Hospital Lymph Node Examination Rates and Survival After Resection for Colon Cancer

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I T MAY BE IMPORTANT THAT A SUFFICIENT number of lymph nodes are obtained and examined at the time of primary resection for colon cancer. More complete node clearance may itself result in lower rates of local or distant cancer recurrence. Obtaining more lymph nodes may also benefit patients to the extent that it allows for more accurate cancer staging and thus more appropriate use of adjuvant chemotherapy for patients with node-positive disease. Numerous observational studies and a recent systematic review suggest that patients in whom a high number of nodes are examined have a considerably lower late mortality after colectomy for colon cancer than patients with fewer nodes examined. Such studies have prompted interest in using minimum lymph node counts as a quality indicator for colon cancer resection.

Recently, in collaboration with the American College of Surgeons, the American Society for Clinical Oncology, the National Comprehensive Cancer Network, and other stakeholders, the National Quality Forum endorsed a 12-node minimum as a consensus standard for hospital-based performance with colectomy for colon cancer. Large private payers have already begun incorporating this measure into their pay-for-performance programs.

For editorial comment see p 2194.

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Using data from the national Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we performed a retrospective cohort study of patients undergoing resection for colon cancer. We explored the extent to which hospital practices vary with regard to lymph node examination after colectomy. Specifically, we assessed whether hospitals' lymph node examination rates were associated with cancer staging, use of adjuvant chemotherapy (indicated for patients with node-positive disease), and 5-year survival.

**Methods**

**Patients and Databases**

For this study, the 1995-2005 national SEER-Medicare-linked database was used. As detailed elsewhere, these files provide a rich source of information on Medicare patients included in SEER, a nationally representative collection of population-based registries of all incident cancers from diverse geographic areas in the United States. The SEER program greatly expanded its coverage in 2001. By the end of the study period, data from population-based cancer registries represented approximately 26% of the US population. For each Medicare patient in SEER, the SEER-Medicare-linked files contain 100% of Medicare claims from the inpatient, outpatient, physician, home health, and hospice files.

From these files, all patients aged 65 to 99 years undergoing major resection for colon cancer between 1995 and 2002 were identified. All Medicare patients with incident cases of these cancers were identified by the appropriate cancer codes from the SEER files. Those patients undergoing colectomy were identified from the Medicare inpatient file using the appropriate procedure codes from the International Classification of Diseases, Ninth Revision. Because lymph node counts are less relevant for this population, patients with distant metastases (stage IV disease) were excluded. The small proportion of patients who received preoperative radiation therapy, which may confound lymph node counts, also were excluded.

**Node Examination Rates**

All US hospitals at which SEER-Medicare patients underwent colectomy during the study period were identified. Each hospital was then characterized according to the proportion of patients in whom at least 12 lymph nodes were examined (the standard endorsed by the National Quality Forum), as determined from the appropriate field within the Patient Entitlement and Diagnosis Summary File from SEER. Hospitals were ranked and sorted into 4 approximately evenly sized patient groups (quartiles). We repeated our analysis after grouping hospitals by their median lymph node counts rather than proportions higher than 12. Because the 2 exposure measures were highly correlated (coefficient of 0.78), results from this sensitivity analysis were nearly identical to those of the baseline analysis and are not presented herein. A separate patient-level analysis also was conducted to address outcomes based on the examination of at least 12 lymph nodes.

**Analysis**

Our primary outcome measure was mortality, determined at 5 years from the date of resection or through 2005, the end of our follow-up period. Cox proportional hazards models were used to examine relationships between hospital node counts and mortality, adjusting for patient characteristics and censoring at the end of the follow-up period. The patient was used as the unit of analysis, with the exposure (lymph node examination quartile) measured at the hospital level. We adjusted for age group (65-69, 70-74, 75-79, 80-84, ≥85 years), sex, race (black, non-black), year of procedure, acuity of the index admission (elective, urgent, emergent), tumor location (right, transverse, left, sigmoid colon), and patient comorbidities. Race was derived from the Medicare Enrollment Database. Race was included in this study to account for its role as a potential confounder or predictor of outcome. We also adjusted for tumor category (Tis, T1, T2, T3, T4). Comorbidities were identified using information from the index admission and inpatient encounters from the preceding 6 months, based on methods described by Elixauser et al. Risk factors were assessed for colinearity, overfitting, and interactions.

Although we subsequently stratified our results by tumor stage, we did not adjust for this variable to avoid introducing bias into our baseline analysis. Hospitals that examine more lymph nodes may appear to have more node-positive patients, even if their patient populations are identical to those at hospitals examining fewer nodes. Risk adjustment would artifactually reward those former hospitals for their “sicker” patients and create a bias toward over-estimating the survival benefit of examining more nodes. As described elsewhere, inpatient, outpatient, and physician claims files were used to identify patients receiving adjuvant chemotherapy, defined as therapy occurring within 6 months before or after surgery. We did not adjust for receipt of adjuvant chemotherapy in our baseline analysis. Chemotherapy for patients with node-positive tumors is hypothesized to be part of the causal pathway underlying potential relationships between higher lymph node counts and improved survival and thus not a true confounder. We did, however, adjust for clinician characteristics potentially associated with improved late survival after cancer surgery, including hospital teaching status, hospital volume, and surgeon volume.

Because patients admitted to the same hospital may have correlated outcomes, marginal survival models that accounted for clustering by hospital were used. Within-cluster correlations in patient failure times (mortality) were first assessed and then robust variance-covariance estimators were derived. These estimators were incorporated into multivariate Cox proportional hazards models assessing relationships between hospital lymph node examination rates and survival. All P values are 2-tailed. The institutional review board of the University of Michigan approved the study protocol. SAS software version 9.1 (SAS Insti-
improved survival, relative to fewer than 12 lymph nodes examined. At the patient level, examination of 12 or more lymph nodes was associated with worse survival than quartile 1 (lowest node examination rate) and quartile 4 (highest node examination rates) had slightly worse survival than quartile 3 (Table 2).

Table 2 also summarizes relationships between survival and hospital lymph node examination rates in various patient subgroups. The AHRs of mortality between the hospitals with the highest node counts and the lowest node counts were lowest among patients with stage II disease (AHR, 0.85; 95% CI, 0.74-0.96) compared with those for stage 0 or I disease (AHR, 0.92; 95% CI, 0.78-1.09) and stage III disease (AHR, 0.98; 95% CI, 0.86-1.11). Patient age and tumor location were not important modifiers of the relationship between hospital lymph node examination rates and late survival after surgery.

We explored the possibility that the importance of hospital lymph node examination rates could be influenced by their relative efficiency in finding positive lymph nodes. For stratified analysis, high and low efficiency was defined according to whether a hospital’s overall ratio of positive nodes to total lymph nodes examined was greater than or less than 8% (the median), respectively. Whether a hospital had high or low ef-

RESULTS

Hospitals in the 4 quartiles varied widely in the number of lymph nodes they examined (Table 1). Only 16% of patients had at least 12 nodes examined at hospitals in the lowest lymph node count quartile vs 61% at hospitals in the highest quartile. Although age and sex did not vary markedly across hospital quartiles, hospitals with the highest proportions of patients with 12 or more lymph nodes tended to treat fewer black patients and more patients who were admitted electively (Table 2). Their patients had fewer sigmoid colon cancers but more right-sided lesions. Hospitals with the highest lymph node examination rates were more likely to be teaching hospitals than hospitals with the lowest rates (58% vs 33%, respectively) and more likely to be high-volume centers (43% vs 20%, respectively). Surgeon volume did not vary considerably across the hospital quartiles (Table 2).

Lymph Node Counts, Staging, and Use of Adjuvant Chemotherapy

Despite wide variation in node examination rates, the number of node-positive tumors found was similar across the hospital quartiles (Table 1). Hospital lymph node examination rates were not associated with the proportion of patients with at least 1 positive node or with the proportion of patients with multiple positive nodes. As a result, cancer stage distributions did not vary considerably across hospital quartiles. Although statistically significant, there were also no clinically important differences in the use of adjuvant chemotherapy, either overall (unadjusted rates of 26% for the highest hospital quartile vs 25% for the lowest hospital quartile) or within cancer stage subgroups.

Lymph Node Counts and Mortality

At the patient level, examination of 12 or more lymph nodes was associated with improved survival, relative to fewer than 12 nodes (adjusted hazard ratio [AHR], 0.83; 95% confidence interval [CI] 0.78-0.88). A similar association was observed within each hospital node count quartile. At the patient level, the association between examination of at least 12 nodes and survival was stronger in patients with stage II disease (AHR, 0.69; 95% CI, 0.63-0.76) than with stage III disease (AHR, 0.89; 95% CI, 0.81-0.98).

However, node examination rates were considerably less predictive of survival when assessed at the hospital level. Before adjusting for confounding patient and clinician factors, hospitals with the highest node examination rates had higher survival rates after resection than hospitals with the lowest rates (FIGURE). Unadjusted 5-year survival probabilities for the 2 hospital groups were 55% and 51%, respectively (P < .001). After risk adjustment, however, hospital lymph node examination rates were no longer associated with survival after surgery (AHR for the highest vs lowest hospital quartile, 0.95; 95% CI, 0.88-1.03; Table 3). In addition to the small differences in survival between hospital groups at the extremes (hospital quartiles 1 and 4), no evidence was found of a dose-response effect in the intermediate quartile comparisons. Although none of these differences were statistically significant, hospital quartile 2 had slightly worse survival than quartile 1 (lowest node examination rates) and hospital quartile 4 (highest node examination rates) had slightly worse survival than quartile 3 (Table 3).
efficiency, there remained no association between hospital node counts and survival rates. This was a post hoc analysis.

**COMMENT**

Our study raises questions about the importance of examining a large number of lymph nodes in patients with colon cancer. Using SEER-Medicare data, we profiled hospitals according to how frequently they achieved the 12-node minimum suggested by many experts and then assessed late survival according to this measure. In addition to reducing risks of patient selection bias within hospitals, comparison at the hospital level most directly simulates survival differences that would be observed if lymph node counts were used as a hospital quality indicator for colon resections. After adjusting for confounding patient and clinician characteristics, we found no evidence of higher 5-year survival at hospitals with higher lymph node examination rates. Our analyses also suggest a simple explanation for these null findings. Regardless of how many lymph nodes hospitals examined, they tended to find the same number of node-positive ones. As a result, higher hospital lymph node examination rates did not result in greater detection of patients with node-positive tumors or higher rates of adjuvant chemotherapy.

### Table 2. Characteristics of Patients Undergoing Resection for Colon Cancer According to Hospital Lymph Node Examination Rates

<table>
<thead>
<tr>
<th>Hospital Lymph Node Count Quartile, No. (%)</th>
<th>Mortality Associated With Variable, HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Quartile (n = 7526)</td>
<td>2nd Quartile (n = 7633)</td>
<td>3rd Quartile (n = 7513)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69 1099 (14.6) 1144 (15.0) 1144 (15.2) 1256 (15.8) 1.28 (1.18-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74 1642 (21.5) 1588 (21.1) 1698 (21.4) 1.59 (1.46-1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79 1586 (24.4) 1869 (24.9) 1972 (24.8)</td>
<td>1.59 (1.48-1.71)</td>
<td></td>
</tr>
<tr>
<td>80-84 1551 (20.3) 1531 (20.4) 1596 (20.1)</td>
<td>2.20 (2.06-2.34)</td>
<td></td>
</tr>
<tr>
<td>≥85 1435 (18.8) 1381 (18.4) 1431 (18.0)</td>
<td>3.44 (2.33-3.66)</td>
<td></td>
</tr>
<tr>
<td>Female sex 4305 (56.4) 4286 (57.1) 429 (56.1) 0.93 (0.90-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black race 1596 (24.4) 1596 (24.4) 1544 (24.1) 1545 (22.5) 0.92 (0.88-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admissio acuity Elective 4410 (57.9) 4519 (60.2) 5050 (63.7)</td>
<td>1.28 (1.19-1.37)</td>
<td></td>
</tr>
<tr>
<td>Emergent 1737 (22.8) 1285 (17.1) 1423 (17.9)</td>
<td>1.62 (1.56-1.69)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity 4814 (63.1) 4823 (64.2) 4907 (61.7) 1.99 (1.91-2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location Right 3650 (55.9) 3619 (56.4) 4032 (58.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse 645 (9.9) 635 (9.9) 665 (9.7) 1.04 (0.98-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left 638 (9.8) 623 (9.7) 633 (9.2)</td>
<td>1.06 (0.99-1.13)</td>
<td></td>
</tr>
<tr>
<td>Sigmoid 1596 (24.4) 1544 (24.1) 1545 (22.5)</td>
<td>0.92 (0.88-0.96)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage (modified AJCC) Stage 0/I 2285 (30.7) 2252 (29.9)</td>
<td>1.28 (1.18-1.37)</td>
<td></td>
</tr>
<tr>
<td>Stage II 2816 (39.5) 2884 (38.3)</td>
<td>1.41 (1.35-1.47)</td>
<td></td>
</tr>
<tr>
<td>Stage III 2386 (31.7)</td>
<td>2.26 (2.16-2.36)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy Overall 2101 (26.4)</td>
<td>0.94 (0.90-0.97)</td>
<td></td>
</tr>
<tr>
<td>Node-negative tumors 927 (17.9) 787 (16.7) 796 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive tumors 1030 (66.5) 965 (60.4) 1137 (47.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician Characteristics Teaching hospital 2917 (38.2) 3708 (49.4) 4636 (58.3)</td>
<td>0.98 (0.96-1.02)</td>
<td></td>
</tr>
<tr>
<td>Hospital procedure volume Low 2903 (38.0) 1670 (22.2) 2206 (27.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium 2400 (31.4) 2855 (38.0)</td>
<td>0.93 (0.89-0.97)</td>
<td></td>
</tr>
<tr>
<td>High 2330 (30.5) 2988 (39.8)</td>
<td>0.90 (0.86-0.93)</td>
<td></td>
</tr>
<tr>
<td>Surgeon procedure volume Low 1740 (35.4) 1742 (34.6) 1715 (31.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium 1637 (33.3) 1643 (32.6)</td>
<td>1.02 (0.97-1.07)</td>
<td></td>
</tr>
<tr>
<td>High 1563 (31.3) 1654 (32.8)</td>
<td>1.08 (1.02-1.13)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio.

Based on data from the 1995-2005 Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The first quartile is considered the lowest lymph node count quartile and the fourth quartile is considered the highest.

Percentages may not equal 100 due to rounding.

Volume categories for hospital and surgeon volume (low, medium, high) are defined by the number of cases (volume) performed that is then divided into evenly distributed terciles.
There are several potential reasons why hospitals that examine more nodes may fail to detect more nodal metastases. First, surgeons may vary in the extent of their resections but not in their ability to include positive nodes with the specimen. For example, some surgeons may tend to resect a relatively small amount of the colon above and below the tumor, but still include within the specimen the mesentry containing the primary vascular pedicle and accompanying lymphatics, which is the primary location for positive nodes. Conversely, surgeons may favor much wider margins. Their specimens may include a broader mesentery and more lymph nodes overall but not necessarily more positive nodes.

A second explanation relates to how surgical specimens are managed in the pathology department, particularly in regard to practices used to dissect lymph nodes from the colectomy specimen. Pathologists, residents, or technicians (depending on the hospital) performing this task may be uniformly successful in finding positive nodes because those nodes tend to be the obvious ones that everyone examines—those that are visible, palpable, or located along the major vascular pedicle supplying the tumor. However, the pathology staff may vary widely in how diligently they search for lower yield nodes in other parts of the specimen. They may also differ in their use of enteric defatting techniques (eg, soaking specimens in alcohol overnight) for extracting additional lymph nodes. Such differences in practice style would explain why hospitals vary in the number of nodes examined but not in the number of positive nodes identified.

A third and related potential explanation is that pathologists or their staff may vary in their skill and efficiency in identifying and dissecting positive nodes from the specimen. If this is the case, more efficient clinicians may feel they need to examine fewer nodes for adequate staging and evolve their practices accordingly. Finally, and perhaps least likely, pathologists may differ in how diligently they examine nodes already dissected from the specimen. For example, some pathologists may simply split (rather than serially section) remaining nodes once they find 1 or 2 positive nodes. If true, we would have expected hospitals with low–node examination rates to have similar proportions of patients with positive nodes, but fewer patients with multiple positive nodes. Our data did not suggest this phenomenon.

Although our findings raise questions about the value of node counts as a hospital quality indicator, they confirm numerous studies suggesting a better prognosis for patients in whom more nodes are examined. A recent systematic analysis summarized data from 17 hospitals that examine more nodes overall but not necessarily more positive nodes.17

Table 3. Association Between Hospital Node Examination Rates and Late Survival After Colectomy for Colon Cancer With Adjustment for Patient and Clinician Characteristics

<table>
<thead>
<tr>
<th>Stage</th>
<th>1st Quartile</th>
<th>2nd Quartile vs 1st Quartile</th>
<th>3rd Quartile vs 1st Quartile</th>
<th>4th Quartile vs 1st Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1</td>
<td>1 [Reference] 1.04 (0.96-1.12)</td>
<td>0.94 (0.87-1.02)</td>
<td>0.95 (0.88-1.03)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 [Reference] 0.99 (0.88-1.13)</td>
<td>0.94 (0.82-1.06)</td>
<td>0.85 (0.74-0.96)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 [Reference] 1.06 (0.93-1.20)</td>
<td>0.91 (0.80-1.04)</td>
<td>0.86 (0.78-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>65-69</th>
<th>70-74</th>
<th>≥75</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference] 1.02 (0.82-1.26)</td>
<td>1.00 (0.84-1.21)</td>
<td>1.05 (0.96-1.14)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Right</th>
<th>Left/rectosigmoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Reference] 1.00 (0.90-1.12)</td>
<td>1.12 (0.98-1.29)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval.

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Lymph node counts and survival after colorectal cancer. We found no significant evidence that patient age is an important modifier of relationships between survival and hospital node examination rates. Nonetheless, the generalizability of our findings to patients younger than 65 years is not known.

Using lymph node counts as a hospital quality indicator is gaining momentum from stakeholders in the health care community. For instance, as part of their pay-for-performance programs, several large private payers have already begun to hold clinicians accountable for recovering at least 12 nodes following resection for colon cancer. Our study also suggests that the potential gains in patient outcomes associated with improvements in this process of care may be small. Further studies based on data sets with more clinical detail would be useful for confirming or refuting our findings, and for identifying more effective levers for improving quality of care in patients with colon cancer.

Author Contributions: Dr Birkmeyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wong, Hollenbeck, Birkmeyer.

Acquisition of data: Morris, Birkmeyer.

Analysis and interpretation of data: Wong, JI, Hollenbeck, Baser, Birkmeyer.

Drafting of the manuscript: Wong, Hollenbeck, Birkmeyer.

Critical revision of the manuscript for important intellectual content: Wong, JI, Hollenbeck, Morris, Baser, Birkmeyer.

Statistical analysis: JI, Baser.

Obtained funding: Birkmeyer.

Administrative, technical, or material support: Wong, Morris, Birkmeyer.

Study supervision: Baser, Birkmeyer.

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REFERENCES


