Identification of 12 or More Lymph Nodes in Resected Colon Cancer Specimens as an Indicator of Quality Performance

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BACKGROUND: Identification of ≥12 lymph nodes in resected colon cancer specimens has been endorsed as a quality indicator. METHODS: The Hoag Hospital cancer registry was used to identify patients diagnosed with colon cancer. The proportion of colon cancer specimens for which ≥12 lymph nodes were identified was determined by anatomic location, stage of disease, patient age, and operating surgeon. Survival was correlated with stage and with whether ≥12 lymph nodes were identified. RESULTS: Pathology procedural changes in 1998 were associated with an increase in the average number of lymph nodes identified from 8.0 to 14.5 (P < .0001); therefore, analysis was limited to 574 patients who underwent surgical resection of colon adenocarcinoma during 1998 to 2005. Identification of ≥12 lymph nodes varied from 57% to 83% by 7 anatomic locations (P < .0001), from 65% to 75% by 5 age cohorts (P = .027), from 59% to 73% by 4 general stages of disease (P = .004), and from 53% to 80% among 12 surgeons who performed at least 17 resections (P = .014). The proportion of resections in which ≥12 lymph nodes were identified was higher for 3 colorectal fellowship-trained surgeons compared with the other 9 surgeons (77% vs 63%, P = .0007), and with 30 surgeons who each performed <10 resections (77% vs 51%, P < .0001). Identification of ≥12 lymph nodes was associated with better survival for patients with stage I (P = .016) and stage II (P = .021) disease. CONCLUSIONS: Anatomic location, colorectal surgical training, and case volume were strongly correlated with the number of lymph nodes identified. Cancer 2009;115:1840–8. © 2009 American Cancer Society.

KEY WORDS: colon cancer, colorectal fellowship training, lymph nodes, pathology procedures.

Colon cancer patients who have metastases to regional lymph nodes (stage III) have worse survival than patients without metastases (stages I and II), and randomized trials prove that such patients benefit from adjuvant systemic therapy.1-5 The accuracy of lymph node staging depends on the adequacy of surgical resection, and identification of lymph node metastases by the pathologist. The sentinel lymph node approach has not proven to be as useful in the staging of colon cancer as in breast cancer and melanoma.6-9

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Therefore, identification and evaluation of all lymph nodes in an appropriately resected specimen is critical for accurate staging to direct therapy.

A variety of studies, including nested cohorts from large randomized trials,10,11 and population-based11-15 and single institution studies,16-25 demonstrate that the number of lymph nodes identified in resected colon cancer specimens is predictive of survival. Various studies support examining at least 7,16,17 9,18-20 10,13,23 11,21 or 1212,15,22,26,27 lymph nodes microscopically. Many trials that emphasized lower thresholds for enumeration of lymph nodes included rectal cancer, which anatomically is associated with fewer lymph nodes, and which increasingly is managed with preoperative radiation and chemotherapy. In recent years, several influential organizations, including the American Society of Clinical Oncology, the Cancer Commission of the American College of Surgeons, the American College of Pathologists, the National Comprehensive Cancer Network, and National Cancer Institute, have endorsed identification of ≥12 lymph nodes from resected colon cancer specimens as a quality performance indicator. Some large payer organizations may use such numbers as a pay-for-performance criterion.28

Obvious questions are: whose performance is actually being evaluated when lymph nodes are enumerated, and what other factors influence these numbers? We used the cancer registry of a high volume, community cancer program to assess clinical correlations with the 12-lymph node threshold. In this analysis we sought to determine the consistency of lymph node enumeration over time, the predictive ability of the 12-lymph node threshold for survival in our patient population, and the association of this 12-lymph node threshold with several variables, including anatomic location, surgeon, patient age, and disease stage.

MATERIALS AND METHODS

Initial Data Set

We analyzed data from the cancer registry of Hoag Hospital, a 498-bed, not-for-profit hospital, nonteaching hospital, located in the coastal community of Newport Beach, in Orange County, California.29 The cancer program is accredited as an “outstanding” comprehensive community cancer program by the Cancer Commission of the American College of Surgeons. Exemption for retrospective analysis of patient data was obtained from the Hoag Hospital Institutional Review Board for the Protection of Human Subjects. Data for Hoag colon cancer patients was compiled annually by Hoag cancer registrars using a software program designed for registry purposes (Electronic Registry Systems, Cincinnati, OH). This registry includes follow-up information for at least 5 years from diagnosis on >90% of patients. Variables included were date of diagnosis, patient age at diagnosis, facility where treatment took place, the surgical procedure that was performed by code and word description, the operating surgeon, anatomic location of the cancer, histology, tumor size, number of lymph nodes identified, number of lymph nodes positive for cancer, general stage (local, regional, or distant), TNM stage per the American Joint Committee on Cancer, date of most recent follow-up or death, and whether patients were living. The database does not include names of individual pathologists who signed pathology reports.

Data Set for Analysis

Data for patients diagnosed with colon cancer were transferred to a Microsoft Excel file for sorting and statistical analyses. Rectal cancer patients were excluded. Patients with subsequent diagnoses of additional colon cancer were entered only once for the first colon cancer diagnosis. The initial data set included 1510 patients. The following cases were excluded: 92 in situ adenocarcinoma, 32 whose surgery took place at a different facility, 244 polyps containing adenocarcinoma (55 underwent only local excision), and 77 for whom the numbers of lymph nodes resected were unknown. This left 1065 patients with invasive colon adenocarcinoma diagnosed during 1989 to 2005, who underwent a surgical resection at Hoag Hospital. More detailed analyses were limited to the subset of 574 patients diagnosed during 1998 to 2005 for reasons discussed below. All statistical measures of probability were 2-tailed. The chi-square test was used for comparisons of multiple proportions. Means were compared using the t test. Survival curves were compared using the log-rank test.
RESULTS

Pathology Processing

In 1998 the Hoag pathology department established a standard protocol for colon cancer resections that included processing by 1 pathology assistant, and the use of fat clearing techniques to facilitate identification of smaller lymph nodes.25,27 The average number of lymph nodes identified increased from 8.0 ± 6.9 during 1989 to 1997 to 14.5 ± 10.2 during 1998 to 2005 (P < .0001).

The average of the median numbers of lymph nodes for successive 3-year periods were 7.5 during 1991 to 1993, 8.3 during 1994 to 1996, 12.3 during 1997 to 1999, 15.2 during 2000 to 2002, and 15.3 during 2003 to 2005. Therefore more detailed analyses were limited to the subset of 574 patients diagnosed during 1998 to 2005. In analyses the numbers of patients ranged from 569 to 574 because of certain missing data. There was also improvement in the quality of pathology reports regarding enumeration of lymph nodes that contained cancer. During 1989 to 1997, 4.7% of colon cancer resections with positive lymph nodes were simply reported as “positive,” compared with 1.3% during 1998 to 2005 (P < .001). The proportion of patients diagnosed with positive lymph nodes increased from 31.6% during 1989 to 1997 to 37.2% during 1998 to 2005 (P = .029). There was no change in the proportion of patients diagnosed with only 1 positive lymph node (10.1% vs 10.6%).

Surgeons Performing Resections

More than 40 surgeons performed colon cancer resections at Hoag Hospital during 1998 to 2005. The median numbers of lymph nodes identified in colon cancer specimens by surgeon ranged from 12 to 19; the proportion of resections with 12 or more lymph nodes identified ranged from 51% to 80% (Table 1). Each of the 12 surgeons (A-L) who performed at least 15 resections averaged 12 lymph nodes per resection. Among these 12 surgeons, there was no clear correlation between number of cases, or cases per year, and the percentage of a surgeon’s specimens associated with 12 or more lymph nodes (P = .24). In contrast, 12 or more lymph nodes were only identified 51% of the time for a cohort of 30 surgeons (M) who each performed <10 colon cancer resections during 1998 to 2005. The surgeon with the highest volume of resections, who performed a fellowship in colorectal surgery, had a higher average number of lymph nodes found in his resections than each of the 3 general surgeons, who performed

<table>
<thead>
<tr>
<th>Surgeon</th>
<th>No. of Cases</th>
<th>Cases per Year</th>
<th>Average No. of Nodes</th>
<th>Median No. of Nodes</th>
<th>% With ≥12 Nodes Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15</td>
<td>3.8</td>
<td>19.1 ± 9.48</td>
<td>19</td>
<td>80.0</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
<td>5.8</td>
<td>18.3 ± 10.07</td>
<td>16</td>
<td>79.3</td>
</tr>
<tr>
<td>C</td>
<td>131</td>
<td>16.4</td>
<td>19.1 ± 10.66</td>
<td>17</td>
<td>77.9</td>
</tr>
<tr>
<td>D</td>
<td>36</td>
<td>7.2</td>
<td>18.8 ± 9.98</td>
<td>15.5</td>
<td>77.8</td>
</tr>
<tr>
<td>E</td>
<td>26</td>
<td>3.7</td>
<td>16.3 ± 9.92</td>
<td>15.5</td>
<td>76.9</td>
</tr>
<tr>
<td>F</td>
<td>21</td>
<td>3.5</td>
<td>17.1 ± 6.51</td>
<td>18</td>
<td>76.2</td>
</tr>
<tr>
<td>G</td>
<td>38</td>
<td>4.8</td>
<td>15.4 ± 7.85</td>
<td>15.5</td>
<td>68.4</td>
</tr>
<tr>
<td>H</td>
<td>22</td>
<td>4.4</td>
<td>16.4 ± 8.10</td>
<td>16.5</td>
<td>68.2</td>
</tr>
<tr>
<td>I</td>
<td>17</td>
<td>2.1</td>
<td>19.6 ± 12.85</td>
<td>15</td>
<td>64.7</td>
</tr>
<tr>
<td>J</td>
<td>43</td>
<td>5.4</td>
<td>14.7 ± 7.66</td>
<td>14</td>
<td>60.5</td>
</tr>
<tr>
<td>K</td>
<td>58</td>
<td>7.4</td>
<td>13.4 ± 6.74</td>
<td>12</td>
<td>55.2</td>
</tr>
<tr>
<td>L</td>
<td>64</td>
<td>8.0</td>
<td>13.6 ± 8.65</td>
<td>13</td>
<td>53.1</td>
</tr>
<tr>
<td>M</td>
<td>71</td>
<td>N/A</td>
<td>13.4 ± 9.13</td>
<td>12</td>
<td>51.4</td>
</tr>
</tbody>
</table>

N/A indicates not available.

M is a cohort of 30 other surgeons who performed less than 10 colon resections on colon cancer patients diagnosed during 1998 to 2005. Differences among identified surgeons in percentages with <12 nodes is significant among the 12 individual surgeons (A-L, P = .012) and with inclusion of cohort M (P = .003). More nodes were identified in specimens from surgeon C than the next three highest volume surgeons, J (P = .012), K (P = .0003), and L (P = .0004). All four of these surgeons performed colon cancer surgeries during all 8 years. Surgeons B, C, and D had completed fellowship training in colorectal surgery.
the second \((P = .012)\), third \((P = .0004)\), and fourth \((P = .0001)\) highest numbers of resections. The 3 colorectal fellowship-trained surgeons (B, C, D) averaged 19 lymph nodes per resection, compared with 15 for the other 9 higher volume surgeons \((P < .0001)\), and 13 for the 30 lower volume surgeons \((P < .0001)\). The difference between noncolorectal fellowship higher volume surgeons and the lower volume surgeons \((P < .0001)\) was not significant \((P = .091)\). The differences among the different surgical cohorts (higher volume vs lower volume and colorectal surgical fellowship trained vs noncolorectal fellowship trained) persisted in an analysis limited to patients ultimately staged as having local or regional disease. This additional analysis was performed in case lower volume and/or noncolorectal fellowship trained general surgeons were more likely to have operated on patients with more advanced disease because of bowel obstruction or other clinical reasons. The proportion of resections in which \(\geq 12\) lymph nodes were identified were, respectively 77% vs 63% for the fellowship-trained vs nonfellowship-trained surgeons \((P = .0007)\), 77% vs 51% for fellowship-trained vs low volume surgeons \((P < .0001)\), and 63% versus 51% for nonfellowship-trained versus low volume surgeons \((P = .066)\).

**Anatomic Locations Within the Colon**

The probability of identifying 12 or more lymph nodes varied with the anatomic site of the resected colon cancer (Table 2). The average and median numbers of lymph nodes were \(\geq 12\) for all anatomic sites, but the range was 57% to 83% for resections in which \(\geq 12\) lymph nodes were identified. Collectively, lesions of the right side of the colon were associated with more lymph nodes, and a higher percentage in which \(\geq 12\) lymph nodes were identified, than left-sided lesions. The highest average numbers of lymph nodes were identified in ascending colon resections, a figure that was higher than cecum \((P < .0001)\), descending colon \((P = .022)\), and sigmoid colon \((P = .0003)\), but not different from the numbers identified in the transverse colon \((P = .11)\) or the splenic or hepatic flexures.

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>No. of Cases</th>
<th>Average No. of Nodes</th>
<th>Median No. of Nodes</th>
<th>% With 12 or More Nodes Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecum</td>
<td>138</td>
<td>14.9±8.06</td>
<td>14</td>
<td>64.5</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>124</td>
<td>19.5±9.25</td>
<td>19</td>
<td>83.1</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>34</td>
<td>18.2±10.64</td>
<td>17</td>
<td>73.5</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>45</td>
<td>16.9±10.62</td>
<td>13</td>
<td>64.4</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>18</td>
<td>16.8±8.71</td>
<td>15</td>
<td>72.2</td>
</tr>
<tr>
<td>Descending colon</td>
<td>30</td>
<td>15.2±8.60</td>
<td>12.5</td>
<td>56.7</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>169</td>
<td>14.6±10.01</td>
<td>13</td>
<td>56.6</td>
</tr>
<tr>
<td>Overlapping lesion</td>
<td>10</td>
<td>16.8±6.36</td>
<td>17</td>
<td>80.0</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5</td>
<td>18.0±6.28</td>
<td>18</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Differences among all sites (first 7 rows) in percentages with 12 or more nodes is significant, \(P = .000004\). Right-sided colon lesions treated by right hemicolectomy, extended right hemicolectomy, or subtotal colectomy (ligation of branches of superior mesenteric artery) had a higher average number of nodes \((17.1±9.27\) vs \(14.7±9.79, P = .0028)\) and a higher percentage of resections with 12 or more lymph nodes compared to left-sided lesions treated by left hemicolectomy (ligation of inferior mesenteric artery) \((258/359 vs 110/197, P = .0001)\). The average numbers of nodes identified in ascending colon resections were higher than the numbers from the cecum \((P = .0002)\), descending colon \((P = .022)\), and sigmoid colon \((P = .0003)\), but not different from the numbers identified in the transverse colon \((P = .11)\) or the splenic or hepatic flexures.
Patient Ages

There were differences in lymph node identification by age cohort (Table 3). Resections from patients <60 years of age were more likely to have ≥12 lymph nodes identified, but there were no differences in the percentages among the 60- to 69-, 70- to 79-, and >80-year age cohorts. The highest average (19.8) and median\textsuperscript{18} numbers of lymph nodes were identified in resections from patients younger than 50 years; there were no differences between any other pairs of age groups.

Disease Stage

The numbers of lymph nodes identified in colon cancer specimens varied with the general stage of disease (Table 4). There were more lymph nodes identified, and higher proportions of resections containing ≥12 lymph nodes, from patients with regional disease (T3 or T4 local extension and/or lymph node metastases) than patients who had either local disease (T1 or T2) or distant metastases. In each stage of disease, the patient cohorts whose samples had <12 lymph nodes identified had a somewhat older average age, but none of these differences reached statistical significance.

Survival

The 12-lymph node threshold was associated with better survival for patients with stage I or stage II disease, but not stage III or IV. Patients with local colon cancer (stage I),
who had \( \geq 12 \) lymph nodes identified, had better survival than stage I patients in whom \(< 12\) lymph nodes were identified (Fig. 1). A similar difference in survival was observed for patients with stage II (T3 or T4 and N0) colon cancer (Fig. 2), and for the 55-patient subset of stage II patients who had T3N0M0 disease (\(P = .025\)). There was no difference in survival for stage II patients whose cancers were resected by the 3 colorectal fellowship-trained surgeons (\(n = 74\)) compared with those resected by other higher volume surgeons (\(n = 85\)) (\(P = .545\)). For those patients who underwent surgical resection, but had distant metastatic disease at diagnosis, there was no difference in survival by the 12-lymph node threshold (\(P = .465\)). It should be noted that these sample sizes are relatively small, and do not take into account other risk factors such as age, performance status, comorbid conditions, or whether adjuvant chemotherapy was used.

**DISCUSSION**

Our study confirms that the numbers of lymph nodes identified in resected colon cancer specimens can be greatly increased by changes in pathology department procedures.\(^{25,27}\) It also shows there is substantial variation in the number of lymph nodes identified by anatomic region, patient age, disease stage, and surgeon. Identification of \( \geq 12 \) lymph nodes in resected colon cancer specimens was predictive of outcome in stage I and stage II disease, even in a hospital in which high volumes of colon cancer resections are performed,\(^{30}\) and in an era when the average number of lymph nodes identified was \(> 12\). We were surprised to find substantial variation in the average numbers of lymph nodes identified in colon cancer resections by individual surgeons. Strengths of this study include: 1) focus on patients diagnosed in a recent era, 1998 to 2005; 2) all patients underwent surgery in 1 facility in which high volumes of colon cancer resections are performed; 3) all colon cancer resections were analyzed in 1 pathology department using a standard procedure that increases the probability of identifying \( \geq 12 \) lymph nodes in colon resections; and 4) only colon cancer resections were analyzed, rectal cancers being excluded.

To our knowledge, this is the first study addressing the implications of the 12-lymph node quality indicator for colon cancer resections by individual surgeons. Although surgeons claim to perform similar surgical resections for colon cancer, there was substantial variation in the numbers of lymph nodes identified, and the rates in which 12 or more lymph nodes were identified. This study raises interesting questions regarding the possible
significance of surgical volumes and training in relation to the number of lymph nodes identified in resected specimens. Three surgeons who had completed fellowship training in colorectal surgery averaged 19 lymph nodes per resection, and >77% of their resections exceeded the 12-lymph node threshold. These figures were higher than those achieved by 9 surgeons who did not have such training. Volume alone was not predictive of high quality performance, but a cohort of surgeons who performed a low volume of resections had the lowest rates of meeting the 12-lymph node threshold. The 3 lowest rates of resections in which 12 or more lymph nodes were identified (51% to 55%) were performed by a cohort of 30 surgeons who performed fewer than 10 colon cancer operations in the time period studied, and by surgeons who had the second and third highest volumes of cases. However, this study demonstrates that several variables are associated with lymph node number, so caution is advised before concluding that inferior quality of care is the explanation for failure to identify at least 12 lymph nodes, especially when the sample size is small. Furthermore, the findings may not be representative of all institutions.

Our study confirms that the numbers of lymph nodes identified in colon cancer resections can be increased by implementation of specific tissue processing procedures. Before 1998, 5 board-certified pathologists performed lymph node dissections according to their individual training. Between 1996 and 1998, a pathology assistant was trained to perform the lymph node dissection on all colon cancer resections, and in 1998 a standard protocol was initiated that included removing the mesentery, fixing it in 10% formalin, and identifying lymph nodes by slicing, visual inspection, and manual palpation. If <12 lymph nodes were identified, the sliced mesentery was fixed overnight in 100% ethanol and reexamined. The median number of lymph nodes in resected samples increased from 9 during 1991 to 1997 to 15 during 1998 to 2005.

The proportion of resections with ≥12 lymph nodes varied by anatomic region. The extent of lymph node resection is determined by en bloc removal of the blood supply, and accompanying lymphatics, to the origin of the primary arterial vessel feeding the cancerous bowel segment. Lymph first drains to pericolic lymph nodes adjacent to the bowel, then to intermediate lymph nodes next to large mesenteric artery branches, and finally to lymph nodes lying adjacent to the origins of the major mesenteric vessels. The right side of the colon, transverse colon, and splenic flexure all drain to lymph nodes that follow the superior mesenteric artery. The left side of the colon drains to lymph nodes that follow the inferior mesenteric artery. Lesions of the cecum and ascending colon ideally are treated by right hemicolectomy with ligation of ileocolic and right colic arteries. Hepatic flexure lesions require an extended right hemicolectomy that adds ligation of the middle colic artery. Transverse colon and splenic flexure lesions require a subtotal colectomy that adds ligation of the left colic artery to the 3 ligated in a subtotal colectomy. Descending and sigmoid colon cancers are treated by left hemicolectomy with ligation of the inferior mesenteric artery. Thus, based on the volume of arterial distribution, one would expect the highest number of lymph nodes for lesions of the splenic flexure, followed by transverse colon and hepatic flexure, then ascending colon and cecum, then descending and sigmoid colon. In our series, more lymph nodes were identified from the distribution of the superior mesenteric than inferior mesenteric artery, but the results were not totally predicted by the volume of arterial distribution. For instance, the average number of lymph nodes was highest for lesions of the ascending colon, not the splenic flexure. In addition, although a right hemicolectomy is supposed to be performed for both cecal and ascending colon lesions, more lymph nodes were identified with lesions of the ascending colon (median = 19) than the cecum (median = 14), whether a hemicolectomy or partial colectomy was performed, according to registry data.

The immune status of patients and cancer-specific immune responses may stimulate reactive lymph nodes that would be easier to identify because of larger size. Increasing age is associated with a decline in immune competence. We found that patients younger than 60 years had a higher number of lymph nodes identified in their cancer specimens than older age cohorts; the greatest numbers of lymph nodes were identified in patients <50 years of age. There was also an association between disease stage and the number of lymph nodes identified. Patients with local extension of disease (T3 or T4) had the highest numbers of lymph nodes identified compared with patients with local disease, lymph node-positive disease, or distant metastatic disease. It is possible this also relates to the immune system.
In our study, the 12-lymph node threshold was predictive of survival for patients with local (stage I, T1, or T2) or locally extensive cancer (stage II, T3, or T4), but not for patients with lymph node-positive (stage III) or distant metastatic disease (stage IV). In a pooled analysis of more than 60,000 colon cancer patients, identification of higher numbers of lymph nodes was associated with increased survival for patients with stage II colon cancer in 16 of 17 studies, and for patients with stage III colon cancer in 4 of 6 studies. However, some studies that suggested a benefit for III patients included a high proportion of patients who did not receive adjuvant chemotherapy, and some included rectal cancers.10,20

In summary, in this community setting there were several variables associated with the failure to identify ≥12 lymph nodes in resected colon cancer specimens, including age, stage, anatomic location, and surgical volume. The suggested significance of a relationship between survival and identification of 12 or more lymph nodes was supported for stage I and stage II disease. The importance of physician training and volume in relation to this indicator requires further investigation.

Conflict of Interest Disclosures

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References


