Close Collaboration Between Surgeon and Pathologist Is Essential for Accurate Staging of Early Colon Cancer

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The postoperative rate of recurrence for stage II colon cancer exceeds 20%, and evidence suggests that some patients with stage II disease have a worse prognosis than those with stage III disease.[1] If patients with high-risk stage II disease could be accurately identified, they might benefit from postoperative chemotherapy, a treatment that is highly effective for metastatic disease but too toxic and expensive for routine use in node-negative colon cancer. Unfortunately, while the prognostic importance of lymph node status is undisputed, there is no consensus or standardization of techniques for sampling and assessment of lymph nodes in a resected specimen. Which and how many nodes should be sampled? How should these nodes be assessed for tumor? What is the clinical significance of micrometastases in the lymph nodes?

Nodes in a resected specimen have traditionally been identified by a combination of visualization and palpation on gross pathologic examination. However, simply removing and examining all palpable lymph nodes[2] is inadequate because metastasis frequently targets nodes <0.5 cm in diameter.[3] The thoroughness of the lymph node harvest from the resection specimen and the number of nodes examined have been stressed by many authors. Joseph et al[4] suggested 40 nodes as a minimum for accurate assessment. At the other end of the spectrum is an increasingly popular selective sampling approach based on identification of the sentinel lymph node (SN). Lymphatic mapping and sentinel node biopsy (SNB) was originally described in melanoma to identify the node(s) most likely to contain any evidence of metastasis from a primary tumor. In both breast cancer and melanoma, SNB is used to identify suboccult nodal metastasis in the tumor-draining lymphatic basin; complete lymphadenectomy is undertaken only when tumor cells are identified in a SN. In colon cancer, SNB also can identify early evidence of nodal metastasis but does not change the extent of surgery, since nodes are routinely removed en-bloc with the primary tumor. Thus, the SN can be identified either before (in vivo mapping) or after (ex vivo mapping) the tumor has been resected. As in melanoma and breast cancer, blue dyes and/or radioactive colloids are used as mapping agents.

However, even when a node is selectively targeted for assessment, metastases may go undetected. Indeed, standard assessment based on hematoxylin and eosin staining of one level of a paraffin-embedded block reportedly can miss as many as 33% of metastases.[5] Techniques such as multilevel sectioning, cytokeratin immunohistochemistry (IHC), and reverse transcription-polymerase chain reaction (RT-PCR) can identify missed tumor cells in nodes,[6] but their impact on staging is unclear.[7]

Still, the importance of small metastases is acknowledged by current staging guidelines from the American Joint Committee on Cancer and International Union against Cancer.[8,9] Nodal positivity corresponds to macrometastases (>2 mm) or micrometastases (between 2 mm and 0.2 mm); although isolated tumor cells and tumor cell clusters (up to 0.2 mm) are not considered to be evidence of nodal metastasis, their inclusion in the guidelines of the American Joint Committee on Cancer and International Union against Cancer is evidence of their potential prognostic importance.

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This issue of *Annals of Surgery* includes reports from 2 large prospective trials that evaluated the role of SNB in colon cancer. Stojadinovic et al[10] demonstrated that conventional pathologic staging was less effective than staging based on ex vivo SNB. Their rate of SN identification was 97%, although the sensitivity of SNB for macrometastases was only 69%. Focused analysis of the SN identified metastases in 57% of patients, as compared with 31% for conventional staging. This upstaging consisted mostly of isolated tumor cells and tumor cell clusters (15 of 56 or 27%); 6 patients (11%) had SN micrometastases. Five medical centers in 3 countries participated in this study with blinded centralized pathologic review. The study was well designed and accrual was completed as expected. The strength of the study was that it required formal SNB training and specimen handling. Additionally, each surgeon completed at least 6 cases prior to entering the study and 6 surgeons performed all 82 SNB cases. The sensitivity in this study was increased by examining at least 4 lymph nodes.

Bembenek et al[11] report a prospective multicenter trial of 315 patients from 19 centers in Germany. The rate of SN detection was 85%; the sensitivity of identifying macrometastases was 54%. Focused analysis of the SN upstaged 21% of cases, 16% with isolated tumor cells and 5% with micrometastases. Aberrant drainage was identified in 1.6% of patients. Unlike the study from Stojadinovic et al,[10] SNB was performed in vivo and an instructional video was given to all participating surgeons. The detection rate and sensitivity of SNB increased when the patient's body mass index was below 24 and when the surgeon had performed more than 22 SNB procedures. Despite different techniques, both studies reported similar rates of nodal macrometastases and similar rates of SNB-based upstaging.

Previously reported rates of successful SN localization vary from 58%[12] to 100%.[13–16] The large variation in sensitivity and specificity has been attributed to differences in technique, experience, patient selection, and perhaps more complex lymphatic pathways in colon cancer. In the 2 studies appearing in this issue of *Annals of Surgery*, reported rates of accuracy and sensitivity reflected surgical experience. A direct correlation between experience and results was reported for the first Multicenter Selective Lymphadenectomy Trial for Melanoma[17] and for the American College of Surgeons Oncology Group multicenter trial for breast cancer; in both trials, adequate training required performance of least 20 to 30 SNB procedures.[18,19] By contrast, the CALGB 8001 study involved 25 surgeons from 13 institutions, who performed SNB in only 72 enrolled subjects. Most surgeons performed fewer than 5 SNB procedures and the SN identification rate was only 66%. The false-negative rate dropped to 12% when nodal specimens were examined by IHC.[20]

The 2 studies in this issue had different definitions of micrometastases; only in the study of Stojadinovic et al[10] were tumor cell clusters classified as nodal positivity. This difference emphasizes the ongoing debate over the prognostic significance of micrometastases. In a recently reported meta-analysis of studies between 1991 and 2002,[21] only 12 trials for patients with stage II colon cancer reported survival data. Micrometastases were identified by IHC in 31.2% of patients (192 of 608) and by RT-PCR in 44% of patients (77 of 173). Three-year rates of disease-free and overall survival were 80.4% and 82.6%, respectively, in IHC-negative patients versus 76.4% and 80.9%, respectively, in IHC-positive patients. Overall survival was significantly higher when RT-PCR findings were negative versus positive (96.5% vs. 77.8%; $P < 0.001$).[21] Micrometastases detected retrospectively by RT-PCR techniques had a stronger correlation with overall survival than did micrometastases identified by IHC. This finding might reflect a more complete nodal analysis by RT-PCR, compared with limited sectioning for IHC. This meta-analysis, however, clearly supports further study and standardization of techniques to evaluate the potential prognostic role of micrometastases in stage II colon cancer.

Although the studies of Bembenek et al[11] and Stojadinovic et al[10] focus on SNB, both also determined the adequacy of lymphadenectomy. The median number of nodes removed was 20 in the Bembenek study and 18 in the Stojandinovic study. These numbers are relatively high, possibly reflecting surgeon skill and meticulous pathologic evaluation. Reinbach et al[17] described a trend toward an increase in the number of nodes (13 vs. 7.5) in colon cancer specimens from surgeons with a particular colorectal interest as compared with those without such an interest. A recent analysis of intergroup trial INT 0089 demonstrated that 5-year survival was 73% for removal of 1 to 10 lymph nodes, as compared with 87% for removal of >20 nodes.[22] In a series of 35,787 cases of stage II colon cancer from the National Cancer Data Base, the 5-year survival rate was 64% if only one or two lymph nodes were examined, versus 86% if more than 25 lymph nodes were examined.[23] The National Cancer Data Base investigators concluded that at least 13 lymph nodes should be retrieved and declared negative for a diagnosis of stage II disease.

We recently reviewed the Surveillance, Epidemiology, and End Results database for all patients undergoing resection of histologically confirmed colon cancer between 1988 and 2000; our purpose was to determine whether increasing the number of resected lymph nodes correlated with improved survival.[24] The median number of nodes sampled in more than 82,896 patients was 9. Resection of at least 15 nodes prolonged median overall survival by 11 months in patients with stage I disease, 54 months in stage II disease, and 21 months in stage III disease. These differences match or exceed the best reported results for even the newest combination adjuvant chemotherapy regimens. In our Surveillance, Epidemiology, and End Results analysis,[24] the most common number of dissected nodes was zero, indicating that many patients received operations not based on standard oncologic principles. While improvement was noted over time, even in the most recent period examined the majority of patients did not have even 10 lymph nodes examined.

Apart from variations in the number of sampled nodes and the technique of nodal assessment, there are variations in pathologic technique and skill. Different pathologists and assistants may have markedly different nodal yields on aver-

age. Failure to pathologically examine all nodes within a specimen might also reflect an increase in inaccuracies in other types of examination such as radial margins of the primary tumor; failure to achieve negative radial, proximal, and distal margins can be a negative prognostic factor.[25] It is also important to recognize that patients may be at high risk for recurrence regardless of micrometastatic involvement. Poorly differentiated primary tumors, the presence of signet-ring cells, and lymphovascular and venous invasion all have an adverse impact.

Although the field is undeniably in a state of flux, rudimentary guidelines can be established. First, the surgeon must apply oncologic principles during a colon resection to increase the yield of lymph nodes. Second, the pathologist must consider techniques that increase the accuracy of nodal analysis. Microscopic examination of one histologic section for each lymph node found on macroscopic examination (standard practice) is inadequate for the detection of micrometastases. Third, the surgeon and the pathologist must collaborate closely to standardize staging and develop a clinically meaningful definition of micrometastases. Until then, the value of supplemental techniques such as SNB and molecular assessment cannot be accurately determined.

It is likely that patients with stage II colon cancer based on adequate nodal sampling without adverse prognostic factors will be cured by surgery alone. If micrometastases are found to be an adverse prognostic risk factor for recurrence, further trials will be needed to examine the effect of chemotherapy for these patients. The improved risk-stratification afforded by standardization of both surgical and pathologic techniques will greatly improve the selection of patients for chemotherapy, thus avoiding its toxicity and expense for those cured by surgery alone.

REFERENCES

1. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with new American Joint Committee on Cancer Sixth edition staging. *J Natl Cancer Inst*. 2004;96:1408–1409.
2. Truong PT, Berthelet E, Lee J, et al. The prognostic significance of the percentage of positive/dissected axillary lymph nodes in breast cancer recurrence and survival in patients with one to three positive axillary nodes. *Cancer*. 2005;103:2006–2014.
3. Rodriguez-Bigas MA, Maamoun S, Weber TK, et al. Clinical significance of colorectal cancer: metastases in lymph nodes <5 mm in size. *Ann Surg Oncol*. 1996;3:124–130.
4. Joseph NE, Sigurdson ER, Hanlon AL, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. *Ann Surg Oncol*. 2003;10:213–218.
5. Feezor RJ, Copeland EM, Hochwald SN. Significance of micrometastases in colorectal cancer. *Ann Surg Oncol*. 2002;9:944–953.
6. Gusterson B. Are micrometastases clinically relevant. *Br J Hosp Med*. 1992;47:247–248.
7. Van Wyk Q, Hosie KB, Balsitis M. Histopathological detection of lymph node metastases from colorectal carcinoma. *J Clin Pathol*. 2000; 53:685–687.
8. Green FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer Verlag; 2002.
9. International Union Against Cancer (UICC). In: Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumors*, 6th ed. New York: Wiley; 2002.
10. Stojadinovic S, Nissan A, Protic M, et al. Prospective randomized study comparing sentinel lymph node evaluation with standard pathological evaluation for the staging of colon carcinoma: results from the United States Military Cancer Institute Clinical Trials Group Study GI-01.
11. Bembenek AE, Rosenberg R, Wagler E, et al. Sentinel lymph node biopsy in colon cancer: a prospective multicenter trial. *Ann Surg*. 2007;245:858–863.
12. Esser S, Reilly WT, Riley LB, et al. The role of sentinel lymph node mapping in staging of colon and rectal cancer. *Dis Colon Rectum*. 2001;44:850–856.
13. Bilchik AJ, Saha S, Wiese D, et al. Molecular staging of early colon cancer on the basis of sentinel node analysis: a multicenter phase II trial. *J Clin Oncol*. 2001;19:1128–1136.
14. Bilchik AJ, Trocha SD. Lymphatic mapping and sentinel node analysis to optimize laparoscopic resection and staging of colorectal cancer: an update. *Cancer Control*. 2003;10:219–223.
15. Trocha SD, Nora DT, Saha SS, et al. Combination probe and dye-directed lymphatic mapping detects micrometastases in early colorectal cancer. *J Gastrointest Surg*. 2003;7:340–346.
16. Wood TF, Saha S, Morton DL, et al. Validation of lymphatic mapping in colorectal cancer: in vivo, ex vivo and laparoscopic techniques. *Ann Surg Oncol*. 2001;8:150–157.
17. Reinbach DH, McGregor JR, Murray GD, et al. Effect of the surgeon's specialty interest on the type of resection performed for colorectal cancer. *Dis Colon Rectum*. 1994;37:1020–1023.
18. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg*. 2005;242:302–313.
19. Posther KE, McCall LM, Blumencranz PW, et al. Sentinel node skills verification and surgeon performance: data from a multicenter clinical trial for early-stage breast cancer. *Ann Surg*. 2005;242:593–599.
20. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med*. 2001;345:1091–1097.
21. Iddings D, Ahmad A, Elashoff D, et al. The prognostic effect of micrometastases in previously staged lymph node negative (N0) colorectal carcinoma: a meta-analysis. *Ann Surg Oncol*. 2006;13:1386–1392.
22. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol*. 2003;21:2912–2919.
23. Swanson RS, Compton CC, Stewart AK, et al. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol*. 2003;10:65–71.
24. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer. *Ann Surg*. 2006;244:602–610.
25. Wright FC, Law CHL, Last L, et al. Lymph node retrieval and assessment in stage II colorectal cancer: a population-based study. *Ann Surg Oncol*. 2003;10:903–909.