

Editorial

Lymphatic Mapping of Nodal Micrometastasis in Colon Cancer: Putting the Cart Before the Horse?

Anton J. Bilchik, MD, PhD, FACS, and Dean T. Nora, MD

Among the numerous prognostic markers investigated in colon cancer, lymph node status remains the most influential in regard to disease-free and overall survival. Not only is it the single most important prognostic factor, but the presence or absence of lymph node metastasis largely dictates whether patients should receive adjuvant chemotherapy. The majority of node-positive patients are treated with regimens based on 5-fluorouracil/irinotecan, with a documented survival benefit. This benefit is typically not seen in node-negative patients.¹ Despite complete resection, however, up to 30% of these patients will relapse and succumb to overwhelming metastasis.²

It has been suggested that patients with node-negative disease relapse because their lymph nodes are not really free of tumor. Tepper et al.³ recently reported that more nodes are examined in patients with node-positive than node-negative disease. They found that rates of overall survival and recurrence were directly correlated with the number of nodes examined: 5-year recurrence was 37% and overall survival was 68% when up to four lymph nodes were examined, versus 19% and 82%, respectively, when at least 14 nodes were examined. Because the extent of resection is relatively standard for colorectal cancer, these data suggest a sampling error. Conventional methods for examining lymph nodes have specific limitations that increase the risk of missing occult disease.

Lymphatic mapping as popularized in melanoma by Morton et al.⁴ not only improves staging accuracy but also reduces the number of unnecessary lymph node dissections. This does not apply to colon cancer where the morbidity of the operation is not dependent on the

number of lymph nodes removed. Instead, the major issue in colon cancer is whether the resection specimen includes an adequate sample of lymph nodes. It is not uncommon for a surgeon to submit a bulky tumor with a generous mesenteric specimen, only to read in the pathology report that six nodes were examined and none contained metastasis.

Intraoperative lymphatic mapping is a powerful technique that elegantly addresses the limitations of conventional nodal examination. Dye-directed mapping identifies the sentinel lymph node (SLN), i.e., the node that has the highest likelihood of harboring metastasis if present. Occasionally, aberrant drainage patterns are detected that change the extent of resection; this has been reported in previous studies^{5,6} and is also mentioned in the report from Paramo's group in this issue of the *Annals of Surgical Oncology*. Finally, focused analysis of the SLN using serial step sectioning and immunohistochemistry (IHC) further enhances the ability to detect nodal tumor and accurately predicts the status of the regional nodal basin.

Using lymphatic mapping, Paramo et al. were able to detect micrometastatic disease in lymph nodes that stained negative for tumor by hematoxylin and eosin (H&E). Their findings were similar to our experience at the John Wayne Cancer Institute^{5,7,8} and to the experience of Saha et al.⁶ Although the authors state that they upstaged 11% (6 of 50) of the cohort using IHC, we believe this to be higher (17%) because they actually upstaged the smaller subset of H&E-negative patients (6 of 36). The universal application of this technique has been questioned because of inconsistencies in sensitivity and accuracy among a variety of authors.^{9,10} However, this article demonstrates that seven surgeons were successful in performing this procedure, with a relatively short learning curve. This supports the simplicity of lymphatic mapping in colon cancer; others have reported a much longer learning curve for breast cancer.¹¹

Received May 16, 2002; accepted May 16, 2002.

From the Division of Surgical Oncology, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California.

Address correspondence to: Anton J. Bilchik, MD, PhD, FACS, John Wayne Cancer Institute, 2200 Santa Monica Blvd., Santa Monica, CA 90404; Fax: 310-449-5261; E-mail: bilchika@jwci.org.

Although there is limited prospective data on the prognostic role of micrometastases (MM), new data indicate a similar prognosis for patients with nodal MM or node-positive disease. Wong et al.¹² suggest that the overall volume of metastases is not as important as the overall number of lymph nodes which are involved. One might then suggest that all lymph nodes should be step sectioned and stained with IHC and that there is no need for lymphatic mapping. Clearly, this is neither cost nor time effective. Wiese et al.¹³ performed multilevel step sectioning with IHC on all lymph nodes and found that nonsentinel MM were rare when the SLN was negative. This validates the power of lymphatic mapping in finding the node(s) that has the highest likelihood of harboring metastases if present.

As mentioned earlier, the prognostic significance of MM is a subject of intense debate. We agree that the presence of cytokeratin-positive cells within a lymph node at present has no known prognostic significance. We are even unsure whether or not they are truly tumor cells. Workers in our laboratory using differential tumor markers are evaluating whether these cells represent degenerating tumor cells, viable tumor cells, or benign mesothelial cells. Earlier studies using IHC to detect microscopic tumor in node-negative patients demonstrated no influence on overall survival, yet studies using more advanced molecular techniques seem to suggest otherwise.¹⁴ A major problem is that there has never been a standardized definition of MM until recently.

The newly published sixth edition of the *AJCC Cancer Staging Manual* makes a clear distinction between MM and isolated tumor cells, and it recommends guidelines for their reporting.¹⁵ Patients whose lymph nodes contain isolated tumor cells (<0.2 mm in diameter) are classified as N0, with a modifier stating how the cells were detected. In the absence of prognostic data, patients with nodal MM (0.2 to 2 mm) are classified as N1. To comply with the new classification system, IHC will need to be performed on all lymph nodes or selectively on the SLN. Lymphatic mapping clearly is a better option because it accurately identifies MM and may help determine their prognostic significance. The other alternative is to ignore the new American Joint Committee on Cancer (AJCC) guidelines until further prognostic data are available.

We agree with Lee Ellis, MD, at M. D. Anderson Cancer Center who recently emphasized that molecular profiling and perhaps gene array analysis of the primary tumor are the future of staging for colon cancer.¹⁶ However, unless standardized techniques are applied prospectively to these promising prognostic markers, they will remain only promising.

Clearly the race is on between technology and science. We believe that lymphatic mapping has an edge because it is relatively simple to perform, has a high degree of accuracy, and can routinely detect microscopic tumor within lymph nodes. Moreover, surgeons and pathologists are far more likely to prefer a focused examination of only a few nodes rather than at least 36 nodes, the number recently reported by Joseph et al.¹⁷ at the Society of Surgical Oncology as the minimum for a 50% chance of accurate staging. The importance of the current study by Paramo's group is its validation of the technical feasibility of lymphatic mapping in colon cancer. Skip metastases can occur, especially in large, bulky tumors with grossly positive lymph nodes and in patients whose lymphatic drainage may have been disrupted by previous surgery. Because the authors excluded all patients who had previously undergone surgery or radiotherapy, their false-negative rate was favorable. Furthermore, lymphatic mapping upstaged a significant proportion of cases in which the nodes were negative by H&E.

We have recently adopted the AJCC guidelines for the reporting of isolated tumor cells and MM. Although we are unsure about their prognostic significance and believe they might unfairly influence choice of adjuvant therapy, our Investigational Review board determined that this information should be included in the pathology report. We think this has created a problem because all of the patients with isolated tumor cells and MM are receiving adjuvant chemotherapy. Even as the medical community becomes more aware of the lack of data to support adjuvant chemotherapy in this setting, oncologists feel the pressure to treat all patients with chemotherapy. This is going to make it extremely difficult for us to determine the prognostic significance of MM. In the era of lymphatic mapping, recommendations for the use of adjuvant chemotherapy in colon cancer may need to be redefined.

Acknowledgments: Supported by grant CA090848 from the National Cancer Institute and by funding from the Rogovin-Davidow Foundation, Los Angeles, CA, and the Rod Fasone Memorial Cancer Fund, Indianapolis, IN.

REFERENCES

1. Impact B2 Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol* 1999;17:1356-63.
2. Cohen AM, Kelsen D, Saltz L, et al. Adjuvant therapy for colorectal cancer. *Curr Prob Cancer* 1998;22:5-65.
3. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001;19:157-63.
4. Morton DL, Wen D, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392-9.

5. Wood T, Saha S, Morton DL, et al. Validation of lymphatic mapping in colorectal cancer: in vivo, ex vivo, and laparoscopic techniques. *Ann Surg Oncol* 2001;8:150–7.
6. Saha S, Bilchik A, Wiese D, et al. Ultrastaging of colorectal cancer by sentinel lymph node mapping technique—a multicenter trial. *Ann Surg Oncol* 2001;8(9 Suppl):94–8.
7. Bilchik AJ, Giuliano AE, Essner RE, et al. Universal application of intraoperative lymphatic mapping and sentinel lymphadenectomy in solid neoplasms. *Cancer J Sci Am* 1998;4:351–8.
8. 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;19:1128–36.
9. Joosten J, Strobbe L, Wauters C, et al. Intraoperative lymphatic mapping in colorectal carcinoma. *Br J Surg* 1999;86:482–6.
10. Merrie A, van Rij A, Phillips L, Rossaak JJ, Yun K, Mccall JL. Diagnostic use of the sentinel node in colon cancer. *Dis Colon Rectum* 2001;44:400–17.
11. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; 220:391–401.
12. Wong JH, Steinemann S, Tom P, et al. Volume of lymphatic metastases does not independently influence prognosis in colorectal cancer. *J Clin Oncol* 2002;20:1506–11.
13. Wiese D, Saha S, Badin J, et al. Pathologic evaluation of sentinel lymph nodes in colorectal carcinoma. *Arch Pathol Lab Med* 2000; 124:1759–63.
14. Liefers GJ, Cleton-Jansen AM, van de Velde CJ, et al. Micrometastases and survival in stage II colorectal cancer. *N Engl J Med* 1998;339:223–8.
15. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer-Verlag, 2002.
16. Ellis LM. A perspective on sentinel lymph node biopsy in colorectal cancer: the race between surgical technology and molecular oncology. *Ann Surg Oncol* 2000;7:475–6.
17. Joseph N, Sigurdson E, Hanlon A, et al. Accuracy of determining nodal negativity in colorectal cancer based on the number of nodes retrieved on resection. Abstract presented at: Annual Meeting of the Society of Surgical Oncology; March 14–17, 2002; Denver, CO.



LIPPINCOTT
WILLIAMS & WILKINS

**Unauthorized Use
Prohibited**