



J.J. Mahany, Jr. *Road to Wonder Lake*, 2002. Photograph. Denali National Park, Alaska.

The combination of lymphatic mapping and sentinel lymph node analysis continues to show promise in improving staging accuracy in colon cancer.

Lymphatic Mapping and Sentinel Node Analysis to Optimize Laparoscopic Resection and Staging of Colorectal Cancer: An Update

Anton J. Bilchik, MD, PhD, FACS, and Steven D. Trocha, MD

Background: *Laparoscopic colectomy for colorectal cancer (CRC) has been criticized because of the potential for inadequate nodal dissection and incomplete staging. Lymphatic mapping (LM) and sentinel lymph node (SLN) analysis can improve the accuracy of staging in open colectomy, but its utility during laparoscopic colectomy is unknown.*

Methods: *Between 1996 and 2002, 30 patients with clinically localized colorectal neoplasms or premalignant polyps underwent subserosal or submucosal injection of isosulfan blue dye via a colonoscope, via a percutaneously inserted spinal needle, or through a hand port. Blue-stained lymphatics were visualized through the laparoscope and followed to the SLN, which was tagged. The colectomy was completed in standard fashion. All lymph nodes were stained by hematoxylin and eosin, and multiple sections of each SLN were examined by immunohistochemical (IHC) staining using cytokeratin antibody.*

Results: *An SLN was identified laparoscopically in all patients. The SLN accurately predicted the tumor status of the nodal basin in 93% of cases. In 8 cases (29%), an unexpected lymphatic drainage pattern altered the extent of mesenteric resection, and in 4 cases (14%), tumor deposits were identified only by IHC and limited to the SLN.*

Conclusions: *This study, which updates a preliminary report (Am Surg. 2002;68:561-565) confirms that SLN mapping during laparoscopic colon resection can alter the margins of resection and may improve staging by allowing a focused pathologic examination of the SLN, although direct comparison with the "gold standard" of open CRC with adequate lymphadenectomy will be required. Better ultrastaging of CRC lymph nodes may more accurately assign patients to prospective protocols to assess the significance of nodal micrometastases or isolated tumor cells.*

From the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California, and the Century City Hospital, Los Angeles, California.

Submitted September 19, 2002; accepted February 20, 2003.

Address reprint requests to Anton J. Bilchik, MD, PhD, John Wayne Cancer Institute, 2200 Santa Monica Boulevard, Santa Monica, CA 90404. E-mail: bilchika@jwci.org

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

Supported in part by funding from the Rogovin-Davidow Foundation, Los Angeles, California, and the Rod Fasone Memorial Cancer Research Fund, Indianapolis, Indiana.

Introduction

We recently reported on our experience with the lymphatic mapping (LM) technique to improve localization and staging of early colon cancer during laparoscopic colectomy.¹ This update further examines the feasibility of LM in laparoscopic colectomy (LCR) and whether sentinel lymph node (SLN) identification can alter staging or the margins of resection.

Colorectal carcinoma (CRC) is the second leading cause of cancer-related deaths in the United States, with more than 57,000 deaths expected in 2003.² LCR for CRC is appealing because it is associated with better cosmesis, shorter hospital stay, and faster return to normal activities.³⁻¹³ However, these potential advantages must be weighed against the risk of port-site recurrences,^{3,8} suboptimal lymphadenectomies,⁹ and prolonged operative time. Few long-term results are available.¹¹⁻¹³

Lymph node positivity remains the most important factor in the selection of patients for adjuvant chemotherapy. Even so, one third of node-negative CRCs will recur. The most likely explanation for failures in such patients is inadequate lymph node resection and/or missed nodal metastases on histologic examination.

Lymphatic mapping of the SLN was originally introduced by Morton et al¹⁴ to avoid unnecessary lymph node dissections in melanoma and to improve staging accuracy. The SLN is the first node to receive lymph flow from a primary tumor and the most likely site of early metastasis in the regional nodal basin.¹⁴ This technique has been applied to other solid neoplasms and has been shown to be effective in the detection of occult nodal metastases in patients undergoing open colon resection (OCR) for CRC.¹⁵⁻¹⁸ It also can identify alternate patterns of regional lymphatic drainage.¹⁶

Patients and Methods

Patient Population

Our preliminary report in 2002 included 14 patients with clinically localized CRC or premalignant polyps who underwent colonoscopic tattooing of the primary site and SLN mapping between 1996 and 2000 at our institute.¹ Since then, the series has increased to include 30 patients (Table 1). All patients had malignant or premalignant polyps that were partially or completely removed during colonoscopy, or they had larger neoplasms that were biopsied colonoscopically. The diagnostic and staging workup included blood tests, chest radiograph, and computed tomography of the abdomen

and pelvis. Distant metastasis was not evident in any of the patients enrolled in the study. Informed consent was obtained from all patients following guidelines of our hospital Institutional Review Board.

Operative Technique

Our operative technique was similar to that described by Tsioulis et al.¹ Laparoscopic abdominal exploration was performed to rule out intra-abdominal metastases. The involved segment of the colon was mobilized without extensive disruption of the lymphatic channels or blood vessels. In 20 patients, LM was performed by injecting 0.5 to 1 cm³ of isosulfan blue dye (Lymphazurin, Ben Venue Laboratories, Inc, Bedford, OH) circumferentially in the submucosa via intraoperative colonoscopy. In 3 patients who had undergone preoperative colonoscopic polypectomy and India ink tattooing of the site, the blue dye was injected subserosally through a spinal needle inserted percutaneously during laparoscopy. Seven patients underwent hand-assisted laparoscopy, and the injection was performed through the hand port.

In all cases, the primary site and the afferent lymphatic channel were laparoscopically visualized, and the first blue-stained nodes (SLNs) were identified within 1 to 5 minutes after injection. Occasionally, minor dissection along the blue-stained lymphatic channel was required to identify the SLN. After each SLN had been marked with a suture or clip, mobilization of the colon was completed. The involved segment of colon and the regional lymph nodes were then resected en bloc through a mini-laparotomy (Figure) or the incision made for the hand port. A hand-sewn or stapled anastomosis was performed extracorporeally.

Table 1. — Key Data on the Patients Undergoing Sentinel Lymph Node Mapping During Laparoscopic Colectomy for Colorectal Cancer

Number of Patients:	30
Gender	
Men:	12
Women:	18
Mean Age (yrs)	64 (range 43–91)
Tumor Location	
Right colon:	20
Left colon:	10
Mean Tumor Diameter:	2.3 cm (range 0.5–5 cm)
T Stage of Primary Tumor	
T0:	6
T1:	14
T2:	4
T3:	6



Lymphatic mapping during laparoscopic colon resection. The colon has been delivered extracorporeally through a mini-laparotomy incision, and the primary tumor, lymphatic channel, and sentinel lymph node (all stained by the blue dye) can be seen. From Tsioulis GJ, Wood TF, Spirt M, et al. A novel lymphatic mapping technique to improve localization and staging of early colon cancer during laparoscopic colectomy. *Am Surg.* 2002; 68:561-565. Reprinted with permission.

The resected specimen was thoroughly inspected for any additional blue-stained SLNs, which were marked appropriately. The entire specimen was submitted for pathologic examination.

Histopathology Protocol

The specimen was processed in a standard fashion for routine microscopic analysis of the primary neoplasm, margins, and all lymph nodes by hematoxylin-eosin (H&E) staining. In addition, each marked SLN was examined by a focused technique developed at our institute.¹⁹ In brief, the pathologist measured each SLN and, depending on its size, bisected it or sectioned it at 2- to 3-mm intervals. Two 4- μ m sections of the paraffin-embedded lymph nodes were cut at two levels separated by 200 μ m. One section from each level was stained with H&E and another with cytokeratin immunohistochemistry (IHC-CK) using the AE-1/AE-3 cytokeratin antibody cocktail (Dako Corp, Carpinteria, Calif). Slides stained with IHC-CK were interpreted according to strict histologic criteria that required strong immunoreactivity combined with microanatomic and cytologic features compatible with CRC.

Results

Our study included 12 men and 18 women, with a mean age of 66 years (range 43–91). Twenty primary neoplasms were in the right colon and 10 were in the left colon. The mean size of the lesions was 2.3 cm (range 0.5–5 cm). Six of the primary tumors were stage T0, 14 were T1, 4 were T2, and 6 were T3 (Table 1).

In 20 cases, colonoscopic identification of the primary site and blue dye injection was successful (Table 2). Eight patients underwent complete polypectomies, and in each case the injection of dye during colonoscopy was helpful in localizing the polypectomy site. In 3 cases with preoperative colonoscopic polypectomy and tattooing of the site, the blue dye was injected percutaneously during laparoscopy. In 7 patients, the mobilization was performed through a hand-assisted port, and mapping was successfully performed extracorporeally.

SLN mapping was accomplished without difficulty in all 30 patients. In 8 cases (29%), LM demonstrated primary drainage outside the margins of the initially planned resection. In all of these, at least 1 SLN was identified deep at the base of the mesentery and resulted in a wider mesenteric resection to encompass the mapped lymphatic channels and SLN(s). In 28 cases (93%), the tumor status of the SLN correctly reflected the tumor status of the entire lymph node basin. There were two false negatives: one in which the lymphatic channel was obliterated with tumor and hence could not take up dye, and the second in a T3 cecal tumor. Of the 28 patients, 6 (21%) had lymph node metastasis. In 4 (14%) of those cases, the SLN was the only tumor-involved lymph node. In all cases, this node contained micrometastasis or isolated tumor cells that were missed by H&E staining but identified by IHC-CK. With a median follow-up of 15 months, there have been no port-site recurrences or regional recurrences.

Discussion

Laparoscopic colon resection is widely accepted for benign colonic disease. However, initial studies of LCR in CRC raised concerns regarding the oncologic safety of this method due to reports of port-site recurrences, inadequate resections, and incomplete lymph node harvesting.^{3,8} Larger and more recent studies

Table 2. — Outcomes From Sentinel Lymph Node Mapping During Laparoscopic Colectomy

No. of Patients	30
Average Number of Lymph Nodes:	14 (range 2–21)
Average Number of SLNs:	1.8 (range 1–3)
Identification of SLN	30/30 (100%)
Accuracy of SLN*	28/30 (93%)
SLN Only Positive Node	4/28 (14%)
Upstaging Based on SLN**	4/28 (14%)
Unexpected Lymph Drainage	8/28 (29%)

* Accuracy of the tumor status of the SLN as an indicator of the tumor status of all regional lymph nodes in the en bloc specimen.
 ** Tumor missed by hematoxylin-eosin staining but identified by cytokeratin immunohistochemistry staining.

have indicated that the risk of port-site recurrences is low.^{7,12,20} Prospective studies are currently investigating the potential advantages (decreased pain, improved cosmesis, more rapid resolution of ileus, shorter hospital stay, and more rapid return to normal activities) and disadvantages (increased cost, the unknown effect of pneumoperitoneum on recurrences [including port sites], prolonged operative time, and inadequate lymphadenectomy) of LCR in malignant disease. A recent comparison of LCR and OCR for CRC reported no port-site recurrences and similar disease-specific survival at 26 months of follow-up.¹² LCR was associated with a longer procedure time (4 hours vs 2.5 hours for OCR), a shorter hospital stay (6 days vs 7 days), and an equivalent number of harvested lymph nodes (8 vs 10). These data are consistent with those of other reports from American^{7,20} and international^{5,10,13} LCR studies. A much-anticipated randomized study reported that although there was a small improvement in global quality of life in patients undergoing LCR vs OCR, the period of follow-up was too short to comment on disease-free and overall survival.²¹ This study concluded that LCR for malignancy continues to be investigational.

There is little doubt that adequate lymph node resection followed by careful lymph node analysis is essential for decision making and may affect survival.²² Inadequate lymph node retrieval during LCR or OCR and the use of conventional methods to examine lymph nodes increase the risk of understaging. We have demonstrated that SLN mapping not only is an accurate means of identifying the regional lymph node(s) most likely to harbor metastasis in patients undergoing OCR, but also can increase the total number of nodes harvested.¹⁶ These results encouraged us to adapt LM for use during LCR.¹ In the present study an SLN was identified in all patients during LCR and demonstrated an accuracy of 93%. Importantly, 4 cases (14%) were upstaged by focused analysis of the SLN using IHC staining. These early results are consistent with our OCR LM and SLN data that demonstrate an accuracy of 85% and upstaging of 15%. The number of lymph nodes removed (14) was also similar to the number of nodes during OCR.¹

In our OCR LM experience, palpation of the tumor is necessary to identify the appropriate location for dye injection. In LCR this is impossible without the use of a hand-assisted port. Alternatively, the site of blue dye injection can be identified by preoperative colonoscopic tattooing with carbon dye. Another option is intraoperative injection of the blue dye through a colonoscope. Use of these techniques allowed us to identify the segment and extent of colon to resect. Eight (29%) of 28 patients had unexpected patterns of lymphatic drainage to lymph nodes at the root of the

mesentery beyond the usual field of resection and, in 2 cases with right-sided colon cancer, to the left of the middle colic artery. The surgical management was therefore altered to include a more extensive mesenteric resection, and in 2 cases, an extended right hemicolectomy was performed.

This study of SLN mapping in conjunction with LCR suggests that the SLN can be accurately identified without adding to the complexity or duration of the operative procedure. In these cases, LM added an average of only 15 to 20 minutes to LCR. The most time-consuming aspect of LM was dye injection via intraoperative colonoscopy. However, as stated above, intraoperative colonoscopy can be avoided by tattooing the lesion preoperatively with a carbon dye. In some cases, the tumor was tattooed preoperatively via colonoscopy, and the blue dye was injected percutaneously at the time of surgery. Percutaneous injection is possible only if the lesion is visible during laparoscopy, if the lesion has been tattooed preoperatively, or if a hand-assisted port is used and the lesion is palpable.

Conclusions

The gold standard for colorectal carcinoma is open colon resection. The addition of LM has the potential for improving staging accuracy. In the advancing era of laparoscopic colectomy, the quality of life advantages must be weighed against standard oncology practices, namely, adequate resections and lymph node harvesting. LM and SLN identification offer the ability to address both of these issues at the same time. As we have shown, 29% of resections were altered because of the location of the SLN. In addition, with a 30% recurrence rate of node-negative colon cancers, standard surgical and pathology techniques may not be enough. Labor-intensive and costly analysis of all the lymph nodes is unnecessary if an SLN is identified. However, the prognostic significance of micrometastases or isolated tumor cell deposits in this node remains unclear. Our ongoing prospective trial of LM in colorectal cancer should indicate the clinical importance of micrometastatic nodal disease.

References

1. Tsioulas GJ, Wood TF, Spirt M, et al. A novel lymphatic mapping technique to improve localization and staging of early colon cancer during laparoscopic colectomy. *Am Surg.* 2002;68:561-565.
2. American Cancer Society. *Cancer Facts & Figures, 2003.* American Cancer Society, Inc: Atlanta, Ga; 2003:6.
3. Berends FJ, Kazemier G, Bonjer HJ, et al. Subcutaneous metastases after laparoscopic colectomy. *Lancet.* 1994;344:58.
4. Ortega AE, Beart RW Jr, Steele GD Jr, et al. Laparoscopic Bowel Surgery Registry: preliminary results. *Dis Colon Rectum.* 1995;38:681-686.
5. Huscher C, Silecchia G, Croce E, et al. Laparoscopic colorec-

tal resection: a multicenter Italian study. *Surg Endosc.* 1996;10:875-879.

6. Lord SA, Larach SW, Ferrara A, et al. Laparoscopic resections for colorectal carcinoma: a three-year experience. *Dis Colon Rectum.* 1996;39:148-154.

7. Franklin ME Jr, Rosenthal D, Abrego-Medina D, et al. Prospective comparison of open vs laparoscopic colon surgery for carcinoma: five-year results. *Dis Colon Rectum.* 1996;39:S35-S46.

8. Vukasin P, Ortega AE, Greene FL, et al. Wound recurrence following laparoscopic colon cancer resection: results of the American Society of Colon and Rectal Surgeons Laparoscopic Registry. *Dis Colon Rectum.* 1996;39:S20-S23.

9. Hida J, Yasutomi M, Maruyama T, et al. The extent of lymph node dissection for colon carcinoma: the potential impact on laparoscopic surgery. *Cancer.* 1997;80:188-192.

10. Stage JG, Schulze S, Moller P, et al. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg.* 1997;84:391-396.

11. Stocchi L, Nelson H. Laparoscopic colectomy for colon cancer: trial update. *J Surg Oncol.* 1998;68:255-267.

12. Bouvet M, Mansfield PF, Skibber JM, et al. Clinical, pathologic, and economic parameters of laparoscopic colon resection for cancer. *Am J Surg.* 1998;176:554-558.

13. Leung KL, Yiu RY, Lai PB, et al. Laparoscopic-assisted resection of colorectal carcinoma: five-year audit. *Dis Colon Rectum.* 1999;42:327-333.

14. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392-399.

15. Bilchik AJ, Giuliano A, Essner R, et al. Universal application of intraoperative lymphatic mapping and sentinel lymphadenectomy in solid neoplasms. *Cancer J Sci Am.* 1998;4:351-358.

16. Wood TF, Tsioulis GJ, Morton DL, et al. Focused examination of sentinel lymph nodes upstages early colorectal carcinoma. *Am Surg.* 2000;66:998-1003.

17. Tsioulis GJ, Wood TF, Morton DL, et al. Lymphatic mapping and focused analysis of sentinel lymph nodes upstage gastrointestinal neoplasms. *Arch Surg.* 2000;135:926-932.

18. Saha S, Wiese D, Badin J, et al. Technical details of sentinel lymph node mapping in colorectal cancer and its impact on staging. *Ann Surg Oncol.* 2000;7:120-124.

19. Turner RR, Ollila DW, Stern S, et al. Optimal histopathologic examination of the sentinel lymph node for breast carcinoma staging. *Am J Surg Pathol.* 1999;23:263-267.

20. Khalili TM, Fleshner PR, Hiatt JR, et al. Colorectal cancer: comparison of laparoscopic with open approaches. *Dis Colon Rectum.* 1998;41:832-838.

21. Weeks JC, Nelson H, Gelber S, et al. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA.* 2002;287:321-328.

22. Wong JH, Steinemann S, Tom P, et al. Volume of lymphatic metastases does not independently influence prognosis in colorectal cancer. *J Clin Oncol.* 2002;20:1506-1511.