Lymphatic Mapping and Focused Analysis of Sentinel Lymph Nodes Upstage Gastrointestinal Neoplasms

George J. Tsioulias, MD, DMSc; Thomas F. Wood, MD; Donald L. Morton, MD; Anton J. Bilchik, MD, PhD

Background: Lymph node analysis is essential for staging gastrointestinal (GI) neoplasms. Intraoperative lymphatic mapping and sentinel lymphadenectomy were originally described for melanoma but have not yet been investigated for most GI neoplasms.

Hypotheses: (1) Lymphatic mapping and sentinel lymphadenectomy is feasible in GI neoplasms, (2) the sentinel node (SN) status reflects the regional node status, and (3) focused analysis of the SN improves staging accuracy.

Design: Prospective patient series.

Patients and Methods: Lymphatic mapping was performed in 65 patients with GI neoplasms by injecting 0.5 to 1 mL of isosulfan blue dye around the periphery of the neoplasm. Blue-stained SNs were analyzed by hematoxylin-eosin staining, multiple sectioning, and cytokeratin immunohistochemistry.

Results: Lymphatic mapping identified at least 1 SN in 62 patients (95%). Of the 36 cases with nodal metastasis, 32 (89%) had at least 1 positive SN and 15 (42%) had nodal metastasis only in the SN. In 11 cases, tumor deposits were identified by multiple sectioning (n = 2) or immunohistochemistry (n = 9) only. In 5 cases (8%), lymphatic mapping identified aberrant lymphatic drainage that altered the extent of the lymphadenectomy.

Conclusions: Lymphatic mapping and sentinel lymphadenectomy are feasible in GI neoplasms and identify aberrant lymphatic drainage. The SN status accurately reflects the regional node status. Focused analysis of the SN increases the detection of micrometastases and may improve selection of patients for adjuvant treatment.

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PATIENTS AND METHODS

Between September 1996 and January 2000, 65 patients with GI neoplasms underwent LM in conjunction with en bloc resection of the primary neoplasm and locoregional lymphadenectomy. Fifty patients had large bowel adenocarcinomas, 6 had gastric adenocarcinomas, 5 had small bowel neoplasms (3 adenocarcinomas and 2 carcinoid tumors), and 4 had pancreatic adenocarcinomas. The diagnostic and staging workup included blood tests, chest x-ray examinations, computed tomography of the abdomen and pelvis, and, where indicated, upper GI tract endoscopy or colonoscopy with biopsy, endoscopic retrograde cholangiopancreatography, small bowel series, and ultrasonography. No study patient had preoperative evidence of distant metastases. Patient participation in this study was in accordance with the informed consent guidelines and restrictions approved by our hospital institutional review board.

Patients were brought to the operating room and placed under general endotracheal anesthesia. Before open laparotomy, an exploratory laparoscopy was performed to rule out intra-abdominal metastasis. The primary neoplasm was mobilized without extensive dissection of lymphatic channels or blood vessels. Lymphatic mapping was performed by injecting 0.5 to 1 mL of isosulfan blue dye (Lymphazurin; BenVenue Laboratories Inc, Bedford, Ohio) circumferentially around the neoplasm using a tuberculin syringe. An afferent lymphatic channel usually was visualized within a minute after injection of the dye. This channel was dissected to the first 1 to 3 blue-stained lymph nodes (Figure 1). Each of these SNs was marked with a silk suture. The lymphatic channel containing the blue dye was then followed proximally to the site of the primary neoplasm to ensure that there were no SNs hidden in the mesenteric fat. On occasion, visualization of the lymphatic(s) and SNs required minor dissection of surrounding tissues. After all SNs were marked, an en bloc resection of the neoplasm and the regional lymph nodes was performed in the standard fashion.

Each marked node (SN) was removed from the surgical specimen by the pathologist for focused examination using a protocol developed at our institute and initially validated for histopathologic analysis of axillary SNs draining primary breast cancers.13 In brief, each SN was measured and, depending on its size, bisected or sectioned at 2- to 3-mm intervals. Two 4-µm paraffin sections were cut at 2 levels 200 µm apart; one was stained with HE and the other with cytokeratin immunohistochemistry (IHC) using the AE-1/AE-3 cytokeratin antibody cocktail (Dako, Carpinteria, Calif).14 An IHC stain was considered positive when strongly positive cell clusters or individual cells with histologic or cytologic features of malignant cells could be identified. The remainder of the surgical specimen was then dissected and its nodes sampled for routine evaluation using HE. The T stage, neoplasm size, number of nodes, and number of positive nodes were recorded. In the case of carcinoid tumors, both sentinel and nonsentinel nodes were also evaluated with special chromogranin and serotonin stains.

RESULTS

The 28 men and 37 women had a mean age of 65.5 years (range, 28-90 years). The mean diameter of the primary neoplasm was 3.4 cm (range, 0.5-8.3 cm). Lymphatic mapping identified at least 1 SN in 62 patients (95%); of the 3 cases in which LM failed to identify an SN, 1 was a cecal neoplasm and 2 were rectal neoplasms. Usually, the lymphatic channel and the first SN were identified within 1 minute after the injection of the blue dye. Lymphatic mapping added an average of only 10 minutes to the surgical procedure. The blue dye caused no allergic reac-
tions or adverse effects, and no complications could be linked to LM.

An average of 15 lymph nodes (range, 2-37) and 1.7 SNs (range, 0-4) were harvested per patient (Table 1). Of the 65 specimens, 36 had tumor-positive nodes. Of the 36, 32 (89%) had at least 1 tumor-positive SN. The remaining 4 specimens had tumor loci identified only in nonsentinel lymph nodes. One of these specimens was a rectal neoplasm from a patient in whom LM had failed to identify an SN. The other 3 cases were associated with locally advanced neoplasms (T3/T4), including 2 low-rectal neoplasms.

Of the 36 specimens with nodal metastasis, 15 had tumor deposits only in SNs (Table 2). Of these 15 tumor-positive SNs, only 4 were identified with routine HE staining. The remaining 11 positive SNs contained micrometastases identified by HE staining on multisectioning (n=2) or by IHC (n=9) (Figure 2). Based on the SN focused analysis, 23% of the neoplasms were upstaged (Table 3).

Nodal deposits in patients with T1 neoplasms were invariably micrometastatic and identified only during focused examination of an SN. With respect to larger primary neoplasms, focused examination of an SN revealed micrometastases in 5 (50%) of 10 patients with T2, 3 (16%) of 19 with T3, and 1 (20%) of 5 with T4 neoplasms. As has been documented in breast cancer, the rate of neoplasms positive for SN only decreased with advanced T stage (Figure 3).

In 5 patients (8%), LM identified an SN in an anatomico- aberrant location (2 colon, 1 pancreas, 1 stomach, and 1 small bowel), altering the extent of resection (Figure 4). In 2 patients with neoplasms on the right side of the colon, the lymphatic channel drained to an SN on the left of the middle colic artery; a planned right hemicolectomy therefore was changed to an extended right hemicolectomy. In a patient with adenocarcinoma of the head of the pancreas, an SN was identified close to the hilum of the liver, and a Whipple procedure with extensive periportal lymphadenectomy was performed. The fourth patient had an antral gastric adenocarcinoma; LM identified an SN in the paracardial region, changing the operation from a subtotal to a total gastrectomy with complete paracardial lymphadenectomy. The fifth patient had a 0.5-cm carcinoid tumor in the ileum, which drained to 2 SNs at the root of the mesentery; a planned sleeve resection therefore was replaced by an enterectomy with wide mesenteric lymphadenectomy extending to the root of the mesentery.

Lymphatic mapping has been proposed as an accurate means of identifying the regional lymph node(s) most likely to contain any tumor cells metastasizing from a primary solid neoplasm via the lymphatics. In this study, we adapted LM for identifying the lymphatic drainage of GI neoplasms and determined whether a focused examination of SNs identified during LM could increase the accuracy of staging. In 62 of 65 LM procedures, the lymphatic channel was readily visualized and at least 1 SN was quickly located and marked with minimal dissection. This 95% success rate in identifying the SN is higher than the 82% initially reported by Morton et al for LM in primary melanoma or the 66% initially reported by Giuliano et al for LM in primary breast cancer. Direct visualization of the lymphatics and a shorter distance from the primary neoplasm to the first SN may have contributed to our higher success rate. Interestingly, of the 3 cases in which an SN was not identified and of the 4 cases with metastases in nonsentinel nodes only, 2 were low-rectal neoplasms. Failure to identify an SN draining in these neoplasms might be due to their infraperitoneal location and the extensive dissection required to mobilize the neoplasm.

Results of LM changed the extent of resection in 5 cases (8%). In each of these cases, the SN was in an anatomico- aberrant position not included in the initial operative field. In the patient with a carcinoid tumor of the ileum, frozen section examination of the 2 SNs identified micrometastasis in the periphery of each node. In the pathology department, chromogranin and serotonin staining of permanent sections from all 37 nodes in this specimen confirmed that metastasis was confined to the 2 SNs. Pathologic examination showed that the SN also was the only tumor-positive node in 3 other cases of aberrant lymphatic drainage. Aberrant drainage patterns are not uncommon in patients with GI neoplasms; Yamamoto et al demonstrated skip-node metastasis (ie,

Table 1. Clinicopathologic Features of Patients Undergoing Lymphatic Mapping for Gastrointestinal Neoplasms

<table>
<thead>
<tr>
<th>Features</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>65</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>65.5 (28-90)</td>
</tr>
<tr>
<td>Location, No.</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4</td>
</tr>
<tr>
<td>Small bowel</td>
<td>5</td>
</tr>
<tr>
<td>Large bowel</td>
<td>50</td>
</tr>
<tr>
<td>Mean size, cm (range)</td>
<td>3.4 (0.5-8.3)</td>
</tr>
<tr>
<td>Total No. of lymph nodes</td>
<td>985</td>
</tr>
<tr>
<td>Mean No. of lymph nodes (range)</td>
<td>15 (2-37)</td>
</tr>
<tr>
<td>Total No. of sentinel nodes</td>
<td>110</td>
</tr>
<tr>
<td>Mean No. of sentinel nodes (range)</td>
<td>1.7 (0-4)</td>
</tr>
</tbody>
</table>

Table 2. Distribution of Metastases in Sentinel and Nonsentinel Lymph Nodes

<table>
<thead>
<tr>
<th>Tumor Status of Nodes</th>
<th>No. (%) of Lymph Nodes</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>985 (100)</td>
<td>65 (100)</td>
</tr>
<tr>
<td>Negative</td>
<td>879 (89)</td>
<td>29 (45)</td>
</tr>
<tr>
<td>Positive</td>
<td>106 (11)</td>
<td>36 (55)</td>
</tr>
<tr>
<td>Nonsentinel only</td>
<td>6 (1)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Sentinel and nonsentinel</td>
<td>82 (9)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Sentinel only</td>
<td>18 (2)</td>
<td>15 (23)</td>
</tr>
</tbody>
</table>

*Four determined by hematoxylin-eosin staining, 2 by multisectioning, and 9 by immunohistochemistry.
a lymph node that is tumor negative when a higher level node is positive) in 10% of 452 patients with colorectal cancer, and Kosaka et al\textsuperscript{16} reported skip metastases in 15% of 51 patients with gastric cancer. Aberrant lymphatic drainage is a possible explanation for inadequate staging and a patient’s failure to respond to adjuvant treatment.

The tumor status of the SN accurately predicted the tumor status of the locoregional lymph nodes in 95% of cases. The SNs were more likely to contain metastases than nonsentinel nodes (49% vs 11%). In 89% of the cases, a negative SN accurately predicted the absence of tumor metastases in all other regional lymph nodes examined by the pathologist. The false-negative rate, excluding rectal tumors, was 4% (2/54). Although focused examination based on multisectioning and immunostaining is too costly and time-consuming for routine examination of

<table>
<thead>
<tr>
<th>Location</th>
<th>SNs Detected, %</th>
<th>SN-Positive Tumors, No. (%)</th>
<th>Hematoxylin-Eosin Positive</th>
<th>Multisection and Immunohistochemistry Positive</th>
<th>Upstaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large bowel</td>
<td>94</td>
<td>22 (44)</td>
<td>2 (3)</td>
<td>8 (17)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Stomach</td>
<td>100</td>
<td>6 (100)</td>
<td>1 (16)</td>
<td>1 (17)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>100</td>
<td>2 (40)</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>100</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>32 (49)</td>
<td>4 (6)</td>
<td>11 (17)</td>
<td>15 (23)</td>
</tr>
</tbody>
</table>

Table 3. Rates of Sentinel Node (SN) Detection and Metastasis

Figure 2. Gastric cancer micrometastases in the sentinel node detected with cytokeratin immunohistochemistry (B), which were missed with the hematoxylin-eosin stain (A) (original magnification ×400).

Figure 3. T stage and percentage of tumor-positive sentinel nodes (SNs) identified only by focused examination based on multisectioning and immunohistochemistry (IHC).
nonsentinel nodes, investigators have examined whether a more sensitive assessment of nonsentinel nodes would reveal tumor foci in the presence of a tumor-negative SN. Wiese et al17 recently performed multiple sectioning on 354 nodes removed from 75 patients with colorectal neoplasms; the rate of positive nonsentinel nodes in the presence of negative SNs was only 0.6%. This finding is similar to the rates previously reported by our group for patients with melanoma and breast cancer.6,13

Results of the present study suggest an inverse relationship between a GI neoplasm’s T stage and the presence of isolated LN metastasis. The SN was the only positive node in all T1, 70% of the T2, 26% of the T3, and 20% of the T4 neoplasms. These findings imply that SN analysis may be particularly relevant in identifying micrometastatic spread from T1-T2 neoplasms. The clinical significance of these micrometastases is unclear. Some studies have associated micrometastasis with a poorer prognosis in gastric and colorectal cancer,18,19 while others have not identified a survival difference.20,21 Prospective studies are required to clarify the prognostic significance of these micrometastases.

This is the first report of LM for patients with a variety of GI neoplasms. Results of this feasibility study indicate that LM can identify the SN(s) that drains a GI neoplasm without adding significantly to the time, cost, or morbidity of the primary surgical procedure. Moreover, LM can identify aberrant lymphatic drainage, which may alter the extent of resection. The histological status of the SN accurately reflects the tumor status of the entire regional node basin in 96% of cases, excluding rectal neoplasms. Focused examination of the SN based on serial

Figure 4. Lymphatic mapping identified sentinel nodes in an anatomically aberrant location, altering the margins of resection in a gastric (A), a pancreatic (B), a small-bowel (C), and a colon (D) neoplasm.
sectioning and IHC further increased staging accuracy. Eventually, the ability to identify a tumor-free SN might enable the surgeon to avoid the morbidity associated with radical lymphadenectomy in patients with gastric and pancreatic cancer. In the meantime, the preliminary findings of this feasibility study suggest that LM with focused examination of the SN(s) improves the staging of GI neoplasms and may affect the selection of patients for adjuvant therapy. This possibility is now being investigated in a prospective phase 2 trial.

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REFERENCES


DISCUSSION

James E. Goodnight, Jr, MD, Sacramento, Calif: Over the last decade, the most influential contribution and change in cancer surgery has been the development of LM/SL.

In the treatment of malignant melanoma and breast cancer, 2 certain outcomes from these procedures are (1) more accurate lymph node staging and (2) much reduced morbidity in obtaining that information. Potentially, LM will guide us to more effective therapy of these various diseases and greatly enhance our knowledge of lymphatic drainage and the spread of cancer. The full range of the clinical relevance of these procedure remains to be defined. Important clinical trials are under way to address these issues.

The reality that a single, identifiable lymph node would accurately predict the tumor status of the regional node basin was hardly a given. Dr Morton, Dr Giuliano, and others are to be congratulated for bringing this procedure to clinical utility. It clearly has advanced the cause. Another member of their group, Dr Bilchik, has appropriately begun to investigate the applicability of LM/SL to GI cancers. In this study, well presented by Dr Tsiossias, the feasibility, staging accuracy, and potential therapeutic utility of the procedure for GI tumors was explored. Quite evidently, the authors can relatively easily identify an apparent SN that for the most part predicts the tumor status of the draining lymph nodes. In selected cases, this information altered their surgical management.

The clinical investigation that has occurred in malignant melanoma and breast carcinoma demonstrates that the SN is a physiologic phenomenon, and our surgical challenge is to find it. Progressive experience in those diseases indicates that the surgeon should find the SN in more than 93% of cases, and when found, the SN, once examined with multiple sections and IHC, should predict the tumor status of the regional lymph nodes with a greater than 99% accuracy.

In this study of 65 patients with GI tumors, 30 patients or 46% of the group had SN biopsies negative for cancer. An additional 3 patients (5%) did not have the SN identified. Within this cohort of 33 patients then, there were 4 patients (12%) who actually had node-positive disease, despite the negative SN, when all the regional nodes were examined. One could argue that the procedure as conducted in this study is not sufficiently accurate to reliably predict the tumor status of the draining lymph nodes. Two possible conclusions are: Even though the authors routinely found a blue lymph node 95% of the time, they...
are not actually identifying the SN or the SN is less predictive of the regional node status in GI cancer. I would ask the authors what refinements of the technique, such as the addition of radioisotope injection and gamma probe mapping, might improve the accuracy of the technique.

It seems likely that with experience and refinement of the technique, the accuracy of LM/SL will improve in GI cancer. Even so, its clinical role remains to be defined. The impact of extensive lymph node dissection (or not) on outcome in patients with GI cancers is uncertain. In contrast to regional lymph node dissection for breast cancer and malignant melanoma, lymph node dissection in operations for GI cancers adds only a small time not significant morbidity.

On the other hand, the upstaging that comes with the intense examination of the SN would be useful, if indeed we have effective adjuvant therapy. Unfortunately, for most GI cancers we do not have that tool. Therefore, one could take the negative view that there is little clinical impact from performing this procedure. I would ask the authors to reiterate their vision for the clinical role of LM/SL in the setting of GI cancer.

Finally, the procedure would seem to be more applicable to colon cancer than other GI cancers because of the ability to vary the surgical resection and the availability of adjuvant therapy. Yet the staging information from colon cancer is relatively easily obtained as we do it now, with no more morbidity than already being in the abdomen. Can you define a role in colon cancer management? Even with these concerns, I do think the authors are very much on the right track.

John T. Vetto, MD, Portland, Ore: I would like to ask the authors what size these tumors were? I heard the word “early” in the presentation once. It does not appear in the abstract, but I suspect these tumors were small. I don’t think that this technique would apply to the tumors that many of us see—big, bulky, obstructing colon cancers, limited to the stomach. Surely these don’t have one SN. My concern is this: in melanoma, these authors have described that 80% of the time the SN is the only positive node. To hear that number was only 39% in these relatively small tumors reinforces what Dr Goodnight said about multifocal nodal drainage in GI tumors. Would the authors comment on this?

Stanley P. L. Leong, MD, San Francisco, Calif: This is an important extension of the SN work for melanoma and breast cancer. I would like to mention the SN study on GI cancer by Dr Kitigawa and his group in Japan, who have shown that the SN predicts quite reliably the status of the nodal basin for esophageal, gastric, and colorectal carcinoma. They have used radioisotope tracer and have shown the utility of prophylactic endoscopic lymhoscintigraphy and intraoperative mapping of SNs using a handheld gamma probe (Kitigawa Y, et al. The role of sentinel lymph nodes in gastrointestinal cancer. In: Leong SPL, Wong JH, eds. Sentinel Lymph Nodes in Human Solid Cancer [Surgical Clinics of North America]. Philadelphia, Pa: WB Saunders; 2000).

Claude H. Organ, MD, Oakland, Calif: I appreciate the fact that they are extending this technique to a variety of tumors in different portions of the body. There has never been a successful experimental preparation to produce chyloperitoneum. The lymphaticovenous connections are extensive. With an assortment of techniques, we have never been able to create chyloperitoneum. What is the efficacy of this technique when these pathways between the lymphatic and venous systems are so enormous?

Dr Morton: To put our study in perspective, you must realize that when we started performing LM for melanoma our rate of SN identification was only 80%. In the present report, the success rate of 93% indicates that mapping the SN is easier in GI neoplasms than in melanoma and certainly easier than in breast cancer. This series represents all our cases, including those undertaken during the learning phase of the procedure. Three of the 4 false-negative cases were in patients with rectal carcinomas. We believe that in vivo LM is probably not useful for identifying the SN draining rectal tumors; by the time dye is injected at the site of the tumor and the rectum/rectosigmoid is mobilized, the dye has passed beyond the SN. We have therefore developed an ex vivo mapping technique for rectal cancers: the resected specimen is placed on a back table in the operating room, and dye is injected at the site of the rectal cancer. Amazingly, the dye passes readily through the effluent lymphatics and stains the SN.

Dr Goodnight, as always, has offered some very astute comments. He asked about improvements in the technique. When I first started mapping the SN in colon cancer in the early 1990s, I used both radioisotopes and blue dye. I found that the handheld gamma counter was not very useful for in vivo mapping of GI neoplasms, because the first SN is usually so close to the primary that the shine-through effect tends to obscure its actual radioactive count. (This is the same problem that our group has noted when attempting to locate axillary SNs receiving drainage from breast carcinomas in the upper outer quadrant.) Of course, the probe can be used on an ex vivo basis to confirm that the dissected nodes with the highest radioactive counts are also blue stained, but we have not found this to be very useful. Moreover, unless the surgeon has a license to use radioisotopes, a nuclear medicine technician must be in the operating room to inject the radioactive tracer. I do have a license for operative use of the radioactive material, but I have not found the probe to be very useful for mapping GI tumors.

It is too early to speculate on the therapeutic implications of GI mapping. About 30% of patients with node-negative Dukes B2 lesions will develop recurrence. We think that these are the patients whose SNs are at risk of harboring micrometastases. Identification and focused histopathologic analysis of the SNs that drain GI tumors should allow us to ultrastage GI neoplasms and thereby increase the number of potential candidates for postoperative adjuvant therapy. Admittedly, there is an urgent need for more effective adjuvant therapy in colon cancer as well as other GI neoplasms.

Dr Vetto’s point is a good one. Our patients had early GI neoplasms measuring 2 to 3 cm or less in greatest diameter. I agree that attempting to map the SNs draining large bulky lesions is not likely to provide more useful staging information, because the nodes are usually grossly involved.

Apropos of Dr Leong’s comment, investigators in Japan also have been using carbon dye to identify the path of lymphatic drainage from gastric cancers. The problem is that the carbon does not travel as fast as the blue dye, so it takes longer, and the carbon seems to go up the chain of nodes. With respect to the practicality of endoscopic techniques for LM, we have achieved a high rate of SN identification during laparoscopic mapping of drainage from colorectal carcinomas. In these patients, the primary tumor is visualized through a colonscope and either tattooed preoperatively with carbon or stained intraoperatively with blue dye.

In regard to Dr Organ’s comment, lymphatic drainage of the tracer material from the primary tumor site is almost immediate and can be followed directly to a specific SN. I do not dispute the existence of lymphaticovenous connections beyond the SN, but these connections are really a marker of systemic metastasis. Of note in our study was the 9% incidence of ectopic drainage from GI tumors. The ectopic SNs were well outside the planned field of en bloc resection. In melanoma and breast cancer, the rate of aberrant drainage is about 14%. Obviously, the lymphatics are not anatomically constant, and their pathways must be determined individually for each patient.