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Aberrant drainage of sentinel lymph nodes in colon cancer and its impact on staging and extent of operation

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Colon cancer; Aberrant lymphatic drainage; Sentinel lymph node mapping

Abstract

BACKGROUND: The role of aberrant lymphatic drainage in changing operations for patients undergoing sentinel lymph node mapping in colon cancer has not been described on a large scale.

METHODS: Patients with colon cancer underwent sentinel lymph node mapping and standard oncologic resection. Aberrant lymphatic drainage was identified outside the standard resection margin, requiring change of the extent of operation. Objectives were to identify the frequency of aberrant lymphatic drainage leading to changes of operation and staging.

RESULTS: Among 192 patients undergoing standard oncologic resection, 42 (22%) had extended surgery because of aberrant lymphatic drainage. Nodal positivity was higher in patients undergoing change of operation, at 62% compared with 43% of those undergoing only standard oncologic resection. In 19 of 192 patients (10%), positive sentinel nodes were found in aberrant locations.

CONCLUSIONS: Sentinel node mapping in patients with colon cancer detects aberrant drainage in 22% of patients, changing the extent of operation.© 2013 Published by Elsevier Inc.

Colorectal cancer is the third most common cancer in the United States and the second most common cause of cancer death. In 2011, approximately 141,000 new cases were diagnosed, and 49,000 people died of colorectal cancer. The presence of nodal metastasis remains one of the most important prognostic indicators in patients with colon cancer. Nodal positivity also helps guide the decision regarding the need for chemotherapy. Examination of an increasing number of nodes has been associated with improved 5-year survival in stage II and III colon cancer. Hence, the accuracy of nodal staging has been intensely studied to improve the technique of identification of the most important nodes harboring metastatic disease.

The hypothesis of a sentinel node and its physiologic basis was first described by Cabanas for penile cancer in 1977. The sentinel node is defined as one of the first few nodes to receive drainage from the primary tumor. The concept of the sentinel node is based on the premise that drainage from a solid organ tumor occurs in an orderly and near linear manner via lymphatics to regional lymph nodes. Identification of these nodes during surgery would identify the “proper nodes” for pathologic examination.
The promise of more accurate nodal staging with reduced morbidity pushed the development of sentinel lymph node (SLN) mapping (SLNM) in melanoma in 1992, breast cancer in 1994, and colorectal cancer in 1997.\textsuperscript{4–6} The development of SLNM in melanoma and breast cancer came with the potential to decrease the morbidity associated with surgical procedures. Since its advent, SLNM has been applied to other solid tumors, including pancreatic and gastric tumors. Kitagawa et al\textsuperscript{7} validated the concept of sentinel nodes for clinically N0 early gastric cancer. In that study, they also showed that selective and modified gastrectomy could be done on the basis of the sentinel node concept. In colorectal cancer, SLNM has been shown to lead to improved staging of the cancer.\textsuperscript{8} Patients identified with true node-positive disease would then be eligible to receive chemotherapy. However, SLNM has not led to large changes in surgical resection for colorectal cancer.

The goal of surgical resection in colorectal cancer is removal of the primary lesion, including the area of lymphatic drainage within the adjacent mesentery. When compared with breast cancer or melanoma, SLNM in colorectal cancer is used primarily for improving the accuracy of staging. SLNM typically does not decrease the extent of surgical resection. Thus, SLNM has not led to a change of operation in colon cancer compared with breast cancer or melanoma. Aberrant drainage is defined as lymphatic drainage to an SLN outside the expected zone of resection. However, little work has been done describing aberrant lymphatic drainage and its impact on the extent of resection in colon cancer. Hence, a prospective study was undertaken with the primary objective of identifying the rates of aberrant lymphatic drainage in colon cancer after SLNM and its impact on staging.

Methods

This study was undertaken under an institutional review board–approved protocol. A total of 192 consecutive patients who provided informed consent between 1997 and 2012 with pathologically proven invasive colon cancer were included in the study. All patients underwent standard oncologic resection with SLNM and resection of regional lymph nodes. Patients with aberrant drainage identified by SLNM underwent standard oncologic resection plus extended mesenteric resection with or without extended colectomy. Each procedure was performed by a single oncologic surgeon experienced in >400 colorectal SLNM procedures.

All patients underwent in vivo SLNM before colonic resection. SLNM was performed by injecting 1 to 4 mL of isosulfan blue or methylene blue into the subserosa along the circumference of the tumor using a 30-gauge needle. A silk suture was placed at sentinel nodes 1 to 4 to assist with pathologic identification. The oncologic surgeon also identified the location of each SLN on a standard colon diagram for each patient. This was later correlated with each node identified in the pathology report to determine the nodal status of each node. All patients had standard hematoxylin and eosin staining with 4 sections of the sentinel nodes. One section with immunohistochemistry staining for cytokeratin was also performed on the sentinel nodes.

Data collected included age, sex, location of the tumor within the colon, number of sentinel nodes, number of total nodes, stage, location of each SLN, and pathology. Patients were excluded if they had previous colectomy, clinically positive nodes, prior major oncologic abdominal operations, or benign pathology. Patients with rectal cancer were also excluded from this study. Patients undergoing changes of operation with either extended colectomy or extended mesenteric resection were then compared with those patients with standard oncologic resection. See Fig. 1 for an example of an extended resection due to the identification of an aberrant draining SLN.

Results

One hundred ninety-two patients were identified who had undergone SLNM with pathologically proven colon cancer. Of these 192 patients, 95 were men and 97 women. The average age was 68.2 years (range, 32–93 years). Of the 192 patients, 42 (22%) underwent changes of operation beyond the field of standard resection margins after the identification of aberrant lymphatic drainage. The average tumor size was 4.2 cm. The average number of lymph nodes harvested was 16.2 per patient. The success rate of

Figure 1  Right colon lesion with aberrant lymphatic drainage on left side of the middle colic vessels.
SLNM was 99% (190 of 192). The average number of sentinel nodes per patient was 3.2.

A majority of our patients had right-sided colon tumors (105 of 192 [55%]). The remainder of the tumors were found in the sigmoid colon (48 of 192 [25%]), transverse colon (29 of 192 [15%]), and left colon (10 of 192 [5%]). The majority of patients (24 of 42 [57%]) who had changes of operation had right-sided colon tumors. The other patients with changes of operation had tumors of the sigmoid (12 of 42 [28%]), transverse (4 of 42 [10%]), and left (2 of 42 [5%]) colon. A majority of our patients undergoing change of operation underwent extended mesenteric resection (40 of 42 [95%]). In some cases, this extended mesenteric resection also required extended resection of the bowel. Two patients were found to have aberrant lymph nodes on the left side of the middle colic vessels and underwent extended right hemicolectomy.

Table 1 describes the T staging of the patient population as well as patients undergoing changes of operation. The majority of the patients with changes of operation had T3 lesions (31 of 42 [74%]). Of the population as a whole, 19 (10%) had changes of operation leading to positive aberrant lymph nodes. The nodal positivity of the 42 patients undergoing changes of operation was 62%, compared with 43% in those undergoing standard oncologic resection. In 2 patients, the aberrant lymph node was the only pathologically positive node. There was also an increased number of lymph nodes harvested per patient in the change-of-operation group, 17.6 compared with 15.8 in those undergoing standard oncologic resection.

Comments

SLNM has led to changes in surgical therapy for breast cancer, melanoma, and gastric cancer. Today, extensive lymphadenectomies are rarely being performed on the basis of SLN status for melanoma and breast cancer. Patients undergoing only sentinel node biopsy for breast cancer and melanoma appear to have less morbidity than those undergoing completion lymphadenectomies. Although SLNM did not decrease the morbidity associated with any of our patients, it did lead to changes in the operations in 22% of our patients. Changing the operation from standard oncologic resection to a more extensive resection has the potential to increase staging and change subsequent therapy.

Our study showed an increase in nodal positivity from 43% in those undergoing standard oncologic resection to 62% undergoing changes of operation. The majority of these patients underwent extended mesenteric resection after aberrant SLNs were identified. Further analysis of the patients with changes of operation revealed that 9.8% of these patients had positive nodes identified outside the standard oncologic resection margins. These positive nodes represent nodes that would have been missed in patients not undergoing SLNM. Nodal positivity in these 19 patients had the potential to change decisions for therapeutic measures such as chemotherapy.

Aberrant lymphatic drainage has been described in melanoma and breast cancer. Other studies have also found aberrant lymphatic drainage in gastric, pancreatic, and colorectal cancer.9,10 In these studies, a SLN for an ascending colon cancer is described on the left side of the middle colic artery. Extended right hemicolectomy was performed on 2 of these patients. This is in accordance with our findings of right-sided colon lesions also having aberrant nodes to the left of the middle colic vessels. A majority of our patients underwent extended mesenteric resection, which has also been described by prior authors.11 Our study is the first to our knowledge to describe a larger number of patients with aberrant drainage in the transverse, left, and sigmoid colon. Although our study describes the position of these aberrant nodes associated with the location of the tumor in the colon, there is no standardization of the nodal positions across our patient population. Work has been done in Asia to describe the positions of the nodal drainage along the vascular supply to the colon. Rectal cancers were excluded from our study, because many patients had been preoperatively radiated. After preoperative radiation, these patients may have had falsely low nodal positivity.

This was the largest study showing how in vivo SLNM may change the planned operation in colon cancer. Our results also suggest that SLNM improves nodal staging. The changes of operation group, 9.8% of patients (19 of 192) had positive SLNs identified outside the area of standard oncologic resection. Without these changes of operation, these patients would have had nodal disease left behind after resection. Additionally, in 2 patients, the aberrant sentinel nodes were the only positive nodes identified.

<table>
<thead>
<tr>
<th>T Stage</th>
<th>T1</th>
<th>27 (14%)</th>
<th>2</th>
<th>25</th>
<th>5 (12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>24 (13%)</td>
<td>3</td>
<td>21</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>129 (67%)</td>
<td>78</td>
<td>51</td>
<td>31 (74%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>12 (6%)</td>
<td>7</td>
<td>5</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>90</td>
<td>102</td>
<td>42</td>
<td>19 (10%)</td>
</tr>
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COP = change of operation; SLN = sentinel lymph node; SLNM = sentinel lymph node mapping.
Overall, this may have an impact on clinical management, staging, and overall survival. Further studies are necessary to explore the impact of aberrant lymphatic drainage on the survival of patients with colon cancer.

**References**


**Discussion**

**Donn M. Schroder, M.D.** (Grosse Pointe, MI): Why did T3 colon cancers have aberrant lymph node drainage according to change of operation 15 times more often than even more advanced T4 cancers and then six to eight times more advanced than the less advanced T1 and T2 tumors? The instance that you report of aberrant lymph nodes is 22 percent change in the operations, much higher than the reported literature of 0 to 10 percent. Why the big difference in your study? Both radioactive tracers and also fluorescent dyes have been reported to detect colon cancer sentinel lymph nodes. Should we expect an increase in the number of aberrant lymph nodes found with these methods, and are they better than blue dye lymph node injection?

**Gregory Johnston, D.O.** (Mt. Clemens, MI): When we looked at T stage, the T1 tumors actually underwent a change of operation approximately 18 percent of the time. With the T2 lesions, about 16 percent of those patients, and you can actually see that in T3 lesions and T4 lesions, we still had about the same percentage. As regard to the second question, I think our incidence of aberrant nodes actually is slightly higher because of how we identify our aberrant drainage. The majority of authors simply identify aberrant drainage as those needing an extended colonic resection. We also identified those needing an extended mesenteric resection. The second point on that, I might make, is that Dr Saha has largely done a large majority of the work on sentinel lymph mapping in colon cancer, and that may lead to better rates of harvest of sentinel nodes, just based on his large number of patients.

The other question in regards to radioactive dyes, we’ve also published on radio sulfur colloid and fluorescent dye along with blue dye in lymphatic mapping. We did not find any increased total number of nodes or number of sentinel lymph nodes found in those patients. We do not think that this wouldn’t have much of a difference in the rate of aberrant drainage between single and multiple dyes. And as regards to micromets, all our patients received IHC, every sentinel node, as well as H&E staining. I know that treating micromets is controversial at this point, however, all of our patients do receive chemotherapy if they are micromet positive. Another paper by Anton Bilchik showed that micromets may have a negative impact when you compare those patients with micromets who are stage II, and stage II patients who are micromets negative.

**Dr William C. Cirocco** (Grosse Pointe, MI): I just wanted to point out what you’re pointing to as an aberrant node, in my experience, I think for most colorectal specialists, is part of our routine mesenteric specimen, that is, that that node that you point out as aberrant is at the IMA, to take off the IMA, which is routinely divided for cancer operation. So I would say that is not aberrant. That’s part of a normal mesenteric resection for a left-sided or rectosigmoid type carcinoma or rectal carcinoma.

**Dr Johnston**: In regards to that, I would say that I agree with you in that sense, however, if the patients had not undergone sentinel node mapping, that node may not have been identified even higher within that mesentery and it may have been missed.

**Dr Zyromski**: How many, quote, “aberrant,” close quote, nodes did you find and how many of those had cancer in them?

**Dr Johnston**: So of the patients who underwent change of operation, we found that 19 of those patients had an aberrant lymph node outside that field of standard resection. I cannot tell you exactly how many nodes were found outside—at this time I can’t tell you how many nodes were found outside that field, but I can tell you how many aberrant positive nodes we found outside that field. All 19 had a positive aberrant node. We had 42 patients who had a change of operation.

**Dr Samantha Hendren** (Ann Arbor, MI): Can you tell from your data whether there were any patients who would have been staged as node negative with a standard resection
who were upstaged to node positive with an extended resection?

**Dr Johnston:** That would be the 19 of the patients that were identified out of the 42 patients who underwent a change of operation.

**Dr Hendren:** Second question is, were any of these procedures laparoscopic?

**Dr Johnston:** No, these procedures are all performed openly, and there is some work on sentinel node mapping in laparoscopic colon cancer, however, we have not published or done any of our work that way.

**Dr Cirocco:** And do you have survival data on the series of patients? If you chase a lymph node up the aorta, I would suspect that the survival of that patient is going to be abysmal, whether you actually remove that atypical node up the aorta or not, but did you have survival data on the series?

**Dr Johnston:** We do have work coming out, which does show improved survival when we found those patients with micromets, however, I don’t believe I have that data for you at this time. Their survival may improve if those patients are identified to have node positive disease and receive chemotherapy.