The Sentinel Node in Colorectal Carcinoma

One of the most important prognostic factors in colorectal cancer is the presence or absence of regional lymph node metastases. In many instances, micrometastatic disease may not be found on routine pathologic analysis using hematoxylin and eosin staining, but may be discovered only with immunohistochemical methods or polymerase chain reaction assay.

Colorectal carcinoma is the most common cancer of the gastrointestinal tract, with over 148,000 cases diagnosed and 56,000 deaths occurring annually in the United States. For carcinomas of the colon and rectum, one of the most important prognostic factors is tumor stage. Management of colon carcinoma in patients with resectable disease involves surgery. Patients with stage I and II histologic node-negative disease have 5-year survival rates ranging from 80% to 90%. The involvement of regional mesenteric lymph nodes indicates stage III disease, for which the 5-year survival rate drops dramatically to 50% or 40%.

In a randomized controlled trial, adjuvant chemotherapy with fluorouracil (5-FU) and leucovorin in stage III and high-risk stage II colon cancer patients resulted in a 5-year survival rate of 74% vs 63% for patients treated only with surgery. Improved survival in stage III colon cancer patients receiving adjuvant treatment has been confirmed by other studies. Therefore, accurate pathologic staging is of the utmost importance.

A key problem in pathologic nodal evaluation is that small lymph nodes may be missed on gross inspection. In addition, microscopic cancerous deposits may be overlooked on routine hematoxylin and eosin (H&E) staining. Either of these problems can result in understaging, which may leave a significant portion of patients without the potential benefit of adjuvant chemotherapy. More sensitive methods of tissue analysis, including polymerase chain reaction (PCR) and immunohistochemistry, could potentially increase the accuracy of tumor staging.

The Sentinel Node

Regional lymph nodes are routinely removed in the surgical management of epithelioid neoplasms in order to stage the disease and assess prognosis. These resections are also helpful in deciding on appropriate adjuvant therapy. However, regional lymphadenectomy for breast cancer and melanoma is associated with well-known morbidities such as lymphedema and nerve injury. Early-stage cancer tends to present with a low incidence of regional lymph node metastasis; thus, regional lymphadenectomy for staging often reveals lymph nodes without histologic evidence of metastasis. A new method of accurately staging the regional nodes without removing the entire lymph node basin was therefore developed.

The sentinel lymph nodes are defined as the first node or nodes in the initial drainage pathway of a tumor, where metastases are most likely to occur. This concept originated with the lymphangiogram studies conducted in the 1960s and 1970s in an attempt to select patients who would benefit from an extended lymph node dissection. The strategy was popularized by Morton and colleagues, who used isosulfan blue dye injections to track the drainage pattern of early-stage melanomas and find the sentinel nodes. The procedure was later applied successfully to breast cancer by Giuliano and colleagues.

Another approach has been to use radioactive-labeled substances such as technetium (Tc)-99m-labeled sulfur colloid with preoperative gamma camera imaging and intraoperative gamma probes to aid in localizing sentinel nodes. A recently completed multicenter trial supports routine use of sentinel node mapping and biopsy in melanoma. Other trials such as the American College of Surgeons Oncology Group Z0010 Breast Sentinel Node Trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 Breast Sentinel Node Trial are exploring the clinical importance of this technique in carcinoma of the breast. In addition, the sentinel node concept has been extended to tumors in a variety of other sites including the head and neck, thyroid, female organs, and gastrointestinal tract.
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Intraoperative Techniques

Attempts to improve tumor staging in colorectal carcinoma have included the use of monoclonal antibodies targeted to antigens expressed by tumor cells such as carcinoembryonic antigen (CEA). These antibodies are labeled with radioactive compounds and injected intravenously several days prior to surgery. An intraoperative gamma probe then scans the pre- and postresection areas that are suspicious for tumor, including the regional and periaortic lymph nodes. This method, called radioimmunoguided surgery, may be helpful in detecting regional metastatic disease that is not obvious by imaging methods and intraoperative inspection. It may also aid in assessing the presence of residual disease after surgical resection, thus providing prognostic information regarding risk of tumor recurrence.[20] Drawbacks associated with this technique include its ineffectiveness in detecting neoplastic cells that do not express the antigen selected, imprecise localization of tumors with extensive necrosis, and uptake of the radioactive compound by organs without tumor.[21]

Localization of sentinel nodes in colorectal carcinoma is achieved using a colored dye such as isosulfan blue (Lymphazurin), which was used by Morton and colleagues in their elegant study in melanoma patients.[10,12] The colorectal tumor is located intraoperatively, and 1 to 2 mL of the dye is injected suberosally into the peritumoral area so that it can reach the draining lymphatics (Figure 1). These lymphatic channels and pericolonic nodes are often visualized within minutes with blue stain (Figure 2). Nodes near the tumor vicinity that first absorb the blue color are marked with sutures on the mesentery because the dye could "wash out" after several minutes. The entire resected specimen is sent for pathologic examination.[22,23] Occasionally, the pathologist may identify a second set of blue nodes that was not initially visualized by the surgeon. Isosulfan blue dye has also been injected suberosally at the tumor site after resection of the colorectal tumor and mesentery (ex vivo). This technique can only be used with visceral malignancies such as colorectal cancers because the bowel segment containing the primary tumor and the mesenteric nodes is resected en bloc.[24]

Node Retrieval Techniques

At the time of surgical resection, it is impossible to know how many lymph nodes have been obtained for staging. The pathologist is responsible for gross retrieval of lymph nodes from the resected mesentery and for the microscopic identification of metastatic cancer within the nodes. In most cases, the search for lymph nodes is performed by visual inspection and palpation of the pericolonic fat and mesentery submitted with the resected segment of bowel containing the primary tumor. The mesenteric fat is sequentially sliced, and round or oval areas with white to tan-pink color suggestive of lymphoid tissue are identified and selected. Palpable firm areas are more closely inspected and sliced to look for the above characteristics as well. Several problems arise with this sampling method. First, a single lymph node might be sectioned into multiple slices during the search for metastatic cancer, and these slices could be misinterpreted as originating from several nodes instead of only one. Given this scenario, the number of positive nodes could be falsely elevated on the final pathology report. Second, identification depends on nodal size, and nodes measuring < 5 mm are more likely to be missed.[6] Although large lymph nodes more probably harbor cancerous deposits, they are not always positive. Conversely, many small nodes
(<5 mm) may actually contain metastases. Other disadvantages of this technique include its tediousness and its dependence on the experience of the pathologist. The clinical disadvantage of this technique is the risk of understaging and the ultimate impact of such staging on treatment. Several studies have attempted to define the minimum number of nodes necessary for accurate staging, or more specifically, to classify patients as stage III. According to the literature, the appropriate range varies, but 6 to 17 lymph nodes have been reported to be adequate.

**Method Refinements**

Several attempts have been made to refine this classic sampling method so as to deal with these difficulties and maximize the number of nodes retrieved. One approach is to separate the node-bearing pericolonic or perirectal fat from the main specimen and to increase the amount of time the fat is exposed to fixating agents. In one study, node positivity increased when fixation with 10% formaldehyde was extended for an extra day vs the more commonplace approaches that neither set a time limit for fixation nor perform fixation of the mesenteric fat separately (55% vs 36% positive nodes). This difference was attributed to the increased accuracy of the local nodal basin evaluation, especially in the area adjacent to the tumor.

Because the main obstacle in the localization of nodes is the surrounding fat, fat-clearing methods have been attempted. By using several types of solvents composed of mixtures of alcohols, formalin, ethers, or acetone, more nodes (including small ones) can be isolated. Koren and colleagues reported retrieving three times as many nodes in 30 patients with a "lymph node-revealing solution" after obtaining 88 nodes with standard dissection methods. However, these fat-clearing methods are time-consuming and expose pathology personnel to potentially toxic substances.

**Immunohistochemistry**

Immunohistochemistry allows more precise characterization of tissues by identifying specific tissue antigens. This involves coupling antibodies with enzymes such as peroxidase, which creates an identifying mark when the enzyme reacts with the substrate and allows visual identification of the tissue or cells bearing the specific antigen.

This method can be applied to microscopic evaluation of lymph node metastases, with the goal of improving detection of small cancerous deposits that would otherwise be overlooked with routine H&E staining. For colorectal carcinoma, relatively characteristic antigens have been identified, including CEA, cytokeratin, and tumor-associated glycoprotein-72, or TAG-72. The term "micrometastasis" has been used to describe very small cancerous deposits (<2 mm), which may only be revealed by such sensitive methods and not by routine histologic examination.

Jeffers and colleagues used the cytokeratin monoclonal antibody combination AE1:AE3 and found micrometastases in 25% of 77 patients with Duke’s B (T3) histologic node-negative colorectal cancer. Cutait and colleagues reported similar results using anti-CEA and anticytokeratin antibodies in 46 patients with Duke’s A and B (T1-3) histologic node-negative colorectal cancer; 26% of the patients were found to have micrometastases. In another study, Adell and colleagues found an even higher percentage of micrometastases (39%) using anticytokeratin antibodies.

**Survival Benefit?**

It is well established that more sophisticated techniques and an increase in nodal sectioning improves the detection of microscopic metastatic disease. However, the ultimate goal is to demonstrate a clinical benefit, such as longer survival. Two of the studies mentioned (Jeffers and Cutait) showed no significant difference in 10-year survival or outcomes of the group with micrometastases on immunohistochemistry vs the group without micrometastases. In the study conducted by Adell and colleagues, a trend toward adverse outcomes was noted in the group with immunohistochemically determined micrometastases, although the difference between groups was not statistically significant.

Finally, Greenson and colleagues found a significant survival disadvantage among patients who were node-positive on cytokeratin staining of microscopic tumor deposits. Further studies are needed to clarify this issue. The use of sentinel nodes should facilitate such studies, since fewer nodes per patient would be required to apply these methods, which are usually more time-consuming and expensive than routine histologic analysis.

**Polymerase Chain Reaction**

Even with the help of immunohistochemistry, a sampling factor must be taken into account, because
only certain sections of lymph nodes may be used for analysis. Multiple sections of a node may be assessed to improve sensitivity, but it is not feasible to view every one of the thousands of slices that can be obtained.[33] Polymerase chain reaction overcomes this limitation by analyzing a complete node for tumor DNA.

The MASA Approach

There are two approaches to PCR amplification of lymph nodes. First, specific mutations that are common in colon cancer, such as K-ras and p53, can be targeted. Some refer to this method as mutant allele-specific amplification (MASA). In one study, 120 patients with an initial diagnosis of Duke’s A and B (T1-3) histologic node-negative colorectal cancer were retrospectively evaluated with MASA for K-ras and p53 mutations within the primary tumor, and mutations were detected in 71 cases. In patients with evidence of lymph node metastasis on PCR, 73% presented with recurrent tumor within a 5-year period, but no recurrences developed in patients with negative PCR results.[30] However, this technique may not be clinically practical, because some tumors do not have DNA mutations that can be detected routinely with PCR amplification.[8] For example, only 40% to 50% of colorectal tumors have K-ras mutations.[30]

RT-PCR

A second approach is to use the reverse transcriptase-polymerase chain reaction (RT-PCR) technique to amplify messenger RNA (mRNA) corresponding to tumor antigens that are more widely present in colorectal cancer. CEA has been used because it is ubiquitous in adenocarcinoma. In a preliminary study by Liefers and colleagues involving 26 patients with stage II colorectal cancer (node-negative), this method revealed micrometastases in 54% of patients. Moreover, the adjusted 5-year survival in the absence of RT-PCR micrometastases was 91%, and only 50% in the RT-PCR node-positive group.[8] Markers other than CEA have also been explored for RT-PCR analysis.[31,34] However, RT-PCR analysis is not without drawbacks. Fresh tissue is required due to the fragility of the mRNA. The technique may also be too sensitive in some cases and identify micrometastatic disease that may not be clinically relevant. Moreover, there is no visual correlate (as there is with immunohistochemistry) i.e., one cannot see the true morphology of what is causing the test to be positive. Even though some of the markers used are reasonably specific for cancer, false-positives may occur. For example, immunohistochemistry studies using the antibody B72.3 against the glycoprotein TAG-72 (once thought to be specific for adenocarcinoma) have shown lymph node positivity in cases of benign disorders such as hyperplastic and adenomatous polyps or inflammatory bowel disease.[35]

Sentinel Node Mapping in Colorectal Cancer

The use of sentinel node mapping has become well established in melanoma and breast cancer. However, for colorectal and other gastrointestinal neoplasms, the success rate of identifying the sentinel nodes varies widely, depending on the technique and experience of the surgeon. Moreover, gastrointestinal cancers are associated with high rates of "skip metastases" i.e., metastatic deposits in higher-level nodes of the tumor lymphatic drainage pathway, with the first nodal basin remaining negative (false-negative).[36] Some investigators advise caution in applying the sentinel node concept to gastrointestinal sites because of an uncertain learning curve, complex lymphatic drainage, and anatomic alterations with prior surgery or radiation therapy.[37]

Clinical Trials

Only a limited number of investigations of sentinel node mapping have been conducted in colorectal cancer (Table 2).[22,23,36,38-41]

Waters et al

In one small pilot study focusing on colon cancer, Waters and colleagues[38] performed sentinel node mapping with isosulfan blue dye in 22 patients with colonic tumors; 18 were confirmed to have invasive cancer on final pathologic assessment. The technique was highly successful, identifying sentinel nodes in all 18 patients with adenocarcinoma. Sections of the nodes were initially analyzed by routine methods such as H&E staining. Immunohistochemistry was reserved for cases that were histologically node-negative. Six patients had metastatic lymph nodes by routine H&E staining, and in those patients, all the sentinel lymph nodes contained metastatic tumor (true-positive). The sentinel node was the only positive node in one patient. The predictive accuracy of the sentinel nodes in staging the entire regional lymph node basin was 100%.

Joosten et al

Joosten and colleagues performed sentinel node mapping with patent blue dye in 50 patients with
colorectal adenocarcinomas.[22] Sentinel nodes were successfully identified in 70% of cases. Lymph node metastases were found in 20 patients who had at least one sentinel node identified and biopsied. The results were disappointing because the sentinel nodes were negative for metastatic disease in 12 of 20 patients, in whom nonsentinel nodes were clearly positive (high false-negative rate).

The authors acknowledged that technical limitations were partially responsible for the results. As noted earlier, a sentinel node was not identified in 30% of patients. The majority of those patients were believed to have received intraluminal rather than subserosal injections. Fat-clearing was performed initially in 10 patients and later abandoned because it had a tendency to wash out the dye.

A significant number of patients with sentinel nodes negative for tumor had bulky disease with gross lymph node involvement. It has been hypothesized that bulky disease in nodes may promote alternative lymphatic drainage due to plugging of the usual pathways. In addition, rectal tumors were included in this study, and lymphatic mapping is technically more difficult for rectal tumors because of a shorter mesentery and a partial extraperitoneal location. This problem has been recognized by other authors as well.[23,36]

Cserni et al
Cserni and colleagues[39] similarly reported disappointing results in a subset of patients who were evaluated for sentinel nodes. The main goal of the study was to determine how many nodes were needed for accurate staging of colorectal cancers. Lymphatic mapping with blue dye was attempted in 25 patients. The predictive value of the sentinel node for regional nodal status was 79%.

In this study, many patients had bulky tumors, and all except two had T3 tumors. Furthermore, the pathologic analysis of the sentinel nodes was less than ideal given that the evaluation of the sentinel nodes did not differ from that of nonsentinel nodes, which was limited to two to three H&E sections per node.

Tsioulias et al
In a comprehensive study that included tumors of the colon, rectum, small intestines, pancreas, and stomach, Tsioulias and colleagues[36] evaluated sentinel node mapping in 65 patients. Focusing only on cases of colorectal cancer, the sentinel nodes were successfully identified 94% of the time. Metastatic disease was found within the sentinel nodes in 10 patients, upstaging 20% of the colorectal tumors.

Interestingly, in two patients with right colon cancer, the sentinel node was at a more distant site than expected. These patients underwent a more extensive resection than planned, suggesting that in some cases sentinel node mapping may not only help to determine the extent of resection but may also increase staging accuracy.

Saha et al
The largest experience to date with colorectal sentinel node mapping was reported by Saha and colleagues.[23] Sentinel node localization was possible in 98.8% of 86 patients, with 38% found to have metastatic lymph nodes. Skip metastases were identified in only three patients, all of whom had unusual presentations. (One presented with recurrent colon adenocarcinoma at the previous anastomosis, and the second patient presented with two synchronous colon cancers. The third patient presented with lung carcinoma metastatic to the colon.) In 18% (n = 15), metastatic disease was found only in the sentinel nodes. Furthermore, in 8% (n = 7), metastatic disease was found only after detailed pathologic analysis focusing on sentinel nodes, including multilevel sectioning and staining with anticytokeratin and anti-CEA antibodies.

The results of this study agree with those of the other studies in that sentinel node mapping is possible in colorectal carcinoma, and the incidence of skip metastases is not as high as previously thought. Saha and colleagues showed their technique to be highly accurate (95%) in predicting regional node status.[23]

Mapping With Isosulfan Blue
Isosulfan blue dye has been the main visualizing aid employed in the study of sentinel nodes in colorectal cancer. It has the advantage of being inexpensive and easy to use. This technique is particularly suitable for colorectal malignancies because unlike the regional nodes for melanoma and breast cancer, the pericolonic mesenteric lymph nodes are in direct view and not masked by the overlying skin. Adverse effects are minimal, occurring in approximately 1.5% of patients.[42]

Isolated case reports of such problems, mainly associated with breast cancer lymphatic mapping, consist of interference with intraoperative pulse oximetry[43] or anaphylaxis.[42]

One disadvantage of this mapping technique is that the blue dye may fade from the nodes, especially after the use of fat-clearing pathologic techniques, as demonstrated in the study by
Joosten and colleagues.[22] For this reason, the mesenteric sentinel nodes should be tagged with sutures within minutes after injection. If enough time has elapsed, the dye may travel to higher-level nodes, and the sentinel nodes may be missed if not marked. The addition of solutions containing mixtures of different-sized carbon particles to isosulfan blue dye has been evaluated in rats with the aim of confirming that the sentinel nodes identified are truly stained with blue dye under the microscope.[44]

Another disadvantage of using subserosal injection of dye in this setting is that small colorectal tumors often cannot be palpated, thus requiring intraoperative localization with colonoscopy.[40]

Radioactive Mapping
Some investigators have used radioactive sentinel node mapping for gastrointestinal tumors. Kitagawa and colleagues[40] used the alternative method of lymphoscintigraphy with Tc-99m-labeled tin colloid to identify the sentinel nodes in a variety of gastrointestinal tumors (including 33 colorectal neoplasms). Their technique involves endoscopic submucosal injection of a radioactive tracer in a four-quadrant pattern around the tumor several hours before the procedure. Between 0.5 and 4.0 mCi of Tc-99m-labeled tin colloid (activity at the time of surgery is approximately 0.3 mCi) in a volume of 1 to 2 mL is injected with a 23-gauge endoscopic puncture needle.

These authors performed preoperative lymphoscintigraphy using a gamma camera, which they consider more useful for rectal cancer because of the lateral location and unexpected sites of the sentinel nodes. However, the "shining" effect (ie, the summation of radioactive tracer uptake by the primary tumor and the sentinel nodes without spacing) seen on preoperative lymphoscintigraphy (by gamma camera) can be a problem with colonic and gastric tumors because of the close proximity of the sentinel nodes to the primary tumor. Thus, a collimated gamma probe is used intraoperatively to detect sentinel nodes, minimizing the interference emanating from the radioactive tracer injection site (or primary tumor). Any nodal tissue with a radioactive count greater than 10 times the background count is considered a sentinel node.

An oncologic resection of the gastrointestinal tumor is performed first. The abdomen is examined postresection with a gamma probe to ensure the adequacy of the primary tumor resection and its associated mesenteric nodes. The sentinel nodes within the resected specimen are confirmed with a final radioactive count using the gamma probe. This method was most accurate for gastric tumors (100%), intermediate for the colon and rectum (93%), and least accurate for the esophagus (92%). Furthermore, these sentinel nodes were invaded by metastatic tumor with a much higher frequency than nonsentinel nodes (13% vs 0.9%).[40]

The authors also commented that routine use of sentinel node mapping may be helpful in determining the extent of lymph node dissection in gastric and esophageal tumors and the extent of lateral lymphadenectomy specifically in rectal tumors.

Combination Mapping
Merrie and colleagues[41] used a combined mapping technique with lymphoscintigraphy and blue dye in 26 patients. Their procedure involved subserosal injection of colonic tumors with a mixture of 40 MBq of Tc-99m colloidal antimony sulfide and 2 mL of patent blue dye V. After a standard resection, the specimen obtained was placed on a grid and imaged with a gamma camera. Visual identification of blue nodes and the gamma image of radioactive nodes were recorded on an anatomic diagram to provide correlation of these sentinel nodes. The mesenteric nodes were then individually dissected on an ultraviolet-irradiated chopping board using a sterile surgical blade. RT-PCR for cytokeratin 20 was used to evaluate the sentinel nodes for occult micrometastatic disease.

The authors acknowledged that their results were not encouraging, given that the sensitivity of their technique was 55% and the false-negative rate, 45%. They concluded that tumor manipulation with temporary occlusion of lymphatic vessels, lack of dynamic scintigraphy, and the relatively large injectate volume may have played a role in the dismal results.[41]

A preliminary 10-patient study by Thorn and colleagues[45] also used a combination of dye and radioactive tracer to identify sentinel nodes and predict the presence or absence of metastatic disease in the locoregional nodes. They injected a combination of blue dye and radioactive tracer subserosally around the primary tumor and marked the blue-colored sentinel nodes with sutures. After resection of the primary tumor, bowel segment, and mesentery, a gamma image of the resection specimen was taken to see if it correlated with the tagged blue nodes. No results were available in their report.

Pathologic Analysis of Sentinel Nodes
For lymphatic mapping to be useful and applicable in the treatment and staging of colorectal cancer, it is necessary to use the special histopathologic techniques that have already been discussed in order to identify sentinel nodes in particular. These techniques differ from those used for routine lymph node evaluation in that the amount of tissue provided is smaller.

**Multiple Sections**
The first and easiest approach is to increase the number of sections per node taken. This should increase the likelihood of detecting small metastatic deposits, even if H&E is the only staining method used. In breast cancer, for example, increasing the number of permanent H&E sections in the axillary sentinel nodes to three additional slides increases the rate at which metastatic disease is discovered.[46]

A feature common to many studies is a stepwise approach to sentinel node evaluation. For example, the initial evaluation may include a frozen section, a method more restricted to cancer sites in which a positive sentinel node dictates further surgery, such as axillary node dissection in breast carcinoma. If the frozen section is negative, additional permanent sections may be taken to increase the efficacy of the search for metastasis.

However, a limit must be set for the number of sections taken, because theoretically these could number in the thousands.[33] One approach that has been proposed in breast cancer is to take three sections (two for H&E staining and one for immunohistochemistry) every 250 µm.[47]

Micrometastases can then be identified without compromising accuracy or cost-effectiveness.

**Multiple Sections Plus Immunohistochemistry**
Immunohistochemistry has been an integral part of sentinel node analysis in several studies. It is especially useful in tumors that invade as a small group of malignant cells or as individual cells—for example, melanoma or lobular carcinoma of the breast.[33] Usually one of the step sections of the sentinel nodes is used for immunohistochemistry. Other methods attempted for the evaluation of sentinel nodes such as imprint cytology and flow cytometry do not appear to be as useful as immunohistochemistry.[33]

Data reported by Wiese and colleagues[48] seem to support the analysis of sentinel nodes in colorectal tumors by the methods just described. These authors evaluated 83 patients with biopsy-proven colorectal cancer. Processing of the nodes included 10 sections at fixed intervals, one of which was stained by immunohistochemistry methods involving anticytokeratin antibodies. An interesting aspect of the study is that, for the first 25 patients, all negative nonsentinel nodes were subjected to the same detailed evaluation applied to the sentinel node. Among cases in which the sentinel node was negative by H&E staining, only two (0.6%) of the nonsentinel nodes were positive on immunohistochemistry.

This small false-negative rate supports the value of restricting special and detailed histopathologic techniques to sentinel nodes. Of the 34 patients with lymph node metastases, 50% had exclusive sentinel node involvement. A total of three patients had involvement of nonsentinel nodes only. The authors concluded that histologic analysis involving multiple sections plus immunohistochemistry has a high accuracy in predicting regional lymph node status (95%). Numerous step sections of lymph nodes are unnecessary. The use of four sections per node did not compromise the accuracy of detecting metastatic disease.

**RT-PCR Analysis**
RT-PCR has also been extended to the analysis of sentinel nodes in colorectal cancer. Bilchik and colleagues found that in 86% of patients whose sentinel nodes were positive for metastatic disease by H&E staining and/or immunohistochemistry (using the following molecular markers: beta-chain human chorionic gonadotropin, hepatocyte growth factor receptor, and universal melanoma-associated antigen-A family), RT-PCR testing of these same nodes was also positive.[34] However, 46% of the sentinel nodes negative by these methods were positive for metastatic disease by RT-PCR. The clinical and prognostic significance of these results has yet to be determined.

**Conclusions**
The current literature on intraoperative sentinel node mapping and biopsy in colorectal carcinoma supports the feasibility of the isosulfan blue dye and radiotracer techniques. However, caution should be exercised because of the variable false-negative rate reported for colorectal sentinel nodes. This could be a reflection of the technique or experience of the investigator.

Novel pathologic assessment of the sentinel nodes, for example, with immunohistochemistry aids in the detection of micrometastases. However, the clinical relevance of micrometastatic disease detected by ultrasensitive techniques has yet to be determined. Further refinement of sentinel node
mapping techniques in colorectal cancer is necessary to increase sensitivity and minimize the false-negative rate. Ultimately, a multi-institutional trial must be conducted to standardize the procedure and provide evidence of clinical benefit.

References:


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