Sentinel Lymphadenectomy: An Emerging New Alternative for Improving Staging of Early Colorectal Cancer

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Colorectal carcinoma is the most common gastrointestinal cancer and the third most common cancer in the United States. Approximately 57,000 Americans die of CRC each year. CRC is the third cause of death in men and women alike, with an estimated annual incidence of 130,000 cases in the U.S. The incidence is equal in men and women. Although 37% of patients are diagnosed with stage I disease, which confers a 91% 5 year survival, another 37% are diagnosed with stage II or III disease. In these patients the 5 year survival rate drops to 75% and 50% respectively. Approximately 30% of patients with stage I or stage II disease will eventually develop diffuse metastatic disease with time [1–4].

In recent years efforts have been made to adjust the treatment given for the true stage of the disease. Improving the staging technique currently used may afford us an opportunity to better assess the patient's prognosis and status, and consequently offer the patient a better suited surgical treatment and adjuvant chemotherapy treatment after surgery, if needed [5]. Although the etiology of recurrence is most likely multifactorial, in virtually all malignant solid tumors it is accepted that lymph node status is one of the most important prognostic indicators of poor survival [6,7].

The propensity of solid tumors to spread to regional lymph nodes was originally observed in the 18th century by François LeDran (1785–1870) [8] in patients with breast cancer. Historically, examples of preferential sites of tumor metastasis have been recognized: Virchow's node for gastric cancer, the Delphian node for thyroid cancer, and Sister Mary Joseph's node [9].

Over 100 years ago, Herbert Snow [10] advocated lymph node dissection as part of the treatment of melanoma. The term sentinel lymph node was first coined by the urologist Cabanas. In 1977, using lymphangiography, he determined that squamous cell carcinoma of the penis initially drains to a group of lymph nodes in the groin [11]. The concept of identifying a lymph node likely to have metastatic melanoma in order to minimize surgery was first proposed by Morton and colleagues [12,13] in patients with stage I cutaneous melanoma. They defined the SLN as the first lymph node or nodes to drain a primary melanoma; therefore these are the nodes most likely to contain metastases if the melanoma has spread to the regional lymph. Thus, they showed that if the SLNs were melanoma-free, the remaining lymph nodes would likely be tumor-free. This subsequently became significant for its application in operative staging of regional lymph node basins. In 1991, Giuliano and co-workers [14,15] modified this procedure in order to apply the technique to patients with breast cancer, and a few years later Kelemen et al. [16] applied the technique to patients with thyroid cancer. More recently, lymphatic mapping for SLN was applied to a variety of solid neoplasms, including CRC [17–20].

The standard procedure today is to send lymph nodes obtained on standard colectomy operation for pathologic assessment. One to two sections are taken from each node, stained by hematoxylin & eosin and examined for metastasis. Over time, an effort was made to find a way to decrease the incidence of missed metastases. One way is to increase the number of lymph nodes obtained during a conservative operation. Another way is to limit the amount of assessed specimen, and within this limited amount of specimen to perform better staining techniques. In some cases, applying these improved techniques allows upstaging of the disease, thereby providing a new prognosis and a different treatment [14,15]. Accurate staging is crucial, since choosing the appropriate treatment in each case depends on the stage of the disease. Surgery and total excision of the tumor is the primary treatment of choice for non-metastatic disease (stages I-III). Operation alone as a curative procedure is appropriate only for stage I and II disease. For stage III, adjuvant chemotherapy is recommended, As a result, recurrence decreases by 39% and mortality by 32%. There is no change in recurrence or mortality rates for stage II, therefore chemotherapy is not indicated for these cases [21].

Definition of a sentinel lymph node

Every region in the body has its own lymphatic draining system. During the course of draining the lymphatic fluid passes through lymph nodes, and the first nodes to encounter the lymphatic fluid from a certain region are the SLNs for this region. The basic assumption behind the recently introduced lymphatic mapping for SLN is that the first nodes to encounter the lymph fluid from a tumor region will most likely be the first to be affected by metastatic deposits, seeded by the tumor via the lymphatic system [22].

LM/SLN in patients with CRC

LM/SLN is a concept taken from melanoma and breast cancer and recently applied to CRC. LM/SLN in CRC is still in its infancy. This

* Deceased

CRC = colorectal carcinoma
SLN = sentinel lymph node

LM/SLN = lymphatic mapping for SLN

approach, however, shows great potential from both the surgeon and pathologist's perspective. For the surgeon, LM/SLN in melanoma and breast cancer usually obviates the need to perform complete lymphadenectomy in patients with negative SLNs. By contrast, in CRC, anything less than optimal standard lymphadenectomy is not recommended. Instead, the benefit of using LM/SLN derives from the ability of LM/SLN to detect aberrant lymphatic drainage patterns in about 4% of patients, which therefore require wider resection to include all the SLNs. For the pathologist, the real benefits of LM/SLN lie in the accuracy of the diagnosis and the ability to detect nodal micrometastatic disease [2].

The first step in assessing the SLNs is to locate them. As mentioned earlier, lymphatic mapping techniques are used in melanoma and breast cancer, but applying them to CRC is easier because the lymphatic channels are easily visualized during surgery [Figure 1].

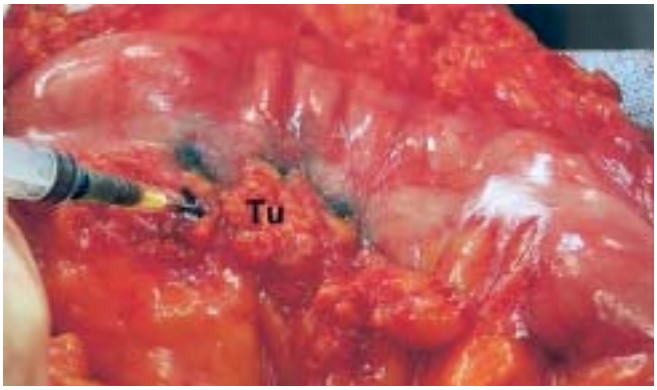

Figure 1. Isosulfan blue dye (3–5 ml lymphazurin R 1%) is injected subserosally around the tumor (Tu) using a tuberculin syringe [3].

Lymphatic mapping using vital-blue dye in patients with CRC

Intraoperative: *in vivo* mapping

In a standard colectomy operation the colon is carefully mobilized without disrupting the lymphatic channels. Isosulfan blue dye (3–5 ml lymphazurin R 1%) is injected subserosally around the tumor using a tuberculin syringe [Figure 2]. Immediately after injection, the dye travels along the lymphatic channels to the SLNs [3]. Visualization of the dye's path occasionally requires precise dissection of the mesentery. The first node(s) (between one and three) to stain blue is identified as an SLN, which is dissected and sent for pathologic examination. Colectomy is then performed in the standard fashion, and the en bloc specimen is sent for pathologic examination [2,3].

In 2000 Tsioulias et al. [17] [Table 1] performed LM/SLN in 65 patients with gastrointestinal neoplasms, using isosulfan blue dye; 0.5–1 ml isosulfan blue dye was injected around the periphery of the neoplasm. Blue-stained nodes were analyzed by hematoxylin & eosin staining, multiple sectioning and immunohistochemistry staining for cytokeratin. LM/SLN identified at least one SLN in 62 patients (95%). Of the 36 cases with nodal metastasis, 32 (89%) had at least one positive SLN and 15 (42%) had nodal metastasis only in the SLN. In 11 cases, tumor deposits were identified by multiple sectioning (n=2) or ICH-CK (n=9) only. In five cases (8%), lymphatic mapping identified aberrant drainage that altered the borders of the planned resection.

In a work by Wood and colleagues [4] [Table 1], LM/SLN was performed in 50 consecutive patients undergoing colectomy for CRC. All lymph nodes in the resection were examined by routine H&E staining. In addition, multiple sections of each SLN were examined by both H&E and IHC-CK. At least one SLN (one to three) was identified in 47 patients (94%), and in 7 patients (14%) LM/SLN identified aberrant drainage that altered the borders of the planned resection. Bilchik et el. [18] [Table 1] published a study that evaluated the sensitivity, accuracy and feasibility of staging based on LM, focused examination, and molecular analysis of the SLN in patients with primary CRC. One hundred patients with CRC underwent LM immediately after peritumoral injection of 1.0 ml isosulphan blue dye. LM was successful in 97% of the cases. Aberrant lymphatic drainage was identified in eight patients (8%), altering the borders of the planned resection.

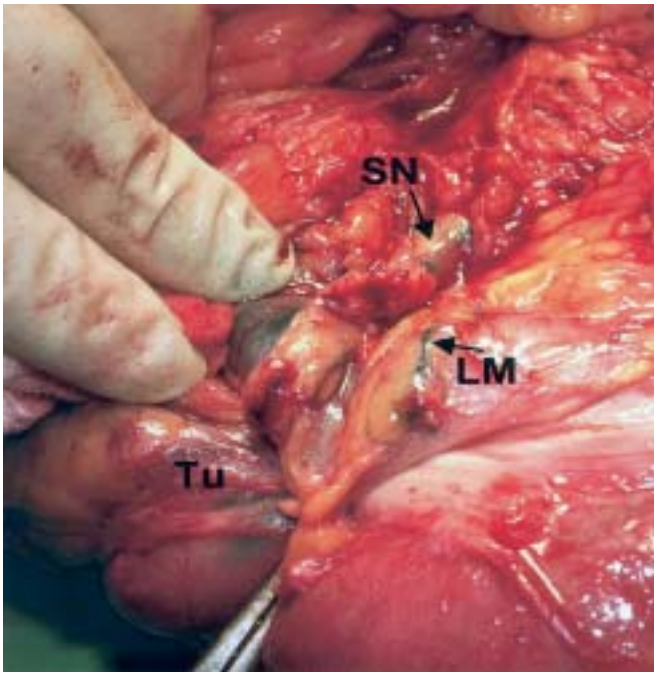

Figure 2. After injection of the isosulfan dye around the primary tumor (Tu), lymphatic mapping (LM) is evident and the sentinel node (SN) is detected.

More recently, Paramo and associates [19] [Table 1] summarized their experience with LM/SLN for colorectal cancer. Fifty-five patients with CRC underwent intraoperative LM/SLN; 1 ml of (1%) isosulfan blue was injected subserosally around the tumor. The first nodes highlighted with isosulfan blue were identified as SLNs, which then underwent multiple sectioning and IHC-CK. The overall learning curve was calculated. LM adequately identified at least one SLN in 45 patients (82%). The overall learning curve stabilized after five cases.

When using isosulfan blue one must be aware of the risks.

IHC-CK = immunohistochemistry staining for cytokeratin
H&E = hematoxylin & eosin

Table 1. Summary of dye-alone LM/SLN

Intraoperative LM using vital-blue dye	SLN identified	LM identified aberrant drainage
Bilchik et el. [18]	97%	8% (5 cases)
Paramo et al. [19]	82%	–
Wood et al. [4]	94%	14% (7 cases)
Tsioulias et al. [17]	95%	8% (5 cases)
***Ex vivo* mapping**		–
Wong et al. [25]	92% (24 of 26)	–
Fitzgerald et al. [26]	88% (23/26)	–

Allergic reaction can vary, from a mild reaction – with blue maculopapular rash, to severe true anaphylaxis – with hypotension, diffuse erythema and edema. Since the incidence of anaphylactic reaction to isosulfan blue was reported to be 0.7–1%, it is recommended that a skin test be performed to assess the potential of allergy [23].

Extraoperative: *ex vivo* mapping

An alternative *ex vivo* approach for harvesting SLN has been reported by Wong and co-workers [24]. This approach follows the en bloc resection of the primary tumor. The specimen is opened on the antimesenteric border, and 0.1–0.2 isosulfan blue is injected submucosally in four quadrants around the primary tumor. The injected site is gently massaged. The peritoneum overlying the mesentery of the specimen is then carefully incised at the base of the bowel wall and, using a technique identical to that described by Morton et al. [13] for intraoperative LM with isosulfan alone, the mesenteric fat is opened. Blue-stained lymphatic channels are identified and traced to blue-stained lymph nodes, which are harvested individually and examined as SLNs. *Ex vivo* mapping has a crucial advantage over the *in vivo* technique: the *ex vivo* approach does not alter the original surgical course and therefore does not prolong its duration. However, there are a few problems with the *ex vivo* approach. First, the regional lymphatic basin might be a considerable distance from the primary tumor and therefore the SLN might be located outside the margins of a conventionally planned mesenteric resection [3]. Second, during a standard operation, irrespective of the surgeon's skill, the lymphatic channels can be damaged; and later, during the staining procedure, lymph nodes might be falsely identified as SLNs. More recently Wong et al. [25] [Table 1] published another study of LM/SLN in which they describe their experience with the *ex vivo* technique to identify the SLN in colorectal carcinoma. Within 30 minutes of resection, colorectal specimens were injected submucosally with isosulfan blue in four quadrants. Blue lymphatic channels were identified in the mesentery and followed to the blue-stained SLNs, which were then harvested. The specimen was fixed in formalin and subsequently analyzed in the usual fashion. Blue-stained nodes that were negative by H&E staining were further analyzed by IHC-CK. The study group comprised 26 patients with CRC undergoing routine resection. Blue-stained SLNs were identified in 24 of 26 specimens. The mean number of SLNs identified per patient was 2.8 $\pm$ 1.6. Seventy-three SLNs were identified from a total of 479 lymph nodes harvested. The mean number of nodes identified per patient was 18.4 $\pm$ 7. The authors concluded that *ex vivo* mapping of the colon and rectum is technically feasible and may provide a useful approach for the ultrastaging of CRC.

Fitzgerald et al. [26] [Table 1] recently reported their study of 26 patients with varying tumor location and stage; the SLN was identified in 23 of the 26 cases (88%). Three failures occurred in patients with rectal cancer. The average number of SLN harvested was 2.5. The status of the nodal basin was accurately predicted in 91% (21 of 23 patients). Two false negative SLNs were harvested in two of three patients with stage III/IV CRC. The SLN upstaged two patients as a result of H&E-stained step sections and IHC-CK in one each.

Radioisotope and gamma probe-guided lymphatic mapping

In contrast to the dye-only method, Krag et al. published the first pilot study of LM/SLN using isotope alone in patients with invasive breast cancer. In this study of 22 patients, unfiltered technetium sulfur colloid injected 1–9 hours before surgery was used to map the lymphatic tract and identify the SLN. The SLN was identified in 18 of 22 cases (82%) and was 100% predictive of the axilla's status. The authors subsequently updated their results in 248 cases. In this cohort, the SLN was identified in 95.5% of patients, with a false negative rate of 6.5% [27].

Until recently, radioisotope was not used for the purpose of identifying SLN in colorectal cancer. It is used to detect locally disseminated disease, which is one of the principal goals of oncologic surgery. These techniques are primarily employed to detect tumor deposits regardless of the histologic location, and its application for identifying SLN was only recently introduced [28].

Radioimmuno-guided surgery

Radioimmuno-guided surgery is a technique in which a radio-labeled monoclonal antibody is injected 3–4 weeks prior to surgery. The antibody becomes attached to the tumor while the body secretes the surplus antibody. The concentration in the blood decreases and a ratio builds up between the tumor and the blood, enabling the surgeon to detect the tumor when using a gamma detection probe during the operation [29].

Tuttle et al. [30], in 1988, studied this intraoperative approach to tumor localization using radiolabeled monoclonal antibodies B72.3, which involves the use of a hand-held gamma detection probe by the surgeon and, subsequently, the pathologist. They reported the use of ^{125}I-labelled MAb B72.3 immunoglobulin G and a gamma detection probe to localize primary and metastatic CRC in 31 patients. The patients were administered radiolabeled MAb intravenously, and all underwent surgical exploration 5–35 days post-injection. *In vivo* localization of the MAb was evaluated using a gamma detection probe, and tumor and normal tissue counts were obtained. In each case, the resultant tumor and normal tissue that were resected were analyzed *in vitro* for MAb localization; this was evaluated by calculating the radio-localization index, i.e., the ratio of the injected dose per gram localized to tumor versus that of normal tissue. When the gamma detection probe was used

MAb = monoclonal antibodies

intraoperatively, MAb B72.3 localized tumors in 21 of 31 patients (68%). MAb B72.3 localized tumor in all sites to which CRC commonly metastasizes, including mesenteric and peri-aortic lymph nodes, liver, lung, and perirectal soft tissue. Lechner et al. [31] recently reported their experience using anti-carcinoembryonic antigen scintigraphy. They investigated 20 patients, 6 with rectal and 14 with colon cancer. Twenty-four hours before surgery the patients were intravenously given 1 ml of a fab'-fragment-antibody to CEA, labeled with 25 mCi of 99mTc (CEA-Scan). During surgery the radioactivity in lymph glands regional to the tumors was measured and compared with the much lower activity in healthy nodes. All lymph nodes of interest were then excised and submitted to frozen section pathology. In 7 of 20 cases scintimetry led to an upstaging of the disease. In addition, they found metastatic spread to lymph nodes that were basically not regional to the primary tumor (retroperitoneum, renal hilum, etc.).

Ex vivo radioisotope and gamma probe-guided lymphatic mapping

Merrie et al. [32] reported their results with an *ex vivo* isotope technique. The aim of this study was to compare the lymphatic drainage of CRC with the anatomic distribution of histologic and submicroscopic lymph node metastases. Patients attending for colectomy were eligible to enter the study. At the commencement of surgery, 40 MBq of 99mTc colloidal antimony sulfide in 2 ml of patent blue dye were injected subserosally around the tumor. Resection was completed in a standard fashion. After resection, specimens were imaged with a gamma camera to determine the site of SLNs, and then dissected, and the position of the lymph nodes was recorded on an anatomic diagram. Recovered lymph nodes were bisected, one-half for routine histology and one-half for assessment by keratin 20 reverse transcription polymerase chain reaction. The kappa measure of agreement was used to assess concordance between SLNs and histologic and submicroscopic metastases. From 26 tumors 456 lymph nodes were dissected and evaluated using lymphoscintigraphy and LM/SLN. SLNs were evident in 23 tumors (88%). The sensitivity of SLN involvement as a predictor of metastatic disease was 55%, with a false negative (non-diagnostic) rate of 45%. SLNs involved the apical group in four tumors and represented anatomic "skip" lesions in four. The authors concluded that direct lymphatic drainage to the apical group does occur in CRC; however, LM/SLN of CRC by this technique is of little clinical value because of the poor concordance between lymph node metastases and SLNs.

LM using a combination of vital-blue dye, radioisotope and gamma probe guidance in patients with CRC

In addition to techniques utilizing only vital-blue dye or radioisotope and gamma probe guidance, there is a technique that uses both vital-blue dye and radioisotope and gamma probe guidance. It requires the injection of radioactive isotope preoperative and intraoperative injection of dye. The combination of these two is expected to increase the ability of the surgeon to identify SLN. This technique is predominately used for breast cancer [33–35]. This combined technique was studied by Nastro et al. [36] for the detection of SLN in CRC in eight patients: SLNs were identified in six patients (75%), two were negative for metastasis by H&E and on IHC-CK (25%), two were positive by both methods (25%), and two were negative for metastasis by H&E and positive on IHC-CK (25%). The study concluded that this technique has potential for application in CRC.

Histopathology

LM/SLN, which adds to the pathologic staging of breast cancer melanoma, might offer the same benefits in CRC. The pathologist can concentrate efforts on detecting metastases in these nodes. Among the many studies underway in the field of LM/SLN, four main methods are being used for the evaluation of the harvested specimens:

- Examination by routine H&E staining
- Examination by step serial sectioning stained by H&E
- Examination by IHC-CK [6]
- Examination by reverse transcription polymerase chain reaction.

Bilchik et al. [18] used H&E staining to examine lymph nodes in CRC specimens from 100 patients. The SLNs were examined by step serial sectioning, IHC-CK and/or RT-PCR analysis in an attempt to identify occult micrometastatic disease. There were five false negative cases, predominately associated with T3/T4 tumors; 26 patients had H&E-positive lymph nodes. In 74 patients who were node-negative by routine H&E, 18 (24%) had occult nodal micrometastases missed on routine H&E examination, but detected by focused analysis of the SLN. RT-PCR analysis of the SLN was performed in 40 patients, 26 of whom were negative by H&E and IHC-CK. In 12 of 26 patients (46%) there was additional evidence of micrometastatic disease.

In the study by Wood et al. [4], all lymph nodes in their resection were examined by routine H&E staining. In addition, multiple sections of each SLN were examined by both H&E and IHC-CK. The SLN correctly predicted node basin status in 44 of 47 cases (94%). There were three false negative SLNs. Sixteen cases had positive SLNs by H&E. An additional 10 cases (20%) were upstaged by a focused examination of SLNs. Micrometastases were identified in three cases by H&E staining of multiple sections of the SLN and in seven by IHC-CK only. In nine cases the SLN was the only node containing tumor cells.

Paramo et al. [19] studied 55 cases from which 87 SLN were obtained. Among the 14 cases that were SLN-positive, 6 patients were positive only by IHC-CK and not by standard H&E staining. The authors concluded that negative SLNs accurately predict the status of non-SLNs 97% of the time. Eleven percent of patients were upstaged by demonstration of micrometastases.

Conclusions

Sentinel lymph nodes are the first nodes to encounter lymph drainage from a cancer region. Therefore, they are the most likely to harbor metastatic deposits if such were sent via the lymphatic

CEA = carcinoembryonic antigen

RT-PCR = reverse transcription polymerase chain reaction

system. Adding LM/SLN with focused pathologic analysis to standard pathologic analysis might improve the ability to identify micrometastasis, thereby providing the clinician with more information to better assess the stage, prognosis and treatment. Liefers et al. [5], studying the prognostic value of micrometstasis detection, detected micrometastases in one or more lymph nodes from 14 of 26 patients (54%). The adjusted 5 year survival rate (for which only cancer-related deaths were considered) was 50% in this group, compared to 91% in the 12 patients without micrometastases. The ability of lymphatic mapping to identify aberrant lymphatic drainage gives the surgeon the opportunity to alter the borders of the performed operation according to true lymphatic regional drainage. Furthermore, the possibility of identifying aberrant lymphatic drainage will enhance the recently introduced laparoscopic technique for colectomy operation [37]. Further studies are still needed to define the significance of micrometastasis in colorectal carcinoma and improve selection of those early-stage patients for whom adjuvant therapy is appropriate.

Acknowledgment. This article is dedicated to the memory of Dr. Oded Cohen.

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