Review Article

Sentinel lymph node biopsy in gastrointestinal malignancies—Where do we stand?

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Abstract

Sentinel lymph nodes (SLNs) are the nodes in direct communication with the primary tumor and are therefore the first group of nodes to be involved in lymphatic metastasis. Though the role of SLN biopsy is well established in cancers of the breast and melanoma, its role in gastrointestinal malignancies is still evolving and controversial. In this paper, the literature is reviewed with respect to the status of SLN biopsy in gastrointestinal malignancies.

Key words: Gastrointestinal malignancies, lymphadenectomy, sentinel lymph node biopsy

Introduction

Sentinel lymph nodes (SLNs) are the nodes directly communicating with the primary tumor through their afferent lymphatic vessels. SLNs are functionally the first echelon or station and therefore this forms the basis of the SLN theory where lymphogenic metastases occur in an orderly fashion, with the SLN being the first site of regional nodal metastases, while the remaining nodes (non-SLNs) are only involved later. It follows further that there will be times where the SLN will be the only node involved with cancer and, in addition, the metastatic deposit may, at this time, be small in size.

History of the Sentinel Lymph Nodes

The concept of the SLN is not new. In fact, it was Virchow who, in the mid-nineteenth century, described the lymphatic drainage from a primary tumor to a "sentinel" node then onward to other nodes.[1] Credit for coining the term sentinel node is however given to Gould *et al.* in relation to parotid cancer.[2] The clinical concept of the SLN was applied in 1977 by Cabanas in his use of lymphangiograms in patients with penile cancer.[3] On this basis, selective inguinofemoroiliac dissection was performed. The clinical application of SLN mapping essentially exploded and became popular following the work of Morton *et al.* when they injected vital blue dye intradermally in patients with early-stage truncal melanoma and the blue-stained SLNs were identified.[4,5] The low incidence of lymph node involvement in early disease and the morbidity associated with potentially unnecessary inguinal lymph node dissection were justifiable concerns. The use of SLN mapping not only allowed for selective lymphadenectomy as directed by the status of Cloquet's node, but was able to identify aberrant lymphatic drainage and therefore guide the dissection.

Another landmark paper came in 1995 when Giuliano *et al.* used the SLN concept in breast cancer.[6] A critical issue from this article was the upstaging potential of SLN biopsy since there was a 13% increase in the lymph node positive rate as detected by SLN biopsy as compared with standard axillary dissection. The difference is explained by the focused pathological assessment of the SLN in terms of nodal step sectioning and immunohistochemistry (IHC) and therefore more accurate detection of micrometastasis (MM). The use

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Website: www.indianjcancer.com

DOI: 10.4103/0019-509X.84940

of the SLN can thus be applied in two broad areas. The first is for tumors in locations where regional lymph node dissection can be performed on a more selective basis depending on the findings of the SLN. Carcinoma of the breast and melanoma will fall in this category. On the other hand, there are tumors located in regions where the state of the SLN will not affect the extent of lymphadenectomy; however, the focused pathological assessment of the SLN can allow for potential upstaging. The obvious implication will be on the need for adjuvant therapy. Some malignancies of the gastrointestinal tract will fall under this category. The status of SLN biopsy will now be discussed in relation to malignancies of different aspects of the gastrointestinal tract.

Status of Sentinel Lymph Node Biopsy in Colorectal Cancer

Lymph node metastasis is the major predictor of survival and recurrence in colorectal cancer and the decision regarding adjuvant therapy depends largely on lymph node status.[7] Yet, up to 30% of patients with node-negative colon cancer staged by standard pathological techniques ultimately suffer disease recurrence and tumor-related mortality following potentially curative surgery.[8] This may reflect either inadequate nodal dissection or inaccurate pathological assessment. At present, the National Comprehensive Cancer Network (NCCN) recommends a minimum of 12 nodes for adequate staging of colorectal cancer.[9] Standard pathological evaluation may overlook low volume nodal metastasis and therefore falsely understage patients. The SLN biopsy allows for selective focused sampling techniques in order to ultrastage patients. Nodal step sectioning and IHC will improve staging accuracy but cannot logically be applied to all harvested nodes since processing time, human resources, and cost would be prohibitive. Directed and detailed examination of a limited number of nodes at highest likelihood of involvement would be a practical method of improving accuracy. The SLN-based ultrastaging can therefore ultimately identify a subset of patients who will benefit from adjuvant chemotherapy.[10] Saha *et al.* pioneered the technique of SLN mapping whereby the affected colon is mobilized with minimum handling of the mesentery to avoid disruption of the lymphatic pathway.[11] Peritumoral injection of 1% isosulfan blue is then performed with care taken to avoid intraluminal injection of the dye. Intraluminal dye can lead to the SLN being identified away from the tumor-bearing area. The first few blue nodes are usually seen within the first 10 minutes and these are marked with sutures for later pathological identification. This is followed by a standard oncological dissection with en bloc resection of the SLNs, together with the other regional nodes. The SLNs were subjected to multilevel sectioning and IHC with cytokeratin. Stojadinovic *et al.*, in a prospective randomized study from the United States Military Cancer Institute Clinical Trials Group Study GI-01, used the *ex vivo* approach whereby, following standard colectomy and lymphadenectomy, 1% isosulfan blue was injected peritumorally and the SLNs were pathologically evaluated as previously described.[12] The metastasis, if present, were categorized as macrometastasis (>2 mm), MM (>0.2 mm and ≤2 mm), or isolated tumor cells (ITCs) (≤0.2 mm). Interestingly, there was a 19% nodal upstaging with the use of the SLN biopsy technique. The difference however was accounted for by the detection of MM and ITCs. A similar study by Bembenek *et al.*[13] revealed upstaging in 21% of patients again due to MM or ITCs. Incidentally, the SLN detection rate was directly related to center experience and inversely related to the patients' body mass index. The conclusion from both studies was that though SLN biopsy does lead to upstaging, the clinical impact of MMs and ITCs in terms of prognosis and need for adjuvant chemotherapy must be clarified. A prospective trial is ongoing to determine this clinical significance. The current NCCN guidelines recommends that the present use of the SLN and the detection of cancer cells by IHC alone should be considered investigational and the results should be used with caution in clinical management decisions.[9]

For the most part, the status of the SLN does not change the extent of resection since standard en bloc resection for colon cancer includes regional lymphadenectomy. On occasion, however, aberrant lymphatic drainage is seen beyond the standard resection margin and SLN mapping will allow extended resection to include this draining basin.[14] This aberrant drainage was seen in 4% of patients undergoing SLN mapping for colon cancer in a study from the Netherlands.[15] In most of these cases, the SLN was identified to the left of the middle colic vessels in ascending colon tumors and therefore changing the extent of resection to an extended right as opposed to a conventional right hemicolectomy. The status of SLN biopsy in rectal cancer is different when compared with colonic cancer. First of all, the dye method appears to be sufficient for colonic cancer; however, in rectal cancer, rectal mobilization is required to identify the blue SLNs, yet this mobilization in itself alters lymphatic flow. The addition of radioactive tracer improves the detection of the SLN in rectal cancer.[16] The other issue is the use of the SLN to select patients who would benefit from lateral pelvic lymph node dissection (LPLD). In this regard, SLN biopsy for rectal cancer is similar to its use in breast cancer or melanoma. A small portion

of the lymphatic drainage from the lower rectum exits the lateral ligament and drains along the internal iliac artery.[17] The incidence of lateral lymph node metastasis is in the region of 15% and the incidence increases with depth of tumor penetration as well as decreasing distance from the anal verge.[18] Although some studies have shown an improved local recurrence and overall survival rate following LPLD,[19] the low rate of lymph node positivity, the poor prognosis of patients with lateral pelvic lymph node metastasis even after dissection, and the increased morbidity of the procedure would not support the routine performance of LPLD. The use of the SLN would therefore allow for a more selective approach to LPLD.

Status of Sentinel Lymph Node Biopsy in Esophageal and Gastric Cancer

The extent of lymphadenectomy in gastric cancer has been a source of controversy for decades. This, together with the complex lymphatic drainage of the stomach as well as the potential for skip lesions[20] make SLN biopsy for gastric cancer even more challenging.

The first evidence of a survival benefit following extended lymphadenectomy came in 1981 when Kodama reported a 39% 5-year survival for D2 dissections compared with 18% for D1 dissections.[21] A D1 dissection is defined as removal of the first echelon of nodes, as described by the Japanese classification, namely the perigastric lymph nodes, while a D2 dissection comprise removal of the perigastric nodes (as in D1) together with the second echelon, that is, nodes surrounding the hepatic, celiac, left gastric, and splenic arteries.[22] Subsequent trials by Cuschieri *et al.* in the United Kingdom[23] and Bonenkamp *et al.* in Holland[24] failed to show any survival benefit of D2 compared with D1 dissections, yet the mortality rate was higher in the D2 group. However, a subset analysis revealed that the mortality was due to a concomitant pancreaticosplenectomy. This finding and that of improved survival of D2 compared with D1 dissection were confirmed in both the German Gastric Carcinoma Study Group[25] as well as the Italian Gastric Cancer Study Group Multicenter Trial.[26] This survival difference can be attributed to the stage migration effect where the more extensive the lymphadenectomy, the greater the chances of detecting involved nodes, and therefore increasing the chances of upstaging the disease.[27] As a result, most western surgeons perform a D1 dissection. In Japan, however, the standard is a D2 dissection. In fact, a study by the Japan Clinical Oncology Group compared D2 dissection to D2 dissection with para-aortic lymphadenectomy and found no difference in the postoperative mortality rate.[28] Further information with regards to any survival difference is pending.

Due to this lack of consensus, individualized approaches based on the lymph node status is required and the clinical potential of focused lymphadenectomy based on the SLN is an attractive candidate. In other words, at this point in time, the SLN concept in gastric cancer is similar to that of breast cancer and melanoma where extended lymphadectomy can be performed on a more selective basis depending on the status of the sentinel node. The first issue in SLN biopsy for gastric cancer is patient selection. The incidence of nodal involvement increases with the depth of penetration of the tumor in that there is a 2 to 18% risk of lymph nodal metastasis in T1 tumors, while this figure increases to over 50% once the muscularis propria or subserosa is involved.[29] As a result, patients with early gastric cancer (EGC) will benefit most from sentinel node biopsy.[30]

The other issue is the method of detection. Hayashi *et al.* have found the dual approach of combining the blue dye and the radiocolloid to have a detection rate of 100% with a false-negative rate of 0% .[31] The current protocol for SLN mapping for gastric cancer at the Keio University Hospital in Japan, indicated for clinically T1 lesions, is the endoscopic submucosal injection of radiocolloid the day prior to surgery as well as the endoscopic submucosal injection of 1% isosulfan blue intraoperatively.[32] A multicenter prospective trial by a study group in the Japan Society of Sentinel Node Navigation Surgery is being conducted using this dual tracer method[33] which will confirm the feasibility of the method used at the Keio University Hospital.

The future direction of SLN biopsy for gastric cancer is toward minimal access surgery or endoscopic mucosal resection in combination with SLN biopsy and, in the event of uninvolved SLNs, avoiding transabdominal surgery.[34]

The support for SLN biopsy in esophageal cancer is not as forthcoming as in gastric cancer. Difficulty does arise in identification of the blue node in a lymph nodal basin already stained with other environmental pigments.[35] In addition, esophageal mobilization is frequently required for node identification resulting in lymphatic pathway disruption. Finally, esophageal cancer, like gastric cancer, invariably presents late in the Western countries, therefore limiting the use of SLN biopsy in this part of the world. The application of SLN biopsy in esophageal cancer may be of some value however in determining the extent of lymph node dissection. Controversy does exist as to the extent of lymphadenectomy with options being a 2-field or 3-field

dissection. The 2-field dissection comprises the removal of nodes in the abdomen and mediastinum, while 3-field will also include the cervical nodes. Though distal esophageal cancers can lead to cervical lymph node involvement and metastasis to celiac lymph nodes may develop in cervical esophageal cancer, SLN biopsy allows for a more selective approach.[36]

Status of Sentinel Lymph Node in Periampullary Cancers

The current standard operation for resectable periampullary carcinoma is the Whipple's pancreaticoduodenectomy; however, the extent of lymphadenectomy is still debatable. Since Joseph Fortner's proposition in 1973 that a more radical resection may improve the cure rate following pancreaticoduodenectomy,[37,38] many trials were conducted yielding contrary results. A multicenter, prospective, randomized trial by Pedrazzoli *et al.* in Italy found no survival difference in patients undergoing standard resection as compared with extended lymphadenectomy.[39] This finding was confirmed by Farnell *et al.*[40] from the Mayo Clinic; in addition, both these studies confirmed long-term diarrhea affecting patients' quality of life in the extended lymphadenectomy group. The Johns Hopkins Institute has conducted the largest and most recent trial comparing standard resection to extended lymphadenectomy.[41-43] Results revealed that there was no survival difference in either group, while the extended lymphadenectomy group revealed higher rates of perioperative complications, including delayed gastric emptying, pancreatic fistula, and wound infections.

To date, there is one article regarding the application of SLN biopsy in pancreatic carcinomas. Ohta *et al.*[44] injected 2% patent blue dye peritumorally and were able to detect an SLN in the posterior pancreaticoduodenal lymph node group (station 13) in eight of nine patients. Following the status of the SLN on frozen section, the need for para-aortic (station 16) lymph node dissection was determined. Of the eight patients in whom the SLN was detected, four revealed metastatic disease and therefore underwent para-aortic nodal dissection. After a three-year follow-up, four patients were alive, three in the SLN-negative group, and one in the SLN-positive group. Incidentally, the three patients in the SLN-negative group underwent a pancreaticoduodenectomy with portal vein resection. The authors' conclusion was that SLN biopsy with curative resection can improve survival and is an alternative to routine para-aortic lymphadectomy. A study by Cubilla *et al.*[45] as well as Kayahara *et al.*[46] confirmed that the posterior pancreaticoduodenal lymph node group is the most commonly involved in pancreatic cancer and Ishikawa *et al.*[47] showed that involvement of second-order lymph nodes, including the para-aortic group, indicated a very poor prognosis with no 5-year survivors. This is in keeping with the many studies revealing no improvement in survival with extended lymphadenectomy. Based on these findings, more data are needed to determine the need, if any, of SLN biopsy in pancreatic cancer.

Status of Sentinel Lymph Node in Hepatobiliary Cancers

Lymph node metastasis is a relatively late event in hepatocellular carcinoma and as a result, it is unlikely that SLN biopsy can play a role in its management. Similarly, although lymph node involvement is a prognostic factor in intrahepatic cholangiocarcinoma, there are no studies to date validating the role of SLN biopsy in this disease.[48] There is however an article by Kane *et al.*,[49] where SLN biopsy is used in colorectal hepatic metastasis in order to ascertain the presence of extrahepatic disease in the periportal and celiac nodes and therefore avoiding the need for a hepatectomy. An SLN was identified in seven of the 11 patients; however, all proved to be free of metastasis. Though there is a potential benefit in identifying patients with nodal involvement prior to undertaking a major hepatic resection, no definite conclusion can be drawn thus far from this study.

Conclusions

The status of the SLN in gastrointestinal malignancies is evolving. The role in the different gastrointestinal cancers is quite diverse as exemplified by its use to allow for focused pathological assessment with the potential for upstaging in colon cancer as opposed to its use to potentially omit lymphadenectomy in EGC. More studies are required for further clarity on this subject.

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How to cite this article: Maharaj R, Shukla PJ, Naraynsingh V, Dan D, Hariharan S. Sentinel lymph node biopsy in gastrointestinal malignancies-Where do we stand?. Indian J Cancer 2011;48:345-50.

Source of Support: Nil, **Conflict of Interest:** None declared.