

Sentinel Node Mapping for Gastric Cancer

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Abstract

Background: Sentinel lymph node mapping is the standard of care for patients with malignant melanoma and breast cancer. Recently, SLN mapping was introduced to the field of gastric cancer.

Objectives: To evaluate SLN mapping in patients with gastric cancer.

Methods: In 43 patients with gastric cancer, open intraoperative subserosal dye injection in four opposing peritumoral points was used. Ten minutes following dye injection, stained LNs were located, marked and examined postoperatively from the surgical specimen.

Results: SLN mapping was performed in 43 patients with gastric cancer; 782 lymph nodes were harvested and evaluated. SLNs were stained in 34 of the patients (79.1%) with a mean of 2.85 SLNs per patient. The false negative rate was 20.9%, the positive predictive value 100%, the negative predictive value 78.6% and the sensitivity 86.9%.

Conclusions: SLN mapping in patients with gastric cancer is feasible and easy to perform. SLN mapping may mainly affect the extent of lymph node dissection, and to a lesser degree gastric resection. However, more data are needed.

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The history of sentinel lymph node mapping dates back to 1977 when Cabanas described and used the technique of lymphangiograms in patients with penile carcinoma [1]. However, this technique was not practiced for many years until it was reintroduced by Morton and co-workers in the treatment of patients with early-stage malignant melanoma [2]. Today, SLN mapping is widely used in the treatment of patients with breast cancer and malignant melanoma [3–6]. SLN mapping has only recently been introduced for the evaluation of patients with colonic and gastric cancer [7–12].

Lymphatic spread is one of the most relevant prognostic factors in patients with gastric cancer resected for cure. Therefore, the evaluation of lymph node involvement is of paramount importance in planning the future treatment approach, estimating the prognosis of the individual patient, and analyzing international treatment results [13].

SLN mapping in patients with gastric cancer has been practiced for the past 10 years [7–12]. Several techniques for the administration of dye or radioactive tracer injection have been

reported. These include: a) preoperative endoscopic injection of dye or radioactive tracer followed by intraoperative mapping [7,10,14–17], b) intraoperative endoscopic injection [12,16,18–20], and c) intraoperative subserosal injection of dye [11,21–23]. After studying the techniques mentioned in the literature, we decided to adopt the intraoperative technique of open dye injection. We report here our initial experience with SLN mapping in 43 patients with gastric cancer.

Patients and Methods

Forty-three patients with gastric cancer underwent SLN mapping during surgery. The abdominal cavity was explored, and disease stage and resectability were assessed. Before any dissection was performed, patent blue (Guerbet Patent Blue V Sodium 2.5%) diluted with 2 ml of normal saline was injected subserosally in four different opposing points around the gastric tumor. Ten minutes following dye injection, dye spread was evaluated and possible SLNs were marked by a stitch. The type of resection was based on tumor location and extent of the disease.

A detailed pathologic assessment of the surgical specimen was performed with special attention to all areas marked by patent blue. All blue-stained lymph nodes were sectioned into 0.2 cm-thick slices and submitted *in toto* for histology. Two sections of 3 μ thick were serially cut at 0.25 mm levels from these lymph node slices: the first was stained with hematoxylin and eosin and the second was placed on a Superfrost Plus Slide. If the H&E slides were negative for metastatic involvement, the unstained consecutive slides were stained with a pancytokeratin antibody (CKMNF116, Dako Corporation, Carpinteria, CA, USA), to highlight micrometastases. All relevant sections were examined. The total sampling of the SLNs with systematic serial sectioning and cytokeratin immunohistochemistry enabled a relatively optimal estimation of the metastatic status of the SLNs.

Results

Forty-three patients diagnosed with gastric carcinoma underwent SLN mapping during gastric resection. The age range of the 17 females and 26 males was 33 to 88 years (mean 68.5 years). In 28 patients, the tumor was located in the antrum or body of stomach, in 12 patients the tumor was located in the cardia, 2 patients had a gastric stump carcinoma following subtotal gastrectomy performed many years previously, and 1 patient had

SLN = sentinel lymph node
H&E = hematoxylin and eosin

linitis plastica. Distal subtotal gastrectomy was performed in 23 patients, total gastrectomy in 10 and proximal gastrectomy in 10. As previously mentioned, 10 minutes following dye injection, dye spread was evaluated and a SLN search performed. The type of resection performed was based on the operative findings.

Altogether, 782 regional lymph nodes were harvested (mean 18.2 lymph nodes per patient, median 18) [Figure 1]. In 33 of the 43 patients (79.1%), blue-stained LNs were detected and examined, varying from as low as 1 to as many as 13 (mean 2.85 nodes per patient, median 2) [Table 1]. The correlation between finding metastatic deposits in these SLNs and in the remainder of the removed lymph nodes in the same patients showed this method to have a high accuracy rate. The accuracy rate (positive correlation with pathologic findings) was as high as 91.2% (31/34 patients). In 20 patients, metastases were found both in stained and non-stained nodes and in 11 patients there were no metastases found in either stained or non-stained nodes. For different types of resection, this index was as follows: for proximal/total gastrectomy, 100% (14/14) and for distal gastrectomy, 85% (17/20 patients). The positive predictive value was 100%, the negative predictive value was 78.6% and sensitivity was 86.9%.

In 34 of the 43 patients (79.1%) we could detect SLNs during the operation. In this particular group, the mean number of SLNs was 2.85. We found that the main factor associated with the number of stained lymph nodes was location of the primary tumor (extension to the proximal stomach) [Table 2]. The mean number of SLNs for the group of patients who underwent proximal or total gastrectomy (n=20) was 2.75, while it was only 1.8 for patients who underwent subtotal distal gastrectomy (n=23) ($P > 0.05$, not significant). These differences were not related to the extent of lymphadenectomy as the mean number of removed LNs in the group of patients who underwent proximal or total gastrectomy was 17.4 as compared to 18.9 for patients who underwent distal gastrectomy.

An absence of staining correlated to local extension of the primary tumor. All patients (19/19) with T1-T2 tumors had stained SLNs, while only 15 of 24 (62.5%) with T3 tumors had stained SLNs [Table 2].

Discussion

Nodal involvement in gastric cancer is defined by two main systems [13]: the 2002 American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) staging system, which is based on the number of positive nodes [24]; and the Japanese system, which is based on the location of positive nodes [25]. While SLN mapping has become standard care in the treatment strategy of patients with breast cancer [3,4] and malignant melanoma [5,6], it is still under evaluation in the field of gastric cancer surgery [1,8,10].

The rationale for SLN mapping in gastric cancer is twofold: to learn the extent of the disease (lymph node involvement), and to try to assess the degree to which SLN mapping might aid in the decision-making process regarding the type of gas-

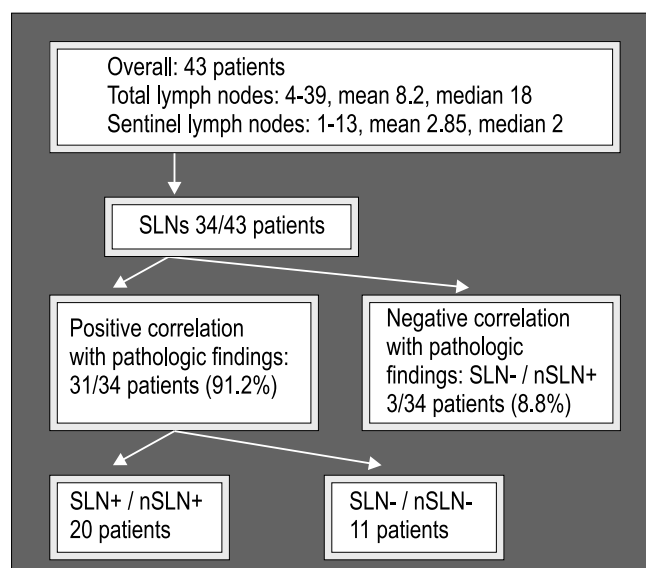


Figure 1. Results of sentinel node mapping in 43 patients with gastric cancer. SLN+ indicates metastases in SLNs, SLN- indicates no metastases in SLNs, nSLN+ indicates metastases in non-SLNs, nSLN- indicates no metastases in non-SLNs

Table 1. Sentinel lymph node staining, tumor localization and the type of surgical procedure

Type of operation	Overall no. of removed nodes (mean)	No. of SLNs (mean)
Subtotal gastrectomy	18.9	1.8
Proximal gastrectomy	16.4	2.4
Total gastrectomy	18.3	3.1

Table 2. Sentinel lymph nodes according to stage of primary tumor

Stage	No. of patients	%	Mean no. of SLNs
T1-T2	19/19	100	3.4
T3	15/24	62.5	2.13

trectomy to be performed – limited or extended. This question has been a matter of debate for years, as extensive resection is also followed by a higher morbidity and mortality rate. SLN mapping may mainly affect the extent of lymph node dissection, and to a lesser degree gastric resection.

Various techniques have been used to map SLNs in patients with gastric cancer. Kitagawa et al. [7], Mori et al. [16] and Parisi et al. [17] used preoperative endoscopic mapping by radioactive tracer; Miwa [18], Mori et al. [16], Nimura et al. [19] and Osaka et al. [20] used endoscopic dye injection; Bilchik et al [21], Hiratsuka et al [22] and Lamont et al. [23] used intraoperative (open) subserosal injection of dye; Aikou et al. [14] used injection of radioactive trace in combination with blue dye injection. As previously stated, in our study we used the open subserosal injection of dye. When reviewing the relevant data,

it becomes evident that the success rate of SLN mapping varies from as high as 99% in the Hiratsuka [22] series to as low as 74% in the Mori [16] series. Our results show a success rate of approximately 79%.

The number of reported series on the subject of SLN mapping for gastric cancer is small and the number of patients reported in each of these series is limited. Since the stage of disease varied among the relatively small number of patients studied overall, no definitive conclusion can be made regarding the contribution of SLN mapping to the decision-making process regarding the extent of resection.

Based on our short and limited experience, we would like to draw attention to some interesting facts that will of course need further evaluation in a larger series of patients. The first and probably most important point is that gastric lymph channels are multidirectional and form a complex network. Hence, in gastric cancer we are probably not dealing with one SLN but rather with groups of nodes, which is best demonstrated by the Japanese classification for gastric cancer [25]. It is interesting to note that we were able to localize SLNs in 79% of our patients, the number of SLNs varying from 1 to 13 with a mean of 2.85 nodes per patient. However, we found that the mean number of SLNs was higher in the group of patients who underwent proximal or total gastrectomy (2.75 nodes per patient), versus 1.8 SLNs for patients who underwent distal subtotal gastrectomy [Table 1] ($P > 0.05$, not significant). These differences were unrelated to the extent of lymphadenectomy: the mean number of lymph nodes harvested in the group of patients who underwent proximal or total gastrectomy was 17.4, as compared to 18.9 in the group of patients who underwent distal gastrectomy. A possible explanation for these differences might be a richer multidirectional lymphatic drainage in proximal gastric tumors.

The second point is that the decision regarding the type of resection to be performed should be based, at least nowadays, on tumor location and stage until a full evaluation of SLN mapping results is available. However, it seems that the decision can be assisted by SLN mapping. In one of our patients with mid-gastric cancer that drained directly to stations 3, 5 and 6, we decided to reduce the extent of the resection. In two other patients in our series, our strategy was modified in compliance with oncologic demands, and instead of performing a total gastrectomy a less extensive surgical procedure was carried out, such as proximal gastrectomy. As mentioned, this was a preliminary study to assess whether or not SLN mapping, with the technique used by us, might help in the surgical decision-making process regarding the extent of surgery. In eight patients (18.6%) SLN mapping failed to produce relevant information. Nevertheless, lymph node dissection according to oncologic principles was performed in all patients.

An interesting observation that we discovered in the literature regarding SLN mapping is also emerging from our study. We found an inverse correlation between the T stage of the tumor and the SLN staging. Of the 34 patients with stained nodes, 19 of 19 patients with T1-T2 tumors (100%) had stained

nodes, while this number decreased to 62.5% (15/24) in patients with T3 tumors. We could not find any explanation for these facts other than that the lymphatic channels were occluded by tumor deposits.

Based on our small series, it is difficult to formulate any valuable conclusion. Further studies, preferable multicentric, are required to gain knowledge on the subject of sentinel node mapping in gastric cancer patients. However, our study showed a high rate of accuracy when comparing SLN status and metastatic involvement of lymph nodes, and SLN mapping may therefore be an additional instrument for planning the extent of surgical resection.

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