Evaluation of a Sentinel Lymph Node Biopsy with Patent Blue in Locally Advanced Gastric Cancer

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Abstract

Background: A sentinel lymph node (SLN) biopsy is an interesting issue in the field of surgical oncology and has recently been introduced to the treatment of gastric cancer. The purpose of this study is to assess accuracy, sensitivity, specificity, and false negative rates (FNRs) of SLN biopsies, and to ascertain whether or not this procedure is useful for locally advanced gastric cancer.

Methods: From December 2013 to March 2014, 22 patients with gastric cancer were enrolled in this study. After laparotomy, patent blue was injected around the tumor subserosaly, resection was then done, and SLNs were detected on a back table. Afterward, D2 dissection was carried out. Finally, SLNs and other specimens were submitted for permanent pathology.

Results: SLNs were detected in 20 of 22 patients. The total number of SLNs was 87. SLNs were positive in 7 patients, and the total number of positive SLNs was 17. In three patients, the SLNs were negative, whereas other LNs were positive, with an FNR of 15%. 18 patients received neoadjuvant. Complete pathologic responses with negative LNs were seen in 3 patients. Accuracy, sensitivity, specificity, and negative predictive values were 80%, 66%, 90%, and 76%, respectively.

Conclusions: This research demonstrated that SLN mapping in advanced gastric cancer is an appropriate method with acceptable levels of accuracy, sensitivity, and negative predictive values, even in those patients who received neoadjuvant treatment.

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Introduction

Gastric adenocarcinoma is the fourth most prevalent form of cancer worldwide, and the second most lethal cancer. Lymphatic spread is a form of distribution of gastric cancer, and one of the most important prognostic factors is the involvement of lymph nodes (LNs) and the number of LN metastases. Surgery and LN dissection are standard treatments of gastric adenocarcinoma. An extensive LN dissection has a better survival rate; thus, D2 dissection seems to achieve better results than D1 dissection. However, D2 dissection is slightly more complicated, even for experienced surgeons (1-8). Hence, a technique that predicts nodal involvement can help in deciding on the type of LN dissection to perform (3). Pre-operative modalities for the detection of metastatic LNs in gastric cancer have a very low sensitivity (9,10). The sentinel LN (SLN) is the first LN that receives drainage from the primary tumor. Based on SLN theory, LN dissection will be limited when there is no metastasis in the SLN (4,5,10-12).

SLN seems to be a reliable method that is able to determine the presence or absence of metastasis in LNs with high accuracy (12). SLN was proposed for parotid malignancy by Gould et al. (13) in 1960. Cabanas (14) used this concept in penile cancer in 1977 but it was not practiced until 1992, when Morton et al. (15) developed SLN biopsy in malignant melanoma. Afterward, this concept was widely used for breast cancer. Palaia et al. (16) used the SLN concept for gastric cancer in 1999; then, Japanese surgeons vastly used SLN biopsy in gastric cancer. The application of SLN mapping in gastric cancer is a more difficult than breast carcinoma and malignant melanoma because the lymphatic stream of the stomach is much more complicated (7,11,17). There are promising studies of SLN biopsies in early gastric cancer, particularly in Japan. The objective of this study is to evaluate the accuracy, sensitivity, and specificity of the SLN mapping of gastric adenocarcinoma in Iran, where the majority of patients are at locally advanced stages.

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Materials and Methods

From December 2013 to March 2014, 22 patients with primary gastric adenocarcinoma, whose disease was confirmed by endoscopic biopsy and were medically fit for surgery, were selected for this study. They had been referred to the Department of Surgical Oncology of the Cancer Institute of Tehran, Iran, and were enrolled in the cross-sectional study of an SLN biopsy. All patients were scheduled for gastrectomy and D2 lymphadenectomy with curative intent. This study was approved by the Institutional Review Board and Committee of Tehran University, and pre-operative informed consent was obtained from patients.

Clinical studies and staging included: esophagogastric endoscopy and biopsy, endoscopic ultrasonography (EUS), chest and abdominopelvic computed tomography-scans, and preoperative laparoscopy for T_3 or N_1 tumors. Exclusion criteria were liver metastasis, peritoneal seeding, nodal involvements at Level III and IV, involvement of celiac, superior mesenteric, and left gastric arteries. Age, tumor depth, tumor size, and neoadjuvant therapy were not the exclusion criteria in this study.

After laparotomy via an upper midline incision, the abdominal cavity was carefully explored in order to assess tumor resectability and metastases. The patients were excluded from the research when the aforementioned exclusion criteria were met. The gastrocolic ligament was then opened and the lesser sac was entered and the tumor was identified by palpation. Before any dissection, 0.5 cc of patent blue was injected subserosaly (SS) at four points around the tumor with a 25-gauge needle. Unlike breast cancer, massage of the injection site of the dye was not done. Then, gastric cancer and perigastric LNs were resected. Total gastrectomy was performed for the tumors located at the upper and middle parts of the stomach, and partial gastrectomy was performed for those at the lower part. The dissecting specimens were then investigated for assessing the number and situation of blue LNs that were considered to be SLNs on the back-table. The LNs locations were described using Japanese Classification of Gastric Carcinoma (18). The operations continued to perform a D2 dissection, and finally, stained blue LNs, which had been isolated on the back-table, the tumor was resected along with the stomach. The D2 dissected specimens were separately submitted for permanent pathology.

The frozen section was not performed on SLNs. SLNs and non-SLNs were fixed in formalin and were engulfed in paraffin. Then, all LNs were sliced for routine hematoxylin and eosin (H and E) stains.

Sensitivity, specificity, positive predictive value, and negative predictive value with a 95% confidence interval were calculated. The chi-square test was applied to assess differences in proportions and a value of $P < 0.05$ was considered significant. The SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used.

Results

Among the 22 patients, SLNs were not detected in 2 patients. The detection rate (DR) was 90.9%. One of the two patients was a 41-year-old man suffering from cancer of the proximal third, with a tumor of 6 cm in size and clinical stage of cT_3N_0. His pathologic type was signet-ring, with 6 positive LNs out of 7; all positive LNs were at Level I. The another patient was a 66-year-old man with a tumor size of 4 cm in the middle third of his stomach and a clinical stage of cT_4N_2, his pathologic type was also signet-ring. 22 LNs were dissected from which 2 were positive in Level II.

Of 20 eligible patients, 19 were male and 1 was female. The average age [± standard deviation (SD)] was 61.9 (± 8.9) years ranged from 43 to 80. From 18 patients who had pre-operative EUS, 2 patients had a clinical stage of cT_2 (11.1%), 14 patients had cT_3 (77.7%), and 2 patients had cT_4 (11.1%). Mean tumor size (± SD) was 4.15 (± 2.0) cm with a range of 1.5-10 cm. Eight tumors (40%) were located on the upper third of the stomach, 5 (25%) were on the middle third and 7 (35%) were on the lower third. 13 patients underwent a total gastrectomy, and 7 had a partial gastrectomy. Altogether, 451 LNs were harvested, with a mean of 22.5 LNs for each patient and a range of 6-42. 87 SLNs were detected with a mean of 4.3 SLNs per patient and a range of 1-9 per patient. Seven patients (35%) had positive SLNs and altogether, 17 SLNs were positive and were all Level I (Table 1).

Table 1. Characteristics of the patients

Total number patients	**20**
Sex (male/female)	19/1
Age (years)	61.9 (range 43-80)
Tumor location	
Upper third	8
Middle third	5
Lower third	7
Gastric resection	
Total gastrectomy	13
Partial gastrectomy	7
Clinical T stage	
T1	0
T2	2
T3	14
T4	2
Tumor size (cm)	4.15 (range1.5-10)
Number of retrieved LN	451 (range 6-42)
Number of retrieved SLN	87 (range 1-9)
Number or retrieved positive SLN	17 (range 1-5)
Number of patients with positive SLN	7

SLN: Sentinel lymph node, LN: Lymph node

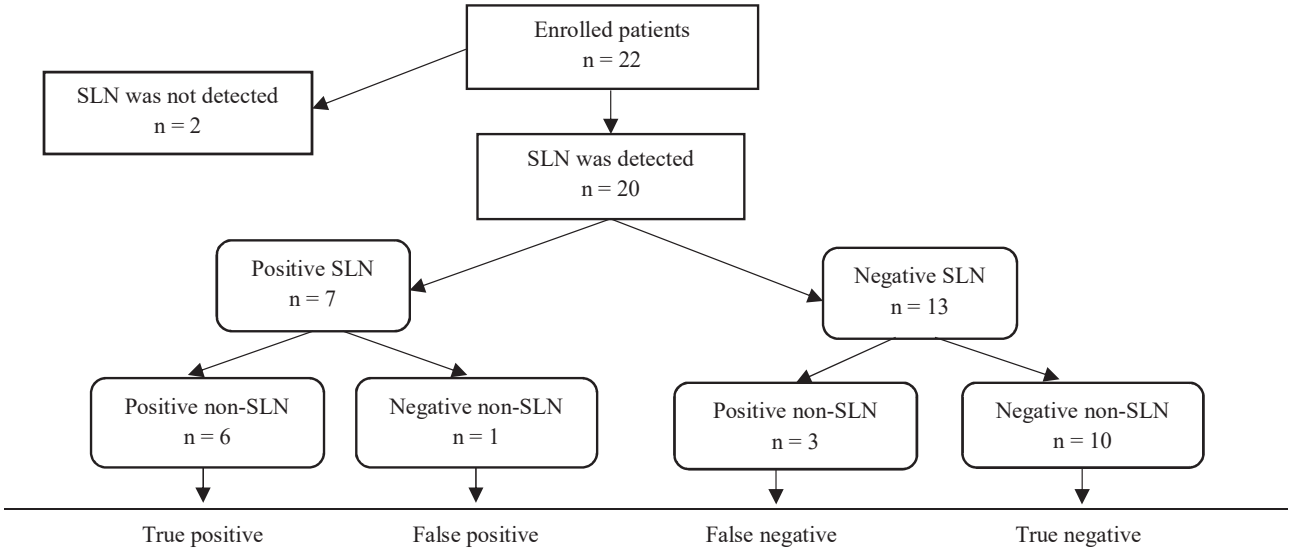

Figure 1. Relationship between status of sentinel lymph node (SLN) and non-SLN

Table 2. Value of sensitivity, specificity, negative predictive value and positive predictive value

Statistics parameters	Estimated value (%)	95% confidence interval (CI)
Sensitivity	66	23-67
Specificity	90	57-99
Negative predictive value	76	45-93
Positive predictive value	85	42-99

In six out of the seven patients with metastatic SLNs, metastases were also found in non-SLNs. For one patient with a positive SLN, metastasis was not seen in non-SLN. Accuracy and positive predictive values were 80% and 85%, respectively.

There were 3 patients with negative SLNs, whereas non-SLNS positive rates and false negative rates (FNRs) were 15%. One of the three patients had tumor on the upper third of his stomach at a size of 5 cm. 28 of his LNs were dissected, 8 of which were SLNs and of these, 3 were non-SLNs positive as one of them was at Level II. The second patient had a 3 cm tumor on the middle third of his stomach, from which 31 LNs were retrieved. 7 of these were SLNs and 6 were non-SLNs positive, and three of them were at Level II. The third patient had a 3.5 cm tumor located on the lower third. 11 LNs were determined, with one SLN and one non-SLN positive at Level I. The pathologic grade of all the patients was G_2.

Of the 20 eligible patients, 18 had EUS and received neoadjuvant therapy and the 2 other patients had no pre-operative EUS or neoadjuvant therapy. In 3 patients (15%), tumors were not seen by a pathologist due to neoadjuvant-induced regression. The relationship between the status of SLN and non-SLN of patients is summarized in figure 1.

Based on the chi-square test, there is a significant correlation between the status of SLN and non-SLN patients ($P < 0.05$). Furthermore, sensitivity, specificity, and negative predictive values are acceptable (Table 2).

Discussion

At the beginning of the 21st century, a SLN biopsy was considered as a method for gastric cancer surgery (19-21). The aim of the SLN biopsy is to facilitate sufficient resection while reducing the risk of morbidity related to unnecessary excision of LNs (3).

To determine SLN, a tracer is needed which must be: easily available, non-toxic, cheap, quickly clearable from the injection site, and rapidly accumulated in SLNs. It must also flow slowly from SLNs to other LNs and be easily recognizable by the surgeon without using sophisticated tools. There are currently no tracers that possess all of these traits. Two tracers are routinely used at present, dye and radioisotope. Dye agents used include: isosulfan blue, patent blue, and indocyanine green. 99_m radiolabeled tin colloid is frequently used as the radio isotope (2,3).

The advantages of dye-guided tracers include ease of use, cost-effectiveness, and real-time observation of lymphatic drainage. However, in dense fat, stained LNs are not visible. Radio-guided tracers should be injected a day before the operation with the endoscopy submocusaly, which is a slightly invasive procedure. Due to the proximity of SLNs to the primary tumor, a shine-through effect distorts the detection of SLNs and is also expensive. It is not available in many clinics, but it can detect LNs even in dense fat (2,3,5,6,22,23).

Some authors merely used dye or radioisotopes, while others used a combination of both. There were no differences between dye-guided and radio-guided tracers in DRs and accuracy but it was reported that dual-guided methods are superior (2,12,24). We used only patent blue because it was cost-effective, available in our operation room and easy to use.

There are two types of injection methods for the tracer: submucosa (SM) and SS. SM injection is done by an endoscopy, 1 day before surgery in radio-guided methods, or immediately before operation in dye-guided methods. The latter method is a difficult technique due to the supine position and incorporation of general anesthesia, as well as endotracheal intubation, which makes endoscope insertion more complicated. It also seems that the injection of tracers by endoscope around lesions that are within the pylorus is not technically easy. Furthermore, it requires a theater equipped with an endoscopic instrument (2,3,12). SS injection, which is done by the surgeon in the operating room, is convenient, time-saving and needs no specific tool. However, it is not useful for non-palpable tumors (5,6,25). Some authors directly compared SM with the SS technique and concluded that, statistically speaking, there is no difference between the two methods (25-27). It seems that accurate injection of the tracers around the tumor, rather than the type of injection, is essential for identifying SLNs (2). In this study, the SS procedure was applied on account of its ease of use.

The majority of researchers that used dye defined SLN as all the LNs stained within 5-20 minutes of the dye injection (4,6,7,23,28,29). Lee et al. (30) and Miwa et al. (31) dissected SLNs after a resection of the stomach on a back-table. In the present research, the researchers also determined SLNs on the back-table after gastric resection. Ishizaki et al. (32) stated that the time interval from injection to dissection of stained-LNs altered the FNR and accuracy as the time became longer, it resulted in an FNR decrease and an accuracy increase.

DR of SLN mapping varies from as high as 100% in Arigami et al. (33), Hayashi et al. (34), and Wang et al. (35) series to as low as 74% in the Simsa et al. (36) series. In this work, DR was 90.9% (20/22). Cozzaglio et al. (4) and Ryu et al. (6) stated that DR decreased in the upper third of the stomach because of the dense fat that hinders the SLNs. In this study, we did not find this to be an issue. Accuracy, sensitivity, and specificity were, respectively, 80%, 66%, and 90% in our research. Mochiki et al. (10) and Kelder et al. (23) stated that an increase of tumor depth could lead to a decrease in SLN DRs and an increase of FNR, presumably due to tumor deposits that occluded the lymphatic drainage. FNR is the most important factor in SLN techniques and can result in local control failure (11). In our theme, FNR was 15%. We could not find correlations between the characteristics of patients and FNR. Lee et al. (37) mentioned that a sufficient number (> 3) of SLNs are needed to prevent FNR. We harvested 87 SLNs from 20 patients with a mean of 4.3 per patient and range from 1 to 9 per patient. Su et al. (5), Isozaki et al. (28), Song et al. (29) and Miyashiro et al. (38), respectively, reported 2.8, 3.3, 2.7 and 3.8 SLNs per patient.

Complexity and multi-directionality of lymphatic drainage of the stomach can lead to skip metastasis in gastric cancer. It implies that metastasis at Level II is without the involvement of Level I LNs. Skip metastasis is a challenge in SLN tactics in gastric cancer that can increase FNR (7,11,17,30). Miwa et al. (31) and Ajisaka and Miwa (39) mentioned that the skip metastases and metastases in non-SLNs were usually found in the same lymphatic basin of the SLNs. Based on this concept, Miwa et al. (31) divided lymphatic flows of gastric cancer into five sections according to their location along with major arteries as follows: left gastric artery, right gastric artery, left gastroepiploic artery, right gastroepiploic artery, and posterior gastric artery. Takeuchi and Miwa (12) therefore recommended that the entire lymphatic basin of SLNs should be dissected instead of the removal of the identified SLNs (pick-up method). Lee et al. (40) showed that lymphatic basin dissection (LBD) is superior to the pick-up procedure in the detection of SLNs metastases. We performed the pick-up technique because LBD is indeed a limited lymphadenectomy as well as a time-consuming option.

Skip metastasis was stated to be 1.4% in early gastric cancer (31). Su et al. (5) reported 9.6%, Kim et al. (41) mentioned 17%, and Lee et al. (30) stated 21.6% of skip metastasis in their researches. In this study, skip metastasis only occurred for one patient, whose SLNs were not detected, as a result, skip metastasis was calculated to be 4.5%. Huang et al. (7) addressed no clinicopathologic factors to be associated with skip metastasis. Although the decrease of survival chance was shown in the patient with skip metastasis, there were no statistically significant differences. Research carried out by Lee et al. (30) showed that tumor size was associated with skip metastasis, but the tumor differentiation and depth did not relate to skip metastasis. He also reported that skip metastasis occurred in advanced gastric cancer because the lymphatic system was blocked by tumor emboli. Yasuda et al. (42) stated that a gastric tumor with a diameter of 5 cm or lower is appropriate for SLN biopsy. Thus, the majority of SLN mapping research in gastric cancer was planned for tumors below 5 cm in size. Lee et al. (30) also reported that the most common regions for skip metastasis are station numbers 7, 8, and 9. Thus, if SLNs were not determined in Level I, station numbers 7, 8 and 9 should be dissected to diminish the skip metastasis and FNR.

Isozaki et al. (43) reported that serial sectioning of SLNs could result in the increase of the accuracy rate. We only sliced one section of the SLNs as serial sectioning was time-consuming and was not routine in the many pathologic laboratories. Some authors used immunohistochemistry and reverse transcriptase polymerase change reactions for increasing the accuracy of SLNs but it should be considered that these techniques are sophisticated, expensive, and time-consuming and are available only in a minority of hospitals. These procedures usually determine micro metastasis and isolated tumor cells that are not diagnosed with routine H and E stains (33,44,45). These entities are controversial in gastric adenocarcinoma treatments and prognosis (12).

Based on the Japanese Gastric Cancer Association guidelines (46), there is no place for neoadjuvant therapy in gastric cancer treatment, even at advanced stages. Hence, in Japanese articles on SLN biopsies in gastric cancer, neoadjuvant therapy was not used. In research conducted in western countries, it is not clearly reported whether neoadjuvant therapy was applied or not (4,17). Based on the MAGIC trial (47), we used perioperative chemotherapy for the treatment of advanced gastric cancer. In this study, neoadjuvant therapy led to complete pathologic responses of tumors and negative LNs in 3 patients. It seems that neoadjuvant therapy can distort the integrity of LN architecture and may interfere with detection of LN metastasis. Thus, if neoadjuvant is used for gastric cancer, the SLN biopsy is in doubt (17). However, in this study, SLN mapping was not affected by neoadjuvant treatment.

Conclusion

As similar to the acceptable results of SLN mapping in early gastric cancer, it seems that this technique is feasible in advanced gastric cancer and the modern approach of neoadjuvant treatment for it. However, further evaluations are required to introduce the SLN concept in locally advanced gastric cancer treatments

Conflict of Interests

Authors have no conflict of interests.

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