



SENTINEL LYMPH NODE NAVIGATION IN GASTRIC CANCER

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Abstract – Objective: This study aims to explore the application value and detection rate of sentinel lymph node (SLN) biopsy in accurate detecting of lymph node metastasis in patients with gastric cancer.

Patients and Methods: A total of 24 patients with Stage I, II or III gastric cancer, from 2015 to 2017, were admitted to our department and underwent D2-gastrectomy plus lymphadenectomy. All 236 nodes were sectioned and stained with immunohistochemical staining (IHC). Lymph node micro-metastasis was defined as evidencing to be positively stained or via the IHC process.

Results: The results indicated that gastric cancer stage 1 was significantly correlated with higher lymphatic metastasis.

Conclusions: Given the very low frequency of malignant non-sentinel lymph nodes was detected in stage 1, it could be logic and safe to merely dissected sentinel nodes without extended lymph node dissection while operation.

KEYWORDS: Gastric cancer, Sentinel lymph node, Gastrectomy, Lymphatic metastasis, Stage.

INTRODUCTION

D2 gastrectomy and lymphadenectomy served as the standard surgical technique in gastric cancer since lymph nodes metastasis is a critical prognostic issue along with the stage or depth of primary tumor invasion¹. The frequency of lymph nodes metastasis seems to be low in early gastric cancer (EGC), with more than a ninety percent 5-year survival rate². Minimally invasive procedures such as endoscopic mucosal resection and laparoscopic wedge resection without lymph node dissection have been carried out in certain EGC patients to improve the quality of life of long-term survivors^{3,4}. For such procedures, the precise extrapolation of

metastatic lymph nodes is decisively necessary to define the range of lymph node dissection^{5,6}.

In theory, lymphadenectomy is not necessary for patients without nodal metastases. Hence, early and precise detection of lymph node metastasis is crucial in making the consequent surgical decisions. Considering the problem of postoperative morbidity and mortality after gastrectomy with extended lymphadenectomy, D2 lymph node resection is considered to be an over invasive surgery for patients with N0 Lymph node metastasis gastric cancer⁵. However, so far, the effective tools to diagnose pre- or intra-operatively the N0 status remains vague. The sentinel node (SN) technique has been introduced in the management of some types of



cancers to avoid unnecessary lymphadenectomy⁶⁻⁸. The sentinel nodes (SNs) are described as the first potential points of metastasis via lymphatic drainage from a primary tumor lesion and were originally introduced, by Cabanas, in cancer of penis⁹. The absence of metastasis in SNs is interpreted as the nonexistence of metastasis in rest of downstream lymph nodes. This theory has been previously developed in breast cancer and melanoma^{10,11}. Minimally invasive surgery like limited lymph node dissection and reduced the extent of resection based on SN plotting is named SN navigation surgery (SNNS). This surgery could avoid the complications of the patient and serve as an advantageous way for avoiding an over invasive surgery. Though, SNNS of gastric carcinoma has not been universal owing to the complicated lymphatic flow from the stomach and skip metastasis, which are sometimes acknowledged in gastric cancer¹²⁻¹⁴; the application of SN biopsy in gastric cancer is still debatable¹⁵⁻¹⁸. Few studies have been reported in gastric cancer¹⁸⁻²²; the SN detection rate and the predictive values of SNs biopsy must be high enough for the clinical application of SNs in gastric cancer¹⁷. In the present study, the SN detection rate and the predictive values of the SN biopsy were determined to evaluate its practicality and significance in gastric cancer. Some clinicopathological characteristics were assessed to detect elements influencing its accuracy.

PATIENTS AND METHODS

Fifty cases of gastric adenocarcinoma, from February 2015 to September 2017, were enrolled in Golestan University of Medical Sciences (GOUMS) General Academic Hospital of 5th Azar, Gorgan, Iran; 24 of them cooperated and took part in the study. They had gastric cancer without invasion of serous layer and distant metastasis based on preoperative assessment and intraoperative judgments. Preoperative assessment involved endoscopic esophagogastroduodenoscopy, abdominopelvic computed tomography, chest X-ray and primary laboratory blood test. Inclusion criteria consisted of well-differentiated mucosal tumors of less than 2 cm without ulcer candidate for endoscopic mucosal resection, and also non-allergic history to drugs. Informed consent was obtained from all participants; the project was approved entirely under supervision of Ethics Committee of GOUMS in accordance with the Helsinki Declaration. EGCs were confined by preoperative endoscopic snipping since such tumors might not be palpable on the serosal surface; just before surgery, three endoscopic clips (HX-600-090Lw, Olympus, Japan) were located at the mucosal layer roughly 1 cm distant in the oral

direction from the proximal margin of the tumor²³. After finishing a laparotomy and a total abdominal probing abdomen, the primary tumor was recognized by palpation and 2 ml of methylene blue 1% via 23-gauged syringe was injected subserosally in four different region around tumor; stomach was not got massaged while the procedures. Five minutes after the injection, blue-stained lymph nodes were recognized and marked as SNs. When blue-stained SNs had been biopsied, D2-gastrectomy plus lymphadenectomy was accomplished. For the pathologic investigation, all dissected lymph nodes were stained with hematoxylin and eosin, and one slice per node was obtained from the mid part of each node then transferred for pathologic assessment. All data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). *p* values were two-sided, and a value of 0.05 was set as statistically significant.

RESULTS

DEMOGRAPHIC DATA

Details of 236 lymph nodes extracting from 24 patients registered in the study are given in Table 1. Forty patients had been classified as stage 1 and forty-six were in stage 3. Lymph node metastasis was observed in 89 of the lymph nodes (38%).

TABLE 1. Baseline characteristics of patients with gastric cancer

Demographic data	Quantity
<i>Age (year± SD)</i>	61.4 ± 7.49
<i>Sex (no.)</i>	
Male	171
Female	65
<i>Residence location (no.)</i>	
Urban	87
Rural	119
Unknown	30
<i>Race (no.)</i>	
Fars	155
Turkmen	56
Unknown	25
<i>Neoadjuvant therapy (no.)</i>	
Yes	70
No	138
Unknown	28
<i>Stage of tumor (no.)</i>	
1th	78
2th	70
3th	88
<i>Lymph node (no.)</i>	
Sentinel	56
Non-sentinel	180

DETECTION RATE

The predictive values of the sentinel nodes biopsy SNs were identified in 21 of 24 patients (detection rate, 87.5%) and the average number of SNs per patient was 9 (range 2-11) (Figure 1). There were no blue-stained lymph nodes in unsuccessful 3 patients

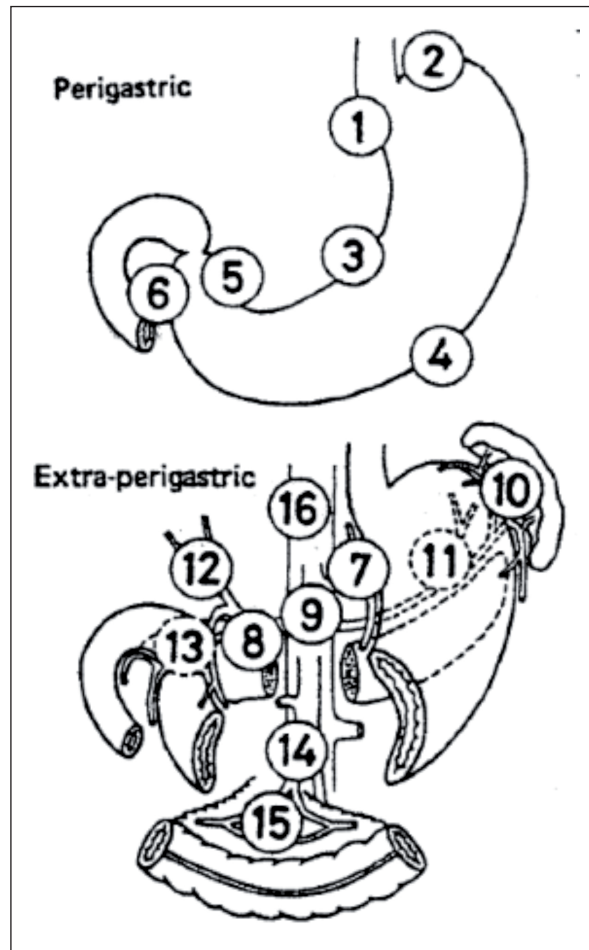


Fig. 1. Gastric regional lymph node mapping^{17,23}.

Lymph node station number	Lymph node station
1	Right pericardial LNs
2	Left pericardial LNs
3	Lesser curvature LNs
4	Left greater curvature LNs
5	Suprapyloric LNs
6	Infrapyloric LNs
7	left gastric artery trunk LNs
8	Common hepatic artery LNs
9	Celiac artery LNs
10	Splenic hilar LNs
11	Splenic artery LNs
12	Hepatoduodenal ligament LNs
13	LNs on the posterior surface of the pancreatic head
14	Superior mesenteric vein LNs
15	Middle colic vessels LNs
16	Paraortic LNs in the diaphragmatic aortic hiatus

although blue stained lymphatic vessels were well pictured. The average number of dissected lymph nodes per patient was 13 (range 5-20). Lymph node metastasis was found in two of three patients in those whose SNs were not recognized. Among the 236 lymph nodes identified, 56 were SNs, metastatic SNs were found in 14 (25%) and the remaining 42 were free of metastasis in SNs. In eight of 182 nodes assessed with metastatic SNs, metastases were also found in non-SNs (positive predictive value, 77%). The metastatic non-SNs located at N1 stations in three patients and at N2 stations in five patients according to the Japanese classification of gastric carcinoma¹⁷. In 207 of 236 nodes assessed without SN metastasis, no metastasis was found in non- SNs (negative predictive value, 88.0%)¹.

DETERMINATION OF FACTORS INFLUENCING THE DETECTION RATE OF SENTINEL NODES AND THE PREDICTIVE VALUES OF THE SENTINEL NODES BIOPSY

Stage of the primary tumor was found to be the most significant factors in SN detection; stage I was significantly related with higher lymph nodes metastasis ($p=0.02$). Other related factors such as; age, race, patients' place of living, histology, angiolymphatic invasion and presence of lymph node metastasis were not correlated with the SN detection rate ($p>0.05$). Table II

DISCUSSION

The logical progress of lymph node metastasis has been well established for both melanoma and breast cancer^{25,26}; the SN concept has been confirmed in these tumors, but debate remains regarding the application of SN biopsy in gastric cancer, owing to the complex lymphatic drainage of stomach and a high frequency of skip metastasis^{15,16}. In our current project, the practicability of the SN biopsy in gastric cancer was reported by an acceptable detection rate of 88% and a positive predictive value of 77% and a negative predictive value of 88%. Negative predictive value was not high enough to allow confidence in using SN biopsy clinically. Positive predictive value of 77 % reinforced that the D2 lymphadenectomy was a mandatory procedure in the patients with stage 2 and 3; in those with stage 1 gastric cancer, simply sentinel lymph node dissection could be enough and safe.

Several technical issues rise about applying a SN biopsy in gastric cancer regarding the kind of tracer used, the method of injecting the tracer and others²⁷; in our study, the subserosal dye injection method



TABLE 2. Multivariable regression analysis of variables related to lymph node metastasis.

<i>Variables</i>	<i>Variables subgroups</i>	<i>Confidence Interval 95%</i>	<i>Odds Ratio</i>	<i>p-value</i>
Lymph node	Sentinel	(0.30-2.68)	0.90	0.85
	Non-sentinel (reference)	—	—	
Race	Fars	(0.94-8.31)	2.79	0.07
	Turkmen and others (reference)	—	—	
Stage	1 (reference)	—	—	<u>0.002</u>
	2	(1.25-8.65)	10.37	
	3	(4.30-323.08)	37.28	

in four regions around was applied due to its more advantages over other techniques. By this method, dye-stained lymphatics are well detectable in peritonealized organs, and the dye is much more controllable than radioactive tracer agents which need be treated according to strict protocols^{28,29}. SNs of gastric cancer are commonly found near the primary site of tumor, so finding of SNs by gamma probe may be difficult because of overlapped radioactivity of the primary lesion. Furthermore, subserosal injection of dye is technically easy compared to the intraoperative submucosal endoscopic injection which is a difficult technique necessitating an expert endoscopist and the accessibility of a specific instrumentation in the operation room. By using localizing methods, like preoperative endoscopic feature for the primary tumor, as implemented in our and some previous studies,³⁰⁻³³ particular instillation of the tracer is possible via subserosal injection. For the settlement of the dye, amount and time interval, pilot study was carried out, in which, subserosal injection of methylene blue more than 1 cc with a time interval more than 5 min marked so many lymph nodes, finally distinguishing of SNs from non-SNs was not clearly possible. Lymph nodes metastasis was not detected in three of our patients via SNs biopsy. In such cases, clinical applications like, wedge resection of the primary tumor without lymph node dissection could be risky, because ignored lymph node metastasis may result in tumor recurrence. No clinicopathological features were found to influence predictive values, possibly due to the small number of study sample size. To decrease the false negatives, in-depth pathologic investigation of SNs by multiple sectioning and immunohistochemistry stains would be obligatory. In our current study, clinical applicability of SN biopsy was assessed, espousing the predictable patho-

logic evaluation, by one section from each single node. Multiple sections and immunohistochemical stains have several practical drawbacks relating to the hospital facilities, which should be deliberated for universal use of SB biopsy. Enhanced detection rates and predictive values have been described in lymphatic mapping for both melanoma and breast cancer by the adjoining use of dying and radio-isotope^{26, 32, 33}. Such a technical methodology may propose balancing processes which improve the SN detection rate and accuracy and reliance on the SN biopsy in gastric cancer³⁴ especially in cases suffering stage 1, as deduced in our current study.

CONCLUSIONS

So the SN biopsy is practicable and enough in early stages of gastric cancer especially in stage 1; it seems that there is no need to perform extended lymph node dissection. However, complementary procedures like, use of combined dye and radioisotope traces (such as Tc99 etc.) plus a longer follow up might be needed to improve detection of positive (malignant) lymph nodes in gastric cancer.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest..

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