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Original article

An assessment of the feasibility of sentinel lymph node-guided surgery for gastric cancer

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Abstract

Background. **Sentinel node-guided surgery has received increasing attention in tumor surgery. To ascertain whether sentinel lymph node (SLN)-guided surgery is feasible for gastric cancers 4 cm or less in size, we conducted a multicenter clinical study.**

Methods. **One milliliter of isosulfan blue was injected endoscopically into the gastric wall at four sites around a gastric cancer lesion. Approximately 15 min after the injection of the dye, the surgeons resected (picked-up) the stained blue nodes (defined as SLNs) around the stomach.**

Results. **SLNs were detected in 140 of 144 patients (97.2%). The average number of SLNs was 3.3. In 99 patients with D2 lymph node dissection, the false-negative rate (FNR) was evaluated. In 14 T1 patients with pathological positive lymph node metastasis (pN(+)), the FNR was 29%. In 9 T2,3 pN(+) patients, the FNR was 44%. In T1 patients with pN(+) but macroscopically normal lymph nodes during surgery (sN0), the FNR was 11% (1/9).**

Conclusion. **T1 and sN0 patients may be a target group for the study of SLN-guided surgery. A larger multicenter trial should be performed to clarify the application of sentinel node navigation surgery for gastric cancer.**

Key words Sentinel lymph node · Lymph node metastasis · Gastric cancer · Limited surgery · Isosulfan blue

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Introduction

The incidence of early gastric cancer has increased in Japan, with the frequent use of limited operations [1,2] for maintaining the quality of life (QOL) after surgery. When curability is achieved, less extensive surgery (wedge resection without lymph node dissection, for example) results in better QOL after surgery. However, when performing limited surgery, lymph node metastasis is a crucial factor, because it is an important prognostic factor in early gastric cancer [3,4].

Since Morton et al. [5] introduced sentinel lymph node biopsy in patients with melanoma, intraoperative lymphatic mapping and sentinel node-guided surgery have received increasing attention in various types of cancer.

To ascertain whether sentinel lymph node (SLN)-guided surgery for gastric cancer is feasible, we conducted a multicenter clinical study.

Patients and methods

This study included patients with gastric cancer 40 mm or less in maximum dimension, age 20–80 years, who gave their informed consent. Patients with serious heart disease, pulmonary disease, liver or renal disease, asthma, or allergic history were excluded. Between July 2000 and February 2002, 144 patients were enrolled at 16 centers. The First Department of Surgery of Okayama University Hospital and its affiliated Public Hospitals participated in this study (EGI Surgical Treatment Study Group).

For each patient, after laparotomy and mobilization of the stomach, an endoscope was inserted via the mouth, and 0.25 ml of isosulfan blue (Lympazurin 1%;

United States Surgical, Ville St. Laurent, Quebec, Canada) was injected endoscopically into the submucosal layer at four sites (total, 1 ml of isosulfan blue) around the cancer. Approximately 15 min after the injection of the dye, the surgeons resected only the stained blue nodes around the stomach, and subsequently gastrectomy with lymphadenectomy was performed. Only the stained nodes were defined as SLNs. Blue nodes detected during lymphadenectomy or after the gastrectomy were not defined as sentinel nodes.

Assessment of lymph node metastasis during surgery (sN, including preoperative clinical findings) was done by surgeons according to gross findings or palpation of the perigastric lymph nodes; also, assessment was done in the fresh specimens. Size (enlarged), shape (round), and firmness (firm) of the lymph nodes were evaluated. However, no strict definition for macroscopic positive lymph node metastasis was made in the protocol of this study.

Histological examination of the lymph nodes was performed by hematoxylin-eosin staining of one section of each node.

The false-negative rate (FNR) by SLN biopsy was defined as: Number of patients with pathological lymph node metastasis (pN(+)) and with negative metastasis in SLN / Number of pN(+) patients.

This report uses the terminology of the *Japanese classification of gastric carcinoma* [6].

Results

SLNs (blue nodes) were detected in 140 of the 144 patients (97.2%).

The average number of SLNs was 3.3 per positive patient (range, 1–9). The average number of removed lymph nodes per patient was 26 (range, 10–69).

Table 1 gives the clinicopathological details of the 140 patients in whom SLNs were detected.

Table 2 shows the distribution of SLNs according to the *Japanese classification of gastric carcinoma*, In 76% of the patients, SLNs were located in compartment 1 only. The first compartment was negative in 2% of the patients with SLNs.

In 99 patients with D2 node dissection, the false-negative rate (FNR) was evaluated (Table 3). It ranged between 11% and 44%, being lowest in T1 patients with pN(+) but macroscopically normal lymph nodes during surgery.

Figure 1 shows the relation between the location of SLNs (stained lymph nodes) and the location of metastatic nodes in the 14 T1 patients with pathological lymph node metastasis and D2 dissection.

In seven patients, SLNs were detected in one node station only. In four of them, SLNs were detected at the lesser curvature side, and all four had metastatic nodes at this side; one patient also had a metastatic node at the left gastric artery. However, in three patients with sentinel nodes at the greater curvature, two patients with sentinel nodes in station 4d also had a lymph node metastasis at the lesser curvature.

Figure 2 is a diagram of a false-negative case in a patient with T1 tumor. The tumor was located at the greater curvature, and SLNs at the greater curvature were normal, but a perigastric node, 1.5 mm in diameter at the lesser curvature was metastatic. Moreover, in this patient, immunohistochemistry revealed micrometastasis along the common hepatic artery.

Figure 3 shows the distribution of false-negative cases by SLN biopsy according to the number of cases in each hospital. False negativity tended to occur early in each series; however, there was no statistically significant difference between numbers of early and late false-negative cases.

Table 1. Clinicopathological features of 140 patients with sentinel lymph node (SLN) detection

	No. of patients
Depth of tumor invasion	
T1	125 (90%)
T2	13 (9%)
T3	2 (1%)
Pathological lymph node metastasis	
pN0	115 (82%)
pN1	21 (15%)
pN2	3 (2%)
pN3	1 (1%)
Macroscopic lymph node staging during surgery	
sN0	128 (92%)
sN1	10 (7%)
sN2	2 (1%)
Lymph node dissection	
D0	12 (9%)
D1	29 (21%)
D2	97 (69%)
D3	2 (1%)

Table 2. Distribution of the sentinel lymph nodes (SLNs)

Location of SLN[a]	No. of patients
Compartment 1 only	107 (76%)
Compartments 1 and 2	29 (21%)
Compartment 2 only	3 (2%)
Compartments 1 and 3	1 (1%)

[a] Regional lymph node compartments according to the *Japanese Classification of gastric carcinoma* [6]

Table 3. False-negative rate (FNR) in 23 patients with pathological lymph node metastasis out of 99 patients with D2 lymph node dissection evaluated for FNR

	Metastasis in SLN	No metastasis in SLN	FNR (%)
T1; All 14 patients	10	4	29
T1 pN(+) sN(−); 9 Patients[a]	8	1	11
T2,3; 9 Patients	5	4	44
T2,3 pN(+) sN(−); 5 Patients[a]	3	2	40

[a] Patients without macroscopic lymph node metastasis during surgery

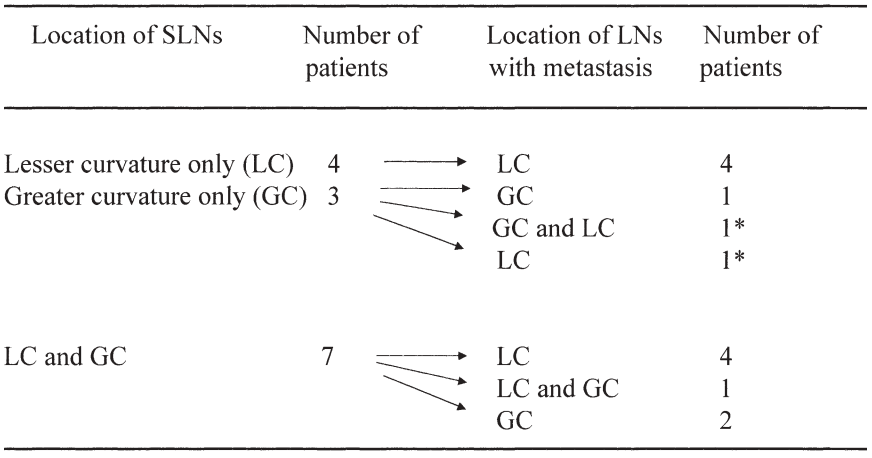

Fig. 1. Relation between the locations of sentinel lymph nodes (*SLNs*) (stained nodes) and of metastatic nodes in 14 T1 patients with pathological lymph node metastasis (pN(+)) and D2 dissection. *Asterisks*, metastasis in locations differing from SLNs

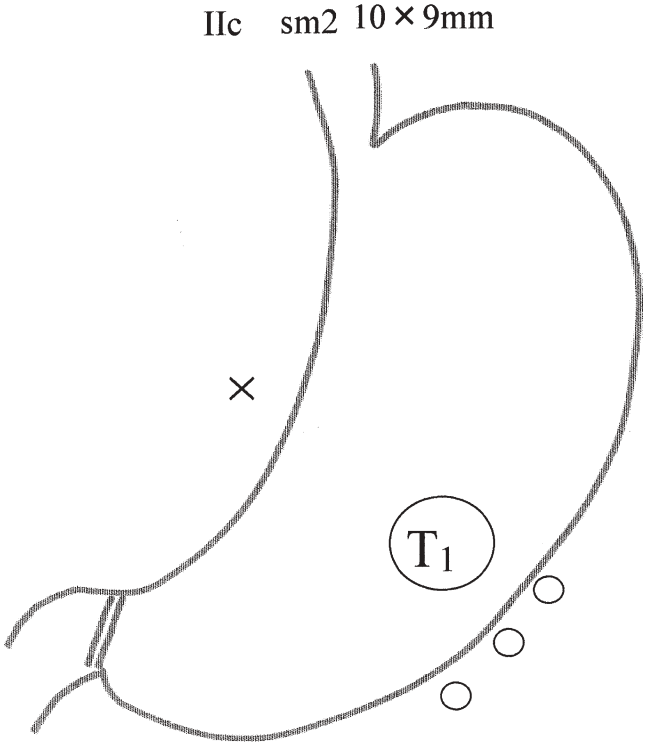

Fig. 2. False-negative *T1* case with node metastasis outside the station containing SLNs. The specimen contained 30 nodes (there were 3 SLNs and another ([non-SNL] metastatic node). *Circles*, SLNs without metastasis; *cross*, non-SLN with metastasis; *sm*, submucosal

Discussion

Sentinel lymph nodes (SLNs), the first draining nodes around a tumor, are expected to be the first nodes which contain metastasis. Intraoperative lymphatic mapping and sentinel lymphadenectomy are currently used to guide the use of complete lymphadenectomy in patients with positive sentinel nodes in melanoma or breast cancer [7,8].

The application of sentinel node tactics in gastrointestinal malignancy and gastric surgery has been controversial [9–11]. In gastric cancer, Hiratsuka et al. [12] reported that, using indocyanine green, the sensitivity for detecting node metastasis by the SLN technique was 100% for T1 tumors and 88% for T2 tumors. However, few patients were studied. Miwa et al. [13] used patent blue and found the sensitivity of SLN for T1 gastric cancer to be 89% (31/35). All their false-negative cases had macroscopic metastasis at surgery, so the sensitivity for SLN in sN0 patients was 100%. Their method to detect SLN was to dissect the stained lymphatic region (lymphatic basin[13]), and then search for SLNs on a back table during surgery. Kitagawa et al. [14], using technetium-99m-labeled tin colloid solution, found the SLN method to be positive in 22 of 24 (91.7%) T1-2, cN0 (evaluated clinically as N0), M0 patients with node metastasis.

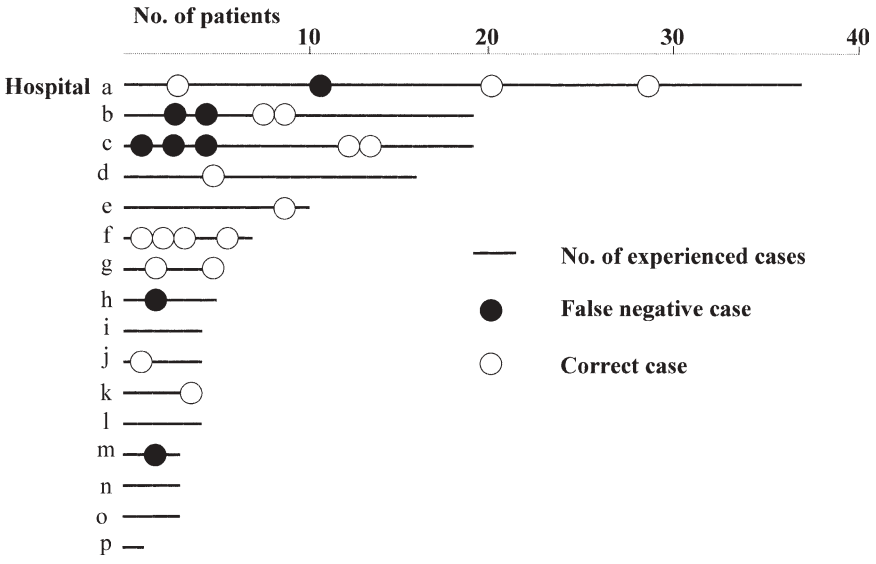

Fig. 3. Distribution of false-negative cases by SLN biopsy according to the number of cases experienced at each hospital (in 140 patients with SLN detection)

When we started this multicenter study, we considered the following items. Firstly, gastric cancer is very common in Japan and is treated surgically at a large number of hospitals. Consequently, these hospitals should be included in multicenter trials, even if they treat few patients. Secondly, in Japan, it is difficult to use radioactive substances at smaller hospitals; consequently, we used a dye (isosulfan blue). Concerning the administration of the tracer, Hiratsuka et al. [12] injected the indocyanine green subserosally via the serosa. Miwa et al. [13] and Kitagawa et al. [14] injected the dye or radioactive colloid into the submucosa endoscopically. We injected the dye endoscopically according to Miwa et al. [13], because many T1 tumors were difficult to palpate.

In our study, SLNs were detected in 97.2% patients, and the average number of SLNs per patient was 3.3. These findings were comparable to single-center experiences, even though Miwa et al. [13] found an average number of SLNs of 6. Our false-negative rate of SLN for the detection of node metastasis was higher than in previous studies. However, when limited to T1 tumors without macroscopic metastasis during surgery, but with pathological positive metastasis, the sensitivity of SLN for lymph node metastasis was comparable with that reported from single centers.

This study indicated that T1 and sN0 patients may be a target group for SLN-guided surgery. The purpose of the SLN biopsy is to avoid extensive node dissection. However, lymphatic flow from the stomach spreads in various directions, and is more complex than that of the breast or extremities. To avoid false-negative cases, multi-directional lymphatic flow should be considered in the application of the SLN technique. Moreover, there is a possible problem of micrometastasis in addition to false-negative cases. Consequently, for patients with T1 SLN(−) tumors which may have node metastases, complete avoidance of node dissection is not yet recommended.

For T2 tumors, the false-negative rate of SLN was high in this study, suggesting that SLN-guided surgery is not applicable. In Japan, most surgeons perform D2 lymph node dissection for these tumors because of the high rate of lymph node metastasis.

In conclusion, T1 and sN0 patients may be a target group for future studies on SLN-guided surgery. A larger multicenter trial with a working definition of sN(+) and a learning period could possibly clarify the role of sentinel node navigation surgery in that situation.

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