When modified gastrectomy was considered feasible for patients with sentinel nodes that stained positive for ICG (preoperative diagnosis of depth after endoscopic treatment is submucosal invasion <0.5 mm), dissection of the ICG positive lymphatic area (lymphatic basin dissection) [6, 7] was performed to remove possible micrometastases in the lymphatic area.

Barium radiographs, endoscopy, abdominal ultrasonography, and computed tomography were performed for preoperative staging and postoperative surveillance.

Results

Patient details and the reasons for additional surgery after endoscopic resection are shown in tables 1 and 2, respectively. All patients were treated within 2 months after endoscopic resection.

The operative procedures are listed in table 3. D1+α or β dissection was performed for distal or proximal gastrectomy. In addition to wedge resection of the stomach or segmental gastrectomy, lymphatic basin dissection was performed in 6 patients in whom the sentinel nodes were examined intraoperatively and were shown to have no metastasis. The extent of lymph node dissection in lymphatic basin dissection is the level of the root of feeding artery (left gastric artery, right gastric artery, left gastric artery, right gastroepiploic artery). As described in figure 2, D2 dissection was performed in 2 patients. Sentinel node detection rates and the incidence of metastasis to sentinel nodes are shown in table 4.

Mapping of sentinel nodes in 3 patients with lymph node metastasis is shown in figure 2. Case 1 (33-mm M signet ring cell carcinoma, ly1, v0) underwent standard distal gastrectomy with D2 dissection because frozen sections (hematoxylin and eosin staining) showed that the No. 4d node (sentinel node) was infiltrated by cancer cells during open surgery. Case 2 (12-mm SM1 moderately differentiated adenocarcinoma including poorly differentiated component in the invasive front, ly1, v0) was converted from laparoscopic wedge resection to open distal gastrectomy with D2 dissection because frozen sections showed the No. 6 node (sentinel node) to be involved. Case 3 (8-mm M well-differentiated adenocarcinoma, ly0, v0) underwent open segmental gastrectomy with lymphatic basin dissection of the left gastric artery area because frozen section examination during surgery showed no sentinel node metastasis. However, postoperative immunohistochemical staining with anticytokeratin antibody revealed micrometastases in the No. 3 node (sentinel node). Micrometastasis could be assessed by CAM5.2 immunohistochemistry in only three nodes of this case 3 among 14 patients after endoscopic treatment.

After a median follow-up of 32 (3–78) months, no patients had tumor recurrence. As to case 3 who underwent only segmental gastrectomy with lymphatic basin dissection, recurrence is not observed after 42 months.

Table 1. Patient details

Age, years	62.2 ± 15.16 (30–82)
Sex ratio, M:F	12:2
Histologic type	
Well-differentiated	4
Moderately differentiated	8
Signet ring cell carcinoma	2
Tumor size, mm	18.0 ± 9.66 (6–33)
Depth of invasion	
m	4
sm	10
Lymphatic invasion	
Positive	6
Negative	8
Venous invasion	
Positive	2
Negative	12

Table 2. Reasons for additional surgery after endoscopic resection

Reasons	Patients
Incomplete resection	4
Submucosal invasion	8
Local recurrence after endoscopic resection	1
Unclear cut margin	1

Table 3. Operative procedures

Type of operation	
Open gastrectomy	7
Laparoscopy-assisted gastrectomy	7
Extent of resection	
Proximal gastrectomy	3
Distal gastrectomy	5
Segmental gastrectomy	3
Wedge resection	3
Extent of dissection	
D1+α	4
D1+β	2
D2	2
Lymphatic basin dissection	6

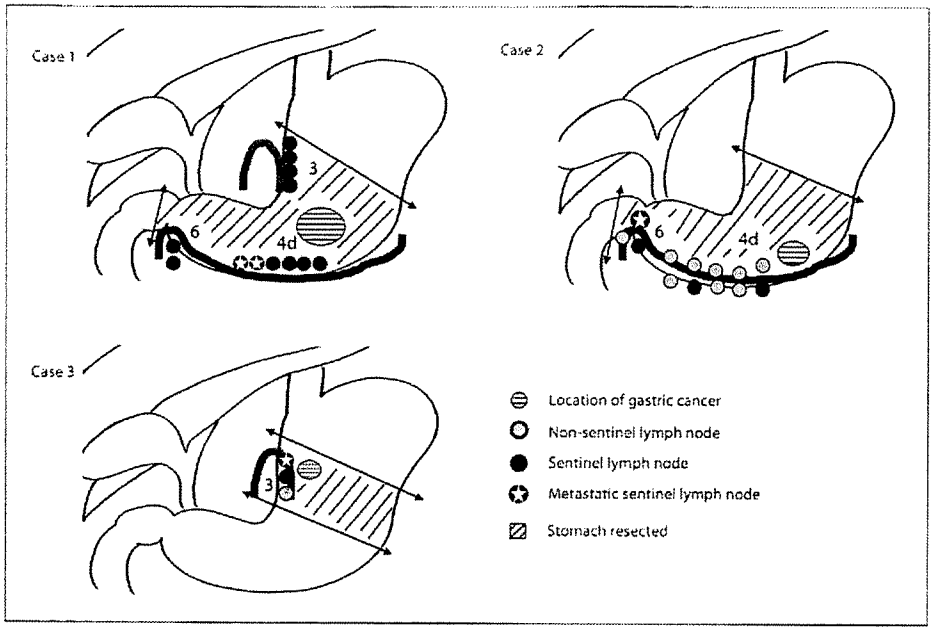

Fig. 2. Lymphatic drainage of patients with metastatic lymph nodes. Case 1 had a 33-mm M signet ring cell carcinoma in the anterior wall (lymphatic invasion: ly1, venous invasion: v0), which had two lymphatic basins (LGA, RGEA), and sentinel nodes in Nos. 3, 4d and 6. Metastatic lymph nodes were located in No. 4d, all of which were sentinel nodes. Case 2 had a 12-mm SM1 moderately differentiated adenocarcinoma (including poorly differentiated component in the invasive front) in the greater curvature (lymphatic invasion: ly1, venous invasion: v0), which had one lymphatic basin (RGEA), and sentinel nodes in Nos. 4d and 6. A metastatic lymph node was located in No. 6, which was a sentinel node. Case 3 had an 8-mm M well-differentiated adenocarcinoma in the lesser curvature (lymphatic invasion: ly0, venous invasion: v0), which had one lymphatic basin (LGA), and sentinel nodes in No. 3. A metastatic lymph node was included in No. 3 (sentinel node).

Table 4. Identification of sentinel node and lymph node metastasis

	Open surgery (n = 7)	Laparoscopic surgery (n = 7)	Total (n = 14)
Sentinel node identification	7 (100%)	7 (100%)	14 (100%)
Lymph node metastasis	2[1]	1[2]	3
Accuracy for rapid pathology for sentinel node metastasis	86% (6/7)	100% (7/7)	93% (13/14)

[1] Cases 1 and 3 in figure 2.
[2] Case 2 in figure 2.

Discussion

Although subsequent gastrectomy after endoscopic treatments should be intended to completely remove residual tumor, there is a large gap between endoscopic resection and open standard gastrectomy with extensive lymph node dissection. Limited surgery has to be considered for patients who received endoscopic resection as an initial treatment for early gastric cancer.

There is growing evidence that sentinel node navigation surgery could be safely used in patients with early gastric cancer and could reduce the extent of gastrectomy and lymph node dissection without increasing tumor recurrence rates [8–11]. According to a recent report [12] of 80 patients, 61 with negative sentinel node metastases underwent a less extensive, function-preserving gastrectomy. In that study, the false-negative rate on sentinel node biopsy was 23% for frozen section and 7% for postoperative pathology, both of which are comparable with the results of the present study. However, the appropriateness of sentinel node navigation surgery for patients who received inappropriate endoscopic treatment for early gastric cancer has been poorly investigated. The concern is that disorganized lymphatic channels caused by endoscopic resection may disturb the lymphatic flow necessary for detecting sentinel node.

In the current protocol for sentinel node mapping for gastric cancer in a university hospital where a high detection rate (292/301) of sentinel node for gastric cancer is achieved, patients who had previous endoscopic treatments are excluded as candidates for sentinel node navigation surgery [13]. However, in a recent report involving 6 patients who underwent laparoscopy-assisted distal gastrectomy after endoscopic mucosal resection, 20 sentinel nodes and 85 non-sentinel nodes were obtained, and the lymphatic tissue after endoscopic mucosal resection was shown to be normal [14].

In the present study, sentinel nodes for gastric cancer could be detected using IREE combined with ICG in all 14 patients who had previously received endoscopic resection during open and laparoscopy-assisted gastric resection. Two of the 14 patients were found to have sentinel node metastases on rapid frozen section pathological examination during surgery, and they underwent standard gastrectomy with D2 lymph node dissection according to the current recommendations. In another patient (case 3, fig. 2), postoperative immunohistochemical staining revealed sentinel node micrometastases that could not be detected at surgery. He underwent segmental gastrectomy with lymphatic basin dissection, leading to eradication of tumor cells (however, if micrometastasis was intraoperatively detected, we think that standard gastrectomy with D2 dissection should be performed in principle until the significance of the micrometastasis becomes definitively determined). For the remaining 11 patients with sentinel nodes free from tumor invasion, less extensive lymph node dissection and/or limited resection of the stomach could be performed.

None of the metastatic cases had indications for endoscopic mucosal resection according to Japanese gastric cancer treatment guidelines [1]. Furthermore, we emphasize the high rate sentinel node metastasis (3/14; 21%) even after endoscopic treatment. Because the whole resected specimen was not evaluated, we cannot show the histological difference of lymphatics between the normal gastric wall structure and the structure of this series. However, we injected the ICG into the normal submucosa away from the scar after endoscopic resection; we consider that this method reproduces the original lymphatic flow from a primary gastric tumor.

Limited surgery with or without sentinel node navigation is still considered partially experimental, technical issues in sentinel node mapping need to be resolved, and the significance of lymph node micrometastases still needs to be confirmed [15]; nevertheless, sentinel node navigation surgery appears to be useful for tailoring treatments for patients with early gastric cancer, even after endoscopic treatments.

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Sentinel Node Navigation Surgery for Early Malignant Tumor of the Duodenum

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ABSTRACT

Introduction: Pancreaticoduodenectomy is a standard operation for duodenal malignant tumor but is associated with a high incidence of postoperative morbidity and impaired quality of life. We report on patients who successfully underwent limited surgery for early duodenal tumors using sentinel node navigation surgery and infrared ray observation.

Methods: Indocyanine green (ICG) was injected submucosally around the tumor through an endoscope. An infrared ray laparoscopy system was used to identify sentinel nodes. These nodes were stained with hematoxylin and eosin intraoperatively or with cytokeratin immunohistochemical staining postoperatively and examined for evidence of metastasis.

Results: In case 1, 1 retropancreatic lymph node (No. 13, Japanese classification) and 1 prepancreatic lymph node (No. 17) were ICG-positive. In case 2, 1 right gastroepiploic lymph nodes (No. 6) and 2 No. 13 lymph nodes were ICG-positive. In case 3, 1 right gastroepiploic lymph node (No. 6) was ICG-positive. These lymph nodes showed no metastasis on frozen-section examination. In case 1, wedge resection of the second part of duodenum and jejunal patch operation were performed, and in cases 2 and 3, wedge resection of the duodenal bulb was performed.

Conclusion: Sentinel lymph nodes in cases of early duodenal cancer could be easily detected with an infrared ray laparoscopy system, which seems to be useful for limited surgery for duodenal malignancy.

(Jikeikai Med J 2009; 56: 11-7)

Key words: sentinel node navigation surgery, malignant duodenal tumor

INTRODUCTION

Pancreaticoduodenectomy is a standard operation for duodenal malignant tumor but is associated with a high incidence of postoperative morbidity and impaired quality of life. We report patients who successfully underwent limited surgery for early duodenal tumors using sentinel node navigation surgery (SNNS) with infrared ray observation.

METHODS AND PATIENTS

SNNS with infrared ray observation was performed in 3 patients with early duodenal tumors. Indocyanine green (ICG, 5 mg/ml, Diagnogreen®, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan) was injected submucosally (0.5 ml per injection) with a 23-gauge endoscopic puncture needle through an endoscope at 4 quadrants around the tumor. Because the duodenal wall was thin, physiological saline was injected into the submucosal layer before ICG was injected.

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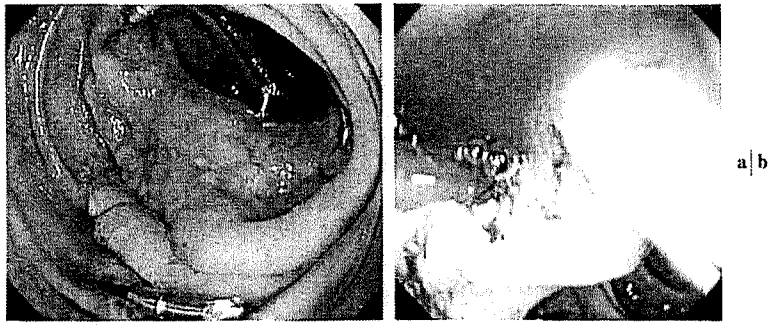
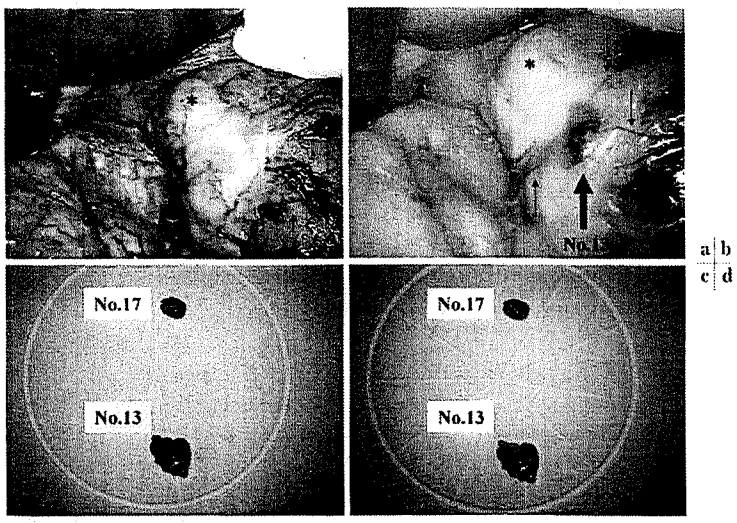


a b

Fig. 1. Endoscopic findings (case 1). a. Early cancer in the second part of the duodenum. b. Intraoperative endoscopy after ICG injection.



a b
c d

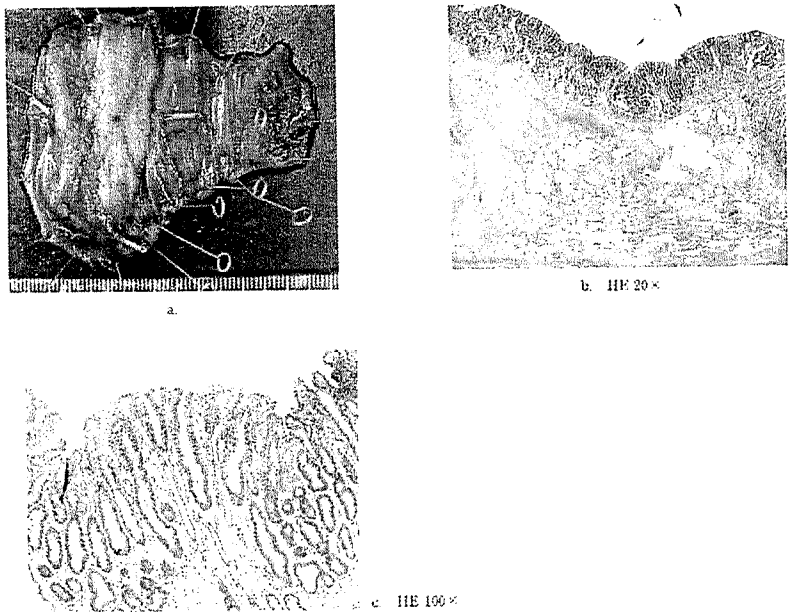
Fig. 2. SNNS (case 1). a. Observation with white light. ICG (+) LNs could not be detected. *; pancreas, ; duodenum (primary lesion). b. Observation with IRLS. ICG (+) lymphatic vessels and LNs were confirmed. Narrow arrows indicate ICG (+) lymphatic vessels. The thick arrow indicates an ICG (+) LN. c. Sentinel LNs. They could not be recognized as green nodes with the naked eye. d. Sentinel nodes. The ICG (+) LNs appeared as black nodes with IRLS.

Twenty minutes after the ICG injection, an infrared ray laparoscopy system (IRLS; Olympus Medical Systems Co., Tokyo, Japan) was used to identify ICG-positive [ICG (+)] lymphatic vessels and LNs through examination of the fatty tissue on the serosa of the duodenum and pancreas. We defined ICG (+) LNs as sentinel nodes. After observation, lymphatic basin dissection was performed. Thereafter, ICG (+) LNs were preserved by freezing, subjected to hematoxylin and eosin staining or with cytokeratin immunohistochemical staining (CAM5.2; BD Biosciences, San Jose, CA, USA), and examined for evidence of metastasis.

Case 1: The patient was a 65-year-old woman with a 50×30-mm tumor of the second part of the duodenum (c0IIa) pathologically diagnosed as well-differentiated adenocarcinoma in adenoma (Fig. 1 and 3).

Case 2: The patient was an 81-year-old woman with a 10-mm-diameter carcinoid of the anterior wall of the duodenal bulb (Fig. 4a). Endoscopic ultrasonography revealed that the carcinoid had reached the submucosa (Fig. 4b).

Case 3: The patient was a 59-year-old man with a 10-mm-diameter carcinoid of the anterior wall of the duodenal bulb. Endoscopic ultrasonography revealed that the carcinoid had reached the submucosa.



a. b. HE 20×

c. HE 100×

Fig. 3. Surgical specimen and pathological findings (case 1). a. Macroscopic appearance of surgical specimen of a duodenal tumor. b, c. Microscopic examination of the duodenal tumors showed well differentiated adenocarcinoma in adenoma (b: hematoxylin and eosin, 20×; c: hematoxylin and eosin, 100×).

Results

Case 1: One retropancreatic LN (No. 13) and 1 prepancreatic LN (No. 17) were ICG (+) (Fig. 2). Although ICG (+) LNs could not be identified with the naked eye (Fig. 2a), such ICG (+) No. 13 LNs appeared black on IRLS (Fig. 2b). The ICG (+) LNs, which were about 5 mm in diameter, were removed (Fig. 2c, d). Intraoperative frozen-section examination revealed no LN metastasis. Wedge resection of the duodenum and jejunal patch reconstruction were performed. Pathological examination showed that the cancer was confined to the mucosa and measured 43×

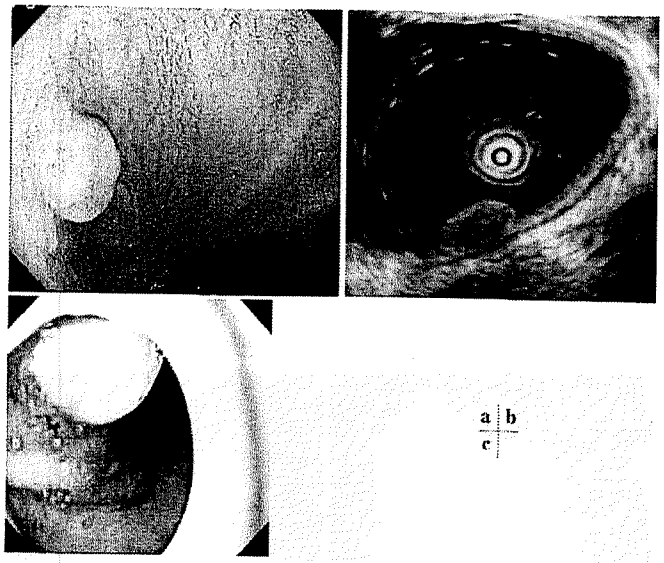


Fig. 4. Endoscopic findings (case 2). a. Duodenal carcinoid in the anterior wall of the bulb. b. Endoscopic ultrasonography. The tumor was confined to the submucosal layer. c. Intraoperative endoscopy after ICG injection.

30 mm (Fig. 3).

Case 2: Although conventional observation failed to identify any ICG (+) LNs (Fig. 5a), 1 ICG (+) right gastroepiploic LN (Fig. 5b) and 2 No. 13 ICG (+) LNs were detected with IRLS and then removed. Intraoperative examination of frozen sections demonstrated no LN metastasis. Wedge resection of the duodenal bulb was performed. Pathological examination showed that the carcinoid was confined to the submucosa and measured 8×7 mm (Fig. 6).

Case 3: One ICG (+) No. 6 LN was detected with IRLS, whereas conventional observation failed to identify any ICG (+) LNs. Intraoperative examination of frozen sections demonstrated no LN metastasis. Wedge resection of the duodenal bulb was performed. Pathological examination showed that the carcinoid was confined to the submucosa and was 5 mm in diameter.

Preoperative abdominal computer tomography of these 3 cases revealed no LNs around the duodenum. The 3 patients are alive without recurrence.

Lymph node (LN) stations were modified from those of the Japanese Classification of Gastric Carcinoma[1].

Discussion

Duodenal tumors are extremely rare in the gastrointestinal tract. Yokoyama et al. have reported that from 1985 through 1991 duodenal adenomas accounted for 0.04% (17 of 39,169 tumors) of gastrointestinal tumors at the National Cancer Center, Japan, and that primary duodenal cancers, excluding cancers of the papilla of Vater, accounted for only 0.01% of tumors (3 of 39,169 tumors)[2]. Primary duodenal carcinoids account for only 2.6% of all carcinoid tumors[3]. Because of the rarity of duodenal cancers and carcinoids, to our knowledge the incidence of LN metastasis of early duodenal cancers has not been reported. A previous report from Japan found that 13% of small (less than 1 cm) duodenal carcinoid tumors are associated with regional LN metastasis[4]. In the United States, Burke et al. have reported that 16 of 77 carcinoid tumors (21%) of the duodenum had LN metastases[5]. Features associated with an increased risk of LN metastasis include involvement of the muscularis propria, size greater than 2 cm, and the presence of mitotic figures. Nevertheless, Mullen et al. have reported that LN metastases were identified in surgical specimen from 7 of 13 patients (54%), including specimens from 2 patients with tumors smaller than 1 cm and confined to the submucosa[6]. Therefore, endoscopic resection alone is inadequate for the treatment of duodenal carcinoids. Moreover, a large-diameter duodenal mucosal cancer, like that in case 1, is difficult to treat with only endoscopic mucosal resection. However, because pancreaticoduodenectomy is major surgery with high rates of morbidity and mortality[6], accurate intraoperative diagnosis of LN metastasis with SNNS would allow a less invasive operation, such as wedge resection of the duodenum.

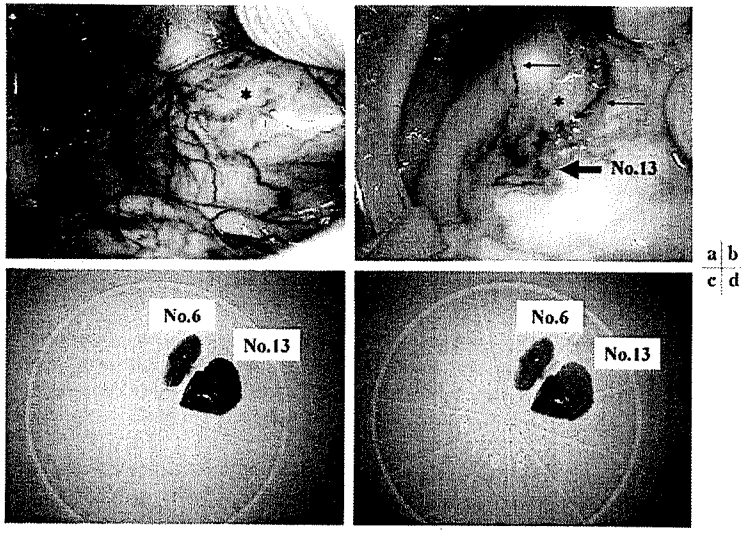
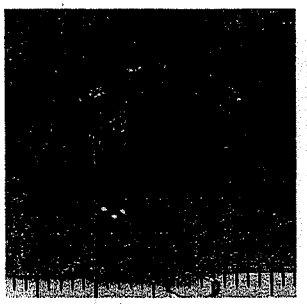


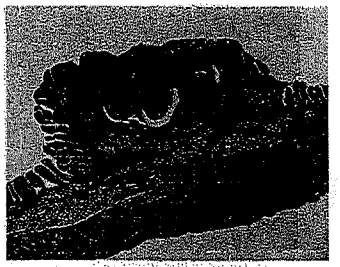
Fig. 5. SNNS (case 2). a. Observation with white light. ICG (+) LNs could not be detected. *, pancreas; ', duodenum (primary lesion). b. Observation with IRLS. ICG (+) lymphatic vessels and LNs could be clearly detected. Narrow arrows indicate ICG (+) lymphatic vessels. The thick arrows indicate ICG (+) LNs. c. Sentinel nodes. These could not be recognized as green nodes with the naked eye. d. Sentinel nodes. These ICG (+) LNs could be recognized as black nodes on infrared ray observation.

Since reported by Morton et al. in 1992, the concept of sentinel lymph nodes in melanoma and breast cancer has been validated, and SNNS is now widely performed[7,8]. Recently, several reports of SNNS for gastric cancer and colonic cancer have been published[9–16]. Since May 2000, we have been using our own technique, IRLS, for gastric cancer; we have obtained excellent results and have reported that SNNS with IRLS is useful for limited gastric surgery for early gastric cancer without compromising curability[17,18].

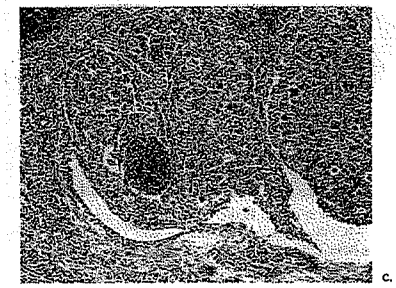
In conclusion, IRLS can be used to detect sentinel LNs in early duodenal malignant tumors, and SNNS is useful for limited duodenal resection.



a.



b. HE 20×



c. HE 100×

Fig. 6. Surgical specimen and pathological findings. a. Macroscopic appearance of a resected surgical specimen, which contained a yellowish submucosal tumor. b. Microscopic findings of the duodenal carcinoid tumor of the submucosal layer (hematoxylin and eosin, 20×). c. Histological examination showed small, round cells that were characteristic of carcinoid (hematoxylin and eosin, 100×).

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Morphological Distribution of Metastatic Foci in Sentinel Lymph Nodes with Gastric Cancer

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Background: The TNM classification defines micrometastasis (MM) and isolated tumor cells (ITC) in lymph nodes (LN). Sentinel node (SN) navigation surgery has been introduced in gastrointestinal cancer. Few reports have examined the morphological distribution of MM and ITC of SN in gastric cancer. The purpose of this study was to clarify the clinical significance of the morphological distribution of cancer cells in SNs according to metastasis (MA), MM, and ITC.

Methods: All dissected LNs obtained from 160 consecutive patients with mapped SNs arising from cT1–2 N0 tumors were examined. Metastasis in these LNs was examined by histology and cytokeratin staining. The distribution of MA, MM, and ITC was classified as marginal sinus (MS), intermediate sinus (IS), parenchymal (PA), and diffuse types (DF).

Results: Nodal metastases were detected in 65 SNs from 30 patients and MA, MM, and ITC accounted for 53.9%, 21.5%, and 24.6%, respectively. MS, IS, PA, and DF accounted for 57%, 6%, 17%, and 20.0%, respectively. Patients with metastasis of non-MS had more nodal metastasis in non-SNs ($P = .025$) and had nodal metastasis in second tier ($P = .009$), compared with the patients with metastasis of MS. The incidence of metastasis in non-MS was higher in tumors larger than 40 mm than those smaller than 40 mm ($P = .011$).

Conclusion: When performing SN navigation surgery in gastric cancer, we should keep in mind that the patients with tumor larger than 40 mm in size and nodal metastasis of non-MS may have non-SN metastasis and nodal metastasis in second tier.

Key Words: Micrometastasis—Isolated tumor cells—TNM classification—Sentinel node—Gastric cancer.

Lymph node metastasis is one of the most important prognostic factors in gastric cancer, even at the early stage.[1,2] Almost all lymph node metastasis occurs in the regional nodes. Lymph nodes play key roles as mechanical and biological barriers against migrating cancer cells in experimental rat model.[3,4] The presence or absence of lymph node metastasis is clinically important for selecting the treatment strategy. If no nodal metastasis is found before or during surgery, less invasive surgery such as endoscopic mucosal resection and reduction of lymphadenectomy are applied in early-stage gastric cancer. The concept of sentinel nodes (SNs) and isolated tumor cells (ITCs) was recently introduced in the Sixth TNM classification,[5] which separates lymph node metastases according to size as follows: metastasis (MA) (> 2 mm), micrometastasis (MM) (0.2–2 mm),

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and ITC (< 0.2 mm). Although lymph node MM has been detected by immunohistochemistry or reverse transcription-polymerase chain reaction, the clinical significance remains controversial.

Several groups have applied SN navigation surgery to melanoma and breast cancer.[6–8] According to this concept, a sentinel node is the first lymph node to receive lymphatic flow from the primary tumor and is therefore the initial site of lymph node metastasis. Thus, MM and ITC are probably located in SNs at the first step of lymph node metastasis.[9,10] We previously described lymph node micrometastasis in SNs of gastric cancer.[11,12] Recently, the microanatomic distribution of metastasis within SNs predicts the non-SNs metastasis in melanoma.[13] We investigated the relationship between microanatomic distribution of SN metastasis and clinicopathologic factors in gastric cancer. The goal of the present study is to clarify the clinical significance of the morphological distribution of cancer cells in SNs according to MA, MM, and ITC based on the TNM classification.

PATIENTS AND METHODS

Patients

We enrolled 160 consecutive patients with gastric cancer, who were preoperatively diagnosed with clinical T1–T2 (cT1, 127 patients; cT2, 33 patients) and cN0. Written, informed consent was obtained from all of the patients based on a document approved by our institutional ethics committee. The patients were clinically diagnosed before surgery based on gastrointestinal fiberscopy, double contrast gastrography, endoscopic ultrasonography, and computed tomography. All underwent curative gastrectomy with lymphadenectomy at the Department of Surgical Oncology and Digestive Surgery, Kagoshima University Hospital, between 2001 and 2006. Patients with endoscopic mucosal resection were not enrolled in this study. None of the patients had undergone preoperative radiation therapy or chemotherapy.

Identification of Sentinel Lymph Node

One day before surgery, 3 mCi (2 mL) of ^{99m}Technetium (^{99m}Tc)-tin colloid was endoscopically injected into the submucosa of the gastric wall at four sites (0.5 mL each) around the tumor using a disposable 23-gauge needle (MAJ-75, Olympus, Japan). Curative surgery then proceeded according to the Japanese classification of gastric cancer.[14] Radioisotope (RI) uptake during surgery was measured in individual lymph nodes using Navigator GPS (TYCO HEALTHCARE, Ltd., Tokyo, Japan). SNs were defined as individual lymph nodes with 10-fold greater RI uptake than background. SNs were separately removed during surgery. After surgery, all dissected lymph nodes were mapped and RI uptake was measured again.

Evaluation of Lymph Node Metastasis by Hematoxylin-Eosin and Immunohistochemical Staining

We examined 3945 lymph nodes from 160 patients. The mean number of dissected lymph nodes per patient was 20 (range, 9–69). All lymph nodes were stained with hematoxylin-eosin (HE) and immunohistochemically using a monoclonal anticytokeratin (CK) antibody cocktail (AE1/AE3, DAKO Corporation, Carpinteria, CA, USA) that reacts with a broad spectrum of human CKs. The sections were deparaffinized in xylene, rehydrated with a graded series of ethanol, and then endogenous peroxidase activity was blocked by a 5-min incubation in 3% hydrogen peroxide in methanol. The sections were then immersed in proteinase K (DAKO Corporation, Carpinteria, CA, USA) to activate the antigen and incubated with CK monoclonal antibody diluted 1:200 for 30 min. After two 5-min washes with phosphate-buffered saline (PBS), the avidin-biotin complex and immunoperoxidase were applied (ABC method; VECTASTAIN ABC Kit, Vector Laboratories, Inc., Burlingame, CA, USA). Cells positive for CK were visualized using diaminobenzidine tetrahydrochloride, and the sections were lightly counterstained with hematoxylin. The negative controls consisted of sections processed in the same manner but without the primary antibody. Consistently CK-positive normal gastric mucosa and primary tumor specimens were used as positive controls. All immunohistochemical stained slides were evaluated by three independent observers (S.Y, S.N, and Y.U).

Based on the Sixth TNM classification, lymph node metastases were separated according to size: MA (> 2 mm), MM (0.2–2 mm), and ITC (< 0.2 mm). SN metastasis was classified into three types in the measurement of metastatic foci: cluster type in which grouping tumor cells were seen in single site (Fig. 1a), multiple cluster type in which grouping tumor cells were seen in multiple sites (Fig. 1b), and diffuse type in which scattered tumor cells were seen (Fig. 1c). Among these, we measured maximal size of metastatic foci in the cluster type, the sum of the maximal size of metastatic

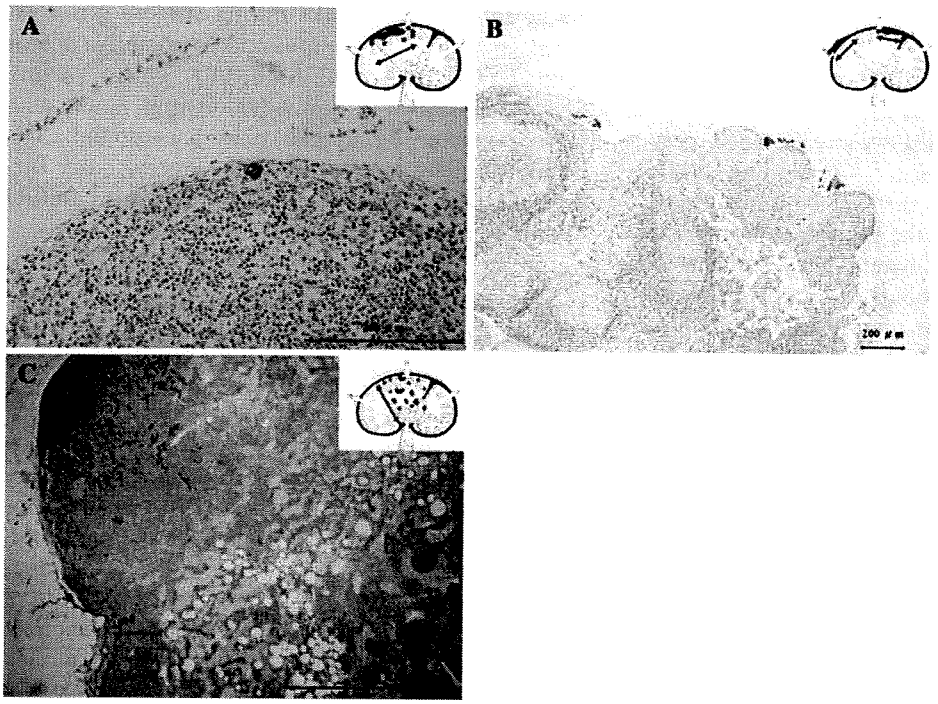

FIG. 1. Measurement criteria for metastatic foci in lymph nodes. Criteria: maximal size of metastatic foci in cluster type, sum of maximal sizes of metastatic foci in multiple cluster type and maximal size of area including cancer cells in noncluster types. (a) Cluster type (400×). (b) Multiple cluster type (100×). (c) Diffuse type (40×).

foci in the multiple cluster type, and the maximal size of the area including cancer cells in the noncluster type (Fig. 1). We classified the distribution of metastatic cancer cells in lymph nodes into four types: marginal sinus type in which tumor cells were present in marginal sinus alone (Fig. 2a), intermediate sinus type in which tumor cells were present in intermediate sinus alone (Fig. 2b), parenchymal type in which tumor cells were seen in parenchyma (Fig. 2c), and diffuse type in which tumor cells were scattered in lymph node (Fig. 2d).

Statistical Analysis

StatView statistical software version 5.5 (SAS institute, Cary, NC, USA) performed all statistical calculations. Data were statistically compared using the χ^2 test. A P value of $< .05$ was considered statistically significant.

RESULTS

Detection of Sentinel Lymph Nodes and Lymph Node Metastasis, Including Micrometastasis

The mean number of SN in 158 of 160 patients (99.7%) was 4.4 (range, 1–17). The rate of detection was 100% and 93.9% (31 of 33) in patients with 127 cT1 and cT2 tumors, respectively.

Lymph node metastasis in SNs was found in 18 of 160 patients (11.9%) by routine histological HE staining. A total number of nodal metastasis was 29. Furthermore, among 142 patients without metastasis by HE staining, CK staining detected 36 metastases in SNs from 12 patients. Accordingly, the total numbers of patients and metastases in SNs were 30 and 65, respectively. Since one patient had false negative result in our SN mapping, sensitivity was accordingly 96.7% (29 of 30) and accuracy rate was 99% (157 of 158).

According to the Japanese Classification of Gastric cancer,[14] 83.3% of patients (25 of 30) had nodal metastasis in first tier and 16.7% of patients (5 of 30) in second tier. Nine patients (30.0%) had nodal metastasis in both SN and non-SN.

Lymph Node Metastasis According to TNM Classification

In 65 nodal metastases, the incidences of MA, MM, and ITC diagnosed by HE staining and CK staining were 53.9% (35 of 65), 21.5% (14 of 65), and 24.6% (1665), respectively (Table 1).

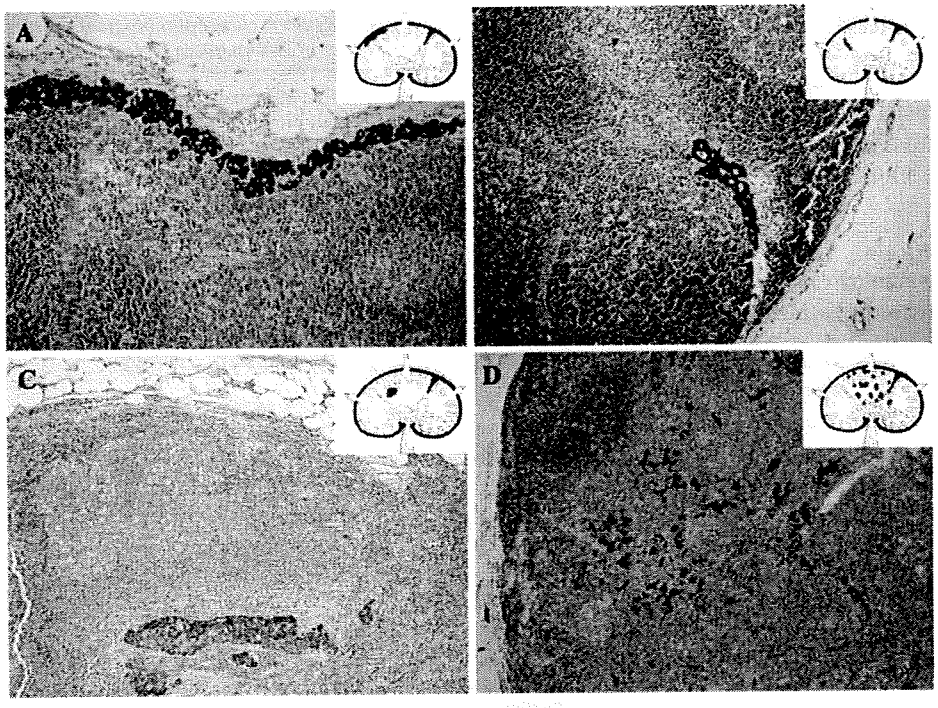

FIG. 2. Classification of distribution of metastatic foci. (a) Marginal sinus type (400×). (b) Intermediate sinus type (400×). (c) Parenchymal type (100×). (d) Diffuse type (100×).

TABLE 1. *Distribution of the metastatic foci and morphology*

	Marginal sinus type	Intermediate sinus type	Parenchymal type	Diffuse type
		Nonmarginal sinus type		
Type				
Incidence	37 (57%)	4 (6%)	11 (17%)	13 (20%)
MA (n = 35)	16 (46%)	1 (3%)	7 (20%)	11 (31%)
MM (n = 14)	10 (72%)	1 (7%)	1 (7%)	2 (14%)
ITC (n = 16)	11 (69%)	2 (12%)	3 (19%)	0

MA, macrometastasis; MM, micrometastasis; ITC, Isolated tumor cell.

Morphological Distribution of Metastatic Foci in Sentinel Nodes

The ratios of marginal sinus, intermediate sinus, parenchymal, and diffuse types of metastatic foci in 65 SNs were 56.9%, 6.2%, 16.9%, and 20.0%, respectively. In the marginal sinus type, the ratio of MA was 43.2%, MM was 27.0%, and ITC was 29.7%. Of metastatic foci, 57% were located in the marginal sinus of SNs (37 of 65 nodes) (Table 1). The remaining 28 nodes were classified as intermediate sinus (n = 4), parenchymal (n = 11), and diffuse (n = 13) types. In MA, 54% of SN metastasis was nonmarginal sinus type. On the other hand, the rate of nonmarginal sinus type in MM and ITC was 28% and 31%, respectively (Table 1).

Correlation between Clinicopathological Factors and Sentinel Node Metastasis

Clinicopathological factors were analyzed between patients with SN metastasis alone and those with SN and non-SN metastasis. The patients with tumor

larger than 40 mm had significantly more non-SN metastasis, compared with patients with tumor smaller than 40 mm (P = .006). Furthermore, the incidence of non-SN metastasis was significantly higher in patients with nonmarginal sinus type than in those with marginal sinus type (P = .025) (Table 2).

Correlation between Clinicopathological Factors and Distribution of Metastatic Foci in Sentinel Nodes

Nonmarginal sinus type was more frequently found in the patients with tumor larger than 40 mm (P = .011). According to the Japanese Classification of Gastric Carcinoma,[14] although the patients with marginal sinus type had no lymph node metastasis in second tier, 36% of patients with nonmarginal sinus type had lymph node metastasis in second tier (P = .009) (Table 3).

DISCUSSION

Lymphatic flows into the afferent lymphatics that connect to the marginal, intermediate, and medullary sinuses and then finally reaches other lymphatics via the efferent lymphatic vessels. Cancer cells detached from the primary tumor flow into intramural lymphatics and enter lymph nodes in the same manner as lymph itself. The SN concept is to detect the first lymph node metastasis using dye and RI colloid. The detection rate of SN in gastric cancer has ranged from 71% to 100%.[15-24] In contrast, we detected 100% and 93.9% of SNs from cT1 and cT2 tumors, respectively. Thus, the SN concept might be a useful diagnostic tool for detecting lymph node metastasis in early gastric cancer.

The concept of MM and ITC has been introduced in the Sixth Edition of the TNM classification. Since the method of measurement of cancer foci was not defined in this source, we propose considering cancer foci as cluster and noncluster types. Few investigators have examined morphological distribution according to TNM classification as MA, MM, and ITC. Understanding this morphological distribution of metastasis seems to be important for SN navigation surgery. Nagata et al. indicate that migrant cancer

TABLE 2. *Correlation between clinicopathological factors and SN metastasis*

Characteristic	SN metastasis	Non-SN metastasis	*P* value
Gender			.389
Male	15	5	
Female	6	4	
Age			.285
≥60	10	5	
<60	11	4	
Tumor size			.006
<40 mm	16	2	
≥40 mm	5	7	
Clinical T			.469
cT1	11	6	
cT2	10	3	
Pathological T			.091
pT1	14	3	
pT2–3	7	6	
Gross type			.523
Elevated	1	1	
Depressed	21	8	
Histology			.593
Differentiated type	3	2	
Undifferentiated type	18	7	
Lymphatic invasion			.139
Positive	13	8	
Negative	8	1	
Venous invasion			.690
Positive	10	5	
Negative	11	4	
SN status			.025
Marginal sinus type	14	2	
Nonmarginal sinus type	7	7	

TABLE 3. *Correlation between clinicopathological factors and distribution of SN metastatic foci*

Characteristic	Total No.	Marginal sinus type	Nonmarginal sinus type [a]	*P* value
Gender				.796
Male	119	11 (55%)	9 (45%)	
Female	41	5 (50%)	5 (50%)	
Age				.696
<60	57	8 (57%)	6 (43%)	
≥60	103	8 (50%)	8 (50%)	
Tumor size				.011
<40 mm	111	13 (72%)	5 (28%)	
≥40 mm	49	3 (25%)	9 (75%)	
Clinical T				.431
cT1	127	8 (47%)	9 (53%)	
cT2	33	8 (62%)	5 (38%)	
Pathological T				.153
pT1	134	11 (65%)	6 (35%)	
pT2–3	26	5 (38%)	8 (62%)	
Pathological N				.009
pN1	25	16 (64%)	9 (36%)	
pN2	5	0	5 (100%)	
Gross type				.118
Elevated	8	0	2 (100%)	
Depressed	152	16 (57%)	12 (43%)	
Histology				.743
Differentiated type	74	3 (60%)	2 (40%)	
Undifferentiated type	86	13 (52%)	12 (48%)	
Lymphatic invasion				.338
Positive	39	10 (48%)	11 (52%)	
Negative	121	6 (67%)	3 (33%)	
Venous invasion				.464
Positive	23	7 (47%)	8 (53%)	
Negative	137	9 (60%)	6 (40%)	

[a] Nonmarginal sinus type: intermediate, parenchymal, and diffuse type.

cells are initially arrested in the marginal sinus, where they evoke a biological response in a rat experimental model.[25] We found that 57% of metastases in SNs of gastric cancer were located in the marginal sinus with the remainder in the nonmarginal sinus. Our data based on the SN concept indicated that more than half of metastases were initially trapped in the marginal sinus, irrespective of metastatic modes (MA, MM, and ITC). However, some cancer cells were detected in the nonmarginal sinus. An examination of multiple sections of nodal metastasis might identify cancer cells even in the marginal sinus. Gaps and fragmentation of the superficial lymph node cortex are considered to provide intranodal shunt flow between afferent and efferent vessels in abdominal and pelvic nodes of elderly Japanese patients.[26]

When analyzing the relationship between microanatomical location of metastasis and clinicopathologic factors, significant correlation was found between tumor size and the distribution of metastatic foci in SNs. Although all patients with marginal sinus type had nodal metastasis in first tier alone, nonmarginal sinus type was found in all patients with pN2. Moreover, we evaluated the relationship between the distribution of metastatic foci in SNs and the incidence of non-SN metastasis. Interestingly, the incidence of non-SN metastasis was higher in the patients with SN metastasis of nonmarginal sinus type than in those with metastasis of marginal sinus type. Dewar et al.[13] suggested that the possibility of non-SNs involvement was extremely low in melanoma patients with the microanatomical location of metastasis with only subcapsular deposits in SNs. This result is in accord with the findings of our study.

Furthermore, CK staining during operation is recommended[27] and improves the diagnosis of SNs.

In conclusion, we demonstrated the microanatomical distribution of cancer foci in SNs. More than half of metastatic foci were located in the marginal sinus, but if the patients had SNs metastasis with nonmarginal sinus type, we should pay attention to the possibility of not only SN metastasis but also non-SN metastasis and pN2. SN navigation surgery in gastric cancer should be carefully performed in such patients.

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Sentinel Node Micrometastases Have High Proliferative Potential in Gastric Cancer

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Background. **The 6th edition of the TNM classification has recently defined "sentinel nodes (SN)," "micrometastasis," and "isolated tumor cells (ITC)." The present study examines the frequency and proliferative activity of such metastases with focus on the SNs of gastric cancer.**

Methods. **We enrolled 133 patients with cT1-2 tumors (cT1: 104, cT2: 29) and mapped SNs. Lymph node metastases were examined by routine histology and by immunohistochemistry with anti-cytokeratin. We used the Ki-67 antibody to detect the primary tumor and lymph node metastases to evaluate proliferative activity.**

Results. **The number of patients with SNs metastases and metastatic SNs was 19 and 52, respectively. The frequencies of macrometastasis, micrometastasis, and ITC were 48%, 25%, and 27%, respectively. Ki-67 expression in the tumor closely correlated with lymphatic invasion ($P = 0.0001$), venous invasion ($P < 0.0001$), and lymph node metastasis ($P < 0.0001$). Cells in 96% of macrometastases, 92% of micrometastases, and 29% of ITCs were Ki-67 positive.**

Conclusions. **We showed that micrometastasis and some ITCs in SNs had proliferative activity. We suggest that micrometastasis and ITCs should be removed, especially during SN navigation surgery, until their clinical significance is clarified.**

Key Words: **micrometastasis; isolated tumor cells; TNM classification; gastric cancer; sentinel node.**

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INTRODUCTION

The incidence of early gastric cancer has recently increased and surgeons have taken several approaches to treat this condition, including endoscopic mucosal and submucosal resection, laparoscopic surgery, and reduction of lymphadenectomy. Sentinel node navigation surgery (SNNS) is among the less invasive surgical options for cancer, and it has recently been introduced for the treatment of gastric cancer [1, 2]. For SNNS to be effective, the presence or absence of lymph node metastases, including micrometastases, must be determined. However, the clinical significance of lymph node micrometastasis remains controversial [3–11]. Various types of micrometastases, such as sentinel node (SN), pNX (sn), pN0 (sn), and pN1 (sn) have recently been added to the 6th edition of the TNM classification system. Furthermore, lymph node metastasis has now been subclassified into three types according to the size of the metastatic foci: metastasis (>0.2 cm), micrometastasis (between 0.2 cm and 0.2 mm), and isolated tumor cells (ITCs; <0.2 mm) [12].

The SN is the first node to receive lymphatic drainage from a primary tumor, leading to the notion that micrometastasis or ITC develops first in the SN [13]. However, whether such metastatic cancer cells can implant and proliferate remains obscure. Ki-67 expression detected by the use an anti-Ki-67 antibody is frequently used to assess proliferative activity in tumor cells because the protein is usually detectable throughout the cell cycle except during the G0 phase [14]. Moreover, Ki-67 expression closely correlates with tumor progression in gastric cancer [15, 16]. The present study uses immunohistochemistry to identify microme-

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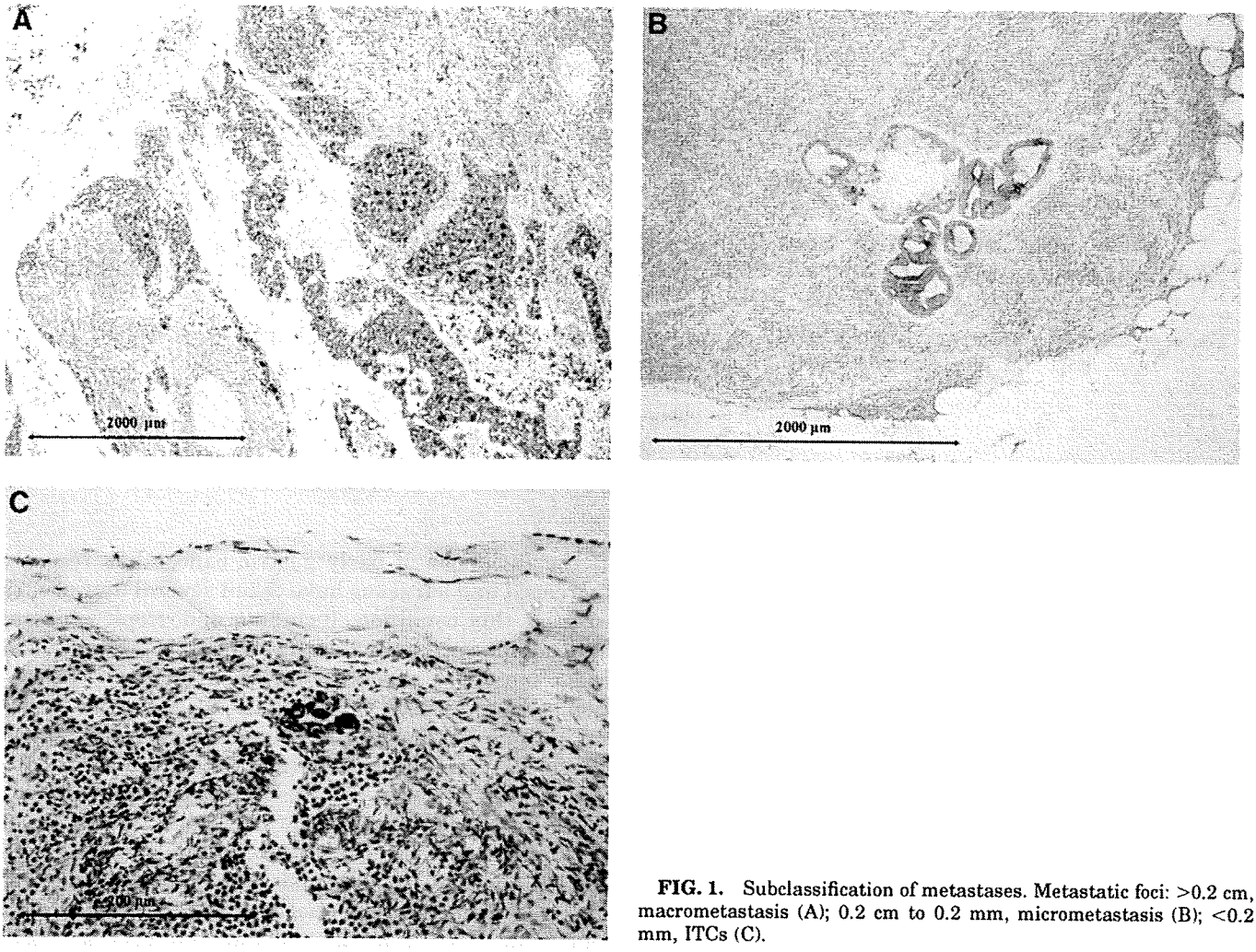

FIG. 1. Subclassification of metastases. Metastatic foci: >0.2 cm, macrometastasis (A); 0.2 cm to 0.2 mm, micrometastasis (B); <0.2 mm, ITCs (C).

tastasis and ITC and then elucidates the proliferative activities of metastatic foci in SNs of gastric cancer.

MATERIALS AND METHODS

Patients

We enrolled 133 consecutive patients with gastric cancer who had been preoperatively diagnosed with clinical grade T1 (n = 104) or T2 (n = 29) between 2001 and 2005. All of them underwent curative gastrectomy with lymphadenectomy and provided written, informed consent to participate based on a document approved by our institutional ethics committee.

Identification of SNs

We mapped SNs as described [17–19]. In brief, 3 mCi (2 mL) of ^{99m}technetium-tin colloid was endoscopically injected into the submucosa of the gastric wall at four sites around the tumor 1 d before surgery. During surgery, radioisotope uptake in each lymph node was measured using Navigator GPS (TYCO Healthcare, Ltd., Tokyo, Japan). All dissected lymph nodes were mapped after surgery and radioisotope uptake was measured once again. Lymph nodes with signals that were 10-fold above background were considered to be SNs.

Diagnosis of Lymph Node Metastasis

Lymph nodes were cut at the plane of the largest dimension, fixed in 10% formaldehyde and embedded in paraffin for sectioning. Some of the sections (3 μm) were stained with hematoxylin and eosin (H and E) and others were immunohistochemically examined. Lymph nodes were stained using AE1/AE3 (20:1 mixture of AE1 to AE3; Boehringer, Mannheim, Germany), a monoclonal antibody cocktail that reacts against a broad spectrum of human cytokeratins (CK). All sections were incubated at 60°C overnight, deparaffinized in xylene and rehydrated through a series of graded ethanols. The sections were incubated in citrate buffer (pH 6.0) for 6 min under pressure, immersed in CK monoclonal antibody diluted 1:100, and then CK reactivity was detected using alkaline phosphatase. We classified lymph node metastases into three categories according to the TNM classification, (Fig. 1) as macrometastasis (>0.2 cm), micrometastasis (between 0.2 cm and 0.2 mm), and ITCs (<0.2 mm). Three independent observers evaluated all of the immunostained slides (SY, SN, and YU).

Detection of Cytokeratin and the Ki-67 Antigen

After lymph node metastasis was determined by CK staining, sections on glass slides were immersed in xylene for a few days to remove the coverslips. The sections were then rehydrated with a graded series of ethanols, autoclaved in 10 mM sodium citrate (pH

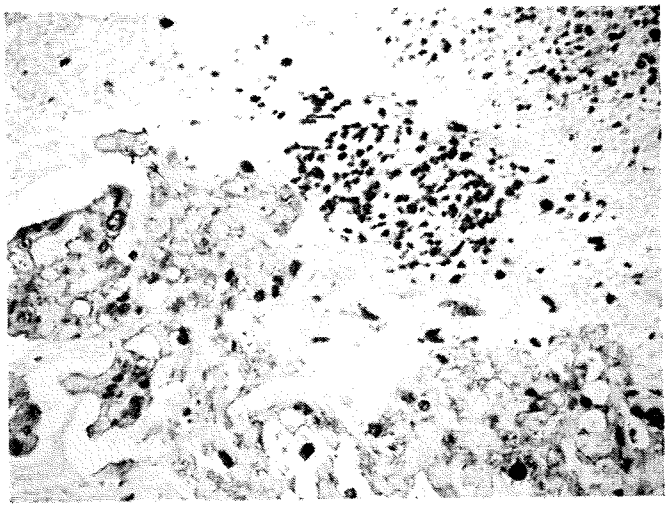

FIG. 2. Proliferative activity in metastatic foci of lymph nodes detected with Ki-67 antigen. Germinal center of the lymph node expresses Ki-67 antigen in nuclei (red) and thus serves as positive control. Cancer cells are framed in cytokeratin (brown) and express nuclear Ki-67 antigen (red).

6.0) for 15 min, and cooled at room temperature. The sections were sequentially incubated at room temperature with 1.5% bovine serum albumin for 30 min, mouse monoclonal Ki-67 antibody (DakoCytomation, Copenhagen, Denmark) diluted 1:50 for 60 min, three washes with PBS for 3 min each and biotin-labeled secondary antibody (VECTASTAIN ABC kit, Vector Laboratories, Inc., Burlingame, CA) diluted 1:200 for 30 min. The sABC steps (DakoCytomation) proceeded at room temperature for 30 min. Alkaline phosphatase (AP) was visualized using fuchsin substrate with the endogenous AP inhibitor, levamisole. Nuclei were not stained with hematoxylin to optimally visualize those that were Ki-67 positive.

The positive control was the germinal center of lymph nodes expressing red nuclear Ki-67 antigen. Cancer cells were framed in brown cytokeratin and nuclear Ki-67 antigen was stained red (Fig. 2).

The Ki-67 labeling index (LI; Ki-67 positive cancer cells/total cancer cells × 100) was determined by observing 1000 tumor nuclei and all nuclei of lymph node metastases in areas of sections with the most intense labeling. Three independent observers evaluated all immunostained slides (SY, SN, and YU).

RESULTS

Detection of Sentinel Node and Lymph Node Metastases

We identified SNs in 131 of 133 patients (detection rate: 98.5%), in all cT1 patients (n = 104; 100% detection rate) and in 27 cT2 patients (n = 29; 93% detection rate). The number of SNs per patient ranged from 1 to 17 (mean, 4.3); we obtained 3264 lymph nodes from 133 patients (range, 13 to 69 per patient; median, 27). Staining with H and E identified lymph node metastasis in 22 SNs from 14 patients. Thirty additional metastatic SNs from five patients were H and E negative but CK positive. Thus, 19 patients had lymph node metastases, and 52 lymph nodes were positive for metastases, including both micrometastases and ITCs in SNs. The overall detection rates of SNs in cT1 and cT2 were 100% and 90%, respectively. All patients in this series with nodal metastasis had lymph node metastasis in SNs. Thus, the detection rate (i.e., sensitivity) for metastasis in SNs in both cT1 and cT2 was 100% and the false-negative rate was 0%.

The incidence of macrometastasis, micrometastasis, and ITCs according to the TNM classification was 48% (25/52), 25% (13/52), and 27% (14/52), respectively. Of these, 16 of 25 macrometastasis (64%), 3 of 13 micrometastasis (23%), and 3 of 14 ITCs (21%) were HE positive. The remainder was CK positive.

Detection of Ki-67 Antigen in Primary Tumors and Metastatic Foci of Lymph Nodes

A comparison of Ki-67 antigen expression and clinicopathologic findings for primary tumors revealed significant differences in tumor depth (P = 0.0119), lymphatic invasion (P = 0.0001), venous invasion (P < 0.0001), and lymph node metastasis (P < 0.0001; Table 1). Nineteen patients had lymph node metastasis, including micrometastasis and ITCs. Cells were Ki-67 positive in 96% of macrometastases (Fig. 3A), 92% of micrometastases (Fig. 3B), and 29% of ITCs (Fig. 3C). In addition, Ki-67 positivity was significantly more frequent in macrometastasis and micrometastasis than in ITCs (P < 0.001; Table 2).

DISCUSSION

Recently, SNNS has been introduced in gastrointestinal intestinal tract cancer, and "sentinel nodes", "micrometastasis," and "isolated tumor cells" have been included in the 6th edition of the TNM classification [20]. For SNNS to be genuinely helpful, lymph node metastases, including micrometastases, must be cor-

TABLE 1

Correlation Between Expression of Ki-67 and Clinicopathological Factors

Variable	Expression of Ki-67 (mean ± S.D.)	P-value
Tumor depth		
pT1	26.3 ± 16.6	0.0119
pT2	36.9 ± 17.2	
Histological type		
differentiated	27.1 ± 15.9	0.7948
undifferentiated	27.9 ± 18.0	
Lymphatic invasion		
negative	24.9 ± 15.3	0.0001
positive	38.2 ± 19.1	
Venous invasion		
negative	25.2 ± 15.4	<0.0001
positive	46.6 ± 16.8	
Lymph node metastasis		
negative	25.1 ± 15.4	<0.0001
positive	49.3 ± 15.2	

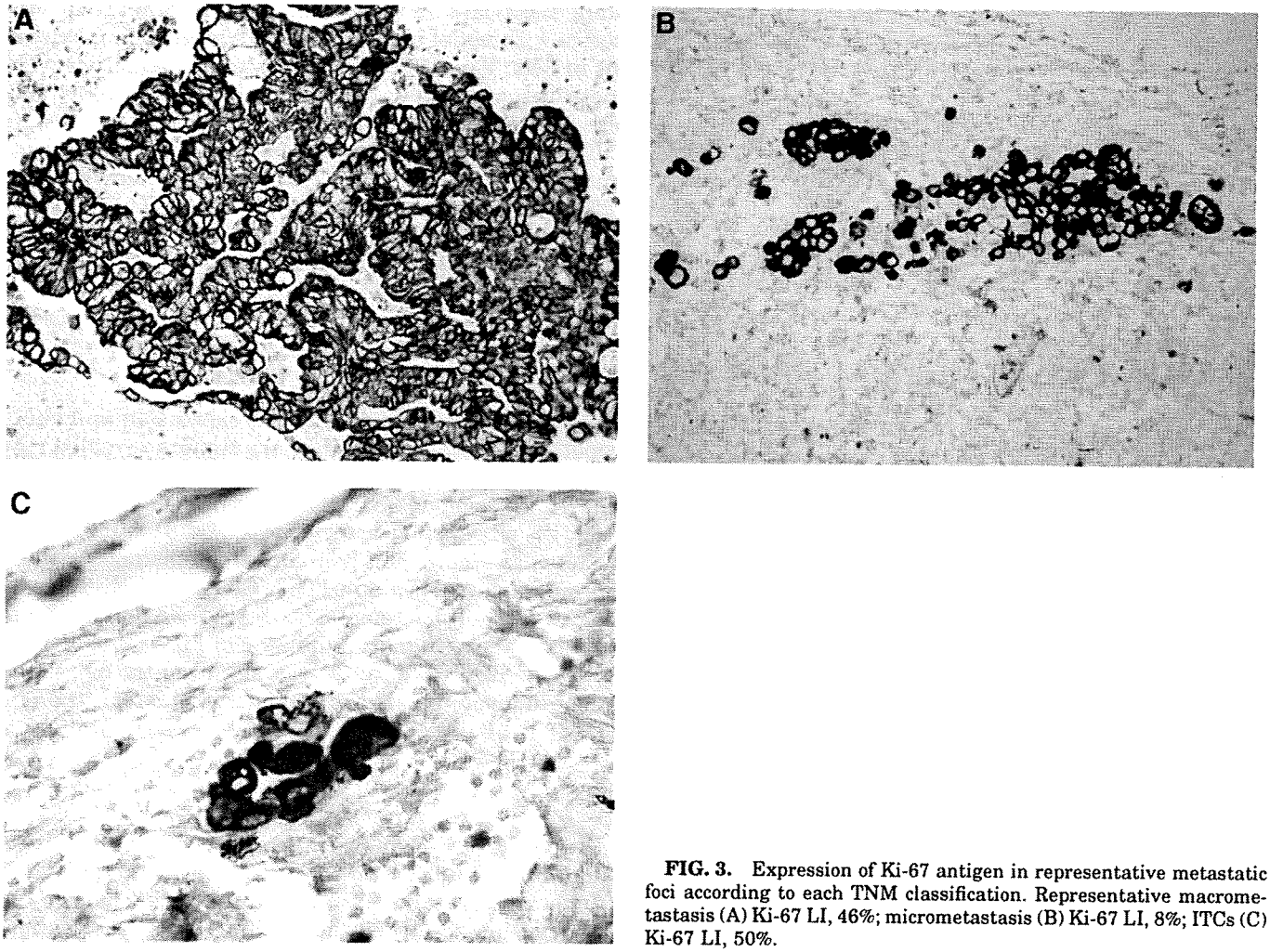

FIG. 3. Expression of Ki-67 antigen in representative metastatic foci according to each TNM classification. Representative macrometastasis (A) Ki-67 LI, 46%; micrometastasis (B) Ki-67 LI, 8%; ITCs (C) Ki-67 LI, 50%.

rectly diagnosed. We selected patients with cT1 or cT2 tumors for the present study because the SN concept seems to be appropriate for patients without nodal metastases [19, 21]. We mapped SNs and used CK staining to detect sparse cancer cells. All lymph node metastases, including micrometastases and ITCs, were contained in SNs.

The clinical significance of lymph node micrometastasis is still debatable. Some authors have described a close relationship between micrometastasis and prognosis, whereas others do not support this notion [3–11].

TABLE 2

Lymph Nodes with Ki-67-Positive Cells

	Ki-67 expression cancer cells	*P*-value
Macrometastasis (n = 25)	96%	<0.001
Micrometastasis (n = 13)	92%	
ITCs (n = 14)	29%	

Natsugoe *et al.* and Harrison *et al.* found that lymph node micrometastasis is clinically significant [3, 4], whereas others have found otherwise [6, 7]. However, the definition of micrometastasis and the stages of patients differed in each of these reports. Since micrometastasis and ITC have been defined in the TNM classification. Lee *et al.* reported that the size and pattern of lymph node metastases could yield prognostic information [11]. Further studies are needed to determine the prognostic significance of micrometastasis and ITC.

The presence or absence of micrometastases is currently an important problem for SNNS, particularly in early gastric cancers for which less invasive surgery is planned [21]. Unresolved issues concerning SNs include the frequency and size of micrometastasis, as well as the proliferative potential of small cancer foci.

Here, we found that HE staining detected metastases in 10% of 133 patients. We clustered metastases by the size of the metastatic foci according to the 6th edition of the TNM classification. Approximately 80%

of micrometastases and ITCs were detected by CK staining alone. Thus, at least an immunohistochemical study seems to be essential for SNNS. However, whether such cancer cells in lymph nodes have proliferative potential remained to be determined. We therefore measured proliferative ability as Ki-67 antigen expression, which reflects the proliferating cell cycle. Ki-67 expression in primary tumors correlates with various tumor progression factors such as tumor depth, lymphatic invasion, venous invasion, and lymph node metastasis, and our results agreed with those of others [15, 16]. When we next examined proliferative activity in various lymph node metastases, Ki-67 expression was positive in 96% of metastasis, 92% of micrometastasis, and in 29% of ITCs. Although proliferative activity was evident even in micrometastasis and ITCs, whether such metastases will become embedded and grow in lymph nodes remains unclear [22]. Yokoyama *et al.* reported that ITCs in regional lymph nodes of an animal model regressed after removal of the primary tumor mainly via natural killer cells [23]. We suggest that micrometastasis and ITCs be removed during less invasive types of surgery including SNNS, from the viewpoint of risk for recurrence, until the clinical significance of such metastases is clarified.

Previous studies and the data presented here suggest that SNNS would be an appropriate strategy with which to treat early-stage gastric cancer [19, 24]. Patients with gastric cancer should benefit from SNNS as the extent of both lymphadenectomy and gastrectomy can be reduced. The goal of SNNS should be to perform curative resection and prevent recurrence. Thus, the detection and subsequent diagnosis of micrometastases with proliferative activity is important when considering SNNS. To help bring this about, we recently introduced a method for rapid immunohistochemical staining during surgery [25]. We predict that rapid RT-PCR methods will soon be routinely applied to diagnose micrometastases during SNNS.

CONCLUSIONS

We identified micrometastases and ITCs and provided evidence of their proliferative activity in SNs. Since the clinical significance of micrometastasis and ITCs in lymph nodes remains obscure, we suggest that, for the time being, such metastases should be removed during the reduction of lymphadenectomy, including SNNS.

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特集 センチネルリンパ節理論の消化器癌への応用

5 センチネルリンパ節生検応用の拡大
(1) EMR/ESDへの応用

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Key words：食道癌，胃癌，センチネルリンパ節，内視鏡的粘膜切除術，内視鏡的粘膜下層剝離術

要 旨

早期消化管癌に対するendoscopic mucosal resection(EMR)やendoscopic submucosal dissection(ESD)は臓器温存，機能温存の観点から優れた治療法の一つである．しかし，これらの治療を選択するうえでリンパ節転移の有無はもっとも重要な因子である．画像診断で診断される明らかなリンパ節転移以外に分子生物学的，遺伝子学的解析により発見される微小転移がある．近年，センチネルリンパ節の概念が消化管癌でも導入されている．センチネルリンパ節を同定し，微小転移を含めたリンパ節転移を診断することは縮小治療には有用である．今後，早期消化管癌に対するEMRやESDの適応拡大に際してはセンチネルリンパ節生検を併用することにより，積極的にかつ安全に施行できると考えられる．

I．センチネルリンパ節の上部消化管癌への臨床応用

この項のポイント
- センチネルリンパ節の同定は治療の個別化の一つである．

センチネルリンパ節理論は乳癌やメラノーマではすでに臨床応用として導入され，リンパ節郭清の標準術式の一つとして確立されている．上部消化管癌にも次第に臨床導入が試みられつつあるが，どのような症例に応用可能であろうか？

センチネルリンパ節は最初に転移が起こると想定されるリンパ節である．血管と同様にリンパ管にも変異があり，さらにリンパ節に流入するリンパ管の数や走行，あるいは腫瘍によるリンパ流の変化により修飾されるため，個々の症例でセンチネルリンパ節は異なると考えられる．また臓器によっても差異があると考えられ，食道癌では早い時期から頸部・胸部・腹部のさまざまな領域に転移がみられる．一方，早期胃癌の場合にはある程度，占居部位に応じて

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