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Long-term outcome following sentinel node navigation surgery for cT1 gastric cancer

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Abstract. Sentinel node navigation surgery (SNNS) has become a standard procedure for early-stage melanoma and breast cancer. However, very few studies have evaluated the long-term clinical outcomes following SNNS for gastric cancer. The present study analyzed 51 patients with cT1 gastric cancer who underwent SNNS at our hospital. Sentinel nodes (SNs) were identified using the dual tracer method. Patients underwent limited gastrectomy with SN station dissection when the SNs were reported as pathologically negative during surgery. When SNs were pathologically positive, standard gastrectomy with D2 lymphadenectomy was performed. Out of the 51 cases, 42 cases (82%) were pathologically diagnosed as SN-negative using a frozen section. The surgical procedures included segmental gastrectomy (n=33) and local resection (n=9). A total of 9 patients (18%) had lymph node metastasis in SNs. The mean observation period was 3,125±167 days, and the 5-year overall survival rate was 98%. There was no recurrence, and body weight loss was minimal following the SNNS. Remnant gastric cancer developed in 4 (8%) of the 50 patients except total gastrectomy. Thus, SNNS was a useful procedure for cT1 gastric cancer from the long-term clinical outcomes, though metachronous gastric cancer should paid further attention to.

Introduction

In recent years, the sentinel node (SN) concept has been widely accepted, and SN navigation surgery (SNNS) is a standard surgical procedure for early-stage melanoma and breast cancer (1). However, the clinical application of SNNS for cT1 gastric cancer had been controversial, because of the complexity of the lymphatic flow compared to breast cancer and melanoma (2).

A prospective multicenter trial verifying the feasibility of SNNS for cT1-2 gastric cancer was conducted (3). This trial showed SN detection rate and the sensitivity of positive SNs are 97.5% (387/397) and 93% (53/57) in cT1-2N0M0 gastric cancer with a tumor <4 cm. Gastric cancer treatment guidelines 2010 (the 3rd edition) by the Japanese Gastric Cancer Association (JGCA) mentioned that local resection of the stomach was promising procedure to maintain the quality of life, which should be reevaluated with development of SNNS in the future.

We previously showed that SNNS was feasible for cT1N0M0 gastric cancer with a tumor <4 cm in size (4) and, this procedure has several advantages over conventional gastrectomy in terms of postoperative functional disorders 1 year after surgery, as well as positive impacts on both the length of postoperative hospital stay and the number of days until the patient's first postoperative oral intake (5). However, there was few reports regarding long-term outcome of SNNS for early gastric cancer.

In this study, we retrospectively evaluated the long-term outcomes after SNNS for early gastric cancer.

Patients and methods

A total 51 patients with cT1N0M0 gastric cancer with a tumor <4 cm who underwent SNNS between 2003 and 2009 at National Defense Medical College Hospital was enrolled in this study. The primary lesion was not eligible for endoscopic submucosal dissection (ESD), and depth of the lesion was diagnosed by endoscopy and fluoroscopy. SNs were identified using the radioisotope (RI) and dye as a tracer. In the RI method, 0.5 ml of 99 mTc-tin colloid solution was injected into each of four sites surrounding the tumor on the day before the surgery, and SNs were defined as lymph nodes with a radioactivity of ≥10 counts per 10 sec. In the dye method, 0.5-1 ml of 1.25% indocyanine green solution was injected into each of four sites surrounding the tumor, and SNs were defined as green-dyed lymph nodes macroscopically or laparoscopically.

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Key words: gastric cancer, long-term outcome, prognosis, sentinel node, sentinel node navigation surgery

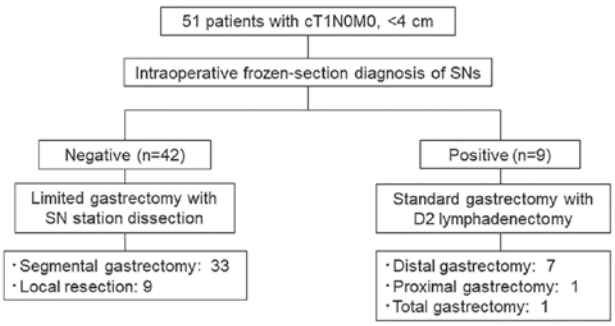

Figure 1. Summary of the results of the 51 patients enrolled in the present study. Out of the 51 cases, 42 cases (82%) were pathologically diagnosed as SN-negative using a frozen section. The surgical procedures included segmental gastrectomy (n=33) and local resection (n=9). A total of 9 patients (18%) who had lymph node metastasis in the SNs during surgery underwent standard gastrectomy with D2 lymphadenectomy. SN, sentinel node.

Limited gastrectomy (segmental gastrectomy or local resection) with dissection of the lymph node stations including the SN was performed, when the SN was pathologically negative based on the frozen-section diagnosis. All resected specimens were confirmed to be free of cancer cells at the surgical margins by intraoperative frozen-section examination. If intraoperative frozen section revealed metastasis in SN, a standard gastrectomy with D2 lymphadenectomy was performed (Fig. 1).

Surveillance after the surgery was followed by JGCA guidelines, and abdominal computed tomography or ultrasonography was taken every six months and endoscopy was done a year. Prognosis of the patients was surveyed by letters to the patients or medical institutions where the patients were followed.

Informed consent. The SNNS procedure reported in this study was reviewed and approved by the institutional review board at National Defense Medical College (Saitama, Japan). Written informed consent was obtained from every patient before the procedures.

Statistical analysis. All data were analyzed using JPM pro 13 for Windows (SAS Institute, Inc., Cary, NC, USA). Data are expressed as the mean ± standard deviation or the standard error. Survival rates were obtained using the Kaplan-Meier method and the significance of the difference in survival rate was determined by log-rank test. $P<0.05$ were considered to indicate a statistically significant difference.

Results

Of the 51 patients, 5 patients (10%) were diagnosed as ≥pT2, and 9 patients (18%) had lymph node metastases (Table I) (6). Forty-two patients (86%) were diagnosed as SN-negative by intraoperative frozen-section examination. Both the detection rate of SN and the sensitivity of metastatic SN were 100%. The surgical procedures included segmental gastrectomy (SG, 33 cases) and local resection (LR, 9 cases). Nine patients (18%) had lymph node metastasis in SNs, for whom DG, PG, and TG with D2 lymphadenectomy were performed in 7 cases (78%), one case (11%), and one case (11%), respectively. The mean observation period was 3,125±167 days. There was one fatal case; secondary gastric cancer of the remnant stomach death within 5 years after the surgery. The 5-year overall survival rate was 98% (Fig. 2).

Table I. Clinicopathological characteristics of the patients (n=51).

Characteristic	Total n
Age, years (mean ± SD)	63±10
Gender	
Male	37
Female	14
Histology	
Differentiated	28
Undifferentiated	23
Depth	
Mucosa	25
Submucosa	21
Muscularis propria	3
Subserosa	1
Serosa	1
Lymph node metastasis[a]	
N0	42
N1	4
N2	5
Tumor size, cm (mean ± SD)	3.1±1.5

[a]According to the Japanese Gastric Cancer Association, 15th edition (6), guidelines.

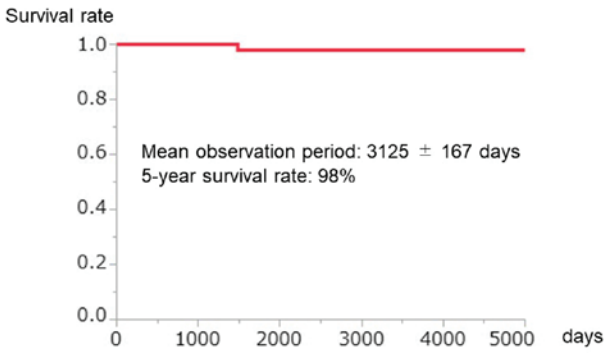

Figure 2. Overall survival using the Kaplan-Meier method. The mean observation period was 3,125±167 days, and the 5-year overall survival rate was 98%.

Remnant gastric cancer developed in four (8%) of the 50 patients with non-TG operation, i.e., SG (n=3) and LR (n=1). Of the four cases, early gastric cancer of the remnant stomach was detected in three cases and advanced gastric cancer of the remnant stomach in one case. For early gastric cancer of the remnant stomach, 1 case was performed completion gastrectomy and 2 cases were performed endoscopic submucosal dissection (ESD). For advanced gastric cancer of the remnant stomach, the patient died 1.5 months after the surgery due to the general development of the metastases (Table II).

The weight loss ratio to the preoperative value in the limited gastrectomy with dissection of the lymph node stations (n=42)

Table II. Residual stomach cancer cases (n=4).

			Primary cancer					Remnant cancer				
Case	Gender	Age, years	Tumor location	Macroscopic type (size, cm)	Tumor depth, histology	Surgical procedure	Postoperative period, years	Tumor location	Macroscopic type (size, cm)	Tumor depth, histology	Surgical procedure	Outcome
1	Male	56	M, Gre	0-IIc (3.0)	SM1, Undifferentiated	Segmental gastrectomy	6	U, Gre	0-IIc (3.0)	SM1, Differentiated	Complete gastrectomy	Survived
2	Male	69	M, Less	0-IIc (4.2)	M, Differentiated	Segmental gastrectomy	4	L, Gre	0-IIa+IIc (1.1)	M, Differentiated	ESD	Survived
3	Male	66	M, Less	0-IIa+IIc (4.5)	M, Undifferentiated	Segmental gastrectomy	6	L, Gre	0-IIa+IIc (1.1)	M, Undifferentiated	ESD	Survived
4	Male	77	U, Post	0-IIc (4.7)	M, Differentiated	Local resection	4	UE, Less-Ant-Post	Type 5 (11.5)	SE, Undifferentiated	Complete gastrectomy	Succumbed

ESD, Endoscopic submucosal dissection; U, Upper; M, Middle; L, Lower; UE, Upper and esophagus; Less, lesser curvature; Gre, greater curvature; Ant, anterior wall; Post, posterior wall; SM1, Submucosa (tumor invasion is within 0.5 mm of the muscularis mucosae).

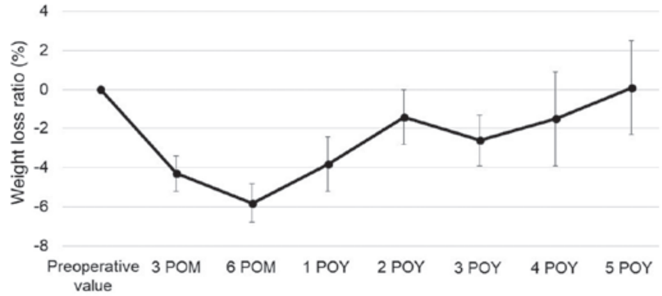

Figure 3. Weight loss ratio with the preoperative value in patients with limited gastrectomy and dissection of the lymph node stations (n=42) was -4.3±0.9, -5.8±1.0, -3.8±1.4, -1.4±1.4, -2.6±1.3, -1.5±2.4 and 0.1±2.4% at POMs 3 and 6, and POYs 1, 2, 3, 4 and 5, respectively. POMs, postoperative months; POYs, postoperative years.

was -4.3±0.9, -5.8±1.0, -3.8±1.4, -1.4±1.4, -2.6±1.3, -1.5±2.4 and 0.1±2.4% at postoperative month 3, 6, postoperative year 1, 2, 3, 4 and 5, respectively (Fig. 3).

Discussion

In this study, we demonstrated that 98% of 5-year overall survival, although 10% of pathological advanced gastric cancer (T2≤) and 18% of positive lymph node metastasis were included in this cohort. We speculated that the cause of the favorable prognosis resulted from accurate staging of the gastric cancer by intraoperative diagnosis of the SN metastasis and relevant surgery according to the staging. It is difficult to adequately diagnose tumor depth and lymph node metastasis before surgery in early gastric cancer (7,8). In this regard, the intraoperative diagnosis of the SN could contribute to the correct staging and relevant treatment strategy.

In this study, there were no false-negative cases due to intraoperative misdiagnosis of the SN and non-SN metastasis. However, there are several limitations to the intraoperative diagnosis on SN metastasis, and the sensitivity of the intra-operative frozen section analyses for identifying lymph node metastases within SNs has been reported to widely vary, from a range of 70 to 90% (9). To improve the sensitivity and convenience for the detection of metastases, we indicated that a new semi-automated molecular method for the rapid diagnosis of SN metastases using one step nucleic acid amplification (OSNA) (10). OSNA is an ideal molecular-based method to intraoperatively detect LN metastasis, takes approximately 30 min to obtain a final result. In addition, we previously reported that metastases including occult ones were always limited to the lymph nodes in sentinel lymphatic station (11). By application of these concepts, the accuracy of SN detection would be improved further.

There were four (8%) remnant gastric cancer cases in this study. The treatment for the remnant gastric cancer was completion gastrectomy in two cases and endoscopic submucosal resection (ESD) in two cases, respectively. Of the two completion gastrectomy cases, one case was early gastric cancer which were compatible for ESD, but it was difficult to perform ESD because the lesion was close to the suture and anastomotic line of the first treatment, which prevented the lesion from lifting up. The reported incidence of remnant gastric cancer was 1-3% after

early gastric cancer surgery (12,13). Nozaki *et al* (13) reported that the risk factors of remnant gastric cancer were male sex, older age, submucosal invasion, and proximal gastrectomy. As possible explanations for the higher incidence of the remnant stomach cancer after proximal gastrectomy, they speculated that the mucosal area in the gastric remnant should be larger than that of a distal or pylorus-preserving gastrectomy, and the larger mucosal area might be associated with a higher incidence of metachronous gastric cancer. We previously reported that the area of the resected stomach in limited gastrectomies was significantly smaller than that in standard gastrectomies (5), resulting in the larger mucosal area in SNNS. It was reported that prophylactic eradication of *Helicobacter pylori* after ESD for early gastric cancer should be used to prevent the development of metachronous gastric carcinoma (14). Similarly, eradication of *H. pylori* after SNNS might be effective for prevention of incidence of remnant gastric cancer.

Malnutrition is among the main postoperative complications of radical gastrectomy for gastric cancer, and a body weight loss continued up to 5 years after the surgery (15). We demonstrated that SNNS has an advantage with lightening of body weight loss over conventional gastrectomy in terms of not only short-term but also a long-term clinical outcome. And, we believe that SNNS procedure should become an option of surgical treatment for cT1 gastric cancer in near future. However, the possibility of the development of malignancy in the remnant stomach should be considered.

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Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

YY contributed to data collection and interpretation, and wrote the initial draft of the manuscript. SH, NI, SN, HH and IK contributed to data collection and interpretation, and critically reviewed the manuscript for important intellectual content. TE, KO, TN, YK, ES and SA contributed to the analysis and interpretation of data, and assisted in the preparation of the manuscript. TI, HT and HU designed the study, and contributed to data analysis and interpretation, and assisted in the preparation of the manuscript. All authors prepared the survey sheet, and read and approved the final manuscript.

Ethics approval and consent to participate

The SNNS procedure reported in this study was reviewed and approved by the institutional review board at National Defense Medical College (Saitama, Japan). Written informed consent was obtained from every patient before the procedures.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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