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REVIEW ARTICLE

Function-preserving gastrectomy based on the sentinel node concept in early gastric cancer

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Abstract Recent meta-analyses and a prospective multicenter trial of sentinel node (SN) mapping in early gastric cancer have demonstrated acceptable SN detection rates and accuracy of determination of lymph node status. SN mapping may play a key role in obtaining individual metastatic information. It also allows modification of surgical procedures, including function-preserving gastrectomy in patients with early gastric cancer. A dual-tracer method that uses radioactive colloids and blue dye is currently considered the most reliable method for the stable detection of SNs in patients with early gastric cancer. New technologies, such as indocyanine green infrared or fluorescence imaging, are also useful for accurate SN mapping in gastric cancer. Theoretically, laparoscopic function-preserving gastrectomy, including partial resection, proximal gastrectomy, segmental gastrectomy, and pylorus-preserving gastrectomy, is feasible in early gastric cancer when the SN(s) is/are nonmetastatic. Our study group conducted a multicenter prospective trial in Japan to evaluate function-preserving gastrectomy with SN mapping for long-term survival and patient quality of life. Non-exposed endoscopic wall-inversion surgery (NEWS) is a new technique for treating gastric cancer with partial resection involving full-thickness resection with endoscopy and laparoscopic surgery without transluminal access. The combination of NEWS and SN biopsy is expected to be a promising, minimally invasive, function-preserving surgery that is ideal for cases of cN0 early gastric cancer.

Keywords Sentinel nodes · Gastric cancer · Laparoscopic · Function-preserving

Introduction

At present, many patients with early gastric cancer in Asian countries are treated with advanced laparoscopic gastrectomy procedures, including laparoscopy-assisted distal gastrectomy (LADG) and laparoscopy-assisted total gastrectomy with standard lymph node dissection [1–4]. Advanced laparoscopic gastrectomy contributes to better esthetics and early postoperative recovery [5]. However, patients' quality of life (QOL) may be affected by late-phase complications, including dumping syndrome and body weight loss resulting from oral intake disturbance. Therefore, careful consideration of minimal invasiveness for early-phase recovery in laparoscopic surgery and additional late-phase function-preserving gastric cancer surgery is important in patients indicated for these procedures.

Function-preserving gastrectomy, such as partial gastrectomy, segmental gastrectomy, and proximal gastrectomy with limited lymph node dissection, is known to improve postoperative late-phase function. In particular, pylorus-preserving gastrectomy (PPG) is a function-preserving surgery for patients with early gastric cancer in the middle third of the stomach [6, 7]. Compared with conventional distal gastrectomy, PPG has a lower incidence of postgastrectomy syndromes, such as dumping syndrome, bile reflux gastroesophagitis, weight loss, and nutritional deficit. Moreover, proximal gastrectomy is recommended

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for patients with early-stage proximal gastric cancer because of the physiological function of the remaining stomach compared with that after total gastrectomy [8–10]. However, adopting function-preserving surgery as the standard procedure is still controversial as function-preserving surgery has uncertain oncological safety [11]. It is also crucial to maintain the balance between QOL and curability when selecting procedures for patients with early gastric cancer. We believe that the sentinel node (SN) concept is a method that can be used to overcome these issues, and has an important role to play in achieving function-preserving surgery in patients with early gastric cancer.

The SN(s) is/are defined as the first draining lymph node or nodes that directly obtain(s) lymphatic flow from a primary tumor [12]. The SN concept identifies the SN (or SNs) as the first place where lymph node metastasis emerges. If the SN(s) is/are negative for metastasis, metastasis to other lymph nodes is also considered negative. This concept has been clinically applied in melanoma and breast cancer [12–14].

The clinical application of SN mapping in early gastric cancer has been controversial for some years. However, single institutional results, including our results and those of a recent multicenter trial of SN mapping in early gastric cancer, are considered acceptable in terms of the SN detection rate and accuracy of determination of lymph node status [15, 16]. Based on these results, we are developing a novel, minimally invasive function-preserving gastrectomy technique combined with SN mapping.

Laparoscopic SN mapping procedures in early gastric cancer

A dual-tracer method using radioactive colloids and blue dye is currently considered most reliable for the stable detection of SNs in patients with early gastric cancer [16, 17]. An accumulation of radioactive colloids facilitates the identification of SNs using a hand-held gamma probe, even in resected specimens. The blue dye is effective for intraoperative visualization of lymphatic flow, including during laparoscopic surgery. Preferred radioactive tracers are technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid. Isosulfan blue and indocyanine green (ICG) are currently the preferred dye tracers.

In our institution, patients with clinical T1 tumors, primary lesions less than 4 cm in diameter, and clinical N0 gastric cancer undergo SN mapping and biopsy. Our procedure involves 2.0 ml (150 MBq) of technetium-99m tin colloid solution injected the day before surgery into four quadrants of the submucosal layer of the primary tumor site, using an endoscopic puncture needle. Endoscopic injections facilitate accurate tracer injection. Technetium-99m tin colloid has relatively large particles that accumulate in the SN(s) after local administration.

Blue dye is injected into four quadrants of the submucosal layer of the primary site with an endoscopic puncture needle at the beginning of surgery. Blue lymphatic vessels and blue-stained nodes can be identified by laparoscopy within 15 min of the blue dye injection. A hand-held gamma probe is simultaneously used to locate the radioactive SN(s), as in esophageal SN mapping. Intraoperative gamma probing is feasible in laparoscopic gastrectomy, using a special gamma detector introduced from trocar ports.

The pick-up method for intraoperative SN sampling is well established in the detection of melanoma and breast cancer. However, it is recommended that the clinical application of intraoperative SN sampling in gastric cancer includes sentinel lymphatic basin dissection, which is a focused lymph node dissection of hot and blue nodes [16, 17]. The gastric lymphatic basins divide into five directions along the main arteries: the left gastric artery area, right gastric artery area, left gastroepiploic artery area, right gastroepiploic artery area, and posterior gastric artery area [18]. Table 1 shows the SN distributions based on the cross-sectional location of the primary tumor in 489 patients with early gastric cancer in our institution.

ICG has excitation and fluorescence wavelengths in the near-infrared range [19]. Some investigators have used infrared ray electronic endoscopy (IREE) to demonstrate the clinical utility of intraoperative ICG infrared imaging as a tracer for laparoscopic SN biopsy [19, 20]. IREE may also improve the visualization of ICG-stained lymphatic vessels and SNs, even in fat tissue. More recently, ICG fluorescence imaging has been developed as a promising novel technique for SN mapping [21, 22]. SNs can be clearly visualized by ICG fluorescence imaging, in contrast to the use of the naked eye. Further prospective studies are needed to evaluate the clinical efficacy of ICG infrared or fluorescence imaging and compare them with radio-guided methods. However, these new technologies may revolutionize SN mapping procedures, not only in gastric cancer but in many other solid tumors.

Results of SN mapping in early gastric cancer

To date, approximately 100 single-institutional studies have demonstrated acceptable SN mapping outcomes in early gastric cancer, with SN detection rates of 90–100 % and accuracies of determination of lymph node status of 85–100 % [17]. These outcomes are comparable with those of SN mapping in melanoma and breast cancer. Wang et al.

Table 1 Distribution of SNs according to the location of the primary tumor (%)

	(*n*)	l-GA	l-GEA	r-GEA	r-GA	p-GA	#2	#9	#10	#11d	#12a	#14v
U												
Less	49	96	4	0	2	6	14	4	0	0	0	0
Gre	4	50	75	25	25	25	25	0	25	50	0	0
Ant	8	100	0	0	0	0	0	13	0	0	0	0
Post	35	97	11	6	0	3	11	0	0	3	0	0
M												
Less	107	95	2	16	12	3	0	5	0	0	0	0
Gre	51	31	35	84	12	0	0	0	0	2	0	0
Ant	47	79	23	74	17	2	0	2	0	0	0	0
Post	67	85	10	43	6	4	3	1	0	0	0	0
L												
Less	43	74	0	42	44	0	0	9	0	0	0	0
Gre	33	30	0	94	12	0	0	0	0	0	0	3
Ant	15	47	7	87	20	0	0	0	0	0	0	0
Post	30	63	7	77	13	0	0	7	0	0	0	7

l-GA lymphatic basin along the left gastric artery, *l-GEA* lymphatic basin along the left gastroepiploic artery, *r-GEA* lymphatic basin along the right gastroepiploic artery, *r-GA* lymphatic basin along the right gastric artery, *p-GA* lymphatic basin along the posterior gastric artery

reported a systematic review evaluating the diagnostic value of SN biopsy in gastric cancer [23]. The results of their large-scale meta-analysis (including 38 relevant studies with 2128 patients) demonstrated a SN detection rate of 94 % and accuracy of prediction of lymph node metastasis based on SN status of 92 % [23]. They concluded that the SN concept is technically feasible in gastric cancer, especially in early T-stage (T1) cases, in combination with the use of tracers and submucosal injection methods during SN biopsy procedures.

In Japan, our group conducted a multicenter prospective trial of SN mapping using a dual-tracer method with a radioactive colloid and blue dye [16]. In that trial, we performed SN mapping in 2004–2008 for approximately 400 patients with early gastric cancer at 12 comprehensive hospitals, including our institution. Eligibility criteria were patients who had cT1N0M0 or cT2N0M0 single tumor with a primary lesion less than 4 cm in diameter, without any previous treatments. We found that the SN detection rate was 98 % and that the accuracy of determination of metastatic status was 99 % [16]. The results of that clinical trial are expected to provide insight into the future of SN navigation surgery in early gastric cancer.

Clinical application of laparoscopic SN mapping in early gastric cancer

Knowledge of the distribution of the sentinel lymphatic basin and the pathological status of the SN(s) is useful when deciding the minimized extent of gastric resection,

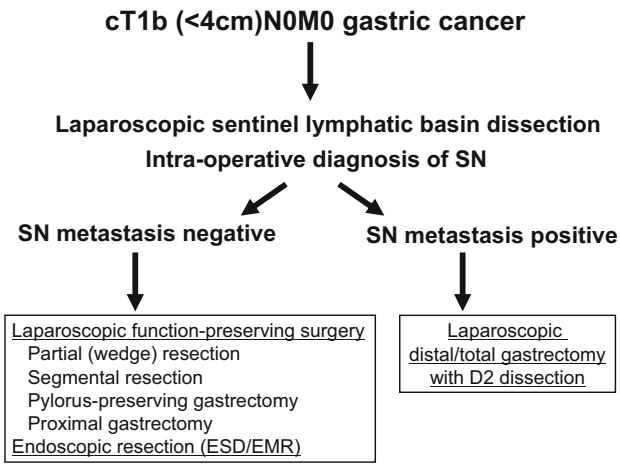

Fig. 1 Personalized function-preserving approaches for cT1N0M0 gastric cancer based on sentinel node mapping. *ESD* endoscopic submucosal dissection, *EMR* endoscopic mucosal resection

and for avoiding the universal application of distal or total gastrectomy with D2 dissection. SN status may also provide individually determined indications for laparoscopic surgeries, including partial (wedge) resection, segmental gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy (LAPG) in cT1N0 gastric cancer (Figs. 1, 2a–c) [17, 24, 25]. Earlier recovery after surgery and preservation of QOL by preventing dumping syndrome or body weight loss during the medium- to long-term follow-up can be achieved by limited laparoscopic gastrectomy with SN navigation. Our study group's multicenter prospective trial aims to evaluate function-preserving

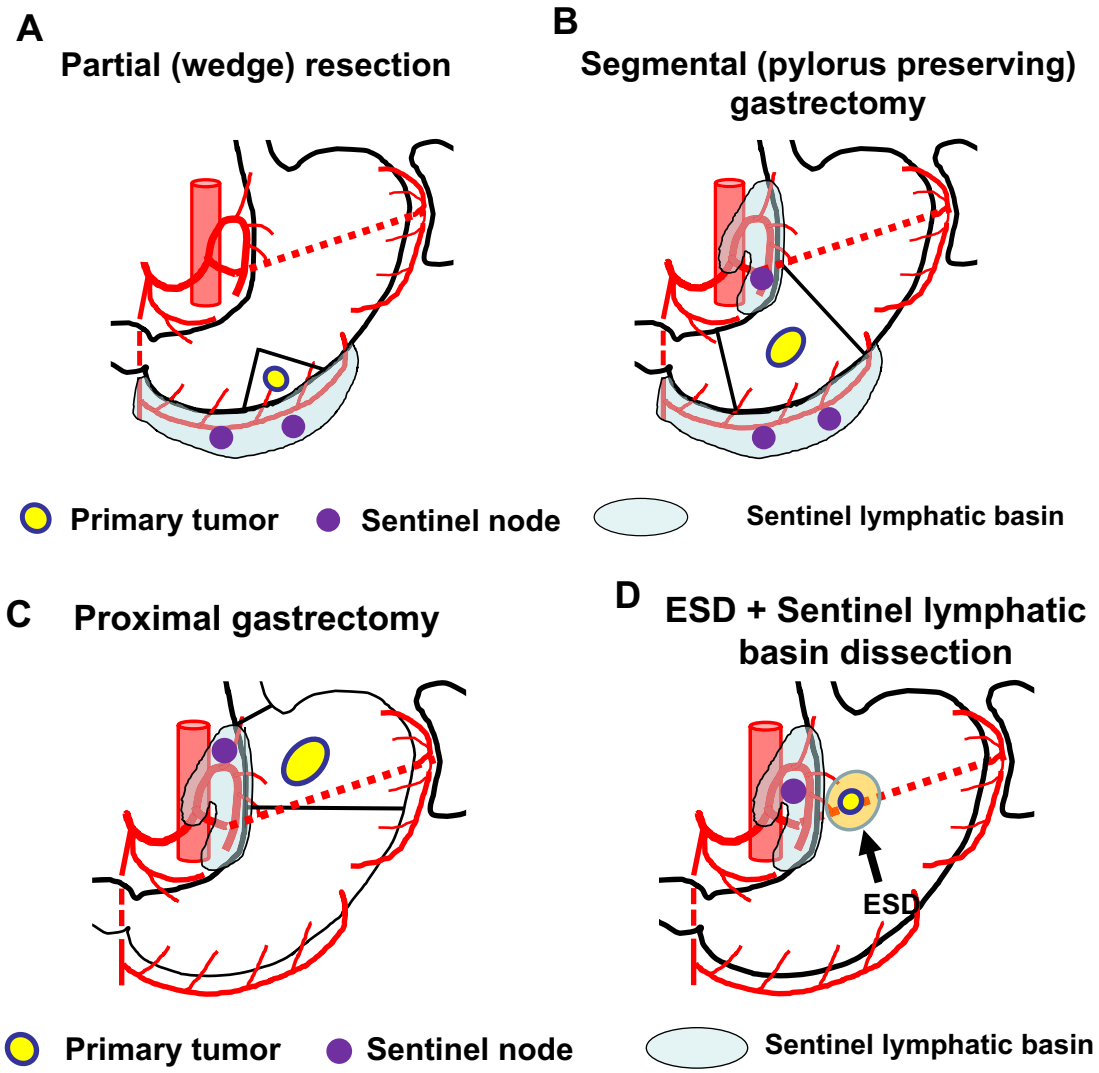

Fig. 2a–d Laparoscopic function-preserving gastrectomy with sentinel lymphatic basin dissection. **a** Partial (wedge) resection; **b** segmental (pylorus preserving) gastrectomy; **c** proximal gastrectomy; **d** sentinel lymphatic basin dissection plus ESD

gastrectomy with SN mapping in terms of long-term survival and patient QOL (UMIN 000014401).

A combination of laparoscopic SN biopsy and endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) in early gastric cancer is another novel, minimally invasive approach that preserves the whole stomach. Theoretically, if the SN(s) is/are pathologically negative for cancer metastasis, EMR/ESD may be sufficient for the curative resection of cT1 gastric cancer beyond the EMR criteria (Fig. 2d) [26, 27]. However, further studies are required to verify the safety and effectiveness of combined treatments involving laparoscopic SN biopsy and EMR/ESD.

LADG or LAPG are currently frequently used for patients with early gastric cancer, based on the results of pathological assessment of the primary tumor following resection by EMR/ESD. However, it is not clear whether SN mapping is feasible after EMR/ESD. An important issue is whether the lymphatic flow from the primary tumor to the original SN(s) changes after EMR/ESD. Our preliminary study showed that the sentinel lymphatic basin was not markedly affected by previous EMR/ESD [26, 27]. Modified gastrectomy based on the SN distribution and metastatic status may be feasible, even for patients who underwent EMR/ESD before surgery.

Non-exposed endoscopic wall-inversion surgery plus SN mapping

Currently, in function-preserving surgeries such as laparoscopic local resection or segmental gastrectomy, the gastrectomy approach is from outside the stomach, where the demarcation line of the tumor cannot be visualized at

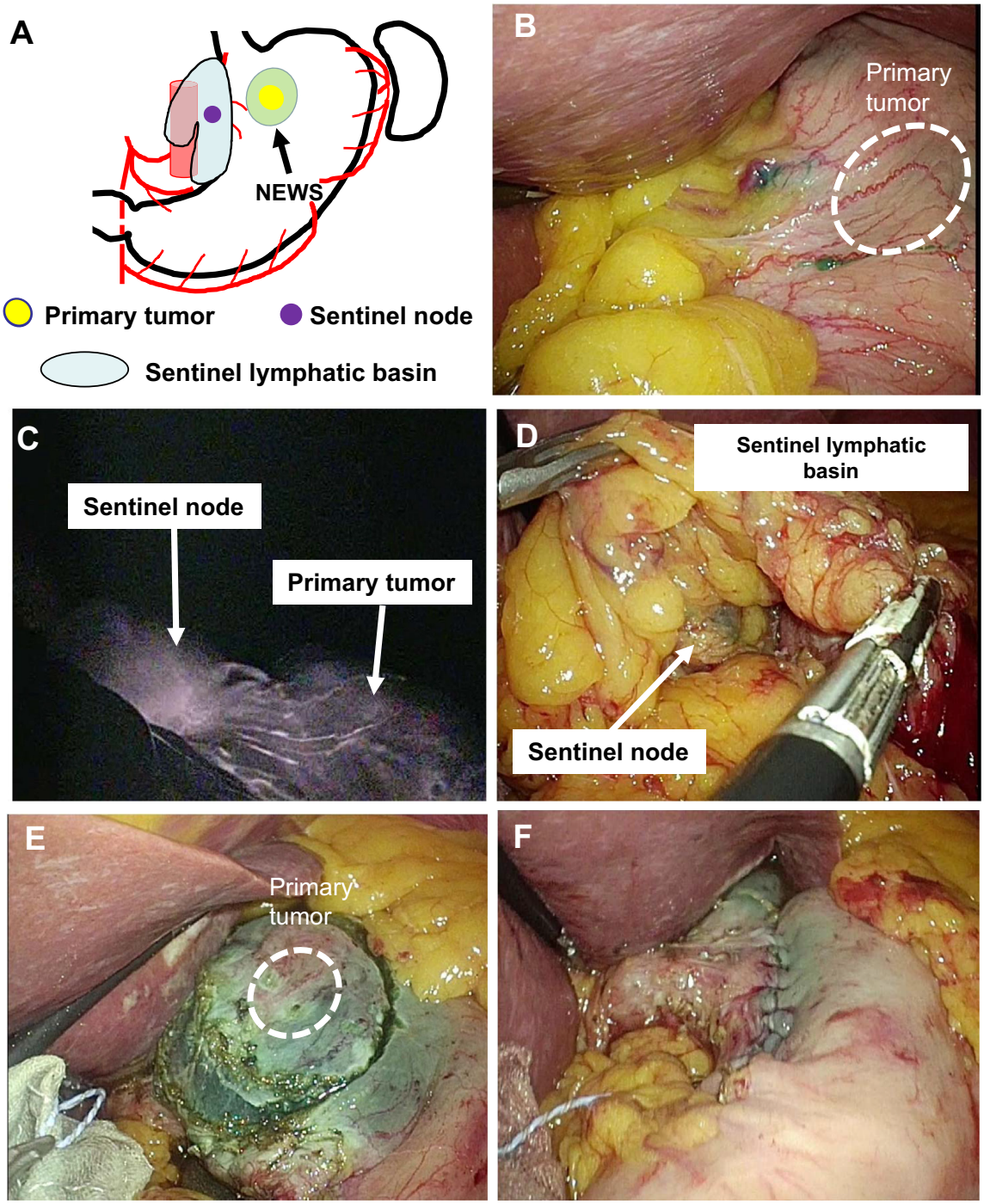

Fig. 3a–f Non-exposed endoscopic wall-inversion surgery and sentinel lymphatic basin dissection. **a** Schema; **b** early gastric cancer located at the anterior side of the *upper* stomach; **c** observation of indocyanine green (ICG) with infrared ray electronic endoscopy; **d** resection of the sentinel lymphatic basin; **e** laparoscopic circumferential seromuscular incision surrounding the primary lesion; **f** laparoscopic seromuscular suturing and inversion of the primary lesion

the resection phase. Therefore, to prevent a positive surgical margin, surgeons cannot avoid a wider resection of the stomach than is desired. Non-exposed endoscopic wall-inversion surgery (NEWS) is a new technique involving full-thickness partial resection. This technique can minimize the extent of gastric resection using endoscopic and laparoscopic surgery without transluminal access, and was mainly designed to treat gastric cancer. We have been

accumulating cases of NEWS with SN biopsy in early gastric cancer with the risk of lymph node metastasis in our clinical trial [28, 29].

In brief, after placing mucosal markings, we injected ICG endoscopically into the submucosa around the lesion to examine the SN(s) (Fig. 3a–f) [28]. The SN basin, including hot or stained nodes, was dissected and intraoperative pathological diagnosis confirmed that no metastasis had occurred. Subsequently, NEWS was performed for the primary lesion. Serosal markings were placed laparoscopically and submucosal injection was added endoscopically. Circumferential seromuscular incision and suturing were performed laparoscopically, with the lesion inverted toward the inside of the stomach. Finally, a circumferential mucosal incision was performed, and the lesion was retrieved perorally.

NEWS combined with SN biopsy can minimize the area of lymphadenectomy and the extent of gastric resection in partial gastrectomy for patients in whom the SN(s) is/are negative for metastasis [28]. Furthermore, as NEWS does not need intentional perforation, the technique can be applied to cancers without risking iatrogenic dissemination. Theoretically, NEWS combined with SN biopsy is applicable to patients with clinical T1N0M0 (primary lesions less than 4 cm in diameter) early gastric cancer. In principle, NEWS with SN biopsy is feasible at any tumor location, although it is important to consider residual stomach deformation after surgery before applying this procedure to a primary lesion near the cardia or pylorus. The clinical benefits of the technique should be evaluated carefully after accumulating patients. Estimation of long-term outcomes is also required to demonstrate its efficacy and safety, especially in terms of patient QOL and the risk of recurrence. Nevertheless, the combination of NEWS and SN biopsy is expected to be a promising, minimally invasive, function-preserving surgery for cases of cN0 early gastric cancer.

In early stage gastric cancer, for which a better prognosis can be achieved through conventional surgical approaches, the next surgical challenge is to establish individualized, minimally invasive treatments that retain the patient's QOL. Although further studies are required for validation, function-preserving gastrectomy based on SN navigation may be a promising strategy to achieve this goal.

Compliance with ethical standards

Human right statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

Conflict of interest There is no potential conflict of interest regarding this study.

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