Minimally Invasive Sentinel Lymph Node Biopsy for Gastric Cancer

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Introduction

In East Asian countries such as Japan and Korea, early-stage gastric cancer [i.e., American Joint Committee on Cancer (AJCC), clinical T1 (cT1) T stage] is found in many asymptomatic patients due to recent advances in endoscopic diagnosis and surveillance programs; and the population at risk currently exceeds 50% in these major institutions [1]. Endoscopic submucosal dissection (ESD) has already been accepted as the most minimally invasive procedure for resection of early gastric cancer [1]. Laparoscopic gastrectomy represents an important intermediate option between ESD and distal or total gastrectomy by open laparotomy for patients with gastric cancer [2]. Currently, laparoscopic distal gastrectomy (LDG) is comparable with conventional open distal gastrectomy and can be performed in routine clinical practice [3, 4]. Many patients with early gastric cancer are currently treated with advanced laparoscopic gastrectomy procedures, such as LDG and laparoscopic total gastrectomy (LTG) with appropriate lymph node dissection in many countries [1–4]. LDG and LTG contribute to better aesthetics and earlier postoperative recovery [5]. However, patients' quality of life (QOL) is mainly affected by late-phase complications including dumping syndrome and body weight loss resulting from disturbances in oral intake due to the extent of gastric resection. Therefore, both minimal invasive techniques for early-phase recovery by laparoscopic surgery and late-phase function-preserving gastrectomy should be carefully considered 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. However, a certain incidence of skip metastasis in the second or third compartment of regional lymph nodes remains an obstacle to wider application of these procedures. To overcome these issues, the concept of sentinel lymph node (SLN) mapping may become a novel diagnostic tool for the identification of clinically undetectable lymph node metastasis in early gastric cancer.

SLNs are defined as the first draining lymph nodes from the primary tumor site [6, 7], and they are thought to be the first possible site of

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micrometastasis along the route of lymphatic drainage from the primary lesion. The pathological status of SLNs can theoretically predict the status of all regional lymph nodes. If SLNs are recognizable and negative for cancer metastasis, unnecessary radical lymph node dissection could be avoided. SLN navigation surgery is defined as a novel, minimally invasive surgery based on SLN mapping and the SLN-targeted diagnosis of nodal metastasis. SLN navigation surgery can prevent unnecessary lymph node dissection, thus preventing the associated complications and improving the patient's QOL.

SLN mapping and biopsy were first applied to melanoma and breast cancer patients and were subsequently extended to patients with other solid tumors [7–9]. The clinical application of SLN mapping for early gastric cancer has been controversial for years. However, single institutional results and a multicenter trial of SLN mapping and biopsy for early gastric cancer observed acceptable SLN detection rate and accuracy of determining the lymph node status [10, 11]. On the basis of these results, we are developing a novel, minimally invasive function-preserving gastrectomy technique combined with SLN mapping and biopsy.

Laparoscopic SLN Biopsy Procedures

A dual-tracer method that utilizes radioactive colloids and blue or green dye is currently considered the most reliable method for stable detection of SLNs in patients with early gastric cancer [10, 11]. An accumulation of radioactive colloids facilitates the identification of SLNs even in resected specimens by using a handheld gamma probe, and the blue dye is effective for intraoperative visualization of lymphatic flow, even during laparoscopic surgery. Technetium-99 m tin colloid, technetium-99 m sulfur colloid, and technetium-99 m antimony sulfur colloid are preferentially used as radioactive tracers. Isosulfan blue and indocyanine green (ICG) are the currently preferred choices as dye tracers.

In our institution, patients with cT1 tumors, primary lesions <4 cm in diameter, and cN0 gastric cancer undergo SLN mapping and biopsy [10, 11]. In our procedures, 2 ml (150 MBq) of technetium-99 m tin colloid solution is injected the day before surgery into four quadrants of the submucosal layer of the primary tumor site using an endoscopic puncture needle. Endoscopic injections to the submucosal layer facilitate accurate tracer injection rather than laparoscopic injection from the seromuscular side of the gastric wall. Technetium-99 m tin colloid with relatively large particle size accumulates in the SLNs after local administration.

The blue or green dye is injected into four quadrants of the submucosal layer of the primary site using an endoscopic puncture needle at the beginning of surgery. Blue lymphatic vessels and blue-stained nodes can be identified by laparoscopy within 15 min after injection of the blue or green dye. Simultaneously, a handheld gamma probe is used to locate the radioactive SLN. Intraoperative gamma probing is feasible even in laparoscopic gastrectomy using a special gamma detector that can be introduced through trocar ports [10, 11].

For intraoperative SLN sampling, the "pick-up method" is well established for the detection of melanoma and breast cancer. However, it is recommended that the clinical application of intraoperative SLN sampling for gastric cancer should include sentinel lymphatic basin dissection, which is a modified focused lymph node dissection involving hot and blue lymph nodes [10, 11]. The gastric lymphatic basins are divided in the following five directions along the main arteries: left gastric artery area, right gastric artery area, left gastroepiploic artery area, right gastroepiploic artery area, and posterior gastric artery area [12].

ICG is known to have excitation and fluorescence wavelengths in the near-infrared range [13]. Until now, some investigators have used infrared ray electronic endoscopy (IREE) to demonstrate the clinical utility of intraoperative ICG infrared imaging as a new tracer for laparoscopic SLN mapping [13, 14]. IREE might be a useful tool to improve visualization of ICG-stained lymphatic vessels and SLNs even in the fat tissues. More recently, ICG fluorescence imaging has been developed as another promising novel technique for SLN mapping [15, 16]. SLNs could be clearly visualized by laparoscopic ICG fluorescence imaging compared to the laparoscopic observation of ICG with normal light. Further studies would be needed to evaluate the clinical efficacy of ICG infrared or fluorescence imaging and to compare those with radio-guided methods in prospective studies. However these new technologies might revolutionize laparoscopic SLN mapping procedures in early gastric cancer.

Results of SLN Mapping in Gastric Cancer

To date, more than 100 single institutional studies have demonstrated acceptable outcomes of SLN mapping for early gastric cancer in terms of the SLN detection rate (90–100%) and accuracy (85–100%) in determining the lymph node status; these outcomes are comparable with those of SLN mapping for melanoma and breast cancer [11]. A large-scale meta-analysis, which included 38 relevant SLN mapping studies with 2128 gastric cancer patients, demonstrated that the SLN detection rate and accuracy of predicting lymph node metastasis based on SLN status were 94% and 92%, respectively [17]. They concluded that the SLN concept is technically feasible for gastric cancer, especially patients with early T stage (cT1) by combining tracers and submucosal injection methods during the SLN biopsy procedures.

Our group in Japan has conducted a multicenter prospective trial (UMIN ID: 000000476) of SLN mapping using a dual-tracer method with a radioactive colloid and blue dye [10]. In the trial, SLN mapping was performed between 2004 and 2008 for 397 patients with early gastric cancer at 12 comprehensive hospitals, including our institution. Eligibility criteria were that patients had cT1N0M0 or cT2N0M0 single tumor with diameter of primary lesion less than 4 cm and without prior treatments.

The SLN detection rate by using the dual-tracer method was 97.5% (n = 387 of 397), and lymph node metastasis was diagnosed in 57 (14.7%) of 387 patients. Of the 57 patients with lymph node metastasis, 53 (93.0%) had positive SLNs. The accuracy of determining the metastatic status based on SLN evaluation was 99.0% (n = 383 of 387). In 32 (60.4%) of 53 patients with positive SLNs, lymph node metastases were limited to only SLNs. Of 21 SLN-positive/non-SLN-positive patients, 15 (71.4%) had metastatic non-SLNs within SLN basins and 6 (28.6%) had metastatic non-SLNs located outside the SLN basins but within the extent of D2 lymph node dissection. Four patients had false-negative SLN biopsy results of whom three had pT2 and/or primary tumors more than 4 cm in size [10]. The results of that clinical trial are expected to provide us with perspectives on the future of minimally invasive SLN navigation surgery for early gastric cancer.

Clinical Application of SLN Navigation Surgery in Early Gastric Cancer

The distribution of sentinel lymphatic basins and the pathological status of SLNs would be useful in deciding on the extent of gastric resection and avoiding the universal application of distal or total gastrectomy with D2 dissection. Appropriate indications for laparoscopic surgery such as partial (wedge) resection, segmental gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy (LPG) for cT1N0 gastric cancer could be individually determined on the basis of SLN status (Figs. 7.1 and 7.2a–c) [18–20]. Earlier recovery after surgery and preservation of QOL in the late phase can be achieved by limited laparoscopic gastrectomy with SLN navigation. Our study group in Japan has currently been conducting the multicenter prospective trial (UMIN ID: 000014401) which will evaluate function-preserving gastrectomy with SLN mapping in terms of long-term survival and patients' QOL. A Korean group is also conducting a multicenter prospective phase III trial to elucidate the oncologic safety including long-term survival of laparoscopic stomach-preserving surgery with

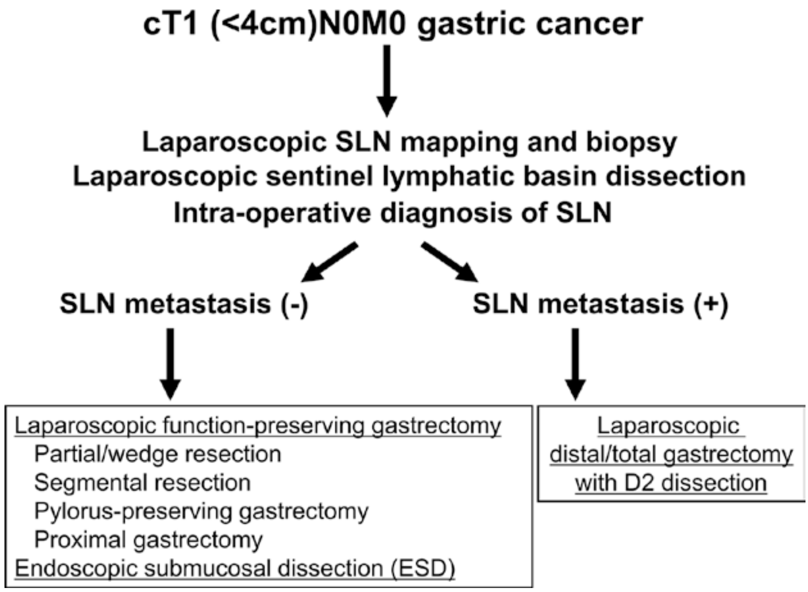

Fig. 7.1 Individualized function-preserving approaches for cT1N0M0 gastric cancer based on sentinel lymph node mapping. ESD, endoscopic submucosal dissection

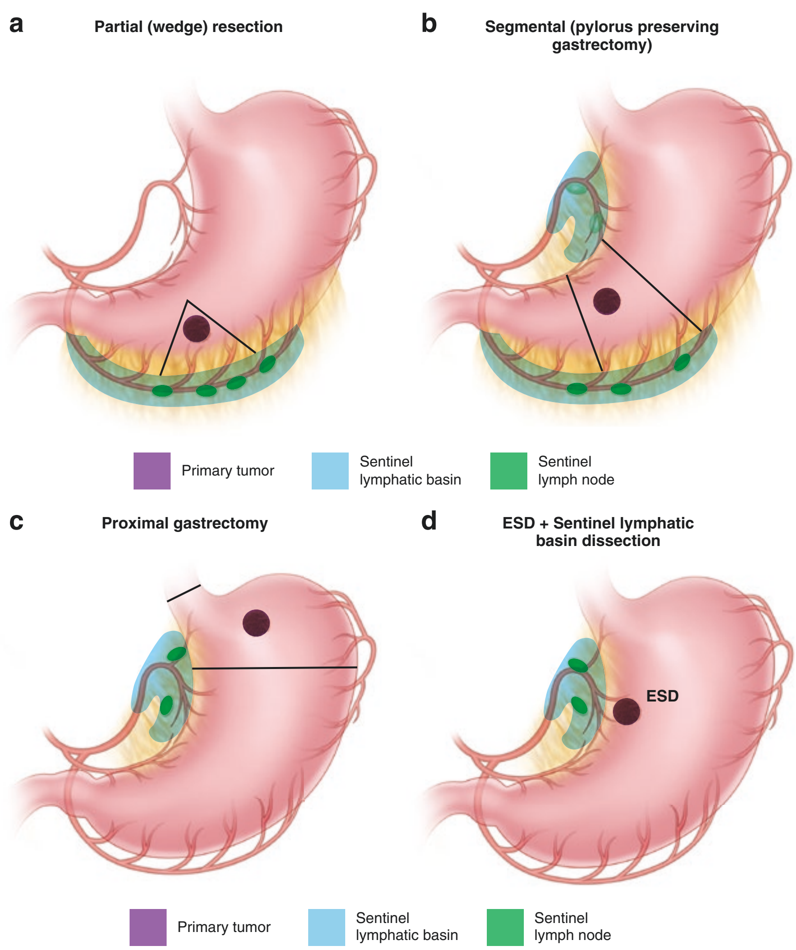

Fig. 7.2 Laparoscopic function-preserving gastrectomy with sentinel lymphatic basin dissection. (**a**) Partial (wedge) resection, (**b**) segmental (pylorus preserving) gastrectomy, (**c**) proximal gastrectomy, and (**d**) sentinel lymphatic basin dissection and ESD

sentinel lymphatic basin dissection compared to a standard laparoscopic gastrectomy [21].

A combination of laparoscopic SLN biopsy and ESD for early gastric cancer is another attractive option as a novel, whole stomach-preserved, minimally invasive approach. If all SLNs are pathologically negative for cancer metastasis, then theoretically ESD instead of gastrectomy may be sufficient for the curative resection of cT1 gastric cancer beyond ESD criteria (Fig. 7.2d) [20, 22]. However, further studies are required to verify the safety and effectiveness of combined treatments involving laparoscopic SLN biopsy and ESD.

Currently, LDG or LPG are frequently applied to patients with early gastric cancer according to the results of pathological assessment of primary tumor resected by ESD. To date, it has not been clarified whether SLN mapping is even feasible after ESD. One of the most important issues is whether lymphatic flow from the primary tumor to the original SLNs might change after ESD. In our preliminary study, however, the sentinel lymphatic basin is not markedly affected by previous ESD [20, 22]. Thus, modified gastrectomy according to SLN distribution and metastatic status might be feasible even for the patients who underwent ESD prior to surgery.

Nonexposed Endoscopic Wall-Inversion Surgery Plus SLN Biopsy (Video 7.1)

In current function-preserving surgery such as laparoscopic local resection or segmental gastrectomy, the approach of gastrectomy is only from the outside of the stomach, in which the demarcation line of the tumor cannot be visualized at the line of resection. Therefore, the surgeon cannot limit resection of the stomach to prevent a positive surgical margin. The recent introduction of a new technique, referred to as nonexposed endoscopic wall-inversion surgery (NEWS), is a technique of partial gastric resection, which can minimize the extent of gastric resection using endoscopic and laparoscopic surgery without opening the gastric wall to treat gastric cancer. During this procedure, a gastrotomy penetrating the full stomach wall is not created, and cancer cells, which are on the mucosal surface, would be neither touched nor disseminated to the peritoneum. The NEWS is thought to be useful to prevent the peritoneal dissemination of cancer cells [23]. We have been accumulating cases of NEWS with laparoscopic SLN biopsy for early gastric cancer with the risk of lymph node metastasis in our clinical trial [23–25].

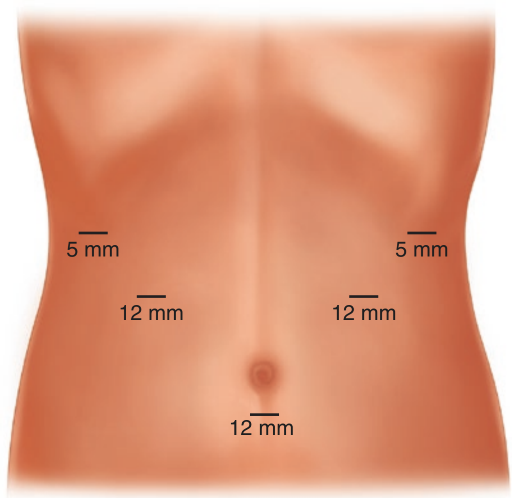

Fig. 7.3 Trocar/port placement for laparoscopic function-preserving gastrectomy with sentinel lymphatic basin dissection

In brief, under general anesthesia, one camera port at the umbilicus and four trocars were inserted for laparoscopic surgery at four quadrants of the upper left, upper right, lower left, and lower right, respectively (Figs. 7.3 and 7.4) [23]. Subsequently, the primary lesion was clearly observed by conventional endoscopy, narrow band imaging with magnifying endoscopy, and chromoendoscopy to demarcate the tumor margin and to decide the resection area, and several circumferential mucosal markings of the primary tumor were placed approximately 5–10 mm outside the lesion using the tip of a 2.0-mm Dual knife (KD-650 L; Olympus Medical Systems,

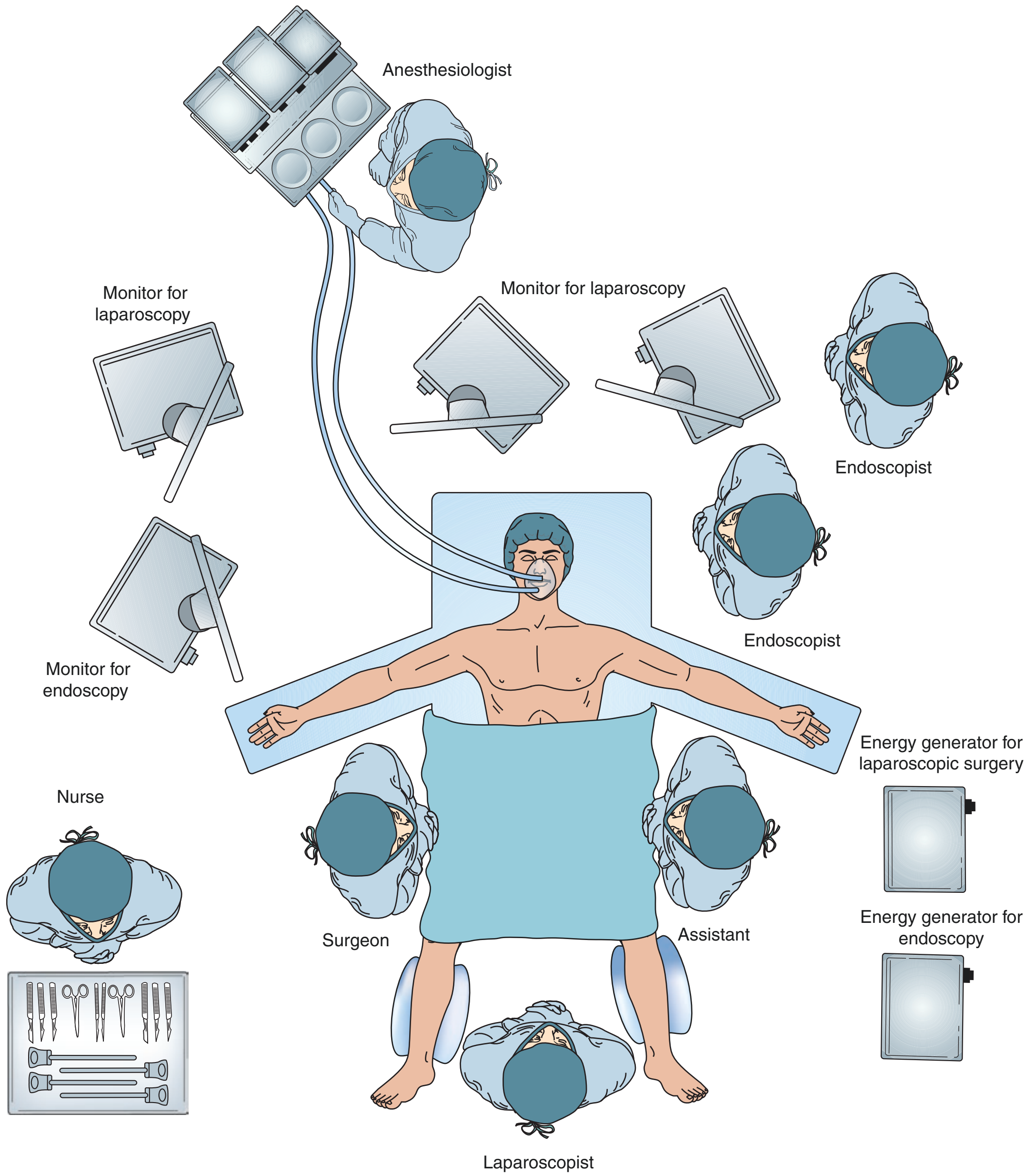

Fig. 7.4 Patient positioning and operating room setup

Co., Ltd., Tokyo, Japan). After placing mucosal markings, ICG was injected endoscopically into the submucosa around the lesion to examine SLNs (Figs. 7.5 and 7.6a–k) [23]. The SLN basin including hot or stained SLNs was dissected, and an intraoperative pathological diagnosis confirmed that no metastasis had occurred. Subsequently, NEWS was performed for the primary lesion (Fig. 7.6f–k) [23].

In the placing of serosal markings using a spatula-type electrode (A6284; Olympus), mucosal markings were protruded toward the outer side

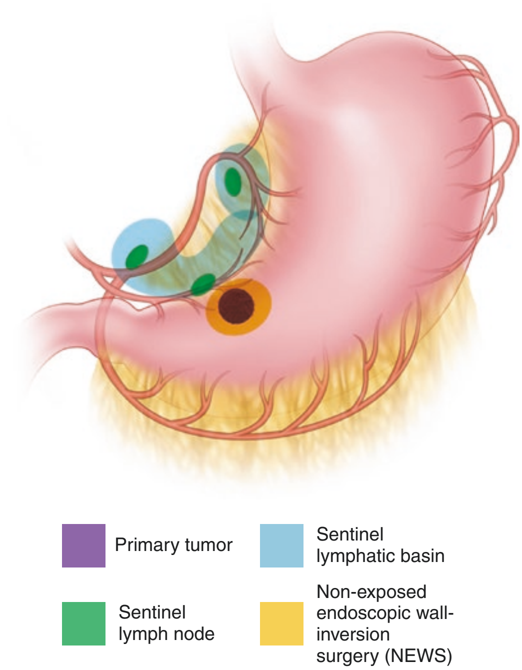

Fig. 7.5 Nonexposed endoscopic wall-inversion surgery (NEWS) with SLN mapping and sentinel lymphatic basin dissection. ESD, endoscopic submucosal dissection

using the Dual knife for the laparoscopist to recognize the location of these markings. A transparently visible shadow of the device from the opposite side was also used to make the serosal markings. Sodium hyaluronate solution (MucoUp; Seikagaku Corporation, Tokyo, Japan) with a small amount of ICG was additionally injected endoscopically into the submucosal layer around the circumference of the primary lesion, followed by a laparoscopic circumferential seromuscular incision 5 mm outside the serosal markings. In order to avoid perforating the mucosa from the outside, the seromuscular layer was cut carefully up to the level of the submucosa stained with green. After deeper cutting of the submucosa toward the outer side to create a flap, the seromuscular layers were linearly sutured, with the lesion inverted toward the inside of the stomach. On the way to the suturing, a laparoscopic surgical sponge (Securea; Hogy Medical Co., Ltd., Tokyo, Japan) that was cut elliptically according to the size of the lesion was inserted between the serosal layer of the inverted lesion and the suture layer, in order to provide a counter-traction to the mucosa and to prevent cutting the suture during the subsequent endoscopic procedure. Finally, the circumferential mucosal and submucosal incision was made endoscopically 5 mm outside of the mucosal markings around the inverted lesion using the Dual knife, while the inserted spacer was dug out. The detached primary lesion and the sponge were retrieved perorally, and the mucosal edges were closed with several endoscopic clips (HX-610-90 L; Olympus). After confirming no air leakage by pooling with normal saline on the serosal side of the suture, endoscopy and laparoscopic devices were withdrawn and scars were sutured (Fig. 7.6f–k).

The NEWS combined with laparoscopic SLN biopsy can minimize not only the area of lymphadenectomy but also the extent of gastric resection with full-thickness partial gastrectomy for patients with negative SLNs [24, 25]. Furthermore, NEWS does not require iatrogenic perforation of the stomach, which enables us to apply this technique to cancers without risk of cancer dissemination. The combination of NEWS with laparoscopic SLN biopsy is expected to become a promising, minimally invasive, function-preserving surgery to cure cases of cN0 early gastric cancer.

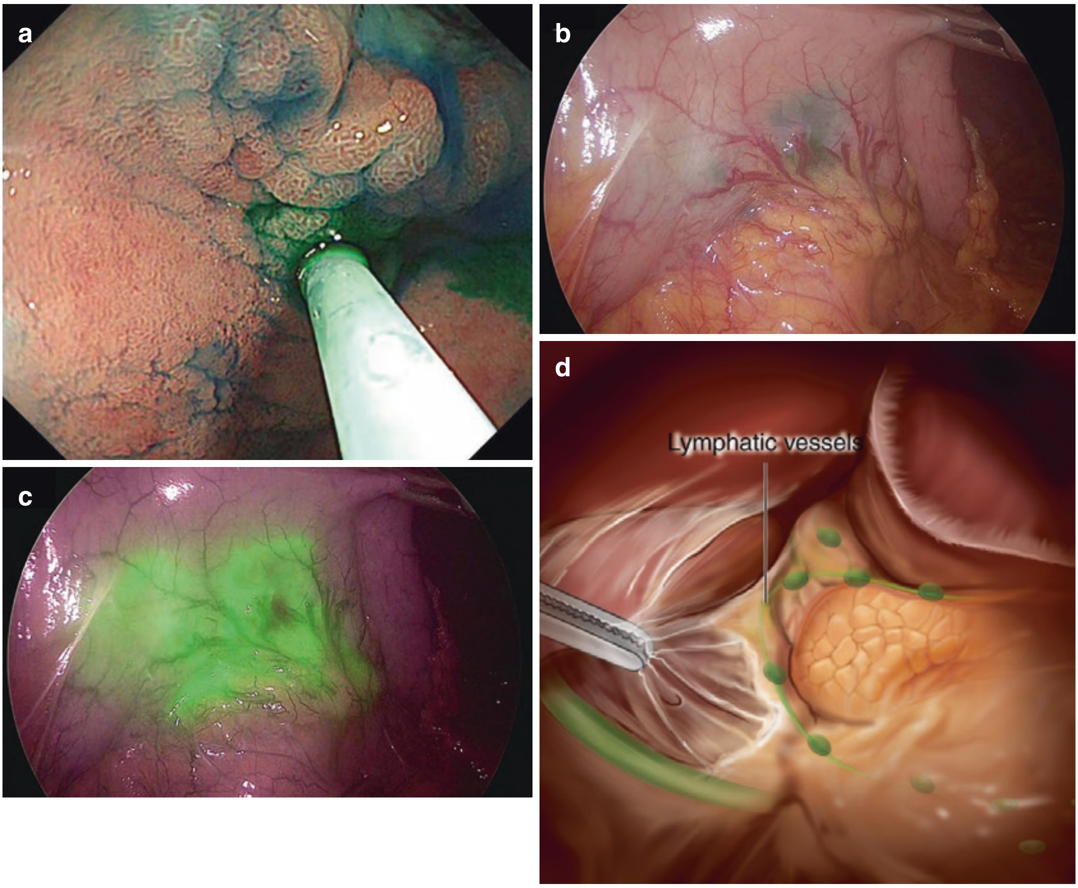

Fig. 7.6 Technique for nonexposed endoscopic wall-inversion surgery (NEWS) with SLN biopsy and sentinel lymphatic basin dissection. (**a**) Indocyanine green (ICG) was endoscopically injected into the gastric submucosal layer surrounding the primary tumor, (**b**) laparoscopic observation of ICG with normal light, (**c**) observation of ICG with infrared ray electronic endoscopy, (**d**) illustration showing ICG within lymphatic vessels and a sentinel lymph node, (**e**) paired intraoperative image showing that infrared ray electronic endoscopy can clearly visualize SNs and lymphatics, (**f**) serosal markings on the primary tumor, (**g**) laparoscopic seromuscular incision around the circumference of the lesion, (**h**, **i**) laparoscopic seromuscular suturing for closure of the circumferential incision and inversion of the primary lesion, (**j**) endoscopic circumferential mucosal incision, and (**k**) endoscopic retrieval of the primary tumor

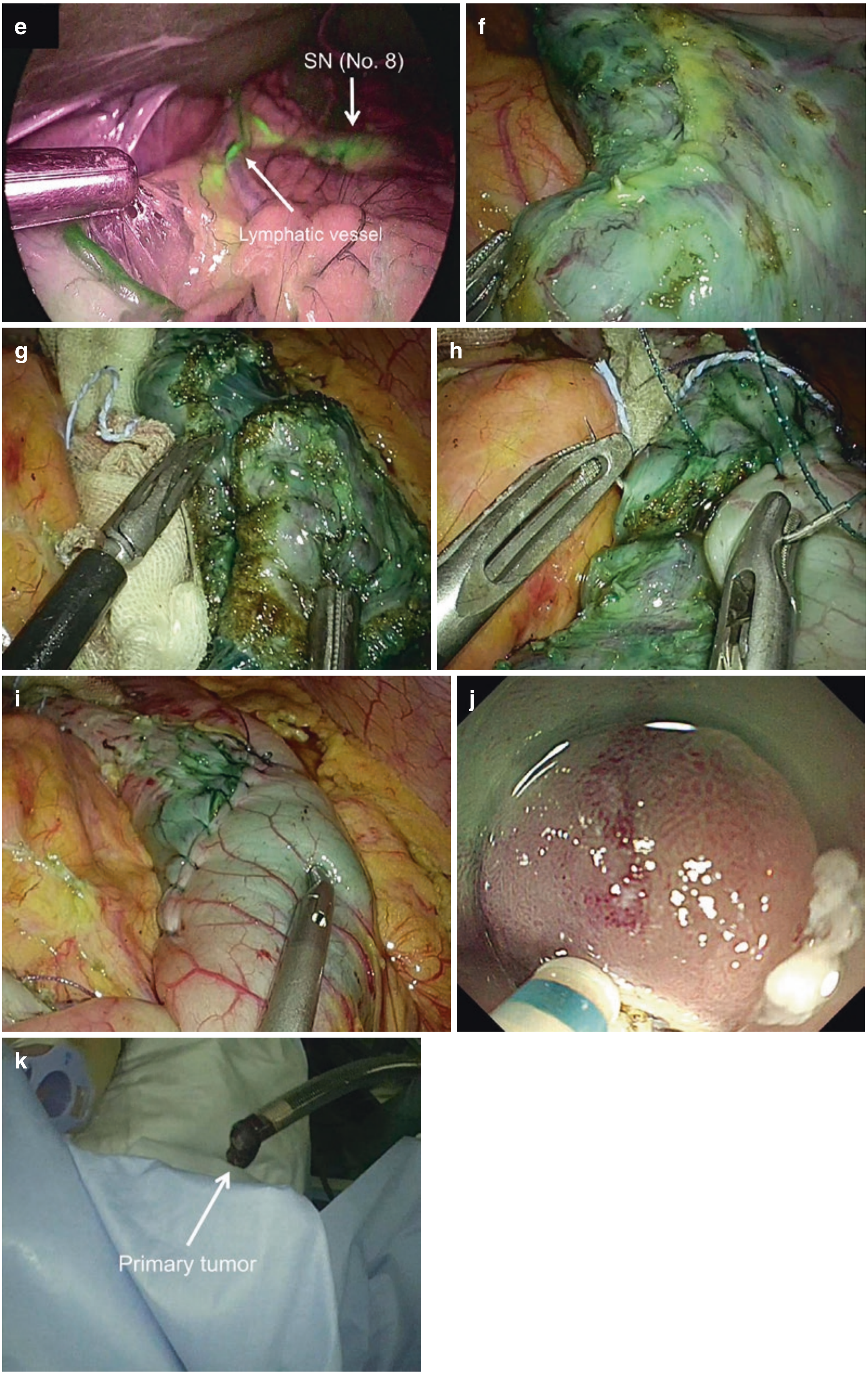

Fig. 7.6 (continued)

Conclusion

For early-stage gastric cancer, the establishment of individualized, minimally invasive treatments that may retain the patients' QOL should be the next surgical challenge. Although further studies are needed for careful validation, function-preserving gastrectomy such as full-thickness partial gastrectomy along with minimally invasive SLN navigation surgery could be a promising strategy for this goal.

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