Minimally Invasive Function-Preserving Gastrectomy with Sentinel Node Biopsy for Early Gastric Cancer

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Keywords

Sentinel node · Gastric cancer · Laparoscopic · Non-exposed endoscopic wall-inversion surgery

Abstract

Background: Recently, minimally invasive approaches such as endoscopic treatment or laparoscopic gastrectomy for early gastric cancer have made rapid progress. However, the extent of gastrectomy and lymphadenectomy in laparoscopic surgery is radical, similar to that of open gastrectomy for patients with early gastric cancer diagnosed as not indicated for endoscopic treatment. Since it is well known that lymph node metastasis is an important prognostic factor, the standard procedure of gastrectomy with radical lymph node dissection has been performed for the purpose of curative resection. The frequency of lymph node metastases is relatively low in patients with early gastric cancer; therefore, function-preserving gastrectomy, a solution between endoscopic treatment and standard gastrectomy in terms of invasiveness, could be considered to avoid excessive invasive surgery. **Summary:** A prospective multicenter trial and meta-analyses of sentinel node (SN) mapping and biopsy for early gastric cancer demonstrated favorable SN detection

rates and accuracy of nodal metastatic status. Personalized function-preserving gastrectomy with limited lymphadenectomy using SN theory will positively impact patients' quality of life (QOL). Specifically, a full-thickness partial gastrectomy by laparoscopic endoscopic cooperative surgery with SN basin dissection could become a reliable technique of minimally invasive gastrectomy for treating patients with clinically node-negative (cN0) early gastric cancer. **Key Messages:** For early gastric cancer, the development of laparoscopic personalized minimized gastrectomy with SN navigation may improve patients' postoperative QOL.

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Introduction

Recently, surgical treatment options for malignant tumors are increasing rapidly due to the improvement of diagnostic technology or the refinement of surgical procedures and devices. Endoscopic submucosal dissection (ESD) has also been performed as a less invasive treatment for cT1 gastric cancer. However, standard gastrectomy with radical lymphadenectomy is generally performed for patients with early gastric cancer diagnosed as

not having an indication for ESD [1]. Although laparoscopic gastrectomy is an intermediately invasive option between ESD and open gastrectomy, patients' quality of life (QOL) is mainly affected by post-gastrectomy syndromes after laparoscopic or open gastrectomy. The development of novel function-preserving, less invasive gastrectomy is essential to reduce perioperative complications and to improve patients' QOL in addition to radical curative resection [2].

Sentinel Node Concept

The sentinel node (SN) is considered as the first lymph node(s) receiving lymphatic drainage from the primary tumor site and is regarded as the first possible node(s) of metastasis from the primary lesion [3, 4]. Theoretically, if SNs are pathologically negative for cancer metastasis, all regional lymph nodes can be predicted as negative for metastasis. Therefore, unnecessary radical lymphadenectomy can be avoided by intraoperative SN biopsy.

In 1992, SN navigation surgery was first applied to melanoma patients using patent blue as a tracer [4]. Minimally invasive surgery performed in accordance with the SN concept can prevent various complications related to unnecessary radical lymph node dissection in cases negative for SN metastasis. The SN concept was subsequently extended to patients with breast cancer or other solid tumors [5–6]. Several studies investigating the SN concept for early gastric cancer showed acceptable SN detection rates and accuracy to predict nodal metastatic status [3, 7]. A large-scale meta-analysis, consisting of 38 studies including 2,128 patients with early gastric cancer, showed that the SN detection rate and accuracy of nodal status diagnosis were 94 and 92%, respectively [8].

Recently, a study group from the Japan Society of Sentinel Node Navigation Surgery (JSNNS) conducted a prospective multicenter trial (UMIN ID: 000000476) to demonstrate the feasibility of SN mapping and biopsy in early gastric cancer [9]. In this study, SN mapping was performed by using dual tracer technique for 397 patients with untreated cT1 or cT2 gastric cancer with primary lesion <4 cm in gross diameter. Following biopsy of the identified SNs, standardized D2 or modified D2 gastrectomy was performed according to current Japanese Gastric Cancer Association guidelines to clarify the accuracy of SN mapping. The study resulted in a SN detection rate of 97.5% and an accuracy for nodal metastatic status of 99.0%. False-negative SN biopsy was observed only in 1.0% (4 of 397), and 3 of 4 patients had primary tumors

with pT2 or >4 cm in size. The study showed that SN mapping for gastric cancer is feasible, reliable, and provides the possibility of using precision medicine based on SN mapping for early gastric cancer. Based on these, a prospective multicenter trial (UMIN ID: 000014401) including our institute about the development of novel strategies by the combination of laparoscopic function-preserving gastrectomy and SN mapping was performed to evaluate the recurrence-free survival, overall survival, and patients' QOL after surgery. This study included clinical T1N0M0 early gastric cancers without indication for ESD with a single primary lesion of less than 40 mm in size to avoid false-negative SN (Fig. 1). In addition, in case of patients with a large primary lesion, it may be difficult to perform stomach-preserving gastrectomy without a postoperative deformity of the remaining stomach. In this study, SN basin dissection, which is a selective lymphadenectomy for en bloc dissection of lymphatic tissue including lymph nodes and vessels, was performed even in patients without SN metastasis to secure the curability of the surgery.

Laparoscopic SN Mapping Procedures

The dual-tracer method using both blue or green dye and radioactive colloids is considered the standard procedure in early gastric cancer patients [2, 9]. The blue or green dye is useful to visualize the lymphatic flow even during laparoscopic surgery. In addition, the accumulation of radioactive colloids in SNs enables the identification of SNs using hand-held gamma probes even in resected specimens. Technetium-99m colloids (tin, sulfur, and antibody sulfur) are preferentially used as radioactive tracers. As dye tracers, isosulfan blue, indocyanine green (ICG), and patent blue are the most frequent options. Moreover, with the recent invention of devices such as the Photodynamic Eye (Hamamatsu Photonics, Hamamatsu, Japan), HyperEye Medical System (Mizuho Medical, Tokyo, Japan), and VISERA ELITE II (Olympus, Tokyo, Japan), ICG fluorescence imaging for SN mapping is currently being used in patients with various types of cancer [10–14].

In our institution, the day before surgery, 2 mL (150 MBq) of technetium-99m tin colloid solution is endoscopically injected into 4 quadrants of the submucosal layer of the primary lesion by using an endoscopic puncture needle. Intraoperatively, the 0.5% ICG solution is also injected in the submucosal layer surrounding the primary lesion in the same manner to function as the radio-

Fig. 1. Study scheme of the clinical trial for laparoscopic function-preserving gastrectomy with SN mapping. SN, sentinel node; ESD, endoscopic submucosal dissection.

active tracer (Fig. 2). Within 15 min after the injection of ICG solution, the lymphatic vessels and lymph nodes are dyed green and visualized. Simultaneously, ICG fluorescence in the lymphatic vessels and lymph nodes is also detected with VISERA ELITE II during laparoscopic operation (Fig. 3). ICG fluorescence imaging enables the easy visualization of SNs and will replace the SN mapping method in many malignancies including gastric cancer [15–17]. Subsequently, a laparoscopic gamma probe introduced from the trocar port is used to locate the radioactive SN. Lymph nodes with radioactivity increased more than 10 times when compared with environmental radioactivity, and are defined as hot nodes. The hot nodes identified by a gamma probe and positive nodes by fluorescence observation are identified as SNs.

Laparoscopic SN Basin Dissection and Precision Medicine

After SN mapping, SN basin dissection is performed. The gastric lymphatic basins are divided into 5 areas along the main arteries as follows: left gastric artery, left gastroepiploic artery, right gastroepiploic artery, right gastric artery, and posterior gastric artery [18]. Harvested SNs are confirmed by fluorescence imaging and gamma probe in resected basins on the back table and subjected

Fig. 2. Intraoperative endoscopic submucosal injection of ICG surrounding the primary lesion. ICG, indocyanine green.

to intraoperative histological examination. Pathological status of SNs and distribution of SN basins provide the necessary information for using precision medicine. If SNs are positive for lymphatic metastasis, standard gastrectomy with radical lymph nodes dissection is per-

Fig. 3. Intraoperative pictures of SN mapping (arrows: SNs, arrowheads: lymphatic vessels). **a** Sentinel lymphatic staining with ICG under ordinary laparoscopy. **b** ICG fluorescence image of the same area. **c** Observation under illumination with infrared ray electronic endoscopy. SN, sentinel node; ICG, indocyanine green.

Fig. 4. Laparoscopic function-preserving gastrectomy with SNBD. **a** Partial gastrectomy with SNBD. **b** Segmental gastrectomy with SNBD. **c** Proximal gastrectomy with SNBD and D1+ lymphadenectomy. SNBD, sentinel node basin dissection.

formed. On the contrary, if SNs are negative for metastasis, function-preserving gastrectomy with SN basin dissection, including partial resection, segmental gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy would be possible for each patient (Fig. 4) [19, 20]. Laparoscopic minimally invasive function-preserving gastrectomy using SN navigation surgery is expected to contribute to the improvement of long-term patients' QOL.

In cases of laparoscopic partial gastrectomy, laparoscopic and endoscopic cooperative surgeries are useful in the determination of the stomach resection line since the demarcation line of the primary tumor cannot be recognized accurately from the outside of the stomach [21, 22]. However, in cancer cases, the full-thickness resection techniques without transluminal access seem to be important to avoid the risk of tumor seeding [23]. Non-exposed endoscopic wall-inversion surgery (NEWS) was developed as a new useful technique of endoscopic full-

thickness resection of the stomach without intentional perforation for early gastric cancer (Fig. 5) [24]. In an ongoing multicenter prospective clinical trial (UMIN ID: 000014401), treatment data of non-exposed endoscopic wall-inversion surgery and SN basin dissection combination have been collected [25]. This strategy is considered to be a promising, ideal, minimally invasive, function-preserving surgical treatment for patients with cT1N0 early gastric cancer.

Present Status and Future Prospects of SN Navigation Surgery for Early Gastric Cancer

The JSNNS study showed that SN biopsy using the endoscopic dual tracer method was safe and effective for the treatment of patients with superficial, relatively small gastric cancers [9]. Ichikura et al. [26] reported that limited gastrectomy with dissection of SN stations for T1N0 gas-

Fig. 5. Intraoperative pictures of non-exposed endoscopic wall-inversion surgery (NEWS). **a** Mucosal markings were endoscopically made around the primary lesion. **b** Serosal markings were made by electric scalpel. **c** Laparoscopic circumferential seromus-

cular incision surrounding the primary tumor. **d** and **e** Laparoscopic seromuscular suturing and inversion of the primary tumor site to the inside of the stomach. **f** Endoscopic mucosal closure using endoscopic clips.

tric cancer was considered safe and acceptable. In contrast, the Japan Clinical Oncology Group (JCOG) also conducted a multicenter prospective trial (JCOG0302) of SN biopsy for cT1N0 gastric cancer [27]. This study was designed to evaluate the feasibility and accuracy of diagnosis using SN biopsy with intraoperative subserosal injection of ICG solution. Patient recruitment was suspended when 440 patients were enrolled because the proportion of false negatives was high. Several causes were involved, including technical problems of the dye-only guided technique with subserosal injection. It might be critical that only 5 cases were required as the minimum experience for the initial learning phase to participate in this study [27].

Similar to our multicenter prospective ongoing clinical trial to assess the long-term survival and postoperative patients' QOL after laparoscopic function-preserving gastrectomy with SN mapping and SN basin dissection, a Korean group has also conducted a prospective multicenter randomized controlled phase III clinical trial (SENORITA trial) to elucidate the oncological safety of laparoscopic stomach-preserving surgery with SN basin

dissection compared to a standard laparoscopic gastrectomy [28]. These proposed trials are expected to verify whether laparoscopic limited gastrectomy with SN basin dissection achieves similar oncological outcomes and improves patients' QOL compared to a standard gastrectomy with radical lymphadenectomy for early gastric cancer patients. A combination of ESD and laparoscopic SN biopsy is another potential option as a novel, whole stomach-preserving minimally invasive treatment when all SNs are pathologically negative for metastasis. In the SENORITA trial, if all the harvested SNs are tumor-free, stomach-preserving primary tumor resection is carried out, including ESD, partial gastrectomy, and segmental gastrectomy. On the contrary, it remains controversial whether SN mapping would be feasible after ESD because the lymphatic flow from the primary tumor site where ESD is performed remains unknown. However, a previous study suggested that at least the SN basin was not markedly changed in patients who underwent ESD prior to surgery [29, 30]. Regarding the combination treatment of ESD and SN biopsy, further studies are required to confirm safety and efficacy.

Results of ongoing Japanese and Korean trials would be expected to establish the ideal, personalized, minimally invasive function-preserving treatment to improve the patients' postoperative QOL with sufficient long-time survival after surgery.

Conclusion

For patients with early gastric cancer, good prognosis is achieved by conventional radical gastrectomy. However, conventional gastrectomy often decreases patients' QOL postoperatively due to post-gastrectomy syn-

drome. In the future, we believe that SN theory could become the ideal treatment option for early gastric cancer patients.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

The present study was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number JP18ck0106300.

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