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Special article

Minimally invasive surgery for gastric cancer — toward a confluence of two major streams: a review

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Abstract
The minimalization of therapeutic invasiveness in order to preserve quality of life (QOL) is a major topic in the management of early gastric cancer. After laparoscopic surgery for gastric cancer was introduced by Kitano et al. in 1991, an enthusiasm to develop laparoscopic procedures has grown steadily. In the initial phase, early gastric cancer limited to the mucosal layer with no risk of lymph node metastasis was treated by laparoscopic wedge resection or intragastric mucosal resection. Since technical and instrumental advances in endoscopic treatment were achieved by gastroenterologists, these cases can be managed by intraluminal endoscopic approaches. The attention of surgeons then shifted to more radical procedures such as laparoscopic gastrectomy with lymph node dissection, which is comparable to open surgery and can be indicated even in advanced cancer. Although this paradigm shift has already been realized in the field of colorectal surgery, we must pay attention to the particular biological nature of gastric cancer in terms of the potential of peritoneal dissemination. While early-phase recovery after surgery has been improved by laparoscopic surgery, preservation of late-phase QOL by function-preserving surgery is also essential in this regard; therefore, the sentinel node (SN) concept has been a much-discussed topic in gastric cancer surgery to approach this aspect. Recently, the validity of the SN concept has been demonstrated by a number of single institutional studies, and prospective multicenter trials are currently ongoing. Theoretically, various types of function-preserving surgery could be applied in cases of early gastric cancer with negative SNs as less invasive surgery to improve long-term QOL. Although we still have to solve several remaining issues in the treatment of gastric cancers, a confluence of these two major streams, laparoscopic surgery and sentinel node navigation surgery, would enable us to apply a novel individualized minimally invasive approach, both in terms of degree of incisional access and extent of function preservation.

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Introduction

The history of laparoscopic surgery for gastric cancer began with the reports of successful laparoscopic distal gastrectomy performed successfully by Kitano in 1991, only a few years after the introduction of laparoscopic cholecystectomy [1]. Laparoscopic surgery appeared as an intermediate option between endoscopic mucosal resection (EMR) and conventional open gastrectomy. In the initial phase, the indications were strictly limited to mucosal gastric cancer with no risk of lymph node involvement. Laparoscopic local resection procedures for these cases were reported by pioneers in the early 1990s [2,3]. Owing to the technical advances in EMR, the indications of laparoscopic local resection for mucosal gastric cancer have gradually decreased. On the other hand, technical and instrumental developments in laparoscopic surgery have allowed more aggressive surgery for gastric cancer with lymph node dissection. Several single institutional studies demonstrated that laparoscopy-assisted distal gastrectomy (LADG) caused less pain and enabled faster recovery and shorter hospital stay, which are parameters of early-phase quality of life (QOL). However, levels of organ function and QOL in the late phase after laparoscopy-assisted gastrectomy should ideally be identical to those of conventional open surgery. From the late 1990s, attempts to solve this issue by individualized function-preserving surgery based on regional lymph node status have focused on the sentinel node (SN) concept as another tributary to the stream of minimally invasive surgery for gastric cancer. Now we must pay attention to both minimal invasiveness for early-phase recovery as well as achieving satisfactory late-phase function after gastric

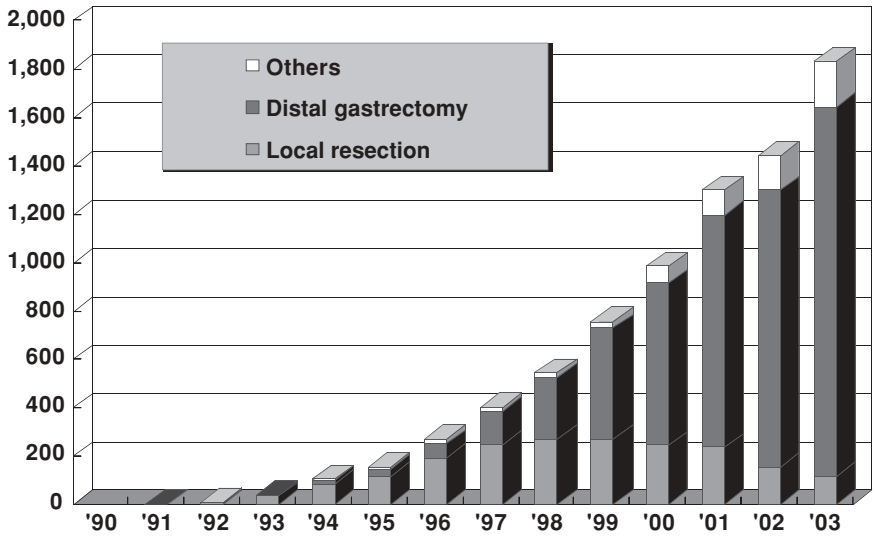

Fig. 1. Nationwide survey of laparoscopic surgery for gastric cancer, 2004. The total number of cases treated by LADG has increased sharply, while the number of cases treated by laparoscopic local resection (LWR and IGMR) has remained unchanged in recent years

cancer surgery. Here we would like to review the past and current status of these two major streams of minimally invasive surgery for gastric cancer and discuss the future direction of this field.

Initial challenges in laparoscopic surgery for gastric cancer

Ohgami and colleagues first developed laparoscopic wedge resection (LWR) of the stomach using a lesion-lifting method [2]. This procedure enables complete local resection with full thickness of the stomach wall and organ preservation by a laparoscopic approach. The indications of this procedure were initially strictly limited to early gastric mucosal cancer with no risk of lymph node involvement. Intragastric mucosal resection (IGMR) developed by Ohashi also enabled a wide range of mucosal resections of lesions located in any part of the stomach except the anterior wall [3]. Although there has been no randomized prospective study to confirm the clinical advantages of these laparoscopic procedures, a survey of the Japan Society for Endoscopic Surgery (JSES) showed limited morbidity (intraoperative: LWR 2.1%, IGMR 4.2%; postoperative: LWR 4.2%, IGMR 6.5%) and no mortality [4,5]. Faster recovery and early discharge from hospital were demonstrated by the survey [4]. The low incidence of local recurrence after LWR and its manageability were also reported [6]. LWR and IGMR have become well accepted as minimally invasive procedures for mucosal gastric cancer since they began to be performed in the early 1990s.

Current trends of laparoscopic gastric cancer surgery

The 2004 national survey conducted by JSES demonstrated that about 7800 patients with gastric cancer underwent laparoscopic surgery from 1991 to 2003 (Fig. 1) [7]. In 2003 LADG, LWR, and IGMR accounted for 83%, 5%, and 1.5% of cases, respectively. The number of instances of LADG has increased rapidly since 1996. Despite the clinical merits of LWR and IGMR, the mode of procedure has been shifted from laparoscopic local resection to laparoscopy-assisted gastrectomy with lymph node dissection, as shown in Fig. 1, mainly because of two reasons. (1) Recent advances in EMR technology, including development of endoscopic submucosal dissection (ESD), have improved local control of mucosal gastric cancer for which laparoscopic local resection was previously indicated [8,9]. (2) Technical and instrumental laparoscopic advances in lymph node dissection enable curative gastrectomy even in cases with potential lymph node involvement [10–12].

Although LWR and IGMR can be technically applicable for submucosal gastric cancer, the limited reliability of preoperative diagnosis of lymph node metastasis in these cases is an obstacle to these applications [13].

Clinical benefits of laparoscopy-assisted gastrectomy for gastric cancer

Compared with conventional open surgery, laparoscopic gastrectomy is reported to have several benefits for patients, including less pain, less inflammatory response, faster recovery of gastrointestinal function,

Table 1. Advantages and disadvantages of laparoscopy-assisted distal gastrectomy in comparison with conventional open surgery

Advantages
Cosmetic benefits
Less pain
Reduced inflammatory response
Faster recovery of bowel function
Less blood loss
Better pulmonary function
Shorter hospital stay
Preserved immune-function
Cost/benefit?
Disadvantages
Complicated procedure
Longer operation time
Cost/benefit?

preserved postoperative immune function, shorter hospital stay, reduced medical costs, and better QOL [14–22] (Table 1). Kitano and colleagues conducted a single institutional prospective randomized study and described several advantages including less pain and better pulmonary function after LADG in comparison with open surgery [23]. Recently Huscher et al. reported the 5-year postoperative results of a prospective randomized clinical trial of laparoscopic versus open subtotal gastrectomy for distal gastric cancer in a total of 59 patients [24]. There is no significant difference in mean number of resected lymph nodes, operative morbidity and mortality, and 5-year overall and disease-free survival between these two groups. Reduced blood loss, shorter time to resumption of oral intake, and earlier discharge from hospital are described in this report as additional benefits of laparoscopic gastrectomy. A large-scale multicenter randomized controlled trial is required to confirm the clinical benefits of LADG. The relatively longer operation time than conventional surgery requires and uncertainty concerning cost benefits are still debated issues.

What are the limits to the indications of laparoscopic gastrectomy?

In March 2001, the Japanese Gastric Cancer Association proposed clinical guidelines for the treatment of gastric cancer in Japan and revised them in 2004 [25,26]. While LADG was recommended for mucosal cancers with limited lymph node metastasis (N1) and submucosal cancers with no or limited lymph node metastasis (N0, N1) in these guidelines, LADG was also described as a practice still under clinical investigation because of the uncertain quality of lymph node dissection and long-term results. Although skilled laparoscopic surgeons demonstrated that complete laparoscopic gastrectomy and D2 lymphadenectomy were technically feasible even in advanced gastric cancer [27], the indications of LADG vary among institutes from cT1N0 to cT2N1 [28]. The extent of lymph node dissection performed with LADG also varies among institutes, from D0 to D2 [28]. Hand-assisted technique is reported as a bridge learning technique to experience laparoscopic surgery [29]. There is a significant learning curve and an entire experienced surgical team including assistants and laparoscopists is required to achieve a stable procedure. Although more complicated laparoscopic procedures such as total gastrectomy and proximal gastrectomy are also technically feasible for experienced surgeons [30,31], these procedures are still not routine in community hospitals.

In colon cancer, advantages of laparoscopic surgery in the early phase after surgery and no impairment of the quality of surgery with regard to long-term survival have been demonstrated [32–34]. Although evaluation of overall cost benefits in laparoscopic colorectal surgery is still controversial [35,36], a major group of laparoscopic colorectal surgeons is oriented to more extensive procedures for more advanced cases. In gastric cancer, however, we must consider the biological behavior of the disease entity including a relatively high risk of peritoneal dissemination, which might be promoted by laparoscopic procedures [37,38]. Recently Hirabayashi et al. demonstrated that cell adhesion molecules integrin and CD44 play an important role in the development of port-site metastasis after laparoscopic surgery and proposed preventive effects through modulation of these molecules [39]. For the further development of laparoscopic gastric cancer surgery, preclinical and oncological research is crucial, in addition to evaluation of the quality control of the procedures.

Function-preserving surgery for gastric cancer: another type of minimally invasive surgery

While early-phase QOL can be improved by laparoscopic surgery, late-phase QOL is more difficult to evaluate as it is closely related to organ and function preservation after surgery. Function-preserving surgery with limited resection extent and modified lymph node dissection has been investigated. In terms of organ preservation, procedures including partial gastrectomy [40], segmental gastrectomy [41], pylorus-preserving distal gastrectomy [42], and proximal gastrectomy [43] should be considered as minimally invasive approaches no matter whether we perform them via laparotomy or laparoscopic surgery. Pylorus-preserving distal gastrectomy and segmental gastrectomy have been reported to

Table 2. Single institutional results of SN mapping for gastric cancer [45–63]

Author	Year	Journal	Method	*n*	Detection rate	Sensitivity
Kitagawa Y et al.	2000	*Surg Clin N Am*	RI	36	97%	100%
Hiratsuka M et al.	2001	*Surgery*	Dye	77	99%	90%
Yasuda S et al.	2001	*Tokai J Exp Clin Med*	RI	26	100%	82%
Ichikura T et al.	2002	*World J Surg*	Dye	62	100%	85%
Kitagawa Y et al.	2002	*Br J Surg*	RI	145	95%	92%
Carlini M et al.	2002	*J Exp Clin Cancer Res*	Dye	40	100%	87%
Hayashi H et al.	2003	*J Am Coll Surg*	RI+Dye	31	100%	100%
Miwa K et al.	2003	*Br J Surg*	Dye	211	96.2%	89%
Gretschel S et al.	2003	*Chirurg*	RI	15	93%	89%
Yasuda S et al.	2003	*Jpn J Clin Oncol*	RI	21	100%	100%
Tonouchi H et al.	2003	*Dig Surg*	RI+Dye	17	100%	100%
Simsa J et al.	2003	*Acta Chir Belg*	Dye	22	100%	56%
Ryu KW et al.	2003	*Eur J Surg Oncol*	Dye	71	92%	100%
Song X et al.	2004	*Am J Surg*	Dye	27	96%	100%
Kim MC et al.	2003	*Hepatogastroenterology*	RI	22	91%	82.2%
Nimura H et al.	2004	*Br J Surg*	Dye	84	99%	100%
Karube T et al.	2004	*J Surg Oncol*	RI+Dye	41	100%	92%
Kim MC et al.	2004	*Ann Surg*	RI	46	93.5%	84.6%
Osaka H et al.	2004	*Clin Cancer Res*	Dye	57	100%	100%

RI, radioisotope-labeled colloid guided method; Dye, dye-guided method

have less frequent dumping syndrome than conventional Billroth I gastrectomy [41,42]. Although limited lymph node dissection and autonomic nerve preservation will help improve functional results after gastric cancer surgery, a certain incidence of skip metastasis in the second or third compartment of regional lymph nodes is an obstacle to the wider introduction of this procedure. As a means to overcome this issue, the sentinel node (SN) concept has attracted attention in recent years and is anticipated to become a novel diagnostic tool for identification of clinically undetectable lymph node metastasis in patients with early gastric cancer.

Introduction of the sentinel node concept in gastric cancer surgery

The first possible sites of metastasis along the route of lymphatic drainage from the primary lesion are known as sentinel nodes (SNs), and these are detectable using injection of either dyes or radioactive tracers, or both. Since Morton et al. demonstrated the concept of SN initially in a feline model, and later in a clinical study involving patients with malignant melanoma [44], the clinical impact of the SN concept has become a major topic with regard to various solid tumors. Until the late 1990s, the application of the SN concept to gastrointestinal (GI) malignancies met resistance because of the multidirectional and complicated lymphatic flow from the GI tract and the relatively high incidence of anatomical skip metastases. In gastric cancer, this clinical evidence supported the validity of D2 lymph node dissection, even for clinically negative node cases.

In the past 5 years, a number of single institutional studies supporting the validity of the SN concept for GI cancers have been reported (Table 2) [45–63]. Despite initial skepticism of experienced GI surgeons concerning this concept in the management of gastric cancer, recent reports support its validity. Unexpected anatomical skip metastases might be accounted for by aberrant drainage routes from primary lesion. Reports indicate that 5%–10% of SNs in cases of gastric cancer are located in the second compartment and not in the perigastric nodes, i.e., the first compartment. Our experience with SN mapping identifying such cases leads us to believe that this technique has great value in identifying these aberrant lymphatic drainage routes in individual patients.

The most common cause for a false negative result of SN mapping in gastric cancer is a lymphatic vessel obstructed by cancer invasion. In these cases, the administered tracer cannot migrate into the real SNs, and its flow will take the path of least resistance, leading it to the second-echelon, or false, SNs. Clinically positive node cases and cases with advanced tumor are not indications for SN mapping for this reason. The most important message from our experience in the recent 5 years is that SN mapping is useful to find clinically undetectable micrometastasis in cT1N0 gastric cancer and that it may change the overall therapeutic approach to this entity.

Multicenter prospective validation study of the SN concept in gastric cancer

Several types of dye and radioactive colloids are used as tracers to detect SN in gastric cancer in the case of various other solid tumors, and consensus has yet to be reached concerning various aspects of the actual procedures, such as the type of dye and colloid, the injection routes (submucosal or subserosal), tracer volume, and observation timing. As with SN mapping of other organs, we must confirm the reliability of the procedure by multicenter prospective clinical trials before the introduction of this technology to actual patient care for gastric cancer. Isozaki and colleagues reported the results of a regional multicenter clinical trial of SN mapping for gastric cancer using the conventional dye-guided method [64]. Although the patient population enrolled in that study was limited, this first multicenter trial of SN mapping for gastric cancer provides several important messages. This study was designed to investigate the feasibility of SN mapping for gastric cancer using the dye-guided method as a simple method that can be conducted even in community hospitals without special equipment. Although the false negative rate reported in the study (29% in T1, 44% in T2) appears disappointing, we must take some extenuating circumstances into account when interpreting the data. The most serious limitations of this study were the inclusion criteria for the participating institutes in terms of prior experience with SN mapping for gastric cancer. In the field of breast cancer surgery, the significance of the technical learning curve for the technique has already been clearly demonstrated. Cox et al. suggested that a 30-case experience with a detection rate of 90% or more is a minimal requirement for institutes to participate in a multicenter study of SN mapping for breast cancer [65]. In the study conducted by Isozaki et al., the learning phase for the procedure had not been completed by most of the participating institutes. Therefore, the relatively high false negative rates demonstrated in this study may be attributed to lack of technical expertise in the initial learning phase. Despite this study design limitation, false negative rates for patients with T1 and sN0 (11%) were similar to those of previous single-institutional reports, lending support to the idea that dye-guided SN mapping may be feasible for T1 sN0 patients after the establishment of a standard procedure and the completion of the learning phase, at least with open surgery.

Recently a poorly designed multicenter prospective trial of SN mapping for colorectal cancer was published with disappointing results [66] (false negative rate: 54%). It is clear that the inappropriate inclusion criteria, which allowed inclusion of patients with advanced tumors, in addition to technical errors in the initial learning phase in participating institutes with limited experience, may well have caused this discouraging result. Fortunately, two major, well-designed large-scale clinical trials of SN mapping for gastric cancer for open surgery have been initiated in Japan. The Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG) organized a multicenter prospective study of SN mapping by the dye-guided method using subserosal injection of indocyanine green. A study group in the Japan Society of Sentinel Node Navigation Surgery (SNNS) is also conducting a multicenter prospective trial of SN mapping by a dual tracer method with blue dye and radioactive colloid. The results of these clinical trials should provide perspectives on the future direction of SN navigation surgery for gastric cancer. If the JCOG study reveals favorable results in terms of false negative rates, the dye-guided method will be utilized as a routine practice for open surgery in a wide range of institutes. If not, we will need to consider introduction of a radio-guided method or add further technical improvements, even for open surgery. Even if the SNNS study demonstrates acceptable detection rates and low false negative rates, we need to conduct a feasibility study of laparoscopic SN mapping for gastric cancer as the next step.

Current clinical applications of the sentinel node concept for gastric cancer

Before actual validation of the SN concept by well-designed large-scale multicenter prospective trials, it may be early to apply less-invasive operative approaches without conventional lymph node dissection for cases with a potential risk of micrometastasis in regional lymph nodes. The concept of a "sentinel lymphatic basin," proposed by Miwa [52], can provide us with an acceptable "safety net" for clinical application during this transitional phase. Prior reports have demonstrated that sentinel lymphatic basins contained truly positive nodes, even in the cases with a false negative SN biopsy. Therefore, the sentinel lymphatic basins are good targets for focused lymph node dissections for cT1N0 gastric cancer. The distribution of sentinel lymphatic basins and the status of SNs would be useful information to decide on the extent of gastric resection. Appropriate indications for proximal gastrectomy, segmental gastrectomy, pylorus-preserving gastrectomy, and partial resection for cT1N0 gastric cancer could be individually determined based on this concept. The extent of resection and lymph node dissection for carcinoma of the esophagogastric (EG) junction can be decided by location and the status of SNs [67]. These approaches have attracted the interest of Western institutes where the incidence of adenocarcinoma of the EG

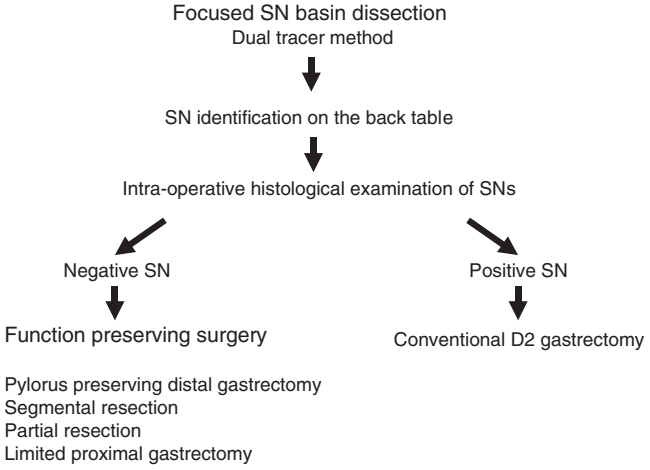

Fig. 2. Current individualized strategy for early gastric cancer based on sentinel-node (*SN*) navigation

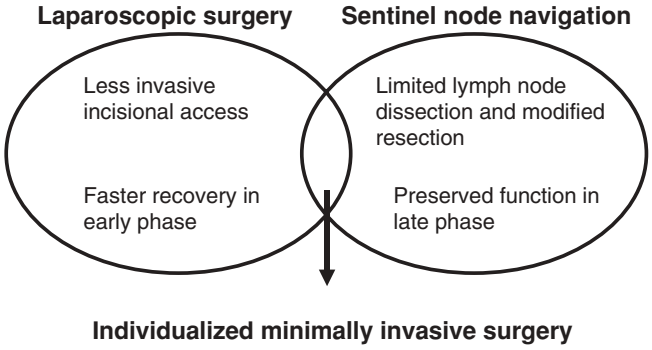

Fig. 3. Confluence of two major streams of minimally invasive surgery for gastric cancer

junction is increasing. These variations of tailored surgery are already feasible in open surgery. Our current strategy for early gastric cancer using SN navigation during this transitional phase is summarized in Fig. 2 [68].

Laparoscopic sentinel node navigation surgery: a confluence of two major streams

Theoretically, earlier recovery after surgery and preservation of QOL in the late phase can be achieved by laparoscopic SN navigation surgery, as shown in Fig. 3. We have introduced laparoscopic pylorus-preserving gastrectomy combined with SN mapping as individualized minimally invasive laparoscopic surgery [69]. In this procedure, the indications of pylorus preservation will be determined by the distribution and status of SNs. In the near future, laparoscopic wedge resection for SN negative superficial gastric cancer will be feasible as minimally invasive surgery. Recently reduced indication of LWR could be expanded to SN negative submucosal gastric cancer.

A combination of EMR or ESD and SN mapping for superficial gastric cancer is another attractive challenge as a less-invasive approach. At this moment, we do not have data on the reliability of SN mapping for the cases with scars after EMR/ESD. Laparoscopic SN mapping and consequent intraoperative EMR/ESD for SN negative cases is likely to soon become an accepted approach. To realize these future clinical applications, there are several remaining issues that require solution.

Laparoscopic SN mapping is still under development owing to various technical and material limitations [70]. Currently available rigid-type laparoscopic gamma probes are fixed by the entry-trocar, thus freedom to search for SN, and to avoid a "shine through" effect from the injection site, is seriously restricted. At present, laparoscopic SN detection is feasible for cases with lesions on the greater curvature of the middle or lower part of the stomach. In cases of carcinoma at the EG junction, a flexible type of gamma probe is required for accurate sampling of SNs.

The clinical significance of micrometastasis and isolated tumor cells in regional lymph nodes with gastric cancer is still controversial. Unlike multimodal options for preventing axillary lymph node recurrence in breast cancer, it is difficult to control lymph node recurrence in patients with gastric cancer. It is essential to deal with micrometastasis and isolated tumor cells in SNs in patients with gastric cancer. The sensitivity of intraoperative histological examination of SN is still unsatisfactory [71]. Although the issue of a false positive study is still controversial, intraoperative utilization of real time reverse transcriptase polymerase chain reaction (RT-PCR) to detect molecular metastasis might well be a useful technology for safer clinical application of the SN concept in GI cancer. We must clear up these unresolved issues very carefully as we proceed.

Conclusions

For early-stage gastric cancer in which generally better prognosis was achieved by conventional surgical approaches, an individualized minimally invasive surgery should be established as the next surgical challenge of the twenty-first century. A combination of laparoscopic surgery with SN navigation surgery has the potential to achieve this goal.

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