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REVIEW

Update on the indications and results of sentinel node mapping in upper GI cancer

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Abstract

The clinical utilization of sentinel node (SN) mapping for early esophageal cancer or gastric cancer has been unclear for a long time. However, previous investigations regarding SN mapping of these cancers have shown relatively good results with regard to the detection rate and diagnostic accuracy for determining the lymph node status. SN mapping helps obtain information about individual metastatic status and allows the modification of the operation in early-stage upper gastrointestinal (GI) disease. Radio-guided methods for identifying SNs in early esophageal cancer have been established via endoscopic injection of technetium-99m tin colloid. Previous studies have reported that the SN concept seems valid, and radio-guided SN mapping can be feasible in cT1N0 esophageal cancer. SN navigation surgery are believed to have potential as strategies for minimally invasive modified surgery for early esophageal cancer. A Japanese study group conducted a prospective multicenter trial of SN mapping for early gastric cancer using a dual tracer method with radioactive colloid and blue dyes; they demonstrated a high detection rate and accuracy for determining the metastatic status based on SN mapping. Subsequently, minimized gastrectomy, including partial gastrectomy and segmental gastrectomy with individualized selective and modified lymphadenectomy for early gastric cancer with a negative SN has been performed to evaluate the long-term survival and postoperative quality of life (QOL) in a multicenter prospective trial. This study verified the SN concept in early-stage upper GI disease with cN0 and found that function-preserving esophagectomy or gastrectomy may help maintain patients' post-surgical QOL.

Keywords Sentinel node · Esophageal cancer · Gastric cancer

Introduction

The clinical utilization of sentinel node (SN) mapping for early-stage esophageal cancer or gastric cancer has been unclear. However, many investigations have already shown that SN mapping of these cancers provides good detection rate and accuracy in determining lymph node status. SN mapping makes an important contribution to the achievement of information about individual metastatic status and enables the modification of the operation in early-stage upper gastrointestinal (GI) disease.

Esophageal cancer

Esophageal cancer is a type of severe malignant cancer, and lymph node metastasis is considered an important predictor of esophageal cancer. As a characteristic of esophageal malignant tumor, in addition to the multi-directional lymphatic route from the primary tumor, there is a complicated pattern of lymph node metastasis from the cervical to the abdominal region [1]. Furthermore, lymph node metastasis is also observed in early stage esophageal cancer, such as pT1b disease [1]. Considering these clinical features, total esophageal resection with two- or three-field lymphadenectomy is currently considered a standard therapy even for cN0 esophageal cancer [1, 2]. However, even though the

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technique of thoracoscopic and laparoscopic procedure have been developed, esophagectomy with extended lymphadenectomy remains one of the high invasive surgery in GI malignancies [3–5]. In order to rule out the universal utilization of these surgeries, SN mapping plays an important role by providing individual information to enable the modification of the surgical tool [6].

SN mapping procedures in esophageal cancer

Generally, in order to identify SNs in esophageal cancer, the radio guide method is more suitable than the conventional blue dye method [7–9]. As per our protocol, we endoscopically inject 2 mL technetium-99 m tin colloid solution (150 MBq) into the submucosa of the gastric wall around the primary lesion in four quadrants using a puncture needle on the day before the surgery. Preoperative lymphoscintigraphy can be performed 3–4 h after the administration of the tracer injection.

Intra-operative SN biopsy is performed using a handheld gamma-probe. Gamma probing can also be performed with SN thoracoscopy or laparoscopy using a special gamma-detector that can be introduced from the trocar ports. Percutaneous gamma probing can be used to identify the SNs located in the cervical area. We carefully investigate the residual SNs in the resected specimens using a gamma-probe and subject all SNs to intraoperative pathological examination. These tasks are performed on a back table.

In esophageal cancer on the abdominal region or adenocarcinoma (AC) of the esophagogastric (EG) junction, we adopt the dual tracer method of the radioactive tracer and blue dye (indocyanine green or isosulfan blue) mainly for SN detection [10]. We endoscopically inject a blue-dye into the submucosal layer of the primary tumor immediately after beginning the surgery. Subsequently, after the tracer has passed through the afferent lymphatics, we identify blue-stained nodes as the SNs approximately 15 min after the injection is administered.

The mediastinal lymph nodes of the thoracic esophagus often pigmentate due to anthracosis; therefore, it is inappropriate to use dye-guided SN mapping for patients with esophageal cancer in the thoracic esophagus. Moreover, without the operative mobilization of the esophagus, real-time observation of the lymphatic pathway using blue dye is impossible; however, mobilization itself may have adverse effect on the active lymphatic flow from the primary tumor. Moreover, the intraoperative radio-guided method is reliable and valuable when evaluating the lymphatic system of esophageal cancer. In contrast, in addition to the radio-guided method, the blue dye method is useful in abdominal esophageal cancer or EG junction cancer because it can relatively easily identify blue-stained lymphatic vessels and lymph nodes without the mobilization of the esophagus in the abdominal cavity compared with that in the mediastinum. Furthermore, pigmentation due to anthracosis is relatively rare in abdominal lymph nodes.

Results of the SN mapping for esophageal cancer

Thus far, numerous single-institution investigations, including our study, have demonstrated important advantages of SN mapping for early esophageal cancer, particularly when utilizing the radio-guided method (Table 1). Clinically T1 esophageal cancers were appropriate targets for SN mapping. However, clinically T3 or T4 tumors, as well as those with clinically evident lymph node metastasis, in which the original

Table 1 Representative results of sentinel node biopsy for esophageal cancer using radio-guided methods

Author (Ref.)	Year	Tracers	Tumor depth	Number of patients	SN detection rate (%)	Sensitivity (%)	Accuracy (%)
Kato et al. [37]	2003	RI (^{99m} technetium rhenium sulfide)	pT1–T4	25 SCC	23/25 (92)	13/15 (87)	21/23 (91)
Yasuda et al. [38]	2003	RI (^{99m} technetium tin colloid)	pT1–T3	23	23/23 (100)	9/12 (75)	20/23 (87)
Lamb et al. [12]	2005	RI(^{99m} technetium nanocolloid)	ND	57 Adeno	57/57 (100)	35/37 (95)	55/57 (96)
Takeuchi et al. [9]	2009	RI (^{99m} technetium tin colloid)	cT1–T2	75 SCC + adeno	71/75 (95)	29/33 (88)	67/71(94)
Kim et al. [39]	2011	RI (^{99m} technetium Neomannosyl HSA)	cT1–T4	23 SCC	21/23 (91)	8/8 (100)	21/21 (100)
Thompson et al. [14]	2011	RI (^{99m} technetium antimony colloid)	pT1a–T3	16 SCC + adeno	14/16 (88)	3/3 (100)	16/16 (100)
Uenosono et al. [15]	2011	RI (^{99m} technetium tin colloid)	cT1–T3	134 SCC + adeno	120/134 (90)	36/57 (63)	99/120 (83)
Takeuchi et al. [40]	2015	RI (^{99m} technetium tin colloid)	pT1	70 SCC + adeno	65/70 (93)	22/24 (92)	63/65 (97)

RI radioisotope, *ND* not determined, *HSA* human serum albumin, *SCC* squamous cell carcinoma, *Adeno* adenocarcinoma

lymphatic routes can be obstructed and altered, led to a high rate of false-negative findings. Therefore, we should exclude cT3 or T4 from the indication for SN mapping.

To evaluate the feasibility of SN biopsy, we performed SN mapping for clinical T1N0 or T2N0 esophageal cancer using radioisotope [9]. SNs were detected in 71 of 75 patients (95%), and the accuracy was as high as 94% in our study. SN mapping was as successful as conventional surgical procedures even during thoracoscopic esophagectomy [9]. Further, it was confirmed that the identified SNs were widely spread from the cervical to the abdominal areas, especially in esophageal squamous cell carcinoma (SCC) [9]. In more than 85% of thoracic esophageal carcinoma cases, one or more SNs spread to the second or third compartment of regional lymph nodes [9]. Generally, lymphatic stations that allow higher metastatic rate in pathological findings were often identified as SNs.

However, in the AC, the SNs are known to be distributed in the peri-esophageal tissue and the abdominal nodes. Grotenhuis et al. [11] indicated a high rate of false-negative (15%) for the SNs in the AC. It may be associated with employing dye-guided SN mapping alone as well as the transhiatal approach that limited lymphadenectomy of the supra-cranial lymph nodes; further, the fact that it comprised a high number of T3 tumors (65%) could account for the low accuracy rate. In contrast, remarkable results were found for SN mapping in 57 patients with AC by Lamb et al. [12]. Burian et al. [13] also showed the feasibility and reliability of SN biopsy in patients with AC located on EG junction. SN mapping may be suitable for patients with AC of the distal esophagus or the EG junction [10].

Generally, accurate diagnosis of lymph node metastasis by performing lymphadenectomy is needed for staging after neoadjuvant treatments and identifying the pattern of nodal metastasis after preoperative therapy could be helpful for planning the surgical procedures. Thus, if the SN techniques can be applied to identify the remaining pathologic lymph nodes after preoperative treatment, extended lymphadenectomy can be avoided, or using SN to establish a new pathological staging disease. Thompson et al. [14] did not indicate any differences between patients who did and did not receive neoadjuvant therapy and difficulty of SN detection. In contrast, Uenosono et al. [15] concluded that esophagectomy using SN mapping is unsuitable for patients who have undergone neoadjuvant chemoradiotherapy because it has a low detection rate and is sensitive for the prediction of metastasis.

Future application of SN mapping in esophageal cancer

SN mapping would provide important information for individualized selective lymphadenectomy without adversely affecting the prognosis. For example, dissection of the cervical lymph nodes is expected to be unnecessary if the SNs are confined to the mediastinum nodes or the abdominal nodes and if there are no pathologically positive SNs in patients with cT1N0 middle or lower thoracic esophageal cancer [9].

In addition, in patients with AC of the distal esophagus or the EG junction, SN mapping and biopsy will be adaptable and reliable [10]. We believe that SN mapping and biopsy for these patients is useful for coordinating and modifying the surgical procedures. For example, if the SNs are identified only in the abdominal area and are pathologically negative in cases with cT1N0 AC of the distal esophagus, we would perform limited resection of the distal esophagus via the laparoscopic transhiatal approach without extensive mediastinal lymph node dissection [9, 10]. However, if the SNs are positive for metastasis during intraoperative diagnosis, we should perform extended thoracoscopic lymphadenectomy. This new method may achieve balance both in the reduction of morbidity and in maintenance of quality of life (QOL) in early esophageal cancer patients with pathologically negative SNs.

Gastric cancer

In eastern Asian region, laparoscopic distal gastrectomy and laparoscopic total gastrectomy are currently performed for patients with early-stage gastric cancer [16–19]. Advanced laparoscopic gastrectomy has contributed in terms of early postoperative recovery and better esthetic outcomes [20]. However, the patients' QOL could be mainly affected by late-phase function, such as the prevention of dumping syndrome or weight loss. Thus, we should carefully consider both minimal invasiveness.

The function-preserving gastrectomies with limited gastric resection and lymphadenectomy may be useful for improving the postoperative late-phase function. For instance, partial gastrectomy, segmental gastrectomy, and proximal gastrectomy are representative examples. However, the use of such treatment is limited by the skip metastasis in the second or third compartment of regional lymph nodes. To resolve these obstacles, the SN mapping concept is expected to serve as a new diagnostic tool for identifying clinically not-identifiable lymph node metastasis.

Although the clinical utilization of SN mapping for patients with early-stage gastric cancer has been examined recently, the SN detection rate and their accuracy were considered acceptable based on the results of single-institution studies, including ours and those from a recent multicenter trial of SN mapping [7, 21]. Based on these results, we aimed to establish a novel, laparoscopic, minimally invasive SN navigation surgery in patients with early gastric cancer.

Laparoscopic SN mapping procedures

A dual-tracer method is one of most dependable system for visualization of SN in early gastric cancer. It utilizes blue dyes combined with radioactive colloids [21, 22]. Radioactivity could be monitored easily using a hand-held gamma probe even in resected specimens, and we also clearly visualized the lymphatic flow using blue dyes during the laparoscopic gastrectomy. Technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid are preferentially utilized as radioactive tracers. Isosulfan blue, patent blue, and indocyanine green (ICG) are the currently favored choices as dye tracers.

Generally, we perform SN mapping and biopsy for patients with cT1 (or T2) tumors, primary single lesion < 4 cm in diameter, and cN0 gastric cancer. In our institute, we endoscopically inject 2 mL (150 MBq) technetium-99m tin colloid solution into the gastric submucosal around the tumor in four quadrants using a puncture needle the day before the surgery. The use of an endoscope enables the accurate injection of the tracer. After topical administration, technetium-99m tin colloid with a relatively large particle size accumulates in the SNs.

At the initiation of the surgical procedure, an endoscopic puncture needle is used to inject the blue dye into the four quadrants of the submucosal layer of the primary site. Blue lymphatic vessels and blue-stained nodes can be recognized with laparoscopy within 15 min of administering the blue dye injection. Simultaneously, as with esophageal SN mapping, we use a hand-held gamma probe to locate the radioactive SNs. By using a special gamma detector that can be introduced from the trocar port, we can perform intraoperative gamma probing in laparoscopic gastrectomy.

In order to perform intraoperative SN sampling, the pick-up method is well established for the identification of melanoma and breast cancer. However, the clinical utilization of intraoperative SN sampling for gastric cancer requires the incorporation of sentinel lymph node dissection, a type of lymphadenectomy that includes hot and blue nodes [21, 22]. The gastric lymphatic compartments were believed to be divided according to the following five directions along the main arteries: left gastroepiploic artery area (l-GEA), right gastroepiploic artery area (r-GEA), left gastric artery area (l-GA), right gastric artery area (r-GA), and posterior gastric artery area (p-GA) [23].

It is known that ICG has excitation and fluorescence wavelengths in the near infrared range [24]. Some studies have attempted to evaluate this new tracer method for clinical application of laparoscopic SN biopsy using an infrared ray electronic endoscopy (IREE) [24, 25]. Recently, ICG fluorescence imaging has emerged as an alternative technique for SN biopsy [26, 27]. Compared to that with the naked eye, ICG fluorescence imaging enables easy visualization of SNs. Although more studies are needed to evaluate the clinical usefulness of this revolutionary method compared with that of radio-guided methods, it will upset the SN mapping strategy not only in gastric cancer but also in several malignancies.

Results of SN mapping for gastric cancer

To date, many researchers have shown acceptable results for SN mapping in early-stage gastric cancer with respect to SN detection rate (90–100%) and accuracy of lymphatic determination (85–100%) based on single-institution studies; these outcomes are equivalent to those of SN mapping for melanoma and breast cancer [22]. Wang et al. evaluated the diagnostic value of SN biopsy for gastric cancer [28]. The results of their large-scale meta-analyses that included 38 related studies of 2128 patients showed that the SN detection rate and prediction accuracy of lymph node metastasis based on the SN status were 94% and 92%, respectively [28]. They indicated that the SN concept has technical feasibility when a combination of tracer and submucosal injection methods during SN biopsy procedure was used, especially for cases with early T stage (T1).

A Japanese study group conducted a multicenter prospective study of SN mapping using a dual-tracer method with a blue dye and radioactive colloid [21]. In this study, SN mapping was performed for about 400 early gastric cancer patients in 12 general hospitals, including our institution. Patients with cT1N0M0 or cT2N0M0 single tumor of primary lesions < 4 cm in size and with previous untreated history were eligible. The SN detection rate was 98%, and the detection accuracy for the metastatic status was 99% [21]. Results of clinical trials provided great expectation in SN navigation surgery in the future.

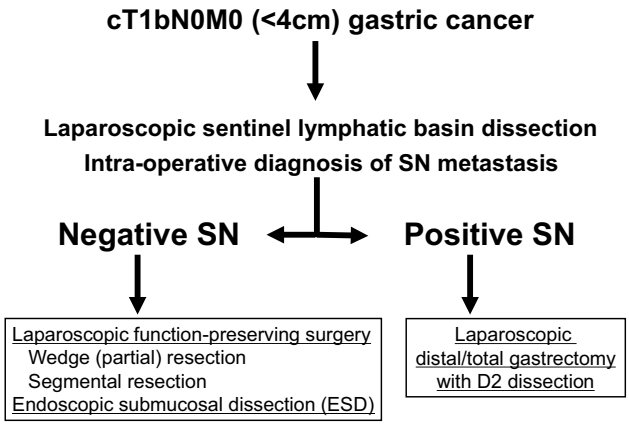

Fig. 1 Individualized function-preserving approaches for cT1bN0M0 gastric cancer based on sentinel node (SN) mapping. *ESD* endoscopic submucosal dissection

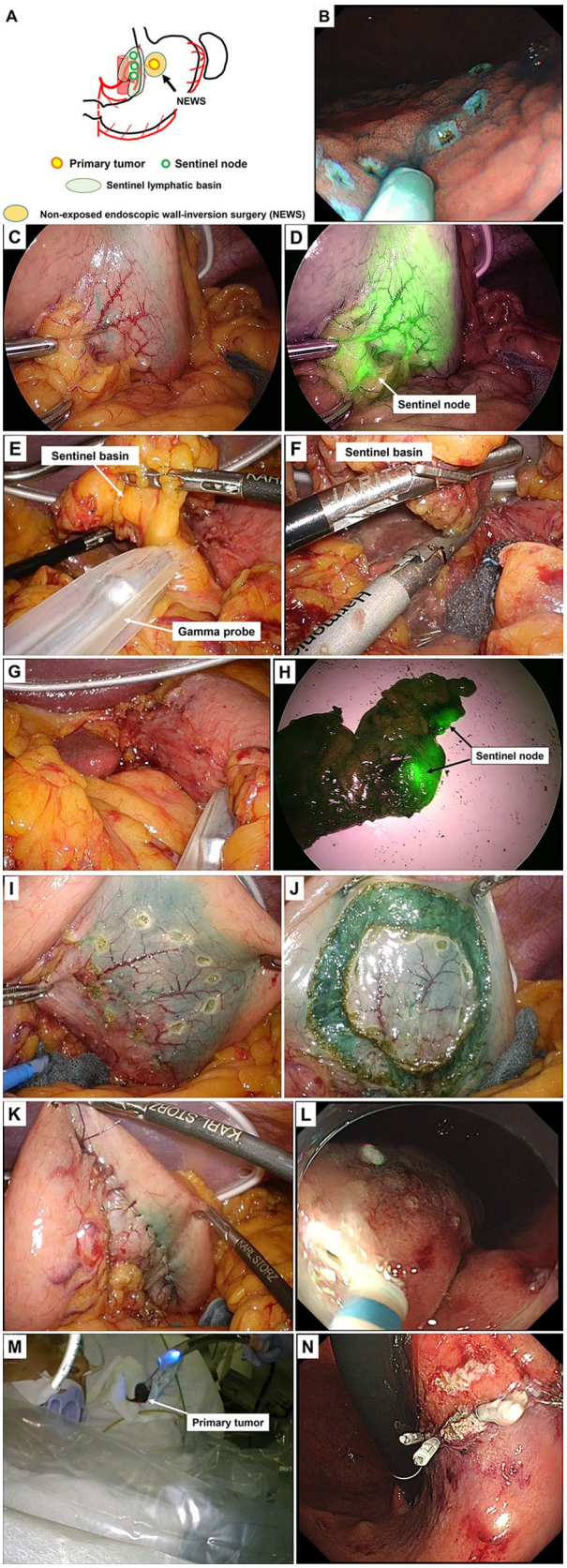

Fig. 2 **a** Schema of non-exposed endoscopic wall-inversion surgery (NEWS) with SN biopsy and sentinel lymphatic basin dissection. **b** Indocyanine green (ICG) is endoscopically injected into the gastric submucosal layer surrounding the primary tumor. **c** Laparoscopic observation of ICG with normal light. **d** Observation of ICG with infrared ray electronic endoscopy. Infrared ray electronic endoscopy can visualize SNs and lymphatics clearly. **e, f** Intraoperative gamma probing and sentinel lymphatic basin dissection including SNs. **g** Sentinel lymphatic basin (#1, #3a, and #7 lymph nodes) including the root of left gastric artery is completely dissected. **h** Identification of SNs with ICG using infrared ray electronic endoscopy on the back table. **i** Circumferential serosal marking surrounding the primary tumor. **j** Laparoscopic circumferential sero-muscular incision. **k** Laparoscopic sero-muscular suturing and inversion of the primary lesion. **l** Endoscopic circumferential mucosal incision surrounding the primary tumor. **m** The detached primary lesion is retrieved perorally. **n** The mucosal edges are closed with several endoscopic clips

Clinical application of laparoscopic SN mapping for early gastric cancer

Knowledge regarding the topographical pattern of sentinel lymphatic basins and the pathological state of SNs helps determine the minimum extent of gastrectomy and avoid radical resection, including distal or total gastrectomy with D2 dissection. We could individually determine the precise indications for laparoscopic surgeries, such as partial (wedge) resection, and segmental gastrectomy for cT1N0 gastric cancer, based on the SN status (Fig. 1) [29, 30]. Laparoscopic limited gastrectomy using SN navigation enables the maintenance of the patients' QOL in the late phase and contributes to early recovery after surgery. Our study group is beginning a multicenter prospective trial to evaluate function-preserving gastrectomy with SN mapping in terms of long-term survival and patients' QOL.

Another potential option of a novel, whole stomach-preserved, minimally invasive approach is the combination of laparoscopic SN biopsy and endoscopic submucosal dissection (ESD) for early gastric cancer. If all SNs are pathologically negative for cancer metastasis, ESD may theoretically be sufficient for the curative resection of cT1 gastric cancer beyond the ESD criteria instead of radical gastrectomy [11, 20]. However, further studies are warranted to confirm the safety and efficacy of the combined approach involving laparoscopic SN biopsy and endoscopic treatment.

Whether SN mapping can be performed after ESD is debatable. In particular, whether ESD affects the pattern of lymphatic route from the primary tumor to the original SNs is still unknown. However, in our preliminary study, the sentinel lymphatic basin was not markedly affected by previous ESD [31, 32]. Even in patients who underwent ESD before surgery, modified gastric resection based on the SN concept may be an adequate method.

A recently emerging new technique called non-exposed endoscopic wall-inversion surgery (NEWS) is a technique of partial gastrectomy that minimizes the extent of gastric

resection using endoscopy and laparoscopy. Since NEWS treats the gastric cancer without opening the gastric wall, it is considered useful for preventing peritoneal dissemination of the cancer cells [33]. We have been collecting data of NEWS cases with SN biopsy for early gastric cancer in the multicenter prospective trial in Japan (Fig. 2) [33, 34]. The combination of NEWS and SN biopsy for the treatment of patients with cN0 early gastric cancer is expected to be established as a promising, ideal minimally invasive, function-preserving surgery [35, 36].

The next surgical challenge in early gastric cancer that can achieve better prognosis by conventional surgical approaches is the establishment of individualized minimally invasive treatments that may preserve the patient's QOL. Although further research is necessary for careful validation, we have high expectation for SN navigation surgery as a promising strategy to achieve this goal.

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