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REVIEW ARTICLE

Sentinel Node Navigation in Gastric Cancer: Where Do We Stand?

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Abstract

Background Early gastric cancer (EGC) is more common nowadays and is related a to low percentage of lymph node metastasis. For this reason, there is enormous interest to implicate minimally invasive approaches. Recently, special efforts have been made towards a potential intraoperative (real-time) lymph node metastasis (LNM) assessment, as nodal disease status could not be identified with precision before or during surgery. In this direction, accurate prediction of the LNM status through sentinel LN mapping has been attempted, as an approach to the intraoperative detection of sentinel lymph nodes (SLNs). A careful literature search was conducted in order to clarify the potential clinical application of SN biopsy in the gastric cancer field.

Conclusion The real clinical application of SN biopsy in gastric cancer treatment has been more than challenging due to the "complicated" nature of gastric lymphatic drainage and the high possibility of "skip" metastasis phenomenon. Notably, sophisticated technical aspects, such as the preferred tracer used and the potential "ideal" method to verify the presence of metastases in the resected SLNs, made SN biopsy application in gastric cancer field extremely demanding. Assessing the potential role of SN navigation for gastric cancer treatment in the era of advanced technology, where the minimally invasive surgical approaches are in the top of the scientific interest, it has to be highlighted that SN navigation for gastric cancer is a topic that remains highly controversial, and the need for future clinical trials on this topic is obvious.

Keywords Gastric cancer · Sentinel lymph node · Lymphadenectomy · Minimally invasive surgery · Sentinel node navigation

Introduction

Gastric cancer (GC) is the fifth most common cause of cancer worldwide with an estimated incidence of around 952,000 cases per year [1]. It is the third leading cause of cancer death in both sexes worldwide accounting for 8.8% of the total deaths from all causes of malignancy [1]. Undoubtedly, the main prognostic factor for patients with GC is lymph node involvement [2]. With the advent of minimally invasive surgery, a shift towards more personalized treatment of GC has been advocated, with the intention of achieving better treatment efficacy for patients with early or advanced disease [1, 2]. It is reported that early gastric cancer (EGC) is more common nowadays and is related a to low percentage of lymph node metastasis. In this way, there is enormous interest to implicate minimally invasive techniques especially for this type of cancer [1, 2]. However, the appropriate extent of lymphadenectomy for gastric adenocarcinoma remains debatable up to date. In high incidence countries in Eastern Asia, more extensive (e.g., D2, D2+) lymphadenectomies represent the standard of care [2]. On the other hand, in the USA and Western Europe, where the incidence of gastric adenocarcinoma is much lower, usually, the majority of patients are treated with less extensive (e.g., D1 or D1+) lymphadenectomy. In an effort to reduce the well-documented morbidity of extensive lymphadenectomy, sentinel node navigation surgery (SNNS) in GC has been intensively investigated recently.

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In this review, an effort has been made in order to assess the potential implication of SNNS in GC field, highlighting the merits and limitations of this challenging and innovative technique. A view towards the future is also provided.

Sentinel Lymph Node

The sentinel lymph node (SLN) is defined as the first lymph node or group of lymph nodes to which cancer cells are most likely to spread from a primary tumor. The concept of SLN biopsy is based on the hypothesis that metastasis in SLN could indicate involvement in downstream lymph nodes, whereas a negative SLN indicates that the rest of the lymph nodes are disease-free. The SLNs are detected with the help of tracers and then resected for intraoperative pathologic examination. The pathologic results of SLNs are believed to predict the lymphatic metastatic status of lymph nodes.

Over the past two decades, it has been proven that SLN biopsy provides nodal status intraoperatively and helps avoid unnecessary lymphadenectomies. SLN biopsy has greatly shaped the modern-day approach to melanoma [3] and breast cancer surgery [4], since limited lymphadenectomy based on the SLN examination has led to a decrease in postoperative complications and improvement in the patient's postoperative quality of life. Although the SLN hypothesis has also been applied to many tissues and organs, its efficacy has not yet been proven in gastrointestinal (GI) cancer field.

The Evolution of Sentinel Lymph Node in Gastric Cancer

The constantly increasing prevalence of EGC among patients, with GC in Japan as a result of the widespread use of endoscopy, has led to the need for a less invasive approach in patients with EGC. There have been many advances in the surgical treatment of GC with the introduction of endoscopic mucosal resection, gastric wedge resection for EGC, and laparoscopic and robotic resection. However, "limited" lymphadenectomy is not universally accepted; hence, the principal treatment for GC remains extended lymphadenectomy along with resection of the primary tumor. EGC was defined in 1971 by the Japanese Society of Gastroenterology and Endoscopy as a carcinoma limited to the mucosa (pT1a) and/or submucosa (pT1b) regardless of the lymph node status [5]. The incidence of node involvement in EGC is reported to be 3.2% (0.0–20.3%) of mucosal EGC and 19.2% (10.2–33.3%) of submucosal EGC [6]. Thus, it is considered that a considerably high portion of patients are free of nodal metastasis and may unnecessarily undergo an extensive lymphadenectomy.

In 2000, Kitagawa et al. [7] introduced the concept of sentinel lymph node biopsy (SLNB) in the treatment of GI cancer aiming for a new organ-preserving therapeutic approach. This study was differentiated from all the previous reports that were mainly focused on the extent of lymphatic flow from the primary lesion and demonstrated the possibility of skip metastases. In 2001, Hiratsuka et al. [8] reported the efficacy of SLNB in the assessment of nodal involvement in patients with T1 GC. Sentinel node biopsy was performed in 44 patients with T1 GC and in 30 patients with T2 GC. Indocyanine green (ICG) was injected intraoperatively around the tumor. The green-stained nodes were then removed, followed by gastrectomy and extended lymphadenectomy. In the patients with T1 cancers, the SN status could diagnose the lymph node status of the patient with 100% accuracy, whereas, in the patients with T2 cancers, sensitivity, specificity, and diagnostic accuracy were 88%. The authors concluded that SLNB is safely applicable in patients with T1 GC, in order to predict the lymph node status, in contrast to patients with T2 GC. Following the study by Hiratsuka et al., a plethora of research studies [9–11] attempted to prove the utility of SLNB for the managements and staging of gastric adenocarcinoma and to introduce new methods of SLNB.

In a study conducted by Kim et al. [9], 99mTc tin colloid was endoscopically injected into the gastric submucosa around the tumor, 3 hours prior to surgery. The SLN was subsequently harvested using a gamma probe, followed by radical gastrectomy and extended lymphadenectomy (D2). They stated that the sensitivity and specificity of this method was 84.6% and 100%, respectively, concluding that this approach is feasible and accurate in the assessment of nodal status. Nonetheless, Song et al. [10] performed SLNB in 27 patients with gastric cancer, using isosulfan blue dye, and concluded that sentinel node navigation surgery is a promising technique in gastric cancer. Nimura et al. [11] reported SNNS for GC by infrared electronic endoscopy (IREE) with ICG injection for the first time. They investigated 84 patients with GC of whom 11 patients had LN metastasis. All of the 11 patients were detected by IREE with ICG injection. However, SLNs detected by ICG injection alone did not include metastasis in 4 of the 11 patients. This result seems to support that IREE significantly increased the number of SLNs detected compared with ICG alone.

In addition, Miwa et al. [12] conducted the first multicenter trial of SN mapping for EGC, reporting that intraoperative endoscopic lymphatic mapping presents high diagnostic accuracy in locating the sentinel nodes in patients with early-stage gastric carcinoma. The detection rate was 96.2%, while the accuracy in LN metastases detection was 98.6%.

However, most reports were from single-institutional studies with a small sample size and inadequate endpoint. Thereafter, numerous reports have been subsequently

published, while Japanese researchers represent the pioneers of sentinel node navigation surgery (SNNS) in GC. However, to date, SNNS is still not widely accepted for the treatment of GC worldwide.

Methodological Problems and Limits for Clinical Application

Mapping Techniques

It has to be highlighted that, up to date, several methods of intraoperative detection of SNs have been studied. The intraoperative identification of SNs in GC is considered to be a major challenge for the operating surgical team. Techniques based on dye and radioisotope agents have been the mainstay for the lymph node detection, each of which has its own merits and shortcomings in SLN detection [13]. In this way, dye agents include isosulfan blue, patent blue, and indocyanine green (ICG). It is more than clear today that ICG is the most commonly used dye being the tracer with the lower rates of allergic reaction. Moreover, the enhanced visibility, the low cost, and the ability to stain not only the LNs but also the lymphatic route are the reason why the ICG is widely used. On the other hand, many reports support that SNs detection using ICG presents high false of negative rate [14, 15].

At present, the topic of suitable tracers in SLN detection in GC is still highly controversial. However, the latest trend in SNNS concerning the tracer method is combining tracers in order to increase the detection accuracy. Double tracer techniques seem to increase the rate of sentinel lymph node identification [16–19]; however, there are some studies that pone under question these findings [20, 21]. Many reports [22–24] suggest the use of isosulfan blue dye combined with technetium 99mTc–labeled tin colloid. However, concerns regarding visualization in fatty tissue, allergy to blue dye, and high cost may cease the widespread use of this dual tracer method.

On the other hand, ICG in combination with IREE or near infrared fluorescent imaging (NIFI) circumvents this issue. The use of infrared ray beam via endoscopy can facilitate the visualization of the used tracer increasing the accuracy of the detection, and growing body of literature investigating the merits of ICG combined with IREE or NIFI for SNNS in GC is underway [25, 26].

Skip Metastases in Gastric Cancer

It has to be emphasized that the SNNS concept in GC is yet controversial and not well established due to several reasons. First of all, the low incidence of EGC in the West makes "difficult" the conduct of clinical trials that could demonstrate the accuracy and ability of SNNS to assess nodal status in EGC. The most important reason is that skip metastases phenomenon is known to occur frequently in GC [27–29]. In this way, skip metastasis refers to the presence of node involvement in the second and third compartments of regional lymph nodes closest to the primary lesion of GI cancer. In GC, skip metastases occurs when extraperigastric lymph nodes are positive for metastatic carcinoma, while perigastric lymph nodes are disease-free [28]. It has been thought that in GC, the patterns of lymph node metastases are very complex due to aberrant lymphatic drainage background, which in turn can cause a high incidence of skip metastasis.

It has to be highlighted that the skip metastasis rate in patients with GC has been reported to be up to 11% among patients with lymph node involvement [30]. However, there is limited information on the incidence of skip metastasis in patients with EGC. For these reasons, skip metastases in GC has been considered a "dramatic" obstacle to the utilization of SNNS. Over the last years, researchers support that understanding the frequency and risk factors of skip metastasis in patients with EGC would overcome this obstacle and would establish SN mapping in patients with GC.

Lee et al. [29] some years ago conducted a retrospective study demonstrating that tumor size and the presence of lymphatic invasion could predict the possibility of skip metastasis in the patients with EGC, supporting that tumor size should be considered during SLN mapping to prevent false-negative results in patients with EGC. They also concluded that the frequency of skip metastasis in EGC was 2.8% and that the most common sites for skip metastases were no. 7 followed by 8 and 9 lymph node stations.

In a recent retrospective study by Kim et al. [28], the researchers reported that tumor size is a risk factor of skip metastasis, and they also stated that skip metastasis was observed in 6.6% of patients presenting EGC in their study. In this study, the most common sites for skip metastasis were no. 8a, 7, and 12a lymph node stations. Su et al. [31] in their study suggested that the only significant influenced factor of skip metastasis is the differentiated degree of the tumor, and they also noted that 20.2% of patients with GC had skip metastases.

Histological Examination

Another conflict in the establishment of SNNS in GC is the optimal method to verify the presence of metastases in the resected SLNs. Traditionally, hematoxylin and eosin (HE) staining for histological examination of frozen section slices has been widely used in SNNS for GC. Nevertheless, the accuracy of intraoperative diagnosis of lymph node metastases based on HE staining presents a wide range in the literature (74–100%). Hence the question arises whether the HE staining is efficient as a standard method of LNM detection. Important efforts have been made towards the identification of alternative,

more reliable options, including immunohistochemical staining and reverse transcription–polymerase chain reaction. Both of these methods present significantly higher metastasis detection rate in the literature than the HE staining technique. Particularly, Arigami et al. [32] reported that the metastatic detection rates concerning SNLB in patients with GC are 8.2% for hematoxylin/eosin, 13.1% for immunohistological staining, and 36.1% for reverse transcriptase–polymerase chain reaction. More studies are necessary in order for safe conclusions to be reached about the optimal method of metastatic detection.

Clinical Trials of SNNS in Gastric Cancer: Where Do We Stand?

A much-anticipated multicenter, phase III clinical trial is currently underway in Korea to verify the oncologic safety of laparoscopic sentinel basin dissection (SBD) with organ-preserving gastrectomy compared with conventional laparoscopic gastrectomy with extended lymphadenectomy for patients with clinical stage T1N0M0 GC.

A prospective multicenter trial conducted in Japan in 2013 by Kitagawa et al. [33] and published in a high-indexed journal demonstrated that endoscopic dual tracer technique for SNB is safe and effective when applied to EGC. Particularly, 397 patients were enrolled in the study with cT1 or cT2 gastric adenocarcinoma of 4 cm or less in diameter. Sentinel node mapping was performed by endoscopic dual tracer injection pre- and intraoperatively. The resected SNs were then examined by hematoxylin and eosin. D2 or modified D2 gastrectomy was then performed for all patients. The sentinel node detection rate was 97.5%, while lymph node metastasis was diagnosed in 14.7% of patients. The incidence of lymph node metastasis was significantly higher in cT2 tumors than in cT1 tumors. Out of 57 patients, 53 (93%) had positive SNs; hence, the accuracy of nodal involvement for metastasis was 99%. Four patients had false-negative SN biopsy results of whom three had either pT2 or primary tumors 4 cm, or both (Table 1).

A single-institution trial conducted in 2013 by Miyashiro et al. [34] assessed the accuracy of SNB with ICG in the intraoperative detection of metastases in SLNs. Two hundred and forty-one patients with cT1 or cT2 gastric adenocarcinoma were enrolled. The researchers report that intraoperatively ICG was injected and all the lymph nodes that stained green were excised and examined. The SNs were detectable in 240 patients, and the success rate of detection was 99.6%. Out of 240, 29 patients were found to have LNM. Of 16 patients with metastases in both SNs and non-SNs, two cases of cT1 gastric cancer were diagnosed as intraoperative SN negative but were later confirmed to be SN positive. Nonetheless, five cases (two patients with cT1 and three patients with cT2) were diagnosed as intraoperative GN negative by histological examinations of frozen sections but positive by imprint cytology. The false-negative rate was 10.3% as an intraoperative diagnosis using SNB and 3.4% as a diagnosis based on the SN concept (Table 1).

Miyashiro et al. [35] (Table 1) conducted a multicenter prospective clinical trial (JCOG0302) in 2013, in order to assess the feasibility and accuracy of diagnosis using SNB in patients presenting T1 GC. However, in this "controversial" study, the proportion of false negatives was much higher than expected. The trial was terminated, because false negatives were found in 13 out of 440 patients, while 7 of 13 false-negative patients had nodal metastases outside the lymphatic basin. The researchers concluded that SN biopsy with ICG and intraoperative histological examination of a single plane is not recommended for clinical use in patients with EGC. Thus, the high false-negative rate (46%) on the interim analysis stopped patient accrual.

In 2015, Lee et al. [36] published a prospective multicenter study including seven institutions. One hundred and eight patients were enrolled in this trial with cT1 or cT2 gastric adenocarcinoma. Above the clinical stage, other eligibility criteria for the study included a tumor of < 4 cm in diameter and tumor at least 2 cm in distance from the pylorus or cardia. Dual tracer was injected via an intraoperative endoscopic approach, and standard gastrectomy with lymphadenectomy D1+ or D2 was

Table 1 Summary of included studies

Study	Year	*n*	Stage	Tracer	Staining	Operation	Detection (%)	Sensitivity (%)
Kitagawa et al. [33]	2013	397	cT1/cT2	Dual	HE	OG	97.5	93
Miyashiro et al. [34]	2013	241	cT1/cT2	ICG	HE	OG	99.6	96.6
Miyashiro et al. [35]	2013	440	cT1	ICG	HE	OG	97.8	46 false negatives
Lee et al. [36]	2015	108	cT1/cT2	Dual	HE	LG	92.6	100
Shimada et al. [37]	2016	156	cT1	Dual	HE	OG	100	99
Nihaara et al. [38]	2016	385	cT1/cT2	Dual	HE	OG/LG	96.6	98.9
Takahashi et al. [39]	2017	44	cT1	Dual	HE	LG	100	100

HE hematoxylin and eosin, *ICG* indocyanine green, *OG* open gastrectomy, *LG* laparoscopic gastrectomy

followed in all patients. Ten patients (19.3%) had lymph node involvement, while there were no patients with metastasis in non-sentinel node alone, without metastatic SN. The results of the study indicate that laparoscopic SNB is feasible and applicable in patients with EGC presenting 100% sensitivity and zero false-negative rates (Table 1).

Moreover, 156 patients were enrolled in a retrospective study by Shimada et al. [37] (Table 1), in order to examine the effectiveness of SNNS in patients with middle-third EGC, with an indication for pylorus-preserving gastrectomy. In this study, technetium 99mTc tin colloid combined with blue dye was used endoscopically as a tracer. The researchers reported that the SN detection rate was 100%, while LNM was seen in 10% of the patients. Out of the 16 patients with LNM, 15 were positive for SN metastases. The accuracy of nodal involvement was 99%.

A single-institutional study by Niihara et al. [38] (Table 1) confirmed the accuracy of SNNS in EGC using dual tracer method, isosulfan blue, or ICG, combined with technetium 99mTc tin colloid. All the 385 patients with cT1 or cT2 GC, who were enrolled, underwent radical gastrectomy and lymphadenectomy. The SLN detection rate was 96.6%, and the accuracy of SLNB for the detection of LNM was 98.9%. The researchers trying to explain the results of this study, combined with a large number of patients enrolled, believe that these are extremely promising concerning the future of SNNS in EGC field.

Takahashi et al. [39] included 44 patients in a prospective multicenter clinical trial, presenting cT1 gastric adenocarcinoma in diameter less than 4 cm. The SNs were identified using ICG combined with infrared ray laparoscopic system (IRLS), and then examined by frozen section with HE staining. All the enrolled patients in the trial underwent D2 or modified D2 laparoscopic gastrectomy. Lymph node metastases were confirmed in 7 patients (16%). The detection rate was 100%, and the accuracy for detecting LNM using the above dual tracer was 100%, indicating that SNNS using infrared ICG is an accurate and effective method to identify lymph node involvement in patients with cT1 GC. However, they highlight that the proportion of false negatives by the ordinary light observation was 57%, indicating that the infrared light observation is the optimal method (Table 1).

However, all these studies have important limitations such as staging of the disease, the staining method, and the heterogeneity of the results.

Future Perspectives

The potential clinical application of SNNS in EGC has long been under extensive debate due to the extremely "complex" lymphatic flow around the stomach. In this way, a multicenter phase III randomized control trial (RCT) is currently underway in Korea enrolling approximately 600 patients. The final results of this trial are expected with great interest from the scientific community to establish or not a potential definitive "place" of SNB in GC treatment. Nevertheless, recent studies revealed that using dual tracer with dye and radioisotope for the detection of SLNs is more accurate than using a single tracer alone.

SNNS for GC is a very attractive treatment option as a novel minimally invasive approach in order to avoid unnecessary lymphadenectomy in patients with EGC. However, it is still under debate, and there is enormous skepticism whether SNNS would be appropriate to perform in patients with GC in the West. Important obstacles to the clinical use of sentinel node navigation surgery have alleviated researchers' interest on the topic; thus, Western countries are less familiar with this treatment option. It is more than clear that SNNS application in the GC field could represent a real "triumph" in the concept of minimally invasive treatment. However, several future well-conducted studies are necessary in order for safe conclusions to be reached. Standardization of technique, skip metastases rates, cost, and minimization of false negatives represent dramatic obstacles for SNNS use in GC field. It is out of the question that there has been an intense and consistent effort over the last decade to apply the SN concept in GC. The scientific community should overcome all the obstacles in the future in order to "allow" the wide clinical application of this innovative minimally invasive approach (SNNS) in the management of GC.

Author's Contribution All authors contributed significantly to the work (conception, design, data acquisition, analysis, drafting, critical revision) and approved the final version of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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