Review Article

Sentinel node navigation in gastric cancer: new horizons for personalized minimally invasive surgical oncology?

Georgios D. Lianos[1,2], Natasha Hasemaki[2], Georgios Vaggelis[2], Anastasia Karampa[2], Zoi Anastasiadi[1], Aikaterini Lianou[1], Sarantis Papanikolaou[2], Grigorios Floras[2], Christina D. Bali[1], Epameinondas Lekkas[2], Christos Katsios[1], Michail Mitsis[1]

[1]Department of Surgery, Ioannina University Hospital & University of Ioannina, Ioannina, Greece; [2]Department of Surgery, General Hospital of Preveza, Preveza, Greece

Contributions: (I) Conception and design: GD Lianos, N Hasemaki; (II) Administrative support: E Lekkas, C Katsios, M Mitsis; (III) Provision of study materials or patients: N Hashemaki, Z Anastasiadi, A Lianou; (IV) Collection and assembly of data: GD Lianos, A Karampa; (V) Data analysis and interpretation: GD Lianos, G Vaggelis; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Georgios D. Lianos, MD, PhD. Department of Surgery, Ioannina University Hospital & University of Ioannina, Ioannina, Greece; Department of Surgery, Genaral Hospital of Preveza, Preveza, Greece. Email: georgiolianos@yahoo.gr.

Abstract: Complete (R0) resection and regional lymph nodes (LNs) dissection represent undoubtedly the basic surgical tools for patients with gastric cancer. It is reported that the LN metastasis rate in patients with early gastric cancer (EGC) is approximately 15–20%. Therefore, the innovative clinical application of sentinel node navigation surgery (SNNS) for EGC might be able to prevent unnecessary LN dissection as well as to reduce significantly the volume of gastric resection. Recent evidence suggests that double tracer methods appear superior compared to single tracer techniques. However, the researchers' interest is now focused on the identification of new LN detection methods utilizing sophisticated technology such as infrared ray endoscopy, fluorescence imaging and near-infrared technology. Despite its notable limitations, hematoxylin-eosin is still considered the mainstay staining for assessing the metastatic status of LNs. In this review, we summarize the current evidences and we provide the latest scientific information assessing safety, efficacy and potential limitations of the innovative sentinel node (SN) navigation technique for gastric cancer. We try also to provide a "view" towards a future potential application of personalized minimally invasive surgery in gastric cancer field.

Keywords: Gastric cancer; surgical oncology; guidelines; lymph node navigation (LN navigation); early gastric cancer (EGC); minimally invasive surgery

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Introduction

Gastric cancer is the fourth most common cancer in the world, accounting for approximately 900,000 new cases per year (1,2). Recently the proportion of gastric cancer at an early stage has been increasing because of the advances in the screening program, such as endoscopic investigation (3).

It is established knowledge that for patients with gastric cancer and clinically suspicious lymph node (LN) metastases, gastrectomy with regional lymphadenectomy is mandatory. This procedure is routinely performed even when the primary tumor is "small". In the past, there has been enormous controversy regarding the application of lymphadenectomy for patients with T1 gastric cancer, since these patients are usually "free" of nodal metastatic involvement; it seems therefore that lymphadenectomy is being conducted at far higher rate than necessary.

We have to highlight that in the countries, such as Japan and Korea, where gastric cancer has become an endemic disease; more conservative surgical procedures

are performed, mainly in early gastric cancer (EGC) cases. However, for many years, experienced surgeons strongly believed in the importance of major gastrectomies with extensive lymphadenectomies. Nowadays, however, minor procedures for EGC have gained popularity among gastric cancer specialists mainly in the East. The diagnostic rate of EGC has dramatically increased in these countries because of technological development and cancer mass screening systems (4). Minor procedures include endoscopic resections and minor surgical gastric resections with D1 or modified D1 lymphadenectomies. These minor procedures have been proved to have improved postoperative quality of life, while maintaining 5-year survival rates >95% (5).

Strong evidence suggests that endoscopic diagnostic algorithms of early gastric tumors along with detailed information from histopathological examinations of biopsies and imaging allow curative endoscopic resections for EGC to be performed safely. Guidelines of the Japanese Gastric Cancer Association determine the indications for endoscopic resections of these gastric tumors with minimum risk of metastatic involvement. However, many patients who are not fit for endoscopic resection still have relatively low risks of LN metastasis. This has led to the innovative idea of sentinel node navigation surgery (SNNS) for EGC.

Materials and methods

We have searched Medline and Embase for works published until June 2016 to identify relevant articles using the following key words: LN navigation; gastric cancer; early gastric cancer.

What is sentinel node (SN) technique?

The SN technique has been established in the management of some types of cancers in order to avoid unnecessary lymphadenectomy (6,7). SN is defined as the first LN to receive cancer cell drainage from the primary tumor, and the LN to which cancer cells metastasize at the beginning. The idea that the tumor status of SN reflects "efficiently" the status of the other LNs represents the main concept of this technique.

In 1992, Morton *et al*. (6) reported that the SN was successfully detected by dye injection into cutaneous melanoma. SN biopsy has been then well assessed in the treatment of melanoma. It is also widely used in breast cancer therapeutic modalities.

Minimally invasive surgery such as limited LN dissection and reduced extent of resection based on SN mapping is termed SN navigation surgery (SNNS). This surgery may prevent the post-operative complications and serve as a useful tool for avoiding an over invasive surgery. However, SNNS of gastric carcinoma has not been universally accepted and adopted due to the complicated lymphatic flow from the stomach and skip metastasis phenomenon, which are sometimes recognized in this type of cancer (gastric cancer).

Nevertheless, patients who undergo standard gastrectomy with D2 lymphadenectomy often suffer a variety of complications (diarrhea, reflux, dumping syndrome) termed postoperative syndrome. Extended LN resection (D2) also presents a significantly higher rate of mortality and a longer hospital stay than D1 lymphadenectomy in Western countries (8).

The proportion of LN metastasis in gastric cancer relies on the depth of cancer infiltration (termed TNM staging): it is found in 2–18% of T1 and in about 20% of T2 tumors. On the other hand, the majority (>90%) of the patients with EGC do survive 5-years and pathological data have suggested that the greater part of LNs resected do not show nodal involvement (8). For these reasons SN concept for gastric cancer surgery represents a real challenge for the upper GI specialists.

SN technique for gastric cancer: indications and contraindications

The SN concept for gastric cancer surgery was first studied at the beginning of the 21st century (9-11). It has to be highlighted that Japanese surgeons represent the pioneers of this technique. Preliminary data for this technique showing a high degree of sensitivity and diagnostic accuracy by the use of an intraoperative γ-probe radiation technique was reported 14 years ago (12,13). At the same period another well conducted study reported that SN biopsy using indocyanine green (ICG) can predict the LN status with a high degree of accuracy (10). In general, SN mapping and biopsy is indicated in (I) patients with T1 or T2 tumors; (II) primary lesions < than 4 cm in diameter; and (III) clinical N0 gastric cancer.

A recent study demonstrated that 91% of patients with T1 tumors and 88% with T2 tumors had stained SLNs as compared to only 68% of patients with T3 tumors, SN mapping in T1 and T2 gastric cancers may be useful in the decision-making process with regard to the extent of

lymphadenectomy (14).

As well as for other cancer types, SN mapping should not be performed in cases with positive LN metastasis identified by preoperative imaging diagnostic modalities such as ultrasonography and CT (15).

SN mapping: how?

Actually, a radioisotope (RI) alone or with a dye is used as tracers for the detection of SN in gastric cancer. In this method (RI method), 99mTc-phytate or 99mTc-tin colloid is applied usually as a tracer. The 99mTc RI tracer is injected endoscopically into the submucosa around the tumor, 1 day before operation, and then, using a γ-probe at surgery, the radioactivity of LNs is measured. An important advantage of the RI method is the objective measurement of the intensity of radioactivity and the detection of SN even in thick intraperitoneal adipose tissues. Furthermore, RI tracers remain in the LNs for a relatively long period of time and, therefore, are preferred in laparoscopic surgery. However, RI tracers are expensive and a radioactivity-controlled area is necessary when using RIs. For these reasons, this breakthrough technique is performed currently only in a limited number of centers in Japan and South Korea (14,16-18).

Commonly, the dye method is widely used nowadays for the detection of SN in gastric cancer. ICG, sulfan blue, and isosulfan blue are used as a tracer, and are injected into the submucosa by intraoperative endoscopy, or into the subserosa from luminal outside. The enhanced visibility, low cost, safety, and the ability to stain not only the LNs but also the lymphatic route are the reason why the dye method is now widely used. Recently, the double tracer method (i.e., dye and RI) has been highly recommended for SN detection in gastric cancer (15). Moreover, a different and innovative type of fluorescence imaging system was recently developed for SN navigation surgery (19). The photodynamic eye (PDE) is able to visualize ICG fluorescence emitted by a light-emitting diode. The PDE visualizes SNs and lymphatic vessels more clearly than the usual ICG method. However, it is necessary to make the operating room pitch-darkness for detecting SLNs while performing SN mapping. Novel, sophisticated ICG fluorescence systems such as the D-light P system do not need for switching off the lights in order to detect SN. What is more, with this novel system, SN examination even in laparoscopic surgery can be safely performed. Therefore, in the near future, this method could become the standard method to detect SN in GI malignancies.

In addition, after detecting the SN, the next step is the biopsy. Intraoperative diagnosis using hematoxylin and eosin (H-E) staining of a frozen section from the LN represents the gold standard technique for SN biopsy. However, the reliability of frozen section examination has been under evaluation (20). In this way, in a Japanese multicenter trial, it was found that ~25% of patients with SN metastases that were diagnosed using permanent sections could not be identified using H-E staining of frozen sections collected intraoperatively (15).

Multistep level sections, immunohistochemistry (21,22), reverse transcription polymerase chain reaction (RT-PCR) (23-26), and the one-step nucleic acid amplification assay (OSNA) (24), have all been developed to reduce the false-negative rates and provide reliable diagnostic tools for micrometastases in SN. By using both complete serial sectioning and immunohistochemistry, LN micrometastases were identified in 4/35 patients, and in 6/1,028 nodes (0.58%), where metastases were not detected with the permanent section method (21). In another important study, Shimizu *et al*. (26) developed a more sensitive real-time PCR method by using cytokeratin 19 mRNA, cytokeratin 20 mRNA, and carcinoembryonic antigen (CEA) mRNA. They have reported that approximately 30% of patients with pathologically negative LNs were positive for RT-PCR. In a study by Sonoda *et al*., LN micrometastases in T1 cases were also limited to the perigastric LNs near the primary tumor and the LN station along to the left gastric artery according to LN mapping (27). Moreover, Kumagai *et al*. (28) demonstrated that the sensitivity and specificity of the OSNA assay was higher than conventional examination. Recently, it has been possible to reduce the detection time to ~30 min (29), and these innovative techniques have also raised the sensitivity to detect SN metastases as part of the intraoperative diagnostic algorithm. It is considered very important to improve the precision of the intraoperative SN metastases by developing new technologies and this represents a major challenge for the researchers in the near future (30-32). It is supported by almost all studies investigating micrometastases in SN examination the oncological safety of lymphatic basin dissection (LBD) in this field. Currently, this method for limited lymphadenectomy in gastric cancer is considered the most appropriate.

Current evidences: indications and problems in clinical application

Despite important recent development, there is still more

and more controversy regarding the potential application of SN mapping in gastric cancer field. Up to date, some researchers support the usefulness of SNNS in gastric cancer, while other studies report important limitations of SNNS. To date, a large number of studies have reported very encouraging outcomes of SN detection in gastric cancer. In these studies, the rate of SN detection was 90–100% while metastasis detection rate was 85–100%.

In accordance with these promising results, two prospective multicenter trials assessing safety and efficacy of SN concept in EGC were conducted. The study group of the Japan Society of SNNS performed a multicenter prospective trial of SN mapping and analyzed the validity of SNNS using the dual-tracer method with a radioactive colloid and isosulfan blue dye (14). Twelve institutions with established SN mapping protocol and experienced surgical staffs were enrolled. Three-hundred and ninety-seven patients with clinical cT1N0M0 or cT2N0M0 single tumor with the diameter of the primary lesion < than 4 cm, were enrolled. The SN detection rate was 97.5% and detection rate of regional LN metastatic involvement was 93%. We have to highlight that based on these important findings, randomized controlled trial to compare individualized gastrectomy based on intraoperative SN biopsy data with conventional distal/total gastrectomy is under construction. In future studies, appropriate indications for function-preserving gastrectomy might be determined individually according to the SN mapping theory. In this way an important roadmap for realistic personalized gastric cancer management could be "opened".

On the other hand, to verify the feasibility of SN technique, Japan Clinical Oncology Group performed a large-scale multicenter clinical trial (33). In this trial, T1 gastric cancer patients with less than 4 cm tumors were enrolled. Injection of 4–5 mL ICG dye was performed from the serosal part of the stomach around the initial tumor. The researchers reported that the detection rate of green nodes was ~97%. However, the rate of false-negative was 46.4%, which was surprisingly high. Recently, another important meta-analysis was performed in order to assess the sensitivity of SN biopsy for patients with gastric cancer (34). Two thousand six hundred and eighty-four cases of SN biopsy-related gastric cancer were enrolled. SN identification rate and sensitivity were 87.8% and 97.5% respectively. Negative and positive predictive values were 91.8% and 38.0%. The researchers concluded that SN mapping in gastric cancer is not clinically applicable for limited LN resection due to its insufficient sensitivity and important differences between surgeons. In the same way, another study enrolled 2,128 cases from 38 studies (35). SN detection rate, sensitivity, negative predictive value and accuracy were 93.7%, 76.9%, 90.3%, and 92.0%, respectively. Combined tracer, submucosal injection method, laparotomy, and immunohistochemical staining revealed a significantly better sensitivity and detection rate. The researchers concluded that although SN mapping is feasible, further studies are necessary in order to assess the best technique and the appropriate algorithm.

The researchers highlight that important controversial issues should be clarified. In this issue, although the dye-guided method is safe and cost-effective, it has important.

Limitations: loss of visibility in dense fat and rapid transit of the dye are some of them. These limitations make this method "less" useful in laparoscopic surgery. From the other hand, legal considerations and costs of radioactive substances limit substantially the probe-guided method. However, it is widely accepted that the combination of dye and radioactive colloid detection substances is more appropriate method for detection (35-39).

Another issue that has to be clarified is the most appropriate site of injection. Appropriate injection of tracer is crucial for detection of SNs. The matter of debate today is whether the injection site of the tracer has to be limited to the submucosa or has to be "expanded" in subserosa.

Another important question that should be "answered" is that the lymphatic flow of the stomach is extremely complicated and skip metastases phenomenon has been described also in EGC.

In general, there have been two types of methods to collect the SN sampling procedures for gastric cancer. One is the picked-up method to remove only hot node or staining LNs and the other method is a LBD (40,41). LBD is recognized as a sort of focused LN dissection involving stained lymphatic vessels and LNs for EGC (42,43). Whether the one or the other method should represent the first choice for the patients with EGC remains under discussion.

Conclusions and future perspectives

SN concept for gastric cancer surgery was first discussed almost a decade ago. However, there are still many issues that should be clarified regarding SNNS in gastric cancer.

The indications for endoscopic treatments such

as endoscopic mucosal resection and endoscopic submucosal dissection are limited to cases with mucosal tumors, histologically differentiated adenocarcinomas, tumors <2 cm in diameter and no ulcer or no ulcer scar in the lesions. If the primary tumor meets these criteria, LN metastasis is considered to be absent. Standard gastrectomy is recommended even for cT1 gastric cancer, outside the general criteria for endoscopic treatments, in the recent Japanese Guideline for Gastric Cancer. However, LN metastasis is present only in 10–20% of such patients (44-46).

In the near future, preserving the function of a residual digestive organ and quality of life in postoperative patients will represent the "centre" of researchers' interest. SNNS is one of the most challenging and attractive method to detect the clinical undetectable LN metastasis of gastric cancer, which may lead to personalized minimally invasive surgical oncology. We have to highlight that although several studies have tried to assess the feasibility and accuracy of SLN in gastric cancer, the results are still very controversial. Multicenter phase III trials assessing oncological safety and feasibility should be conducted in the near future in order safe conclusions to be reached.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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