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REVIEW

Sentinel lymph node biopsy for gastric cancer: Where do we stand?

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Abstract

Development of sentinel node navigation surgery (SNNS) and advances in minimally invasive surgical techniques have greatly shaped the modern day approach to gastric cancer surgery. An extensive body of knowledge now exists on this type of clinical application but is principally composed of single institute studies. Certain dye tracers, such as isosulfan blue or patent blue violet, have been widely utilized with a notable amount of success; however, indocyanine green is gaining popularity. The double tracer method, a synchronized use of dye and radio-isotope tracers, appears to be superior to any of the dyes alone. In the meantime, the concepts of infrared ray electronic endoscopy, florescence imaging, nanoparticles and near-infrared technology are emerging as particularly promising alternative techniques. Hematoxylin and eosin staining remains the main method for the detection of sentinel lymph node (SLN) metastases. Several specialized centers have begun to employ immunohistochemical staining for this type of clinical analysis but the equipment costs involving the associated ultra-rapid processing systems is limiting its widespread application. Laparoscopic function-preserving resection of primary tumor from the stomach in conjunction with lymphatic basin dissection navigated by SLN identification represents the current paramount of SNNS for early gastric cancer. Patients with cT3 stage or higher still require standard D_2 dissection.

Key words: Sentinel lymph node biopsy; Gastric cancer; Laparoscopy; Lymph node dissection; Lymphatic metastasis; Staining and labeling

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INTRODUCTION

Over the past two decades, sentinel lymph node (SLN) biopsy in surgical oncology has been so successful that it is now considered as the gold standard procedure in breast cancer surgery. There is also a growing body of published research supporting the utility of SLN biopsy for gastrointestinal cancers, particularly with colorectal and gastric adenocarcinomas[1,2]. Compared to colorectal cancer surgery, however, investigations into SN biopsy for gastric malignancies are not as prevalent as those involving colorectal surgery. Concurrent advances in

laparoscopic techniques have stimulated many gastrointestinal surgeons to seek out new ways to easily perform SLN biopsy and to make more precise decisions as to the extent of lymphatic tissue that should be removed during laparoscopic resection of gastric cancer.

As one of the commonest cancers and the second most frequent cause of cancer-related deaths worldwide, carcinoma of the stomach affects hundreds of thousands of people every year[3]. Two of the most important prognostic factors for patients with gastric cancer are tumor depth and lymph node involvement. While complete resection of any gastric primary tumor can be sufficiently ensured by frozen section examination of the resected margins, the most effective means by which to manage the associated lymph nodes and lymphatic channels draining the tumoral area remain undefined. This clinical inconsistency stems from the fact that a given proportion of patients who present no lymph node metastasis undergo routine D2 lymphadenectomy as a standard procedure[4]. The emergence of new technologies, however, have facilitated the use of SN biopsy as a sufficiently reliable guide towards defining the boundaries of tissues to be resected during oncological surgery; this concept is now generally referred to as "sentinel node navigation surgery (SNNS)"[4].

GENERAL PERSPECTIVE OF THE STUDIES ON SNNS FOR TREATMENT OF GASTRIC CANCER

The principal objective of using sentinel node biopsy and SLN mapping is to limit the extent of tissue dissection around the primary organ. Ultimately, the SNL is expected to facilitate precise and sufficient resection while decreasing the risk of morbidity caused by unnecessary removal of tumor-free areas. Studies on the clinical use of SNNS for gastric cancers first appeared in the English literature in the early 2000s and have since led many oncological researchers and clinicians to develop new methods by which to improve the feasibility and usefulness of sentinel node mapping. In fact, over 50 studies to date have investigated SNNS for its specific applicability to treat gastric cancer. The majority of these studies have been published in journals indexed in the Medline® database[5-55] (Table 1). Not surprisingly, most of the studies in this field have been conducted in Japan, where adenocarcinoma of the stomach is considered endemic and remains the leading cause of cancer-related deaths[56]. Authors from South Korea are the second most prevalent publishers on this topic. Researchers interested in evaluating the effectiveness of SNNS for treating gastric cancer are usually practicing clinicians, probably since those tracers and methods commonly used in any form of SNNS were previously established by experimental studies in breast and colon cancer models. As a result, only one-tenth of the gastric cancer-related contributions have had a laboratory-based design[38,40,42,49,55]. Considering knowledge accessible through the Medline® database, we can say that the total number of patients enrolled in studies evaluating SNNS feasibility for gastric cancer treatment - irrespective of the method used for the removal of primary tumor - stands at approximately 2800 (Table 1). In order to determine the potential of SNNS to detect lymph node involvement and identify the most accurate SNNS strategies, studies have examined a wide array of technical aspects, including but not limited to, the effectiveness of novel tracers, different injection sites

Table 1 Relevant publications reporting on sentinel node concept for gastric cancer

Author	Yr	Country	Study design	*n*
Hiratsuka *et al*[5]	2001	Japan	Clinical	74
Kitagawa *et al*[6]	2002	Japan	Clinical	145
Hundley *et al*[7]	2002	USA	Clinical	14
Ichikura *et al*[8]	2002	Japan	Clinical	62
Hayashi *et al*[9]	2003	Japan	Clinical	31
Ajisaka *et al*[10]	2003	Japan	Clinical	35
Miwa *et al*[11]	2003	Japan	Clinical	211
Ishigami *et al*[12]	2003	Japan	Clinical	27
Uenosono *et al*[13]	2003	Japan	Clinical	?
Ryu *et al*[14]	2003	South Korea	Clinical	71
Tonouchi *et al*[15]	2003	Japan	Clinical	17
Isozaki *et al*[16]	2004	Japan	Clinical	144
Nimura *et al*[17]	2004	Japan	Clinical	84
Kim *et al*[18]	2004	South Korea	Clinical	46
Tanaka *et al*[19]	2004	Japan	Clinical	3
Yasuda *et al*[20]	2004	Japan	Clinical	18
Osaka *et al*[21]	2004	Japan	Clinical	57
Tonouchi *et al*[22]	2005	Japan	Clinical	37
Lee *et al*[23]	2005	South Korea	Clinical	121
Gretschel *et al*[24]	2005	Germany	Clinical	34
Uenosono *et al*[25]	2005	Japan	Clinical	104
Zulfikaroglu *et al*[26]	2005	Turkey	Clinical	32
Arigami *et al*[27]	2006	Japan	Clinical	61
Ichikura *et al*[28]	2006	Japan	Clinical	80
Ishizaki *et al*[29]	2006	Japan	Clinical	101
Park *et al*[30]	2006	South Korea	Clinical	100
Lee *et al*[31]	2006	South Korea	Clinical	64
Mura *et al*[32]	2006	Italy	Clinical	10
Saikawa *et al*[33]	2006	Japan	Clinical	35
Ohdaira *et al*[34]	2007	Japan	Clinical	161
Morita *et al*[35]	2007	Japan	Clinical	53
Ishigami *et al*[36]	2007	Japan	Clinical	5
Rino *et al*[37]	2007	Japan	Clinical	43
Kitayama *et al*[38]	2007	Japan	Experimental	-
Gretschel *et al*[39]	2007	Germany	Clinical	35
Koyama *et al*[40]	2007	Japan	Experimental	-
Ishikawa *et al*[41]	2007	Japan	Clinical	16
Koyama *et al*[42]	2007	Japan	Experimental	-
Yaguchi *et al*[43]	2008	Japan	Clinical	63
Miyashiro *et al*[44]	2008	Japan	Clinical	3
Orsenigo *et al*[45]	2008	Italy	Clinical	34
Lee *et al*[46]	2008	Korea	Clinical	21
Yanagita *et al*[47]	2008	Japan	Clinical	133
Tajima *et al*[48]	2009	Japan	Clinical	56
Cahill *et al*[49]	2009	France	Experimental	-
Ichikura *et al*[50]	2009	Japan	Clinical	35
Ohdaira *et al*[51]	2009	Japan	Clinical	30
Park do *et al*[52]	2011	Korea	Clinical	68
Rabin *et al*[53]	2010	Israel	Clinical	80
Kelder *et al*[54]	2010	Japan	Clinical	212
Jeong *et al*[55]	2010	Korea	Experimental	-

and methods and type of surgery performed. These efforts have yielded a rapid advancement in SNNS-based procedures compatible with newly developed technologies and have improved the ability of physicians to readily and precisely detect metastatic sentinel LNs. Today's questions regarding the usefulness of SNNS for treating gastric cancer may, therefore, be categorized into three groups: (1) What tracer should be used, and by which means, to identify SLNs? (2) What method should be selected for the detection of SLN metastasis? and (3) Which patient is suitable for SNNS and what strategy should be used to manage tumor load?

WHAT TRACER SHOULD BE USED, AND BY WHICH MEANS, TO IDENTIFY SLNs?

An acceptable rate of success for detecting metastasis in SLN for gastric cancer can only be achieved by accurately identifying real sentinel nodes in a timely manner during the operation. Any ideal tracer for SNNS in gastric cancer would be characterized as a nontoxic, readily available and cost-effective substance that is capable of accumulating in the SLN within a few minutes, stays there for hours and does not escape beyond the sentinel nodes. This ideal tracer would also be expected to be conducive to use during both open and minimally invasive surgical techniques and easily recognizable by the surgeon without use of sophisticated equipment. To date, an ideal tracer that meets all of the above mentioned criteria has yet to be developed. In early studies of SNNS for use in gastric cancer surgery, dye-guided and radioisotope-guided methods represented the procedures of choice[5-12,14-16]. The dye agents most often used are isosulfan blue, patent blue violet and indocyanine green (ICG), while Technetium 99m-radiolabeled tin Colloid is the most frequently used radioisotope. Introduction of infrared ray electronic endoscopy (IREE)[17,34,41] followed these techniques to facilitate visualization of dyed SLNs and lymphatic basins draining the tumor as they are contrasted from the fatty areas surrounding the stomach. More recently, it has been suggested that fluorescence imaging of the lymphatic structures stained by ICG can be used to visualize the dye within thin lymphatic vessels and those SLNs situated deep within the tissue that might otherwise have been overlooked[44,48]. The most recent investigations into the development of precise detection methods for SLNs in gastric cancer are quite promising. For example, near-infrared fluorescence (NIR) technology combined with the use of quantum dots, a well-known nanoparticles group, as the tracer has been used successfully in pigs, allowing the surgeon to see both natural anatomical structures and SLNs in real time[57,58]. Furthermore, quantum dots rapidly map lymphatic vessels, accumulate into the SLNs within 1 to 3 min and do not flow toward non-sentinel nodes at any time over a 4 h period[58]. ATX-S10Na(II), a novel lisosomal photosensitizer, has been characterized for its ability to sustain the original injected concentration for an extended period of time and can be visually identified by its bright red coloration in the lymphatic tissue; this chemical has been investigated in animal studies for its potential as a valid tracer[36,38,40,42]. Research continues to determine the properties of toxicity of these next generation tracers and it seems likely that in the near future these novel tracers will advance to replace conventional dye-guided and radioisotope-based methods in SNNS.

The issue of how to best administer any tracer has been another topic of debate. Traditional application mandates preoperative submucosal administration of radio-isotopes or intraoperative submucosal injection of dye tracer around the primary tumor, depending on the mapping method preferred by the physician. Both of these methods are carried out *via* endoscopy. A few studies have performed direct comparisons of submucosal vs subserosal injection of dye to determine which method yielded superior SLN detection rates. In a study of 121 patients, Lee *et al*[23] compared the subserosal and submucosal injection of isosulfan blue. They found no significant difference between the two methods in terms of the proportion of successfully identified SLNs (92 and 94 percent, respectively) or the number of SLNs determined per patient (2.5 and 2.9, respectively). Likewise, Yaguchi *et al*[43] determined that submucosal application by intraoperative endoscopy had similar rates of node identification as the subserosal injection of ICG introduced by physicians relying only on naked vision. Still, many other reports have presented data in favor of the endoscopic approach and most surgeons prefer endoscopy-assisted submucosal administration.

An overview of all the relevant studies on this topic on Medline demonstrated that two major trends have emerged in SNNS over the past 5 years. Firstly, a general preference for the double-tracer (dye plus isotope) method to visualize SLNs has arisen[31-33,35,39,43,46,52]. A number of authors have reported significant increases in the rate of successful identification of SLNs by combined use of both techniques[31-33,46,52,59], although some studies have presented evidence that does not support this idea[39]. Hayashi *et al*[9] concluded that use of only a single dye-guided or radio-guided method resulted in a reduced success rate; specifically, each method achieved only 90% of success in identifying SLNs and 4%-7% of skip metastasis to the non-SLNs. The second trend witnessed over the last 5 years is a remarkable increase in the use of ICG as the dye tracer for SNSS, as compared to the previously preferred isosulfan blue and patent blue violent dyes[28,30,34,35,48,51,54]. It is a fact that globalization has allowed increased availability to next generation tools and research materials to more countries and has enabled researchers to explore novel techniques within their own clinics.

In summary, although there still is no clear consensus as to the nature of tracer or superior method to accurately identify SNLs by SNNS in gastric cancer, some conclusions may be drawn. Firstly, the dual-mapping procedure continues to increase in popularity. Secondly,

endoscopic administration of the tracers (radio-isotope: 3 h to 1 d before surgery; dye: intraoperative) remains the procedure of choice. Thirdly, ICG with fluorescent imaging is rapidly gaining proponents. It should be recognized that the procedure selected will be dependent upon the capabilities of the surgeon and the medical facility where the health service is offered. This reality is a particular limiting factor for laparoscopic SNNS, which requires technical expertise and costly equipment. Most importantly, recent reports of novel products, such as quantum dots, and techniques, such as IREE and NIR, are highly promising for the future of SNNS.

WHAT METHOD SHOULD BE SELECTED FOR THE DETECTION OF SLN METASTASIS?

An intraoperatively detected metastasis of an SLN during SNNS is the key factor that will determine whether a patient will proceed with conventional D2 lymph node dissection or not. As such, it is our opinion that the false negative and accuracy rate are of the utmost importance in SNNS for gastric cancer. Unfortunately, the outcomes of not performing a standard extended lymph node dissection on patients who were clear on SLN biopsy but actually had lymph node metastasis include increased rate of omitting adjuvant therapy and mortality rates.

The traditional practice of SLN for gastric carcinoma biopsy has been largely based on the use of hematoxylin and eosin (HE) staining for histological examination of frozen section slices. However, the issue of whether HE is adequate for intraoperative detection of LN metastasis remains controversial. Kitagawa *et al*[59] reported that accurate intraoperative diagnosis using HE with a single slice was possible in only 74% of cases. Contrary to that conclusion, other authors have reported satisfactory accuracy rates (between 93.8% and 100%) with HE staining of SLN biopsied tissue[5,9,23,30,33,41,50]. Because of this controversy, efforts have been directed towards identifying more reliable histopathological methods. What we find interesting is that most of the studies that compared the conventional HE method with more sophisticated methods, such as immunohistochemical staining (IHC) and reverse transcription-polymerase chain reaction (RT-PCR), reported a significant improvement in the detection rate where the presence/absence of metastasis was confirmed using a sophisticated method. For example, in the study by Arigami *et al*[27] that included 61 patients with cT1 and cT2 cN0 disease, HE was used to determine that five (8.2%) of the patients had SLN metastasis, whereas eight (13.1%) were found to have metastatic disease by the IHC method. This rate rose to 36.1% (22 patients) when RT-PCR was used for the diagnosis of metastasis. The difference in findings from the IHC and RT-PCR methods were due to micrometastases being demonstrated in 14 additional patients by the sensitive PCR-based technique. As the significance of micrometastases for gastric carcinomas is still undefined, the presence of micrometastases, especially in early gastric cancer with no clinically evident lymph node metastasis, should be interpreted thoughtfully and rationally. Similarly, Osaka and colleagues showed that IHC and RT-PCR were able to detect micrometastases in 8 and 21 LNs, respectively, from 10 out of 57 patients with confirmed early gastric cancer[21]. None of those metastases were identifiable by conventional tissue staining. The results of the two latter studies suggest that the conventional HE method may not be sufficient to manage patients with early gastric cancer *via* the SLN concept. Unfortunately, methods relying on the amplification of certain mRNAs associated with malignant cells or staining by given monoclonal antibodies that react with a broad spectrum of human cytokeratins have two major drawbacks: firstly, the technical equipment is unavailable in many hospitals across the globe; and secondly, obtaining a timely result during surgery is difficult. It is clear that the rationality of a technique for SNNS is correlated with its applicability to intraoperative decision-making. Despite the time requirement being only 30-40 min to obtain an IHC result, only a limited number of centers around the world have the equipment and trained staff necessary to carry out such a test.

To summarize, it is necessary to note that the method selected to detect any metastasis in SLNs for gastric cancer is as important as the method used to identify those SLNs. However, for routine clinical care, HE with multiple slices seems the best available option that enables surgeons to make an intraoperative decision, despite its high risk of overlooking some micrometastases. If possible, supplementing the HE procedure with ultra-rapid IHC will definitely contribute to the reliability of the results. The RT-PCR method has yet to be established as a standard practice, mainly due to cost restrictions. Another solution may be that the entire lymphatic basin corresponding to the stained and/or radio-labeled SLNs is removed, regardless of the presence or absence of metastasis in SLNs.

WHICH PATIENT IS SUITABLE FOR SNNS AND WHAT STRATEGY SHOULD BE USED TO MANAGE TUMOR LOAD?

Unlike breast cancer, carcinoma of the stomach has the distinctive property of loco-regional invasion. Multidirectional, rather than single-course, flow of lymphatic fluid from the primary tumor allows metastatic cells to move to multiple SLNs. This flow can be directed toward any number of SLNs situated anywhere throughout the lesser curvature (LNs No. 1, 3 and 5) (according to classification by the Japanese Gastric Cancer Association[3]) or the greater curvature (LNs No. 2, 4 and 6) in a manner that is generally relevant to the location of the primary lesion. However, this is not always the case. Multiple SLNs can also be present along both the lesser and greater curva-

tures concurrently[54]. Another probability is that some SLNs can be situated at the second echelon (LNs No. 7, 8, 9 and 11)[7,59]. This complicated drainage structure has been one of the most challenging obstacles that has restricted the efficacy of SNNS in patients with gastric cancer.

Perusal of the relevant literature reveals a truth unquestionable at this moment: it is possible to undertake SNNS but only for a certain subset of patients with gastric cancer, with proportions ranging from approximately as low as 3% to as high as 50%, depending on the country where the procedure is performed[1,53,56,60]. Studies from Japan and Korea have selectively included clinically node-negative cT1 and cT2 patients[6,9,10,17,18,21,23,43,52,54], while studies originating from countries in the western regions have included cases with cT3 (serosal infiltration) tumors as well[7,24,26,53]. However, skip metastasis in gastric cancer has been associated with lymphatic obstruction by tumor cells that usually is accompanied by aberrant lymphatic pathways; this event makes the consideration of SNNS of cT3 tumors having a higher risk of LN involvement controversial[45,46,53]. Moreover, some authors have asserted that cT1, rather than cT2, tumors represented the best candidates for SNNS[30,48,52,59]. Fortunately, in many cases the skip metastasis is encountered in non-SLNs at the same lymphatic basin as the SLN. Therefore, removal of entire relevant lymphatic basin, rather than selective excision of identified SLNs, appears to be the most reliable procedure[11,46,52,59].

As SNNS for gastric cancer aims to protect the patient from unnecessary morbidity by means of a less invasive dissection, the optimal procedure would integrate the use of laparoscopic or other minimally invasive approaches. Studies investigating SNNS for gastric cancer during open surgery first appeared in the literature in the early 2000s[5-11,18,21,24]. Over the last 5 years, data has been presented from use of the technique in amalgamated subsets of open and laparoscopic treatment[17,54] and in patients undergoing laparoscopic resection[22,45,46,48,52]. Interestingly, in a recent report based on an experimental study, Cahill *et al*[49] claimed that SNNS could also be performed during natural orifice transluminal endoscopic surgery. Meanwhile, the laparoscopic approach is rapidly evolving into a key strategy in the armamentarium of gastric cancer surgery, owing to novel facilitating devices which may be used for both radical and partial resection of the stomach. The current knowledge supports the practice of laparoscopic lymphatic basin dissection plus function-preserving (partial or wedge) resection of the primary tumor, providing that it is smaller than 4 cm in diameter. The issue of whether patients with a primary lesion confined to the mucosa might also be viable candidates for endoscopic mucosal resection with SLN biopsy is under investigation and preliminary trials are reporting encouraging outcomes[61,62]. It seems feasible to perform distal, proximal or total gastrectomy, depending upon the lesion location, for those patients with more extensive lesions. Given promising instrumental revolutions and the growing body of knowledge, it is logical to predict that the laparoscopic approach will soon become the standard of care for patients with clinically diagnosed node-negative early gastric cancer as it is complementary to the SNNS concept.

In conclusion, recent advances in SNNS and minimally invasive interventions have significantly impacted our current approaches to gastric cancer surgery. A number of reports representing single institute experiences have augmented the relevant knowledge base. The currently established double tracer method (dye and radio-isotope tracers) appears to be the most efficacious and reliable procedure for identifying true sentinel nodes. While conventional dye tracers, such as isosulfan blue or patent blue violet, are still useful, ICG deserves more attention for the current applications. IREE, florescence imaging, nanoparticles and near-infrared technology represent the future direction in which the SNNS concept is advancing. Across the globe, detection of SLNs harboring metastasis is mainly accomplished by HE staining. Immunohistochemical staining has considerable potential for routine clinical use; however, ultra-rapid processing systems must first become more prevalent among each country's hospitals. Laparoscopic function-preserving resection of the tumor from the stomach with lymphatic basin dissection navigated by SLN identification represents the current dominant choice of SNNS for early gastric cancer. Patients with cT3 or more advanced disease are still advised to receive standard D_2 dissection for yielding satisfactory survival rates.

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