

Sentinel node navigation surgery in gastric cancer: Current status

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Abstract

The theory behind using sentinel node mapping and biopsy in gastric cancer surgery, the so-called sentinel node navigation surgery, is to limit the extent of surgical tissue dissection around the affected organ and subsequently the accompanied morbidity. However, obstacles on the clinical correspondence of sentinel node navigation surgery in everyday practice have occasionally alleviated researchers' interest on the topic. Only recently with the widespread use of minimally invasive surgical techniques, *i.e.*, laparoscopic gastric cancer resections, surgical community's interest on the topic have been unavoidably reflat. Double tracer methods appear superior compared to single tracer techniques. Ongoing research is now focused on the invention of new lymph node detection methods utilizing sophisticated technology such as infrared ray endoscopy, fluorescence imaging and near-infrared technology. Despite its notable limitations, hematoxylin/eosin is still the mainstay staining for assessing the metastatic status of an identified lymph node. An intra-operatively verified metastatic sentinel lymph node will dictate the need

for further conventional lymph node dissection. Thus, laparoscopic resection of the gastric primary tumor combined with the appropriate lymph node dissection as determined by the process of sentinel lymph node status characterization represents an option for early gastric cancer. Patients with T3 or more advanced disease should still be managed conventionally with resection plus standard lymph node dissection.

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Key words: Sentinel node; Gastric cancer; Minimally invasive surgery

Core tip: Sentinel node navigation surgery can change the current surgical treatment of gastric cancer expanding the indications of minimally invasive surgical options such laparoscopic techniques. However, the complex lymphatic drainage of the stomach and the ubiquitous fear of skip metastasis make the selection of patients extremely important. Currently, laparoscopic resection of the tumor from the stomach with lymph node dissection navigated by sentinel lymph node identification represents an option only for early gastric cancer patients. Unfortunately, patients with T3 or more advanced disease should still be managed conventionally with resection plus lymph node dissection.

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INTRODUCTION

Melanoma was the first malignancy that the concept of sentinel node found application for. However, the indications and uses of this attractive procedure have been

Table 1 Lymph node stations of the stomach

Lymph node stations	Anatomic location	Group	Lymphadenectomy
1	Right cardia	N1	D1
2	Left cardia		
3	Lesser curvature		
4	Greater curvature		
4a	Short gastric vessels	N2	D2
4b	Left gastroepiploic vessels		
4c	Right gastroepiploic vessels		
5	Suprapyloric		
6	Infrapyloric	N3	(N1 + N2)
7	Left gastric artery		
8	Common hepatic artery		
9	Celiac trunk		
10	Splenic hilus	N4	D3
11	Splenic artery		
12	Hepatoduodenal ligament		
13	Posterior surface of the head of the pancreas		
14	Root of the mesentery	N4	(N1 + N2 + N3)
14A	Superior mesenteric artery		
14V	Superior mesenteric vein		
15	Para-aortic		
16	Paracolic		

recently expanded in many fields of surgical oncology such as breast cancer, thyroid cancer, gynecological malignancies, colorectal and, recently, gastric cancer. Sentinel node mapping and biopsy in gastric cancer surgery, the so-called sentinel node navigation surgery, aimed to limit the extent of surgical tissue dissection around the affected organ. By convection, any unnecessary dissection, *i.e.*, dissection of virgin-tumor free areas unrelentingly increase morbidity without always respective survival benefits. Within this context, sentinel lymph node navigation surgery could, at least theoretically, facilitate precise and sufficient resections. However, in some instances, insurmountable obstacles on the clinical correspondence of the sentinel node navigation surgery concept in everyday practice have occasionally alleviated researchers' interest on the topic. Only recently with the widespread use of minimally invasive surgical techniques, *i.e.*, laparoscopic gastric cancer resections, surgical community's interest on the topic have been unavoidably reflagged.

Nowadays, the following questions regarding the utility of sentinel lymph node mapping and biopsy in clinical practice need to be precisely answered: (1) which are the available techniques for sentinel lymph node mapping? (2) which is the best way to administer the tracer? (3) which is the optimal method to verify the presence of metastasis in the identified sentinel lymph node? (4) which is the gastric cancer patient subgroup suitable for sentinel node mapping and biopsy? and (5) which are the available options for primary tumor control?

LYMPH NODE STATIONS

In 1973, the Japanese Research Society for the study of gastric cancer published a manual standardizing lymph node dissections in gastric cancer by recognizing 16 dis-

tinct anatomic lymph node stations. Further grouping of these lymph node stations took place, *i.e.*, N1, N2, N3 and N4 to achieve correspondence with respective lymph node dissection extents, *i.e.*, D1, D2, D3 and D4^[1] (Table 1).

LYMPHATIC STREAM IN GASTRIC CANCER

Trying to decipher the lymph route out of a malignant lesion within the stomach, a few anatomical considerations are of paramount importance. Briefly, from the anatomic viewpoint, lymph from the gastric wall is drained *via* lymphatic vessels which form a complex sub-peritoneal plexus surrounding the stomach both anteriorly and posteriorly. Depending on the location, the lymph of the upper left part of the stomach is routed to the left gastric and pericardial nodes. Lymph originated from the pylorus is filtered through the supra-pyloric and the right supra-pancreatic nodes. The region of the fundus filters lymph along the gastrosplenic ligament and splits with lymph flowing to the left supra-pancreatic nodes and the left gastroepiploic nodes via the splenic nodes. Lymph from the pyloric and the distal portion of the corpus collects in the right gastroepiploic nodes and then flows to the sub-pyloric nodes. From all regions, the lymph stream continues to the celiac nodes^[1].

When dealing with malignant lesions, clarifying the lymphatic drainage pattern is crucial for performing proper lymph node dissections especially from sites "susceptible" to metastasis. However, as briefly discussed above, the lymphatic stream of the stomach appears particularly complex and multidirectional and in many occasions ill-investigated. Certainly, having even a rough idea of how lymph drains out of the stomach will render upper gastrointestinal (GI) surgeons capable of performing effective and, up to a point, targeted lymph node dissections^[2]. Nevertheless, tumors at any location within the stomach have a non-negligible chance of atypical metastasis. Tumors located longitudinally or circumferentially in the lower part of the lesser curvature appear to be of higher chance for an atypical metastasis compared to other locations^[3]. It becomes obvious that the efficiency of the sentinel node concept is compromised when dealing with tumors at these locations as an unacceptable increase of false-negative results should be anticipated. Studies raise the incidence of skip metastasis up to 29%^[3]. Apart from the location, the degree of tumor differentiation has been inconsistently implicated as to increase skip metastasis potential^[4].

Generally, the severity of gastric malignancy, *i.e.*, tumor size and depth of invasion is positively correlated with the lymph node metastasis rate^[5]. In addition, studies using a retrospective methodology and including patients with sole lymph node involvement have shown that the majority of sentinel lymph nodes are located in the regional area at a close proximity to the tumor^[6]. It is recommended, that if nodes are not identified in the usual locations, then No. 7, 8 and 9 lymph node stations should

be investigated as well^[7].

WHICH ARE THE AVAILABLE TECHNIQUES FOR SENTINEL LYMPH NODE MAPPING?

Numerous methods in order to increase the usefulness and effectiveness of sentinel node mapping have been proposed to date^[8-18]. The clinical evaluation and assessment of these modalities within studies have led to a breathtaking progress in the field rendering sentinel lymph node tracking techniques familiar to surgeons. However, the main problem is on the logistics of each technique. Identifying sentinel lymph nodes intra-operatively in a timely and effective pattern is by definition a challenging process. The tracer used should meet the minimum requirements of (1) non-toxicity; (2) easy availability; and (3) cost-effectiveness. Ideally, the tracer should accumulate within the sentinel nodes for a period of time long enough to render detection possible. Furthermore, it should be readily identifiable without the need for using sophisticated and unfamiliar to surgeons equipment. As no single tracer to date incorporates all of the above characteristics, the quest for the optimal compound seems to be ongoing.

Dye-based and radioisotope-based techniques have been the mainstay for lymph node detection so far^[8-18]. Dye agents include isosulfan blue, patent blue and indocyanine green (currently, the most commonly used dye). On the other hand, technetium 99 m represents the most commonly used radioisotope. The use of infrared ray beam *via* endoscopy can, at least theoretically, facilitate the visualization of the used tracer increasing the accuracy of the detection^[19,20]. Similarly, fluorescence imaging is another available adjunct which is suggested to increase the detection rates of traditional dye agents such as indocyanine green^[21,22].

However, sentinel lymph node mapping of the GI tract by using available techniques is often limited by various factors. The multidirectional lymph drainage patterns and, practically, the inability to image surgical anatomy in real time in relation to the used tracer can compromise the whole process. In this direction, the use of invisible near-infrared light might have the answers. In this technique, an intraoperative near-infrared fluorescence imaging system that simultaneously displays surgical anatomy is utilized. Near-infrared fluorescence images of the surgical field are generated to illustrate intra-parenchymally injected near-infrared fluorescent quantum dots. The final result is the visualization of the draining lymphatic tree and of the nodes as well. The technique promises dissection under real time vision^[23].

Generally, there is a trend for combining tracers in order to increase the detection accuracy. Double tracer techniques (dye plus isotope), almost consistently, seem to increase the rate of sentinel lymph node identification^[24-30], however there are indeed studies which question

this finding^[31,32]. In addition, pre-clinical research is in progress for inventing the optimal tracer and visualization system. It seems pretty likely at this point that research will overcome the traditional dye-based techniques and it will open new perspectives in sentinel node mapping.

WHICH IS THE BEST WAY TO ADMINISTER THE TRACER?

Traditionally, endoscopy has been used in order to inject the tracer sub-mucosally around the primary tumor. The administration was carried out either preoperatively in case of isotopes and intra-operatively in case where a dye was the used tracer. Sub-serosal injection of dye has been tested, as well, without however notably superior results compared to the standard sub-mucosal injection^[33,34].

WHICH IS THE OPTIMAL METHOD TO VERIFY THE PRESENCE OF METASTASIS IN THE IDENTIFIED SENTINEL LYMPH NODE?

The traditional practice of sentinel node biopsy for gastric cancer has been largely based on the use of hematoxylin and eosin (HE) staining for histological examination of frozen section slices. As the accuracy of intraoperative diagnosis of metastasis based on Hematoxylin/Eosin staining ranges significantly in the literature (74%-100%), the issue of whether this certain staining is efficient as a standalone modality remains controversial^[35-42]. Because of this controversy, efforts have been directed towards identifying more reliable histopathological methods. Immunohistochemical staining and reverse transcription-polymerase chain reaction have been both tested in this direction yielding a significantly higher metastasis detection rate than the standard staining technique.

Having this comparative principles, Arigami *et al*^[43] reported the following metastatic detection rates: 8.2% for hematoxylin/eosin, 13.1% for immunohistological staining and 36.1% for reverse transcriptase polymerase chain reaction. These major differences in the detection rates can be explained by the fact that the more sensitive and sophisticated the technique used is, the more likely the detection of micrometastasis is. As the prognostic significance of micrometastasis in gastric cancer has yet to be confirmed, the aforementioned differences require careful interpretation. However, whatever the natural history of gastric cancer micrometastasis is, the widespread use of these sophisticated techniques is quite problematic. Firstly, the penetrability of these techniques among institutions is still poor because of the unavailability of the technical equipment. Secondly, due to the logistics, obtaining a definite result in a timely manner, *i.e.*, before the end of the procedure is still mainly futile. Thus, despite its limitations hematoxylin/eosin staining remains the standard method for examining the detected sentinel

lymph nodes.

WHICH IS THE GASTRIC CANCER PATIENT SUBGROUP SUITABLE FOR SENTINEL NODE MAPPING AND BIOPSY?

Although attractive as a concept, sentinel node biopsy is indicated only for a strict subgroup of gastric cancer patients. Depending on the geographic distribution of each study's institution, eligibility ranges from 3% to 50% of all gastric cancer patient population^[44-47]. Eastern studies have included clinically node-negative T1 and T2 patients^[48-51]. On the other hand, studies originating from Western institutions have included T3 tumors as well^[52]. The complex lymphatic drainage of the stomach and the ubiquitous fear of skip metastasis make the selection of patients extremely important. Fortunately, skip metastasis is encountered usually within the same group of nodes as the identified sentinel lymph node. An approach of removing the entire group of nodes rather than focusing on the identified represents the safest choice^[28,53].

WHICH ARE THE AVAILABLE OPTIONS FOR PRIMARY TUMOR CONTROL?

The "less invasive" theory behind sentinel lymph node biopsy has its benefits based on the limitation of morbidity caused by unnecessary dissection. At least theoretically, combining the method with minimally invasive surgical procedures such as laparoscopic surgery sounds attractive. Studies have already tested the sentinel node concept for both open, laparoscopic gastrectomies and even natural orifice transluminal endoscopic surgery^[54-56]. Generally, there is no consensus regarding the optimal primary tumor control during sentinel node navigation surgery^[57]. Endoscopic resection may be safely applied to small mucosal cancers, but other surgical options such as minimally invasive function-preserving resection of the stomach should be employed for larger lesions, given their tendency for diffuse invasion^[57].

CONCLUSION

In conclusion, sentinel node navigation surgery can change the current surgical treatment of gastric cancer. The applications and ultimately the indications of minimally invasive surgical options such as laparoscopic techniques can be significantly expanded and boosted with the generalized use of sentinel node navigation surgery. Currently, the double tracer method (indocyanine green and radio-isotope tracers) appears to be the method of choice due to its increased efficacy in detecting nodes compared with single tracer techniques. Research is focused on the invention of new lymph node detecting methods utilizing infrared ray endoscopy, fluorescence imaging and near-infrared technology. Despite its limitations and given that the use of more sophisticated techniques

is still in a developing stage, hematoxylin/eosin remains the standard staining for assessing the metastatic status of a detected lymph node.

An intraoperatively detected metastasis of a sentinel lymph node is the factor that will determine whether a patient will proceed with conventional lymph node dissection or not. Laparoscopic resection of the tumor from the stomach with lymph node dissection navigated by sentinel lymph node identification represents an option only for early gastric cancer patients. Unfortunately, patients with T3 or more advanced disease should still be managed conventionally with resection plus lymph node dissection.

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