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UPDATE

Sentinel Lymph Node Mapping In Gastric Cancer Surgery: Current Status

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Lymphonodular metastases remain an important predictive and prognostic factor in gastric cancer development. The precise determination of the lymphonodular invasion stage can be made only by extended intraoperative lymphadenectomy and histopathological examination. But the main controversy is the usefulness of extended lymph dissection in early gastric cancer. This increases the duration of the surgery and the complications rate, and it is unnecessary without lymphonodular invasion . The identification of the sentinel lymph nodes has been successfully applied for some time in the precise detection of lymph nodes status in breast cancer, malignant melanoma and the use for gastric cancer patients has been a controversial issue. The good prognosis in early gastric cancer had been a surgery challenge, which led to the establishment of minimally invasive individualized treatment and acceptance of sentinel lymph node mapping. The dual-tracer method, submucosally administered endoscopically is also recommended in sentinel lymph node biopsy by laparoscopic approach. There are new sophisticated technologies for detecting sentinel lymph node such as: infrared ray endoscopy, florescence imaging and near-infrared technology, carbon nanoparticles, which will open new perspectives in sentinel lymph nodes mapping.

Keywords: sentinel lymph node, gastric cancer, lymphonodular metastases

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Introduction

Despite the individualized therapy, gastric cancer (GC) occupies the top places in both the incidence and cancer mortality [1]. Lymphonodular metastases remain an important prognostic and predictive factor, therefore optimizing the technique for proper identification and removal are required [1]. Identifying the sentinel lymph node (SLN) could however lead to a precise detection of lymph nodes in gastric cancer status.

The SLN concept is based on the theory of lymphatic sequential dissemination of tumor cells [2]. When the lymphatic dissemination occurs, the invasion initially is in the first lymph node (LN) that drains the lymph fluid from the tumor [2,3]. This LN was also named SLN and, depending on positive or negative status, one can determine the presence or absence of metastases in the regional remaining LNs [2,3]. The importance of therapeutic lymphadenectomy is represented by the local control of the disease by reducing local recurrence, while being one of the most important prognostic factors. SLN biopsy is an oncology technique relatively recently introduced into clinical use, and aims to reduce morbidity related to lymphadenectomy, to reduce the extent of surgery and improve LN assessment accuracy [3]. SLN is defined in the literature as a LN that drains the tumor directly, the LN which is closest to the primary tumor, the most radioactive LN, the first LN identified by lymphoscintigraphy, the stained LN, the LN visualized by infrared radiation. In 1960, Gould has used the term "sentinel node" as a node positioned usually in patients with parotid carcinoma [2,3]. In 1977, Cabanas described a new approach to staging carcinoma of the penis, using the term SLN assessed by contrast lymphangiography [2,3]. He found that patients with negative SLN and negative lymph dissection presented the best prognosis compared to patients with positive SLN [2,3]. Wong and Morton used blue dye to determine its effectiveness in locating SLN [2,3]. In 1991, Morton used lymphoscintigraphy to determine the activity of SLN, and Krag, Reingten and Giuliano have later enacted this concept [2]. These groups helped develop sentinel lymphadenectomy as the usual procedure in oncology surgery in melanoma and breast carcinoma, later SLN technique became known and applied for thyroid, vulvar, prostate, colorectal, gastric cancers [2,3]. For SLN have a high predictive value, there must be used effective techniques for its identification, and the histopathology examination must be thorough and accurate.

SLN mapping techniques

SLN identification may be performed using vital dye, radioactive tracer or associating the two methods [2,4,5]. Both dye and radioactive tracer injected in proximity to the tumor are taken up by the lymphatic system and driven towards the lymphonodular area where the SLN limits themselves.

The SLN dye identification method:

Is very useful due to visibility, being a simple, cheap technique performed intraoperatively coloring not only the LN, but the lymphatic vessels as well [6,7]. Dye administration

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can be made intraoperatively subserous around the tumor, or preoperatively endoscopically, submucosal, the results obtained by the two methods in the literature not being different [8,9]. Endoscopic submucosal dye administration is recommended by laparoscopic SLN biopsy because the tumor may be palpable during a surgery intervention [4,5]. The intraoperative injection of dye into subserous is performed prior to mobilization to not alter the lymphatic drainage [2]. The injection is made with the aid of a tuberculin syringe, around the tumor in a circumferential manner, in the four cardinal points [7,8]. Shortly after injecting the dye, colored lymphatic channels that lead to the colored LN are visualized. The time interval in which SLN can be identified is limited because the vital dye is circulated rapidly, extending to other nods. The vital dye method has been widely used due to cost effectiveness and benefits in detecting vessels and LNs, but is not suitable for patients with thick fat tissue, where there is a high rate of false negative [5,6]. The dye marking can be done using several types of dyes, among which the most used are: blue isosulfan (Lymphazurin), methyl blue, indocyanine green (ICG) [6,9]. Isosulfan blue was the dye most commonly used in the past, but may cause allergic reactions ranging from urticaria and hypotension, to anaphylactic shock [10-12]. Methyl blue dye has been shown to be an effective and cost-efficient alternative for isosulfan. The dye is excreted in urine and causes a blue-green coloration of urine [2,12]. Isosulfan blue and methyl blue were the most frequently dyes used in the past, being more visible than a green dye (ICG) on a yellow fat tissue [8,9]. Thus, in SLN mapping, the blue dyes were more widespread, but recently ICG replaced blue dyes because of allergic reactions, especially in Japan [2,9]. Fluorescein appear to successfully cross the lymphatic way to reach the afferent SLN, the LNs turning from blue to yellowish green [8,9]. The phenomenon can be confirmed by a special Wood lamp in a darkened room, the nods being visualized like bright yellow fluorescent spots [8,9]. The rate of identification and sensitivity (detection) of the SLN was lower in ICG mapping due to low visibility, but has developed a new system of infrared ray electronic endoscopy (IREE) (Olympus Optical, Tokyo, Japan) to observe the ICG absorption by infrared [5,8,13]. Using IREE has increased the identification rate in comparison with ICG from 85.8% to 99.5%, and the sensitivity from 48.4% to 97.0% [5-9]. The identification of SLN by IREE combined with ICG presented a higher sensitivity and precision, with the possibility of being applied by thick fat tissue, too [5,8,13]. For visualizing SLN a dark operation theater was required [5,8]. Newly developed ICG fluorescence systems like HyperEye Medical System (Mizuho Medical, Tokyo, Japan) and D-light P system (Karl Storz, Tuttlingen, Germany) don't need dark room for SLN detection [5,8,13].

The radioactive tracer method:

In 1993, Alex and Krag introduced radioisotopes (sulfuric colloid marked with Technetium) in SLN localization administered before surgery and the intraoperative use of a gamma radiation detection probe [2,5,8]. Using the radioactive tracer method involves injecting radioactive tracer, performing a preoperative scintigraphy and using an intraoperative gamma probe [5,8,14]. The radioguided techniques offered a simple technique for identifying and harvesting SLN simultaneously minimizing surgical dissection extension, but has high costs, requires specific technical equipment and interdisciplinary collaboration [5,8]. A big advantage of the method is that it objectively measures the intensity of radioactivity and detects radioactivity even in the thick intraperitoneal fat tissue and the radioisotope tracers remain within the LN for a relatively long time, so are preferred for laparoscopic surgery [5,8].

The radioactive agent technetium-99m sulfur colloid has the advantage of quickly moving throughout the regional lymph nodes and concentrating in that level for a few hours [5,8,15]. The half-life of Tc-99m is about 6 hours. 1-2 ml of radio-colloidal solution is endoscopically submucosally injected the day before surgery (12 hours before surgery) in four peritumoral quadrants [8,16,17]. The scintigraphy is useful in that it identifies the area in which SLN is located and reveals the place of the incision, where with the use of a gamma probe the LN with radioactive activity is detected [4,5]. The radioguided method has higher sensitivity and specificity in identifying SLN in comparison with the vital dye method, even in patients with a thick adipose tissue, making it suitable for laparoscopic surgery due to the longer time of persistence in the LN [17,18]. In literature, the success rate of locating the SLN by radioactive tracer varies between 80-90% [5,8].

The dual-tracer method, using radioactive colloids and vital dye:

Is currently considered the safest method for the detection of SLN in patients with early gastric cancer (EGC) [4,8,16]. The colloidal solution Technetium-99m is injected the day before surgery in four quadrants of the tumor submucosal layer with an endoscopic puncture needle, and the dye during surgery subserous (in open surgeries) or endoscopic submucosa (in laparoscopic surgeries) [17,18]. Several studies have reported that there is no difference in the number and identification of SLN between the subseries and submucosal injection method [3,9].

The ideal method of SLN mapping should allow accurate and secure SLN detection and real-time observation of lymph flow during surgery. The ideal marker for SLN in CG must be a non-toxic, easily accessible and cost effective substance, which is able to accumulate within SLN within a few minutes, remains within SLN for hours, is suitable for use during both surgical techniques (open and minimally invasive), and be easily recognized by the surgeon without the use of sophisticated equipment [15].

There are new SLN detection technologies using sophisticated technology such as infrared ray endoscopy, florescence imaging and near-infrared technology, car-

bon nanoparticles, CT lymphography with ethiodized oil [5,14,15,19]. It seems that at this time research will exceed traditional dye-based techniques and will open new prospects for SLN mapping.

The current state of SLN for GC

The reports on SLN identification in GC surgery began to be published in 2001 by Japanese authors [4,5,20,21]. Hiratsuka used ICG dye administered intraoperatively subserous for SLN mapping, achieving a success rate of 99%, with a sensitivity of 90% for T2 tumors, respectively 100% in T1 and 100% specificity [21]. He concluded that the identification of SLN using ICG can be performed with a high success rate, and the state of SLN may predict the lymph nodes status with a high degree of accuracy, especially in patients with EGC (T1) [21]. In identifying SLN in GC, Aikou used the dual tracer method, blue dye and radioactive colloids, obtaining an identification rate of 94% [20]. In the cases of negative SLN to hematoxylin-eosin (HE), he used immunohistochemistry examination (IHC) with anti-cytokeratin antibodies to detect micrometastases, concluding that it is a promising technique for the GC; SLN can be used to determine the required lymphadenectomy in patients with EGC [20]. After the first good results, there have been many studies with poor results (false negative rate over 40%) achieved especially in cases with T2, T3 tumors more than 4 cm in size [4-6]. Meta-analyzes were conducted by collecting several studies (46) with SLN biopsies in GC and there were reported detection rates and sensitivity between 97.5% and 38.0%, warning that SLN biopsy might not be clinically applicable for limited lymphadenectomy because of its low sensitivity and interstudy heterogeneity [8]. This meta-analysis showed that the number of SLN collected (more than four) is the only factor that affects the sensitivity [8].

Another meta-analysis (with 38 items) report that the rate of identification and sensitivity is higher in cases of GC in the early T1 stage (93.7% and 76.9%), using the dual tracer method by submucosa injection, combined with the histopathological diagnostic by immunohistochemistry [8].

Japan Society of Sentinel Node Navigation Surgery conducted a multicenter prospective trial study using the double tracer method with a radioactive colloid and isosulfan blue in 397 patients with GC, with cT1N0M0 or cT2N0M0, with unique primary lesions smaller than 4 cm [8]. They reported a SLN detection rate of 97.5% and a sensitivity of 93%.

In 2004, Japan Clinical Oncology Group (JCOG) conducted a multicenter prospective clinical trial of SLN biopsy in GC, in cT1N0 stage, to evaluate the feasibility and accuracy of diagnosis [8,22,23]. SLN mapping was performed with ICG dye administered intraoperatively subserous, but the trial was stopped because of an unexpectedly high false negative rate of 46% [8,22,23]. The study authors analyzed a sample of 28 cases, and during the pathological examination conducted several sections of SLN (instead of one section as previously), thus reducing the rate of false negativity to 14% [8,22,23]. They assumed that intraoperative histological examination using just one section and a small learning curve (5 patients) for SLN mapping has caused a high rate of false negativity [8,22]. Japan Society of Sentinel Node Navigation Surgery recommends at least 30 cases for the initial learning curve [4,8,22,23].

The results reported in the specialty literature on SLN biopsy in GC are very different, many Asian authors reported an accuracy of better than 98% [13,14,21], especially in the early stages (T1-T2), while in the Western countries the accuracy was approximately 80%, with a false negative rate ranging from 15% to 20% [4,8,11]. This variation may be explained by the difference in the method of mapping the learning curve.

There has been much controversy regarding the usefulness of SLN mapping. The complicated and multi-direction lymphatic drainage of the stomach and the presence of skip metastasis explain why some surgeons were quite skeptical about applying the SLN in GC method, occasionally mitigating the interest in this subject [24].

Following the progress in screening systems, the proportion of EGC has been growing due to endoscopic investigations, so in Japan half of the patients undergoing surgery for GC are in the early stage (T1) [5]. EGC is defined as a cancer limited to the mucosa and submucosa, regardless of lymphonodular metastases and/or distant metastases. The 5-year survival rate for EGC is 90% or higher, Japanese studies reaching up to 99% for intramucosal carcinoma and 96% for submucosal carcinoma, but EGC may recur [24-26]. The most important prognostic factor for EGC patients is the presence of LN metastases, their preoperative evaluation still being an aspiration [24]. The incidence of lymphonodular metastasis in EGC is 3-24%, depending on the mucosal or submucosal invasion [25,26]. Standard gastrectomy is a surgical procedure performed with curative intent, involving resection of at least two thirds of the stomach by D2 lymphadenectomy. But the main controversy is the usefulness of extensive lymphatic dissection (D2) in EGC. This increases the duration of the surgery and the complications rate, and in absence of lymphonodular invasion it is unnecessary, so that it should not be performed in all cases. The good prognosis in EGC was a surgical challenge and has led to the minimally invasive treatment of strictly selected individual cases. Conventional surgery may be excessive in many patients with EGC, and the minimally invasive one (endoscopy, laparoscopy) can maintain a better quality of life. The Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4) accepts less invasive interventions such as endoscopic mucosal resection or endoscopic submucosal dissection and distal laparoscopic gastric resection in EGC, in well-selected cases [27].

Endoscopic resections are recommended in patients with EGC in T1aN0 stage: tumors of a differentiated type with/without ulceration (Ulcer findings) under 3 cm in

diameter and undifferentiated tumors without ulceration, less than 2 cm in diameter [24,27]. In EGC cases of T1 stage, which are not appropriate for endoscopic resection the laparoscopic surgery is recommended [17,18,27]. The frequency of lymphonodular metastases in EGC was studied and correlated with the clinicopathological characteristics of the tumor and was found that the depth (of the submucosal invasion), the size (bigger than 2 cm), the Ulcer findings, the histological form (undifferentiated), and lymphovascular invasion are the risk factors that significantly increase the presence of lymphonodular metastases [24,27]. The D1 lymphadenectomy standard gastrectomy, or at least D1 + (D1 enlarged) is recommended for patients with EGC, which proved the presence of risk factors for LN metastases [24,27]. The widespread use of minimally invasive surgical techniques and the modern trends to maintain the functions of a residual digestive organ and the quality of life in postoperative patients were also felt in the GC surgery, which is why lately SLN identification has again become of actuality. SLN mapping is one of the most attractive instruments to detect clinically undetectable GC lymphonodular metastases, which may result in a less invasive, individualized surgical approach.

In 2013, Kitagawa reports the results of a prospective multicenter study of SLN mapping for GC with dual tracer method using isosulfan blue dye and endoscopically submucosal administered radioactive colloid [22]. The study selected patients with GC in T1N0M0 or T2N0M0 stage with tumors of ≥4cm in diameter [22]. The results of this prospective multicenter study showed that the method is feasible and safe [22]. The detection rate of SLN and the sensitivity of detecting the metastasis in regional LNs by SN biopsy were comparable to the previously reported data relating to breast cancer and melanoma [22]. Kitagawa concluded that SLN mapping is indicated in cT1 lesions because the false negative rate was significantly higher in cT2 tumors than in cT1 tumors in this study [22]. The method is accepted in patients with EGC to change the current surgical treatment and expanding the indications of minimally invasive therapeutic options (laparoscopic, endoscopic techniques) [22]. Following the results obtained in different studies and meta-analyzes, the technical aspects of SLN sampling have undergone changes; the dissection of the sentinel lymph basin (BLS) instead of SLN biopsy was recommended [5,8,22]. SLN biopsy (picked-up method) is harvested in colored or radioactive LNs, the method being used to determine the SLN in breast cancer and malignant melanoma. The dissection of the BLS is selective lymphadenectomy, which dissects through the colored area to the so-called lymph basins containing the lymph vessels and the colored LNs [5,8,22]. The possibility of BLS containing true positive LNs when SLN is false negative exists, being reported a lymphonodular metastasis detection rate of 92.3% in the BLS group, while in SLN biopsy it was of 50% [5]. There are five lymphatic basins on the main arteries of the stomach: the left gastric artery, the right gastric artery, the left gastroepiploic artery, the right gastroepiploic artery, and the posterior gastric artery [5,8,22]. The type of surgery chosen depends on the location of the tumor and the number and location of the lymphatic basins [8]. Following the favorable results obtained by SLN mapping, the function-preserving gastrectomy associated with the BLS dissection have been introduced in surgical practice [8]. The gastrectomies used to preserve the stomach functions in EGC treatment are local resection, segmental resection on the stomach (transectional gastrectomy), upper pole resection, antral resection with pylorus preservation, performed by open or laparoscopic surgery [8,17,18,22]. BLS dissection is also recommended in the endoscopic treatment of EGC with potential lymphonodular metastases [8]. In the suspected cases, the endoscopic treatment is combined with SLN mapping; if there aren't metastasis in SLN, endoscopic therapy is sufficient, while D2 gastrectomy is necessary if SLN metastasis are found [8]. In the cases where endoscopic resection is not sufficient, the block endoscopic resection (full-thickness resection) is recommended or laparoscopic resection associated with BLS dissection (technical CLEAN-NET or NEWS) [8].

The histopathological examination of the SLN

The conventional histopathological examination of a single section of the resected LN was inappropriate. To increase the accuracy of identifying LN metastasis, the multi-serial examination with HE was proposed, thus reducing the rate of false negativity to 14% [8,22,23]. To identify micrometastases and reducing the rate of false negativity, IHC techniques and polymerase chain reaction (RT-PCR) were used, which are more sensitive techniques and are applied if the result is negative for HE [5,20,22]. The conventional RT-PCR method to obtain a finding of micrometastases is not applicable for rapid diagnosis during surgery because of the time required [5]. There have been studies that have shown that the sensitivity and specificity of the one-step nucleic acid amplification assay compared with histological examination in detecting cytokeratin 19 mRNA were higher [5,8]. Recent developments in molecular biological techniques have reduced the detection time to 30–40 min [8]. These molecular biological methods have dramatically improved sensitivity in the diagnosis of intraoperative SLN metastases, but remain incomplete [8].

Conclusion

SLN mapping is recommended in patients with EGC to avoid unnecessarily extended lymphadenectomy and related complications, and can thus expand the indications of minimally invasive treatment options. The dual-tracer method using radioactive colloids and vital dye is currently considered the safest method for the detection of SLN in patients with EGC. Since recently, the SLN dissection is also recommended in patients with ECG after endoscopic resection with potential lymphonodular metastases. In the

near future, preserving the function of a residual digestive organ and the quality of postoperative life will be more emphasized. SLN is one of the most attractive instruments to detect clinically undetectable GC lymphonodular metastases, which may result in a less invasive individualized surgical approach. Thus, the laparoscopic resection of the primary gastric tumor combined with the proper LN dissection determined by the SLN status is by an option for EGC. One potential strategy to validate the concept of SLN in GC would be advancing fast intraoperative histopathology. One-step nucleic acid amplification assay, an automated system that uses the reverse-transcription loop-mediated isothermal amplification method for gene amplification, may be an ideal to replace the histological examination with a quick and simple molecular approach.

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Conflict of interest

The authors declare no conflict of interest

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