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Sentinel Lymph Node Sampling for Early Gastric Cancer—Preliminary Results of A North American Prospective Study

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Abstract

Introduction Although endoscopic resection for early gastric cancer is well established, anatomical resection with regional lymphadenectomy is recommended for lesions at high risk for occult lymph node metastasis (e.g., lymphovascular invasion, poor grade, and deep submucosal invasion). However, 75–95% high-risk early gastric cancer (HR-EGC) patients ultimately have node-negative disease and could potentially have undergone organ-sparing resection. Due to the inadequacy of standard modalities to reliably rule out nodal metastases in HR-EGC patients, sentinel lymph node (SLN) sampling was developed in Asia with promising results. However, the applicability of this technique in the West has been brought into question due to potential differences in tumor histology and body habitus. This prospective study aimed to test SLN sampling for North American EGC patients.

Methods All patients with biopsy-confirmed T0–2 N0–1 M0 gastric adenocarcinoma at the Montreal General Hospital-McGill University Health Centre were eligible for enrollment. Esophageal and GEJ cancers were excluded due to the high rate of intrathoracic lymph node involvement. Peritumoral submucosal injection with T^{99} radiocolloid was performed endoscopically 24–30 h prior to surgery. Methylene blue dye injection was performed after induction of anesthesia. SLN basins were identified as those having > 10% of baseline tumor radiation signal or blue color, or both. After basins were individually removed, standard laparoscopic anatomical resection was then performed with D2 lymphadenectomy. (ClinicalTrials.gov identifier: NCT03049345). Data are presented as median (interquartile range).

Results From July 2016–April 2018, 253 patients with esophagogastric adenocarcinoma were evaluated. Of these, 10 met inclusion criteria (90% male, age 66(30) years). Subtotal gastrectomy was performed in nine patients (90%) and length of stay was 4 (2) days. At least one SLN basin was identified in nine cases (90%). The median #SLN basins identified was 2(2) with a median of 5(5) total SLNs retrieved per patient. In the one case for which no SLN basins were identified, only blue dye injection was used, whereas SLNs were identified in all cases using the dual tracer method. Final T-stage was pT1b/T2 in four (40%), pT1a in two (20%), and Tx in four (40%). Two patients (20%) had lymph node metastases on final pathological analysis, both of which were identified by SLN sampling (accuracy 100%; false negative rate 0%). No adverse events related to SLN retrieval were identified.

Conclusions This study represents the first prospective feasibility evaluation of sentinel lymph node sampling for early gastric cancer in North America with promising preliminary results. The dual tracer method was superior to single agent blue dye in identifying sentinel nodal basins. Considerable further study is necessary to verify the safety and utility of SLN mapping in North American patients with early gastric adenocarcinoma.

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Keywords Early gastric cancer · Sentinel lymph node · Endoscopic submucosal resection · Innovation

Introduction

Gastric cancer incidence in North America is 7.4/100,000 population, with 24,590 new cases diagnosed annually in the USA.[1] Of these, approximately 15% is detected at the early gastric cancer (EGC) stage with no spread to regional lymph nodes.[2] Gastric cancers detected at an early stage have an excellent prognosis, with reported long-term overall survival rates of 71–92%.[3–6]

Recently, organ-sparing techniques have emerged which allow select early gastric cancers to be treated without anatomical resection. These techniques, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), allow for curative resection with complete organ preservation.[5] The shortcoming of these organ-sparing resection techniques is that lymphadenectomy is not performed, limiting the application of these techniques to only those patients at acceptably low risk of occult lymph node metastases.[7,8] Even among "high-risk" patients, however, the majority are found to have no lymph node metastases after anatomical resection with regional lymphadenectomy,[7,9] suggesting these patients too could undergo organ-sparing resection if only accurate lymph node staging were achievable without extensive dissection.

Current staging modalities for gastric cancer are unable to accurately predict which EGC patients harbor micro-metastases in regional lymph nodes.[10–12] As such, the mainstay of treatment for moderate and high-risk EGC remains anatomical resection with regional lymphadenectomy. This approach, while oncologically sound, is often associated with complications and unpleasant short-term and long-term side effects.[13,14] Given the long-life expectancy of patients after resection of EGC, curative resection with organ preservation to improve postoperative quality of life should be a treatment goal.

To address the gap in the ability to accurately detect nodal metastases in EGC, gastric sentinel lymph node (SNL) sampling was pioneered in Asia and has undergone refinement and study there since the early 2000s.[15] Following the success of SLN sampling in gastric cancer, select Asian institutions are now applying this technique to diverting sentinel node-negative (SLN–ve) T1 and T2 gastric cancer patients away from anatomical resection with extensive lymphadenectomy and towards organ-sparing endoscopic or wedge resection.[16] Despite the success of this technique in Asia, gastric SLN sampling has not been adopted in the West potentially due to increased rates of obesity in North America[17] and differences in tumor location and histology between Asian and North American patients,[18] limiting generalizability of techniques and treatments from one region to another.

The purpose of this prospective study is to determine the utility, feasibility, and accuracy of SLN sampling for early gastric cancer in a North American context.

Methods

Patient Selection

Study subjects were patients undergoing curative-intent upfront anatomical resection with extended D2 lymphadenectomy for cT0–2, N0–1, M0 gastric adenocarcinoma. The study protocol is outlined in Fig. 1. As this is a feasibility study, patients with only one clinically suspicious lymph node were eligible for study inclusion. Preoperative staging included physical examination, upper endoscopy with estimation of lesion size and location, endoscopic ultrasound (EUS), and contrast-infused CT chest/abdomen/pelvis for all patients. Positron-emission tomography (PET) scan was done selectively. Patients who had undergone endoscopic resection and were found to be at high risk for lymph node metastases or had incomplete tumor removal were also eligible.

Sentinel Lymph Node Detection

A dual tracer method using both radioactive tracer and visible dye has been repeatedly shown to produce greater SLN detection rates than single tracer injection alone.[19] Radioactive colloid has been found to reach the sentinel nodes within 2 h and remain there for more than 20 h,[20] while blue dye reaches the sentinel lymph nodes within 5–10 min after injection.[21]

At 20–24 h before surgery, 3.0 mCi of 99 m technetium sulfur colloid filtered at 0.22 μm and diluted in 3.5 cc of saline was injected submucosally at 4 points around the tumor. At the time of surgery, 3 cc of methylene blue dye was similarly injected. At surgery, the gastrocolic ligament and pars flaccida are opened to expose all gastric lymph node drainage basins. Using visual inspection and the Navigator GPS 10 mm straight laparoscopic gamma probe (Dilon Diagnostics, Newport News, Virginia), blue nodes, and those emitting > 10% of tumor signal were considered sentinel nodes and extracted as individual specimens. According to published protocols to maximize SLN detection,[15, 22] SLNs were extracted as a "bundle" taking the surrounding perigastric fat. Any nodes which were malignant in appearance but not part of a sentinel nodal bundle were removed and sent for permanent section as separate specimens.

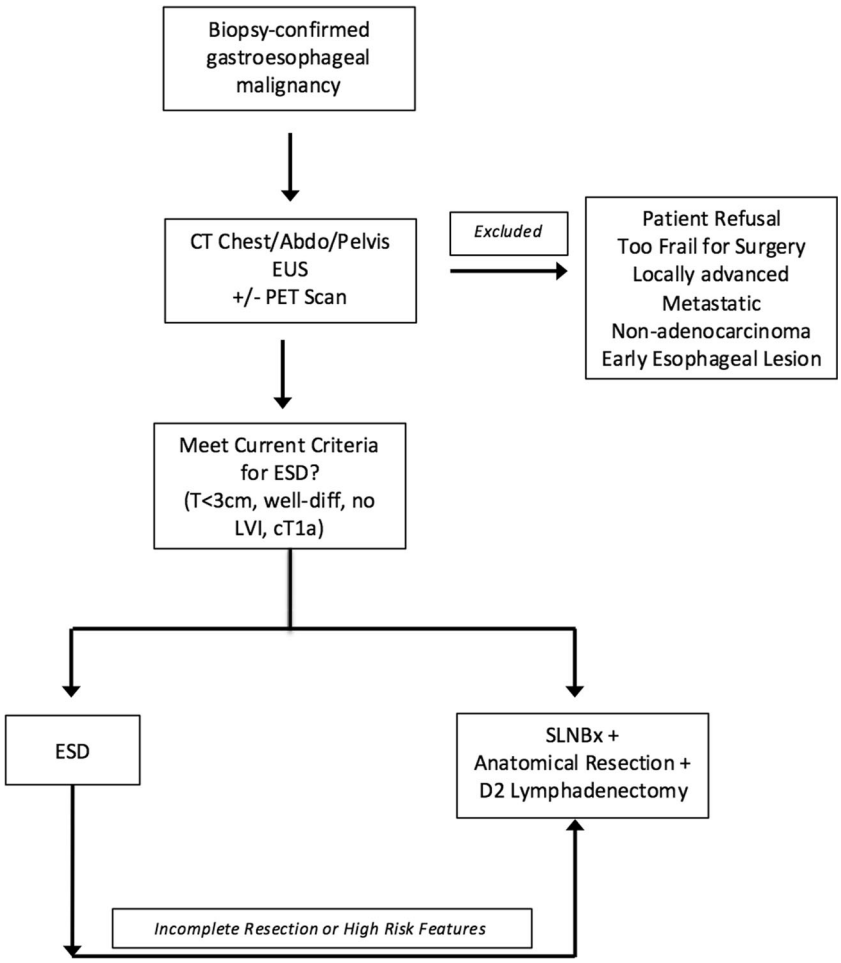

Fig. 1 Patient treatment algorithm. This figure outlines the criteria for study enrollment and management of gastric cancer patients at our center. CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography, cN + ve, clinically node positive; cM + ve, clinical evidence of distant metastases; SLNBx, sentinel lymph node biopsy; ESD, endoscopic submucosal dissection; locally advanced: ≥ cT3 or ≥ 1 clinically positive LN

Surgical and Perioperative Care

All patients were operated by one of two experienced foregut surgeons (CM and LF) who each perform > 50 D2 lymphadenectomies per year. Following extraction of sentinel nodal bundles, patients underwent standard anatomical resection with D2 lymphadenectomy as determined by the study protocol (Fig. 1). All patients underwent Roux-en-Y reconstruction as a standard practice in our group. Patients were managed perioperatively according to a standardized enhanced recovery pathway based on recently published guidelines[23] and approved for use by the institution. All postoperative complications were captured prospectively using the Clavien-Dindo grading system.

Pathologic Examination

All surgical specimens, including sentinel nodal bundles, were analyzed using permanent section by a pathologist with expertise in gastric cancer.

Primary Outcomes

The main outcome measures of this study were success of sentinel lymph node identification and accuracy of SLN staging in comparison to final pathological stage.

Secondary Outcomes

Patient demographics and American Society of Anesthesiologists (ASA) score[24] at diagnosis, pre- and post-treatment staging scores, final pathological tumor characteristics, adjuvant treatment details (if any), recurrences, and 30-day procedure-related complications were prospectively recorded. Surgical complications were cataloged according to the Clavien-Dindo system[25] for reporting postoperative adverse events.

Statistical Analyses

Continuous variables are reported as median (interquartile range) unless otherwise specified. Statistical analyses were performed using IBM SPSS Statistics (©IBM, 2015).

This study was approved by the Internal Review Board of the McGill University Health Centre and registered at ClinicalTrials.gov identifier: NCT03049345.

Results

From July 1, 2016, to April 30, 2018, a total of 253 gastroesophageal cancer patients were screened for study eligibility, of which 10 met inclusion criteria (Fig. 2). Three patients had undergone prior endoscopic submucosal dissection for early lesions and were found to be at high risk of nodal metastases based on histological features. The remaining patients underwent upfront anatomical resection for lesions not amenable to endoscopic resection (deep submucosal or muscularis propria invasion). Tumors were located in the body or distal stomach in all the cases. Characteristics of study subjects are listed in Table 1.

The surgical approach was laparoscopic in all cases. One case required conversion to open for retroperitoneal bleeding due to adhesions from previous pancreatitis. One patient underwent total gastrectomy for early gastric cancer in the context of hereditary gastric cancer (CDH1 gene carrier status); the remainder were treated with subtotal gastrectomy. No adverse events were encountered as a direct result of the sentinel lymph node sampling procedure. Three patients experienced adverse events postoperatively, of which two were minor (CD class ≤ 2 and one required re-operation for evacuation of intraperitoneal hematoma (CD 3b). No deaths occurred within 30 days of surgery. Operative outcomes are described in Table 2.

Table 1 Characteristics of study subjects

Number	10
Male (%)	9 (90)
Age (years)	66 (30)
BMI	22 (4)
ASA score (%)	
1	0
2	5 (50)
3	5 (50)
4	0
Differentiation	
High-grade dysplasia	1 (10)
Well	1 (10)
Moderately	2 (20)
Poorly	6 (60)
Pretreatment stage	
TxN1	1 (10)
T1aN0	1 (10)
T1bN0	3 (30)
T2 N0	4 (40)
Tumor location	
Body	3 (30)
Antrum	4 (40)
Incisura	3 (30)
Tumor size (cm)	3 (3)

Results are presented as median (interquartile range) unless otherwise specified. *ASA*, American Society of Anesthesiology[24]; *BMI*, body mass index

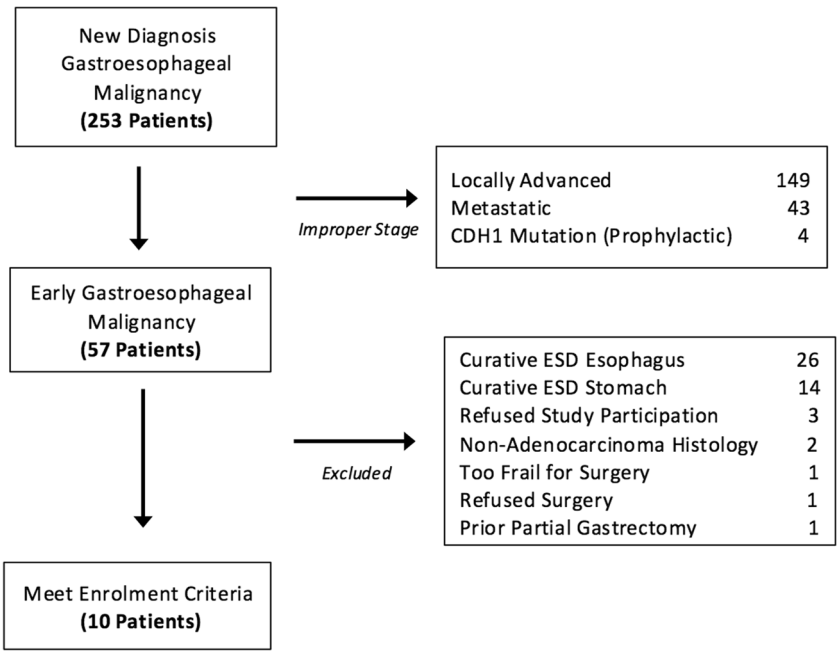

Fig. 2 Patients screened for study eligibility. This figure describes the number and type of patients screened for study eligibility as of publication. CDH1, cadherin-1 gene; ESD, endoscopic submucosal dissection

Table 2 Operative details

Surgical outcomes		
Completed laparoscopically	9 (90)	
Subtotal gastrectomy	9 (90)	
Length of stay (days)	4 (2)	
Surgical complications		Clavien-Dindo[25] score
Bleeding	2 (20)	2
Re-operation 30 days	1 (10)	3b
Delayed gastric emptying	1 (10)	1
Ileus	0	
Pneumonia	0	
DVT/PE	0	
ICU admission	0	
Myocardial infarction	0	
Aspiration	0	
UTI	0	
Duodenal stump leak	0	
Anastomotic leak	0	

SLNSx. sentinel lymph node sampling; *DVT/PE*, deep vein thrombosis/pulmonary embolism; *ICU*, intensive care unit; *UTI*, urinary tract infection

On final pathological analysis, four patients had no identifiable tumor in the stomach. One of these had multi-focal high-grade dysplasia with a single focus of carcinoma in situ preoperatively, two had lymphovascular invasion and poorly differentiated tumor histology after complete endoscopic submucosal dissection (high-risk features for nodal metastases[7]), and one had positive deep margin after endoscopic resection. Of these, one patient was found to have a single nodal metastasis after anatomical resection. All patients underwent preoperative, peri-tumoral methylene blue dye injection as per study protocol. Radiotracer-guided sampling was not done in one patient who failed to present for preoperative injection. Sentinel nodal bundles could not be found in this case using the single tracer method (blue dye alone). Sentinel nodal sampling was successful in the remaining nine cases (90%) with a median of two bundles and five total nodes identified per patient. The maximum number of sentinel nodal bundles identified was five (two patients), and the most individual SLNs identified in a single case was 18. Number of sentinel lymph nodes identified per case increased over the study period (Fig. 3). Among patients in whom SLNs could be identified, concordance of SLN samples to final pathology with respect to nodal involvement was 100% in this series. Two patients (20%) had lymph node–positive disease on final analysis, of which both had positive LNs identified in the SLN basins (true positive rate = 100%). The first patient had 2/19 LNs positive, of which one node was identified among the sentinel nodes; the second patient had 1/47 LNs positive (Table 3).

Discussion

This series describes the first prospective trial in North America examining feasibility and efficacy of sentinel lymph node sampling for early gastric cancer patients. The results of this study demonstrate early success with the technique, with 90% success rate of identifying SLNs and 100% accuracy of SLNSx in predicting nodal stage. Importantly, no false negatives and no adverse events related to SLNSx were encountered.

Treatment of early gastric cancer (EGC) has been revolutionized by the advent of organ-sparing resection for lesions at low risk of lymph node metastases. According to the Japanese Gastric Cancer Treatment Guidelines,[8] EGC lesions are deemed appropriate for organ-sparing resection if they meet the following criteria: confined to the mucosa (T1a), tumor size < 2 cm, no ulceration, and well-differentiated tumor grade. Together, tumors with these features have a very low risk of lymph node metastases (< 1%). Long-term outcomes of organ-sparing resection in well-selected patients are highly favorable, with local recurrence and overall survival rates comparable to anatomical resection.[4,5] For tumors that do not meet the above criteria, however, risk of lymph node involvement is increased, with submucosal invasion, ulceration, tumor size > 3 cm, poorly differentiated tumor type, and lymphovascular invasion conferring risk of lymphatic metastases of 4–25%.[7] For this reason, current best practices recommend EGCs with high-risk features continue to undergo anatomical resection with regional D2 lymphadenectomy. However, 75–96% of such patients will ultimately have no regional metastases on final pathological analysis, suggesting they could have been spared anatomical resection if only their lymph node basins had been definitively staged prior to surgery.

Sentinel lymph node sampling (SLNSx) addresses a gap in the care of early gastric cancer patients at high risk of LN metastases by providing a means to definitively stage regional lymph nodes without necessitating anatomical resection. Presently, several preoperative imaging modalities are available to determine lymph node stage for gastric cancer, including endoscopic ultrasound (EUS), computed tomography (CT), and positron emission tomography (PET). Unfortunately, the sensitivity of these modalities is woefully inadequate to accurately predict microscopic lymph node metastases.[10–12,26] With this in mind, a nationwide, prospective multi-institutional trial in Japan recently confirmed the safety and accuracy of SLNSx to identify nodal metastases in high-risk ECG patients.[15] As a result, SLNSx is now being used in Japan to select high-risk EGC patients for organ-sparing resection.[16] If proven successful in North American patients, SLNSx may similarly provide a staging modality that is currently missing from the treatment armamentarium of EGC in the West.

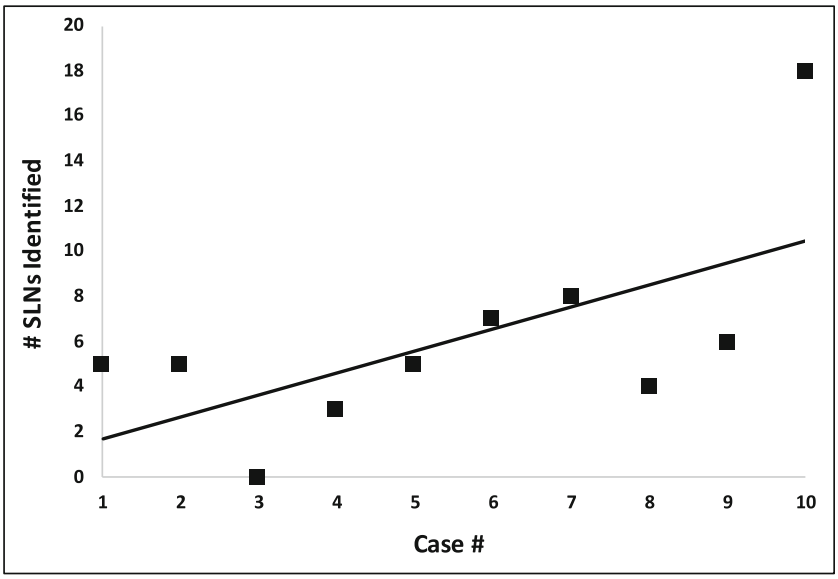

Fig. 3 Chart depicting increasing total number of sentinel lymph nodes identified per patient with advancing case number

Table 3 Postoperative pathological data and sentinel lymph node sampling (SLNSx) procedure details

Final pathology	
R0 resection	10 (100)
T-stage	
Tx	4 (40)
T1a	2 (20)
T1b	3 (30)
T2	1 (10)
N-stage	
N0	8 (80)
N1	2 (20)
Median total LNs/patient	25 (20)
SLNSx data	
Methylene Blue Injected (%)	10 (100)
T99 Sulfur Colloid Injected (%)	9 (90)
Number of patients SLN identified (%)	9 (90)
Median number of SLN bundles/patient	2 (2)
Median number of SLNs/patient	5 (5)
Number of SLN bundles "hot" only (%)	4 (21)
Number of SLN bundles "blue" Only (%)	8 (42)
Number of SLN bundles "hot" and "blue" (%)	7 (37)
Number of LN + ve patients (%)	2 (20)
Number of SLN + ve patients (%)	2 (20)
False negative rate	0%
Accuracy	100%

SLN, sentinel lymph node; *LN*, lymph node; False Negative Rate = (# of −ve SLN patients with +ve LNs on D2 dissection)/all LN + ve patients; Accuracy = (true positives + true negatives)/(all patients in whom SLNs were identified)

Interestingly, in this series of 10 patients with early gastric cancer, extensive lymphadenectomy was found to be non-therapeutic after final pathological analysis in six (60%). These patients could thus have potentially been spared anatomical resection had a less invasive means of definitive nodal staging been available. Of the four who required anatomical resection, one was a CDH1 gene carrier with a small T1a lesion who underwent total gastrectomy, and one had a focus of carcinoma-in-situ in a field of multi-focal high-grade dysplasia, making anatomical resection unavoidable in both cases. The remaining two patients had lymph node–positive disease on final analysis, both of which were identified in the SLN bundles. The rate of LN-positive disease in this study is in line with rates reported for similar patients in a much larger series[7] and underlines the need for a more accurate LN-staging technique to reduce the rate of non-therapeutic anatomical resection in these patients.

Technical factors affecting the success of SLNSx were identified during this study which were addressed as experience with the technique advanced. Volume of both methylene blue and T99 sulfur colloid injected was increased from 2 to 3 cc after the first case, which seemed to enhance visibility of blue nodes and radiotracer signal. Shine-through signal from the primary tumor was found to obscure nodal detection using the laparoscopic gamma probe due to limitations in angulation. Introducing the probe from multiple ports oriented at different angles to the stomach and approaching the nodal basins from behind by lifting the primary tumor away were maneuvers that helped in identifying true SLN basins. Similarly, completely mobilizing the stomach by dividing the gastrocolic ligament up to the first short gastric vessel and opening the pars flaccida allowed ready access to all possible SLN basins both visually and with the gamma probe.

Visual identification of SLNSx proved challenging at times, most importantly since they are often encased in perigastric adipose tissue. The median body mass index (BMI) of patients in this series was 22, substantially lower than the average BMI of adult Canadians. According to recent statistics, 76% of adult males over the age of 40 had a BMI > 25 in 2011.[27] Patients in this series were not selected for enrolment based on weight, however, the low BMI may have contributed to a high SLN detection rate among study patients. Further study with patients whose body compositions are more representative of the general population is necessary to confirm the utility of gastric SLNSx in North America.

Use of the dual tracer method was important to the high success rate of SLN identification in this study. While blue nodes could be easily seen in several patients (Fig. 4), they were frequently difficult to find by visual inspection alone. Indeed, the only case in which SLNs could not be identified had failed to undergo injection of the radioactive tracer. Anecdotally, the radiotracer signal seemed to guide dissection of SLN bundles, at which point the blue dye became more visible. Similarly, blue color alone did lead to the dissection of some nodes which did not emit a radioactive signal, implying both tracers are important for complete SLN detection. Injection of T99 sulfur colloid is logistically difficult as it must be done endoscopically 24 h before surgery, mandating an extra procedure for the patient and limiting flexibility in surgical timing. It is nevertheless the opinion of the study authors that radiotracer use is necessary for the success of this technique. While studies have demonstrated the feasibility of using immunofluorescence dye as a single tracer for gastric SLNSx, this approach has been associated with a high false negative rate,[28,29] and at present, there is insufficient evidence demonstrating a single agent is equivalent to the dual tracer method for SLNSx in gastric cancer.

Limitations of this study include most importantly the small sample size. Recruitment could have been increased by offering enrolment to all patients with EGC lesions at low risk of LN metastases, however this was not done for two reasons: firstly, our program has offered endoscopic submucosal dissection for these cases since 2007 with excellent results,[30] so it was not feasible to begin offering unnecessary anatomical resection to these patients for the purposes of this study. Secondly, since finding positive LNs among these low-risk patients is extremely unlikely, recruitment into this study would not have furthered the aim of this study in determining accuracy and false negative nodal detection rates with SLNSx. In order to address the small numbers in this preliminary series, ongoing recruitment and study are planned. Finally, this study was carried out at a single institution in relatively low-BMI patients, limiting greatly the generalizability of these results. The authors felt it was important to learn and perfect the technique locally before expanding to other sites in order to ensure uniformity of approach. Ultimately, multicenter involvement and recruitment of patients with higher BMI will be needed to determine the applicability of SLNSx to North American gastric cancer patients generally.

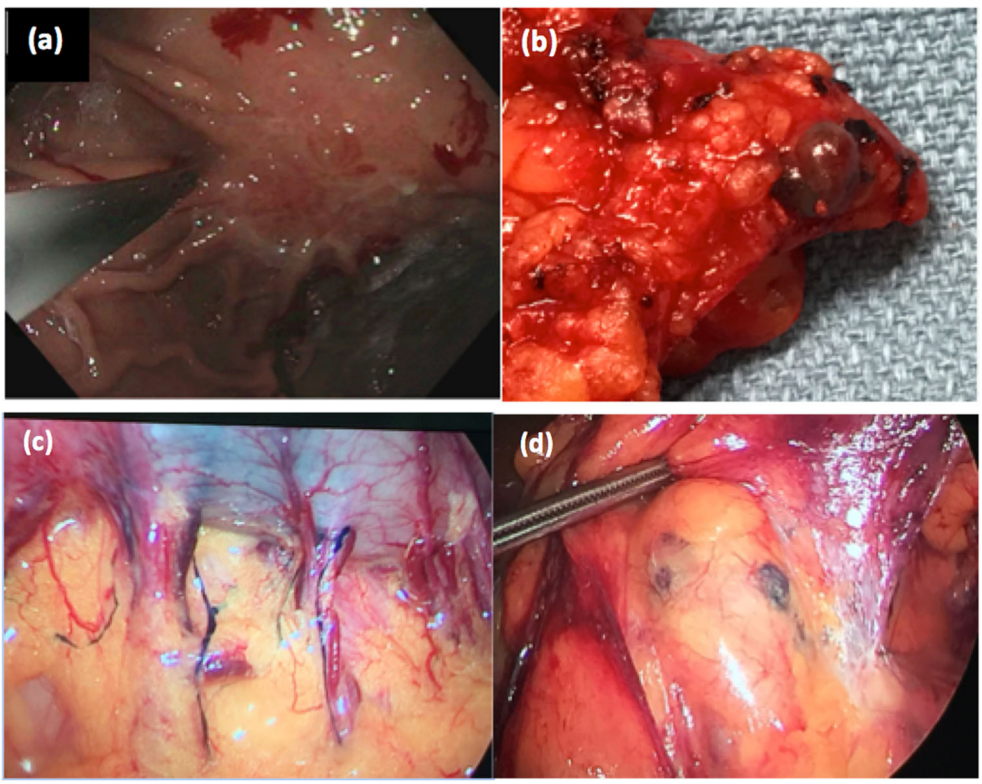

Fig. 4 Dual tracer method for sentinel lymph node identification. **a** Peritumoral injection of 3 cc of 99mTechnetium sulfur colloid, performed endoscopically 24 h before surgery; **b** ex vivo photograph of sentinel lymph node identified using dual tracer method (gamma probe signal > 10% of tumor background and visual inspection of blue color); **c** visible lymphatic drainage along gastric greater curvature of methylene blue injected 20 min prior to surgical incision; **d** Blue-stained nodes seen at base of right gastroepiploic artery approximately 45 min after peritumoral injection of methylene blue

Conclusions

This study represents the first prospective evaluation of sentinel lymph node sampling for early gastric cancer in North America with promising preliminary results. The dual tracer method was superior to single agent blue dye in identifying sentinel nodal basins. Further study involving greater numbers of participants is necessary to verify the safety and utility of SLN mapping in North American patients with early gastric adenocarcinoma.

Author Contributions Project conception—Mueller, Ferri, Lisbona
Data acquisition and Analysis—Mueller, Sorial, Siblini
Drafting and revising the work—all
Approved final version—all

Compliance with Ethical Standards

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

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