

Sentinel Lymph Node Navigation Surgery for Early Gastric Cancer: Is It a Safe Procedure in Countries with Non-Endemic Gastric Cancer Levels? A Preliminary Experience

Guilherme Pinto Bravo Neto, Elizabeth Gomes Dos Santos¹, Felipe Carvalho Victor¹, Marcelo Soares Neves², Márcia Ferreira Pinto², and Carlos Eduardo De Souza Carvalho³

Department of Surgery, Faculty of Medicine, Federal University of Rio de Janeiro (UFRJ),

¹Division of Esophageal and Gastric Surgery, General Surgery Service of the Clementino Fraga Filho University Hospital (HUCFF-UFRJ),

²Gastroenterology Service of the Clementino Fraga Filho University Hospital (HUCFF-UFRJ),

³Pathology Service of the Clementino Fraga Filho University Hospital (HUCFF-UFRJ), Rio de Janeiro, Brazil

Purpose: Early diagnosis of gastric cancer is still the exception in Western countries. In the East, as in Japan and Korea, this disease is an endemic disorder. More conservative surgical procedures are frequently performed in early gastric cancer cases in these countries where sentinel lymph node navigation surgery is becoming a safe option for some patients. This study aims to evaluate preliminary outcomes of patients with early gastric cancer who underwent sentinel node navigation surgeries in Brazil, a country with non-endemic gastric cancer levels.

Materials and Methods: From September 2008 to March 2014, 14 out of 205 gastric cancer patients underwent sentinel lymph node navigation surgeries, which were performed using intraoperative, endoscopic, and peritumoral injection of patent blue dye.

Results: Antrectomies with Billroth I gastroduodenostomies were performed in seven patients with distal tumors. The other seven patients underwent wedge resections. Sentinel basin resections were performed in four patients, and lymphadenectomies were extended to stations 7, 8, and 9 in the other 10. Two patients received false-negative results from sentinel node biopsies, and one of those patients had micrometastasis. There was one postoperative death from liver failure in a cirrhotic patient. Another cirrhotic patient died after two years without recurrence of gastric cancer, also from liver failure. All other patients were followed-up for 13 to 79 months with no evidence of recurrence.

Conclusions: Sentinel lymph node navigation surgery appears to be a safe procedure in a country with non-endemic levels of gastric cancer.

Key Words: Sentinel lymph node biopsy; Stomach neoplasms; Gastrectomy; Lymphadenectomy; Neoplasm micrometastasis

Introduction

For many years, Japanese and Korean surgeons have emphasized the importance of major gastrectomies with extensive

lymphadenectomies as a part of curative treatment for gastric cancer. Nowadays, however, they perform minor procedures for these malignancies, thus individualizing gastric cancer treatment. This has been possible due to early diagnosis of gastric cancer in those countries, as surgery for patients with early gastric cancer (EGC) has accounted for more than 50% of all surgical procedures for gastric cancer in these countries. Minor procedures include endoscopic resections and minor gastric resections with less extensive lymphadenectomies, such as D1 or modified D1, and have improved postoperative quality of life while maintaining 5-year survival rates above 95%.^{1,2} The high gastric cancer

Correspondence to: Guilherme Pinto Bravo Neto

Department of Surgery, Faculty of Medicine, Federal University of Rio de Janeiro (UFRJ), Rua Engenheiro Enaldo Cravo Peixoto, 65/201, Rio de Janeiro (RJ) 20540-106, Brazil

Tel: +55-21-999844679, Fax: +55-21-25371222

E-mail: guilhermebravo@gmail.com

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incidence has enabled better studies of the disease, therefore enhancing the experience levels of many professionals from different medical fields and improving diagnosis and treatment. Thus, accurate endoscopic diagnosis of early tumors along with detailed information from histopathological examinations of biopsies and imaging allow curative endoscopic resections that treat EGC to be performed safely. Most importantly, all of these safety increases can be attributed to analysis of background statistical data on lymph node metastasis for each type of tumor that is based on thousands of patients who previously underwent extensive gastrectomies with D2 lymphadenectomies. Guidelines of the Japanese Gastric Cancer Association¹ determine the indications for these endoscopic resections, which have negligible risks of metastasis. However, many patients who do not fit these indications still have relatively low risks of lymph node metastasis, and that what has led to expanded indications for endoscopic resections and supported the idea of sentinel node (SN) navigation surgery (SNNS) for EGC.³⁻⁶

This study aims to evaluate the outcomes of patients with EGC who underwent SNNS as a primary surgery in a university hospital in Brazil, a country with high, but still non-endemic, rates of gastric cancer.

Materials and Methods

We evaluated 14 patients with EGC out of 205 gastric cancer patients who were treated at the Clementino Fraga Filho University Hospital at the Federal University of Rio de Janeiro from September 2008 to March 2014. These patients represented half of our EGC patient population, and this subset underwent SNNS with intraoperative endoscopic peritumoral injection of patent blue dye. All 14 patients had an endoscopic finding of EGC, which was confirmed by endoscopic ultrasound (EUS) and histological examination of gastric biopsies. Preoperative clinical staging with EUS and computed tomography (CT) displayed disease that was limited to the stomach. Other EGC patients did not have clear cT1N0 clinical preoperative staging and underwent standard gastrectomies with D2 lymphadenectomies. The follow-up cutoff date was April 10, 2015.

All gastroscopies were performed with the patient on the operating table and after open surgical access to the peritoneal cavity to locate the lesions, and intraoperative endoscopic submucosal injections of 0.5 ml of patent blue dye were administered in each of the four quadrants of the tumor. Within 3 to 5 minutes, the

SNs were stained and then excised for frozen section histological examinations. Each SN was histologically examined in one plane through its largest dimension after hematoxylin and eosin staining. If the nodes were negative for metastatic disease, we proceeded to minor gastric resection, the characteristics of which depended on the location of the gastric lesion. Likewise, a sentinel basin resection was performed according to SN mapping. All harvested lymph nodes were histologically examined using paraffin-embedded sections after surgery. Ambulatory monitoring was performed using endoscopy and abdominal CTs every six months in the first two years and then annually.

This research complies with the guidelines for human studies and animal welfare regulations. Our institute's committee on human research (Research Ethics Committee/Institutional Review Board) has approved the study protocol (139/11 – CEP), and all patients provided informed consent.

Results

Among the 14 patients, there were 6 female and 8 male patients aged between 36 and 83 years, with an average age of 64.6 years. Tumor sizes averaged 2 cm and varied from 0.5 cm to 4.3 cm. Type III tumors, which were either isolated or found in combination with other tumor types, were observed in 11 patients. Tumors were well-differentiated, moderately differentiated, and poorly differentiated in 6, 3, and 5 patients, respectively, and were located in the lower third, middle third, and upper third of the stomach in 7, 5, and 2 patients, respectively. The average number of sentinel lymph nodes was 2.5 (range, 1~5 nodes). With the exception of 2 patients with SNs in station 8, patients had SN located exclusively in N1 stations. All SNs were negative for metastasis upon frozen section examination. Antrectomies with Billroth I gastroduodenostomies were performed in the seven patients with distal tumors. The others underwent wedge resections with direct visualization of the tumor using gastrotomy since the lesions were neither apparent at the serosa nor palpated. This allowed resections with safe margins of 3 to 5 cm while gastric deformation levels were evaluated, thus avoiding major anatomical deformations of the remaining stomach. Sentinel basin resections were performed in 4 patients with well-differentiated cT1a tumors who had sentinel lymph nodes located exclusively in N1 stations. These basin resections were extended to stations 7, 8, and 9 in the remaining 10 patients. The average number of resected lymph nodes was 9.7 (range, 2~19 nodes). One patient received a

Table 1. SLN navigation surgery for early gastric cancer

Patient No.	Sex	Age (yr)	Size (cm)	Macroscopic feature*	Site	Lauren's classification	Histologic type	SLN (n)	LN station	Operation/ date	Lymphadenectomy	pTNM	Follow-up
1	F	77	2.2	Type III	L	Intestinal	Well differentiated	3	4, 7, and 8	Antrectomy/ 09/2008	BR+stations 7, 8, and 9	T1bN0M0	A, DF
2	F	78	1.8	Types IIa+IIc	M	Intestinal	Moderately differentiated	4	3	Wedge GR/ 09/2008	BR+stations 7, 8, and 9	T1bN0M0	A, DF
3	F	53	1.5	Types IIc+III	M	Diffuse	Poorly differentiated	2	3	Wedge GR/ 10/2008	BR+stations 7, 8, and 9	T1aN0M0	2nd EGC 2 years PO: TG; A, DF
4	M	60	1.7	Type III	M	Intestinal	Well differentiated	2	3	Wedge GR/ 10/2009	BR	T2N0M0	2nd EGC 1 year PO: TG; A, DF
5	M	60	1.7	Type I	L	Intestinal	Well differentiated	3	5 and 6	Antrectomy/ 01/2010	BR	T1aN0M0	A, DF
6	M	54	3.5	Type IIb	L	Intestinal	Moderately differentiated	3	3	Antrectomy/ 05/2011	BR+stations 7, 8, and 9	T1bN0M0	Dead 2 years PO (LF); DF
7	F	76	2.0	Type III	L	Intestinal	Well differentiated	1	3	Antrectomy/ 05/2011	BR	T1aN0M0	A, DF
8	M	72	4.3	Types IIa+III	M	Intestinal	Well differentiated	2	3	Wedge GR/ 03/2012	BR	T1aN0M0	A, DF
9	M	79	1.8	Type III	U	Intestinal	Well differentiated	3	3	Wedge GR/ 03/2012	BR+stations 7, 8, and 9	T1bN0M0	Dead 5 days PO (LF)
10	M	83	2.0	Types IIa+III	U	Intestinal	Moderately differentiated	2	4	Wedge GR/ 04/2012	BR+stations 7, 8 and 9	T1aN0M0	A, DF
11	F	71	1.5	Type III	M	Diffuse	Poorly differentiated	3	4	Wedge GR/ 04/2012	BR+stations 7, 8, and 9	T2N1M0 (micro metastasis)	A, DF
12	M	36	2.0	Type III	L	Diffuse	Poorly differentiated	1	3	Antrectomy/ 09/2012	BR+stations 7, 8, and 9	T3N1M0 (1 false negative SLN)	A, DF (RTx+Qt)
13	M	54	0.5	Type III	L	Diffuse	Poorly differentiated	1	5	Antrectomy/ 10/2012	BR+stations 7, 8, and 9	T1aN0M0	A, DF
14	F	51	2.2	Type III	L	Diffuse	Poorly differentiated	5	3 and 8	Antrectomy/ 03/2014	BR+stations 7, 8, and 9	T3N0M0	A, DF

SLN = sentinel lymph node; LN = lymph node; F = female; M = male; L = lower third; M = middle third; U = upper third; GR = gastric resection; BR = basin resection; A = alive; DF = disease-free; EGC = Early gastric cancer; PO = postoperatively; TG = total gastrectomy; LF = liver failure; RTx+Qt = radiotherapy and chemotherapy. *Macroscopic type according to Japanese classification of gastric carcinoma: 3rd English edition (Gastric Cancer 2011;14:101-112).

false-negative result from SN biopsies, and another patient had micrometastases in 2 of the resected lymph nodes. Four patients were diagnosed with higher T stage disease after histopathological examination of the surgical specimens, with 2 patients actually having T2 tumors and the other 2 having T3 tumors. There was one postoperative death from liver failure in a cirrhotic patient. Except for this patient and an additional patient who underwent a Billroth I antrectomy and exhibited poor gastric emptying in the immediate post-operative period, the other patients recovered uneventfully with restoration of oral diet on the third day. Another cirrhotic patient died after two years also from liver failure without recurrence of gastric cancer. All other patients were followed up from 13 to 79 months (mean follow-up, 47.8 months) with no evidence of recurrence. Two patients were diagnosed with a second EGC, 1 and 2 years after surgery, and underwent total gastrectomies with D2 lymphadenectomies. In both cases, all removed lymph nodes were disease free (Table 1).

Discussion

Lymph node metastases in gastric cancer patients are frequent, appear early in the disease course, and depend on many variables, among which are depth of gastric wall invasion, histologic type, ulcerative findings, lymphovascular involvement, and tumor size. EGC patients have low incidences of lymph node metastasis that range from 0% to approximately 20%. Unfortunately, these metastases usually cannot be identified before or even during surgery, which has made gastrectomy with D2 lymphadenectomy the standard surgical treatment for EGC. On the other hand, background statistical knowledge of risk for lymph node metastasis in patients with EGC based on thousands of patients who previously underwent extensive gastrectomies with D2 lymphadenectomies has allowed the safe performance of more conservative procedures, such as endoscopic resections. Those patients who are not suitable for endoscopic resection still may undergo conservative gastrectomies with less extensive lymphadenectomies through SNNS.

But SNNS still has some issues, such as false-negative results on histological examination of sentinel lymph nodes, the possibility of undetected micrometastases in frozen section biopsies performed with hematoxylin and eosin staining, and the occurrence of skip metastases.⁷⁻¹³ These problems may be minimized using new available methods, for instance those that allow quick detection of micrometastases in the operating room through

semi-automated molecular-based rapid diagnostic methods that detect lymph node metastases using one-step nucleic acid amplification.¹⁴ The significance of these micrometastases for prognosis also needs to be better evaluated, but the possibility of making diagnoses intraoperatively is a reality and will soon become routine worldwide. Because the incidence of skip metastases is less than 3% and mostly occurs in lymph nodes stations 7, 8, and 9, some authors suggest that lymphadenectomies should be extended to those stations depending on the location of the tumor.^{1,10,15,16} Taking all these points into consideration, it is important to emphasize that pick-up biopsies of SNs are inadequate and risky, and basin resection should be considered mandatory for SNNS.¹⁷

In Western countries, where gastric cancer incidence has decreased over the years and early diagnosis is still the exception, treatment outcomes for gastric cancer patients are still poor and are reflected in the overall 5-year stage-specific survival rates that have been consistently superior in studies from Japan and Korea when compared with large Western trials. These differences are due to many factors, but we would like to emphasize stage migration and differences in tumor biology, as Chen et al. recently described.¹⁸ The rate of EGC lymph node metastasis in our previous study, for instance, was higher than that observed in East Asian countries. In this recently published study of 178 patients treated for gastric cancer, 27 patients (15.2%) were diagnosed with EGC, and almost 30% of them already had lymph node metastases.¹⁹ This rate ranged from 15.4% for patients with tumors restricted to the mucosa (T1a) to 42.8% for patients with tumors with submucosal involvement (T1b). Despite the small number of cases, these data made the decision to conduct SNNS for EGC difficult and emphasized our decision to extend basin resection to other lymph node stations in patients with moderately and poorly differentiated tumors since these were the most important risk factors for lymph node metastasis in our study. On the other hand, more than two-thirds of our EGC cases involved patients with other serious diseases, including portal hypertension, since the majority of EGC was diagnosed from findings of endoscopic procedures performed to complement other diagnostic evaluations. Extended gastrectomies and lymphadenectomies in gastric cancer patients with cirrhosis can lead to severe postoperative morbidity and mortality. Choosing the appropriate surgical strategy in such cases is still controversial.²⁰ Minor surgeries for these patients should always be considered.

In 2012, we published our first seven cases of EGC for which we performed minor gastric resections with sentinel basin resec-

tions in patients undergoing sentinel lymph node mapping using patent blue dye.²¹ Our current study examines 14 patients, with two deaths from causes unrelated to gastric cancer. There was one postoperative death from liver failure in a cirrhotic patient, and another cirrhotic patient died also from liver failure after two years without gastric cancer recurrence. All other patients were followed up for 13 to 79 months with no evidence of recurrence. Among these 12 cases, one patient received a false-negative result from SN biopsies (8.3%), and another patient had micrometastases in two of the resected nodes (8.3%). Since we always resect all SN stations and all other lymph nodes from other resected stations were negative for metastasis, we chose not to reoperate on the patients. In our study, we decided that sentinel basin resections would be performed in four patients with well-differentiated tumors, only one of which had a tumor larger than 2 cm. In the other cases, specifically for tumors that were not well-differentiated, we performed sentinel basin resections with extended lymphadenectomies to include stations 7, 8, and 9, not only because of our high rates of EGC lymph node metastases but also due to possible skip metastases. Blood supply to the remnant stomach was carefully preserved. For the same reason, postoperatively diagnosed T2 and T3 tumor patients were kept under clinical observation. Patients 4 and 11 (T2) presented with small clusters of neoplastic cells in the superficial muscularis propria. However, in T2 tumors, although lymph node metastasis rates can reach 50%, about half of patients have metastases in N1 nodes, particularly when the tumor involvement occurs in the most superficial muscle layer, as occurred in our patients. In both cases, all resected lymph nodes were negative for metastases, which led us to maintain clinical observations and tomographic control. Some authors have demonstrated that patients with gastric cancer without lymph node metastases but with limited invasion of the muscularis propria had similar outcomes to those with EGC, with similarly good prognoses.²² The absence of serosal involvement also suggested that peritoneal carcinomatosis were unlikely. In a large Japanese study, patients preoperatively staged as cT1N0 that were postoperatively diagnosed as pT2N0, had better prognoses, lower N staging and limited lymph node metastasis in 98% of cases. Five-year survival rates were greater than those with preoperative diagnoses of T2 advanced tumors.^{23,24}

For patient 12, a 36-year-old man with a 2-cm type III poorly differentiated tumor who received a false-negative result from SN biopsies and was postoperatively staged T3N1M0, we decided to administer adjuvant radiotherapy and chemotherapy.

Patient 14, a 51-year-old woman with a 2.2-cm type III poorly differentiated tumor and stage pT3N0 disease, underwent a distal gastric resection and a sentinel basin resection with an extended lymphadenectomy to include stations 7, 8, and 9. This patient had 16 lymph nodes resected, all of which were negative for metastasis, and thus, we opted for clinical observation. These diffuse type tumors based on Lauren classification are usually disseminated beyond the distal gastric wall layers, do not exhibit mass effects, and are often downstaged during EUS. Major resections with more extensive lymphadenectomies should be considered for these patients.²⁵

Two of our patients (cases 3 and 4) had second early tumors found on endoscopy scans performed 1 and 2 years after surgery, and we chose to complete gastrectomies in those cases. Metachronous gastric tumors after resection of EGC occurred in approximately 3% of patients in a large Japanese study of 1,281 cases, but in a smaller study of patients undergoing EGC laparoscopic wedge resection, this rate reached 12%.^{26,27} The main independent risk factors revealed from multivariate analysis were male gender, advanced age, invasion of the submucosa, and proximal gastrectomy. Leaving an almost entire stomach after these minor resections results in an additional risk for a second EGC that often occurs within the first two postoperative years.

Patent blue, lymphazurin, and the indocyanine green (ICG) are preferable dyes for SN mapping and are widely used due to the cost effectiveness. They can detect lymphatic vessels as well as lymph nodes, but they may not be suitable for obese patients who have dense adipose tissue, which would cause a high false-negative rate. ICG dye seems to be more suitable for SNNS due to its high accuracy, but it is poorly visible compared to blue dyes. The use of infrared ray electronic endoscopy combined with ICG; however, may overcome those visibility problems, and stained nodes can also be identified through dense adipose tissues when using this method.²⁸⁻³⁰ Sometimes radioisotopes are used to increase sensitivity of node identification. In our study, patent blue dye injected intraoperatively through endoscopy identified SNs in 100% of patients. There were no allergic reactions to the blue dye. Patent blue dye was chosen mainly because of its cost effectiveness.

Although still yielding controversial results that range from a false-negative rate of 46.4% for biopsies¹³ to a 99% accuracy for evaluation of metastatic EGC status,²⁸ SNNS will probably soon be an attractive tool to detect clinically undetectable lymph node metastasis of EGC.²⁹ Laparoscopic sentinel basin dissection is be-

coming more safe and more feasible according to well-conducted prospective multicenter studies and will allow safe organ preserving surgeries for gastric cancer.¹⁷

Although our small patient sample revealed unexpected variables, the complete absence of tumor recurrence suggests that SNNS is a safe procedure in a country with non-endemic gastric cancer levels and will probably be a safe option for treatment in the near future. Especially if associated with minimally invasive surgery, this procedure may ensure better quality of life, low rates of postoperative complications, and shorter hospital stays for many patients. It is urgent to increase histological examination accuracy of SN frozen sections in order to reduce the risk of false-negative results as well as to identify micrometastases.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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