

Minor gastric resections with modified lymphadenectomy in early gastric cancer with negative sentinel node

Ressecções gástricas menores com linfadenectomia modificada em câncer gástrico precoce com linfonodo sentinela negativo

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A B S T R A C T

Objective: To study the sentinel lymph node in early gastric cancer as a diagnostic method of unsuspected lymph node metastasis, which may allow the performance, in those with negative lymph nodes, of smaller gastric resections with limited lymphadenectomy. **Methods:** We studied seven patients with early gastric cancer treated at the Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, from September 2008 to May 2011, who underwent sentinel lymph node exams, performed by intraoperative peritumoral endoscopic injection of patent blue dye. **Results:** We found an average of three sentinel nodes per patient. The frozen biopsy of lymph nodes was negative for metastases, which allowed the realization of atypical gastric resection in three cases and antrectomy with BI reconstruction in four. The performed lymphadenectomy was modified D1. There was no operative mortality. The duration of postoperative follow-up ranged from five to 37 months, without evidence of recurrence. One patient developed a second early tumor 13 months after the initial surgery and underwent total gastrectomy. **Conclusion:** The sentinel lymph node proved to be an effective method for the evaluation of nodal metastases in seven patients with early gastric cancer and allowed for smaller gastric resections and limited lymphadenectomies. These minor procedures reduce the risk of postoperative complications, maintaining, on the other hand, the oncological radicality that is required in the treatment of gastric cancer.

Key words: Sentinel lymph node biopsy. Stomach neoplasms. Lymph node excision. Gastrectomy. Lymphatic metastasis.

INTRODUCTION

In patients with gastric adenocarcinoma, lymph node metastases are the main determinants of the extent of the surgical procedure, which consolidated broad gastrectomies, with D2 lymphadenectomies, as standard procedures in advanced gastric tumors¹. In early gastric cancer (EGC), however, the incidence of lymph node metastases is around 20%, varying from 0% to 6.4% for those confined to the mucosa and from 2.2% to 24% when there is extension to the submucosa, these variations also depending on other factors, such as tumor grade, tumor size and presence or absence of angiolymphatic invasion²⁻¹¹. Thus, the possibility of EGC metastases is greater when the tumor diameter exceeds 4cm in undifferentiated histological types and when there is angiolymphatic invasion. On the other hand, well-differentiated, smaller

than 2cm and non-ulcerated tumors are treatable even by endoscopic resection, with virtually no likelihood of lymph node metastases¹²⁻¹⁴. Endoscopic resections of submucosal EGCs have also been made in some centers when lymph node secondary implants are ruled out^{12,15}. Imaging methods, however, are not able to accurately identify metastatic lymph nodes, which stimulated the research use of sentinel lymph nodes, as traditionally used in melanoma and breast tumors¹⁶⁻¹⁸, in patients not eligible for endoscopic resection. The injection of dyes and/or submucosal peritumoral radioisotope allows early identification of lymph nodes draining the region responsible for the tumor that, when negative for metastases on frozen section histopathology, infer the lack of lymph node metastases with a high degree of reliability¹⁹⁻²⁷. In these patients, atypical, limited gastric resections, with modified D1 lymphadenectomy, are able to provide results oncologically

Study Conducted at Clementino Fraga Filho Hospital, Federal University of Rio de Janeiro (HUCFF-UFRJ), Brazil.

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comparable to large resections with extensive lymphadenectomies, but with lower morbidity and mortality rates. In countries like Japan and Korea, where gastric cancer is endemic and preventive endoscopic examinations are the rule, about 70% of diagnosed tumors are EGC¹⁵. In Brazil, the incidence of EGC is about 15%, this diagnosis usually being made in patients with other diseases, such as chronic liver diseases, which led to the indication of the endoscopic procedure^{14,28}. In these patients, limited gastric resections, besides being curative, reduce the risk of postoperative complications.

The objective of this work is to study the sentinel lymph node in EGC as a diagnostic method of unsuspected lymph node metastasis and to allow individualization of the procedures to treat these patients.

METHODS

We evaluated seven patients with early gastric cancer treated at the Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, from September 2008 to May 2011, who underwent sentinel lymph node, performed by intraoperative endoscopic, peritumoral, injection of vital blue dye.

We included patients seen in HUCFF-UFRJ with endoscopic finding of EGC, confirmed by endoscopic ultrasound (EUS), histopathological examination of gastric biopsy and clinical staging, by EUS and computed tomography (CT), of disease limited to the stomach.

We performed the sentinel lymph node research with the patient on the operating table. After surgical access to the peritoneal cavity, the endoscopist performed the endoscopic exam, with location of the lesion and injection of 0.5 ml of patent blue dye in each of the four quadrants of the tumor. Within minutes the sentinel nodes were stained (Figure 1) and were then resected for frozen section histological examination. If negative for metastatic disease, we proceeded to atypical, localized gastric resection, whose characteristics were dependent on the location of the lesion in the stomach. Likewise, a regional, modified perigastric lymphadenectomy was performed, also according to the topographical location of the tumor and to the Japanese Association criteria for Gastric Cancer²⁹. Definitive histopathological examination, with confirmation of pathologic stage T1 N0 M0, free resection margins and negative lymph nodes, were criteria for outpatient treatment. Positive margins and/or lymph nodes rendered the patient a candidate for reoperation, a classic gastrectomy with D2 lymphadenectomy. The ambulatory monitoring is being done with endoscopy and abdominal CT every six months in the first two years and then annually.

All patients were informed of the risks and benefits of the procedure and signed a consent form.

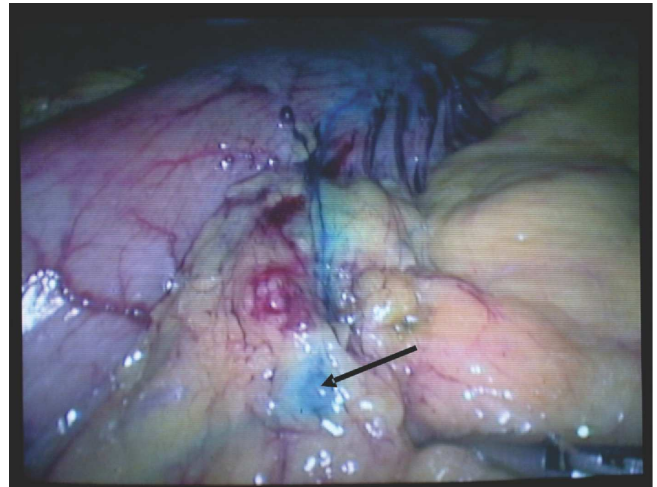


Figure 1 - Sentinel lymph node stained with blue dye.

RESULTS

From September 2008 to May 2011 seven patients with early gastric cancer were admitted to the Division of Surgery of the Esophagus and Stomach HUCFF-UFRJ. Once submitted to a complete preoperative staging for EGC, they matched the inclusion criteria for sentinel lymph node study. The epidemiological characteristics, size of tumors and their macroscopic, microscopic and TNM classifications are shown in table 1.

The location of the lesions, the number and chains of sentinel nodes and type of surgery performed are shown in table 2.

Atypical stomach resections were performed under direct visualization of tumors via a gastrotomy, as shown in figure 2.

The nodal stations resected and the number of removed lymph nodes of each patient are shown in table 3.

All patients had comorbidities, among which stands out hypertension, chronic vascular diseases and diabetes. One patient had hepatitis B and portal hypertension and one had incipient renal failure. All had surgical risk classified as ASA III.

There was no operative mortality. One patient undergoing antrectomy with BI transit reconstruction presented with difficulty in gastric emptying and was submitted to a gastrojejunostomy on the 21st day after surgery. One patient had wound infection.

In one patient (case 4) histopathological examination of the surgical specimen revealed the nucleus of neoplastic cells in the muscularis propria not identified by the EUS, which brought the patient to the stage T2 N0 M0. Because of their high surgical risk, the presence of free surgical margins and the absence of metastases in 23 lymph nodes resected with the stomach segment, we opted for clinical monitoring for him. Another patient (case 3)

Table 1 - Epidemiological characteristics, size of tumors and macroscopic, microscopic and TNM classifications.

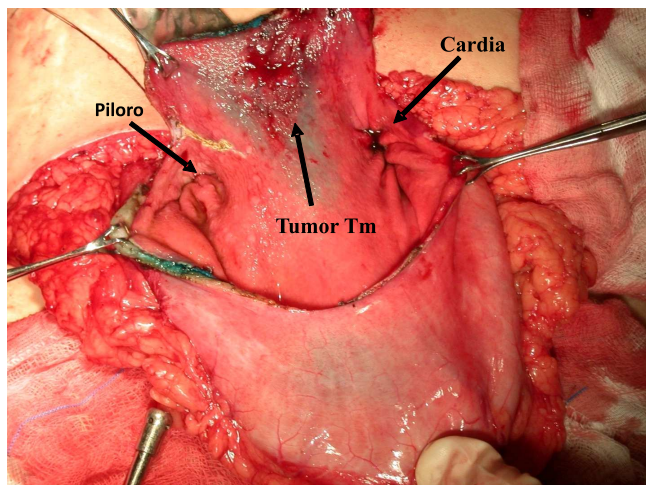
Patient	Age	Macroscopic Classification	Size cm	Microscopic Classification	TNM Classification
1	77	Type III	2,2 x 2,0	Well Differentiated Intestinal Type	T1sm N0 M0
2	78	Types IIa + IIc	1,8 x 1,0	Moderately Differentiated Intestinal Type	T1sm N0 M0
3	53	Types IIc + III	1,5 x 1,5	Poorly Differentiated Difuse Type	T1m N0 M0
4	60	Type III	1,7 x 1,1	Well Differentiated Intestinal Type	T2a N0 M0 *
5	60	Type I	1,7 x 1,4	Well Differentiated Intestinal Type	T1m N0 M0
6	54	Type IIb	3,5 x 2,5	Moderately Differentiated Intestinal Type	T1sm N0 M0
7	76	Type III	2,0 x 2,0	Well Differentiated Intestinal Type	T1m N0 M0

* Small nucleus of neoplastic cells in the superficial muscularis propria identified in the histopathology of the specimen.

Table 2 - Location of lesions, number of sentinel nodes and their chains, and type of surgery performed.

Patient	Location Of Tumor	Number Of Nodes	Node Chains	Surgery Performed
1	Aterior wall of distal antrum	3	4, 7	BI Antrectomy
2	<i>Incisura angularis</i>	4	3	Atypical gastric resection
3	<i>Incisura angularis</i>	2	3	Atypical gastric resection
4	Posterior wall of body	2	3	Atypical gastric resection
5	Aterior wall of distal antrum	3	5, 6	BI Antrectomy
6	Aterior wall of distal antrum	3	3	BI Antrectomy
7	Aterior wall of distal antrum	1	3	BI Antrectomy

Os linfonodos sentinelas corados com azul patente podem ser vistos na Figura 1.

**Figure 2** - Atypical gastric resection.

presented with a second early tumor in an endoscopic exam performed 13 months after the atypical gastric resection and underwent total gastrectomy with D2 lymphadenectomy. Histopathological examination of the specimen confirmed that it was a second early tumor, with no lymph node metastases. The median survival of patients was 23.5 months, ranging from five to 37 disease-free months.

DISCUSSION

Early gastric cancer is defined as adenocarcinoma confined to the mucosa and submucosa layers, regardless of the presence or absence of lymph node metastases¹⁷. Considering that about 80% of these patients have no lymph node involvement, it seems reasonable to seek to identify those without metastases in order to perform minor surgical procedures with less morbidity and mortality, and even endoscopic or laparoscopic resections, individualizing their treatment²⁶. Imaging studies are flawed in the preoperative characterization of these lymph node metastases, being suggestive only when there is perigastric lymph node enlargement³⁰. In these cases, by endoscopic ultrasound, one can not only confirm the endoscopic impression of early tumor, but mainly diagnose the presence of suspicious lymph nodes and have them aspirated for histological evaluation. However, more distant nodes of the gastric wall cannot be visualized by endoscopic ultrasound, and in addition, in most cases, the absence of enlarged lymph nodes does not exclude the possibility of metastases.

Thus, the search for sentinel lymph nodes may contribute to the identification of metastases, following the principle that the lymph nodes of the rich lymphatic chain of the stomach that drain a particular tumor region should also be the first to receive its metastatic implants³¹. Negative

Table 3 – Nodal chains and number of lymph nodes resected.

Patient	Resected Lymph Node Chains	Number Of Nodes Resected
1	3,4c,5,6,7,8 ^a	10
2	3,5,7,8 ^a	9
3	3,5,7,8 ^a	17
4	2,3,4a,4b,4c,7	23
5	3,4a 5,6,7, 8 ^a	10
6	3,4a 5,6,7, 8 ^a	9
7	3,4a 5,6,7, 8 ^a	9

sentinel lymph nodes suggest the absence of implants in more distant chains, allowing the realization of limited lymphadenectomies, or even none. Most authors, however, advocate the complete resection of the chains in which lymph nodes are stained. The Japanese Gastric Cancer Association²⁹ recommends modified lymphadenectomies depending on the location of the tumor in the stomach and the possibility of skip metastases. In these cases the lymph node metastases occur in more distant nodal chains, preserving those closest to the tumor. The incidence of those skip metastases was 2.8% in a large Korean series and was associated with larger tumors and the presence of invasion of lymphatic vessels³². All occurred in nodes extra-perigastric, mostly in chains 7, 8 and 9. In our patients the modified D1 lymphadenectomy followed guidance of the Japanese Gastric Cancer Association²⁹, as shown in Table 3. Unlike the single sentinel lymph nodes, which are identified in breast tumors and malignant melanoma, in gastric cancer the number of sentinel lymph nodes usually range from three to four and may occur in more than one nodal station, as identified in our patients (Table 2).

The sentinel lymph node exam can be made by endoscopic, submucosal, peritumoral injection of various dyes such as patent blue and indocyanine green, and identified by direct vision or, in the latter case, with the help of infrared rays¹⁹. The injection of radioisotopes has also been used alone or in association with the dye injection, in an attempt to increase the sensitivity of the method²⁴. We opted for the use of patent blue due to its proven efficacy, lower cost and easy endoscopic manipulation. The time interval between injection of the dye and the staining of the first nodes ranges from three to ten minutes, as observed in our patients. We started the sentinel lymph node research by laparoscopy in two patients (cases 1 and 2), which allowed for smaller incisions for gastric resection after negative results of the frozen section examination. The remaining patients were obese or patients with previous abdominal surgery, which led us to prefer laparotomy as the initial access.

Regarding the type of gastric resection, we chose antrectomy with BI reconstruction in four patients with tumors of the distal antrum-pyloric or ptr-pyloric. In the remaining we performed atypical resections with direct visualization

of the tumor through gastrotomy, since the lesions were not apparent at the serosa and were difficult to palpate, especially those confined to the mucosa. This allowed the resection with safe margins, while the level of gastric deformation was evaluated, thus avoiding anatomical deformations of the remaining stomach. Except for one patient undergoing BI antrectomy, who showed poor gastric emptying in the immediate postoperative period, the others recovered uneventfully, with restoration of oral diet on the third day.

The pathology of the surgical specimens confirmed the preoperative diagnosis of early tumor, except in one patient (case 4), which presented a small nucleus of neoplastic cells in the superficial *muscularis propria*. However, in T2 tumors, although the rate of lymph node metastasis could reach 50%, about half of patients have metastases in level 1 nodes, particularly when the tumor involvement occurs in the most superficial level of the muscular layer, as occurred in one of our patients^{33,34}. In this case, all 23 resected lymph nodes were negative for metastases, which led us to keep the patient under clinical observation and tomographic control. The absence of involvement of the serosa also deemed the possibility of peritoneal implants unlikely. In a large series studied in Japan, patients with T2 tumors diagnosed on histopathological examination, but with a preoperative diagnosis of early tumor, had a better prognosis, lower N staging and limited extent of lymph node metastases in 98% of cases and five-year survival greater than those with a preoperative diagnosis of T2 advanced tumor³⁵.

One of our patients (case 3), 53 years old, had a second early tumor in an endoscopy scan performed 13 months after surgery and in this case we chose the completion of gastrectomy. Metachronous gastric tumors after resection of EGC occurred in approximately 3% of patients in a large Japanese series of 1281 cases, but reached 12% in a smaller study of patients undergoing EGC laparoscopic wedge resection^{36,37}. The main independent risk factors outlined in the multivariate analysis were male gender, advanced age, invasion of the submucosa and proximal gastrectomy, none of the factors presented by our patient.

This preliminary study of patients with EGC demonstrates that minor surgical procedures, with atypical gastric resections and limited lymphadenectomies, can be safely performed in selected patients with disease limited to the stomach, based on the sentinel lymph node exam. In Brazil this diagnosis is

usually made by endoscopy for the detection of other diseases in patients with high surgical risk. These smaller procedures can have a positive impact on the risk of postoperative complications, maintaining, on the other hand, the oncological radicality required for the treatment of gastric cancer.

R E S U M O

Objetivo: Estudar a pesquisa de linfonodo sentinela em câncer gástrico precoce como método diagnóstico de metástase ganglionar insuspeita, e que permita a realização, naqueles com gânglios negativos, de ressecções gástricas menores, com linfadenectomia limitada. **Métodos:** Foram avaliados sete pacientes portadores de câncer gástrico precoce, tratados no Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro, no período de setembro de 2008 a maio de 2011, e submetidos à pesquisa de linfonodo sentinela, realizada através da injeção endoscópica, peritumoral, transoperatória, do corante azul patente. **Resultados:** Foram encontrados, em média, três linfonodos sentinelas por paciente. A biópsia por congelação destes linfonodos foi negativa para metástases, o que permitiu a realização de ressecção gástrica atípica em três casos e antrectomia com reconstrução a B1 em quatro. A linfadenectomia realizada foi a D1 modificada. Não houve mortalidade operatória. O tempo de acompanhamento pós-operatório variou de cinco a 37 meses, sem evidências de recidivas. Uma paciente apresentou um segundo tumor precoce 13 meses depois da primeira cirurgia e foi submetida à gastrectomia total. **Conclusão:** A pesquisa de linfonodo sentinela em câncer gástrico precoce, nos sete pacientes estudados, mostrou-se um método eficaz para a avaliação de metástases ganglionares e permitiu a realização de ressecções gástricas menores e linfadenectomias limitadas. Estes procedimentos de menor porte diminuem o risco de complicações pós-operatórias, mantendo, por outro lado, a radicalidade oncológica que se exige no tratamento do câncer gástrico.

Descritores: Biópsia de linfonodo sentinela. Neoplasias gástricas. Excisão de linfonodo. Gastrectomia. Metástase linfática.

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