

FREQUENCY AND PREDICTIVE FACTORS RELATED TO LYMPHATIC METASTASIS IN EARLY GASTRIC CANCER

Frequência e fatores preditivos relacionados a metástase linfática em câncer gástrico precoce

Leonardo Medeiros **MILHOMEM**¹, Daniela Medeiros Milhomem **CARDOSO**¹, Eliane Duarte **MOTA**¹,
Ailton Cabral **FRAGA-JÚNIOR**¹, Edésio **MARTINS**², Orlando Milhomem da **MOTA**¹

From ¹Cancer Hospital Araújo Jorge and
²Catholic University of Goiás, Goiânia, GO,
Brazil.

ABSTRACT – Background - The standard treatment of gastric cancer still has high morbidity and mortality in western populations. Groups of patients with negligible risk of lymph node metastasis may benefit from less invasive treatments. Data regarding the frequency and predictive factors related to lymphatic metastasis in early gastric cancer are rare. **Aim** – To perform the analysis of frequency and predictive factors related to lymphatic metastasis in patients with early gastric cancer treated in a tertiary center in Brazil. **Methods** - Nine hundred and twenty three patients underwent gastrectomy for gastric adenocarcinoma at the hospital. Of these, 126 had early tumors and were included in the analysis. Clinical and pathological related findings and lymphatic metastasis were evaluated. **Results** - Lymph node metastases were observed in 7.8% of patients with mucosal tumors and 22.6% of submucosal tumors. The presence of ulceration, Lauren histologic type, tumors larger than 50 mm, submucosal invasion, and presence of lymphatic or vascular invasion were significant factors in univariate analysis. The presence of ulceration, lesions larger than 50 mm, infiltration of the submucosal layer and lymphatic invasion were factors independently related to lymphatic metastasis in multivariate analysis. **Conclusion** - Ulceration, lesions larger than 50 mm, infiltration of the submucosal layer and lymphatic invasion are independent risk factors related to lymphatic metastasis in early gastric cancer.

HEADINGS – Stomach neoplasms.
Lymphatic metastasis. Adenocarcinoma.
Predictive value.

Correspondence:

Leonardo Medeiros Milhomem,
e-mail: leonardo2m@yahoo.com.br e
leommilhomem@gmail.com

Financial source: none
Conflicts of interest: none

Received for publication: 09/06/2012
Accepted for publication: 10/09/2012

DESCRITORES - Neoplasias gástricas.
Metástase linfática. Adenocarcinoma.
Valor preditivo

RESUMO – Racional - O tratamento padrão do câncer gástrico ainda apresenta alta morbidade e mortalidade em populações ocidentais. Grupos de pacientes com risco negligenciável de metástase linfonodal podem se beneficiar de tratamentos menos invasivos. Dados referentes à frequência e fatores preditivos relacionados a metástase linfática em câncer gástrico precoce são raros. **Objetivos** - Realizar a análise de frequência e fatores preditivos relacionados à metástase linfática em pacientes com câncer gástrico precoce tratados em centro terciário do Brasil. **Métodos** – Novecentos e vinte e três pacientes foram submetidos à gastrectomias por adenocarcinoma gástrico. Destes, 126 tinham tumores precoces e foram avaliadas características clínicas e patológicas relacionadas e metástases linfáticas. **Resultados** - Metástases linfonodais foram observadas em 7,8% dos pacientes com tumores mucosos e 22,6% dos tumores submucosos. A presença de ulceração, tipo histológico de Lauren, tumores maiores que 50 mm, invasão de submucosa e presença de invasão linfática ou vascular foram fatores significativos em análise univariada. A presença de ulceração, lesões maiores que 50 mm, infiltração da camada submucosa e invasão linfática foram fatores independentemente relacionados à metástase linfática em análise multivariada. **Conclusão** - Ulceração, lesões maiores que 50 mm, infiltração da camada submucosa e invasão linfática são fatores de risco independentes relacionados à metástase linfática em câncer gástrico precoce.

INTRODUCTION

Gastric cancer is the second cause of cancer death in the world today. It is observed decrease in incidence in several countries related to reducing the prevalence of risk factors, improvement of basic sanitation, food changes and reduction of smoking³². However, gastric cancer is still diagnosed in advanced

stages. The early gastric cancer, which represents the lesions limited to the mucosa and submucosa layers, independent of lymph node metastases¹², corresponds in our country about 15% of cases of this disease^{11,19}. Similar rates are observed in European countries and China³. In other Asian countries like Japan and Korea about 50-60% of cases of gastric cancer are diagnosed in the early stages²².

The early lesions, unlike advanced lesions, have a favorable prognosis, with survival rates at five years over 90%^{26,29}. The operation associated with radical lymphadenectomy remains the gold standard treatment in cases of gastric cancer, even in early stages. However, therapeutic modality is associated with high morbidity and mortality in Western countries^{4,28}.

Less invasive therapeutic methods and associated lower morbidity and mortality, such as endoscopic resection, can be used in specific groups of patients with negligible risk of lymph node metastases; the oncological results are similar to standard treatment, avoiding unnecessary radical treatments in these situations.

Data related to the frequency and factors associated with lymph node metastasis in early gastric cancer are rare in Western countries.

The aim of this study was to perform frequency analysis and predictive factors related to lymph node metastasis in patients with early gastric cancer treated at a tertiary center in the Central-Western Brazil.

METHODS

This study was approved by the Research Ethics Committee of the Cancer Association in Goiás with Protocol No 035/2011.

Variables analyzed included macroscopic characteristics such as size of lesions, presence of ulceration, histological factors (Lauren classification), grade of differentiation, depth of invasion, presence of lymphatic and vascular invasion, associated with *Helicobacter pylori* infection and the presence of lymph node involvement.

The macroscopic appearance of the lesions was determined according to criteria of the Japanese Society for Research in Gastric Cancer (Japanese Research Society for Gastric Cancer)¹².

The *Helicobacter pylori* infection was diagnosed by histological method. The size of each lesion was determined by measurement according to the largest diameter, performed by a pathologist and divided into three groups: lesions less than 20 mm, between 20 and 50 mm and larger than 50 mm. The depth of invasion was measured according to the finding of malignant cells at the point of greatest penetration

into the layers of the gastric wall. In cases of multifocal tumors deeper lesion was considered for analysis. All dissected lymph nodes were analyzed for the presence of metastatic disease.

Poorly differentiated tumors, carcinomas with signet ring cell and mucinous adenocarcinomas were classified as undifferentiated tumors. Tubular papillary adenocarcinomas and tumors were classified as differentiated. Histological evaluation by classifying Lauren was also performed.

The data were compiled in a database with the program Microsoft Excel 2007. Statistical analysis was performed using SPSS for Windows version 18.0. The chi-square test was used to compare variables. Multivariate analysis was performed using logistic regression method of Mantel-Hansell. P values <0.05 were considered statistically significant.

RESULTS

From January 1998 to December 2010, 923 patients underwent gastrectomies with curative or palliative intent for gastric adenocarcinoma in Araújo Jorge Hospital Cancer of Goiás. Of these, a total of 126 patients (13.65%) with tumors restricted to gastric mucosa and submucosa layers were included in the analysis. The mean age was 60.73 years (28-93), with 66 men (52.38%) and 60 women (47.61%). Clinical characteristics and information pertaining to the treatment are shown in Table 1.

TABLE 1 - Clinical characteristics of patients with early gastric cancer

	Number	%
Sex		
Male	66	52,38
Female	60	47,61
Location		
Proximal	6	4,76
Middle third	32	25,39
Distal	86	68,25
Mouth anastomotic	1	0,7
No information	1	0,7
Endoscopic classification		
High (I and IIa)	7	5,55
Plain (IIb)	8	6,34
Depressed (IIc and III)	90	71,42
No information	21	16,66
Surgical treatment		
Segmental gastrectomy	3	2,38
Distal gastrectomy	104	82,53
Total gastrectomy	18	14,28
D1 lymphadenectomy	18	14,28
D2 lymphadenectomy	108	85,71
Dissected lymph node	3.050	Média 24,59 (5-98)

Of the 126 patients with early gastric cancer, 21 (16.6%) had lymph node metastases, 17 cases N1 and four N2 (3.17%). Of the 51 patients with lesions restricted to the mucosal layer four (7.8%) had lymph node metastases and among 75 patients with submucosal lesions, 17 (22.6%) had lymph node metastases.

The association between the variables and the presence of lymph node metastasis is exposed in Table 2.

TABLE 2 - Association between clinicopathological factors and lymph node metastases, univariate analysis

Variable	Lymph nodes				P	ORIC95
	Negative		Positive			
	N	%	N	%		
H. Pylori						
Negative	41	53,9	5	41,7		
Positive	35	46,1	7	58,3	0,420	1,64(0,47-5,62)
Ulceration						
Negative	43	44,3	3	15,0		
Positive	54	55,7	17	85,0	0,01	4,51 (1,24-16,41)
Classification						
High	6	7,0	1	5,3		
Plain	7	8,1	1	5,3	0,91	0,85(0,04-16,85)
Depressed	73	84,9	17	89,5	0,76	1,40(0,15-12,38)
Lauren						
Bowel	67	66,3	9	42,9		
Diffuse	34	33,7	12	57,1	0,04	2,62(1,01-6,84)
Differentiation						
Good	22	23,4	4	21,1		
Bad	72	76,6	15	78,9	0,82	1,14(0,34-3,81)
Size						
<2Cm	36	34,3	3	14,3		
2-5Cm	57	54,3	11	52,4	0,21	2,31(0,60-8,87)
> 5Cm	12	11,4	7	33,3	0,001	7,00(1,56-31,43)
Depth						
Mucosal	47	44,8	4	19,0		
Submucosal	58	55,2	17	81,0	0,02	3,44 (1,08 -10,93)
Lymphatic invasion						
No	103	98,1	18	85,7		
Yes	2	1,9	3	14,3	0,03	8,58(1,34-55,02)
Vascular invasion						
No	102	97,1	18	85,7		
Yes	3	2,9	3	14,3	0,02	5,66 (1,05 - 30,11)

Infection with *Helicobacter pylori*, endoscopic classification of lesions and degree of differentiation were not factors associated with metastasis.

Regarding the diameter of lesions was observed that the probability of lymph node metastases lesions was greater in lesions more than 50 mm (p = 0.01). The presence of ulceration was also a significant factor, with 6.5% of cases without ulceration presenting lymph node metastases and 23.9% with ulceration had lymph node metastases (p = 0.01).

The depth of lesions, diffuse type of Lauren and the presence of lymphatic and vascular invasion were also factors associated with lymph node metastasis.

Was conducted multivariate analysis of the variables associated with lymph node metastasis. Were independent factors associated with lymph node metastases: the presence of ulceration (OR 4.035, 95%

CI 1.085 to 15.023, p = 0.03), lesion size greater than 50 mm (OR 5.22, 95% CI, 1.18 to 23, 02, p = 0.02), invasion of the submucosal layer (OR 3.45, 95% CI, 1.08 to 11.03, p = 0.03) and lymphovascular invasion (OR 11.08, 95% CI, 1.4 - 87.77, p = 0.02) (Table 3). The presence of vascular invasion showed no association with lymph node metastases in multivariate analysis

TABLE 3 - Association between lymph node metastases and clinical histological factors, multivariate analysis

Variable	P	OR IC 95%	p' adjus	OR' adjus IC 95%
Ulceration				
Negative				
Positive	0,01	4,51 (1,24-16,41)	0,03	4,035 (1,08 -15,023)
Size				
<2Cm				
2-5Cm	0,21	2,31(0,60-8,87)	0,35	1,93 (0,48 - 7,69)
> 5Cm	0,001	7,00 (1,56- 31,43)	0,02	5,22(1,18-23,02)
Depth				
Mucosal				
Submucosal	0,02	3,44 (1,08-10,93)	0,03	3,45(1,08-11,03)
Lymphatic invasion				
No				
Yes	0,03	8,58 (1,34-55,02)	0,02	11,08(1,4-87,77)
Vascular invasion				
No				
Yes	0,02	5,66(1,05-30,11)	0,06	5,35 (0,92 - 30,98)

*Adjusted by Lauren

DISCUSSION

Although epidemiological studies show decreasing worldwide incidence of gastric cancer, this disease still represents one of the cancers with highest incidence rates and mortality worldwide³². In Brazil are estimated for the year 2012 about 12,670 new cases, representing mostly the lesions classified as advanced lesions⁵. It stands out among the prognostic factors of this tumor to lymph node metastases^{10,16,27,31}, considered as the only independent prognostic factor in multivariate analyses^{9,20,25}.

The early gastric carcinomas correspond to lesions limited to the mucosa and submucosa independent of lymph node metastases¹², representing in our country in about 15% of cases^{1,19}. It is observed in these lesions probability of incidence of lymph node metastases ranging from 2.6% to 23.6% according to the level of invasion of the primary tumor⁸. Among the lesions restricted to the mucosal layer this probability varies between 2.6% to 4.8%, and between the submucosal from 16.5% to 23.6%, according to retrospective Eastern and Western studies^{14,26}.

In the present study, the incidence of lymph node metastasis in mucosal lesions was 7.84% of cases, incidence greater than that observed in other series. The incidence of lymph node metastasis in submucosal tumors was 22.66%, similar to other published reports. The incidence of lymph node metastases in lymph nodes N2 was found in about 2-3% of patients with early gastric cancer¹⁶, and was 3.17% in this study.

The gold standard treatment of gastric cancer with curative intent is radical operation generally associated with D2 lymphadenectomy¹³. This treatment has a high success rate in early cases, but is associated with not negligible morbidity and mortality^{4,28}. Certain groups of patients with early gastric cancer have negligible risk of lymph node metastases, allowing these situations to adopt less invasive treatment strategies^{7,33}. In general, currently available imaging methods have low diagnostic accuracy for the presence of lymph node metastases, because they are based on parameters of low reliability^{8,33}. Retrospective studies conducted in Eastern countries, concerning the analysis of predictive factors, clinical and pathological features associated with lymph node metastasis in early gastric cancer, led to the adoption of criteria widely used today in the indication of endoscopic surgeries in these populations^{4,7,28,34}. The application of the same criteria in Western populations remains uncertain and questionable.

Among the clinical and pathological factors assessed in this study, the presence of ulceration, tumors of the diffuse type of Lauren, lesions with a diameter greater than 50 mm, depth of invasion in the submucosal layer, and the presence of vascular or lymphatic invasion, showed association with lymphatic metastasis in univariate analysis. Multivariate analysis of these factors showed that independent predictors associated with lymph node metastasis in early gastric cancer were ulceration, tumors larger than 50 mm, the submucosal layer invasion and lymphatic invasion.

The presence of ulceration is questionable factor^{15,18,37}, depending on the natural history of these lesions and the criteria for determining the presence of ulceration. Studies show that up to a third of them may undergo gross changes and even healing, plus a large inter-observer variation. In a previous study of Gotoda et al.⁶, with a significant number of patients, the presence of ulceration was an independent factor associated with lymph node metastases. Recent studies indicate not only the presence of ulceration as a biomarker for lymph node metastases, but also the diameter of ulceration^{35,36}.

The depth of invasion of the lesion proved to be an important factor, a finding similar to other studies, and accepted by many researchers as the main factor associated with the presence of regional lymph node metastases^{1,6,18,24}.

The diameter of the lesions was found to be an independent factor related to regional lymph node metastases. In this study the difference between the larger and smaller lesions than 50 mm was statistically significant. Other reports in the literature show that the diameter greater than 20 mm is an independent predictor of lymph node metastases^{2,17,23,34}, parameter currently used as a

criteria for indication of endoscopic resection¹³.

The presence of lymphovascular invasion was also confirmed as an important predictor of lymph node metastases, a finding similar to descriptions of several other authors^{2,6,34}.

The selection of patients, performing less invasive therapeutic modalities, endoscopic or surgical, respecting oncological security is difficult. The determination of predictive factors related to regional lymph node metastasis established the criteria currently used in the therapeutic application of these methods in oriental populations. Its acceptance is still low and questionable in the West, where the number of studies on the subject is limited.

CONCLUSION

Ulceration, lesions larger than 50 mm, infiltration of the submucosal layer and lymphatic invasion are independent risk factors related to lymph node metastasis in early gastric cancer.

REFERENCES

1. Abe N, Watanabe T, susuki K, Machida H, Toda H, Nakaya Y, Masaki T, Mori T, SugiyamaM, Atomi Y. Risk factors predictive of lymph node metastasis in depressed early gastric câncer. *Am J Surg.* 2002;183:168-72.
2. An JY, Baik YH, Choi MG, Noh JH, Sohn TS, Kim S. Predictive factors for lymph node metastasis in early gastric cancer with submucosal invasion: analysis of a single institutional experience. *Ann Surg.* 2007;246(5):749-53
3. Borie F, Millat B, Fingerhut A, Hay JM, Fagniez PL, De Saxce B. Lymphatic involvement in early gastric cancer. *Arch Surg.* 2000;135:1218-23
4. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomized controlled surgical trial. *Lancet.* 1996; 347: 995-9.
5. Estimativa 2012: Incidência De Câncer No Brasil. Instituto Nacional De Câncer.- Rio De Janeiro: Inca, 2009, Disponível Do Site: <http://www.inca.gov.br/estimativa/2012/>
6. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric câncer: estimation with a large number of cases at two large centers. *Gastric Cancer.* 2000;3:219-225.
7. Gotoda T, Sasako M, Ono H, Katai H, Sano T, Shimoda T. Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer. *BR J Surg.* 2001; 88(3): 444-9.
8. Hölscher AH, Drebber U, Mönig SP, Schuklte C, Vallböhrer D, Bollschweiler E. Early Gastric Cancer. Lymph node metastasis starts with deep mucosal infiltration. *Annals of Surgery.* 2009; 250:791-797.
9. Huguier M, Houry S, Landen S. Prognostic significance of lymph node involvement in gastric carcinoma resected with curative intent. *Dig Surg.*1994;11:68-71.
10. Itoh H, Oohata Y, Nakamura K, Nagata T, Mibu R, Nakayama F. Complete ten-year postgastrectomy follow-up of early gastric cancer. *Am J Surg.* 1989; 158:14-16.
11. Jacob CE. Early Gastric Cancer: Clinical And Pathologic Features; Correlation with Late Survival (Doctoral Dissertation; In Portuguese). Sao Paulo Universidade De Sao Paulo, Faculdade De Medicina, Departamento De Gastroenterologia; 2003.

12. Japanese Gastric Cancer association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer*. 1998;1: 10–24.
13. Japanese Gastric Cancer Association. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer*. 2010.
14. Kim DY, Joo JK, Ryu SY, Kim YJ, Kim SK. Factors related to lymph node metastasis and surgical strategy used to treat early gastric carcinoma. *World J Gastroenterology*. 2004;10:737-740.
15. Kitamura K, Yamaguchi T, Taniguchi H, Hagiwara A, Sawai K, Takahashi T. Analysis of lymph node metastasis in early gastric cancer: rationale of limited surgery. *J Surg Oncol*. 1997;64:42-47.
16. Kunisaki C, Shimada H, Nomura M, Akiyama H. Appropriate lymph node dissection for early gastric cancer based on lymph node metastasis. *Surgery*. 2001; 129(2):153-7.
17. Kunisaki C, Takahashi M, Nagahori Y, Fukushima T, Makino H, Takagawa R, Kosaka T, Ono HA, Akiyama H, Moriwaki Y, Nakano A. Risk factors for lymph node metastasis in histologically poorly differentiated type early gastric cancer. *Endoscopy*. 2009;41(6):498-503.
18. Maehara Y, Orita H, Okuyama T, Moriguchi S, Tsujitani S, Koregana D, Sugimachi K. Predictors of lymph node metastasis in early gastric cancer. *Br J Surg*. 1992;79:245-247.
19. Marchesini JB, Brenner S, Buffara Junior VA, Moreira M. Early Gastric Cancer: Analysis Of 12 Cases (In Portuguese). *Rev Bras Cir* 1992;82:77–81.
20. Msika S, Chastang C, Houry S, Lacine F, Huguier M. Lymph node involvement as the only prognostic factor in curative resected gastric carcinoma: a multivariate analysis. *World J Surg*. 1989;13(1):118-23.
21. Nitti D, Marchet A, Mammano E, et al. Extended lymphadenectomy (D2) in patients with early gastric cancer. *Eur J Surg Oncol*. 2005;31:875-81.
22. Okabayashi T, Kobayashi M, Nishimori I, et al. Clinicopathological features and medical management of early gastric cancer. *Am J Surg*. 2008;195:229-32.
23. Park JM, Kim SW, Nam KW, Cho YK, Lee IS, Choi MG, Chung IS, Song KY, Park CH, Jung CK. Is it reasonable to treat early gastric cancer with signet ring cell histology by endoscopic resection? Analysis of factors related to lymph-node metastasis. *Eur J Gastroenterol Hepatol*. 2009;21(10):1132-5.
24. Park YD, Chung YJ, Chung HY, Yu W, Bae HI, Jeon SW, Cho CM, Tak Wy, Kweon Yo. Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating poorly differentiated adenocarcinoma of the stomach. *Endoscopy*. 2008;40:7-10.
25. Roder JD, Böttcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ. Results of German Gastric Cancer Study. *Cancer*. 1993;72(7):2089-97.
26. Roviello F, Rossi S, Marelli D, Pedrazzani C, Corso G, Vindigni C, Morgagni P, Saragoni L, de Manzoni G, Tomazzoli A. Number of lymph node metastases and its prognostic significance in early gastric cancer: a multicentric Italian study. *Journal Surg Oncol*. 2006;94:275-280; discussion 274.
27. Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer - follow-up of 1475 patients and review of the Japanese literature. *Cancer*. 1993; 72: 3174-8.
28. Sasako M. Risk factors for surgical treatment in the Dutch gastric cancer trial. *Br J Surg*. 1997; 84: 1567-71.
29. Sasako M. Principles of Surgical Treatment for Curable Gastric Cancer. *JCO*. 2003;21:274-5.
30. Shen L, Huang Y, Sun M, Xu H, Wei W, Wu W. Clinicopathological features associated with lymph node metastasis in early gastric cancer: analysis of a single-institution experience in China. *Can J Gastroenterol*. 2009;23(5):353-356.
31. Shiu MH, Moore E, Sanders M, Huvos A, Freedman B, Goodbold J et al. Influence of extent of resection on survival after curative treatment of gastric carcinoma. A retrospective multivariate analysis. *Arch Surg*. 1987; 122:1347-51.
32. Stewart BW, Kleihues P. *World Cancer Report*. Lyon: IARC Press, 2003
33. Sung CM, et al. Predictive factors for lymph node metastasis in early gastric cancer. *World J Gastroenterology*. 2010;16(41): 5525-56.
34. Tajima Y, Murakami M, Yamazaki K, Masuda Y, Aoki S, Kato M, Sato A, Goto S, Otsuka K, Kato T. Risk factors for lymph node metastasis from gastric cancers with submucosal invasion. *Ann Surg Oncol*. 2010;17(6):1597-604.
35. Xu C, Shen J, Xie S, Jiang Z, Chen W, Wang L. Impact of Malignant Ulcer Size on Lymph Node Stages in Gastric Cancer with Ulcerative Growth. *Hepatogastroenterology*. 2011; 31;59(114).
36. Xu CY, Shen JG, Shen JY, Chen WJ, Wang LB. Ulcer size as a novel indicator marker is correlated with prognosis of ulcerative gastric cancer. *Dig Surg*. 2009;26(4):312-6.
37. Yasuda K, Shiraishi N, Suematsu T, Yamaguchi K, Adachi Y, Kitano S. Rate of detection of lymph node metastasis is correlated with the depth of submucosal invasion in early stage gastric carcinoma. *Cancer*. 1999;85:2119-2123.