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Original Article

Assessment of lymphovascular invasion in gastric carcinoma; do they always indicate lymph node metastasis?

Pande Kricha[1], Rauniyar Shyam Kumar[1], Pudasaini Sujata[1]

[1]*Department of Pathology, Nepal Medical College and Teaching Hospital, kathmandu, Nepal*

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ABSTRACT

Background: Stomach cancer is one of the leading causes of cancer death. The grading and staging of this cancer plays an important prognostic role. Lymphovascular invasion predicts poor outcome in gastric cancer. Among the others, lymphovascular invasion provides useful information for the clinical management of patients with gastric cancer. Nevertheless, data about lymphovascular invasion in early-stage and in lymph node-positive gastric cancer are lacking. Hence, significance of lymphovascular invasion to metastatic lymph nodes impacting nodal status in gastric cancer has been studied in this study.

Materials and methods: This is a retrospective analysis of twenty nine (29) histologically confirmed gastric carcinoma cases received in the department of Pathology at NMCTH dating from October 2014 to September 2016.

Results: There was male preponderance to gastric carcinoma with male to female ratio of 2.2:1. The age varied from 31- 84 years. There were 17 cases (59%) of intestinal type and 11 cases (38%) of diffuse type of gastric carcinoma and 1 case (3%) of adeno-neuroendocrine carcinoma. Microscopic evaluation for depth of invasion showed tumor invasion till the subserosal connective tissue layer (69%) suggesting pT3 stage. lymphovascular invasion was identified in 21 cases (72%). There was statistically significant correlation (P value 0.01) between lymphovascular invasion and nodal status (N0) status.

Conclusion: Presence of lymphovascular invasion is considered as poor prognostic marker in case of gastric adenocarcinoma. Pathologist have been reporting their presence or absence in each gastrectomy reports related to gastric carcinoma.This study has established a significant relation between presence of lymphovascular invasion and nodal staging of gastric carcinoma.

Correspondence:
Dr. Kricha Pande (MBBS, MD
Lecturer, Department of Pathology
Nepal Medical Collage and Teaching hospital & Green city Hospital.
Email: krichapande@gmail.com
ORCID ID: 0000-0002-9303-831X

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INTRODUCTION

Stomach cancer is one of the leading causes of cancer death. Though the incidence is decreasing worldwide, yet on global scale, stomach cancer remains one of the most common causes of cancer death.[1] The grading and staging of this cancer plays an important prognostic role. The number of metastatic lymph nodes (N stage) is known to be an important prognostic factor of gastric carcinoma after curative resection.[2] There have been studies suggesting that metastatic status of the regional lymph node is the most significant prognostic factor for gastric cancer.[3] Lymphovascular invasion (LVI) predicts poor outcome in several malignancies, including gastric cancer. Recently,

LVI emerged as a prognostically promising factor, which independently predicted survival and was associated with advanced tumor stage (T stage), prompting some authors to suggest that LVI should be included in risk stratification and selection of patients for entry into clinical trials.[4] There have been many biological and pathological factors besides tumor and nodal (T and N) categories as possible prognostic indicators, but often with conflicting results. Among the others, lymphatic and blood vessel invasion (LVI) seems to possess the necessary potential to provide useful information for the clinical management of patients with gastric cancer.[5]

In fact, it has been suggested that venous infiltration could be a valuable prognostic factor in gastric cancer involving muscularis and subserosal layer and lymphatic and vascular invasion was shown to be an independent risk factor for recurrence and poor prognosis in patients with node-negative cancer of the stomach.[6,7]

Nevertheless, data about lymphatic and/or blood vessel invasion in early-stage and in lymph node-positive gastric cancer are lacking.[5] The presence of LVI, a common pathological finding for a variety of different cancer types, has been of considerable interest in the last few decades as a potential biomarker. The effectiveness of LVI as a reliable indicator of cancer recurrence and prognosis has been clearly established for both hepatocellular carcinoma and testicular cancer, supporting its incorporation into the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM (tumor-node-metastasis) staging guidelines and staging system.[8,9]

In the regards further clarification on significance of lymphovascular invasion to metastatic lymph nodes impacting nodal status in gastric cancer has been studied in this report. The aim of this study was to establish a relationship between lymphovascular invasion and lymph node involvement and nodal status in the patient with gastric cancer.

MATERIAL AND METHODS

A retrospective analysis was done for all gastrectomy cases received in the department of Pathology at NMCTH. Prior to the data collection, permission was obtained from institutional review committed. From October 2014 to September 2016, a total of twenty nine histologically confirmed gastric carcinoma was enrolled for the study. Other malignancies like lymphomas or sarcomas were excluded from this study. The cases were retrieved from the medical record section for history and patient's particulars and histopathological findings were fetched from the files in the department of Pathology. Information regarding clinicopathological features were noted down from the file. In each case, the following pathological data were noted:

• lesion topography (cardia, fundus, body and antrum),

• tumor size in centimeters in the longest axis of the lesion,

• macroscopic configuration of advanced lesions according to Borrmann's classification.[10]

The paraffin blocks of each case were retrieved from store room. Standard pathological procedure was followed for all blocks. The slides of the primary tumors and regional lymph nodes were prepared first. Hematoxylin and Eosin stain was used for all slides. These slides were numbered and were reviewed. They were assessed to determine differentiation degree/ grade (poorly differentiated, moderately differentiated, and well-differentiated), histological subtype according to Lauren's classification (intestinal, diffuse, or mixed), degree of invasion (mucosa, submucosa, muscular, serosa), presence of metastases in perigastric lymph nodes, staging according to the TNM classification, the depth of tumor and lymphovascular invasion (LVI). The diagnostic criteria for the tumor stages was in agreement with the AJCC 7th edition TNM staging system.

LVI is defined as the invasion of vessel walls by tumor cells and/or the presence of tumor emboli within an endothelial-lined space; with no distinction between vascular and lymphatic vessels.[11]

The following criterion has been used to identify the lumen of blood and/or lymph vessels:

(i) lined by endothelium;

(ii) with supporting smooth muscle or elastica;

(iii) filled with lymphatic fluid or red blood cells.

All sections showing retraction artifacts were excluded considering them to be due to peritumoral edema and tissue shrinkage.

The World Health Organization (WHO) Classification of Tumours of the Digestive System (2010 version) was used to determine tumor differentiation. The depth of tumor infiltration, the lymph node status and the tumor stage was determined utilizing the UICC/AJCC TNM.[12]

Ethical approval was taken from Institutional review board/ committee of NMCTH.

Statistical analysis

The data were subjected to manual analysis. Statistical analysis was performed using tables and descriptive variables. In order to establish a relationship between the presence of lymphovascular invasion and nodal status,

Table 1: Different variables with their number and percentage

Variables	Type	Number (n)	Percentage (%)
Gender	Male	20	69
	Female	09	31
Age	≤ 50	07	24
	>50	22	76
Tumor size	<6	14	48
	≥6	15	52
Tumor location	Antrum	**21**	**72**
	Body	06	21
	Body till antrum	02	07
Bormann classification	Type I	04	14
	Type II	05	17
	Type III	15	52
	Type IV	05	17
Microscopic depth of invasion	Mucosal invasion	0	00
	Submucosal invasion	03	10
	Muscularis invasion	06	21
	Subserosal connective tissue invasion	20	69
Histologic type (Lauren classification)	Intestinal	17	59
	Diffuse	11	38
	Other (adenoneurocrine carcinoma)	01	03
Degree of differentiation	Well differentiated	03	10
	Moderate differentiated	17	59
	Poorly differentiated	09	31
Lymphovascular invasion (LVI)	Present	21	72
	Absent	08	28
Pathological stage (T stage)	T1	03	10
	T2	02	07
	T3	20	69
	T4	04	14
	T4	04	14
Number of lymph node (N stage)	N0	06	21
	N1	06	21
	N2	10	34
	N3	07	24

chi-square and Fisher's exact tests were used. Results were considered significant at a level of maximum significance of 5% (P-value of <0.05).

RESULTS

A total of twenty nine cases were included in the present study. Male to female ratio was 2.2:1 with 20 male and 9 female patients. The age ranged from 31 years to 84 years with mean of 59.5 years. Young patients (≤ 50 years) were 7 cases and 22 cases of older patients (> 50 years).

Pathological status:

Out of total, 7 were total gastrectomy, rest 22 were subtotal gastrectomy specimens. All of them had tumor mass on them. Most of the tumor masses were located in the antrum and pylorus region amounting to 21 cases followed by body (6 cases) and 2 cases revealing tumor extending from body till antrum region. Bormann classification showed 4 cases of Type I (polypoid), 5 cases of Fungating tumor (Type II), 15 cases of ulcerated tumor (Type III) and 5 cases of infiltrating type (type IV) on gross morphology. The size of the tumor varied from 2.5 cm to 10 cm. 14 cases (48%) had tumor size less than six cm in maximum diameter whereas

Table 2: Correlation between lymphovascular (LVI) status and Nodal (N) status

LVI status	Nodal status N0	Nodal status N1	Nodal status N2	Nodal status N3	P –value
Present (21)	**01**	05	09	06	0.007
Absent (08)	05	01	01	01	

Table 3: Correlation between Tumor size and pathological Tumor (pT) stage

Tumor size	T stage	Nodal status N1	Nodal status N2	Nodal status N3	P –value
Size <6 cm (14)	**02**	01	08	03	0.05
Size ≥6 cm (15)	01	01	12	01	

15 cases (52%) had tumor size equal to or more than six cm. Most of the tumor showed tumor invasion till the serosa (52%), followed by tumor infiltrating till the muscularis (38%), submucosal invasion (7%) and (3%) mucosal invasion by tumor grossly. (Table 1)

Microscopic finding:

There were 17 cases (59%) of intestinal type and 11 cases (38%) of diffuse type of gastric carcinoma and 1 case (3%) of adeno-neuroendocrine carcinoma when categorized as Lauren's classification. Most of the tumor showed moderate degree of differentiation 17 cases (59%), followed by poor differentiation in 9 cases (31%) and only 3 cases (10%) of them were well differentiated. Microscopic evaluation for depth of invasion showed that the majority of the cases had tumor invasion till the subserosal connective tissue layer (69%) suggesting pT3 stage, muscularis invasion (21%) and submucosal invasion in 10% of cases. The intramucosal carcinoma was not seen in the present study. LVI was identified in 21 cases amounting to 72 per cent. (Table 2). Lymphovascular invasion correlated with the nodal status with P value <0.05.

Correlation between the tumor size and tumor stage is shown in table 3. Most of the tumor were of stage 3 (n=20; 68.9%). Tumor size was not only the defining features of tumor staging (P=0.5). Despite being of larger size (≥6 cm), T4 stage was seen only in 1 case (6.6%), whereas most of the larger tumor were of stage 3 (n=12; 80%). Correlation between lymphovascular invasion and nodal status was statistically significant. (P= 0.01)

DISCUSSION

Gastric cancer is one of the most common malignancies occurring globally. The identification of prognostic factors is very important for predicting gastric cancer patient's survival and determining therapeutic strategies. It is universally acknowledged that the most significant factors affecting prognosis of gastric cancer patients are the depth of invasion (T staging) and the status of lymph node metastasis (N staging).[13-15]

The present study constituted 29 cases of gastric carcinoma. There was male preponderance to gastric carcinoma with male to female ratio of 2.2:1 (20 male and 9 female). The age varied from 31- 84 years with mean of 59.5 years. This correlated well with other studies done by Lazar et al consisting of 61 patients (43 male and 18 female), with ages between 30- 80 years (average age = 59.34 years).[16]

LVI was identified in 21 cases amounting to 72%. This data correlated well with other studies. Dicken et al stated that the incidence of LVI in gastric cancer varies from 5.4% to 86%, with the lowest incidence reported in patients with node-negative tumors.[4] Variations in the incidence of vascular invasion may be due to differences in the detection methods, criteria for pathological evaluation, and percentage of advanced GC as stated by Li et al.[17]

Only H and E stain were used to identify LVI which was similar to other researchers as well. In the study done by Li et al which included 1148 cases of gastric cancer out of which LVI was detected in 404 patients (35.2%) through the use of hematoxylin and eosin (H&E) staining.[18]

Similarly, Del Casar et al had previously reported that 31.9% of GC patients had presented with LVI as detected using H & E staining complemented by immunostaining with CD34.[19] However, a study by Kim et al had indicated that LVI was detected in 44.3% of GC patients by immunostaining with D2-40 and CD31. Because of lack of immunohistochemistry, LVI was detected using H and E stain only in this study.[20]

This study showed that there was statistically significant correlation between LVI and nodal status (N0) status at the significance level of 0.05. P value of 0.01 was achieved. This correlated well with study done by Michelassi et al, which also showed P value of less than 0.001 when LVI was correlated with nodal status.[21]

There have been many studies suggesting vascular invasion was an indepen¬dent risk factor for recurrence in patients with node-negative advanced GC as stated by Hyung et al.[7] Talamonti et al also showed that, along with other clinicopathologic factors, LVI is independently associated with disease-free survival. This study reported 5-year overall survival rates of 26.2% in LVI positive compared

with 49.9% in LVI-negative tumors.[22]

Lazar et al also concluded that there is a direct proportional relationship between the lymphovascular invasion and the number of positive lymph nodes. Hence, survival after 5 years decreases significantly in the presence of lymphovascular invasion.[23] Lim et al reported that tumor size, depth of invasion, macroscopic type, and lymphovascular invasion were related to lymph node metastasis in early gastric cancer. However, this study showed that the relation between tumor size and pT stage was statistically not significant (p- value of 0.5). This may be because of relatively less sample size in this study.[24]

Scartozzi M et al did a multivariate analysis with 734 patients, divided into two groups: group A for patients with LBVI/PNI (26%) and group B for patients without LBVI/PNI (74%). The disease-free survival (DFS) for patients in group A was 32.1 months, whereas it was not reached for patients in group B; the median overall survival was 45.5 months for patients in group A, whereas it was not reached for patients in group B. Hence, the presence of LBVI/PNI appeared an independent prognostic factor for DFS and OS.[5]

The observation of lymphovascular invasion as prognostic marker seems to integrate well to what has been already suggested by other studies hypothesizing that LVI may represent a prognostic factor in oesophageal squamous cell cancer and gastric cancer and that the prognostic value of these factors is not influenced by tumour stage, grade of differentiation or lymph node involvement as suggested by Gabbert, Kooby and Burkhard et al.[25-27]

CONCLUSION

Presence of lymphovascular invasion is considered as poor prognostic marker in case of gastric adenocarcinoma. Pathologists have been reporting their presence or absence in each gastrectomy reports related to gastric carcinoma. This study has established a significant relation between presence of LVI and nodal staging of gastric carcinoma.

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