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Intestinal and diffuse gastric cancer: a retrospective study comparing primary sites

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ABSTRACT

Objective: We assessed differences in primary sites and spread patterns of the intestinal and diffuse subtypes of gastric carcinoma. We also compared survival outcomes based on spread patterns.
Materials and methods: For this retrospective IRB-approved study, our institutional imaging database was mined for patients with gastric cancer. We included 99 treatment-naïve patients. Patient demographics, pathologic data, tumor classification, primary tumor site, and metastasis sites were recorded. Pearson's chi-squared test was used to correlate tumor pathology with metastatic sites. Kaplan–Meier survival curves were compared between baseline metastatic types. A heat map was created based on the relative frequencies of metastatic sites for each primary tumor site.
Results: Of the 99 patients, 66 patients had intestinal and 33 had diffuse gastric carcinoma. The intestinal subtype was significantly associated with hepatic metastases ($p < 0.001$). Diffuse subtype was associated with peritoneal metastases, including omental metastases ($p < 0.006$), gastrosplenic ligament involvement ($p < 0.004$), and mesocolonic implants ($p < 0.008$). Patients with primary gastric tumors occurring at the greater curvature had longer overall survival than those with primary sites at the antrum, GE junction and lesser curvature ($p = 0.0015$). Patients with peritoneal metastases had a significantly shorter overall survival than patients without peritoneal metastases ($p < 0.001$). Patients without mesocolon, gastrohepatic ligament, and gastrosplenic ligament involvement had a better survival ($p = 0.005$, $p = 0.0002$, and $p = 0.0005$, respectively). Presence of hepatic metastases had no effect on survival ($p = 0.16$).
Conclusion: Recognizing distinctive spread patterns for intestinal versus diffuse gastric carcinoma can aid radiologists in diagnosis and guide clinical management.

1. Introduction

Gastric carcinoma is the fourth most common cancer, the most prevalent cancer in Eastern Asia, and the second most fatal cancer globally [1,2]. When patients present with gastric carcinoma, it is important to classify the primary tumor type, identify the primary location of the tumor, and identify the pattern of disease spread in order to guide optimal treatment.

Gastric carcinoma is divided into 2 main histological subtypes according to Lauren's criteria – intestinal (also known as well-differentiated) and diffuse (also known as undifferentiated) [3]. The two subtypes each have unique pathogenesis, genetic background, epidemiology, and morphology.

On a molecular level, the initiating factor for development of diffuse carcinoma is loss of expression of the key surface protein E-cadherin, which maintains the organization of epithelial tissues and establishes intracellular connections. When a somatic or germline mutation, epigenetic silencing of gene transcription, or allelic imbalance occurs, there is biallelic inactivation of CDH1 (cadherin 1), the gene encoding cadherin. Diffuse carcinoma is associated with loss of E-cadherin expression and CDH1 mutations [4–7]. Diffuse carcinoma exhibits a lack of adhesion molecules, which enables tumor cells to proliferate and

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invade adjacent structures without forming glands or tubules. Therefore, diffuse carcinoma is characterized by rapid disease progression and a poor prognosis.

Intestinal carcinoma, on the other hand, is usually initiated by *Helicobacter pylori* infection, triggering a multistep process. A long precancerous process ensues, which usually takes decades to convert from an infectious process to cancer [8]. Intestinal-subtype tumors are associated with the CDX-2 (caudal type homeobox-2) gene, which is important in the development of intestinal mucosa [9,10]. It is found in the presence of intestinal metaplasia. The proto-oncogene Her-2/neu (HER2) tends to be overexpressed in the intestinal subtype (in 30% of cases, vs 6% of diffuse-subtype cases) [11]. HER2 is located on chromosome 17q21 and encodes a transmembrane tyrosine kinase growth factor receptor. Proliferation of HER2 has been shown in gastroesophageal and gastric tumors [11,12]. In addition, the beta-catenin/wnt signaling pathway has been associated with intestinal carcinoma [13].

The spread patterns of the subtypes of gastric carcinoma differ. The tumor can spread directly, through the lymphatics, or hematogeneously [14,15]. The pattern of direct contiguous spread involves invading the lymphatics, extending to the ligaments, including the hepatoduodenal, gastrocolic, gastrosplenic, and gastrohepatic ligaments (Fig. 1). The direct contiguous spread pattern has been associated with the diffuse subtype (Fig. 2).

Some studies have shown that a phenotypic peritoneal spread

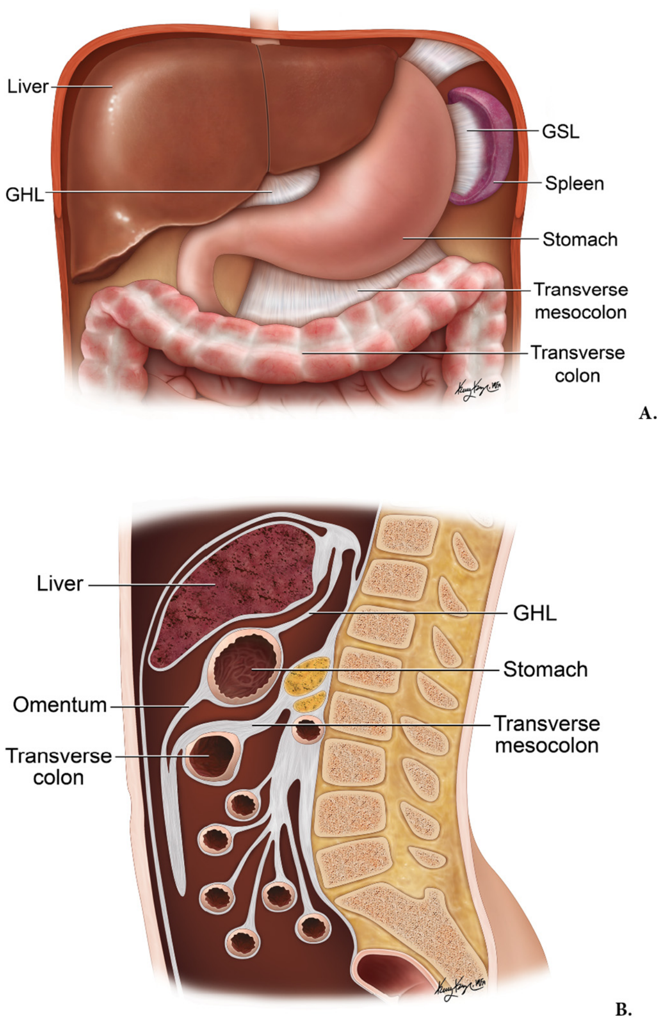


Fig. 1. Anatomy of the gastric ligaments.
A, Coronal image. GSL: Gastrosplenic ligament.
B, Sagittal image. GHL: Gastrohepatic ligament.

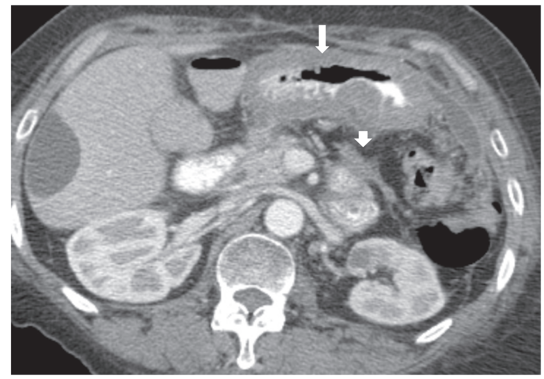


Fig. 2. 53–Year-old female with diffuse-subtype gastric carcinoma. Axial postcontrast CT image demonstrating circumferential involvement of the gastric body (arrow), with gastrosplenic carcinomatosis (arrowhead), and ascites scalloping around the liver.

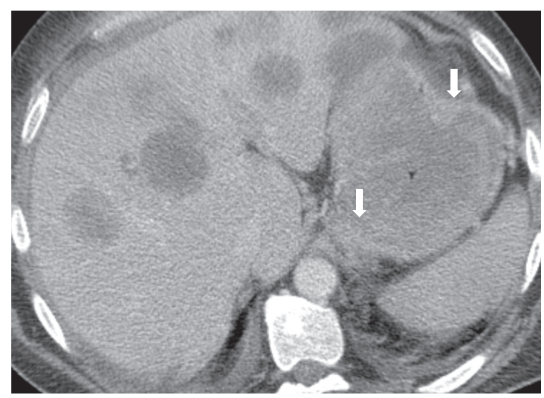


Fig. 3. 62-Year-old male with intestinal subtype gastric carcinoma. Axial postcontrast CT demonstrating circumferential tumor involvement of the fundus and proximal stomach (arrows). There are bilobar liver metastases and small bilateral pleural effusions.

pattern can be associated with certain gastric cancer subtypes [15–17] so we investigated for a correlation in this study. A hematogenous spread pattern, typical of intestinal-subtype gastric carcinoma, is less common, stemming from the portal venous drainage pattern of the stomach to the liver, lungs, and bone [16] (Fig. 3).

To our knowledge, there is a paucity of research investigating the specific spread patterns of the intestinal and diffuse subtypes of gastric carcinoma on imaging. We hypothesized that the intestinal versus diffuse subtypes have characteristic spread patterns of peritoneal disease. We also hypothesized that presence and spread patterns of peritoneal disease, and presence of hepatic metastases would affect patient survival. We tested these hypotheses in a retrospective study of patients with intestinal or diffuse gastric carcinoma.

2. Materials and methods

After IRB approval, we searched our imaging database for patients diagnosed with gastric cancer from January 2005 to January 2009. Patients who had a contrast-enhanced CT scan in the portal venous phase were included. 99 treatment-naïve patients with pathologically confirmed intestinal- or diffuse-subtype gastric carcinoma were included.

For each patient, the medical records, pathology reports, and CT scans were reviewed. Patients' age, sex, primary tumor subtype (intestinal versus diffuse), primary tumor site (gastroesophageal junction, greater curvature, lesser curvature, antrum), pathological grade (well-differentiated, moderately differentiated, poorly differentiated), and

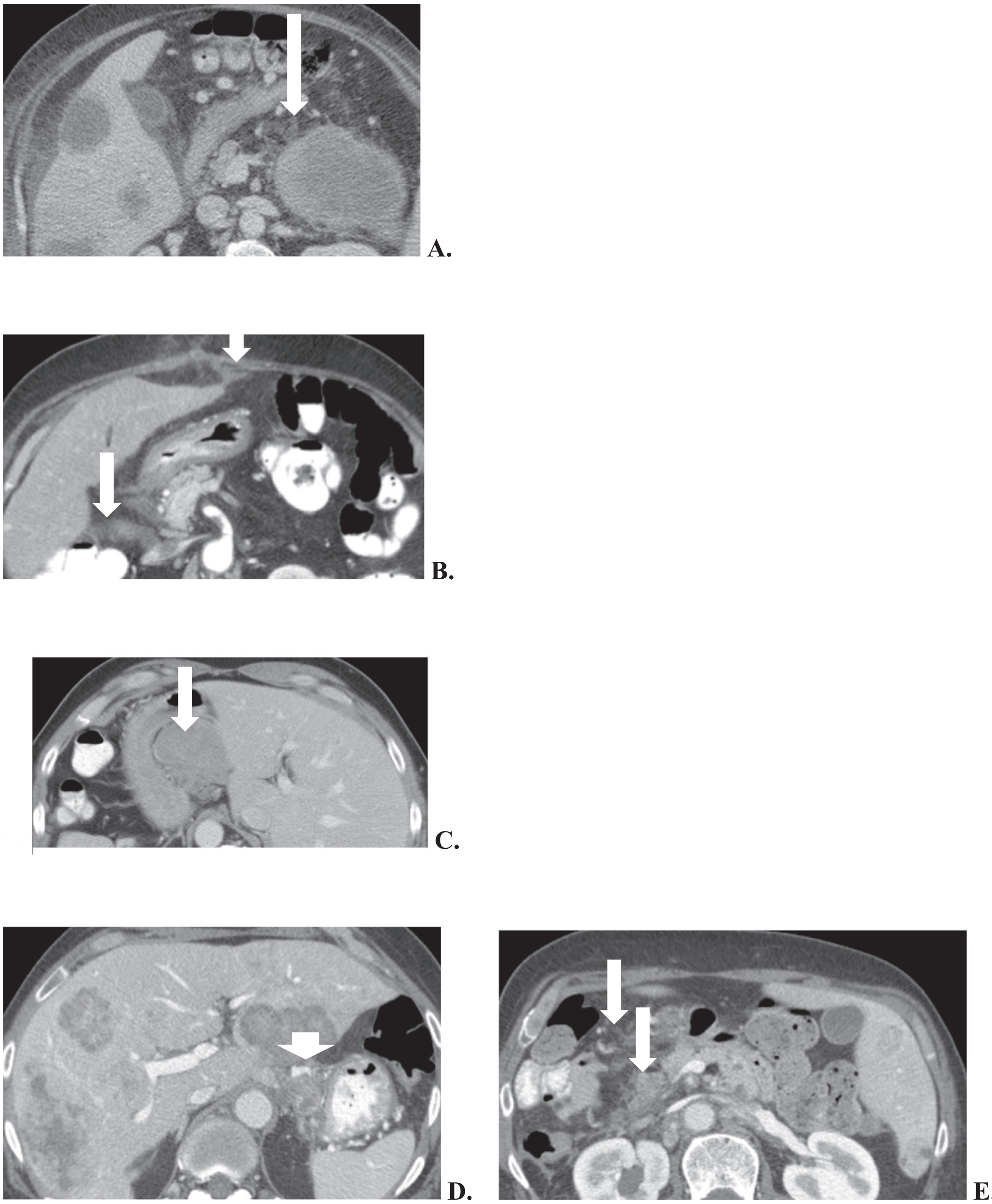


Fig. 4. Phenotypes subtypes of peritoneal spread utilized for this study for both intestinal and diffuse subtypes.
A, 65-Year-old male with gastric carcinoma. Stranding was documented as wispy haziness within the ligaments (arrow).
B, 72-Year-old female with gastric carcinoma. A sheet pattern was described as a thick linear rind of soft tissue (arrows).
C, 60-Year-old male with gastric carcinoma. A nodular pattern was described with the peritoneal disease appeared as discrete nodules (arrow).
D, E, 53-Year-old female with gastric carcinoma. A mixed pattern was defined as a combination of nodular (arrowhead), stranding (arrows), and thickened linear bands.

Table 1
Summary statistics of patient demographics and pathology.

Factor	Total	Intestinal	Diffuse	p-Value
	(N = 99)	(N = 66)	(N = 33)	
Age, years (mean ± _)	61.5 ± 13.7	64.2 ± 12.3	56.0 ± 14.7	0.004
Sex				0.01
F	34 (34.3)	17 (50.0)	17 (50.0)	
M	65 (65.7)	49 (75.4)	16 (24.6)	

sites of metastatic disease were documented from patients' electronic medical records. The tumor classification (T1-T4) based on the TNM system was recorded [18,19]. Date of patient death if applicable was tabulated.

All CT images were acquired on a 16 detector scanner (GE Healthcare, Milwaukee, WI). All patients had portal venous and delayed phase imaging at 2.5 mm axial slice reconstructions through the abdomen and pelvis, based on the standard-of-care protocol at our institution. CT parameters included pitch of 0.9375, revolution time of 0.8 s, table feed/rotation of 18.75 mm, peak kilovoltage of 120 kVp and collimation of 0.625 mm. The study was obtained following administration of 125 mL of Omnipaque 350 (GE Healthcare), which was

Table 2
Cross tabulation of pathological subtypes of primary tumor with metastatic sites.

Factor	Total (N = 99)	Intestinal (N = 66)	Diffuse (N = 33)	p-Value
Omental metastases[a]				0.006
No	33 (33.7)	28 (84.8)	5 (15.2)	
Yes	65 (66.3)	37 (56.9)	28 (43.1)	
Gastrohepatic metastases				0.44
No	16 (16.2)	12 (75.0)	4 (25.0)	
Yes	83 (83.8)	54 (65.1)	29 (34.9)	
Gastrosplenic metastases				0.004
No	54 (55.1)	43 (79.6)	11 (20.4)	
Yes	44 (44.9)	23 (52.3)	21 (47.7)	
Mesocolon metastases				0.008
No	36 (36.4)	30 (83.3)	6 (16.7)	
Yes	63 (63.6)	36 (57.1)	27 (42.9)	
Peritoneal metastatic spread pattern[a]				0.19
Sheet & stranding	25 (32.1)	18 (72.0)	7 (28.0)	
Nodular & mixed	53 (67.9)	30 (56.6)	23 (43.4)	
Hepatic metastases				< 0.001
No	39 (39.4)	14 (35.9)	25 (64.1)	
Yes	60 (60.6)	52 (86.7)	8 (13.3)	

Values presented as N (row %).
p-Values: Pearson's chi-square test.
[a] Missing values: Mets_at_Omentum = 1, Mets_at_Gastrosplenic = 1, Peritoneal mets spread pattern = 21.

injected at the rate of 2.5–3 mL/s with bolus tracking. A Hounsfield unit trigger value of 100 in the abdominal aorta at the level of the celiac artery and a scan delay of 45 s were used. Barium sulfate (Bracco Diagnostics, Monroe Township, NJ) was utilized as an enteric contrast agent.

Review and tabulation of the findings from the CT scans (portal venous phase of contrast) were performed independently by two board-certified fellowship-trained abdominal radiologists specializing in oncologic imaging ([initials masked]), who have 20 years and 16 years of experience, respectively.

Sites of peritoneal spread (gastrohepatic ligament, gastrosplenic ligament, mesocolon, omentum) were assessed. The phenotypic pattern of peritoneal disease (stranding and sheetlike in one category, and nodular and mixed in another category) were described (Fig. 4). Stranding was documented as wispy haziness within the ligaments. A sheetlike pattern was described as a thick linear rind of soft tissue present in the peritoneum. A nodular pattern was described if the peritoneal disease appeared as discrete nodules. A mixed pattern was defined as combination of nodular, stranding, and other morphologies such as thickened linear bands.

The presence of liver metastases was also assessed. Lesions within the liver were characterized as metastases if they had rim enhancement and/or irregular margins and demonstrated decreased enhancement on the delayed phase of the exam.

Patient demographics, primary tumor features, and metastatic sites were summarized using descriptive statistics. These features were compared between intestinal gastric carcinoma and diffuse gastric carcinoma using two-sample *t*-test and Pearson's chi-squared test. Primary tumor sites were cross-tabulated with metastatic sites and tested using Fisher exact test. Survival curves of different baseline peritoneal or hepatic metastatic status were estimated using the Kaplan–Meier method and compared by log-rank test. A heat map based on the relative frequencies of metastatic sites for each primary site was created to examine the relationship between the metastatic sites and the primary sites. The rows and columns in the heat map were clustered by using hierarchical clustering. All tests were two-sided and *p*-values of 0.05 or less were considered statistically significant. Statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC). The heat map and survival curves were plotted using R version 3.1.1 with the packages "gplots" and "survminer" (R Foundation, Vienna, Austria).

3. Results

The study population consisted of 65 men and 34 women (Table 1). The mean age was 61.5 years. The intestinal subtype was found in 66 patients and the diffuse subtype in 33 patients.

The peritoneal metastases were divided into omentum, gastrohepatic ligament, gastrosplenic ligament, and mesocolon metastases. Omental, gastrosplenic ligament, and mesocolonic peritoneal implants were associated with the diffuse subtype ($p = 0.006$, 0.004, and < 0.008, respectively; Table 2). Fig. 5A and B illustrates a representative pattern. The phenotypic appearance of the peritoneal disease was categorized as either stranding and sheetlike, or nodular and mixed. There was no significant association between the phenotypic pattern of peritoneal disease and the cancer subtype ($p = 0.19$).

Of the 99 patients, 60 had hepatic metastases, of which 52 had intestinal and 8 had diffuse primary tumor subtypes. Hepatic metastases were significantly associated with being intestinal (odds ratio, 10.8; 95% confidence interval, 4.19 to 27.84; $p < 0.001$). A representative pattern is shown in Fig. 5C and D. The risk of an intestinal gastric carcinoma developing hepatic metastases was approximately ten times

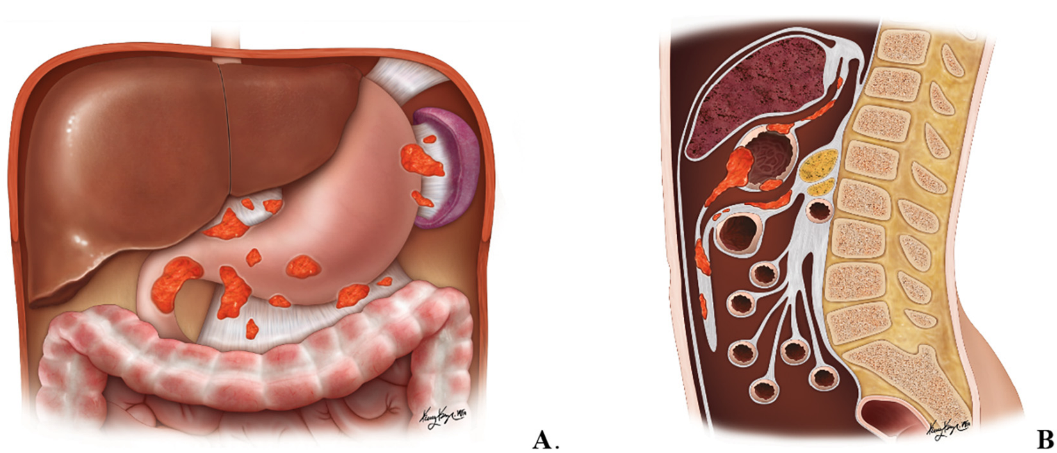


Fig. 5A, B. Spread pattern of diffuse-subtype gastric carcinoma. The perigastric ligaments, primarily the gastrosplenic ligament, gastrohepatic ligament, and mesocolon, are involved. Red deposits mark sites of tumor involvement.
A, Coronal view.
B, Sagittal view. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

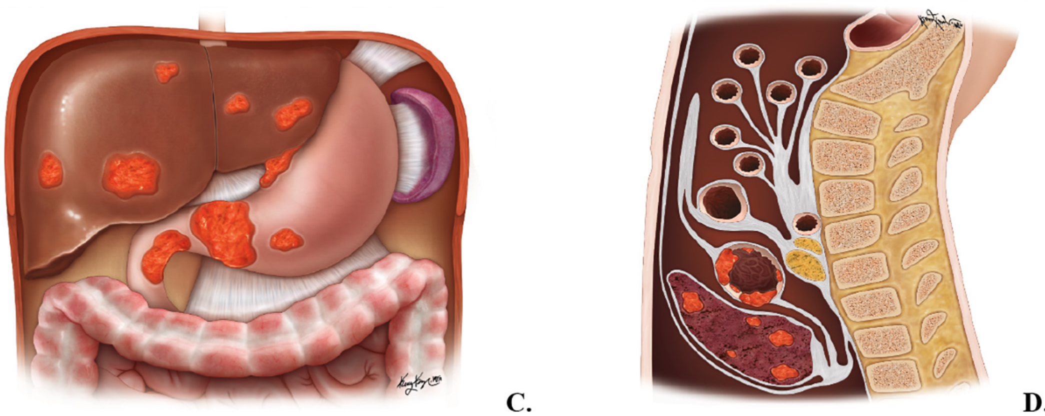


Fig. 5C, D. Spread pattern of intestinal-subtype gastric carcinoma. Spread is primarily hematogenous to the liver. Red deposits mark sites of tumor involvement. C, Coronal view.
D, Sagittal view. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

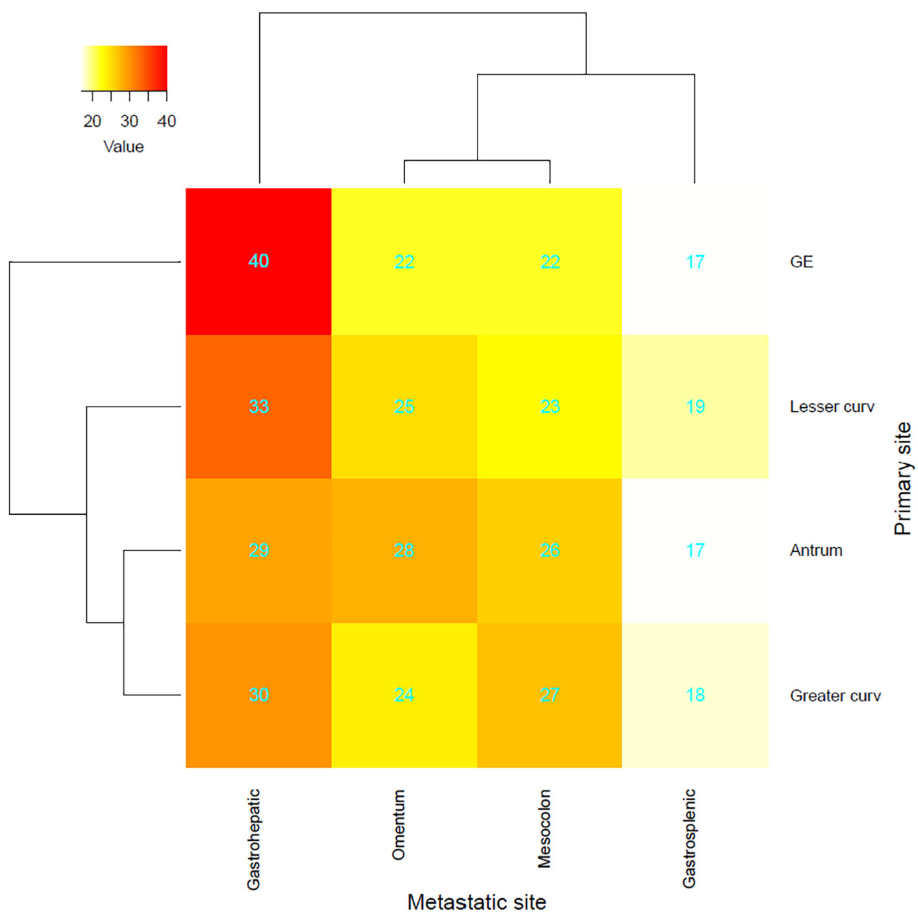


Fig. 6. Heat map of observed frequencies from primary gastric sites (rows) to metastatic sites (columns). The numbers in each cell are counts. The clusters' ordering shows similarity between primary sites with respect to metastatic pattern.

compared to the risk of a diffuse cancer acquiring hepatic metastases.

Heat maps were generated to measure the observed frequencies of primary gastric cancer sites to their metastatic site (Fig. 6). We found that tumors with primary sites in the gastroesophageal (GE) junction and lesser curvature were associated with peritoneal metastases. For the patient group as a whole, a primary tumor at these sites was associated with metastatic disease in the gastrohepatic region (Table 3).

Univariate overall survival analysis results for survival time from the baseline CT scan were generated. Kaplan-Meier curves by CT scan metastasis at baseline were generated. Patients with peritoneal metastases had a significantly lower survival than patients without peritoneal metastases ($p < 0.001$) (Fig. 7a). Patients without involvement of the mesocolon, gastrohepatic ligament, and gastrosplenic ligament had better survival ($p = 0.005$, $p = 0.0002$, and $p = 0.0005$, respectively). Presence of hepatic metastases had no effect on predicting survival ($p = 0.16$; Fig. 7b). Patients with primary gastric tumors occurring at the greater curvature had better survival than did those with primary sites at the GE junction, antrum, and lesser curvature ($p < 0.0015$).

Table 3
Cross tabulation of primary tumor sites with metastatic sites.

Factor	Total	GE	Greater curv	Lesser curv	Antrum	p-Value
	(N = 99)	(N = 28)	(N = 15)	(N = 20)	(N = 36)	
Omentum metastases[a]						0.002
No	33 (33.7)	15 (45.5)	6 (18.2)	8 (24.2)	4 (12.1)	
Yes	65 (66.3)	13 (20.0)	8 (12.3)	12 (18.5)	32 (49.2)	
Gastrohepatic metastases						0.16
No	16 (16.2)	4 (25.0)	5 (31.3)	4 (25.0)	3 (18.8)	
Yes	83 (83.8)	24 (28.9)	10 (12.0)	16 (19.3)	33 (39.8)	
Gastrosplenic metastases[a]						0.52
No	54 (55.1)	18 (33.3)	9 (16.7)	11 (20.4)	16 (29.6)	
Yes	44 (44.9)	10 (22.7)	6 (13.6)	9 (20.5)	19 (43.2)	
Mesocolon metastases						0.012
No	36 (36.4)	15 (41.7)	6 (16.7)	9 (25.0)	6 (16.7)	
Yes	63 (63.6)	13 (20.6)	9 (14.3)	11 (17.5)	30 (47.6)	

Values presented as N (row %).
p-Values: Fisher's exact test.
[a] Missing values: Mets_at_Omentum = 1, mets_at_Gastrosplenic = 1.

4. Discussion

Our study results support our hypothesis that the intestinal versus diffuse subtypes of gastric carcinoma have characteristic spread patterns of peritoneal disease. Our results also support our hypothesis that presence and type of peritoneal disease and spread patterns of peritoneal disease affect patient survival. However, our results suggest that presence of hepatic metastases from gastric cancer does not affect patient survival.

Our study demonstrates a higher tendency for peritoneal disease in patients with diffuse subtype when compared with the intestinal subtype, which is concordant with other studies [3,17,20,21]. We did not find any literature that has discussed the frequency of specific sites of peritoneal spread. In our study, we found that the diffuse gastric carcinoma subtype tends to spread to the gastrosplenic ligament, transverse mesocolon, and omentum.

Both diffuse and, less frequently, intestinal gastric cancer tend to spread contiguously from the tumor. The pattern of direct contiguous spread involves invading the lymphatics, extending to the ligaments, including the hepatoduodenal, gastrocolic, gastrosplenic, and gastrohepatic ligaments [15]. From the ligaments, the tumor spreads to the peritoneal cavity, including the greater and lesser omentum depending on the primary tumor type. Gastric tumors can also spread in a direct manner to adjacent organs such as the duodenum. Diffuse carcinoma tends to have a disseminated pattern [16]. In our study, peritoneal metastases were more common with the diffuse subtype than with the intestinal subtype, concordant with other research. Therefore, we can deduce the diffuse subtype is associated with a lower survival than intestinal gastric carcinoma.

Our study demonstrated that intestinal-subtype gastric carcinoma is significantly associated with liver metastases, which is also concordant with the literature [16]. Metastatic disease occurs through a hematogenous spread pattern stemming from the gastric vein draining into the portal venous system that supplies the liver. Other sites of hematogenous spread aside from the liver include the lungs, soft tissues, and bones. Intestinal gastric carcinoma tends to grow in a localized regional distribution within the stomach and is masslike on imaging [20].

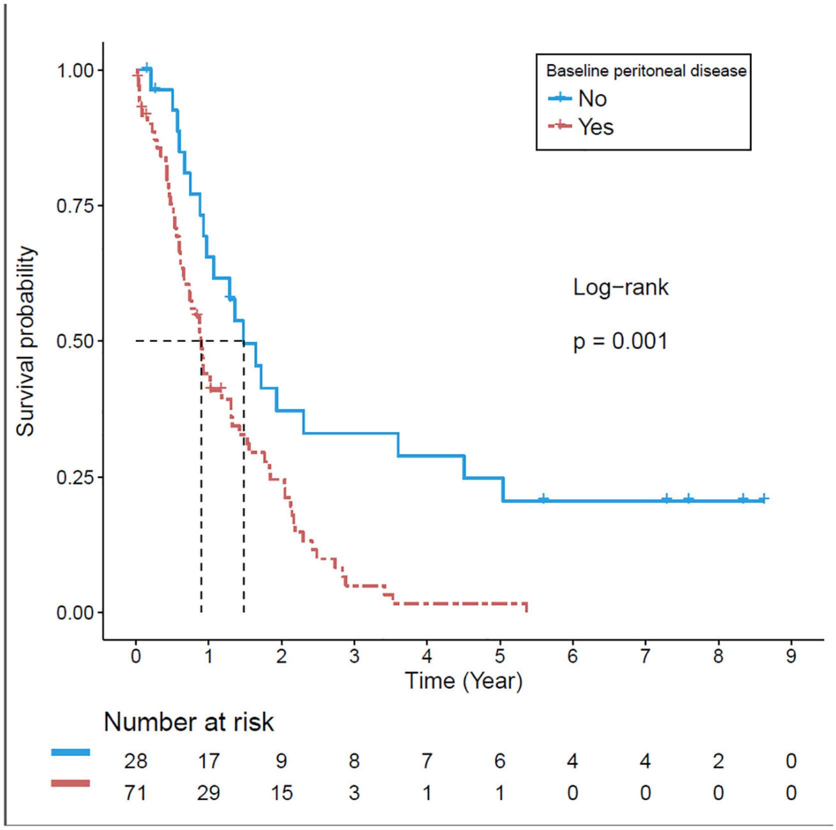
Studies demonstrate that diffuse carcinoma typically is more prevalent than the intestinal subtype [21–24]. Two studies determined that the diffuse subtype occurs more frequently in the distal stomach and antrum of the stomach [20,21]. The intestinal subtype has been linked to being located more commonly in the distal stomach and antrum, and also to being well differentiated with less lymphovascular invasion [20,24]. Interestingly in our study, the majority of both intestinal and diffuse subtypes were found at the gastroesophageal junction, lesser curvature, and antrum.

Our results demonstrated that the presence of hepatic metastases in the intestinal subtype of gastric cancer did not significantly affect survival outcomes. We also demonstrated that presence of peritoneal metastases, which is strongly associated with diffuse gastric cancer, adversely affects survival rate, which is concordant with other research [21]. In this study, patients with peritoneal disease had a significantly lower survival rate than did patients without involvement of the omentum or gastrohepatic and gastrosplenic ligaments. This finding is concordant with prior investigations that determined that diffuse gastric carcinoma tends to have peritoneal metastases and a worse prognosis than intestinal-subtype carcinoma [21]. A study by Yamashita et al. suggests that the tendency of the diffuse subtype to have deeper invasion and peritoneal cells is a factor in the worse prognosis of the diffuse subtype [22]. We found that the pattern of peritoneal disease (nodular, stranding, sheet, mixed) had no significant association with spread pattern or survival. Our study showed that primary gastric tumors occurring at the GE junction gastric cardia had the worst survival, which is similar to the findings by Hansson et al. [25].

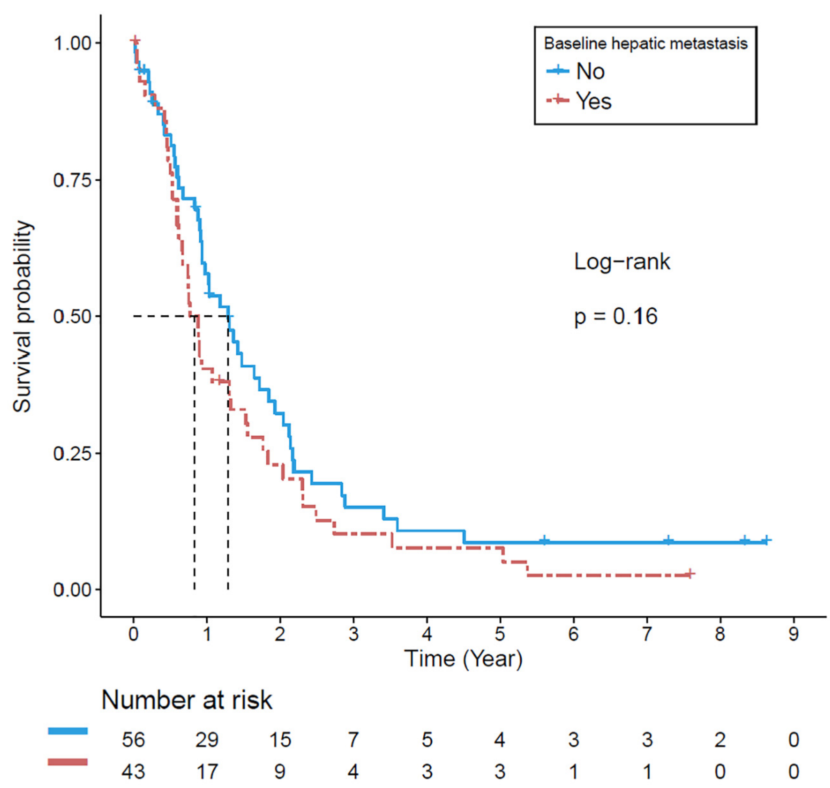
Surgical treatment of diffuse gastric carcinoma may have a high probability of positive margins on resection as this subtype can be poorly receptive to adjuvant chemotherapy [26]. Thus, knowledge of the tumor subtype and the pathway of spread of tumor may help guide the radiologist to optimally assess for peritoneal disease and thus preclude intended surgical resection. Since diffuse gastric carcinomas tend to spread to the peritoneum, finding peritoneal disease may guide the oncologist to administer higher doses of chemotherapy, which result in higher peritoneal concentrations of drug, which are gradually absorbed into the lymphatic system. Several studies have demonstrated that intraperitoneal injection of paclitaxel or intraperitoneal injection along with intravenous chemotherapy (allied systemic chemotherapy) may be a promising treatment option for diffuse gastric carcinoma [27–29].

This study has limitations, as it is a retrospective study from a single institution. The sample size was relatively small, with fewer cases of diffuse carcinoma (33 cases) in comparison to intestinal carcinoma (66 cases). Also, with the retrospective nature of the study, it is difficult to assess the temporal pattern of disease. A prospective, larger study would be beneficial to validate the associations we observed between each gastric subtype and spread pattern, as well as survival analysis.

In conclusion, this study demonstrates there is a significant difference in the spread patterns of intestinal versus diffuse gastric cancer. It found that tumors in the GE junction, lesser curvature and antrum in descending order respectively tend to spread to the peritoneum, particularly the gastrohepatic ligament and omentum, which to our knowledge has not been investigated before; this primary location



A.



B.

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Fig. 7. Kaplan-Meier survival analyses.
A, Survival comparison based on presence of baseline peritoneal disease on CT.
B, Survival comparison based on presence of baseline hepatic metastasis on CT.

portends a worse prognosis than when the primary is located along the greater curvature. Hepatic metastases associated with intestinal carcinoma have no effect on predicting survival rate. Understanding the spread patterns of each subtype of carcinoma is important for radiologic interpretation as well as clinical management. It is beneficial when the primary site is known to be able to predict the spread pattern of disease, or conversely observing a characteristic spread pattern may aid in finding the primary tumor.

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