Gastric Cancer: Correlation of Histologic Type with Commonly Used Prognostic Variables

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Abstract

Background: Gastric cancer is one of the most common cancers among Iranian men and women.
Objectives: The aim here was to investigate different histopathologic types and features of this cancer in association with selected prognostic variables.
Methods: A retrospective cross-sectional study was performed to reevaluate the pathologic samples of 100 cases of gastric cancer referred to Shohadaye Tajrish Hospital, Tehran, Iran from 2017 to 2022.
Results: We evaluated 100 cases of gastric cancer in this study. They had a mean age of 62.4 ± 13.44 years old (range 28 - 84 years) and were mostly men (n = 66, 66 %). On histopathologic evaluation, tubular carcinoma was the most common type (n = 45, 45%). We found a statistically significant correlation between the histologic type and perineural invasion (P-value = 0.024), lymphovascular invasion (P-value < 0.001), tumoral involvement of surgical margin (P-value = 0.012), infiltration depth of the primary tumor (pT) (P-value = 0.049) , number of metastatic lymph nodes (pN) (P-value = < 0.001) , tumor location in the antrum (P-value=0.033) and body (P-value = 0.013) , and tumor size (P-value = 0.002 and P-value = 0.031 in small and large size groups respectively).
Conclusions: According to the findings, histologic type of gastric cancer correlates with perineural invasion, lymphovascular invasion, tumoral involvement of the surgical margin, pT, pN, and tumor location and size.

Keywords: Gastric Cancer, Perineural Invasion, Lymphovascular Invasion, Surgical Margin, WHO Classification System, TNM Staging System

1. Background

While gastric cancer is the fourth most common cancer globally, Iran is one of the several South Central Asian countries where gastric cancer is the most common cause of cancer-related death (1). Gastric cancer is also the first and third most common cancer in males and females in Iran, respectively (2).

Based on anatomic location, gastric cancers are classified into two groups: Cardia and non-cardia. Several studies have shown that the survival rate of adenocarcinomas in the cardia and upper third of the stomach is noticeably low (3-5).

Unlike anatomic classification, a lot of classification systems have been proposed and used for gastric cancer based on histology. However, the prognostic value of all of these histopathologic classifications is still controversial due to the high heterogeneity among these tumors and the lack of reproducible histopathological criteria (6-8).

Among these classifications, the Laurén classification was established in 1965 and since then has been the most popular system, but its value in the prognostic area is still controversial (9). The World Health Organization (WHO) classification, established 12 years ago, is another popular classification system that includes all types of gastric tumors. Some of the major variants in the latest WHO classification (2019) are tubular adenocarcinoma, parietal cell carcinoma, adenocarcinoma with mixed subtypes, papillary adenocarcinoma, NOS, micropapillary carcinoma, mucoepidermoid carcinoma, mucinous adeno-

carcinoma, signet ring cell carcinoma, poorly cohesive carcinoma, medullary carcinoma with lymphoid stroma, hepatoid adenocarcinoma, and Paneth cell carcinoma.

Along with these classifications, some other histologic features such as perineural and lymphovascular invasions have been identified by many studies as poor prognostic factors ([10]-[13]). However, the clinical stage is still the most important determinant of prognosis and the TNM staging system is the means that is generally applied as the primary method for assessing the extent of disease and correlates with the prognosis of patients ([14]). This system is also a great help in choosing the most proper management for patients with gastric cancer. In this study we used the 8th edition of this system for our staging purposes.

Although most cases of gastric cancers in Iran are diagnosed at advanced stages ([15]), the 5-year survival rate is estimated for 25% of the patients ([16]); however, early detection and accurate diagnosis of gastric cancer can reduce the mortality rate, advanced-stage diseases, need for chemotherapy and/or chemoradiation, and surgical resection of the tumor and lymph nodes ([17], [18]).

2. Objectives

With regard to the high prevalence of this cancer in Iran and mentioning the importance of an accurate histopathologic evaluation, classification and staging for choosing the most proper management, the purpose of this study was to investigate the correlation of the histologic type of gastric cancer with some important variables. Most of these variables have been identified to have prognostic value including perineural invasion, lymphovascular invasion, surgical margin tumoral involvement, pT, pN, and tumor location and size.

3. Methods

We performed a retrospective cross-sectional study on 100 selected patients with gastric carcinoma referred to Shohadaye Tajrish Hospital from 2017 to 2022.

University's research ethics committee approved this academic work. Informed consent was acquired from all patients.

Inclusion criteria included the presence of primary epithelial neoplasms confirmed by surgical resection specimen and no history of chemoradiotherapy or other synchronous malignancy. Those who refused to allow researchers to use their clinical data or those with incomplete information were excluded from the study.

The clinicopathological data of all patients were obtained from the hospital information system. Variables included demographic data (age and sex), preferred surgical

approach, histological classification, primary tumor location, tumor size, tumor grade, surgical margins, lymphovascular invasion, perineural invasion, T stage (AJCC 8th edition), N stage, and lymph node metastasis. The International Union Against Cancer clinicopathological staging (TNM) was applied for tumor evaluation. World Health Organization classification (2019) was used for histological typing and differentiation grading. Histology was exclusively used as the gold standard for the T stage. The gold standard for assessment of lymph node involvement was the histologic examination of tissue obtained in patients undergoing either lymphadenectomy or a peri gastric lymph node biopsy.

By calculating the median tumor size and using it as the standard, we categorized tumors into 2 groups: Small size (≤ 6) and large size (> 6) ([19]).

Statistical analysis was performed using IBM SPSS Statistics (version 21; IBM Corporation). A chi-square test was used to investigate correlations between the pathological and clinical findings. Data were considered significant if $P < 0.05$.

4. Results

A total of 100 patients were enrolled in this study. The patients had a mean ± SD age of 62.4 ± 13.44 years old (range 28 - 84 years) and were predominantly men (n = 66, 66 %).

The histopathological findings of the specimens are summarized in Table 1. Tubular carcinomas were most commonly found histologic type (n = 45, 45%); followed by mixed tubular & papillary, poorly cohesive, mucinous 25 (n = 25, 25.0%), poorly cohesive carcinomas (signet-ring cell carcinoma & poorly cohesive carcinoma NOS) (n = 24, 24%), and papillary carcinoma (n = 6, 6%). Other histologic types were not found among the evaluated tumors.

Table 1. Histopathological Findings

Tumor Histologic Type	No. (%)
Tubular	45 (45.0)
Mixed tubular & papillary or poorly cohesive or mucinous	25 (25.0)
Poorly cohesive (signet-ring cell carcinoma & poorly cohesive carcinoma NOS)	24 (24.0)
Papillary	6 (6.0)

4.1. Histologic Type Correlation with Demographics and Significant Features

4.1.1. Age and Sex

There was no statistically significant correlation between the sex of patients and tumor histologic type ([Ta-

ble 2). The average age of patients with poorly cohesive carcinoma (signet-ring cell carcinoma & poorly cohesive carcinoma NOS) was lower than other types. The highest age was related to patients with tubular tumors (P-value = 0.007).

4.1.2. Lymphovascular/Perineural Invasion

Lymphovascular invasion was detected in 67 (67%) patients and showed a significant correlation with tumor type (P-value < 0.001) (Table 3). Most of the cases with lymphovascular invasion were patients with tubular type of carcinoma while none of the papillary cases showed this type of invasion.

Perineural invasion was found in 57 (57%) cases and significantly correlated with tumor histologic type (P-value = 0.024) (Tubular Tubular and poorly cohesive carcinomas had similar numbers of cases with perineural invasion, while papillary carcinoma again had the least number of perineural invasions.

4.1.3. Surgical Margin Tumoral Involvement

Microscopic evaluation of surgical margins revealed that the margins of the majority of specimens (n = 88, 88.0%) were free of tumoral lesions, but it also had a significant correlation with the type of tumor (P-value = 0.012) (Table 3).

4.1.4. TNM Staging

The T stage of the majority of patients was T3 (n = 37, 37.0%) and T4a (n = 30, 30.0%) and the N stage showed a significant correlation with the type of tumor (P-value = < 0.001) (Table 3).

4.1.5. Tumor Location

The relationship between tumor type and location is summarized in Table 4. Tumors in the antrum region were more of the tubular type (P-value = 0.033) while tumors of the body region were more of the papillary type (P-value = 0.013).

4.1.6. Tumor Size

Table 5 shows the relationship between histologic type and tumor dimension.

4.1.7. Type of Surgery

No significant correlation was found between tumor histologic type and type of surgery (P-value = 0.434) (Table 6).

5. Discussion

Gastric cancer is the most common cause of cancer death in Iran (1) and although the overall incidence of gastric cancer has declined over past decades, the cardia group in anatomic classification has shown an increase (20). These statistics illustrate the importance of further investigations in this area, especially in countries like Iran.

In our study males (n = 66, 66.0%) were more affected by this cancer than females (n = 34, 34.0%). This result ties well with previous studies where the male-to-female ratio was 2 : 1 (21).

Different histologic types have been shown to have different presentations, for example mixed carcinoma had great size (22) and correlated with nodal involvement (23, 24) In our investigation, we examined tumor size among different tumor types in two categories: Small and large size (Table 4). While both groups showed statistically significant correlation with different histologic types, most of the poorly cohesive tumors had large size, whereas other histologic types were mostly in the small-size group. We also examined nodal involvement according to the updated AJCC/UICC TNM staging system (Table 3). It has to be noted that the prognosis prediction abilities of the 8th and 7th editions of the AJCC/UICC TNM staging system for gastric cancer were analyzed in a recent study and proved that the 8th edition of the AJCC/UICC TNM staging system is superior to the previous edition (25). The majority of the poorly cohesive tumors which as mentioned above were large, had pN2 stage in this study. Lymph node involvement is considered a sensitive prognostic factor in patients with gastric cancer. Accordingly, a higher lymph node ratio that is defined as metastatic nodes to the total number of examined lymph nodes was found to be the predictor of a worse prognosis (26). In assessing the depth of tumor invasion according to the considered staging system, we found that most of evaluated tumors had the pT3 stage. A similar pattern of results was obtained in another study by Zhu et al. (27). They showed that most of their cases (418 of all 932 cases) had pT3 stage. They also compared histologic type and pT stage in pure and mixed histologic types and found significant relationships similar to our study. However, contrary to our findings, they did not show a significant correlation between tumor location and histologic type (P-value = 0.96).

It should be mentioned that one of the most important determinants in treatment of gastric cancer is histologic type (27-29). In histopathologic evaluation we also evaluated two factors proposed as negative prognostic factors, lymphovascular invasion and perineural invasion. Dobrițoiu et al. (30) showed that these factors are more prevalent among mixed type gastric carcinoma. Contrary

Table 2. Age and Sex Distribution of Different Histologic Types of Gastric Cancer

Variables	Total	Tumor Histologic Type				P-Value
		Tubular	Mixed Tubular & Papillary or Poorly Cohesive or Mucinous	Poorly Cohesive	Papillary	
Gender, No. (%)						0.559 [a]
M	66 (66.0)	31 (68.9)	18 (72.0)	13 (54.2)	4 (66.7)	
F	34 (34.0)	14 (31.1)	7 (28.0)	11 (45.8)	2 (33.3)	
Age	62.4 ± 13.44	66.62 ± 11.83	62.68 ± 13.02	55.5 ± 14.28	57.17 ± 13.04	0.007 [b]

[a] Based on chi-square
[b] Based on ANOVA

Table 3. Histologic Types of Gastric Cancer and Some Proposed Prognostic Variables [a]

Variables	Total	Tumor Histologic Type				P-Value
		Tubular	Mixed Tubular & Papillary or Poorly Cohesive or Mucinous	Poorly Cohesive	Papillary	
Margin						0.012 [b]
All free	88 (88.0)	44 (97.8)	22 (88.0)	16 (66.7)	6 (100.0)	
Radial involve	7 (7.0)	1 (2.2)	1 (4.0)	5 (20.8)	0 (0.0)	
Proximal involve	5 (5.0)	0 (0.0)	2 (8.0)	3 (12.5)	0 (0.0)	
LV						< 0.001 [b]
-	33 (33.0)	19 (42.2)	5 (20.0)	3 (12.5)	6 (100.0)	
+	67 (67.0)	26 (57.8)	20 (80.0)	21 (87.5)	0 (0.0)	
PNI						0.024 [b]
-	43 (43.0)	26 (57.8)	9 (36.0)	5 (20.8)	3 (50.0)	
+	57 (57.0)	19 (42.2)	16 (64.0)	19 (79.2)	3 (50.0)	
PT						0.049 [b]
t1a	7 (7.0)	3 (6.7)	2 (8.0)	0 (0.0)	2 (33.3)	
t2	8 (8.0)	4 (8.9)	2 (8.0)	2 (8.3)	0 (0.0)	
t3	37 (37.0)	15 (33.3)	10 (40.0)	8 (33.3)	4 (66.7)	
t4	15 (15.0)	10 (22.2)	3 (12.0)	2 (8.3)	0 (0.0)	
t4a	30 (30.0)	13 (28.9)	8 (32.0)	9 (37.5)	0 (0.0)	
t4b	3 (3.0)	0 (0.0)	0 (0.0)	3 (12.5)	0 (0.0)	
PN						< 0.001 [b]
n0	18 (18.0)	11 (24.4)	3 (12.0)	1 (4.2)	3 (50.0)	
n1	18 (18.0)	14 (31.1)	1 (4.0)	0 (0.0)	3 (50.0)	
n2	39 (39.0)	17 (37.8)	9 (36.0)	13 (54.2)	0 (0.0)	
n3a	17 (17.0)	0 (0.0)	10 (40.0)	7 (29.2)	0 (0.0)	
n3b	8 (8.0)	3 (6.7)	2 (8.0)	3 (12.5)	0 (0.0)	

[a] Values are expressed as No. (%)
[b] Based on Fisher exact test.

to their findings, the incidence of lymphovascular and perineural invasions in our study were highest among poorly cohesive groups (87.5% and 79.2%, respectively).

Others have shown that surgical margin tumoral involvement correlates with a poorer prognosis (31). In evaluation of this negative prognostic factor, we found a signifi-

Table 4. Tumor Location in Relation to Histological Type of Gastric Cancer [a]

Tumor Location	Total [b]	Tumor Histologic Type				P-Value [b]
		Tubular	Mixed Tubular & Papillary or Poorly Cohesive or Mucinous	Poorly Cohesive	Papillary	
Cardia						
No	72 (72.0)	36 (80.0)	15 (60.0)	18 (75.0)	3 (50.0)	0.19
Yes	28 (28.0)	9 (20.0)	10 (40.0)	6 (25.0)	3 (50.0)	
Lesser curvature						
No	59 (59.0)	25 (55.6)	18 (72.0)	13 (54.2)	3 (50.0)	0.494
Yes	41 (41.0)	20 (44.4)	7 (28.0)	11 (45.8)	3 (50.0)	
Antrum						
No	80 (80.0)	31 (68.9)	20 (80.0)	23 (95.8)	6 (100.0)	0.033
Yes	20 (20.0)	14 (31.1)	5 (20.0)	1 (4.2)	0 (0.0)	
Whole gastric wall						
No	88 (88.0)	42 (93.3)	21 (84.0)	19 (79.2)	6 (100.0)	0.242
Yes	12 (12.0)	3 (6.7)	4 (16.0)	5 (20.8)	0 (0.0)	
Pylorus						
No	92 (92.0)	40 (88.9)	23 (92.0)	23 (95.8)	6 (100.0)	0.661
Yes	8 (8.0)	5 (11.1)	2 (8.0)	1 (4.2)	0 (0.0)	
Body						
No	89 (89.0)	41 (91.1)	22 (88.0)	23 (95.8)	3 (50.0)	0.013
Yes	11 (11.0)	4 (8.9)	3 (12.0)	1 (4.2)	3 (50.0)	
Fundus						
No	96 (96.0)	43 (95.6)	25 (100.0)	22 (91.7)	6 (100.0)	0.477
Yes	4 (4.0)	2 (4.4)	0 (0.0)	2 (8.3)	0 (0.0)	

[a] Values are expressed as No. (%)
[b] Based on Fisher Exact test and chi-square.

Table 5. Tumor Size and Histologic Type of Gastric Cancer

Tumor Size	Total	Tumor Histologic Type				P-Value
		Tubular	Mixed Tubular & Papillary or Poorly Cohesive or Mucinous	Poorly Cohesive	Papillary	
Max size, No. (%)	7.59 ± 6.25	5.76 ± 4.63	9.05 ± 7.4	10.62 ± 6.72	3.08 ± 2.27	0.002 [a]
≤ **6**	57 (57.0)	30 (66.7)	14 (56.0)	8 (33.3)	5 (83.3)	0.031 [b]
> **6**	43 (43.0)	15 (33.3)	11 (44.0)	16 (66.7)	1 (16.7)	

[a] Based on ANOVA.
[b] Based on Fisher exact test.

cant difference between different histologic types (P-value = 0.012). The highest incidence of positive surgical margins (radial and proximal totally) was among poorly cohesive groups, while all the surgical margins in the papillary group were free of tumor.

The main limitation of this study was the lack of follow up of the patients for assessing survival rate.

5.1. Conclusions

Overall, our results demonstrate a correlation between tumor histology and our selected studied variables including perineural invasion, lymphovascular invasion, tumoral involvement of surgical margin, pT, pN tumor location, and size.

Table 6. Type of Surgery and Histologic Type of Gastric Cancer [a]

| Type of Surgery | Total | Tumor Histologic Type | | | | P-Value [b] |
		Tubular	Mixed Tubular & Papillary or Poorly Cohesive or Mucinous	Poorly Cohesive	Papillary	
Total gastrectomy	37 (37.0)	16 (35.6)	7 (28.0)	10 (41.7)	4 (66.7)	0.434
Subtotal gastrectomy	13 (13.0)	6 (13.3)	6 (24.0)	1 (4.2)	0 (0.0)	
Gastrectomy	19 (19.0)	9 (20.0)	5 (20.0)	4 (16.7)	1 (16.7)	
Partial gastrectomy	20 (20.0)	9 (20.0)	3 (12.0)	7 (29.2)	1 (16.7)	
Resection	7 (7.0)	4 (8.9)	1 (4.0)	2 (8.3)	0 (0.0)	
Distal gastrectomy	4 (4.0)	1 (2.2)	3 (12.0)	0 (0.0)	0.(0.0)	

[a] Values are expressed as No. (%).
[b] Based on Fisher exact test.

Footnotes

Authors' Contribution: Study concept and design, Statistical analysis: A. T; Drafting of the manuscript, statistical analysis, critical revision of the manuscript for important intellectual content: A. KH; Acquisition of data: M. SA; Collected the clinical data: R. S.; Acquisition of data: M. B.; Collected the clinical data: M. HP.; Statistical analysis: S. Z.; Collected the clinical data: H. HF.; Acquisition of data: R. M.; Acquisition of data: S. S.; Acquisition of data: P. N.; Acquisition of data: HR. E.; Administrative, technical, and material support: Z. S.; Administrative, technical, and material support: M. H.; Critical revision of the manuscript for important intellectual content, Study supervision: A. M; Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content, Study supervision: L. B. KH.

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Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available because they contain names, phone numbers and addresses of the patients.

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