Original Article

Clinicopathological Characteristics of Gastric Cancer in Iranian Patients Referred to Imam Reza Hospital During 2008 to 2017

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Abstract

Background and Aim: There are a limited number of studies regarding the clinicopathological features of gastric cancer. Here, the clinicopathological features of gastric cancer including tumor type and size, degree of differentiation, tumor operability, and immunohistochemically results of E-cadherin and *P53* expression was investigated in Iranian patients.

Methods: This retrospective study was performed on patients who were admitted at Imam Reza Hospital in Tehran-Iran from 2008 to 2017 with a diagnosis of gastric cancer. Required information including age, sex, type of cancer, pathology, and immunohistochemistry (IHC) results and treatment were extracted from the hospital archive.

Results: Out of 264 enrolled patients (with the mean age of 70.03±14.01 years), 180 cases were men. The frequency of intestinal-type, Diffuse-type, lymphoma and GIST tumor were 54.5%, 27.7%, 12.25% and 5.92% respectively. In addition, 67.58% and 13.83% of the tumors were undifferentiated and poorly differentiated respectively.

Surgery was less probable in less differentiated tumors (r=0.582 P=0.001). The surgery rate in GIST, intestinal-type, and Diffuse-type tumors were 100%, 57%, and 14.4%, respectively. IHC results showed that E-cadherin expression was present in 78.6, of which 50.9% were weakly positive (+1). Also, the high expression of *P53* was observed in 60.7% of patients.

Conclusion: According to the data, we can conclude that poorly differentiated tumors, decreased expression of E-cadherin, and increased expression of *P53* is linked to poor prognosis in Iranian patients with gastric cancer. In this regard, further clinical trials and multicenter studies should be done to evaluate the possible factors for improving the prognosis and survival rates of Iranian patients with gastric cancer.

Keywords: Gastric cancer; Tumor; Surgery; E-cadherin; P53; Differentiation.

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Introduction

Gastric cancer is the 5th most common cancer, the third leading cause of cancer death worldwide (1), and the most common malignancy in Iranian men. The annual incidence of gastric cancer is 7300 in Iran and it is the first cause of Iranian cancer death in both sexes (2, 3). There are distinct histological subtypes of gastric cancer, which differ in their epidemiology, pathogenesis, genetic profile, and clinical outcomes (4, 5). In recent years, the discovery of different genes has increased our knowledge about the pathogenesis and clinical course of cancers. Different gene mutations can affect the prognosis as well as the treatment of choice. Gastric cancer has a variable distribution in the world, being the most common in Asian countries such as Japan and China, on the other hand, in Eastern Europe, gastric cancer incidence and mortality showed a continuous decline in the last decades, and this is more related to the intestinal type of gastric cancer rather than diffuse type (6, 7). In Iran, the highest incidence rate was observed in Ardabil, a northwestern province, with

an age-standardized incidence rate of 49.1 and 25.4 in men and women respectively (8) However, gastric cancer is still the fourth most common malignancy worldwide and the second leading cause of cancer death (9).

Numerous studies have evaluated the role of different genes such as p53 and E-cadherin and their expression or mutation in the development, severity, prognosis, and type of gastric cancer (10-12). Studies show that the prevalence, prognosis, and genetic characteristics of gastric cancer vary by race and region (1, 13, 14). A study was revealed that nearly 50% of patients with diffuse gastric cancer had the mutation of E-cadherin (15). Also, different studies showed the effect of P53 expression in patients with gastric cancer (16, 17). In this regard, because of the effect of P53 and E-cadherin's mutations on the progression and survival of patients with gastric cancer, the current study was designed.

We know about the epidemiology of gastric cancer in Iran, but little is informed about its clinicopathological features. Therefore, in this study, we intend to examine these features, including tumor type and size, degree of differentiation, tumor operability, and immunohistochemical (IHC) reports on E. cadherin and P53 expression.

Methods

This retrospective study was performed on patients diagnosed with gastric cancer and who underwent biopsy or surgery during 2008-2017 in Imam Reza Hospital, Tehran, Iran. The inclusion criteria consisted of all patients older than 15 years old who had the pathology report of gastric cancer from 2008 to 2017. However, the exclusion criteria implied patients who were referred to finalize their treatment or were lost to follow-up. The sample size of patients calculated by Cohen's table should enroll at least 150 patients with P-Value <0.05.

Informed consent was obtained from all individuals. The Ethics Committee at the Research Center approved the consent form and the protocol for Cancer Screening and Epidemiology, AJA University of Medical Sciences, Tehran, Iran (project code 91000321A).

By referring to the hospital pathology ward and examining samples' registries, all pathological reports of the patients in the mentioned period had been studied. The data collection form was completed based on the information in pathology reports, including patients' age, sex, tumor location, sample size, final diagnosis and tumor size, and tumor grade; Meanwhile, a number of samples were deficient in the information that was corrected and completed by referring to patients' admission records at the archives and phone calls to patients. Finally, 264 patients were enrolled in this study.

Descriptive tests were applied for data presentation, also fisherman tests and Spearman correlation were done for comparisons. P-values less than 0.05 were considered statistically significant. SPSS version 24 (Chicago, Illinois) was used for data analysis.

Results

There were 264 patients implied in this study (180 men and 84 women). The age range of patients was 15 to 118 years old with a mean age of 70.03±14.01 years.

Tissue samples were taken endoscopically in 169 patients and surgically in 95 patients. These numbers include 35 studied cases that went under surgery after the endoscopic evaluation through the period of study.

The diagnosis of gastric cancer was definite in 253 patients. The pathology results are summarized in Table 1. The location of the sampling was determined in 185 cases. Samples were taken from the proximal gastric sections in 25 patients, the body in 12 cases, and distal sections in seven patients. Sampling was performed on multiple sections in 140 cases by either surgery or endoscopic evaluation. Sampling was performed only on gastric mucosa in 126 cases while it included other gastric levels as well in the rest of the cases.

Among the 264 study cases, 253 (95.8%) were diagnosed with cancer, two were undetermined and 9 patients did not have any malignancies in this regard. The type of tumor was determined in 177

cases. Pathology results indicated that type of tumors in order of prevalence was as the following;

intestinal, diffuse, lymphoma, and gastrointestinal tumor (GIST).

Table 1: A summary of pathological findings

Characteristics	Pathology	n (%)
Cancer type	**Intestinal-type**	138 (54.5%)
	Diffuse-type	69 (27.27%)
	Lymphoma	31 (12.25%)
	GIST	15 (5.92%)
Degree of differentiation	**Well**	4 (1.6%)
	Moderate	43 (17%)
	Poor	35 (13.83%)
	undifferentiated	171 (67.58%)
Local lymph node metastasis		38.3%
Tumor size		8.05±8.72cm

Further histopathological evaluations of tumor grades indicated that in 1.6% of cases the tumor cells were well differentiated while 17.1% were moderately and 13.7% were poorly differentiated. No differentiation was observed in 67.7% of cases.

In addition, 101 cases (38.3%) showed local lymph node metastasis. In the available results of tumor size in surgically treated patients (53 patients), results revealed that tumor volume was between 2 to 45 square centimeters. However, the mean tumor size was 8.05 ± 8.72. Follow-ups indicated that among 264 studied patients, 109 cases (41.3%) had finally undergone surgical operations for tumor removal.As it shows, 54.5% of the tumors were intestinal-type and 67.58% of the tumors were undifferentiated. Spearman correlation showed that in men the tumor is larger (r=0.283 P=0.039) but

more differentiated (r=0.373 P=0.006). Surgical resection was possible in 109 patients (41.3%). Spearman correlation showed that less differentiated tumors are less operable (r=0.582 P=0.001). In addition, the type of tumor was also influential in the tumor operability, so that the rate of surgery in GIST, intestinal-type, and Diffuse-type tumors were 100%, 57%, and 14.4%, respectively. The relationship between the possibility of surgery and other variables is summarized in Table 2. IHC results showed that E-cadherin expression was present in 78.6%, of which 50.9%% were weakly positive (+1) and 27.7% were strongly positive (+2). In addition, P53 high expression was observed in 60.7% of patients. There is no relationship between age, gender, tumor grade and size and IHC results.

Table 2: IHC analysis of E-cadherin and P53 expression

Characteristics	IHC	n(%)
E-cadherin expression	negative	48 (21.42%)
	Weakly positive (+1)	114 (50.89%)
	Strongly positive (+2)	62 (27.67%)
P53 expression	High	136 (60.7%)
	low	88 (39.3%)

Discussion

Gastric cancer is the 5th most common cancer, but it is the third leading cause of cancer death worldwide(1). Similar to the results of other

countries, our study shows that in Iran, the majority of patients with gastric cancer are men (68.18% vs. 31.82%). This is related to more smoking and alcohol consumption by men and the protective role of estrogen in women(18, 19).

The histologic type of cancer and its degree of differentiation are two important factors in predicting disease progression and patient survival. Also, increasing the depth of tumor invasion in the stomach wall is associated with a poor prognosis(20, 21). In our study, 67.58% of tumors were undifferentiated and 13.83% were poorly differentiated, indicating that gastric cancer is associated with poor prognosis in a large percentage of Iranian patients. In addition, local lymph node metastases were seen in 38.3% of patients, which further worsens the prognosis. Similar studies in other areas show that most gastric cancers are in the advanced stage at diagnosis and have a poor prognosis, with a five-year survival of less than 25%(22, 23).

Surgery is the primary treatment for resectable tumors and increases patients' survival. patients with respectable localized tumors have the highest survival. In such cases, the surgical cure is possible in up to 90% of cases (24, 25).

In our study, it was observed that most Iranian patients had undifferentiated or poorly differentiated tumors. In addition, in our study surgery was possible in only 109 patients (41.3%). Spearman correlation showed that surgery is less possible in poorly differentiated tumors (P =0.001 r =0.582). These results are consistent with the results of the study of Sun et al.(26). They showed that the rate of partial gastrectomy was 87.5% in well and moderately differentiated tumors and 25% in less differentiated tumors. In their study, all the well-differentiated cases were operable (partial or total gastrectomy) while less differentiated tumors were operable in only 62.5% and 37.5% of them were inoperable even after chemotherapy. In inoperable tumors, neoadjuvant chemotherapy can significantly increase the possibility of surgery (27-29).

In our study, the most common type of gastric cancer was intestinal-type followed by diffuse-type, which is similar to other regions (30, 31). Tumor type is another factor that affects the possibility of surgery. In our study, the surgery rate for GIST, intestinal-type, and diffuse-type tumors was 100%, 57%, and 14.4%, respectively. It is known that Diffuse-type gastric cancers are undifferentiated

tumors, highly Metastatic, less operable, and with poor prognosis(30).

E-cadherin is a tumor suppressor and Loss of E-cadherin expression can lead to dedifferentiation and invasion of cells(32). In our study, IHC results showed that EE-cadherin expression was negative in 21.4% and positive in 78.6% of cancers, which was weakly positive (+1) in 50.9% and strongly positive (+2) in only 27.7%. This indicates that in Iranian patients the E-cadherin expression has decreased in a large percentage of gastric cancers. In a meta-analysis, Xing et al.(22) Showed that E-cadherin loss of expression is associated with decreased overall survival (HR = 1.87), higher TNM stage (OR = 2.52), lymph node metastasis (OR = 2.39), distant metastasis (OR = 2.23), and less differentiated tumors (OR=2.26). In addition, in their study, E-cadherin expression was significantly lower in patients with diffuse-type cancers compared to intestinal-type (OR = 4.22).

Finally, p53 high expression is an independent predictor of shorter survival and tumor recurrence in gastric cancer (33, 34). In our study, most of the patients had P53 high expression (60.7) which was not related to gender, age, tumor size, and tumor grade. Sankalecha et al. (35) showed that P53 expression was present in 90% of gastric cancers. In their study, 63.8% of patients showed P53 high expression and 36.2% of them showed P53 low expression and in contrast to our study, p53 high expression was associated with age, sex, tumor size, and tumor grade, but the data are somewhat conflicting, since in the study by Victorzon et al (36). P53 expression was not associated with gender, age, metastasis and it wasn't an independent predictor of survival. It should be noted that due to the retrospective design of the study, the expression of E-cadherin and P53 were reported qualitatively, while the quantitative results provide more accurate information.

Conclusion

Most patients with gastric cancer are men and the most common type of gastric cancer in Iran is intestinal-type. The majority of Iranian patients have poorly differentiated or undifferentiated tumors, which reduces the possibility of surgery and

survival. In addition, a large number of patients had decreased E-cadherin expression and increased *P53* expression, both of which are associated with poor prognosis.

Conflict of Interest

The authors declared that they have no conflict of interest.

Ethics

The study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The ethics committee of AJA University approved this study (No. AJA-0003-04-95). In addition, written informed consent was obtained from the patients for publication of this study.

Author Contributions

Babak Sattartabar and Mahyar Nourian: writing the manuscript draft; Mahyar Nourian and Narjes Mehrvar: data analysis and editing; Shahrokh Iravani: primary investigator in collaboration with Azim Mehrvar and Hassan Jalaeikhoo: critical reviewing and editing; Esmaeil Samizadeh: performing experimental tasks.

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