Original Article

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Clinicopathologic Characteristics of Multifocal Gastric Adenocarcinoma

M. Kalbasi (MD)[1], S. Siadati (MD)[2], S. Kamali Ahangar (BSc)[3], N. Nikbakhsh (MD)[4*]

1.Student Research Committee, Babol University of Medical Science, Babol, I.R.Iran

2.Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran

3.Clinical Research Development Center, Shahid Beheshti Hospital, Babol University of Medical Sciences, Babol, I.R.Iran.

4.Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol I.R.Iran

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ABSTRACT

BACKGROUNDANDOBJECTIVE: Gastric cancer is the fifth prevalent cancer in worldwide. Among of this, adenocarcinoma is more than 95% of all case and most prevalent. According to gastric adenocarcinoma is resistant to adjuvant therapy, surgical resection is the cardinal strategies of treatment. One of the problems with treating adenocarcinoma of the stomach is that its main causes are malignant or pre-malignant changes in the residual gastric tissue that may be neglected during resection. By recognizing these lesions and resection, they can be expected to reduce the malignancy. Therefore, this study was conducted to investigate the characteristics of non-tumoral gastric tissue in terms of malignant or pre-malignant changes.

METHODS: In this retrospective cross-sectional study, 112 patients who had undergone total gastrectomy in the hospitals affiliated to Babol University of Medical Sciences during the period of 2013-2017 were examined and analyzed for age, sex, type and location of tumor.

FINDINGS: Of 112 cases that studied,72 cases (64.3%) were male and 40 cases (35.7%) were female. The mean of ages was 64.7±8.6 year. Poorly differentiated pathology in 60.7% and well differentiated pathology in 39.3% of patients were seen. In 64 patients (57%), there was synchronous lesions in addition to primary pathology. These synchronous lesions were related statistically significant to pathology, cancer stage and gender.

CONCLUSION: Based on the results of this study, it can be concluded that resection should be accompanied by considering simultaneous lesions in addition to primary pathology, which can be a reason for total gastrectomy as a standard treatment for gastric cancer.

KEY WORDS: *Adenocarcinoma, Gastric, Recurrence, Synchronous Lesions*.

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***Corresponding Author: N. Nikbakhsh (MD)**
Address: Department of Surgery, School of Medicine, Babol University of Medical Sciences, Babol, I.R.Iran
Tel: +98 11 32199596
E-mail: novinsu@hotmail.com

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Introduction

Gastric cancer is the most common cancer in the world in the past century, but in the latest comprehensive epidemiological studies, it is known to be the fifth most common cancer and the third cause of death from cancer (1). In Iran, the north and northwest areas include Mazandaran, Golestan and Ardebil provinces with high prevalence (2). Among stomach cancers, more than 95% is formed by adenocarcinoma, so that the term "gastric cancer" is consistent with gastric adenocarcinoma. The etiology of stomach adenocarcinoma is a multi-factorial nature and includes environmental characteristics, diet and family and genetic factors, among which the role of environmental processes is very prominent. H. pylori infection plays a fundamental role in the progression of the pro-malignant stages and transforms it into malignant stage (3). The two main gastric adenocarcinoma subgroups include well differentiated and poorly differentiated, which has different backgrounds and pathology. Well differentiated adenocarcinoma is a type of papillary and tubular pathology and is equivalent to the intestinal subunit of Lauren's classification. The poorly differentiated adenocarcinoma includes a signet ring pathology and is in accordance with the diffuse subgroup. Mucinous pathology based on IHC criteria can be categorized well or poorly in each of the subgroups. Regarding the limitation of alternative treatments for gastric adenocarcinoma, standard surgical resection of R0 is the basis of treatment. Therefore, the presence of simultaneous lesions and the identification of related factors can be one of the factors to change the resection strategy. Of course, even after total gastrectomy, there have been cases of renormalization in the anastomosis line or the jejunal arm, the theory of the mechanism of this problem is the development of sub-serous and sub-mucosal of tumor cells (9). In a study by Buzzoni et al., radical surgeries were reduced by a reduction in recurrence or an increase in disease-free period (10).

One of the major challenges in the treatment of gastric adenocarcinoma is its recurrence which is associated with an ominous nature, and this is a factor that the prognosis of adenocarcinoma of the stomach is still disappointing. The recurrence of adenocarcinoma in the residual gastric tissue is due to the presence of precursor lesions or due to altered malignancy in the tissue. Therefore, it can be expected that, along with the first malignant pathology, there may be pre-malignant or malignant precursor in other parts of the stomach. Regarding the nature of gastric adenocarcinoma, attempts to obtain a comprehensive protocol for chemo radiation before or after surgery for locally and systemic control of the disease are not associated with scalloping results (4), therefore, the extent of the resection of gastric adenocarcinoma should be effective, the incidence in the future is reduced (5). This study was conducted with the aim of examining the characteristics of non-tumoral tissue of the stomach in terms of malignant or pre-malignant changes.

Methods

In this retrospective cross-sectional study, after approval of Ethics Committee of Babol University of Medical Sciences in Babol, the demographic and pathological information of all patients who were undergoing total gastrectomy due to gastric cancer were assessed and analyzed from 2013 to 2017. All patients with adenocarcinoma who had undergone total gastrectomy surgery were enrolled in the study. Samples with incomplete records and non-cooperation patients were excluded from study. Diagnosis of the patient's adenocarcinoma was performed by a gastroenterologist on the basis of upper endoscopy, biopsy, pathologic confirmation and staging, and was referred to a surgery specialist, depending on the clinical condition, if the stage of the disease was different from stage 4. Patients underwent surgery in the presence of physiological conditions and lack of evidence that they were not resectable on the basis of imaging. The type of surgery, if possible, was total gastrectomy at D1 level and reconstruction using one of the common techniques. The gastric tissue was then sent to the pathology unit along with the lymph nodes of stations 1 to 8. The pathology of the specimens was evaluated in terms of primary pathology, invasion to lymph nodes, and the gastric tumor of the stomach was also evaluated in the blocks for simultaneous pathology and lesions. Data were entered into SPPS 23 software and analyzed by t-test, Chi Square, pearson logistic regression and $p < 0.05$ was considered significant.

Results

Of the 112 patients, 72 were men and 40 were women. The mean age of the patients was 64.7 ± 8.6 years, the age range of the patients was 43-83 years old and the age of the patients in this study had normal distribution. The mean age of men was 64±9 years and the range was between 83-43 years. The mean age of women was 65±8 years and the age range was 50-81

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years, and there was a significant difference between the two groups. The location of the primary tumor was consistent according to the location of the anatomical location, with the highest prevalence of cardia (39.3%), followed by gastric body- fundus (32.1%) and anthrome and pylorus (28.6%), respectively. 39.3% of the tumors were well differentiated and 60.7% were poorly differentiated, indicating a remarkable superiority of poorly differentiated pathology in this study. Also, there was a significant relationship between type of pathology and gender, and poorly pathology in males and well differentiated pathology in females were more prevalent (p = 0.033). In patients with stage II disease, stage 3 was the most frequent (7.7% 53%), followed by stage 2 (28.5%) and stage one (17.8%), respectively. In the blood group A, there was the highest frequency (50%) and the AB blood group was the lowest (7%) (Table 1). Concurrent lesions of the malignant or pre-malignant nature of the non-tumoral tissue of the stomach in all of the pathologic pathologies were 64 cases (57%), most of which were accompanied by poorly differentiated pathology. The relationship between the lesions with different clinical and pathologic characteristics was evaluated. Concurrent lesions based on analysis showed a significant relationship with gender, type of pathology, stage of disease, but no significant relation was found with the anatomical location of the primary tumor and the blood group (Table 2).

Table 1. Frequency of variables

Variable		Frequency N(%)
Gender	male	72(64.3)
	female	40(35.7)
Pathology	Well differentiated	44(39.3)
	Poorly differentiated	68(60.7)
Location of primary tumor	Cardia	44(39.3)
	Gastric body and fundus	36(32.1)
	Antrum and pylorus	32(28.6)
Lesions simultaneous	+	64(57)
	-	48(43)
Blood group	A	56(50)
	B	32(28.5)
	AB	8(7)
	O	16(14.5)
Tumor stage	I	20(17.8)
	II	32(28.5)
	III	60(53.7)

Table 2. Statistical relationship between clinical and pathological characteristics with concurrent lesions

Varible		Synchronous lesion +	Synchronous lesion -	P-value
Gender	male	48	24	0.009
	female	16	24	
Pathology	Well differentiated	8	36	0.00
	Poorly differentiated	56	12	
Location of primary tumor	Cardia	20	24	0.125
	Gastric body and fundus	24	12	
	Antrum and pylorus	20	12	
Blood group	A	36	20	0.06
	B	20	12	
	AB	4	4	
	O	4	12	
Tumor stage	I	0	20	0.00
	II	12	20	
	III	52	8	

Discussion

In this study, 39.3% of patients were well differentiated and 60.7% had poorly differentiated pathology and according to the gender abundance, poorly differentiated pathology in men and well differentiated pathology in women was more prevalent. The type and degree of histologic differentiation, the depth of involvement and lymphatic metastasis are effective in prognosis of patients with gastric adenocarcinoma (7). In the study of Adachi et al., which was based on the demographic and pathologic differences in gastric adenocarcinomas, patients with well differentiated, compared to poorly differentiated, had higher age (67 versus 58 years), male gender superiority, maximal anatomical distribution in the lower third of the stomach, smaller size, serous involvement and lymphatic metastasis (8). The presence of simultaneous lesions along with primary pathology is one of the challenges in the treatment of adenocarcinoma because these pathologies are largely microscopic and cannot be detected in endoscopic studies either before or after surgery, and leaving these lesions can lead to future illness. In this study, 57% of gastric tissue samples were present in non-tumoral parts of the same microscopic lesions that were either pre-malignant or malignant, and these lesions had a significant relationship with the type of pathology and were very similar to the signet ring adenocarcinoma. In this study, the mean age of the patients was 64.7 ± 8.6

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years and the age range was 83-43 years. The incidence of gastric cancer is directly related to age, and Karimi and his colleagues studied the median age of gastric cancer patients (70).

64.3% of the patients were male and 35.7% were female, and in the major comprehensive epidemiologic studies, the ratio of male to female is 2 to 1, and this proportion is similar in the study of Malekzadeh et al. in Iranian epidemiology (2). Regarding the different distribution of gastric cancer in Iran and especially the maximum prevalence in the north and northwest of the country, it seems that the distribution of gender is approximately 2 to 1 in this study, which was conducted in one of the most prestigious universities in the north of Iran and Mazandaran province, and can be an accurate statistic. The extent of gastric adenocarcinoma resection from endoscopic mucosal resection to total and radical gastrectomy will be different, and determination of the resection strategy depends on a variety of factors, including the stage of the disease, the location of the tumor, the type of pathology, and the protocols governing the health system.

The standard resection for poorly diffuse (includes the signet ring pathology) is total gastrectomy, because on the one hand this pathology is not prominent from the pre-malignant lesions and the malignant changes cannot be controlled, and on the other hand, in addition to the primary focus, there may be other malignant cancers that need to be resected (11). In a study by Charlton and his colleagues for the evaluation of hereditary gastric juvenile disseminated adenocarcinomas in 6 patients with prophylactic gastrectomy due to the positive CHD-1 marker, despite the absence of a macroscopic site, multiple signet ring microscopic focal regions were scattered (12). In this study, 83% of poorly pathologies were associated with simultaneous lesions in other parts, indicating the need for greater resection rates to eliminate all the disease's focal points. In the intestinal adenocarcinoma (well), the extent of resection to achieve an un-pathologic margin is of interest in western countries, with more tendency toward more limited surgical procedures and in contrast to East Asian countries, tend to undergo more radical surgeries, and this difference in the approach is the result of a difference in the profile of the illness and patients in the east and west. In the present study, there were 18% of the primary tumors of the same lesions in the non-tumor tissue of the stomach. A challenge is due to the mucinous pathology because this pathology is based on the type of behavior and the IHC criteria can be located in either well or poor subgroups. Therefore, it should be noted that reaching a resection of R0 in the adenocarcinoma of the stomach was not easily achieved by the general rule of subtotal gastrectomy in all patients, and other aspects should be considered.

There was another association between lesions at the same time as the disease stage and most lesions were in stage 3. Although tumors with high degree of penetration or adjacent organs are blocked out en block, the relationship between the extent of the resection and the stage of the disease (both the depth of tumor invasion and lymphatic involvement) has not been discussed before. The total number of lymph nodes and, on the other hand, positive lymph nodes are two independent factors associated with survival (13), and it can be verified that lymphatic involvement in the second and third glands in proximal tumors is more than distal. Despite these Western surgeons, the increase in lymphatic resection is considered unnecessary in increasing the survival. In a study by Yildirim et al., total gastrectomy with D2 lymphadenectomy would be better with survival when the invasive tumor of muscolaris propria and serous without visceral involvement were less than 15 lymph nodes (14).

There was a significant relationship between sex and multiple lesions in this study, and these lesions are more common in male patients. Therefore, the extent of resection in men is more important. In the study of Sun et al, in general, prognosis of early adenocarcinomas in men was better than that of women (15). Although the location of the tumor is one of the determinants of resection, the relationship between tumor location with concurrent lesions in this study has not been proven ($p = 0.125$). In cases that the therapeutic program is partial gastrectomy, a safe margin relative to the primary tumor should be observed, which is expressed in different studies in different numbers. In order to obtain an appropriate margin, the sub-serousal and sub-mucosal extension of the tumor, which is microscopic, should also be considered (9), because the lack of resection in a suitable margin with adverse effects is associated. To perform partial gastrectomy, depending on the initial location of the tumor, the margin should be at least 5 cm from the palpable edge of the tumor, on the other hand, there is a clear limitation on having an appropriate margin of at least 2 cm to the gastric bypass to the esophagus (EGJ).

Therefore, for partial gastrectomy, in case of non-involvement of serous, 7 cm margin is needed, and in case of serous involvement, at least 8 cm margin resection is required from the stomach attachment to the esophagus (16). In this study, the blood group A was

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more prevalent in comparison with other blood groups, and it was associated with several lesions, but its relationship was not significant. In the study of Wang et al., there was a clear relationship between the blood group A and the incidence of gastric adenocarcinoma, and the O blood group also had a more protective effect on it (17).

One of the important features that was evaluated in this study was the presence of malignant or pre-malignant lesions with primary tumors, which could be a factor in future recurrence of the disease. Decision making for partial gastrectomy in stomach adenocarcinoma should be based on correct patient selection, advanced pathology report, correct staging, biopsy mapping, accurate radiologic assessments, intraoperative esophagodeodenoscopy, and frozen section (16). Otherwise, total gastrectomy is a more appropriate treatment suggestion. According to the results of this study, resection should be considered in the presence of simultaneous lesions in addition to primary pathology, which can be a reason for total gastrectomy as a standard treatment for gastric cancer.

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