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Effect of *H. pylori* eradication on gastric preneoplastic lesions and gastritis progression

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ABSTRACT

Aim: It is assumed that the sequence of events in gastric cancer is as follows: chronic gastritis, atrophy, intestinal metaplasia (IM), dysplasia and carcinoma. It is also known that *Helicobacter pylori* (H.pylori) can be involved in the chain of these chronic phenomena. This study investigated to compare the changes in the grades of gastric preneoplastic lesions over time in cases with *H. pylori* eradication and in cases where *H. pylori* could not be eradicated. In addition, it was aimed to retrospectively examine whether there was a significant change in the severity of gastritis and the degree of gastric preneoplastic lesion in cases in which *H. pylori* could be eradicated.

Material and Method: Patients who had dyspeptic complaints and were diagnosed with *H. pylori* gastritis, atrophy and intestinal metaplasia or dysplasia were enrolled in the study between January 2009- January 2016. Patients who underwent *H. pylori* eradication therapy were included in the study in terms of surveillance programs for gastric carcinoma. The medical records of the patients were reviewed retrospectively. Atrophy, intestinal metaplasia and dysplasia grades were determined during the first endoscopy. The Operative Link for Gastritis Assessment (OLGA) and The Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) scores were recorded. Severe gastsitis define as OLGA stage III-IV and/or OLGIM stage III-IV.

Results: In total, 5736 patients were enrolled. 97 patients who were diagnosed with intestinal metaplasia and/or atrophy as a result of endoscopic biopsy and were followed up regularly by surveillance were included in our study. According to the initial endoscopy, gastric atrophy was detected in 75.3% (73) of the cases and intestinal metaplasia was detected in 75.3% (73). Severe was detected in 17.5% (17) and low-grade dysplasia was detected in 3.1% (3). According to the latest endoscopic biopsy results *H. pylori* was eradicated in 27.8% (27) of the cases. In the group with successful eradication of H.pylori, a statistically significant decrease was observed in the frequency of atrophy and intestinal metaplasia at the last visit. A nearly significant decrease was observed in the frequency of severe gastritis (p=0.06). Significant decreases were detected in OLGA (1.2±1.0 vs. 0.4±0.5) and OLGIM (1.3±1.2 vs. 0.7±0.9) scores. ($p < .001$ and p=.03. respectively). In the group with successful eradication of H.pylori in a mean follow-up of 23.6 months, dysplasia disappeared in 2 patients who were found at the first visit. In the group with unsuccessful eradication of H.pylori there was no significant change in the frequency of severe gastritis or dysplasia. Nearly significant (0.8±0.6 vs. 0.5±0.8. p=.052) change was detected in the OLGA score, while in the OLGIM score (1.4±1.1 vs. 1.0±1.1. p=.002) a significant decrease was detected.

Conclusion: A statistically significant decrease in the frequency of atrophy and intestinal metaplasia, a significant decrease was also detected in OLGA and OLGIM scores were observed with the success of eradication of *H. pylori* in gastric cancer. A nearly significant decrease was observed in the frequency of severe gastritis. We believe that *H. pylori* eradication treatment should be performed in *H. pylori*-positive precancerous gastric lesions

Keywords: Gastric cancer, *Helicobacter pylori*, OLGA-OLGIM, dysplasia

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. Precancerous gastric lesions are one of the most blamed factors in the etiology of gastric cancer. As a result of epidemiological and pathological studies, it is accepted that the sequence of events in intestinal type gastric carcinogenesis is chronic gastritis, intestinal metaplasia, dysplasia and carcinoma. It has been explained by the World Health Organization (WHO) that *Helicobacter pylori* (*H. pylori*) plays an important role in that initiate the process leading to cancer. In societies with a high incidence of gastric cancer the frequency of *H. pylori* infection is also higher (1-3).

H. pylori infection is frequently observed in the world. It was detected in 95% of patients with duodenal ulcer and in 70-80% of patients with gastric ulcer. This rate is 50% in patients with functional dyspepsia. The risk of peptic ulcer in patients with *H. pylori* is higher than those without. Similarly, 50-90% coexistence of *H. pylori* has been observed in gastric cancer and lymphomas. In general. *H. pylori* is pathogenic for humans only (4).

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After the relationship between *H. pylori* infection and chronic gastritis and ulcers was reported studies on gastric cancer have intensified. There are results suggesting that the main factor in cancer development is the age at which the infection was acquired and that a long induction time is required for carcinogenesis. Kuipers et al. (5) showed that *H. pylori* infection causes atrophy and intestinal metaplasia which are important risk factors for cancer development. Correa et al. (6) suggested that hyperproliferation caused by *H. pylori* gastritis is the starting point of the cascade of events leading to gastric cancer. All of these changes are seen histopathologically as superficial gastritis with multifocal atrophy, intestinal metaplasia and ultimately dysplasia and cancer.

In this study, it was aimed to compare the changes in the grades of gastric preneoplastic lesions over time in cases with *H. pylori* eradication and in cases where *H. pylori* could not be eradicated. In addition, in cases where *H. pylori* could be eradicated, whether there was a significant change in the severity of gastritis and the degree of gastric preneoplastic lesion was retrospectively examined.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 06.07.2015, Decision No: 19/13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, we included patients who applied to Kırıkkale University Medical Faculty Gastroenterology Department between January 2009 and January 2016 with dyspeptic complaints and who were found to have gastric atrophy-intestinal metaplasia, dysplasia and *H. pylori* positivity by upper gastrointestinal endoscopy. After *H. pylori* eradication, 5736 patients aged 18-90 years who were included in the gastric adeno cancer surveillance program were retrospectively screened. 97 patients who met the criteria for case selection were included in the study. Initial and final endoscopic biopsy results of the cases were analyzed. As a result of the histopathological examination; the *H. pylori* density, intestinal metaplasia and atrophy degrees detected in the initial and final histopathological examinations were determined according to The Updated Sydney Classification (reference) and the OLGA and OLGIM stages determined according to these results were recorded. Cases with OLGA or OLGIM stage III or IV according to both initial and final histopathological examinations were defined as "severe gastritis". Patients with peptic ulcer. malignancy, gastric resection history, and chronic disease (liver cirrhosis. chronic kidney disease, decompensated heart failure) were excluded from the study.

The data of the study were recorded with the Statistical Package for the Social Sciences (SPSS) version 25 (IBM corporation. New York. United States) program and statistical analyzes were made. Descriptive statistics are summarized as numbers. percentages. mean and standard deviation. Average age was calculated by Student's t test. Chi-square test was used to compare qualitative data. P values <0.05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

Among the cases who applied to Kırıkkale University Medical Faculty Hospital Gastroenterology Department with dyspeptic complaints between January 2009 to January 2016. 97 patients who were diagnosed with intestinal metaplasia and/or atrophy as a result of endoscopic biopsy and were followed up regularly by surveillance were included in our study. 55.7% (54) of our patients were men and 44.3% (43) were women. The mean age of the patients was 57.9±13.1 years. The mean age of female patients was 54.2±13.2 years while the mean age of male patients was 60.8±12.3 years.

According to the initial endoscopy, gastric atrophy was detected in 75.3% (73) of the cases and intestinal metaplasia was detected in 75.3% (73). Severe gastritis was detected in 17.5% (17) cases and low-grade dysplasia was detected in 3.1% (3) cases. The mean follow-up period of the patients was 23.6±16.1 months (min-max: 3-70).

While eradication of *H. pylori* was successful in 27.8% (27) of the patients, eradication was unsuccessful in 72.2% (70) patients. There was no statistically significant difference between the groups with successful and unsuccessful eradication in terms of age (p=.6) and gender (p=.1). Demographic and clinical characteristics of our patients are given in **Table 1**.

Table 1. Demographic and clinical characteristics

No	97 (43f/54m)
Age	57.9±13.1years
H.p eradication successful	27 (27.8%)
H.p eradication unsuccessful	70 (72.2%)
Initial Visit Gastric Atrophy	73 (75.3%)
Initial Visit Intestinal metaplasia	73 (75.3%)
Initial Visit Severe gastritis (OLGA III-IV or OLGIM III-IV)	17 (17.5%)
Initial Visit Low-grade dysplasia	3 (3.1)
Follow-up time	23.6±16.1 months

Changes Observed in Histopathological Findings at the End of the Follow-up Period

At the end of the follow-up period; Regardless of *H. pylori* eradication success a significant decrease was detected in the frequency of atrophy (p<.001) and intestinal metaplasia (p<.001) compared to baseline. A nearly significant decrease was observed in the frequency of severe gastritis (p=.057) (**Table 2**). Significant reductions in OLGA (0.94±0.80 vs. 0.054±0.79) and OLGIM (1.39±1.16 vs. 0.95±1.10) scores (p<.001 for both) were detected.

Table 2. Changes observed in histopathological findings at the end of the follow-up period

	First visit	Final visit	p
Atrophy (n.%)	73 (75.3)	38 (39.2)	<.001
Intestinal metaplasia (n.%)	73 (75.3)	44 (45.4)	<.001
Severe gastritis (n.%)	17 (17.5)	9 (9.3)	.057
Dysplasia (n.%)	3 (3.1)	2 (2.1)	1.0

Comparison of First Visit Histopathological Findings According to Eradication Success

According to the histopathological findings of the unsuccessful eradication and successful eradication groups; presence of atrophy,intestinal metaplasia, severe gastritis and dysplasia were similar.(**Table 3**). In addition, baseline and final visit OLGA (1.2±1.0 vs. 0.8±0.6. respectively) and OLGIM (1.3±1.2 vs. 1.4±1.1. respectively) scores were also similar in successful and unsuccessful eradication groups.

Table 3. Comparison of first visit histopathological findings according to eradication success

	Eradication (+) n=27	Eradication (-) n=70	p
First Visit			
Atrophy (n,%)	22 (81.5)	51 (72.9)	.3
Intestinalmetaplasia(n,%)	19 (70.4)	54 (77.1)	.4
Severe gastritis (n,%)	5 (18.5)	12 (17.1)	1.0
Dysplasia (n,%)	2 (7.4)	1 (1.4)	.1

Changes Observed in Histopathological Findings at the End of the Follow-up Period in Patients with Successful *H. pylori* Eradication

In the group with successful eradication of H.pylori, the change in histopathological findings was examined, a statistically significant decrease was observed in the frequency of atrophy and intestinal metaplasia at the Final visit compared to baseline. A nearly significant decrease was observed in the frequency of severe gastritis (p=.06). It was observed that dysplasia disappeared in the follow-up in 2 patients who were found to have dysplasia at the beginning (**Table 4**). Significant decreases were detected in OLGA (1.2±1.0 vs. 0.4±0.5) and OLGIM (1.3±1.2 vs. 0.7±0.9) scores. (p<.001 and p=.03, respectively) (**Figure 1**).

Table 4. Changes observed in histopathological findings at the end of the follow-up period in patients with successful *H. pylori* eradication

	First visit	Last visit	p
Atrophy (n,%)	22 (81.5)	11 (40.7)	.002
Intestinal metaplasia(n,%)	19 (70.4)	12 (44.4)	.03
Severe gastritis (n,%)	5 (18.5)	1 (3.7)	.06
Dysplasia (n,%)	2 (7.4)	-	0.2

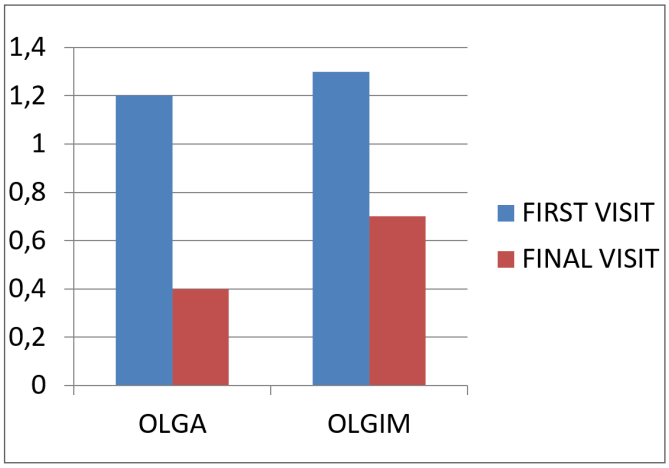

Figure 1. OLGA and OLGIM scores in the group with successful eradication of H.pylori

Changes Observed in Histopathological Findings at the End of the Follow-up Period in Patients with Unsuccessful *H. pylori* Eradication

In the group with unsuccessful eradication of H.pylori, the change in histopathological findings showed a statistically significant decrease in the frequency of atrophy and intestinal metaplasia at the last visit compared to baseline. There was no significant change in the frequency of severe gastritis or dysplasia (**Table 5**). Nearly significant (0.8±0.6 vs. 0.5±0.8. p=0.052) change was detected in the OLGA score. while OLGIM (1.4±1.1 vs. 1.0±1.1. p= .002) score was significantly decreased (**Figure 2**).

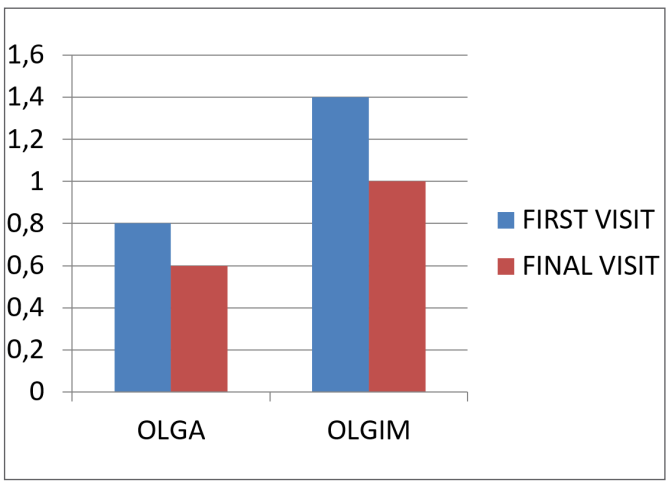

Figure 2. OLGA and OLGIM scores in the group with unsuccessful eradication of *H. pylori*

Table 5. Comparison of the initial and final histopathological findings of the cases whose *H. pylori* eradication failed

	First visit	Last visit	p
Atrophy (n,%)	51 (72.9)	27 (38.6)	<.001
Intestinalmetaplasia (n,%)	54 (77.1)	32 (45.7)	<.001
Severe gastritis (n,%)	12 (17.1)	8 (11.4)	.03
Dysplasia (n,%)	1 (1.4)	2 (2.9)	1.0

DISCUSSION

It has been known for years that *H. pylori* can cause stomach cancer. However not all people with *H. pylori* develop gastric pathology. Some studies suggest that eradication of *H. pylori* in patients with premalignant gastric lesions has a very limited effect on the incidence of subsequent gastric cancer (7,8).

In addition, the presence of *H. pylori* and the role of age and male gender in the progression of premalignant lesions are contradictory. Age and male gender were not found to be independent risk factors for the progression of premalignant lesions in the studies of Borody et al. (9) However You et al. (10) found that there is a relationship between age and intestinal metaplasia and dysplasia and they found that these lesions accumulate and progress with increasing age. They found a faster progression in men than in women in all premalignant lesions.

In our study group, a mean age of 57.9 years. 43 (44.3%) of whom were female. total 97 patients. while the eradication of *H. pylori* was successful in 27.8% (27) of the patients. eradication was unsuccessful in 72.2% (70) of the patients. There was no statistically significant difference in terms of age (p=.6) and gender (p=.1).

Ji Hyung Nam et al. (11) In a cross-sectional study examining the distribution of OLGA and OLGIM scores with age on 632 patients in Korea, it was found that the *H. pylori* positivity rate was 59% (373/632) and that *H. pylori* eradication of OLGA/OLGIM stage III, IV patients which was defined as especially severe gastritis was successful or unsuccessful. It was found that advanced age (>40 years) was significantly higher in both groups. (p<.01) In addition, age, smoking and *H. pylori* positivity were determined as independent risk factors for both groups. They concluded that *H. pylori* eradication is necessary to prevent precancerous lesions.

In our study, according to the histopathological findings of the unsuccessful and successful eradication groups; presence of atrophy, intestinal metaplasia, severe gastritis and dysplasia were similar. In addition, baseline and final visit OLGA (1.2±1.0 vs. 0.8 ±. respectively) 0.6) and OLGIM (1.3±1.2 vs. 1.4±1.1. respectively) scores were also similar in successful and unsuccessful eradication groups.

In our country Erdem et al. (12) had studied on patients with dyspepsia, they found atrophic gastritis in 8%,intestinal metaplasia in 21%, dysplasia in 4% of the patients. While 90% of patients with precancerous lesions for gastric cancer were *H. pylori* positive, 61% of patients without precancerous lesions were *H. pylori* positive.

In our study, gastric atrophy was found in 75.3% (73) of the cases and intestinal metaplasia was detected in 75.3% (73) according to the initial endoscopy. Severe gastritis (OLGA III-IV and/or OLGIM III-IV) was detected in 17.5% (17) cases. and low-grade dysplasia was detected in 3.1% (3) cases.

In Korea, Cho et al. (13) found that 46.2% of the patients diagnosed with gastric cancer were OLGA III and IV, and this rate was significantly significant. (p<0.001) in cases with OLGA III and IV. they found that the development of intestinal type gastric cancer was at the forefront (62.2%).

In ours, at the end of the median follow-up period of 23.6 months; Regardless of *H. pylori* eradication success, a significant decrease was detected in the frequency of atrophy (p<.001) and intestinal metaplasia (p<.001) compared to baseline. A near-significant decrease was observed in the frequency of severe gastritis. (p=.057) OLGA (0.94±0.80 vs. 0.054±0.79) and OLGIM (1.39±1.16 vs. 0.95±1.10) scores (p< for both) .001) significant reduction was detected.

In a study conducted in China, while *H. pylori* eradication treatment did not reduce the risk of gastric cancer in patients with *H. pylori*-positive precancerous lesions; In patients without *H. pylori*-positive precancerous lesions, gastric cancer development has been shown to be significantly reduced after eradication therapy (14).

In a retrospective study in which the first and Final OLGA and OLGIM scores of the patients who applied to the gastroenterology outpatient clinic with the complaint of dyspepsia were found to be positive for *H. pylori*. and received standard eradication therapy, were compared. It was found that the rates of gastric atrophy and intestinal metaplasia were significantly higher in the eradication unsuccessful group(p=.001) found that the group with OLGA stage III.IV and OLGIM stage III.IV. which was evaluated as severe gastritis in the eradication-successful group, was high and that severe gastritis played an important role in eradication failure as an independent risk factor (p=.03 and p=.01) (15).

In our study, in the group with successful eradication of H.pylori, the change in histopathological findings was examined. A statistically significant decrease was observed in the frequency of atrophy and intestinal

metaplasia at the Final visit compared to the baseline. A nearly significant decrease was observed in the frequency of severe gastritis (p=.06). It was observed that dysplasia disappeared in the follow-up in 2 patients who were found to have dysplasia at the beginning. Significant decreases were detected in OLGA (1.2±1.0 vs. 0.4±0.5) and OLGIM (1.3±1.2 vs. 0.7±0.9) scores ($p < .001$ and p=.03, respectively).

It is controversial that *H. pylori* eradication can regress the lesions in patients with precancerous lesions in the stomach. In a study conducted in China, where the death rate due to gastric cancer was 153 per 100 thousand. Eradication treatment did not reduce the risk of gastric cancer in patients with *H. pylori* (+) precancerous lesions; In patients without *H. pylori* (+) precancerous lesions, gastric cancer development has been shown to be significantly reduced after eradication therapy (14). There are conflicting statements about the benefit of eradication therapy in patients with precancerous lesions in the stomach (16).

In our study. when the change in histopathological findings was examined in cases where eradication of *H. pylori* was unsuccessful, a statistically significant decrease was observed in the frequency of atrophy and intestinal metaplasia compared to the baseline but no significant change was detected in the frequency of severe gastritis or dysplasia. While a minimal change was detected 0.8±0.6 vs. 0.5±0.8, p=.052) in OLGA score, there was a significant decrease in OLGIM (1.4±1.1 vs. 1.0±1.1, p=.002) score detected.

CONCLUSION

A statistically significant decrease in the frequency of atrophy and intestinal metaplasia was observed with the success of eradication of *H. pylori* in gastric cancer. A nearly significant decrease was observed in the frequency of severe gastritis. A significant decrease was also detected in OLGA and OLGIM scores after *H. pylori* eradication treatment. We believe that *H. pylori* eradication treatment should be performed in *H. pylori* positive precancerous gastric lesions.

The weak points of our study are that it was designed retrospectively, the number of patients was small and it was not known which eradication protocol was applied to the patients.

Clinical guidelines for the treatment or endoscopic follow-up of premalignant gastric lesions are strongly needed as follow-ups in premalignant gastric lesions are not compatible with the potential risk of gastric cancer these lesions have. We believe that more studies should be done on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 06.07.2015, Decision No: 19/13).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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