RESEARCH ARTICLE

# Outcome of Intestinal Metaplasia in Gastric Biopsy of Patients with Dyspepsia in Guilan Province, North Iran

**Fariborz Mansour-Ghanaei[1,2]*, Farahnaz Joukar[2], Fatemeh Soati[2], Alireza Mansour-Ghanaei[3], Zahra Atrkar-Roushan[2]**

## Abstract

**Background: It is generally accepted that gastric carcinomas are preceded by a sequential multistage process that includes chronic gastritis, gastric atrophy, usually with intestinal metaplasia (IM), and dysplasia. This series of changes in gastric carcinogenesis is often initiated by *Helicobacter pylori* (*H pylori*) infection. The aim of the present study was determination of gastric histopathologic changes in IM patients after at least one year in Guilan province, Iran. Materials and Methods: This case-series study was conducted in Guilan Gastrointestinal and Liver Disease Research Center (GLDRC) during 2010 to 2011. Gastric biopsy was performed for all 71 known cases of IM and precanceric lesions including gastric atrophy, IM, dysplasia and *H pylori* infection were determined after at least one year. Results: Of the total of 71 patients with established IM who were enrolled, 50 had complete-type IM and 21 had incomplete-type IM. Fifty two people had *H pylori* infection. *H pylori* eradication was achieved in 39 patients (75%). Secondary pathology findings of patients with IM were complete metaplasia (39.4%), incomplete metaplasia (32.4%), dysplasia (23.9%) and other precanceric lesions (4.2%). Dysplasia (20% vs 33%) occurred in patients who had complete and incomplete IM at baseline respectively (p>0.05). Age, gender, family history of gastric cancer(GC); smoking habits and NSAIDs use were not associated with gastric premalignant lesions in initial and secondary pathologies (p>0.05). The difference became statistically significant between *H pylori* infection in patients with more than 3 years diagnostic intervals (p<0.05). Statistical difference between eradicators and non-eradicators was not significant. Conclusions: We found that incomplete IM increased the risk of subsequent dysplasia in this study.**

**Keywords:** *H pylori* infection - histopathologic changes - intestinal metaplasia

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## Introduction

Gastric cancer (GC) represents the fourth most common cancer and is the second prevalent leading cause of death in the world and approximately 700,000 people succumb each year to gastric adenocarcinoma (Ferlay et al., 2010; Herszenyi and Tulassay, 2010; Yaghoobi et al., 2010; Wroblewski et al., 2010). In Iran GC is the most common cancer in male and it is reported to be the third cancer after breast and colorectal cancers in female (Babaei et al., 2010). About 7300 cases in Iran (10.5 per 100000 individuals) are affiliated to GC annually (Mehrabian et al., 2010).

According to the Lauren's classification, two subtypes of GC can be distinguished basing on their different histology: the intestinal-type adenocarcinoma and the diffuse-type GC (Wroblewski et al., 2010; Lastraioli., 2012). The accepted model for the development of gastric adenocarcinoma of the intestinal type consists of the following precancerous steps: non-atrophic gastritis, multifocal atrophic gastritis, intestinal metaplasia (first "complete" and then "incomplete") and dysplasia, first low grade and then high grade (Correa et al., 2010; Correa and Piazuelo, 2012). Intestinal metaplasia (IM) and gastric dysplasia are the main precancerous lesions of the stomach; IM also being the most frequently encountered (de Vries and Kuipers, 2007a; Cazacu et al., 2009; Zullo et al., 2012).

Identified risk factors for IM include *H pylori* infection, first degree relatives of gastric cancer patients, high salt intake, smoking, alcohol consumption and chronic bile reflux (Peleteiro et al., 2007; Camorlinga-Ponce et al., 2008; de Vries et al., 2009a; Roesler et al., 2012; Zullo et al., 2012).

Two third of patients with gastric carcinomas are diagnosed in the advanced stages of the disease and in these stages just palliative therapies are possible; If diagnose is performed in the early and premalignant stages, surgical therapy will result in 10-year survival in more than 85% of cases (Testino, 2006). As a primary prevention *H pylori* eradication by antibiotics together with proton pump inhibitors are considered as it is able

*[1]Division of Gastroenterology and Hepatology, [2]Gastrointestinal and Liver Diseases Research Center (GLDRC), Guilan University of Medical Sciences, Rasht, [3]Shahid Beheshti University of Medical Sciences, Tehran, Iran *For correspondence: ghanaei@gums.ac.ir*

to reduce gastric cancer incidence (Konturek et al., 2009; Fuccio et al., 2010). Few studies indicated that endoscopic histological follow-up in patients with IM is able to detect gastric cancer in an early stage with a considerable mortality reduction (Correa et al., 2010; de Vries et al., 2010; Dinis-Ribeiro et al., 2012; Zullo et al., 2012). Considering the high prevalence of gastric carcinoma in the northern regions of Iran (Talebi et al., 2011) and especially Guilan province, and the fact that histopathologic changes might have been made during a long period, even if the disease has been diagnosed soon before, we set a survey to analyze the histologic changes in patients with IM after at least one year in this area.

## Materials and Methods

*Study subjects*

It was a case-series which was done in Gastrointestinal and Liver Diseases Research Center (GLDRC) of Guilan university of Medical Sciences Rasht, Iran in 2010-2011. Study population consisted of all dyspeptic patients with documented IM diagnosed at least one year ago. These patients had under previous upper gastrointestinal endoscopy in private or public centers in Rasht and their pathology specimens exist in various pathobiology laboratories. Their pathology reports were extracted from the labs and the patients were invited to come for filling some questionnaires and undergoing another gastrointestinal upper GI endoscopy to study their gastric histopathologic changes. Patients who had undergone gastrectomy surgery for any reason, patients who had other precancerous lesions (eg. Gastric polyps and ulcers) in the first pathology and those who didn't consent for endoscopy were excluded. The study protocol was first approved by ethics committee of GLDRC.

*Specimens*

Upper gastrointestinal endoscopies were performed after local lidocaine 10% sedation and by video endoscopy (Olympus Optical Co, Ltd, GIF type V) and one expert endoscopist reported it. Biopsy specimens were taken from five different regions of the stomach; four specimens were taken for histologic exams, two from antrum, one from fundus and one from body. Rapid urease test (RUT) was also used performed for diagnosis of *H pylori* infection in a specimen from the antrum. Each specimen was placed in a separate bottle of formalin 10% and sent to the hospital pathology lab. After fixation, staining and microscopic exam, various premalignant lesions including atrophic gastritis, intestinal metaplasia (grade I to III), dysplasia and *H pylori* infection were determined and classified by Sydney criteria (Sakaki and Kozawa, 2001). The pathologist was blinded to the patient's data, index diagnosis, and endoscopic findings. Also data on patient's age, sex, family history, smoking habits, NSAIDs use, and treatment of *H pylori* eradication were recorded.

Patients were classified into three groups according to the interval between the initial and second pathologies (group 1: 1-2 years; group 2: 2-3 years; group3: >3 years). IM was classified to complete (grade I) and incomplete (grades II and III).

*Data analysis*

Data were analyzed by SPSS 18 software and by descriptive studies and compare means. $X^2$ test when appropriate was used for comparison of proportions. The analysis of the "initial" and "secondary" in the *H pylori* positive group was evaluated with the Mc-Nemar test. Significance of differences and relations were determined by p value ≤0.05.

## Results

Totally 71 patients with established IM were enrolled, 50 had complete-type IM and 21 had incomplete-type IM. Patients' mean age was 48.66 (±12) years, (range: 21-79 years) and there were 40 males and 31 females. The mean (±SD) interval between the initial endoscopy and the current endoscopy was 3 (±1.1) years with max duration: 4.5 years. Seventeen patients (22.5%) were categorized in group 1, 14 (19.7%) in group 2 and 41 (57.7%) in group 3. Fifty two (73.3%) patients had positive *H pylori* in the initial endoscopy; the remaining 19 (26.7%) patients had no signs of *H pylori* infection.

*The second pathology findings were as follow*

Twenty eight patients (39.4%) had confirmed having complete metaplasia, 23 patients (32.4%) showed incomplete metaplasia and 3 patients (4.2%) showed other precancerous lesions (gastritis with gastric atrophy). Also in the second pathology, dysplasia was diagnosed in 23.9% of the patients. In 20% of patients that had complete IM and 33% of those who had incomplete metaplasia at baseline, the dysplasia accrued (p>0.05).

Various precancerous changes in initial and secondary pathologies in 3 patients' groups are shown in Table 1. There was no significant difference between the histologic changes in initial and secondary pathologies among the three groups (p<0.05).

Age, gender, family history of GC; smoking habits and NSAIDs use were not associated with gastric premalignant lesions in initial and secondary pathologies (p>0.05) (Table 2).

*H pylori* negative was significantly more in the patients in the secondary pathology than the first pathology (p<0.05). No significant change was seen in *H pylori* positive and negative subjects in the first and

**Table 1. Various Precancerous Lesions Changes in Initial and Secondary Pathologies in 3 Patients' Groups**

| Group: Initial pathology | | Secondary Pathology | | | | Total |
|---|---|---|---|---|---|---|
| | | Gastritis with gastric atrophy (3) | Complete IM (28) | Incomplete IM (23) | Dysplasia (17) | |
| 1: | Complete | 1 (11.1) | 2 (22.2) | 5 (55.6) | 1(11.1) | 9 (56.2) |
| | Incomplete | 0 (0) | 5 (71.4) | 2 (28.6) | 0 (0) | 7 (43.8) |
| | Total | 1 (6.2) | 7 (43.8) | 7 (43.8) | 1 (6.2) | 16 (100) |
| 2: | Complete | 2 (20) | 4 (40.0) | 4 (40) | 0 (0) | 10 (71.4) |
| | Incomplete | 0 (0) | 1 (25.0) | 3 (75) | 0 (0) | 4 (28.6) |
| | Total | 2 (14.3) | 5 (35.7) | 7 (50) | 0 (0) | 14 (100) |
| 3: | Complete | 0 (0) | 15 (48.4) | 7 (22.6) | 9 (29) | 31 (75.6) |
| | Incomplete | 0 (0) | 1 (10.0) | 2 (20) | 7 (70) | 10 (24.4) |
| | Total | 0 (0) | 16 (39.0) | 9 (22) | 16 (39) | 41 (100) |

*group 1: 1-2 year interval between two pathologies, group 2: 2-3 year interval between two pathologies, and group 3: >3 year interval between two pathologies

**Table 2. Relation between Initial and Secondary Pathology Changes with Age, Sex, Family History, Smoking Habits, and NSAIDs Use**

| Variables | | In initial pathology N (%) | | In secondary pathology N (%) | | | | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | | Complete IM | In Complete IM | Gastritis with gastric atrophy | In Complete IM | Complete IM | Dysplasia | Total | |
| | | 50 (%) | 21 (%) | 3(%) | 23 (%) | 28 (%) | 17 (%) | 71 (%) | |
| Age | <40 | 14 (77.8) | 4 (22.4) | 1(5.6) | 5(27.8) | 8(44.8) | 4(22.2) | 18(100) | NS |
| | >40 | 36(67.9) | 17(32.1) | 2(3.8) | 18(34) | 20(37.7) | 13(24.5) | 53(100) | |
| Sex | Male | 28(70) | 12(30) | 0(0) | 13(32.5) | 15(37.5) | 12(30) | 40(100) | NS |
| | Female | 22(71) | 9(29) | 3(9.7) | 10(32.3) | 13(41.9) | 5(16.1) | 31(100) | |
| Family history | No | 29(67.4) | 14(32.6) | 2(4.7) | 16(37.2) | 18(41.9) | 7(16.3) | 43(100) | NS |
| | Yes | 21(75) | 7(25) | 1(3.6) | 7(25) | 10(35.7) | 10(35.7) | 28(100) | |
| NSAID | No | 31(67.4) | 15(32.6) | 1(2.2) | 17(37) | 17(37) | 11(23.9) | 46(100) | NS |
| | Yes | 19(76) | 6(24) | 2(8) | 6(24) | 11(44) | 6(24) | 25(100) | |
| Smoking | No | 35(70) | 15(30) | 3(6) | 17(34) | 21(42) | 9(18) | 50(100) | NS |
| | Yes | 15(71.4) | 6 (28.6) | 0(0) | 6(28.6) | 7(33.3) | 8(38.1) | 21(100) | |

**Table 3. Relation between the Premalignant Lesions in Patients With and Without *H pylori* Infection in Initial and Secondary Pathologies**

| | | In initial pathology N (%) | | | p value | In secondary pathology N (%) | | | | | p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Complete IM | In Complete IM | Total | | Gastritis with gastric atrophy | Complete IM | In Complete IM | Dysplasia | Total | |
| | | 50 (%) | 21 (%) | 71% | | 3(%) | 28 (%) | 23 (%) | 17 (%) | 71 (%) | |
| *H pylori* Infection | Negative | 19(100) | 0 (0) | 19(26.7) | 0.001 | 1(2.1) | 21(43.8) | 12(25) | 14(29.2) | 48(67.6) | NS |
| | Posetive | 31(59.6) | 21(40.4) | 52(73.3) | | 2(8.7) | 7(30.4) | 11(47.8) | 3(13.1) | 23(32.4) | |

second groups, but these changes were significant in the third group ($p<0.05$). Ten people who hadn't had *H pylori* infection in baseline became *H pylori*-positive in secondary pathology. Various precancerous changes in patients with and without *H pylori* infection in initial and secondary pathologies are shown in Table 3.

From 52 people who had *H pylori* infection treatment prior to the baseline endoscopy, *H pylori* eradication was achieved in 39 patients (75%). The presence of complete IM was confirmed at surveillance endoscopy in 16 of 39 patients (41%), in 11/39 patient (28.2%) incomplete IM was detected and in 1/39 patients (2.6%) was diagnosed atrophic gastritis. Eleven (28.2%) of 39 patients showed progression to dysplasia. Among non-*H pylori*-eradicated individuals who were 13 (25%), premalignant lesions were detected as follow: complete IM (38. 5%), incomplete IM (30.8%) and dysplasia (30.8%). There was no significant difference in the changes of premalignant lesions in eradicated and non–eradicated subjects ($p>0.05$).

## Discussion

Atrophic gastritis, intestinal metaplasia, and epithelial dysplasia of the stomach are common and are associated with an increased risk for gastric cancer (Dinis-Ribeiro et al., 2012). *H pylori* is an important risk factor for gastric cancer due to the fact that it causes chronic inflammation of the gastric mucosa in virtually all infected patients (Capelle et al., 2010; Wroblewski et al., 2010; Correa and Piazuelo, 2012). Patients with incomplete type IM harbor a higher risk of GC compared to those with complete type IM. However, incomplete type IM is much less frequent than complete type (de Vries et al., 2010).

In the present study, 29.6% of the patients showed incomplete IM in the first pathology which increased to 32.4% in the second pathology. In our study incomplete IM had the higher possibility of progression to dysplasia. There was no significant difference between the histologic changes in initial and secondary pathologies.

In Erikson's study, the total prevalence of IM was 19%. In those patients, prevalence of metaplasia type III was 2.8%; type II, 4.4%; and the complete metaplasia, 11% (2008). In a study by de Vries, 24% of patients had gastric atrophy and 67% of them had IM. They reported that incidence of gastric cancer was 0.1% for patients with gastric atrophy and 25% for IM 5 years after diagnosis. It was determined in their study that premalignant lesions increased the risk of GC (2009b). In the study of Dinis-Ribeiro et al. (2004) on patients with atrophic chronic gastritis and IM, 12% of the patients with atrophic chronic gastritis had progressed to low grade dysplasia. Eight percent of patients were diagnosed to have grade I IM, 38% with grade II and III, and 32% with low grade dysplasia. IM type II and III had the higher possibility of progression to dysplasia and cancer. In a recent study performed in Spain, gastric carcinoma developed in 16 (18.2%) out of 88 patients with incomplete IM and in only 1 (0.96%) out of 104 patients with complete IM after a mean follow up of 12.8 years; incomplete IM also showed the highest risk of developing a GC at multivariate analysis (Gonzalez et al., 2010). In a study in Slovenia, the cumulative incidences of GC in those patients previously diagnosed with IM were 1.3% incomplete IM-type I, 2.8% in incomplete IM-type II and 9.8% in incomplete IM-type III patients (Filipe et al., 1994).

In the present study, there was no significant difference between the premalignant lesions according to smoking habits; also in the study of Chacaltana et al. (2009) there was not any significant relationship between gastric premalignant lesions and smoking or

alcohol consumption. In the study of Peleteiro et al. (2007) smoking was related significantly with complete and incomplete metaplasia, and this shows the different modes of gastric carcinogenesis. In Cazacu (2009) they mentioned a strong relation between smoking habit and pathological-diagnosed atrophy. According to a prospective cohort study Cigarette smoking was associated with risk of of developing GC (Steevens et al., 2010). In Shikata' (2008) study findings suggest that cigarette smoking and *H pylori* infection are significant risk factors for gastric cancer in Japanese men.

Family relatives of GC patients have a higher risk of GC and premalignant gastric lesions (Leung et al., 2005). In the present study, there were no significant difference between gastric premalignant lesions according to family history. In the study of Chacaltana et al. (2009) there was not any significant relationship between gastric premalignant lesions and patients' family history while. In the recent study in Guilan province results confirmed that precancerous lesions such as dysplasia, atrophy and chronic gastritis were significantly higher in GC relatives rather than control group (Mansour-Ghanaei et al., 2012). Zendehdel et al. (2010) found in 808 first-degree relatives a similar IM prevalence between those subjects with 1 and those with >1 cases in the family, with no difference when the index case was male or female.

In our study there was no significant relationship between patients' age and gastric premalignant lesions; while in Cazacu's et al. (2009) study at patients with gastric atrophy diagnosed by endoscopy, OR has statistical significant risk for age above 50 years (OR=8.54, CI 95% 2.95-14.42) and for IM, a statistically significant risk was noted above 60 years, rural residence (OR=3.25).

In our study, there was significant difference between gastric premalignant lesions in patients with and without *H pylori* infection in initial pathology but there was no significant differences between secondary pathology. *H pylori* is the most important risk factor for gastric cancer and its precursor lesions. The systematic review article of Peleteiro et al. (2008) with the data from 29 countries reported the prevalence of IM in *H pylori* positive patients. This prevalence varies from 3% in Argentina to 55% in News land. In countries exhibiting a simultaneously high prevalence of infection and low incidence of gastric cancer, IM was also relatively infrequent (Thailand, 6%; India, 8.2%; Nigeria, 11.1%; Gambia, 11.8%; Saudi Arabia, 15.5%; Iran, 15.6%; Egypt, 24.4%). Zhang et al. (2005) showed that progression of gastric premalignant lesions, glandular atrophy and IM has a significant relationship with *H pylori* infection. In the study of Kang et al. (2008) the prevalence of IM type I, II, and III were respectively 28.1% , 57.8% , and 14.1% in gastric body. There was no significant relationship between this distribution and *H pylori* infection. They showed that the type of IM played an important role in progression of gastric carcinoma in Chorea. IM type III had a relationship with age and metaplasia type II was shown to be related with gastric carcinogenesis in the presence of *H pylori* infection.

In our study, *H pylori* was eradicated in 75% of people. There was no significant difference in gastric premalignant lesions in non–eradicated and eradicated subjects. There are different ideas about this issue whether *H pylori* eradication halts progression or can even cause regression of premalignant gastric lesions (de Vries and Kuipers, 2007b; Roesler et al., 2012). After 1.5-year follow-up by Satoh et al. (1999) after *H pylori* eradication, no significant improvement was seen in atrophic gastritis and IM. In the study by Sakaki and Kozawa (2001) even 2 years after *H pylori* eradication, there was no significant regression in metaplasia. While two randomized studies, the first with a 5-year follow up and the second with a 1-year follow-up, observed that *H pylori* eradication was beneficial in preventing progression of atrophy and intestinal metaplasia of the gastric mucosa (Roesler et al., 2012). Some studies reported a significant improvement in atrophy after *H pylori* eradication, but IM didn't change significantly after eradication (Lahner et al., 2005; Lee et al., 2007; 2013; Rokkas et al., 2007; Vannella et al., 2011; Massarat et al., 2012) while some randomized studies with longer follow-up periods of over two years have shown evidence of IM regression (Ciok et al., 1997; Correa et al., 2000; Kim et al., 2000; Kokkola et al., 2002; Mera et al., 2005; You et al., 2006).

In the present study patients with IM who had a >3 year interval between two pathologies were significantly more *H pylori* negative but the patients with 1 or 2 year interval didn't. *H pylori* infection may provide the proper environment for atrophic gastritis and IM to occur. But at the final stage of the disease, gastric atrophy with IM is not a hospitable environment for *H pylori* and is associated with a dramatic reduction or even disappearance of the organism (Zhang et al., 2005).

In conclusion, it was determined in our study that incomplete-type IM increased the risk of dysplasia. Also there was significant difference in *H pylori* infection in the group who had a >3 year interval between two pathologies. Of course getting to more documented results needs further prospective surveys with larger samples and longer follow up duration. Also future surveys should concentrate on determining various *H pylori* subtypes, their virulence, and its relationship with premalignant lesions.

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