Turk J Gastroenterol *2014; 25: 226-8*

Utility of diagnosing *H. pylori* in presence of intestinal metaplasia

To the Editor,

In February 2014 issue of Turkish Journal of Gastroenterology, Galiatsatos P. et al. (1) reported that, biopsy alone for the detection of *H. pylori* may be less accurate in the context of intestinal metaplasia, and additional use of breath urea test would increase the accuracy of diagnosis. *H. pylori* causes intestinal type gastric cancer via chronic active gastritis-multifocal atrophic gastritis-intestinal metaplasia-dysplasia-cancer cascade. Authors states that after treatment of *H. pylori*, intestinal metaplasia can revert to normal mucosa so progression to gastric cancer may be prevented.

This study is well organized and planned. However, we believe that there is no point establishing *H. pylori* diagnosis and treating it after intestinal metaplasia and atrophic gastritis develop. Even though authors mentioned about controversies regarding reversibility of intestinal metaplasia after eradication, according to the Maastricth IV/Florence consensus report, eradication treatment is only effective in preventing gastric cancer before the atrophic gastritis and intestinal metaplasia developed (2). This result has been validated by the long term and large scaled studies (3-5).

Early eradication of *H. pylori* for prevention of gastric cancer has also been shown in experimental studies completed with mongolian gerbils (6). Chronic active gastritis disappears completely a few months after bacterial eradication while atrophy, intestinal metaplasia or dysplasia remains. Mucosal atrophy and intestinal metaplasia confer a high risk for the development of gastric cancer (7). Relative risk for gastric cancer after eradication has been found as 0.65 according to pooled analysis of 6695 patients (5). In a study, presence of H. pylori was evaluated in 1,833 gastric cancer patients with rapid urease tests, serology examinations, and histological evaluations and most of gastric cancers showed evidence of past *H. pylori* infection (8). These findings suggest that early eradication is most effective if completed before intestinal metaplasia and atrophic gastritis develop (9).

Another important point is the importance of H. pylori antibodies in diagnosis of past infection. Therefore, in patients with atrophic gastritis, the use of serology is encouraged in diagnosing *H. pylori* infection. In a study, most of the gastric cancers were found *H. pylori* negative and diagnosis can only be done by serum antibody testing (8). It seems that, other mechanisms are coming into prominence than *H. pylori* after intestinal metaplasia and gastric atrophy developed. It should not be forgotten that some of *H. pylori* species and CagA positivity plays an important role on the progression to the gastric cancer even though the patient is treated for *H. pylori*. So, what would change after eradication? Furthermore, *H. pylori* is not the only etiopathogenetic mechanism for gastric cancer. *H. pylori* negative gastric cancers are also present. In a study from South Korea, *H. pylori* negative gastric cancer rate was found as 5.4% and they seem to have a poorer prognosis than *H. pylori*-positive cases (10).

In summary, it seems that eradication is important before the intestinal metaplasia develops; there would not be any gain of eradication after it develops.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Ali Tüzün İnce

Department of Gastroenterolgy, Bezmialem Vakıf University Faculty of Medicine, İstanbul, Turkey

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Adress for Correspondence: Ali Tüzün İnce, Department of Gastroenterolgy, Bezmialem Vakıf University Faculty of Medicine, İstanbul, Turkey
E-mail: dralince@gmail.com
Received: 13.5.2014 **Accepted:** 18.5.2014

Author's Reply

To the Editor,

Your comments are valid and appreciated, and highlight the ongoing controversies with regards to this topic, as we had also mentioned in our paper. In the Maastricht IV consensus report, *H. pylori* is implicated in 71%-95% of gastric cancer cases, while eradication is said to be proven by studies to reduce gastric cancer risk, albeit more likely in patients without precancerous lesions (1). However, as the authors point out, "the exact point of no return has not been identified" (1). Moreover, the consensus panel themselves recommend eradication of *H. pylori* for the prevention of gastric cancer in patients with severe atrophy (statement 16, grade of recommendation A) (1).

There are a non-negligible number of well-designed trials that have demonstrated regression or improvement of atrophy or gastric intestinal metaplasia (IM) following eradication of *H. pylori,* mainly located in the gastric antrum. At the very least, there are studies that show stability of IM severity scores post eradication, suggesting that treating the organism may prevent progression to more advanced lesions. In an older prospective study of 63 patients post *H. pylori* cure, although there was no change in IM after 4 years, there was significant reduction in antral atrophy by the third year (p=0.02) (2). Amongst 76 Finnish patients with H. pylori and atrophic gastritis, mean atrophy score declined significantly at one year post treatment of infection (3). In a study of 587 infected patients randomized to treatment or placebo, there was an improvement in the activity of antral IM one year post successful eradication (p=0.014) (4). At 5 years post treatment, the degree of IM in the antrum was reduced or stable in the eradicated patients, as opposed to significantly increased in the control arm (p=0.032) (5). In a separate randomized prospective trial of 435 patients with *H. pylori* infection, those with IM who remained infected after 5 years had a significantly higher rate of IM progression than those who were treated (OR 2.13, p<0.001) (5). Ito et al. also demonstrated a significant decrease in grades of atrophy and IM (both corpus and antrum) 5 years post successful eradication of H. pylori (6).

Proving that reversal of atrophy or IM translates into reduced gastric cancer rates is of course more difficult. The problem is that it takes a very long time for regression of IM to occur, and consequently it would take even longer to appreciate a significant reduction in gastric cancer rates, which is why it is challenging to demonstrate and likely underestimated. However, one recent study has successfully proven decreased gastric cancer risk post H. pylori eradication in patients with irreversible high-risk lesions, namely 1007 patients with low-grade/high-grade dysplasia, or early gastric cancer, having undergone endoscopic resection (7). These patients were prospectively followed for 60 months, and the risk of metachronous gastric neoplasm was significantly higher amongst patients with persistent H. pylori infection than those eradicated (hazard ration 1.9, p=0.02). Intuitively, the resolution of inflammation, decrease in oxygen free radical formation, and reduction in cell turnover following successful eradication of *H. pylori* seem worthwhile pathophysiological processes in cancer prevention, regardless of reversibility of IM.

Ultimately, it would take a blinded randomized eradication trial with large numbers of patients and follow-up over 20-30 years to prove a difference, however the odds of such a trial ever being done is slim to none. Because of this, we believe that eradication of *H. pylori*, which is generally safe and not very costly, is a worthwhile pursuit, particularly in younger and higher risk patients (atrophy, IM) if the risk does not outweigh the potential benefit.

Polymnia Galiatsatos, Andrew Szilagyi
Department of Gastroenterology, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Canada

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Adress for Correspondence: Polymnia Galiatsatos, Department of Gastroenterology, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Canada
E-mail: pgaliatsatos@jgh.mcgill.ca