

Surveillance of Gastric Intestinal Metaplasia: Is It Warranted?

Polymnia Galiatsatos

Polymnia Galiatsatos, Division of Gastroenterology, Department of Medicine, Jewish General Hospital, McGill University, Montreal, Quebec, Canada

Correspondence to: Polymnia Galiatsatos, MD, FRCP(C), Division of Gastroenterology, Department of Medicine, Room E-110, Jewish General Hospital, McGill University, 3755 Cote-Ste-Catherine, Montreal, Qc, H3T 1E2, Montreal, Quebec, Canada

Email: pgaliatsatos@jgh.mcgill.ca

Telephone: +1-514-340-8144

Fax: +1-514-340-8282

Received: July 3, 2014

Revised: September 1, 2014

Accepted: September 6, 2014

Published online: December 21, 2014

ABSTRACT

Despite a decline in incidence over time, gastric adenocarcinoma remains one of the most common and lethal malignancies worthwhile. Nonetheless, endoscopic surveillance of gastric intestinal metaplasia (IM), a precursor lesion, remains controversial with lack of uniform guidelines. Trials have shown a roughly 6-fold increased risk of gastric cancer in the context of IM, with evidence of earlier stage detection and improved 5-year survival with routine surveillance protocols. Thorough pursuit and treatment of *Helicobacter pylori* infection seems warranted, as IM severity scores appear to improve post eradication. Conventional and digital chromoendoscopy may be the way of the future, while appropriate and cost-effective intervals for surveillance still need to be determined.

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Key words: Gastric intestinal metaplasia; Gastric adenocarcinoma; *Helicobacter pylori*

Galiatsatos P. Surveillance of Gastric Intestinal Metaplasia: Is It Warranted? *Journal of Gastroenterology and Hepatology Research* 2014; 3(12): 1364-1366 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/965>

SURVEILLANCE OF GASTRIC INTESTINAL METAPLASIA: IS IT WARRANTED?

Despite a steady decline in gastric cancer incidence since the 1930s, it remains the fifth most common malignancy (after lung, breast, colon, and prostate) and the third leading cause of cancer death worthwhile, with 723,000 deaths in 2012^[1]. Most gastric cancers are adenocarcinomas, which are further subdivided into 2 groups, namely intestinal or well-differentiated (50%), and diffuse or undifferentiated (33%), the latter of which affects younger patients and is phenotypically more aggressive^[2]. Intestinal-type gastric adenocarcinoma is more common in older patients, and has been causally linked to *Helicobacter pylori* (*H. pylori*) through a series of events starting with long-standing non-atrophic body-predominant gastritis, to multifocal atrophy, gastric intestinal metaplasia (IM), dysplasia, and invasive cancer. In fact, *H. pylori* is a recognized class I carcinogen, and thought to be solely responsible for gastric cancer in 36-47% of cases^[2].

Because of its poor prognosis and high mortality rate, attempts have been made to identify preventative strategies. Unfortunately, unlike Barrett's esophagus and colon cancer which have established surveillance recommendations (despite recent scrutiny and periodic need for revision), similar guidelines with respect to gastric cancer or its precursor lesions had been essentially lacking for the Western world up until recently. The 2006 guidelines from the American Society for Gastrointestinal Endoscopy state that endoscopic surveillance for IM without dysplasia could not be "uniformly recommended" due to insufficient evidence^[3]. Meanwhile, in 2012 the Europeans came up with guidelines recommending use of magnification chromoendoscopy and/or narrow band imaging with at least 4 biopsies of the proximal and distal stomach as a baseline, followed by endoscopic surveillance every 3 years for patients with extensive mucosal atrophy and/or IM^[4].

To evaluate benefit of surveillance, we must first understand what is the risk of progression of IM to gastric cancer. A Dutch study estimated the annual incidence of gastric cancer to be 0.1% for

atrophic gastritis (AG), 0.25% for IM, 0.6% for presence of mild to moderate dysplasia, and 6% for severe dysplasia^[5]. A Japanese trial quoted a 6-fold increased risk of gastric cancer in the presence of IM^[6], while in a Korean trial the relative risk varied from 7.52 to 9.25 depending on the location of IM, lesser curve being worse than antrum^[7].

Unfortunately, there is a true paucity of prospective studies investigating surveillance gastroscopy for IM in the Western world. In a UK study, patients over age 40 who underwent an initial gastroscopy for dyspeptic symptoms were offered annual surveillance endoscopies for high-risk lesions (namely ulcers, polyps, dysplasia, IM, AG, foveolar hyperplasia and regenerative changes)^[8]. Amongst 93 patients with IM who accepted annual endoscopic surveillance, 10 gastric cancers (11%) were discovered over a 10-year period. Tumors detected by routine surveillance were of an earlier stage that open access endoscopy, and the five-year survival was also significantly higher (50% vs 10%, $p=0.006$)^[8]. In an Italian study of 471 patients with IM undergoing surveillance biennially, 45 (9.55%) developed neoplasia over a 52-month follow-up period, specifically 17 cases of dysplasia alone, 26 gastric cancers, and one high-grade lymphoma^[9]. In this trial, age >65, persistent *H. pylori* infection, and indefinite-for-dysplasia lesions were independent risk factors for neoplastic transformation on multivariate analysis. IM extension $\geq 20\%$ also correlated with higher neoplasia risk (hazard ratio 9.25).

One major issue of screening IM for cancer risk is cost-effectiveness. This is difficult to estimate, given the variable incidence of gastric cancer in different geographic locations, as well as the widely differing costs of endoscopy, even between countries in close proximity. An American decision-analysis model of annual surveillance endoscopy for IM determined that the number of gastroscopies required to detect one cancer was 556, and to prevent a gastric cancer-related death was 3,738, at a cost of 72,519 \$ per life-year gained, deemed cost-effective^[10]. In another US simulation model of surveillance in men over 50 with precancerous gastric lesions, endoscopic surveillance was only deemed to be cost-effective post endoscopic mucosal resection (EMR) of dysplastic lesions, at a cost of 39,800 \$ per quality-adjusted life year (QALY)^[11]. Routine surveillance of IM every 10 years reduced lifetime gastric cancer risk by 61%, but at a cost of 544,500 \$ per QALY.

Advocating gastric cancer prevention by means of surveillance gastroscopies for IM would be incomplete without a parallel recommendation for pursuit and eradication of *H. pylori* in this patient cohort, as it confers a higher risk of neoplasia. Despite ongoing controversy regarding the reversibility of IM with *H. pylori* eradication, there are now a non-negligible number of studies demonstrating improvement in IM severity^[12-17], or at the very least stability of IM scores with eradication^[18-20]. Treatment of *H. pylori* has also been shown to decrease metachronous cancer risk in patients with dysplasia or early gastric cancer post endoscopic resection^[21]. Whether biopsies obtained during surveillance endoscopies could reliably diagnose the infection is yet another area of uncertainty, as studies have cast doubt on biopsy accuracy for *H. pylori* in the context of IM^[22-24]. A recent retrospective analysis estimated sensitivity of gastric biopsy to be as low as 78.7%, with negative predictive value of 76.7% in this patient population^[22].

The way of the future in IM surveillance may be to incorporate newer endoscopic tools such as confocal microscopy (CM), conventional chromoendoscopy, and digital chromoendoscopy such as narrow band imaging (NBI). In an earlier trial, the sensitivity of magnification chromoendoscopy using methylene blue was 76% for IM, and 97% for dysplasia^[25], compared to rates less than 50% for

conventional endoscopy^[26]. In a Dutch study of 36 patients with premalignant gastric lesions, the sensitivity of NBI versus white light endoscopy for detection of IM or dysplasia was 71% versus 51% respectively ($p<0.001$), compared to random and targeted biopsies^[27]. This was at the expense of specificity, which was significantly lower with NBI (58% vs 67%, $p=0.04$). The diagnostic accuracy of NBI was also impressively higher than magnifying white light endoscopy for small depressed gastric lesions in a Japanese trial (79% versus 44%, $p=0.0001$), with a sensitivity for small gastric cancer in the range of 70% as opposed to 23% respectively, and no significant difference in specificity^[28].

Considering the risks associated with upper endoscopy are generally low, I think it is reasonable to offer surveillance gastroscopy to patients with IM without dysplasia if they have extensive IM involvement, a family history of gastric cancer, if they are smokers, or have ongoing *H. pylori* infection. I also advocate thorough testing and treating of *H. pylori* infection, with consideration of a second confirmatory modality (preferably urea breath test) in the context of negative biopsy. While conventional chromoendoscopy could be laborious and time-consuming, digital chromoendoscopy, if available, could increase diagnostic accuracy without increased risk or cost. The biggest question that remains to be answered is what the appropriate surveillance interval should be, to maximize benefit at a reasonable cost for a given population. This should be the focus of prospective studies to come.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests and received no financial support.

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- Peer reviewer:** Raffaele Capasso PhD, Department of Experimental Pharmacology, University of Naples Federico II, Via D. Montesano 49, I-80131 Naples, ITALY.