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FIELD OF VISION

Intestinal metaplasia surveillance: Searching for the road-map

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Abstract

Atrophic gastritis and intestinal metaplasia (IM) of the stomach are common and are associated with an increased risk for gastric cancer. In the absence of guidelines, a pragmatic management has been performed in Western countries in patients with these premalignant conditions. Recently, formal European guidelines have been delivered on this topic. Basically, it has been recommended that patients with extensive atrophic gastritis (AG) and/or extensive IM should be offered endoscopic surveillance every 3 years. On the contrary, no scheduled endoscopic/histological control has been advised for those patients with precancerous conditions confined to the antrum. In this commentary, we highlighted some potential weaknesses in the management formally recommended by the new guidelines. In detail, we discussed that AG and IM patients do not share the same gastric cancer risk, at least in Western countries, deserving a different approach. Some factors significantly associated with gastric cancer risk, such as IM type, first-degree family history of gastric cancer, and smoking habit have not been considered in tailoring the endoscopic follow-up. Finally, some data would suggest that a 3-year follow-up in patients with extensive gastric precancerous conditions could result in an inadequate secondary prevention.

Key words: Intestinal metaplasia; Guidelines; Atrophic gastritis; Gastric cancer; Follow-up

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COMMENTARY ON HOT TOPICS

We read with great interest the recent article by Dinis-Ribeiro *et al*[1] reporting the first European Guidelines on management of precancerous conditions and lesions in the stomach (MAPS), and strongly recommend it to readers. Despite gastric cancer incidence is decreasing, such a neoplasia remains the fourth most prevalent tumor and second most frequent cause of cancer-related mortality in the world[2]. The endoscopic-based screening programs performed in a few Asian countries[3], where the gastric cancer incidence is extremely high, are not feasible in other countries due to a distinctly lower frequency of such a neoplasia. Therefore, in the Western countries, surveillance of precancerous conditions [gastric atrophy and intestinal metaplasia (IM)] and lesions (dysplasia) is the only reliable procedure able either to reduce gastric cancer onset - *i.e.*, by removing dysplasia areas at endoscopy or to diagnose an already-developed cancer in an early stage, so that patient survival is distinctly improved[4,5]. However, the American Society for Gastrointestinal Endoscopy Guideline recommended against the surveillance

for patients with IM[6]. Until few months ago, no European guidelines were available on the management of these precancerous lesions, leaving both gastroenterologists and general practitioners (GP) to empirically manage these patients without any actual reference standard. For this reason, Dinis-Ribeiro *et al*[1] should be commended for having organized a workshop involving a vast panel of experts, in order to deliver the first European guideline on such a topic.

According to these new guidelines, it has been recommended that patients with extensive atrophy gastritis (AG) and/or extensive IM - *i.e.*, involving both antral and gastric body mucosa - should be offered endoscopic surveillance (evidence level 2++, recommendation grade B) every 3 years (evidence level 4, recommendation grade D). On the contrary, no scheduled endoscopic/histological control has been advised for those patients with precancerous conditions confined to the antrum. Therefore, both gastroenterologists and GPs have now a "road map" to systematically schedule the surveillance in patients with either AG or IM.

Although any guideline is better than no guideline, we would further discuss some potential flaws entailed in the management recently recommended. First, it might appear questionable that the same endoscopic follow-up has been advised for both AG and IM patients. In a nationwide study[7], the 10-year gastric cancer incidence was estimated to be 0.8% and 1.8% in 22 365 AG and 61 707 IM patients, respectively, corresponding to an adjusted yearly incidence of 0.055% and 0.1%[8]. Given the two-fold different gastric cancer risk, perhaps a differently scheduled endoscopic surveillance should be proposed for AG and IM patients. Differently from IM[9], a strict follow-up in AG patients may be not cost-effective in Western countries[10].

Secondly, appropriateness of the suggested interval for endoscopic follow-up is not well documented. The 3-year interval selected for patients with extensive AG or IM does not appear to be corroborated by any prospective study. Indeed, the panel of experts downgraded this statement as level 4, grade D. However, at least two studies demonstrated that only 36% and 38% of detected gastric cancers were in an early stage (*i.e.,* stage I disease), when scheduling the endoscopic surveillance interval at 1- or 2-years, respectively[11,12]. Therefore, despite patients underwent a more intensive follow-up than the 3-year interval now officially recommended[1], gastric cancer was diagnosed in an advanced stage in as many as 62%-64% of the cases. Based on these observations, an even worse scenario cannot be excluded when a 3-year interval follow-up is to be implemented in clinical practice. The dismal prognosis of gastric cancer diagnosed in an advanced stage poses ethical concerns about recommending a 3-year surveillance interval for IM patients. On the other hand, it is also unquestionable that an appropriate use of endoscopic procedures is essential to the rational use of finite resources. To dissipate economic resources in performing yearly endoscopic controls in all IM patients - most of which would never develop gastric cancer - would also be unethical. A possible solution could be represented by a patient-tailored approach. Similarly to the extensive spreading of AG or IM in the stomach - the only risk factor considered in the MAPS guidelines[1] - several studies demonstrated that other factors increased gastric cancer risk, including IM type, first-degree family history of gastric cancer, and smoking habit. Presence of incomplete type IM significantly increased the hazard ratio of gastric cancer as compared to complete IM (hazard ratio: 11.3, 95%CI: 3.8-33.9)[13]. A first-degree family history of gastric cancer also increases such risk by 2.6-3.5 times, with a calculated attributable risk of 8%[14,15]. Indeed, the gastric carcinogenetic cascade in these subjects seems to start earlier than in controls[16]. A meta-analysis, considering 14 442 cases and 73 918 controls, found that smoking significantly increased gastric cancer risk, with an overall odds ratio (OR) of 1.48 (95%CI: 1.28-1.71), and an OR of 1.69 (95%CI: 1.35-2.11) for current smoker status in comparison to never smokers[17].

Therefore, IM patients with at least 1 of these risk factors (incomplete IM, family history, smoking habit) - information easily available in clinical practice - would appear at a further increased risk of gastric cancer and may probably beneficiate of a more intensive endoscopic surveillance, rather than the 3-year follow-up uniformly suggested for all patients[1]. We recently proposed a patient individualized follow-up with an yearly endoscopic control in those patients with adjunctive risk factors, and a less intensive (2-3 years) follow-up in the remaining IM patients[18]. For instance, a patient with incomplete IM confined to the antral mucosa would not appear to be at lower gastric cancer risk as compared to a patient with extensive, complete IM. Similarly, a smoker patient with complete IM in the antrum or with a family history of gastric cancer likely deserves endoscopic surveillance, contrary to what recommended by the MAPS. However, further studies on this topic are needed.

Finally, the gastric biopsy sampling proposed in the MAPS includes $\geqslant$ 2 biopsies in the antrum and $\geqslant$ 2 biopsies in the gastric body. However, in the updated Sydney System, 5 biopsies were recommended, including 1 additional specimen on the *incisura angularis*[19]. The need of this additional biopsy was based on the evidence that IM prevalence is higher in this gastric site as compared to any other part of the stomach[20]. Indeed, IM generally initiates in the *incisura angularis*, subsequently spreading in both antrum and gastric body[21]. Despite it could be argued that IM only located in the angulus does not increase gastric cancer risk, it is also true that IM would presumably spread to both antrun and body in the majority of patients[21]. Therefore, by simply taking 1 biopsy on the angulus it is possible to early detect IM - that is a generally irreversible, precancerous lesion[22]. Taking 1 further biopsy on the angulus is a simple and rapid procedure, without any additional patient discomfort and cost.

Indeed, as suggested in the Operative Link for Gastritis Assessment (OLGA) system, the additional biopsy specimen taken on the angulus should be pushed in the same vial of antral biopsies[23]. The MAPS guideline did not include angulus biopsy among the recommendations[1]. However, the guideline suggested that biopsies should be histologically assessed according to the OLGA/OLGIM system[23,24], for which 5 biopsies (1 on the angulus) are required. Therefore, it would appear reasonable to include *incisura angularis* in the biopsy sampling.

In conclusion, while waiting for large prospective, randomized, multicenter studies comparing different follow-up strategies, it would appear reasonable to take into account some additional risk factors for gastric cancer in the follow-up strategy for management of gastric precancerous lesions. A simple, patient-tailored surveillance may be probably more appropriate than a single schedule proposed for all patients. Despite MAPS represents a good start, a more patient-orientated road-map(s) could be also considered.

REFERENCES

1 **Dinis-Ribeiro M**, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, Pereira C, Pimentel-Nunes P, Correia R, Ensari A, Dumonceau JM, Machado JC, Macedo G, Malfertheiner P, Matysiak-Budnik T, Megraud F, Miki K, O'Morain C, Peek RM, Ponchon T, Ristimaki A, Rembacken B, Carneiro F, Kuipers EJ. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy* 2012; **44**: 74-94 [PMID: 22198778 DOI: 10.1055/s-0031-1291491]

2 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

3 **Leung WK**, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, Wu KC, Wu DC, Sollano J, Kachintorn U, Gotoda T, Lin JT, You WC, Ng EK, Sung JJ. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 2008; **9**: 279-287 [PMID: 18308253 DOI: 10.1016/S1470-2045(08)70072-X]

4 **Repici A**, Pagano N, Hassan C, Cavenati S, Rando G, Spaggiari P, Sharma P, Zullo A. Endoscopic submucosal dissection of gastric neoplastic lesions in patients with liver cirrhosis: a systematic review. *J Gastrointestin Liver Dis* 2012; **21**: 303-307 [PMID: 23012672]

5 **Yeh JM**, Hur C, Kuntz KM, Ezzati M, Goldie SJ. Cost-effectiveness of treatment and endoscopic surveillance of precancerous lesions to prevent gastric cancer. *Cancer* 2010; **116**: 2941-2953 [PMID: 20564399 DOI: 10.1002/cncr.25030]

6 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854 DOI: 10.1016/j.gie.2006.02.004]

7 **de Vries AC**, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008; **134**: 945-952 [PMID: 18395075 DOI: 10.1053/j.gastro.2008.01.071]

8 **Zullo A**, Hassan C. How harmful is the presence of intestinal metaplasia in the stomach? *Gastroenterology* 2009; **136**: 1461-1462; author reply 1462 [PMID: 19245871 DOI: 10.1053/j.gastro.2008.11.064]

9 **Hassan C**, Zullo A, Di Giulio E, Annibale B, Lahner E, De Francesco V, Ierardi E. Cost-effectiveness of endoscopic surveillance for gastric intestinal metaplasia. *Helicobacter* 2010; **15**: 221-226 [PMID: 20557364 DOI: 10.1111/j.1523-5378.2010.00752.x]

10 **Vannella L**, Lahner E, Annibale B. Risk for gastric neoplasias in patients with chronic atrophic gastritis: a critical reappraisal. *World J Gastroenterol* 2012; **18**: 1279-1285 [PMID: 22493541 DOI: 10.3748/wjg.v18.i12.1279]

11 **Whiting JL**, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JW. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut* 2002; **50**: 378-381 [PMID: 11839718 DOI: 10.1136/gut.50.3.378]

12 **Tava F**, Luinetti O, Ghigna MR, Alvisi C, Perego M, Trespi E, Klersy C, Fratti C, Fiocca R, Solcia E. Type or extension of intestinal metaplasia and immature/atypical "indefinite-for-dysplasia" lesions as predictors of gastric neoplasia. *Hum Pathol* 2006; **37**: 1489-1497 [PMID: 16949645 DOI: 10.1016/j.humpath.2006.05.012]

13 **González CA**, Pardo ML, Liso JM, Alonso P, Bonet C, Garcia RM, Sala N, Capella G, Sanz-Anquela JM. Gastric cancer occurrence in preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. *Int J Cancer* 2010; **127**: 2654-2660 [PMID: 20178099 DOI: 10.1002/ijc.25273]

14 **Palli D**, Galli M, Caporaso NE, Cipriani F, Decarli A, Saieva C, Fraumeni JF, Buiatti E. Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Biomarkers Prev* 1994; **3**: 15-18 [PMID: 8118379]

15 **La Vecchia C**, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. *Cancer* 1992; **70**: 50-55 [PMID: 1606546 DOI: 10.1002/1097-0142(19920701)70]

16 **Marcos-Pinto R**, Carneiro F, Dinis-Ribeiro M, Wen X, Lopes C, Figueiredo C, Machado JC, Ferreira RM, Reis CA, Ferreira J, Pedroto I, Areias J. First-degree relatives of patients with early-onset gastric carcinoma show even at young ages a high prevalence of advanced OLGA/OLGIM stages and dysplasia. *Aliment Pharmacol Ther* 2012; **35**: 1451-1459 [PMID: 22548492 DOI: 10.1111/j.1365-2036.2012.05111.x]

17 **La Torre G**, Chiaradia G, Gianfagna F, De Lauretis A, Boccia S, Mannocci A, Ricciardi W. Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. *Tumori* 2009; **95**: 13-22 [PMID: 19366050]

18 **Zullo A**, Hassan C, Romiti A, Giusto M, Guerriero C, Lorenzetti R, Campo SM, Tomao S. Follow-up of intestinal metaplasia in the stomach: When, how and why. *World J Gastrointest Oncol* 2012; **4**: 30-36 [PMID: 22468181 DOI: 10.4251/wjgo.v4.i3.30]

19 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022 DOI: 10.1097/00000478-199610000-00001]

20 **de Vries AC**, Haringsma J, de Vries RA, Ter Borg F, van Grieken NC, Meijer GA, van Dekken H, Kuipers EJ. Biopsy strategies for endoscopic surveillance of pre-malignant gastric lesions. *Helicobacter* 2010; **15**: 259-264 [PMID: 20633186 DOI: 10.1111/j.1523-5378.2010.00760.x]

21 **Genta RM**. Screening for gastric cancer: does it make sense? *Aliment Pharmacol Ther* 2004; **20** Suppl 2: 42-47 [PMID: 15335412 DOI: 10.1111/j.1365-2036.2004.02039.x]

22 **Rokkas T**, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of Helicobacter pylori eradication

on gastric histology: a systematic review and meta-analysis. *Helicobacter* 2007; **12** Suppl 2: 32-38 [PMID: 17991174 DOI: 10.1111/j.1523-5378.2007.00563.x]

23 **Rugge M**, Correa P, Di Mario F, El-Omar E, Fiocca R, Geboes K, Genta RM, Graham DY, Hattori T, Malfertheiner P, Nakajima S, Sipponen P, Sung J, Weinstein W, Vieth M. OLGA staging for gastritis: a tutorial. *Dig Liver Dis* 2008; **40**: 650-658 [PMID: 18424244 DOI: 10.1016/j.dld.2008.02.030]

24 **Capelle LG**, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, van Dekken H, Meijer J, van Grieken NC, Kuipers EJ. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc* 2010; **71**: 1150-1158 [PMID: 20381801 DOI: 10.1016/j.gie.2009.12.029]

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