Gastric cancer

Secondary prevention of gastric cancer

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A matter of definitions

When I was young(er), my mentor, Pelayo Correa, who taught a generation of researchers orbiting around gastric oncology, encouraged me to spend some sabbatical time at the European Cancer Agency in Lyon ''...to gain, among other things, a better perception of the crucial clinical impact that epidemiological data really have in clinical practice''. I did not follow this good piece of advice... and it was a mistake! This was the first thought that came to me as I read the manuscript produced by de Vries *et al* in this issue of *Gut* (**page 1665**)—a well conducted study that will be mentioned by every paper addressing gastric precancerous lesions.[1]

The paper provides valuable insight on the declining prevalence of gastric precancerous lesions (that is, atrophic gastritis and gastric non-invasive neoplasia) in the Netherlands between 1991 and 2005: 15 years is a long enough time to give us a historical perception of how fast our world is changing. The abundance of data presented by the authors prompts a few general considerations on our current strategies for dealing with gastric precancerous lesions/conditions, making us look to the near future in the light of a critical review of our recent past.

Let us start from the conclusions: the Dutch data confirm that gastric cancer usually arises in the second half of life and its incidence is declining in the western world—a victory without a battle. Less optimistically, however, we could argue that gastric epithelial malignancies still have a major oncological impact in both Asian and South-American countries. Even in large areas of southern and eastern Europe, gastric cancer is still a leading oncological problem and surgeons are still faced with advanced gastric tumours in their daily practice (just to give an example, the incidence of gastric cancer in the Russian Federation exceeds 32/100 000 population/year; personal communication from Professor Victor Pasechnikov, Stavropol Medical Academy, Russia). de Vries's prediction of a 24% drop in the worldwide incidence of gastric cancer still seems out of reach (outside the Netherlands, at least).

Assuming that gastric cancer (and the intestinal type in particular) remains a major health problem in more than two-thirds of the world's population, any efforts to improve the secondary prevention of gastric cancer will have to include each of the following points: non-invasive tests for selecting high-risk subjects, gastric endoscopy procedures and biopsy sampling protocols, consistent (internationally validated) histological assessment of gastric precancerous lesions and finally histology reports.

de Vries's data suggest a few concise comments on each of these major points.[1]

NON-INVASIVE TESTS AND GASTRIC CANCER RISK

There is evidence that serology can give us an overall clinical perception that a field ''cancerisation'' process has taken place in the stomach. Several studies[2–8] (albeit with some notable controversy[8]) have consistently pinpointed pepsinogens, gastrin-17 and anti-*Helicobacter pylori* (and/or Cag-A) serology as the most promising among the serological markers for identifying patients at high risk of gastric cancer. There is no evidence, however, to support the claim that available blood tests can provide information on already established focal precancerous/cancerous lesions: such wishful thinking would have a negative fallout on the credibility of the tests and, more importantly, on our patients. Taking the particular epidemiological context into account, pepsinogens and gastrin have proved highly specific (but scarcely sensitive) in detecting atrophic gastritis, whereas anti-*H pylori* antibodies have shown a marked sensitivity (and a low specificity).[2–7] By simplifying and combining tests that perform differently, serology could be useful for screening populations at high risk of gastric cancer. Such a strategy may improve the secondary prevention of a cancer that is ''much more common than many other disorders for which screening and prevention have long been accepted in many populations''.[5]

ENDOSCOPY AND BIOPSY IN THE ASSESSMENT OF (ATROPHIC) GASTRITIS

While we wait for non-invasive, reliable tests to come to light, the only way to assess pre-malignant lesions remains upper gastrointestinal endoscopy (which is bloody, expensive and time consuming). In non-Japanese hands, the endoscopic detection of atrophic changes and even advanced precancerous alterations is inconsistent, which brings us to the next point: the biopsy sampling protocol. As a pathologist, I am reluctant to consider a diagnostic assessment satisfactory if the gross and histological features are not merged together, and the stomach should be no exception. Endoscopy without biopsy is usually done to contain the costs of the diagnostic procedure (or so we are led to believe!). I am convinced that gastroenterologists and pathologists would agree that healthcare costs need to be contained by pursuing the appropriateness of a procedure not by inappropriately performing necessary procedures. In this respect, the Dutch policy of involving general practitioners in the preparation of guidelines to restrict referrals for upper gastrointestinal endoscopy makes good sense (and should be implemented more widely in our daily clinical practice).[9]

When endoscopy is appropriate, the Sydney biopsy sampling protocol should be applied because of its worldwide acceptance.[10] By sampling the incisura angularis, the oxyntic and the antral mucosa, we can effectively explore different functional areas of the stomach and the resulting information has a major clinical impact at single patient level.[11 12] Moving from daily clinical practice to larger cohorts of patients, by consistently applying the Sydney protocol we can also learn more about the topography of gastric pre-malignant lesions. Such information would significantly improve our current knowledge about the phenotype(s) of gastritis at high risk of cancer progression: is ''oxyntic gastritis'' an autonomous phenotype of cancer-prone gastritis (as Uemura suggested[13]) or is it the most advanced (multifocal, spreading) stage of an earlier antrum-predominant atrophic gastritis?[14 15]

More extensive biopsy sampling protocols should be restricted to clinical research or specific situations—for example, a previously established diagnosis of non-invasive neoplastic lesions.[16]

RECOGNISING AND SCORING BASIC HISTOLOGICAL LESIONS

Evidence-based pathology means applying reliable, internationally validated diagnostic criteria to histological assessment. The international community of pathology experts should provide practising pathologists with clear guidelines for unequivocally recognising and scoring histological anomalies and, here again, gastric pathology is no exception. In the case of precancerous lesions in the stomach, the

definition of atrophy as the ''loss of appropriate glands'' is widely accepted and its sub-classification as metaplastic or non-metaplastic phenotypes has been established by an international group of pathologists of eastern and western cultural extraction.[17] With or without metaplasia (intestinal and/or pseudopyloric), atrophy has been brought back down to a single entity, albeit with differences in cancer risk (undoubtedly higher for the metaplastic variant).[18] Genta's visual analogue scales for scoring atrophy are a valuable, additional, step in efforts to standardise the grading criteria.[19]

Recognising and grading dysplasia is a long, seemingly endless, story. de Vries is probably right in saying that stricter criteria for assessing dysplasia may have contributed to a decline in the number of new cases in recent years.[1] Both the recent re-definition of dysplasia as non-invasive neoplasia (which is not a semantic touch-up) and the more detailed description of its phenotypic spectrum (as proposed by the WHO Agency) may have reduced the number of cases too lavishly classified as dysplastic.[20–22] A histological report of non-invasive neoplasia assigns the patient to a well defined (distressing and expensive) follow up protocol, which might sometimes be avoided if a second opinion is obtained from a pathologist with elective experience.[16]

HISTOLOGICALLY REPORTING ON GASTRITIS

The Sydney System and its Houston-updated version attempt to provide a scoring system to help pathologists grade the severity of different histological variables (inflammation, activity, metaplasia, *H pylori*) belonging to the spectrum of gastric inflammatory disease.[10 23] The Sydney matrix, however, was unable to provide a clear biopsy reporting format for unequivocally defining the gastritis phenotype and ranking its cancer risk that was easy for both clinicians and patients to understand. All these limitations clash with our current knowledge about the biological place of gastritis in the gastric carcinogenic process.[10 14 18] A sizeable body of literature proves that different phenotypes of gastritis are associated with different cancer risks and the extent/location of gastric atrophy (particularly the metaplastic subtype) consistently correlates with the risk of cancer onset.[13 15 18 20 24 25] The success of the Hepatitis Staging System[26] induced an International Group of Gastroenterologists and Pathologists (Operative Link on Gastritis Assessment; OLGA) to propose a histological gastritis staging system designed to enable a plain ranking of the severity of disease of the stomach as a whole.[27 28] The OLGA system uses the biopsy sampling protocol suggested by the Sydney System and considers gastric atrophy as the key lesion for assessing disease progression (and its related cancer risk). Gastritis is staged by combining the extent of atrophy scored histologically with its topographical extent, as identified by biopsy mapping. It is also suggested that the diagnostic report should include information about the likely aetiology (*H pylori,* autoimmune and so forth*)*.

Pilot studies have demonstrated that the OLGA system accomplishes its initial task by associating different gastritis stages with a different cancer risk.[29] Prospective multicentre studies in different epidemiological contexts are needed to further validate the new reporting format.

Coming back to the de Vries study, it would have been useful to compare the OLGA stage of gastritis over the period considered. Expressing the declining incidence of gastric precancerous diseases in terms of stage would have given the reader a more immediate perception of a changing situation (as in oncological practice, when a successful screening programme results in an increasing prevalence of low-stage cancers).

Consistent diagnostic protocols, unequivocal definitions, and structured and straightforward histology reports are all matters that are by no means marginal to our good daily practice in clinical oncology: as de Vries's study demonstrates, they are an integral part of evidence-based preventive, diagnostic and therapeutic procedures. A reliable exchange of information remains a major problem —even in the Wikipedia era.

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