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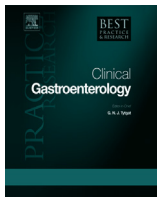

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Individual risk stratification of gastric cancer: Evolving concepts and their impact on clinical practice

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A B S T R A C T

Gastric cancer (GC) is the third leading cause of cancer-related death worldwide and it mostly develops in long-standing inflammatory conditions, and *Helicobacter pylori*-gastritis, in particular. Despite the increasing understanding of both the phenotypic alterations and the molecular mechanisms occurring during GC multi-step carcinogenesis, no reliable biomarker is available to be reliably implemented into GC secondary prevention strategies. Multidisciplinary diagnostic approaches integrating endoscopy, serology, histology and molecular profiling currently appears as the most appropriate approach for patients' stratification into different GC risk classes.

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Introduction

Despite its declining incidence, gastric cancer (GC) is still the third most frequent cause of global cancer-related mortality [1–3]. At diagnosis, virtually half of GC patients presents with an advanced disease, with a 5-year survival rate lower than 30% [4,5].

GCs can be syndromic/hereditary, being associated to specific mutational profiles [6–9]. However, most frequently, GCs are sporadic and they result from a progressive accumulation of genotypic and phenotypic changes, triggered by a longstanding gastritis, primarily due to *Helicobacter pylori* infection [10–12]. In this setting, the so-called epidemic, intestinal-type GC is the most broaden GC type, and the most studied for the introduction of secondary prevention approaches.

The chronic mucosal inflammation results in structural changes of gastric mucosa, leading to both an absolute loss of resident glands, and/or a metaplastic modification of the native glandular structures: this atrophic transformation of the gastric mucosa is the cancerization field in which gastric cancer develops [10–12]. In a subsequent step, the metaplastic epithelia might undergo de-differentiation, acquiring most of the biological characteristics of a neoplastic cell, but still lacking of the invasion-capability (intra-epithelial neoplasia [IEN], formerly defined as dysplasia). With stromal intrusion, IEN ultimately results in invasive cancer [12].

Such natural history, universally known as Correa's oncogenic cascade, provides the rationale enabling multidisciplinary strategies for cancer primary and secondary prevention [11,13]. Several operative inconsistencies, however, affect significantly the attempt to anticipate GC detection: (i) reliability of clinical/serological data in the assessment of gastric precancerous conditions; (ii) endoscopic assessment of pre-neoplastic lesions; (iii) biopsy sampling protocols to be applied; (iv) discrepancies in the histological classifications; (v) inter-observer variability in the histology assessment.

Histology in the assessment of gastric cancer risk: from the Sydney system to the gastritis staging

Gastric mucosa includes two structural/functional compartments: (i) distal muco-secreting, and (ii) proximal oxyntic: this biological heterogeneity results in different histology patterns of the gastric inflammatory diseases [14]. As a consequence, any histology phenotyping of gastritis does require a separate assessment of an adequate number of biopsy specimens obtained from each of the two mucosal compartments. Hence, five biopsies (three from the antrum [including *incisura angularis*], and two from the gastric body) have to be available in the assessment of both the aetiology, and the severity of inflammatory disease (including its associated risk of malignancy) [14].

Several studies consistently associated (extensive) gastric atrophy to an increased risk of GC; according to this evidence, any strategy addressing GC secondary prevention specifically focuses on this precancerous condition [10–13,15].

Gastric atrophy is defined as 'loss of appropriate glands'. This definition basically includes two phenotypes of atrophic transformation (Table 1): (i) shrinkage or complete disappearance of glandular units, replaced by fibrotic expansion of the lamina propria (i.e. a reduced glandular mass, with no modification of the native glandular phenotype); or (ii) replacement of the native by metaplastic

Table 1
Atrophy in gastric mucosa.

Atrophy	Histological type	Site and key lesions		Grading
		Antrum	Corpus	
0 Absent (=Score 0)				
1 Indefinite (no score is applicable)				
2 Present	2.1 Non-metaplastic	Glands: shrinking/vanishing	Glands: shrinking/vanishing	2.1.1 Mild = G1 (1–30%)
		Lamina propria: fibrosis	Lamina propria: fibrosis	2.1.2 Moderate = G2 (31–60%)
				2.1.3 Severe = G3 (>60%)
	2.2 Metaplastic	Intestinal metaplasia	Intestinal metaplasia	2.2.1 Mild = G1 (1–30%)
			Pseudopyloric metaplasia	2.2.2 Moderate = G2 (31–60%)
				2.2.3 Severe = G3 (>60%)