ORIGINAL ARTICLE

A follow up model for patients with atrophic chronic gastritis and intestinal metaplasia

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Aim: To devise a follow up model for patients with gastric cancer associated lesions, such as atrophic chronic gastritis (ACG) and intestinal metaplasia (IM).

Methods: Cohort study of 144 patients, followed for a minimum of one year, in whom at least two upper gastrointestinal endoscopic biopsies in flat gastric mucosa provided a diagnosis of ACG, IM, or low grade dysplasia (LGD).

Results: Of those diagnosed with ACG at first endoscopic biopsy (entry biopsy), 12% progressed to LGD in outcome biopsy, as did 8% of those with type I IM, 38% with type II or III IM, and 32% with LGD. Type of IM at entry independently predicted progression to LGD and cancer. Type II and III IM had a higher rate of progression to LGD than type I IM, which showed an indolent behaviour similar to ACG. Patients with type II or III IM were at higher risk for development of dysplasia, and 7% of patients with type III IM at first biopsy progressed to high grade dysplasia (HGD), whereas no cases of ACG or type I/II IM progressed to HGD during the first three years.

Conclusion: Patients with ACG or IM could possibly be allocated to different management schedules, based on differences in rate and proportion of progression to LGD or HGD. Less intensive follow up (two/three yearly with "serological evaluation" (pepsinogen)) may suit those with ACG or type I IM. Patients with type III IM may benefit from six to 12 monthly improved endoscopic examination (magnification chromoendoscopy).

The prognosis of gastric carcinoma depends on its stage at diagnosis.¹ A cascade of mucosal lesions, from chronic gastritis, atrophy, intestinal metaplasia (IM), to dysplasia has been consistently identified, at least for Lauren's intestinal subtype of gastric cancer.^{2–4}

In the Vienna classification of 1998, low grade dysplasia (LGD) was considered to be itself a non-invasive neoplasm, and not just a premalignant lesion. It is agreed that patients with these lesions should at least be followed up, because this might lead to the early diagnosis of gastric carcinoma.⁵ Other lesions, such as atrophy, or IM, have been considered as non-dysplastic, but associated with cancer. Until now, no definitive proposals have been made for the management of these patients. There is no consensus on treatment for these patients or on the follow up schedule or its cost effectiveness.

"The prognosis of gastric carcinoma depends on its stage at diagnosis"

In our present study, we describe a cohort of patients in whom associated lesions or LGD have been diagnosed. Similar to current practice in Barrett's oesophagus⁶ and colon polyps,⁷ we hypothesised that the follow up of these patients could be scheduled according to the most severe lesion, in terms of gastric carcinogenesis, found at baseline.

We aimed to devise and validate a follow up model, based on the allocation of patients to different diagnostic methods and schedules.

METHODS

Type of study, clinical variables, and patients

A retrospective cohort study was performed on patients who had been followed up at our institution since at least July 2000. By the end of 2002, those in whom at least two upper

gastrointestinal endoscopic biopsies of flat gastric mucosa had been carried out were included in our analysis ($n = 144$). At first biopsy, the gastric mucosal changes were LGD, IM, or atrophic chronic gastritis (ACG). In all patients, a minimum of two endoscopic biopsies had been performed, although 40% of patients had at least three biopsies, and more than 15% of patients had more than four biopsies performed. The maximum number of biopsies was eight.

Because these lesions, particularly atrophic changes and IM, are expected to be multifocal, sampling error can occur. Therefore, we only considered progression to more severe lesions. Pairs of endoscopic biopsies ($n = 239$) were considered, including intermediate biopsies (between the first and last).

Biopsies were defined as entry biopsies (first or intermediate) and outcome biopsies (second or last). The diagnoses of the entry biopsies were: ACG ($n = 58$); type I complete IM ($n = 62$); type II or III, incomplete IM ($n = 57$); and LGD ($n = 62$). For patients with more than two biopsies, it was possible to measure the time or duration of known disease, because we had at least one previous endoscopic biopsy ($n = 47$). No significant differences were found according to the histopathological lesion in the entry biopsy. For patients whose most severe lesion was ACG or type I IM, the median (minimum–maximum) time of disease was 12.5 months (range, 3.2–36.2). For those patients with type II or III IM, the median time of follow up before first biopsy was 16.8 months (range, 2.5–25.2) and 17.0 months (range, 6.0–188.7) for those with LGD.

Abbreviations: ACG, atrophic chronic gastritis; HGD, high grade dysplasia; IM, intestinal metaplasia; LGD, low grade dysplasia

Helicobacter pylori infection was diagnosed in 53% ($n = 76$) of patients at entry. No previous eradication treatment had been carried out in these patients. These patients had a median age (defined as that at first endoscopic evaluation with biopsy) of 55 years (range, 42–74), and 48% of them were men. There were no significant differences with regard to age, sex, or prevalence of *H. pylori* infection in the different groups of patients.

Our study was fully approved by the ethical committee of the Instituto Português de Oncologia–Centro do Porto, Porto, Portugal. Patients' data were analysed after informed consent was given.

Histological classification

The endoscopic biopsies were assessed for histopathological variables. We performed a retrospective analysis, so that a standardised endoscopic protocol was not possible to define. Two pathologists (CL, MG) reviewed all the slides. Agreement was achieved in 85% of cases. In case of disagreement, a consensus was obtained according to the Vienna classification. Lesions such as chronic gastritis, atrophy, and IM were considered as non-dysplastic but possibly associated with gastric cancer, according to the Vienna classification. Chronic gastritis was defined as a chronic diffuse inflammatory infiltrate with lymphocytes and plasmocytes, expanding the lamina propria and epithelium, with no atypical cellular nuclei. Atrophy was defined as the disappearance of the normal glands in a certain area of the stomach, and classified as mild or severe according to the Sydney classification.⁸ IM (fig 1) was classified as complete (type I) and incomplete (types II and III), according to sulfomucin or sialomucin staining.⁹ Gastric dysplasia, classified as low grade (fig 2) or high grade (fig 3), and

Figure 1 Histopathological evaluation of an endoscopic biopsy showing a case of incomplete intestinal metaplasia (haematoxylin and eosin staining; original magnification, $\times 200$).

Figure 2 Histopathological evaluation of an endoscopic biopsy showing low grade dysplasia (haematoxylin and eosin staining; original magnification, $\times 200$).

invasive carcinoma were defined according to the Vienna classification.⁵ Each individual case was classified as the most severe lesion found at one endoscopic biopsy, in accordance with the gastric carcinogenesis cascade into carcinoma. Modified Giemsa staining and specific immunohistochemistry using anti-*H. pylori* antibodies (rabbit polyclonal antibody; Novocastra Laboratories, Newcastle upon Tyne, UK; and Vectastain Elite ABC kit; Vector Laboratories, Peterborough, UK) were used to identify *H. pylori* in the gastric biopsies.

Statistical analysis

Statistical Package for Social Sciences (SPSS 11.0 Package Facility®) was used for data support and analysis. Non-parametric tests (Pearson's χ^2 and Kruskal-Wallis tests) were

Figure 3 Histopathological evaluation of an endoscopic biopsy showing high grade dysplasia (haematoxylin and eosin staining; original magnification, $\times 200$; inset, $\times 400$).

used to evaluate differences in outcome proportions (at least LGD or at least HGD), and to assess the patients' characteristics, such as age, sex, *H pylori* infection prevalence, and duration of disease. Survival analysis was performed to define the rate of progression to outcome at first year of follow up and on a yearly basis (at third year of follow up). For survival analysis, the most severe lesion found at baseline biopsy was defined as the inclusion criterion, and time between endoscopic biopsies as time to event. Outcome was considered as progression to lesions as severe as LGD. For estimation of risk, a multivariate analysis of progression to dysplasia was performed with the use of the Cox regression model, with both forward stepwise inclusion of factors, and an inclusion criterion of $p \leq 0.05$.

RESULTS

Progression to dysplasia

Table 1 describes the 239 pairs of biopsies in the 144 patients analysed in our study.

According to the most severe histological diagnosis found at first endoscopic biopsy (entry biopsy), the proportion of cases that progressed to LGD in the outcome biopsy was assessed. In 11 patients, the outcome was HGD ($n = 7$) or invasive carcinoma ($n = 4$). All carcinomas were early forms. All these patients had either incomplete IM or LGD in their entry biopsy, as did 31 of the 43 patients who progressed to lesions as severe as LGD ($p = 0.001$). In contrast, only 12 patients with LGD had had complete (type I) IM or ACG as the worst histological diagnosis in their entry biopsy. In other words, from all cases of ACG in the entry biopsy, 12% progressed to LGD, as did 8% of those in which the first biopsy revealed ACG with type I IM, whereas 37% of patients with incomplete IM (22 of 59) progressed to LGD ($p < 0.001$).

Rate of progression

Figure 4 shows the rate of progression to lesions as severe as LGD according to the diagnosis at entry biopsy. Type III and type II IM have a higher rate of progression than type I IM, which behaved in an indolent manner, similar to ACG (Breslow's test; $p < 0.001$; table 2). In the first and third years the rate of progression to LGD was 5% and 13%, respectively, for those patients with ACG without metaplasia; 4% and 7% for complete type I IM, respectively; 11% and 33% for type II IM, respectively; and 22% and 39% for type III IM, respectively. Median time to outcome was 34.6, 32, 15, and 11.3 months for ACG without metaplasia, type I, type II, and type III IM, respectively.

Progression to more severe lesions such as HGD and invasive carcinoma occurred in the first year after diagnosis of type III IM and LGD (Breslow's test; $p = 0.001$). Fifteen

per cent of individuals with type III IM at their first biopsy progressed to HGD in the first year. In addition, 7%, 11%, and 14% of those with LGD progressed to HGD during the first year, the second, and the third year, respectively. No cases with ACG, complete IM, or type II IM progressed to HGD during the first three years.

Risk estimates

Two groups of patients were now considered for further analysis: (1) those with ACG without IM or with type I complete IM ($n = 110$); and (2) those with incomplete (type II or type III) IM ($n = 57$).

In our sample, age (hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.97 to 1.05), male sex (HR, 1.18; 95% CI, 0.48 to 2.87), and *H pylori* infection (HR, 0.73; 95% CI, 0.28 to 1.92) were not independent factors for progression (as had been expected and stated in the Methods). As for time under follow up for those patients with more than two biopsies ($n = 47$), no increase risk was clearly defined (HR, 0.93; 95% CI, 0.78 to 1.11).

The type of histopathological lesion found at entry biopsy was the only variable found to be independently related to progression to dysplasia in multivariate analysis. Those patients whose entry biopsy revealed either type II or type III IM had a four times greater risk of developing dysplasia than did those with ACG without metaplasia, or with type I complete IM (HR, 4.64; 95% CI, 1.83 to 11.81).

DISCUSSION

Several studies have highlighted the need for intensive follow up protocols in patients with dysplasia. Namely, HGD may represent a synchronous lesion that can quickly develop into gastric invasive carcinoma, and it should therefore be treated as carcinoma.^{5 10-16} Although low grade gastric epithelial dysplasia is now considered to be a true premalignant, non-invasive low grade tumour, questions still remain on the best management for patients with these lesions. Because these lesions may progress to early forms of carcinoma, some authors have suggested an intensive follow up, even though some will never progress to invasive carcinoma.¹⁰⁻¹²

However, for patients with lesions such as atrophy or IM several issues remain unanswered, such as the need and cost effectiveness of follow up.¹⁷ Although several studies have investigated the issue of progression of associated lesions into gastric cancer, the cumulative results remain inconclusive and sometimes controversial. The great variability that exists in the interpretation of the concept of atrophy, the patchy distribution of IM (which results in sampling error), and differences in endoscopic and diagnostic protocols may account for some of the discrepancies, in addition to a lack of consistency among studies, namely concerning progression

Table 1 Histological lesions found at outcome endoscopic biopsy according to histopathological evaluation at baseline or entry biopsy ($n = 239$)

	Outcome						Total
	ACG	IM			LGD	HGD/Ca	
		Type I	Type II	Type III			
First biopsy							
ACG	33 (57%)	6 (10%)	12 (21%)		7 (12%)		58
IM							
Type I	8 (13%)	24 (39%)	25 (41%)		5 (8%)		62
Type II	7 (15%)	13 (27%)	13 (27%)		14 (29%)	1 (2%)	48
Type III			1 (10%)	2 (20%)	4 (40%)	3 (30%)	10
LGD	13 (21%)	15 (24%)	13 (21%)	1 (2%)	13 (21%)	7 (11%)	62
Total	60	58	64	3	43	11	239

ACG, atrophic chronic gastritis; IM, intestinal metaplasia; LGD, low grade dysplasia; HGD/Ca, lesions as severe as high grade dysplasia or high grade non-invasive neoplasia.

Figure 4 Progression into lesions as severe as low grade dysplasia (LGD) in the outcome biopsy according to the diagnosis on the entry biopsy (Breslow's test; $p = 0.009$). The time to event (in months) was the time between the entry and outcome biopsies. Type III and II intestinal metaplasia (IM) show higher rates of progression to LGD in the outcome biopsy. Median time to lesions as severe as LGD is 34.6, 32, 15, and 11.3 months for atrophic chronic gastritis (ACG), type I, type II, and type III, respectively.

or reasonable regression. A matter of concern may also be variability in the assessment of the severity of dysplasia.¹⁸⁻²⁰ The classification into LGD and HGD may reduce inter-observer disagreement, as stated in the Vienna classification,⁵ and may simplify outcome assessment in clinical practice.

In our present study, we aimed to clarify some of the issues reported before, and to define a protocol schedule based on the assumption that the prognosis of patients could be defined by their lesions at diagnosis. Even though our analysis is retrospective, and no systematic endoscopic protocol was under evaluation, no significant differences existed in age, sex, *H pylori* infection prevalence, and time of follow up between cases according to the histological diagnosis of the first lesion. At entry or baseline biopsy, all lesions (ACG, complete IM, incomplete IM, or LGD) were equally prevalent. Because of the problems stated previously, we decided to investigate the progression of lesions only, because regression may be overestimated.

In our group of patients we found that only histological evaluation was independently related to progression to gastric neoplastic lesions. In those patients in whom a first biopsy showed either ACG or IM type I, no cases of HGD or

cancer occurred during the following three years, and less than 10% progressed to LGD. However, incomplete IM, namely type III, did progress to lesions as severe as LGD, and even to HGD, mostly in the first years after diagnosis.

These differences offer us the opportunity to improve follow up protocols and to study treatment aimed at inhibiting progression through intervention targeting previously identified aetiological factors.¹⁵⁻¹⁷

The prediction of the progression of these lesions according to the severity at baseline has been referred to by others.²¹⁻²³ In addition, Lahner and colleagues²⁴ suggested that the follow up of patients with body predominant atrophic gastritis need not to be earlier than four years after diagnosis, stating that this interval is satisfactory for the detection of potential neoplastic lesions. More than 10 years ago, type III IM²¹⁻²⁵⁻²⁷ was stated as a lesion with an increased risk for dysplasia and cancer, and it was suggested that its follow up should be intensive.

However, this proposal is very restricted because it does not take into account the individual response and ecological variation. Other factors, such as genetic polymorphisms, diet, etc were not addressed. In our study, *H pylori* infection was

Table 2 Rate of progression at first and third year after diagnosis according to lesion found at entry biopsy

	Rate of progression (95% CI)	
	12 months	36 months
ACG	5.4% (2.4% to 8.5%)	13.5% (7.4% to 19.7%)
Type I IM	4.1% (1.2% to 7.0%)	7.4% (3.1% to 11.7%)
Type II IM	11.1% (6.4% to 15.9%)	32.7% (24.0% to 41.3%)
Type III IM	22.2% (8.3% to 36.0%)	38.8% (20.8% to 56.8%)

Type III and II IM found at entry biopsy progressed at a higher rate than type I IM or ACG, both at 12 and at 36 months after their diagnosis at baseline or entry biopsy.
ACG, atrophic chronic gastritis; CI, confidence interval; IM, intestinal metaplasia.

found not to be an independent risk factor for the progression of lesions. *Helicobacter pylori* is a risk factor for cancer, because it causes chronic gastritis and, very early in the carcinogenesis cascade,² leads to atrophy. However, no agreement exists on its role in the progression of these lesions, although some studies have shown that *H pylori* eradication can prevent or revert atrophy,^{28–29} but there has been no consistency on the reversibility of IM or dysplasia after eradication treatment.^{30–33}

“In those patients in whom a first biopsy showed either atrophic chronic gastritis or intestinal metaplasia type I, no cases of high grade dysplasia or cancer occurred during the following three years, and less than 10% progressed to low grade dysplasia”

As stated before, the diagnosis of these lesions relies on the histological examination of endoscopic biopsies. Conventional endoscopy shows neither a reasonable inter-observer agreement nor a good correlation with histology, and is not well accepted by patients, particularly those who are asymptomatic. The use of new endoscopic methods, such as magnification chromoendoscopy, could increase the diagnostic yield for these areas.³⁴ A reasonably reproducible classification of mucosal patterns has been developed, which appears to be valid for the diagnosis of IM and at least for the exclusion of dysplasia.³⁴ It may be useful for the diagnosis and follow up of these patients because it has a very high negative predictive value. Nonetheless, endoscopic examination throughout the entire gastric cavity may still fail to diagnosis dysplasia and cancer.

The measurement of serum pepsinogen I (PGI) and PG II concentrations, to estimate the PGI/II ratio, can provide a “serological biopsy” for gastric mucosa.³⁵ This technique is particularly useful because of its high negative predictive value, even in selected groups of patients.

Therefore, we may be able to diagnose IM with new endoscopic methods and to exclude severe lesions such as dysplasia by combining these methods with non-invasive serological techniques.

As improvements in diagnosis are made, we could plan the follow up of patients based on their gastric mucosal histology, as we do after the resection of polyps in the colon or in Barrett's oesophagus. A better allocation of resources and a more patient friendly follow up schedule could be designed.

It seems reasonable to propose that patients with ACG without metaplasia or those with completely differentiated IM could be allocated to a less intensive follow up protocol—for example, at a two or three yearly interval, with serological

evaluation. In contrast, in those patients with previously report LGD or incomplete IM (namely type III), a “hunt” for high grade neoplasia should be performed. These patients should be submitted each six to 12 months for evaluation with both improved endoscopic examination (with magnification chromoendoscopy) and the pepsinogen test.

Further controlled longterm prospective studies and guidelines are needed to address the validity of this model. Such improvements may allow better measurements of disease progression or regression in intervention studies,³⁶ and may provide new insights into gastric carcinogenesis.

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Take home messages

- Because of differences in the rate and proportion of progression to low grade dysplasia (LGD) or high grade dysplasia, patients with atrophic chronic gastritis (ACG) or intestinal metaplasia (IM) could possibly be allocated to different management schedules
- A less intensive follow up regimen (two/three yearly with “serological evaluation” (measurement of serum pepsinogen)) may be suitable for those with ACG or type I IM, which behave in a more indolent manner
- Because of the more aggressive behaviour shown by type III IM and LGD, patients with these lesions may benefit from six to 12 monthly improved endoscopic examination (magnification chromoendoscopy)

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