Original article

A micrometric classification of intramucosal carcinomas of the stomach

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Abstract

Background. The aim of this study was to assess whether the results of micrometric measurements could be correlated with the macroscopic-endoscopic classification of intramucosal carcinomas of the stomach.

Methods. The thickness of 86 consecutive intramucosal gastric carcinomas (IMGCs) was micrometrically assessed. IMGCs having more than twice the thickness of the non-involved gastric mucosa (NIGM) were regarded as protruding (type I) and those having twice or less of the thickness of the NNGM, as non-protruding (type II). Non-protruding IMGCs were subclassified as elevated (thicker than NNGM, or type IIa), flat (the same thickness as NNGM, or type IIb), and depressed (thinner than NNGM, or type IIc).

Results. Only 9.3% ($n = 8$) of the 86 IMGCs were protruding and 90.7% ($n = 78$) were non-protruding. Of the 78 non-protruding IMGCs, 46.2% ($n = 36$) were elevated (type IIa), 38.5% ($n = 30$) were flat (type IIb), and the remaining 15.4% ($n = 12$) were depressed (type IIc). A low correlation was found when the micrometric and a similar gross classification were compared. Protruding and elevated IMGCs were often histologically of intestinal type (60.3%), whereas flat and depressed IMGCs were often of diffuse type (73.9%).

Conclusion. Tumor differentiation may be related to the micrometric profile of the tumor. Non-protruding IMGCs (type II) may expand laterally, without “becoming” protruding and without invading the submucosal layer.

Key words Intramucosal carcinoma · Stomach · Micrometry

Introduction

Based on the degree of tumor penetration, adenocarcinomas of the stomach are classified as early and advanced carcinomas [1,2]. In early carcinomas, the tumor invades the mucosa and may even invade the submucosa, but not beyond. When the tumor invades

beyond the lower limit of the submucosa, carcinomas are regarded as advanced.

In 1993, the Japanese Research Society for Gastric Carcinoma [3] proposed a macroscopic classification for early gastric carcinomas. The macroscopic appearance of early carcinomas was classified as: type I carcinoma (“protrusion into the gastric lumen is eminent”), type II early gastric carcinoma (“unevenness of the surface is inconspicuous”), and type III excavated early gastric carcinoma (“an excavation of the gastric wall is prominent”). The superficial type was subdivided into type IIa (elevated type; “the surface is slightly elevated”), type IIb (flat type; “almost no recognizable elevation or depression from the surrounding mucosa”), and type IIc (“the surface is slightly depressed”) [3]. Two combined macroscopic types often occur in the same lesion.

A histologic classification similar to the macroscopic classification has not yet been proposed.

In a previous publication [4], we reported the results of micrometric measurements in gastric adenomas. Quantitative assessment of the thickness of the lesions in relations to the non-involved gastric mucosa (NIGM) permitted the accurate differentiation of protruding (type I) from non-protruding or superficial (type II) gastric adenomas.

The aim of the present work was to explore the possibility of histologically classifying intramucosal gastric carcinomas (IMGCs) according to their micrometric thickness.

Material and methods

Filed sections from 86 gastrectomy specimens with an intramucosal carcinoma from patients seen during a 10-year period (between 1988 and 1998 [5]) at the Department of Pathology, University of Florence, were investigated.

The tissue blocks were carefully oriented before embedding, with the aim being to obtain perpendicular sections (to the muscularis mucosae). Semi-stepwise sections were made. No fewer than three sections per block were available.

With the aid of a calibrated ocular microscale, the shortest linear distance between the surface epithelium and the upper border of the muscularis mucosae was assessed in both the non-involved gastric mucosa (NIGM) and the intramucosal gastric carcinoma (IMGC). As the height in both the IMGC and the NIGM could vary in individual sections, measurements were carried out in areas having the maximal height.

Definitions

Non-involved gastric mucosa (NIGM) was regarded as the adjacent mucosa that was either histologically normal or atrophic, with or without chronic inflammation and/or with or without intestinal metaplasia.

Five measurements were done in well oriented sections in the NIGM and in the IMGC. The mean height of the NIGM in individual cases was multiplied by a factor of two. The result was regarded as the limit between protruding IMGC (type I, with mean values surpassing two times those of NIGM) and superficial IMGC (type II, with mean values being twice or less those of NIGM). Superficial IMGCs (type II) were subdivided (Fig. 1) into:

- Superficial elevated IMGCs, thicker than NIGM (type IIa)
- Superficial flat IMGCs, with a similar thickness to NIGM (type IIb), and
- Superficial depressed IMGCs, thinner than NIGM (type IIc)
- Excavated IMGCs (type III) were those IMGCs which were below the level of the adjacent NIGM's muscularis mucosae.

The width of each IMGC was also recorded, with the aid of a calibrated ocular micrometer.

The mean difference between the measurements of the NIGM and of the IMGCs in individual specimens was calculated, and the results were analyzed by the McWhitney non-parametric method.

When all the histo-micrometric results had been obtained, the results of the gross classification obtained at the time of surgical removal were de-coded.

Results

Patients

Of the 86 patients, 81.4% ($n = 70$) were men and the remaining 18.6% ($n = 16$) were women. Of the 86

Fig. 1. Micrometric types of intramucosal gastric carcinomas (IMGC; diagonally shadowed areas). Non-involved gastric mucosa (NIGM) was regarded as the adjacent mucosa that was either histologically normal or atrophic, with or without chronic inflammation and/or with or without intestinal metaplasia. The mean thickness of the NIGM (from the muscularis mucosae [m.m.] to the luminal border) was multiplied by a factor of two. The result was regarded as the limit between protruding IMGC (type I, with mean values surpassing two times those of NIGM, dotted lines) and superficial IMGC (type II, with mean values being twice or less those of NIGM). Superficial IMGCs (type II) were subdivided into: superficial elevated IMGCs (thicker than NIGM, or type IIa), superficial flat IMGCs (with a similar thickness to NIGM, or type IIb), and superficial depressed IMGCs, (thinner than NIGM, or type IIc). Excavated IMGCs (type III) were those IMGCs which were below the level of the adjacent NIGM's m.m.

patients, 9.3% ($n = 8$) were younger than 59 years of age, 44.2% ($n = 38$) were aged 60–69 years, 37.2% ($n = 32$) were aged 70–79 years, and the remaining 9.3% ($n = 8$) were older than 80 years of age.

Thickness of non-involved gastric mucosa (NIGM)

The median thickness of the NIGM in the 86 patients was 15.7 μm (range, 5–30 μm). The median thickness in the NIGM in protruding (type I) IMGCs was 14.2 μm (range, 12.3–18.3 μm); in the 12 superficial elevated (type IIa), it was 15.3 μm (range, 5–30 μm), in the 30 superficial flat (type II b), it was 14.9 μm (range, 13.3–

Table 1. Median thickness (in μm) and median width (in mm) as well as ranges (in parentheses) in 86 intramucosal gastric carcinomas (IMGCs)

	Type I (<i>n</i> = 8)	Type IIa (<i>n</i> = 36)	Type IIb (<i>n</i> = 12)	Type IIc (<i>n</i> = 30)
Thickness of NNGM	14.2 μm (12.3–18.3 μm)	15.3 μm (5–30 μm)	14.9 μm (13.3–17.3 μm)	16.9 μm (9.3–26.7 μm)
Thickness of IMGCs	42.5 μm (26.3–68.7 μm)	20.3 μm (9–57.7 μm)	15.2 μm (13–18 μm)	12.3 μm (8.3–18.3 μm)
Width of IMGCs	22.1 mm (8–39 mm)	15.8 mm (9–33 mm)	17.3 mm (7–30 mm)	14.8 mm (7–45 mm)

The maximal expected thickness for classifying types I and II IMGCs was calculated by multiplying the thickness of the non-neoplastic gastric mucosa (NNGM) in individual cases by a factor of two. IMGCs with a measured thickness exceeding two times the thickness of the NNGM were regarded as type I (protruding) and those not exceeding that limit as type II (non-protruding)

17.3 μm), and in the superficial depressed (type IIc), it was 16.9 μm (range, 9.3–26.7 μm).

Thickness of intramucosal gastric carcinomas (IMGCs)

The results in Table 1 show that 8 of the 86 IMGCs (9.3%) were micrometrically protruding (type I) and the remaining 78 (90.7%) were non-protruding or superficial (type II). No micrometric type III was recorded.

The median thickness in the 86 IMGCs was 18.9 μm (range, 8.3–68.7 μm). Table 1 shows that in the 8 protruding IMGCs (type I), the median thickness was 42.5 μm (range, 26.3–68.7 μm).

In the 78 non-protruding IMGCs (type II) the median thickness was 15.6 μm (range, 8.3–57.7 μm). When the various subtypes were analyzed, it was found that the median thickness in the 36 superficial elevated IMGCs (type IIa, i.e., thicker than NIGM) was 20.3 μm (range, 9–57.7 μm). In the 12 superficial flat IMGCs (IIb, or with similar values to those recorded in the NIGM), the median thickness was 15.2 μm (range, 13–18 μm). In the 30 superficial depressed IMGCs (type IIc or thinner than the NIGM), the median thickness was 12.3 μm (range, 8.3–18.3 μm).

The difference between the mucosal thickness in protruding (type I) and superficial types (type II) IMGCs and their corresponding NIGMs was significant ($P < 0.5$). Similarly, differences between the mucosal thickness in superficial elevated (type IIa), superficial flat (type IIb), and superficial depressed IMGCs (type IIc) were significant ($P < 0.05$).

IMGC thickness and histologic phenotype

Results showed that of the 86 IMGCs, 63 were of intestinal type and the remaining 23 of diffuse type.

Of the 63 intestinal type IMGCs, 60.3% ($n = 38$) were protruding and elevated (micrometric types I and IIa),

and of the 23 diffuse type IMGCs, only 26.1% ($n = 6$) were protruding and elevated. Of the remaining 25 intestinal type IMGCs, 39.7% ($n = 10$) were flat and depressed (micrometric types IIb and IIc), but 73.9% of the remaining 17 diffuse type IMGCs were flat and depressed.

Thus, protruding and elevated IMGCs were often of histologic intestinal type, whereas flat and depressed IMGCs were often of histologic diffuse type ($P < 0.05$).

Comparison of micrometric and macroscopic assessments

A correlation between lesions having a single macroscopic IMGC (either type I, IIa, IIb, IIc, or III) and micrometric type I, IIa, IIb, or IIc, was found in only 26% (13/50) of the lesions. In the remaining 35 composite macroscopic types (IIa + IIb, IIa + IIc, IIb + IIc, IIb + III, and IIc + III) a comparison with micrometric types was difficult, because the latter were registered as belonging to one particular type.

Width of intramucosal gastric carcinomas (IMGCs)

The median width of the 86 IMGCs was 16.2 mm (range, 7–39 mm). In the 8 protruding IMGCs, the median width was 22.1 mm (range, 8–39 mm).

The median width of the 78 non-protruding IMGCs (type II) was 15.5 mm (range, 8.3–39 mm). In the 36 superficial elevated IMGCs (type IIa), the median width was 15.8 mm (range, 9–33 mm), in the 12 superficial flat IMGCs (type IIb), it was 17.3 mm (range, 7–30 mm), and in the 30 superficial depressed IMGCs (type IIc), it was 14.8 mm (range, 7–45 mm).

Discussion

Based on endoscopic and/or on gross examinations of resected stomachs, the Japanese Research Society

for Gastric Carcinoma has proposed a macroscopic classification of early gastric carcinomas [6]. Type I is a "tall, nodular or polypoid lesion than often shows an irregular surface"; type II lesions are further subdivided into three types. "Type IIa lesions (superficial and slightly elevated type), consist of a slight elevation of the lesion approximately twice or greater than the thickness of the mucosa up to 5 mm". "Type IIb lesions (superficial and flat type) are approximately level with the surrounding mucosa, and type IIc lesions (superficial and slightly depressed type), have a shallow depression." [6].

In the present work, we studied the thickness of intramucosal gastric carcinomas (IMGCs) by micrometry. The values obtained were compared with the thickness of non-involved gastric mucosa (NIGM) in individual cases. Because measurements of the NIGM demonstrated wide individual variations in thickness, micrometric IMGC values were considered valid only when the height of the NIGM in individual cases was known.

With micrometry, it was possible to differentiate two types and three subtypes of non-protruding IMGCs. Micrometric results showed that 9.3% of the IMGCs were type I, 41.9%, type IIa; 13.9%, type IIb; and 34.9%, type IIc. Thus, more than 90% of the lesions fulfilled the micrometric criteria of non-protruding IMGCs (type II).

When lesions having a single macroscopic type were considered ($n = 50$) the correlation between the micrometric and the macroscopic classifications was low (26%). Apparently the micrometric and the macroscopic classifications are non-concordant and independent.

The macroscopic classification of early gastric cancer is based on visual empirical interpretation and judgment, both subjective assessments much influenced by the personal experience of the observer. The descriptive characteristics for each of the macroscopic types [3] are vague and may give rise to different individual interpretations. Actual measurements have not been reported.

Despite these limitations, the macroscopic classification (mainly related to the thickness of the lesions) has attracted the interest of endoscopists [7,8], because, in their experience macroscopic types IIc and III may be associated with a carcinoma invading the submucosal layer or beyond. Thus, the macro-structural outline of the neoplastic lesions appears to be an important parameter in predicting submucosal invasion in early neoplasias in the stomach [7,8].

A predictive classification of gastric intramucosal carcinomas based on micrometric-structural outlines has not yet been entertained.

In the present work we found that protruding and elevated IMGCs (types I and IIa) were often of

intestinal type, whereas flat and depressed IMGCs (types IIb and IIc) were often of diffuse type. These results suggest that there may be a relationship between the micrometric-structural profile of IMGCs and their histological phenotype. In this connection, it may be of interest to mention that Ikeda et al. [9] demonstrated that the frequency of undifferentiated type early gastric carcinoma increased with tumor progression.

Micrometric studies also suggested that non-protruding IMGCs (superficial or type II) may expand laterally — in an intramucosal fashion — without "becoming" protruding (i.e., exophytic) and without invading the submucosal layer.

The objective micrometric assessment reported here is easy to perform. Nonetheless, the significance of the present micrometric classification as a predictor of tumor progression remains to be elucidated. In this endeavor, the method is being applied to routine materials, not only for adenomas and intramucosal carcinomas of the stomach but also for adenomas and intramucosal carcinomas of the colorectal mucosa [10].

Neoplasias in the gastro intestinal tract evolve through a series of molecular events, which include mutations of the *APC* gene in chromosome 5, and of the *ras* proto-oncogenes in chromosome 12 and deletions of the suppressor gene *p53* in chromosome 17, of the *DCC* suppressor gene in chromosome 18, and of the presumptive suppressor gene *MCC*. However, those molecular events do not explain why some IMGCs grow in a protruding (type I) and others in a lateral, superficial, non-protruding fashion (types II). The cause(s) of this behavior remains elusive.

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