Gastrointestinal epithelial neoplasia

We can see only what we already know

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Over the past two decades we have learnt much from Japanese endoscopists about how to recognize and how to endoscopically treat the early stages of gastrointestinal neoplasia. The Japanese are ahead of us not only because of earlier use of technical progress and because of their endoscopy skill but also for their consistent and much more precise classification with practical clinical (i.e. therapeutical) consequences, thus significantly influencing daily routine practice. Dr. Urban et al. having published their experience with endoscopic diagnosis and the treatment of superficial non-polypoid neoplasms in this issue of the Journal (19) have been much influenced by their Japanese colleagues, too, not only because of their close personal contacts and practical cooperation.

Unlike the positive influence of the East for endoscopy in the West, there have been several misunderstandings in histology descriptions, terminology and interpretation of microscopic findings between the West and the East. Both for endoscopy and histology, it holds true that we can see only what we already know (16). However, to fulfil this wisdom it is necessary to speak the same language. Several consensus meetings have been organized recently to bring both views, Eastern and Western, closer together.

The greatest merit belongs to Professor Mařatka for his continuous effort to unify basic endoscopy terminology (8). An original Japanese macroscopic classification was applied for early gastric cancer first and then extended to superficial oesophageal carcinoma and early colorectal neoplasia in the late seventies. The macroscopic classification of early neoplasia in the digestive tract was based on the gross evaluation of the extent of elevation and depression limited to the mucosa and submucosa (12). The advanced cancer, coming out from the Borrmann classification published in 1926, has been classified into type 1 (protuberant, polypoid, usually attached on a wide basis), type 2 (ulcerated with sharply demarcated and raised margins), type 3 (ulcerated, infiltrating without definitive limits), type 4 (non-ulcerated, diffusely infiltrating without definite limits) and type 5 (unclassifiable) (12,17). The Paris endoscopic classification of superficial neoplastic lesions (17) distinguishes polypoid and non-polypoid lesions. Polypoid lesions (0-I) can be protruded pendulated (0-Ip) or protruded sessile (0-Is). Non-polypoid lesions are divided into superficial slightly elevated (0-IIa), flat (0-IIb), superficial slightly depressed (0-IIc) and excavated type (0-III) (17). Several combinations in one lesion are possible (i.e. 0-IIa + 0-IIc, 0-I + 0-IIc. 0-IIc + 0-III etc.) (12). It has been advocated that the prefix "type 0" (0-I, 0-IIa etc.) be used to distinguish these early and superficial carcinomas from advanced cancer. However, in recent years it has become general practice to apply the classification to the endoscopic gross appearance of any tumour resembling early carcinoma, including adenoma/dysplasia and advanced cancer, and to omit using the prefix "0" (12). In the colon and rectum, a superficial elevated lesion greater than 10 mm is sometimes called a "laterally spreading tumour" (10), subclassified into homogenous granular, mixed-nodular and non-granular types. However, this term is based on an assumption about its growth pattern and should be separated from the macroscopic classification of gross morphologic appearance. In early gastric cancer type II-c is the most common, in colorectal adenomas and early cancer type I and II-a are mostly seen, types II-c, IIb and I are usually found in oesophageal superficial cancer (according to Japanese papers cited in ref. 12).

Recently, several papers have been published highlighting significant differences in histopathologic

interpretation of neoplastic proliferation of the gastrointestinal tract between Japanese and Western pathologists (18,20). To overcome these discrepancies the Vienna classification of gastrointestinal epithelial neoplasia was proposed in 1998 (14). The Vienna classification distinguished five groups: (1) negative for neoplasia/dysplasia, (2) indefinite for neoplasia/dysplasia, (3) non-invasive low-grade neoplasia (low-grade adenoma/dysplasia), (4) non-invasive high-grade neoplasia (high-grade adenoma/dysplasia, non-invasive carcinoma and suspicion of invasive carcinoma), and (5) invasive neoplasia (intramucosal carcinoma, submucosal carcinoma or beoynd) (14). There is some confusion in the use of the terms dysplasia and adenoma: in the West, protruded or slightly elevated noninvasive neoplastic lesions are called adenomas, while flat or depressed neoplastic noninvasive lesions are called dysplasia, although the terms "flat adenoma" and "depressed adenoma" are accepted and commonly used for discrete lesions. In the East, both types of lesions are called adenomas and described as protruding (polypoid), flat or depressed. In the Vienna consensus classification for intramucosal neoplasia, the terms adenoma and dysplasia are both replaced by "intraepithelial neoplasia" (7). Even after Vienna classification, there was area of disagreement in the differentiation of high-grade dysplasia versus invasive carcinoma between Western and Japanese pathologists. The major cause of these disagreements was that Japanese pathologists counted upon nuclear cytologic and glandular architectural abnormalities to diagnose "carcinoma" whereas Western pathologists considered the presence of invasion as the sine qua non of carinoma (20). Recently, Dixon (1) proposed revised Vienna classification, see Table 1. The most important change is moving the intramucosal carcinoma into group 4, together with high-grade adenoma/dysplasia and non-invasive carcinoma (carcinoma in situ) (1). The new system with markedly improved levels of agreement between Japanese and Western pathologists is based on clinically meaningful categories from which patient management options have been traditionally focused. The consensus terminology (17) makes a distinction between high-grade intramucosal neoplasia with no invasion of the lamina propria and high-grade intramucosal neoplasia with invasion of the lamina propria. The latter is called intramucosal carcinoma in the oesophagus or stomach. In the large bowel, the risk of nodal invasion is nil in this situation, and there is a tendency in the West to avoid the terminology "carcinoma" for lesions without submucosal invasion, because they are completely cured with local excision. Beyond this stage, all neoplastic lesions with invasion of the submucosa are called invasive carcinoma (1,7). The rate of lymph node metastasis is very low in mucosal cancers, 2 - 3 % for oesophageal and gastric cancer and nil for colorectal carcinoma, but becomes much higher in case of submucosal invasion namely 37 - 53 % for oesophageal, 14 - 20 % for gastric and 3 - 18 % for colorectal cancer (13). The name "de novo" cancer applies to small (often less than 5 mm), flat or depressed cancerous lesions, when there are no adenomatous glands in the operative specimen, suggesting that the carcinoma did not develop from an adenomatous or dysplastic precursor (17).

As the various types of superficial lesions reflect differences in expected depth of invasion, the Paris classification (17) is helpful when one has to decide

Table 1
The revised Vienna classification of gastrointestinal epithelial neoplasia.
Adopted from MF Dixon (ref. 1).

Category	Diagnosis	Clinical management
1	Negative for neoplasia	Optional follow-up
2	Indefinite for neoplasia	Follow-up
3	Mucosal low-grade neoplasia Low-grade adenoma Low-grade dysplasia	Endoscopic resection or follow-up
4	Mucosal high-grade neoplasia 4.1 High-grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ) 4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma	Endoscopic or surgical local resection
5	Submucosal invasion by carcinoma	Surgical resection

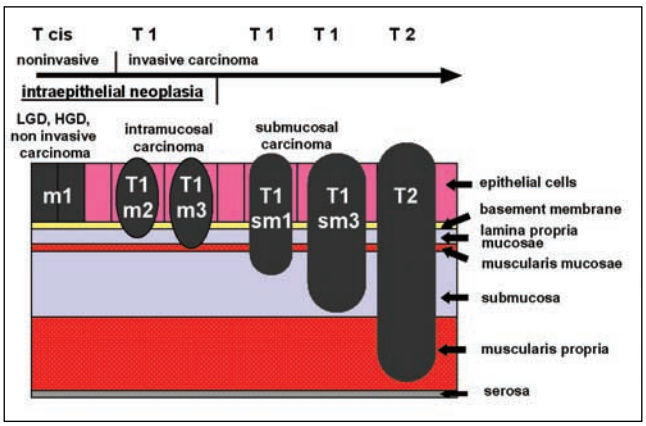

Figure 1
Classification (T stage) of gastrointestinal neoplasia.

between endoscopic treatment and surgical resection (2,3,11,12). There are three distinct layers in the mucosa, corresponding to the epithelium (m1), lamina propria (m2) and muscularis mucosae itself (m3), see Fig. 1. The submucosa is arbitrarily divided in three successive sectors of equivalent thickness (sm1, sm2, sm3). Cancer invading only the superficial levels (m1 + m2) can usually be treated successfully with endoscopic mucosal resection (5,15). Invasion into deep levels (sm2 + sm3) usually requires surgery for a cure. Middle level invasion (m3 + sm1) requires balancing clinical factors with surgery, which is preferred when a patient's status is appropriate. However, in a specimen obtained after endoscopic mucosal resection, the full thickness of the submucosa is not available, and this division is not valid. Therefore, invasion in the submucosa is measured with a micrometric scale, from the bottom of the mucosal layer. The cut-off limit between sm1 and sm2 is 500 µm for the oesophagus and stomach, and 1,000 µm for the colon and rectum (17). Choice of treatment will depend not only on the depth of invasion as assessed endoscopically or ultrasonographically but also on the overall size of the lesion, presence of non-lifting sign, and on general factors such as the patient's age and comorbid conditions (1-3,15).

Endoscopic staging can be improved by endoscopic ultrasonography, particularly with high frequency probes (20 MHz), see Fig. 2. Both endoscopic gross morphologic staging and endoscopic ultrasonography have their limits (3,10,17). Endoscopy tends to understage superficial lesions, ultrasonography tends to overstage them (21,22).

Despite all the progress there are some questions remaining to be answered. For instance, why are Japanese endoscopists after colonoscopy able to reduce the risk of subsequent colon cancer by more than 95 %, compared to the 50 - 76 % risk reduction achieved in the West? Perhaps the most likely explanation for the success of Japanese screening is that Japanese endoscopists are more aware of non-polypoid adenomas and remove flat and depressed premalignant lesions that may be unrecognized in the West (9).

Magnifying endoscopy with the help of contrast chromoendoscopy has considerably improved the analysis of the endoscopic morphology in metaplasia (especially in Barrett's oesophagus) and neoplastic lesions (6). The orifices of the glandular crypts are referred to as "pits" and the specific arrangement of the openings of the glands in various kinds of lesions is called the "pit pattern". Kudo et al. (4) divides the pit pattern of the large intestine into six groups: I (normal mucosa, roundish pits with a regular distribution), II (non-neoplastic hyperplastic, large star-like or onion-like pits), IIIL (tubular large pits), IIIS (tubular small pits), IV (branched or gyrus-like pattern) and V (VI irregular in shape, size and arrangement or VN nonstructural). The invasive pattern (irregular and distorted

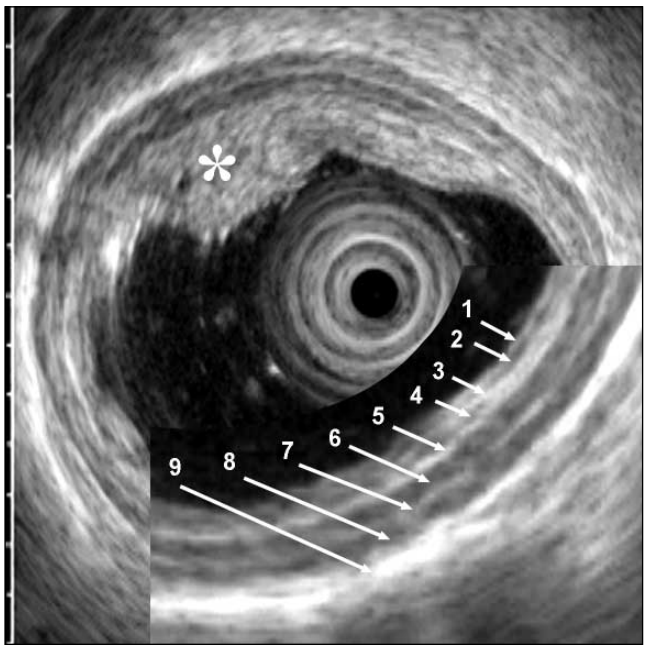

Figure 2
Adenocarcinoma in the Barrett's oesophagus. Endoscopic ultrasonography. EUS miniprobe 20 MHz (Olympus). The adenocarcinoma (asterisk) penetrates deep into the submucosa (T1 sm3).
Inlay: a 9-layer structure of the oesophageal wall in detail. Epithelium (1 and 2), lamina propria mucosae (3), muscularis mucosae (4), submucosa (5), circular (6) and longitudinal (8) part of the muscularis propria muscle with interface of connective tissue (7) and adventitia (9).

epithelial crests) suggests submucosal invasion in more than 1,000 μm (Matsuda et al. 2003, cited from ref. 17) and thus is not an appropriate indication for endoscopic treatment.

The awareness of non-polypoid lesions and significant technical progress (using chromoendoscopy, high-resolution/high-magnifying endoscopes and endoscopic ultrasonography etc.) have contributed to a higher detection rate of superficial oesophageal cancer, early gastric and early colorectal carcinoma.

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