Superficial oeso-gastric cancer and endoscopic mucosal resection : the pathologist's approach

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Abstract

Dysplasia is the earliest phase in cancer development that can be recognized by routine morphology. High grade dysplasia, intraepithelial carcinoma and in situ carcinoma are synonymous terms identifying a non invasive lesion whereas superficial (early) carcinoma is defined as a lesion confined to the mucosa or to the mucosa and sub-mucosa with or without lymph node metastasis. In the Vienna classification, proposed by a panel of Western and Japanese experts in 2000, the term "dysplasia" was replaced by the term "intraepithelial neoplasia" because this term defines more clearly the nature and the extent of the lesion, allowing recommendations for further diagnostic and therapeutic measures. Intraepithelial neoplasia is divided into two groups : low grade and high grade. Superficial oeso-gastric cancer can be treated by endoscopic mucosal resection (EMR). EMR provides specimens that must be handled and reported as surgical specimens by the pathologist. (Acta gastroenterol. belg., **2006**, 69, **316-320**).

Key words : superficial oeso-gastric cancer, early oeso-gastric cancer, dysplasia, intra-epithelial neoplasia, Vienna classification, endoscopic mucosal resection.

Early recognition and diagnosis of superficial gastrointestinal tumours is essential, particularly since recent developments in endoscopic techniques allow local endoscopic resection such as mucosectomy instead of heavy surgical procedures. Although histology plays a pivotal role in the diagnosis of superficial cancer, pathologists and clinicians still struggle with a host of various terms describing neoplastic or preneoplastic lesions along the gastrointestinal (GI) tract, such as dysplasia, intraepithelial neoplasia, superficial cancer, early cancer, intramucosal cancer, intraepithelial cancer,… This multiple terminology often hampers the discussion between pathologists and clinicians, leading to misunderstandings and either delayed or even erroneous diagnoses.

The aim of the present manuscript is to clarify the terminology and to facilitate its common use in order to allow the appropriate management of each pathological state. After a brief overview of the oesophageal and gastric mucosal and submucosal histology, the authors give a definition of each term used in the field, highlight the Vienna classification and finally summarize the work of the pathologist for endoscopic mucosal resection specimens.

1. Histology (1)

Oesophagus

The oesophagus is lined by squamous epithelium and in its lower part by a surface mucin-secreting columnar epithelium with underlying mucous glands. The mucosa is composed of a non-keratinizing stratified squamous epithelium with a subjacent lamina propria, which rests on the underlying muscularis mucosae composed of smooth muscle cells. The lower border of the squamous epithelium is irregular due to the presence of numerous papillae of vascularised connective tissue, part of the lamina propria, which projects upwards up to two-thirds of the total thickness of the epithelium. In addition to connective tissue, the lamina propria contains lymphocytes and occasional eosinophils. The muscularis mucosae has a variable pattern. It consists of isolated or irregularly arranged smooth muscle bundles rather than a continuous sheet. The muscularis mucosae is therefore not always easy to spot (Figs. 1A and B). In the lower part of oesophagus, it usually becomes a continuum of smooth muscle fibres. The submucosa contains the blood vessels and a ramifying lymphatic plexus in a network of loose connective tissue.

Stomach

The gastric mucosa is composed of a surface epithelium which consists of a single layer of columnar mucus-secreting cells. Gastric crypts (pits, faveoli) are lined by surface epithelium and are separated from each other by the lamina propria. In the gastric body, the superficial zone encompasses about 25% of the total thickness of the mucosa and the deep zone consists of straight tubules, which are perpendicular to the surface and extend from the base of the crypts to the muscularis mucosae. In the antral or pyloric region, the superficial zone forms 40% of the total mucosal thickness and the

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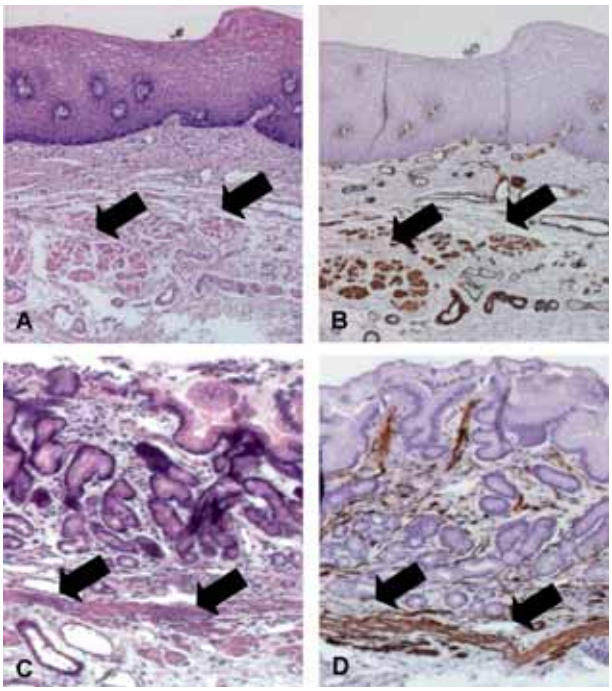

Fig. 1. — A-B. Mucosa and superficial submucosa of the superior part of the oesophagus. The muscularis mucosae is not easy to identify on haematoxylin-eosin stained sections (A) and is more obvious after immunohistochemical detection of actin (Arrows) (B).
C-D. Mucosa and superficial submucosa of the gastric antrum. The muscularis mucosae has a variable thickness but represents a continuum (C. haematoxylin-eosin and D. actin immunoperoxydase).

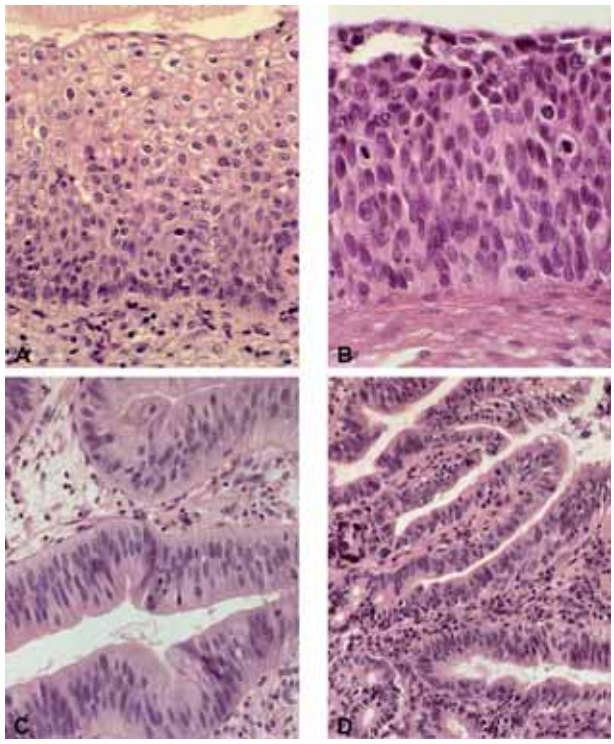

Fig. 2. — A. Low grade intra-epithelial neoplasia in squamous epithelium of the oesophagus.
B. High grade intra-epithelial neoplasia in squamous epithelium of the oesophagus.
C. Low grade intra-epithelial neoplasia in Barrett oesophagus.
D. High grade intra-epithelial neoplasia in Barrett oesophagus (haematoxylin-eosin).

deep zone consists of coiled tubules separated from each other by the lamina propria. Some of these are branched and separated by upgrowths of muscularis mucosae. The lamina propria consists of a network of connective tissue fibres with blood vessels, lymphatics, nerve fibrils and lymphocytic cells. There is a rich supply of blood capillaries at all levels of the mucosa, running closely both to the basal lamina of gastric glands and to the surface epithelium. Lymphatic capillaries only occur in the deep lamina propria adjacent to and within the muscularis mucosae. The muscularis mucosae varies in thickness but always consists of a continuum of smooth muscle fibres (Figs. 1C and D). As for the oesophagus, the gastric submucosa contains the blood vessels and a ramifying lymphatic plexus in a network of loose connective tissue.

2. Definition of terms used to define precancerous lesions or superficial cancers

Dysplasia is the earliest phase in cancer development that can be recognized by routine morphology because of well established architectural and cytological abnormalities of the mucosa. Dysplasia has been defined in 1983 by Riddell *et al.* as an "unequivocal, noninvasive (confined within the basement membrane) neoplastic transformation of the epithelium excluding all reactive changes" (2). The confusion of the term "dysplasia" has led to replace it by the expression "*intraepithelial non-invasive neoplasia"* which defines more clearly the nature and extension of the lesion. According to the severity of the alterations, intraepithelial neoplasia is divided into different categories. Nowadays, the international community recommends the use of a "two grade" classification (3). Low grade intraepithelial neoplasia includes the "former" mild and moderate dysplasia whereas high grade intraepithelial neoplasia corresponds to severe dysplasia and *in situ carcinoma* as well as to some cases of moderate dysplasia with major architectural alterations (Figs. 2A-D).

Intraepithelial carcinoma is synonymous with *in situ carcinoma*. It is a non- invasive carcinoma limited to the epithelial surface such as the stratified epithelium of the oesophagus or the columnar glandular gastric epithelium.

Intramucosal carcinoma is defined as a carcinoma that invades the lamina propria of the mucosa with or without involvement of the muscularis mucosae, without trespassing.

Table 1. — **Vienna classification (7)**

1. Negative for neoplasia/dysplasia
2. Indefinite for neoplasia/dysplasia
3. Non-invasive low grade neoplasia
4. Non-invasive high grade neoplasia
4.1. high grade neoplasia/dysplasia
4.2. non-invasive carcinoma (carcinoma in situ)
4.3. suspicion of invasive carcinoma
5. Invasive neoplasia
intramucosal carcinoma
submucosal carcinoma

Table 2. — **Revised Vienna classification (8)**

1. Negative for neoplasia/dysplasia
2. Indefinite for neoplasia/dysplasia
3. Mucosal low grade neoplasia
4. Mucosal high grade neoplasia
4.1. high grade neoplasia/dysplasia
4.2. non-invasive carcinoma (carcinoma in situ)
4.3. suspicion of invasive carcinoma
4.4. intramucosal carcinoma
5. Invasive neoplasia
submucosal carcinoma

Submucosal carcinoma is a carcinoma infiltrating the lamina propria of the mucosa, trespassing the muscularis mucosa and affecting the submucosa.

Early cancer is a clinical term. It suggests that the lesion is still limited and has a low risk of metastasis and a potential for complete cure after adequate excision. This term should not be used in pathology because it implies a time notion and is not a precise description of tumoral invasion. However it is frequently used in the literature.

Superficial cancer is an endoscopic term used to describe a lesion with a depth of invasion restricted to the mucosa or the submucosa. Therefore it regroups the following categories : intraepithelial carcinoma, intramucosal carcinoma and submucosal carcinoma. In the TNM classification of the upper GI cancer, superficial cancers correspond to pTis and pT1 lesions, including pT1m and pT1sm.

3. The Vienna classification (Table 1)

The use of proper definitions and terminology is essential for an international classification of neoplastic GI lesions, to facilitate the standardization of their therapeutic management. The use of both conventional Western and Japanese classification systems of GI epithelial neoplasia has resulted in large discrepancies among pathologists in the diagnosis of oesophageal, gastric and colorectal cancer (4,5). In Western series, early gastric cancers represent between 15% to 21% of all newly diagnosed cancers whereas in Japan they account for 50% of cases (6). This difference not only results from earlier detection in Japan but also from differences in diagnostic criteria. Indeed, invasion is mandatory for a Western diagnosis of carcinoma and is defined as being present when the lamina propria of the stomach or the oesophagus is involved. By contrast, the diagnosis of carcinoma in Japan is based on cytological and architectural changes without criteria of invasion. In order to solve these discrepancies, a new terminology has been proposed by a panel of Western and Japanese experts resulting in the classification of epithelial neoplastic lesions into five categories (7), with consequences for the management of the patient :

– Category 1 : negative for neoplasia/dysplasia. A follow-up of the lesion is not necessary from a carcinological point of view.

– Category 2 : indefinite for neoplasia/dysplasia. The follow-up is necessary because of the uncertainty of the actual nature of the lesion.

– Category 3 : Non-invasive low grade neoplasia (former low grade dysplasia). The follow-up is made according to endoscopic recommendations.

– Category 4 : Non-invasive high grade neoplasia. In this lesion, the risk of developing invasion and metastases is increased. It regroups the three former categories of high grade dysplasia, in situ carcinoma and intraepithelial carcinoma as well as lesions for which the pathologist suspects an invasive carcinoma.

– Category 5 : Invasive neoplasia (intramucosal and submucosal carcinoma).

Local treatment such as endoscopic mucosal resection (EMR) is indicated for the lesions of categories 4 and 5.

This classification is practical and might facilitate a clear understanding between various pathologists and also between pathologists and clinicians, thereby improving the care of GI neoplastic lesions. In 2002, a clinically meaningful revised version of this classification has been proposed (8), including the intra-mucosal carcinoma in category 4 (Table 2).

4. Superficial cancer classification

Superficial oesophageal and gastric cancer must be subdivided into carcinoma of the mucosal (m-type) and submucosal (sm-type) layers (9). In the oesophagus, for squamous cancer, mucosal type can be subdivided into pm1, pm2 and pm3 types. Pm1 is a cancer limited to the epithelium, pm2 a lesion infiltrating the lamina propria and pm3 a lesion infiltrating the muscularis mucosae. Submucosal type is subdivided into 3 types : psm1 means infiltration of the upper part of the submucosa (superficial invasion of the submucosa) ; psm2 corresponds to a cancer involving the middle part of the submucosa and psm3 the deep of the submucosa. Barrett's carcinoma is subdivided into a mucosal and submucosal type (pm and psm 1-3) similar to gastric carcinoma. In 1991, Takubo *et al.* (10) described a double muscularis mucosae in Barett's oesophagus, reason why a new subdivision of the different layers was proposed by some authors : m1 for a cancer limited to the mucosa ; m2 for a cancer infiltrating newly formed muscle tissue ; m3 for a cancer infiltrating the lamina propria and m4 for a cancer infiltrating the original muscularis mucosae (11).

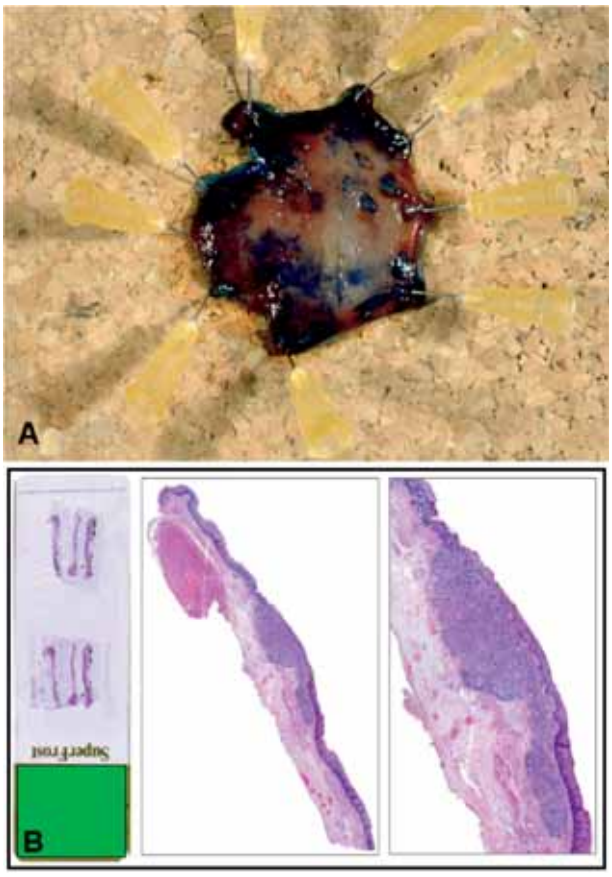

Fig. 3. — Endoscopic mucosal resection. The fresh specimen is pinned down on a cork base (A). After fixation, it is serially sectioned and submitted for microscopic examination (B). This technique allows the recognition of the lesion in the centre and the examination of lateral and deep margins.

The description of the exact depth of infiltration is crucial since the depth of penetration allows the evaluation of the risk of lymph node metastases : the deeper the infiltration, the higher the risk of lymph metastases (12-14).

5. Endoscopic mucosal resection

Superficial carcinomas can be treated by endoscopic mucosal resection (EMR). EMR is a standard technique in Japan, increasingly used in Western countries (15-17). It provides a resected specimen that should be handled and reported as a surgical specimen by the pathologist (18,19). Indeed, this technique is a diagnostic and potentially therapeutic tool but it has also an important role to play as a staging method that gives crucial indications for further therapeutic management of the patient. The specimen can consist in a large en-bloc resection or in several pieces of mucosa. The endoscopist should stretch and pin down each specimen on a firm base and give the pathologist all the indications for a correct orientation of the samples. In the pathology department, the deep and lateral resection margins are marked out with India ink and the specimen is fixed in formaldehyde for 24 hours. It is then step-sectioned at 2 mm intervals along the main axis. Sections are serially submitted in two or three cassettes, routinely processed and stained with haematoxylin-eosin (Figs. 3A and B). In its evaluation the pathologist will consider successively the nature of the lesion, the depth of infiltration, the presence of lymphatic and/or vascular infiltration and the margins (19,20).

In the literature, the diagnosis made on EMR gastric specimens is in concordance with that made on biopsies in 63% of cases. Up to 37% of lesions will be in fact more severe than previously thought (19). Regarding the depth of infiltration, for example in Barrett's specimens, 70% are in concordance with the evaluation before EMR by endoscopic ultrasonography. Among the incorrect 30% of cases, 18% are deeper located and 12% are less deep than thought (20). If the lesion invades the submucosa, the depth of this invasion is mentioned as well as the presence of lymphatic infiltration because these two features are strongly correlated with the risk of lymph node metastases. In the oesophagus for example, m2-m3 squamous lesions will have lymph node metastases in 4.8% of cases and an sm3 lesion in 48.4% of cases. In the stomach, lymph nodes are affected in 2.3% of mucosal cases and 18% of submucosal cases (11). For Barrett oesophagus, in case of mucosal infiltration only, the risk is very low (0-3%) whereas it increases severely in submucosal lesions (8-41%) (21). Finally, the status of the lateral and deep margin is assessed. If the deep margin is affected, recurrence is the rule whereas in case of positive lateral margins, recurrence occurs in half of the patients (19). In 10% of cases, lateral margins are indefinite because of coagulation artefacts (18).

In conclusion, the Vienna classification attempts to unify all the terminologies regarding superficial oesogastric lesions. It should be used by the pathologists as well as by the endoscopists to ensure good reciprocal understanding and optimal patient care. Endoscopic mucosal resection is one emerging therapeutic approach for such superficial lesions in Western countries. It has the same precise requirements as surgical specimens in their management by the pathologist.

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