Endoscopic Assessment of Early Neoplasia in the Gastrointestinal Tract

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Abstract

Endoscopic detection and evaluation of early neoplasia in the gastrointestinal tract should be carried out by systematic assessment of a standard set of lesional characteristics. First of all, attention should be given to the microvasculature and pit pattern of the mucosal surface. These features can distinguish neoplastic from non-neoplastic lesions and are used to assess the presence of dysplasia or malignancy. High resolution endoscopy combined with narrow band imaging usually provides sufficient detailed visualisation for characterisation. Secondly, estimating the risk of invasion beyond the mucosal layer is important, because the depth of invasion corresponds to the risk of lymph node metastasis. This prediction can be based on the gross morphology according to the Paris classification, but also size, the presence of converging folds with clubbing, ulceration and discoloration are considered predictive characteristics. This editorial provides a practical approach to assessing early neoplasia in the gastrointestinal tract. We would encourage endoscopists to appreciate these features systematically before proceeding to endoscopic or even surgical resection.

Disclaimer: There is no potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology,* 2012:1:45-52

Introduction

By definition, all malignant tumours throughout the gastrointestinal tract arise from precursor lesions. Discrete premalignant epithelial changes are the first step in the progression to early carcinoma, ultimately leading to advanced cancers. Endoscopy is the most effective method to detect these precursor lesions or the neoplastic lesions restricted to the superficial layers. A neoplastic lesion is called "superficial" when the depth of penetration in the digestive wall is limited to the mucosa or submucosa, i.e. there is no infiltration of the muscularis propria.[(1)] The term early carcinoma refers to the same depth of invasion confined to the mucosa or submucosa, irrespective of lymph node metastasis. Because superficial neoplastic lesions are usually asymptomatic, they are often incidental findings or are detected during screening or surveillance programs. Accurate recognition and assessment of such lesions is essential and should be done carefully before endoscopic therapy is considered. Assessment of mucosal surface characteristics allows making a presumptive in vivo histological diagnosis. It can assist in differentiating between non-neoplastic and neoplastic (pre)malignant lesions. Additionally, the morphological features predict the extent of invasion into the submucosa which corresponds with the risk of lymph node metastasis. This information is crucial to determine the appropriateness of endoscopic resection and the need for en bloc or piecemeal resection. Despite improved quality with high-resolution (HR) images composed of 850K to 1 million pixels, detailed evaluation of such lesions can still be difficult and operator dependent. New endoscopic technologies have been developed in recent decennia aiming to improve detection, visualisation and characterisation of neoplastic lesions. High magnification endoscopes are capable of enlarging the image up to 150 times with the same pixel density, providing an even more detailed image.[(2)] Because most endoscopists are not familiar with the use and interpretation, magnifying endoscopy has not gained wide-spread acceptance in Western countries. Chromoendoscopy is an endoscopic intravital staining technique using absorptive and

contrast stains to enhance visual characteristics.[3]

Chromoendoscopy is usually applied in combination with optical magnification to improve examination, although its use has also been adopted in standard magnification endoscopy. Narrow band imaging (NBI) is a relatively new optical technology using special narrow band filters in the endoscopic system and highlights the superficial vasculature and mucosal pattern of gastrointestinal neoplasia.[4] Another diagnostic modality that is frequently performed in staging of digestive tract cancer is endoscopic ultrasound (EUS), either using radial or linear array ultrasonography endoscopes or more recently developed miniature ultrasound probes. High frequency ultrasound visualizes the distinctive layers of the gastrointestinal tract, allowing pre-treatment determination of the T-stage.

This review focuses on the different aspects of adequate assessment of superficial neoplastic lesions in the colon, stomach and esophagus, including Barrett's esophagus. It is written from a practical point of view and should be helpful in daily practice to every endoscopist using modern endoscopes. The value of HR endoscopy, chromoendoscopy and NBI is discussed, considering the wide availability of these techniques in both academic and community centres. Because high magnification endoscopy has been the first diagnostic modality providing detailed micromorphological differences, the yield of this technique is also described. Furthermore, the additional value of EUS is discussed.

Assessment of mucosal surface

Examining the mucosal surface is an important aspect in the endoscopic assessment of a superficial lesion. Most knowledge has been gained from examination of colorectal lesions. To classify colorectal neoplastic lesions, the pit pattern classification according to Kudo is usually applied.[5] The type of pit pattern can be assigned after closely examining the mucosal surface of the lesion (Fig.1). It appears valuable in the histological prediction according to five types of pit pattern. Lesions with type I and II are considered nontumorous epithelial tissue, i.e. normal or hyperplastic. In contrast, type IIIS, IIIL, IV and V are neoplastic adenomatous lesions, potentially harbouring carcinoma. Incorporating a technique during standard colonoscopy that can accurately differentiate between adenomatous and hyperplastic polyps is desired. This could prevent unnecessary removal of nonadenomatous polyps, resulting in decreased risk of complications and costs. The original Kudo classification was based on assessment using magnifying endoscopy with white light (WL) after spraying the lesion with indigo carmine or cresyl violet. Whereas this classification relies on the variation of intestinal crypt openings, NBI also provides detailed visualisation of the microvasculature. Because superficial vascular structures change during the process of tumour angiogenesis, proper recognition is an essential component of characterising neoplastic lesions. Several studies have shown that magnification in combination with NBI is able to satisfactorily differentiate neoplastic from non-neoplastic lesions.[6-7] Furthermore, it could possibly provide a prediction of submucosal invasion, in particular massive invasion depths.[8] Although these results are encouraging, magnifying endoscopy is not routinely available in most Western endoscopy centers. HR endoscopy is generally used instead because most endoscopists feel more comfortable with this technique. However, the diagnostic accuracy of HR endoscopy in distinguishing neoplastic colorectal lesions is suboptimal. Without the use of optical magnification,

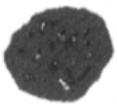
I		Round, regular (normal)
II		Stellar or papillary pits
IIIL		Large tubular or roundish pits
IIIS		Small tubular or roundish pits
IV		Branch-like or gyrus-like pits
V		Non-structural pits

Figure 1. Kudo's pit pattern classification. Adapted from reference [5]

assessment of the lesions with NBI alone seems to be an advancement. NBI without magnification has been compared with WL endoscopy in three large studies, both with HR images. For predicting adenomas, NBI was significantly superior to WL with a sensitivity ranging from 80-96% vs 38-69% and diagnostic accuracy ranging from 80-93% vs 61-77%.[9-11] The results of non-magnifying endoscopy using NBI with HR closely resembles the results obtained with magnifying endoscopy. It may represent a functional tool, which is able to assist endoscopists in making determinations regarding polyp histology prior to resection. One should be aware though that results do not indicate that this technique can replace histopathological examination. Furthermore, adequate interpretation of NBI produced images is preceded with a learning curve in which dedicated training and feedback is essential.[10]

For assessment of the mucosal surface of esophageal or gastric superficial lesions, still no internationally accepted validated classification system is available. However, adequate evaluation in these areas relies on the presence of distorted microvasculature and mucosal morphology, similar as in colorectal lesions.

In superficial esophageal squamous cell tumours, grading the microvasculature is based on different shapes of intraepithelial papillary capillary loops (IPCL), as suggested by two studies.[12-13] IPCL's were visualised using magnifying endoscopy in both studies. The reported level of distortion correlates to the degree of malignancy. It may even be possible to predict invasiveness based on these characteristics. Theoretically, NBI could have an additional value because it accentuates the vasculature. However, two studies have demonstrated that the use of NBI for differentiating superficial esophageal squamous cell carcinomas is not beneficial. Although a higher contrast ratio has been demonstrated with NBI compared to WL endoscopy, prediction of the depth of invasion is equally effective between both diagnostic modalities with an accuracy rate of approximately 80%.[14-15] Chromoendoscopy has not been investigated as a tool for differentiating early esophageal squamous cell cancers. On the other hand, lugol staining might improve visualization of the lateral margins of the lesion.[16]

Surveillance of Barrett's esophagus (BE) primarily focuses on the presence of high grade dysplasia (HGD) or carcinoma. Detailed observation of the mucosal morphology can assist in the distinction of HGD or carcinoma from nondysplastic specialized intestinal metaplasia (SIM). Several studies using magnifying endoscopy with NBI have demonstrated that HGD is associated with irregular/disrupted mucosal patterns and irregular/abnormal vasculature. NBI has also been evaluated as a potential diagnostic tool for BE, mostly in non-comparative studies. It seems effective in differentiating HGD or carcinoma from LGD with a reported sensitivity of 93-100% and specificity of 58-100%.[17-21] Only one randomised cross over trial evaluated the detection capability of NBI versus WL HR endoscopy in Barrett's esophagus.[20] In this study 28 patients referred for occult HGD underwent two separate endoscopies with an interval of 6-8 weeks. Although NBI detected a limited number of additional lesions, the sensitivity for identifying patients with HGD or carcinoma with NBI was similar compared to HR endoscopy. Also based upon our own experience, we would recommend WL HR endoscopy for evaluating BE using NBI as a supportive imaging technique. Standard resolution endoscopy should not be used for detection of dysplasia in BE as it is proven to be inferior compared to HR endoscopy with NBI.[22] The role of chromoendoscopy for the detection of dysplasia in BE is limited. A recent meta-analysis demonstrated no significant incremental yield with methylene blue compared to conventional random biopsies.[23] As for the methylene blue staining characteristics, it still remains unclear which staining pattern is predictive for HGD or early carcinoma and therefore routine use is not advocated at this time.[24-25]

With regard to early gastric neoplastic lesions, several Japanese researchers have adopted various classification systems, based on changes of microvascular architecture and glandular structure. Most studies have used magnifying endoscopy with NBI, demonstrating an accurate relationship of the type of microvessel pattern with the pathological diagnosis.[26-28] This classification corresponds with the histopathological differentiation grade as well as the presence of submucosal invasive cancer. In contrast to the esophagus, the additional value of NBI is more clearly established in evaluation of gastric lesions, although benefit has only been demonstrated in combination with magnifying endoscopy. Magnifying endoscopy with NBI allows for identification of small gastric lesions more accurately with a higher sensitivity compared to

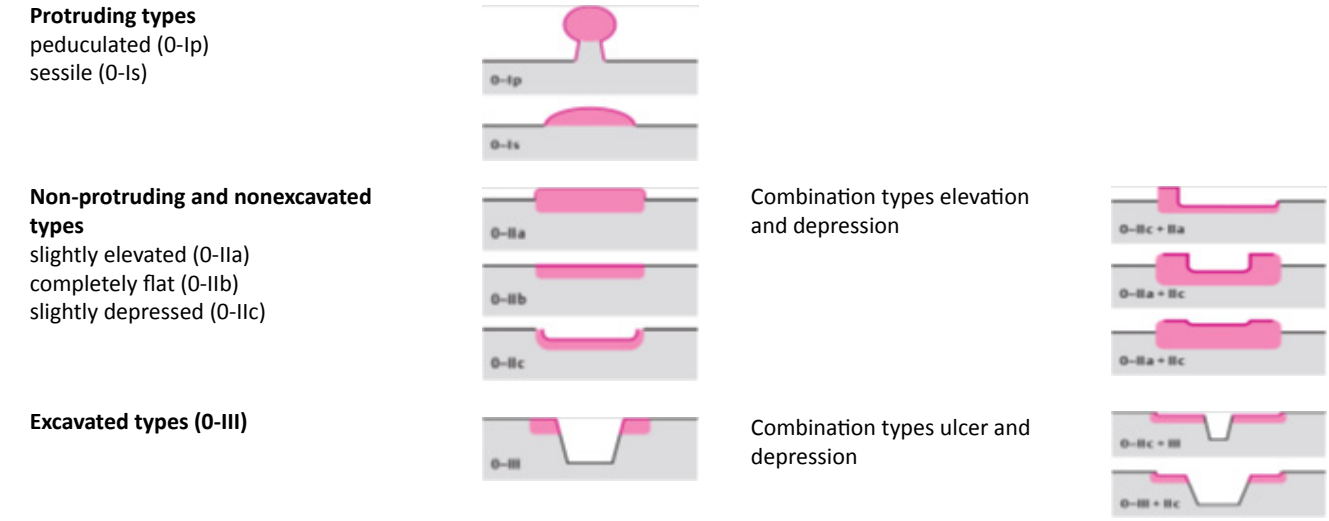


Figure 2. Paris Classification; Endoscopic appearance of superficial neoplastic lesions. Adapted from reference [35]

WL HR endoscopy.[29] Furthermore, several studies have shown a superior accuracy in the differential diagnosis of superficial gastric lesions.[30-31] One study of 204 gastric lesions, including 14 proven cancers, demonstrated a high diagnostic accuracy of predicting cancer (sensitivity 92.9% and sensitivity 94.7%) based on a triad (disappearance of fine mucosal structure, microvascular dilation and heterogeneity) observed using ME with NBI.[30] These results were significantly better compared to ME with WL (sensitivity 42.9% and sensitivity 61.0%). In a different study, ME with NBI was superior in distinguishing low grade adenoma from early gastric cancer.[31] The use of chromoendoscopy has been studied in early gastric cancer, with indigo carmine, methylene blue and Congo red as the most frequently used dyes. The clear benefit in increasing the detection of gastric lesions has never been confirmed in randomized trials. Instead, it can be helpful for determination of the lateral border of the lesion which is essential to achieve complete resections. Three studies have confirmed a better diagnostic performance of identifying the lateral margin in differentiated adenocarcinoma using a mixture of indigo carmine with acetic acid compared to HR WL endoscopy.[32-34] However, this advantage has not been confirmed in undifferentiated adenocarcinoma.[33]

Assessment of gross morphology

Besides the mucosal surface, another crucial element is the assessment of the gross morphological appearance. The most widely accepted classification system is the Paris classification (Fig.2).[1,35] Although initially used to assess superficial tumours in the stomach, this classification was later adopted for early neoplasia throughout the entire gastrointestinal tract. The classification assists in predicting the extent of invasion into the submucosa. Because this depth of invasion correlates with the risk of lymph node metastasis, appropriate treatment of each lesion is largely depending upon this assessment. Superficial lesions are classified as either protruding (0-I), non-protruding, non-excavated (0-II) or excavated and often ulcerated lesions (0-III). The protruding lesions (0-I) can further be divided in pedunculated (0-Ip) or sessile (0-1s) lesions. Type 0-II lesions are subdivided in 0-IIa, 0-IIb and 0-IIc, corresponding to slightly elevated, completely flat and slightly depressed type lesions respectively. Lesions which have both elevated and depressed components are classified into two groups: depressed lesions in which most of the surface is depressed and there is elevation in a portion of the peripheral ring are classified as 0-IIc + IIa, while elevated lesions with a central depression encircled by the elevated ring at the periphery are called 0-IIa + IIc. The combined patterns of excavation and depression are called 0-III + IIc or 0-IIc + III, depending on the relative surface area of the ulcer and of the depressed area.

The corresponding incidence of submucosal infiltration varies between the different subtypes and the location in the gastrointestinal tract.[35] True protruding (0-I) lesions in the stomach demonstrate a 57% relative frequency of submucosal invasion, whereas nonprotruding, nonexcavated lesions (0-II) demonstrate submucosal invasion in 20-40%.The

incidence also differs between the three subtypes of type 0-II lesions. Especially type 0-IIc lesions have a substantial risk of penetration into the submucosa with a reported incidence of 40%. In excavated gastric lesions (0-III), the muscularis propria is often already involved. Although the exact percentage of involvement of the muscularis propria is not reported in the literature, this number comes close to 100%. This latter assumption also accounts for excavated lesions in the large bowel, although exact numbers are lacking. In type 0-II colorectal lesions, the proportion of submucosal infiltration is highest (61%) for type 0-IIc lesions, similar to gastric neoplasia. Regarding early neoplasia of the esophageal squamous epithelium, submucosal invasion most frequently occurs in protruding (0-I) or excavated (0-III) types, both with an incidence of approximately 80%. However, one should be aware that also type 0-II lesions, especially 0-IIa, are at risk of submucosal invasion with a rate of 15-48%.

Representative frequencies in Barrett's esophagus cannot be provided as there is relative paucity on data regarding this subject.

Other neoplastic features

Additional characteristics which should be taken into account and include larger size, converging folds with clubbing, presence of discolorations (remarkable redness) and ulceration. These adverse features are associated with deeper invasion and higher risk of lymph node metastasis. The diameter of a lesion has been analysed as a prognostic factor for submucosal invasion in various studies. For instance, submucosal infiltration occurs in less than 1% when a colorectal lesion measures less than 10mm and this rate increases in proportion to the diameter. This applies for every morphological type, except for depressed (type 0-IIc) type lesions, of which also small diameter lesions are associated with a substantial risk of submucosal invasion.[1] In the stomach, small (<1 cm) lesions with submucosal invasion of more than 500µm (sm2) also carry a considerable risk of lymph node metastasis. The incidence even rises in larger lesions. On the other hand, when invasion into the submucosa is limited to the upper 500µm (sm1), the risk of lymph node metastasis is low, even when the diameter increases.[36] Thus, it is important to realise that further management should not solely be based on the size of a lesion. Another feature that should be taken into account is the relation with the peristaltic waves. Lesions that are confined to the mucosa tend to floatingly move over the peristaltic waves, whereas peristaltic waves seem to curve around tumours that have invaded the muscularis propria.

In most endoscopic resection techniques, submucosal injection of fluid is used to lift the lesion from the muscularis propria. The amount of lifting also provides information on the invasion depth of the lesion. Mucosal or superficial submucosal lesions usually demonstrate complete lifting, whereas the lesions which infiltrate into the deeper submucosal layers often lift incompletely. In the first situation the lesion is generally amenable for endoscopic resection, while in the latter the efficacy of an endoscopic approach is doubtful. A non-lifting sign most often represents invasion into the muscularis propria, precluding endoscopic resection. One should be aware that the presence of fibrosis, for example after previous attempts at removal, can also hinder complete lifting.

Endoscopic ultrasonography

In our opinion, the addition of EUS as a diagnostic modality does not substantially impact management decisions of early neoplastic lesions. Even the recently developed miniprobe EUS, which provides excellent resolution, is not more reliable than conventional endoscopy prior to treatment. A systematic review, evaluating the performance of EUS in gastric cancer, reported a diagnostic accuracy ranging from 65% to 92.1% for overall T staging.[37] When the accuracy of EUS is limited to early gastric cancer, the overall accuracy in differentiating mucosal (T1m) from submucosal (T1sm) lesions, is 67.4%, as shown in the largest series to date including 955 cases.[38] In this comparative study conventional endoscopy, using criteria predominantly based on the Paris classification, appeared superior with an accuracy rate of 73.7%. Approximately 40% of cases were assessed by a miniprobe, which indeed showed a significantly higher accuracy compared to radial EUS, but this was not different from conventional endoscopy. The imperfection of EUS can be explained due to various reasons. EUS has a tendency to overstage tumours due to ulceration and peritumoral inflammation. On the other hand, understaging can occur due to undetected microinvasion. The most important limitation of the miniprobe EUS is the restricted

field of visualisation. Therefore, there is a risk of misdiagnosing the invasiveness in larger lesions. In our opinion, EUS should not routinely be applied in pretreatment staging of early gastric cancer. The same limitations impede the regular use of EUS in early esophageal cancer. The diagnostic performance on determining the exact T-stage is unsatisfactory as demonstrated in a recent systematic review.[39] In our opinion, the role of EUS is also limited in early rectal cancer since careful conventional endoscopic assessment is usually sufficient to predict deep submucosal invasion. However, it should be noted that there are no comparative studies with regards to early esophageal and rectal cancer.

Criteria for endoscopic resection

Critical appraisal of all these aforementioned features enables us to choose the appropriate resection modality, either an endoscopic or surgical resection. Endoscopic resection can be performed using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). While ESD allows radical, en bloc, resection independent of the size of the lesion, en bloc EMR can only be achieved in lesions <2 cm using a snare technique. The advantage of en bloc resection is accurate assessment of the depth of invasion in the obtained specimen.

This is less important in neoplastic lesions with predicted low- or high-grade dysplasia without submucosal invasion. These can safely be removed by piecemeal EMR for example using snare polypectomy. On the other hand, en bloc resection is indicated for lesions potentially harboring carcinoma based on endoscopic appearance. Current widely adopted guidelines suggest that ESD or en bloc EMR is justified for intramucosal, well or moderately differentiated carcinomas, because the incidence of submucosal lymphovascular involvement in these cases is close to zero. In case of submucosal ingrowth, the extent of infiltration into the submucosa is measured from the lower limit of the muscularis mucosae. It is well known that deeper invasion is clearly associated with a higher rate of lymphangitic spread. The currently adopted cut-off limit is dependent on the location in the gastrointestinal tract.[35] Invasion should be less than 200µm in the squamous epithelium of the esophagus, less than 500µm in the stomach or in Barrett's esophagus and less than 1000µm in non-pedunculated neoplastic lesions of the colon. Studies have shown that with only limited submucosal invasion, in the absence of other adverse qualitative criteria, the rate of nodal metastases is very low. Although the rate is not zero, and reported even up to 26% for esophageal squamous cell carcinoma[40] and up to 16% for Barrett's neoplasia based on limited data,[41] it is suggested that in these patients endoscopic resection is justified and surgery can be avoided.[35] Many endoscopists however tend to be more conservative. Usually in these esophageal cases invasion limited into the muscularis mucosae is accepted as a cut-off for endoscopic resection. In these cases, the risk of lymph node metastasis is negligible compared to mortality rates reported for esophageal resection. Thus, accurate histological examination of the obtained specimen by a dedicated pathologist is of major importance as it may guide further management.

Conclusion

Every endoscopist will encounter early neoplastic lesions on a regular basis, either as an incidental finding or during screening or surveillance endoscopy. Selecting the most appropriate resection method largely depends on accurate assessment of a standard set of lesional characteristics using the correct imaging techniques. Relying on glandular structure and microvasculature patterns, it is possible to categorize lesions as non-neoplastic or neoplastic lesions and to assess the presence of dysplasia or even malignancy. Magnifying endoscopy is capable of delivering the most detailed information. However, it is not widely available, is time-consuming, requires extensive training and should therefore only be used in the hands of experienced endoscopists. We believe that HR images are sufficient for accurate inspection of the vast majority of lesions. NBI may contribute to a more detailed visualisation and characterisation of microvessels, although improved accuracy has only been suggested in gastric and colorectal lesions. Another critical point of evaluation is the estimated risk of submucosal invasion, which is an important predictive factor for the development of lymph node metastasis. The value of EUS for staging depth infiltration in early neoplasia is limited and should not be routinely advocated at this time. However, assessment of the gross morphology according to the Paris classification as well as other endoscopic features, give a reliable real-time prediction of invasion into the submucosa or beyond. Appreciation

of the combination of these endoscopic findings should be used as a tool in deciding further treatment. It plays a pivotal role in the decision making which lesion can be safely resected in a piecemeal fashion and which lesion should be resected en bloc or even be referred for surgery.

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