The challenge of high-resolution endoscopy

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**Synopsis**

The dramatic improvement in the images obtained by the newer electronic video endoscopes has resulted from a number of factors, including the high density of pixels in the charge-coupled device, new processors and high-definition monitors, image processing with structure enhancement, color enhancement, narrow-band imaging, and magnification with optical or electronic zoom.

High-resolution endoscopy is a development in diagnostic endoscopy that opens up a new era in the endoscopic diagnosis of early cancer: the focus is now on flat precancerous and cancerous neoplastic lesions, which the technique has made more visible and conspicuous. On the other hand, the spectrum of clinically irrelevant abnormalities of the mucosal surface that can now be detected is also considerably increased, with an attendant increased risk of overtreatment.

While the diagnosis of polypoid lesions is easy, the endoscopic diagnosis of nonpolypoid lesions requires a step-by-step strategy. The first step is the detection of an abnormal area, such as a discolored area or a sharp demarcation line. The next step is characterization of the lesion, based on the microvascular pattern, the gross morphology, and the degree of magnification available. The final step is a treatment decision based on the provisional diagnosis: no resection of lesions considered to be without clinical relevance, resection or surveillance for low-grade dysplasia, resection for high-grade noninvasive dysplasia, and resection or direct surgical treatment for early cancer, according to the estimation of the depth of invasion in the submucosa.

**Gastrointestinal endoscopy in the era of digital imaging**

In addition to improved mechanical properties and field of vision, the recent video endoscopes are equipped with new charged-coupled devices (CCD) and processors, facilities for image processing, and optical and electronic zoom. In the era of digital imaging, endoscopy maintains its gold standard status for the exploration of the gastrointestinal mucosa and should now be known as “high-resolution endoscopy.”

**Miniaturization of the charge-coupled device**

Recent CCD models contain a higher number of pixels in the same small surface, adapted to the diameter of the endoscope. The higher image resolution requires new processors and coupling to specific red-green-blue (RGB) monitors in the RGB
system. The greater number of lines available with the high-definition television (HDTV) standard is an adaptation of the increased pixel density of the new CCDs.

**Image processing**

Image processing is the modulation of specific frequencies, either in the reflected photons from the surface of the gastrointestinal mucosa or in the incident photons emitted by the light source. The image reflected by the mucosa can be processed to enhance the contrast between two areas of mucosa with different architecture (e.g. normal versus neoplastic) – this is “structure enhancement” (Olympus Systems Corp., Tokyo, Japan). The image displayed on the color monitor can also be processed with spectral enhancement of the color of hemoglobin – this is the “index of hemoglobin” (IHb, Olympus Systems) [1,2]. Computed images with enhanced sharpness, tone, or color can be processed at three distinct wavelengths in RGB and combined to develop an artificial chromoscopy. This is the “Fuji Intelligent Chromo Endoscopy” or “FICE” system available in the EPX 4400 model (Fujinon Co., Omiya, Japan), which has both optical and electronic magnification.

In the Olympus narrow-band imaging (NBI) system, a filter is interposed after the xenon light source. In the prototypes the filter displayed three narrow bands (blue, green, and red), but in the commercially available instrument (Exera II or Lucera Spectrum) only two narrow bands are displayed (blue light at 415 nm and green light at 540 nm) and all the wavelengths of light that are not absorbed by hemoglobin are filtered out. The remaining light passing across the two narrow bands of the filter will either be absorbed by the vessels containing hemoglobin, providing a highly contrasted image, or will be reflected by the surface of the surrounding tissue. The 415-nm image channel analyzes the fine surface architecture of the mucosa and the superficial capillary network. The 540-nm image channel analyzes the collecting vessels in the deeper mucosa. In the final mixed image, superficial and deep details are superimposed as one color image, enhancing the visibility of flat lesions. The subepithelial capillaries are displayed in brown and the collecting veins in the submucosa in cyan [3–6].

**Magnification**

Magnification allows visualization of the surface architecture (pits and ridges) of the gastrointestinal mucosa. The optical zoom (with a power range of ×60 to ×150) requires distance adjustment of the focal length (the plastic cap at the tip of the endoscope is useful for this). The macro objective lens is less powerful but easier to use. With the electronic zoom the resolution loss does not affect practical examination if the image is processed in the HDTV standard. The recently developed Olympus endocytoscope that uses white light and the Optiscan-Pentax confocal endoscope that uses laser light both offer a facility for in vivo cytology or histology [7–9] but these endoscopes are not used in routine endoscopy. As a rule, NBI is combined with magnification, either using a macro objective and electronic zoom (Olympus Evis Exera II) or an optical zoom (Olympus Evis Lucera Spectrum).

**Chromoscopy**

The NBI and FICE techniques have been proposed as substitutes for chromoscopy (in which a dye is injected through the operating channel of the endoscope to stain the surface of the mucosa). However, there are still specific indications for chromoscopy [10–12]: staining with 1.5%–2% iodine-potassium iodide Lugol solution is the easiest way of assessing the limits of flat (unstained) neoplastic areas in the squamous-cell epithelium; and staining with 0.5% indigo carmine
solution shows the morphology of nonpolypoid neoplastic lesions during standard endoscopy or their pit pattern in magnifying endoscopy. Other absorbed dyes have specific indications: acetic acid (3%–5% dilution) at the squamocolumnar junction, methylene blue (0.5% solution) to stain intestinal metaplasia, and cresyl violet (0.2% solution) for the analysis of pit patterns in magnification endoscopy.

**Morphology of superficial neoplastic lesions in the gastrointestinal mucosa**

Endoscopy is the gold standard procedure for the early detection of neoplastic lesions. Benign or malignant neoplastic lesions of the gastrointestinal mucosa are classed as superficial when their endoscopic appearance suggests that invasion is limited to the mucosa (m) or to the submucosa (sm); their morphology is classified as type 0 according to the Paris classification [13] (types 1 to 5 are advanced cancers). Type 0 benign or malignant lesions can be polypoid (0-I), nonpolypoid (0-II), or (rarely) excavated (0-II). In a further subdivision, polypoid lesions can be pedunculated (0-Ip) or sessile (0-IIs); and nonpolypoid lesions can be slightly elevated (0-IIa), completely flat (0-IIb), or slightly depressed (0-IIc).

**Non-neoplastic and neoplastic lesions of the gastrointestinal mucosa**

Hyperplastic polyps, whether pedunculated, sessile, or slightly elevated, are often misdiagnosed as neoplastic lesions. Hyperplastic polyps form as a result of noncancerous proliferation of foveolar cells and they feature elongated pits. Although most hyperplastic polyps do not undergo neoplastic change, a small proportion of these lesions have a mixed hyperplastic and adenomatous structure and can progress to malignancy – these are known as “serrated adenomas.”

Neoplastic lesions of the gastrointestinal mucosa are circumscribed areas of altered epithelium with cellular atypia and evidence of hyperproliferation. Premalignant lesions carry a significant risk of progression to malignancy. Malignancy is also characterized by invasion of the lamina propria in the mucosa or the submucosa. Malignant lesions are classed as superficial when the invasion is limited to the mucosa or submucosa. Pathologists use the Vienna classification for the description of superficial neoplastic lesions, which are classified into categories 3, 4, and 5: low-grade intraepithelial neoplasia (category 3); high-grade, noninvasive or invasive, intraepithelial neoplasia (category 4); and submucosal carcinoma (category 5). In this classification, high-grade intraepithelial neoplasia and intramucosal carcinoma are in the same category (category 4).

Premalignant lesions develop either in normal epithelium or in preneoplastic epithelium, under the combined influence of environmental and genetic susceptibility factors (similar to those thought to be responsible for the development of cancer). Columnar metaplasia in the esophagus with a specialized epithelium [14], chronic gastritis with *Helicobacter pylori* infection [15], and chronic epithelial lesions in inflammatory bowel disease are all classified as preneoplastic lesions. A preneoplastic lesion may qualify as a precursor of neoplasia when prospective studies have shown that it carries a significantly increased risk of developing into cancer. Prenec biplastic lesions are classified into categories 1 and 2 of the Vienna classification (as negative or indefinite for neoplasia), which correspond to non-neoplastic lesions.
The role of endoscopy in screening for gastrointestinal cancer

Screening strategies

The early detection of neoplastic lesions in the gastrointestinal mucosa is the objective of “organized” protocols for population-based screening programs proposed by health authorities for asymptomatic people. Screening may also be done on an occupation-related or insurance-related basis. "Nonorganized" or individual screening, also known as “opportunistic” screening is screening of asymptomatic people who have contacted their own doctor or who have gone to private health-check facilities. Most population-based programs use a relatively simple “filter” test, such as gastrophotofluorography for stomach cancer or the fecal occult blood test for colorectal cancer; endoscopy is offered only to the small number of people who test positively on these simpler tests.

The benefits and drawbacks of screening

Prevention is based on the early detection and treatment of potentially curable cancers and of precursor lesions that have a significant risk of progression to malignancy. Limiting factors in terms of the benefit of early detection include: (a) interval cancers revealed after a negative diagnostic test – the early-diagnosis miss rate is probably particularly high for small and evolving lesions, which then have a poorer prognosis; and (b) overdetection and overtreatment of lesions with a very low risk of malignant progression – this results in increased morbidity and cost.

The roles of organized and individual screening

Population-based screening and individual screening cooperate in the reduction of the burden of cancer. The contribution of individual screening increases as a consequence of the implementation of population-based mass screening, which is the source of reference for guidelines, quality control, and evaluation of the screening process. In Japan, population-based screening for stomach cancer has been organized by the government for more than 20 years [16]. The filter tests used in Japan are gastrophotofluorography for stomach cancer (from 1983) and an immunochemical fecal occult blood test for colorectal cancer (from 1992). However, organized screening detects only a small proportion of cancers in this country: in 2003 the total number amounted to fewer than 7000 cases of stomach cancer and fewer than 11,000 cases of colorectal cancer, while the total numbers of cancers diagnosed in the same year were estimated to be 110,000 for stomach cancer and 95,000 for cancers of the colon and rectum. The low yield results from three cumulative factors: a low take-up of the filter test by the population being screened, the small proportion of screened people who have a positive filter test, and poor compliance with further exploratory investigations by the people who have tested positive to the filter test.

In spite of the low yield revealed by these Japanese figures, however, the trend for early detection has increased through nonorganized screening, when gastroscopy and colonoscopy are often used as the primary procedure for screening. A recent analysis (2000) in ten cancer registries confirmed that the proportion of localized stomach and colorectal cancers in Japan is very high, accounting for more than 50% of all cancers. The trend toward early detection is associated with improved survival: the 5-year survival rate for gastric cancer (all stages), calculated from seven population-based registries for the period 1993–1996 was found to be 58%, a higher figure than that recorded in Western countries. The origin of patients referred to the
National Cancer Center Hospital in Tokyo from 2001 to 2003 for endoscopic or surgical treatment of early gastric cancer confirms the general trend of early detection: 64% patients were referred by outpatient clinics, 28% were referred by private health check-up units, and only 7.6% were referred from the organized mass screening program. In this series, gastroscopy was the initial detection procedure in 68.8% of asymptomatic people and in 91.7% of symptomatic people [17].

A strategy for endoscopic diagnosis

The concept of selective growth of a clone of neoplastic cells into a conspicuous polypoid lesion in the gastrointestinal mucosa is now challenged and the new techniques of high-resolution endoscopy are facilitating the detection of flat nonpolypoid lesions, bringing in a whole new range of diagnostic and therapeutic options for the Western endoscopist. A sharper image is obtained using these methods, but to make a correspondingly sharper diagnosis more care and more reflection is required in the observation of the mucosa – the single-step strategy (resection of any superficial lesion followed by a wait for histology) must become a step-by-step, analytical process. Abnormalities that are clinically relevant must now be selected from a much wider range of appearances – a greater number of variations of the normal pattern and more localized abnormalities that have no clinical relevance. The risk of overdetection and overtreatment of lesions is therefore increased. Endoscopic diagnosis now comprises three steps: (a) detection of an abnormal area which is selected as a target area; (b) characterization of the nature of the lesion and its clinical relevance; and (c) a decision on whether and which treatment is required.

Endoscopic diagnosis also requires complete cleanliness of the mucosal surface. Small nonpolypoid lesions in the colon can be hidden by any solid or liquid matter persisting on the surface of the mucosa if the precolonoscopy bowel preparation has been incomplete. During upper gastrointestinal endoscopy, all particles inside the stomach should be dislodged with a jet of water and aspirated, and oral premedications (simethicone or pronase) can be administered before the procedure.

Detection of a lesion during endoscopy

Abnormal areas in the gastrointestinal mucosa can be detected by standard endoscopy without the help of image processing and chromoscopy. In upper gastrointestinal endoscopy, the esophagogastric junction and the corpus of the stomach are explored under direct vision and in retroflexion. In colonoscopy, the surface of the mucosa is explored segment by segment, avoiding any blind areas, and the recommended scope withdrawal time is 8 minutes.

Polypoid and benign neoplastic lesions have been considered in Western countries to be the usual precursors of cancer in the gastrointestinal mucosa. They are easily detected, even when small, but can be missed at the gastric cardia below the esophagogastric junction, the distal border of the angulus in the stomach, and on proximal edges of colonic valves.

Nonpolypoid lesions can be missed when the operator lacks training in the recognition of the following signs: a slight change in color of the mucosa (paler or redder); and a strict line of demarcation within the normal mucosa surface with interruption of the subepithelial vascular network at this line. Etched in the long-term memory of Western endoscopists is the invariable image of a neoplastic lesion as a protruding abnormality, and flat, discolored spots are not recognized in the absence of a corresponding template in the brain linking the image to neoplasia [18]. In Japan,
as early as in the 1975–1980 years, endoscopists began to realise that nonerosive flat areas of mucosa could be neoplastic and that flat lesions with a depressed morphology deserved special attention, even when they are less than 10 mm in diameter. Japanese descriptions of these lesions met with some skepticism, however, before similar findings were reported by Japanese workers in English and North American centers.

**Characterization of a lesion after detection**

Once an abnormal area has been detected using a video endoscope equipped with these recently developed technical facilities, the lesion should be characterized using the following steps:

1. Analysis of the microcirculation at a low magnification power in standard view (without chromoscopy) and then with NBI: slight vascular alterations suggest either a non-neoplastic lesion or low-grade neoplasia; severe vascular alterations with numerous corkscrew vessels of irregular caliber suggest high-grade noninvasive or invasive neoplasia.

2. Assessment of the gross morphology in standard vision with the help of chromoscopy.

3. Analysis of the surface microarchitecture (depressions and ridges) when there are severe vascular alterations present. This is done under magnification with an optical zoom and chromoscopy (using indigo carmine or cresyl violet). Whether NBI and optical magnification without chromoscopy are as effective as with chromoscopy remains a debatable question.

**Gross morphology of the lesion.** The limits and the relief of the target lesion are assessed under standard endoscopic vision. The diameter of the lesion is estimated by comparison with a guide (a graduated probe or biopsy forceps). The gross macroscopic appearance, enhanced by chromoscopy with indigo carmine for detecting depressions and ridges, is classified into subtypes of type 0 superficial neoplastic lesions. The proportion of nonpolypoid neoplastic lesions is estimated to be 80% in the esophagus, 95% in the stomach, and 45% in the colon, where small flat adenomas are common and progress either to polyps or to flat lesions. Many flat (nonpolypoid) lesions remain superficial as they increase in diameter in a transverse-type growth pattern; other flat lesions progress to invasive carcinoma in spite of their small size in a vertical-type growth pattern and these lesions usually correspond to the depressed type of superficial neoplastic lesion (0-IIc).

**The microvascular network.** The superficial vascular network in the suspect area is best explored without chromoscopy and with the help of magnification [19–21]. Small vessels are clearly contrasted in dark green using the NBI technique. The subepithelial capillaries reproduce the microarchitecture (crests and pits) of the normal epithelium: intrapapillary capillary loops with a hair-clip appearance in the esophageal squamous epithelium; a honeycomb network around the neck of gastric pits in the gastric oxyntic mucosa and transverse collecting venules visible more deeply; coiled subepithelial capillaries in the gastric antral mucosa; and hexagonal capillaries around the pits in the colon.

In areas with chronic inflammation, various degrees of alterations are seen: in esophagitis, the intrapapillary capillary loops are elongated (type II according to the Inoue classification) compared with type I appearances. In the stomach, *H. pylori*
infection causes a diffuse reddening of the surface of the oxyntic mucosa with regression of the honeycomb pattern and of collecting venules.

In areas with neoplasia, various degrees of change are observed: in the squamous epithelium of the esophagus, tumoral neoangiogenesis results in a punctuated pattern, corresponding to types III, IV, and V of the Inoue classification. The average diameter of the small vessels increases with the depth of invasion in the mucosa (from m1 to m2 to m3) or submucosa (sm). In the columnar-lined esophagus, the microvascular network on the surface of neoplastic areas also has some relevance for assessment of the depth of invasion and for making decisions on endoscopic treatment. In the stomach, intramucosal cancer is shown by abnormal superficial vessels (mesh, coil, or corkscrew), their appearance depending on the degree of tumor differentiation. The pattern of neoangiogenesis has been less documented in the large bowel.

The microarchitecture of the epithelium. When using NBI or chromoscopy with the optical zoom or the macro objective lens, pits and ridges are enhanced at the surface of the mucosal depressions [22,23]. Magnification is particularly helpful in the columnar-lined esophagus for identifying areas with intestinal metaplasia or with a disorganized structure, suggesting low- or high-grade intraepithelial neoplasia. Magnification is also helpful in the large bowel for classification of the pit pattern of a neoplastic lesion into the five types described by Kudo [24]: type I pit pattern with regular and narrow pits, seen in normal epithelium; type II pit pattern with enlarged, star-shaped colonic pits, seen in hyperplastic polyps; type III, type IIIs, and type IV pit patterns for low- and high-grade intraepithelial neoplasia; and type V pit pattern with an amorphous surface, seen in invasive cancer.

Treatment decisions during endoscopy

Characterization of the target abnormal zone avoids the unnecessary resection of lesions with a very low malignant potential as well as inappropriate endoscopic treatment of lesions that should be treated directly by surgery. When the morphology suggests that a small lesion is non-neoplastic, with no potential for malignant progression, the endoscopist will decide whether a biopsy is needed and no endoscopic treatment is proposed. When the morphology is benign, suggesting a low potential for malignancy (low-grade dysplasia) the decision lies between endoscopic resection or surveillance. When the morphology suggests noninvasive malignancy (high-grade dysplasia) the treatment of choice is endoscopic resection.

Piecemeal resection is easier than en-bloc resection for neoplastic lesions larger than 2 cm in diameter, but the risk of recurrence is higher. En-bloc resection is preferred in theory, but the location of the lesion in the esophagus, stomach, or colon may be the deciding factor in the choice of the technique. When the morphology suggests malignancy with invasion into the submucosa, the choices for treatment are either endoscopic resection or surgery if deep invasion in the submucosa is suspected.

References


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