Screening for
Early GI Cancer

Seeing beyond naked eyes

Joseph Sung  MD, PhD
Professor of Medicine
Institute of Digestive Disease, CUHK
How Common is GI Cancers?

<table>
<thead>
<tr>
<th>Condition</th>
<th>New Cases (M+F, million)</th>
<th>Death (M+F, million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Lung</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Breast</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>GU</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>GYN</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Mortality of GI Cancers

- **Colorectal**
- **Stomach**
- **Liver**
- **Esophagus**
- **Pancreas**

**New Cases**

**Death**

No. of patients (M+F, thousand)
Why bother to diagnose Early GI Cancer

• Carcinoma involving the mucosa or submucosa

• Excellent prognosis
  – Risk of lymphovascular metastasis is low

• Difficult to diagnose
  – Early stage, asymptomatic
The management process
Early Gastric Cancer

- Recognition of Early Gastric Cancer
- Histopathology
- Staging of EGC
- Management

Endoscopy, Endoscopy, Endoscopy, Endoscopic resection
Aim of Endoscopic Assessment
Early Gastric Cancer

- To establish the diagnosis
- To assess the depth of invasion
- To define the margin of involvement
Key to diagnose Early GI Cancer

“High index of suspicion”
1. Classification of EGC (Type 0)

- **I** – protruded
- **II** – superficial
  - IIa – elevated
  - IIb – flat
  - IIc – depressed
- **III** - excavated
Chromo-endoscopy
Contrast endoscopy

- Indigocarmine (0.5%)
- Cells not stain
  - Pooling between pits
  - Aim –
    - to improve the contrasting effect
    - For delineation of early gastric cancer / possible lesions
S-colon: 8mm IIc, sm1 (microscopically extended submucosal cancer)
High-grade dysplasia in the long-standing UC (19yrs aft. Onset)
BE by chromoendoscopy

• 400 patients with suspected SSBE

• Chromoendoscopy with 0.5% crystal violet

• Detecting BE with sensitivity 89.2% specificity 85.7%

Amano Y et al. Am J Gastro 2005
Disadvantages of dye spraying method

- Spray to the entire stomach or colon:
  time consuming and relatively high cost

- Methylene blue:
  less expensive and obtain good images
  induce oxidative damage of DNA when photosensitized by white light


Alternative safe and convenient method instead of dye spray?
Magnifying endoscopy
Early gastric cancer

- 80 times optical magnification
- Subepithelial microvascular architecture (MV)
- Muscosal pit pattern / Microsurface structure (MS)
Magnifying endoscopy
Early gastric cancer

Subepithelial capillary network (SECN)

1. Density of vessel
2. Extend of branching
3. Diameter & length of vessels
4. Direction of vessels

Akisato et al. Keio J Med 1973
Magnifying endoscopy
Early gastric cancer

• SECN

• Microvasculature size
  – EGC vessels significantly larger than benign gastric lesions upon magnifying endoscopy

  – $4.45 \pm 0.29$ vs $4.03 \pm 0.25$ (p<0.0001)

Ohashi et al. Endoscopy 2005
Magnifying endoscopy
Early gastric cancer

- Microsurface structure (MS)
- Loss of regular pit pattern
  - 83% accuracy
  - 97% sensitivity
  - 81% specificity

Dinis-Ribeiro et al. GIE 2003
Yoshida et al. GIE 2005
Chromoendoscopy
Disadvantages

- Need dye assisted assessment
- Need time to prepare
- Vigorous wash of mucus before application
- Dye induced discomfort
Novel Endoscopic Technology
Towards Optical Chromoendoscopy...

Recognition of Early Gastric Cancer

Narrow band imaging

Autofluorescence endoscopy
NBI plus magnifying endoscopy
Normal gastric mucosa

- Subepithelial capillary network (SECN)
- Normal Gastric Body
  - Polygonal loop
  - Connecting venules (CV)

Yao et al GIE 2002
White light is composed of various wavelengths. Looks White

NBI Filter = Specially Coated Glass

Narrow Band Illuminations

#1

#2
Narrow-band imaging system changes conventional optical filters (red, green, blue) to spectral narrow band filters.
Narrow-band imaging system

- visible blue light penetrating only superficial areas of the tissue
- blue light with NB filter (415 nm) is well absorbed well by Hb so that NBI can image the superficial capillary structures
Structure of Vessels in Human Tongue

415nm 445nm 500nm 540nm 600nm
Magnifying NBI image of gastric mucosa
NBI plus magnifying endoscopy
Normal gastric mucosa

- Normal Gastric Antrum
  - **SECN**: coiled shaped
  - No connecting venules
  - **CV** occurs in deeper part of lamina propria of antrum than body

Yao et al 2007
Mucosal Vessel Network

NBI showing not only thick veins but also fine capillaries
Comparing conventional vs NBI Colonoscopy

A 0-IIa lesion (7mm in diameter) seen as a brown lesion. The pit pattern (IIIs, IIIL) by Kudo is seen in magnification
NBI plus magnifying endoscopy
Early Gastric Cancer limit to mucosa

- **Microvascular pattern / SECN**
  - Irregular
  - Torturous

- **Microstructure pattern / pit**
  - Irregular
  - Absence of central pit

Yao et al. 2007
NBI plus magnifying endoscopy

Early Gastric Cancer beyond submucosa

- Microvascular pattern / SECN
  - Neovascularization

- Microstructure pattern / pit
  - Loss of pit pattern

Yoshida et al GIE 2005
Blue fringe⇒
Light blue crest:
A fine, blue-white line on the crests of the epithelial surface/gyri

LBC may be originated by dense reflection of the short \( \lambda \) at the ciliated tissue structure.

*An image of Beroe cucumis Fabriciiu was provided by Ito K.

Duodenal mucosa
<table>
<thead>
<tr>
<th></th>
<th>Fine network</th>
<th>Cork screw</th>
<th>Unclassify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiated</td>
<td>66.1%</td>
<td>3.7%</td>
<td>30.3%</td>
</tr>
<tr>
<td>(109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>3.6%</td>
<td>85.7% *</td>
<td>10.7%</td>
</tr>
<tr>
<td>(56)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $P = 0.0011$

Nakayoshi et al. Endoscopy 2005
AFI images of early gastric cancers

Pyloric growth

Fundic atrophy

Uedo N, Gastrointest Endosc 2005;62:521-8
**Optical Chromoendoscopy**

Autofluorescence imaging (AFI)

- Difference in endogenous fluorophores between normal & cancer

- **Xillix LIFE**
  - Need fibreoptic endoscope

- **Olympus AFI (Q240FZ)**
  - Videoscope
Autofluorescence imaging
Early Gastric Cancer
## Diagnostic accuracy for EGC

<table>
<thead>
<tr>
<th></th>
<th>No of lesions</th>
<th>WLI</th>
<th>AFI</th>
<th>Chromo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>22</td>
<td>8 (36%)</td>
<td>15 (68%)</td>
<td>20 (91%)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>6</td>
<td>1 (17%)</td>
<td>2 (33%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Flat extension</td>
<td>5</td>
<td>5 (20%)</td>
<td>4 (80%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

Uedo et al Dig Endosc 2006
Color difference in background mucosa

Fundic

Atrophic
<table>
<thead>
<tr>
<th></th>
<th>Color of the gastric body</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Purple (n=36)</td>
<td>Green (n=26)</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>0.9 ± 0.7</td>
<td>0.9 ± 0.8</td>
<td>0.624</td>
</tr>
<tr>
<td>Inflammation</td>
<td>2.1 ± 0.8</td>
<td>1.9 ± 0.5</td>
<td>0.975</td>
</tr>
<tr>
<td>Atrophy</td>
<td>1.6 ± 0.6</td>
<td>1.9 ± 0.8</td>
<td>0.030</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>0.8 ± 1.2</td>
<td>2.0 ± 1.0</td>
<td>0.000</td>
</tr>
</tbody>
</table>
AFI/NBI in diagnosis of Hp associated gastritis

- AFI shows extent of mucosal atrophy as green areas in the gastric body
- NBI visualizes areas containing intestinal metaplasia as whitish patchy areas
- LBC in magnifying NBI is an accurate sign for the diagnosis of intestinal metaplasia
- It requires neither drug administration nor dye spraying
Why is the lesion?
What is it?
How extensive?
How deep?

EMR with ESD – T1m
What to do?

ESD – T1m
Is it an ulcer?
Probably not
Virtual Histopathology
Virtual Histopathology
Early Gastric Cancer

Recognition of Early Gastric Cancer

Histopathology

Endocytoscopy

Confocal endomicroscopy
Endocytoscopy

- **Prototype**
  - 400x or 1100x

- **Contact endoscope**
  - From working channel

- **Observation to cellular level**
Endocytoscopy

Results

- 87 cases
  - 95.4% high quality images
  - 18 cases gastric cancer
  - 4 of these cannot get good images because of mucus

Inoue et al Endoscopy 2006; Inoue et al Gastrointest Endoscopy Clin N Am 2004
Endocytoscopy
Early gastric cancer
Confocal endomicroscopy

Argon ion laser wavelength 488nm
Scan rate 0.8 (1024x1024 pixels)-1.6 (102x/512 pixels) frames/sec
Optical slice thickness 7μm
Lateral resolution 0.7μm

Pentax (EC3870K)
Diameter 12.8mm
Distal tip: air and water nozzle
2 Light guides
Auxiliary water jet
2.8mm working channel
Confocal endomicroscopy

Acraflavine stain superficial epithelial cells

Fluorescin stains deeper laminar propria and vessels
Detection of aberrant crypts

Keisslich et al. GE 2004

Normal colonic mucosa
1. Goblet cell
2. Crypt lumen
3. Stroma

Aberrant colonic crypt

Fusion of crypts with irregular shape

A

B

80 μm

A

B

80 μm
Confocal Endomicroscopy
Confocal endomicroscopy
Early gastric cancer

- 2004 - 2006
- 54 patients: confocal endomicroscopy examination
  - 27 EGC
  - Pathologist interpretation
  - Accuracy of diagnosis 94.2% to 96.2%

Kitabatake et al Endoscopy 2006
Seeing beyond naked eyes

White light endoscopy

Screening through AFI

No suspicious area
Capsule Endoscopy

Suspicious lesion
Magnifying endoscopes
NBI: vascular and pit pattern
EUS: depth of lesion
Endocytoscopy
Confocal Endomicroscopy
Endoscopic Submucosal Dissection
Conclusions

• Novel technology enhanced the endoscopic detection and assessment for early cancers to determine the size and depth

• Optical biopsy is feasible with endocytoscopy and confocal endomicroscopy

• One-step endoscopic management is possible from diagnosis, staging to curative resection
Prince of Wales Hospital
The Chinese University of Hong Kong