INTRODUCTION

- Diagnostic difference of gastric epithelial neoplasia between Japanese and Western pathologists
- We have same problems in diagnosis of gastric epithelial neoplasia in Korea, due to confused and complicated criteria between pathologists
Topics

- Classification & Terminology
- Problems of Current Diagnosis of Gastric Epithelial Neoplasm:
  - Current Problems
  - Suggestion in Pathologic Diagnosis
- EMR/ESD
- Case Review and Consensus
Classification & Terminology (I)

- **Dysplasia**: atypical changes in the epithelium considered to be precancerous.
- **Adenoma**: a circumscribed benign neoplasm composed of tubular and/or villous structures lined by dysplastic epithelium (WHO).

Morphological classification of Gastric adenoma:

- Polypoid
- Flat
- Depressive
Lining epithelium is same as dysplastic

Dysplasia = Adenoma

Classification & Terminology (II)

- Japanese Classification
  - Group I: normal mucosa and benign lesion with no atypia
  - Group II: lesions showing atypia but diagnosed as benign
  - Group III: borderline lesions between benign and malignant
  - Group IV: lesions strongly suspected of carcinomas
  - Group V: Carcinoma

Classification & Terminology (II)

- The Padova International Classification of Gastric Dysplasia
  1. Negative for dysplasia
  2. Indefinite for dysplasia
  3. Non-invasive neoplasia
     1) low-grade
     2) high-grade: including carcinoma without invasion (intraglandular)
  4. Suspicious for invasive carcinoma
  5. Invasive adenocarcinoma


Classification & Terminology (III)

- Korean Grading System for Gastric Epithelial Neoplasia
  I. Normal epithelium or atypical changes interpreted as regenerative process
  II. Atypical changes interpreted as questionable dysplasia
  III. Low grade dysplasia
  IV. High grade dysplasia
  V. Overt carcinoma

Problems (I)

Japanese viewpoint

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>L</th>
<th>H</th>
<th>S</th>
<th>D</th>
<th>Tot</th>
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<td>2</td>
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<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Tot</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>29</td>
<td>35</td>
</tr>
</tbody>
</table>

Agreement: 13/35 = 37%
Kappa coefficient: 0.16
(95% CI 0.05–0.26)

Problems (II)

Big Diagnostic Discrepancy in Gastric Epithelial Neoplasia in Korea


The Vienna classification of gastrointestinal epithelial neoplasia

Category 1. Negative for neoplasia/dysplasia
Category 2. Indefinite for neoplasia/dysplasia
Category 3. Non-invasive neoplasia low grade neoplasia
Category 4. Non-invasive high grade neoplasia
  4.1 High grade adenoma/dysplasia
  4.2 Non-invasive carcinoma (carcinoma in situ)
  4.3 Suspicious of invasive carcinoma
Category 5. Invasive neoplasia
  5.1 Intramucosal carcinoma
  5.2 Submucosal carcinoma or beyond


But Still Problems in Category 4

By Vienna Classification
Vienna Classification Category 4

- Category 4. Non-invasive high grade neoplasia
  - 4.1 High grade adenoma/dysplasia
  - 4.2 Non-invasive carcinoma (carcinoma in situ)
  - 4.3 Suspicious of invasive carcinoma

Still Big Discrepancy

Most Western Pathologist still think that
“ It is still High grade” (4.1)
(Most Japanese Pathologist still think that
“ It is still adenocarcinoma” (4.2 or 4.3)

Japanese Point of View

- Histological diagnosis of biopsy materials in submucosal invasive cancer confirmed by surgical specimen
  - C 4.1 (high-grade) 1%
  - C 4.2 (Non-invasive carcinoma (carcinoma in situ) 29%
  - C 4.3 (Suspicious invasive carcinoma) 0%
  - C 5.1 (Intramucosal ca) 37%
  - C 5.2 (submucosal ca) 33%
Problems (II)

Big Diagnostic Discrepancy in Gastric Epithelial Neoplasia in Korea and Japan

Differential Diagnosis between atypical regenerative change and well differentiated adenocarcinoma

The 8th Korea–Japan Gastrointestinal Pathology Seminar Japan–Korea GI Meeting Consensus Conference, Yokohama, 2008, Feb

Problems of
- Well-differentiated adenocarcinoma with low-grade atypia by Japanese Pathologist
- Definition of invasion (lamina propria)

The 8th Korea–Japan Gastrointestinal Pathology Seminar Japan–Korea GI Meeting Consensus Conference, Yokohama, 2008, Feb
Problems of Well-differentiated adenocarcinoma with low-grade atypia by Japanese Pathologist and definition of invasion (lamina propria)

The 8th Korea–Japan Gastrointestinal Pathology Seminar Japan–Korea GI Meeting Consensus Conference, Yokohama, 2008, Feb
Summary of Problems

- Big discrepancy in diagnosis of gastric epithelial lesion between Korea and Japan, same as between Korean pathologists

Main Causes of Problems
- definition of high-grade and low-grade
- definition of adenocarcinoma
- definition of invasion

Grading of Gastric adenoma

- Two tier system (low and high grade)

- 핵의 길이가 세포길이의 ½이하: low
  핵의 길이가 세포길이의 ½이상: high
  (위암병리보고서표준화, 2005)

- 위암병리보고서표준화, 2005
  Vienna Classification
  Pavoda Classification
  Japanese Classification
Grading of gastric adenoma

- Architectural Features
  - Glandular disarray
  - Intralumina foldings
  - Glandular budding, branching, dilatation

- Cytologic Features
  - Nuclear pleomorphisms
  - High N/C ration
  - Loss of nuclear polarity with pseudostratification

Grading adenoma by Korean Pathologists

Grading adenoma by Western Pathologists

Low grade

High grade

Grading adenoma by Japanese Pathologists

Tubular Adenoma with moderate dysplasia

Well differentiated Adenocarcinoma

<table>
<thead>
<tr>
<th>Low-Grade Dysplasia</th>
<th>High-Grade Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architectural Features</strong></td>
<td><strong>Architectural Features</strong></td>
</tr>
<tr>
<td><em>mild to moderate glandular disarray and crowding</em></td>
<td><em>marked glandular disarray</em></td>
</tr>
<tr>
<td><em>mild to moderate branching</em></td>
<td><em>glandular crowding with back to back glands</em></td>
</tr>
<tr>
<td><em>rare budding</em></td>
<td><em>moderate to marked branching with frequent budding</em></td>
</tr>
<tr>
<td><em>intraluminal folding and cribriforming</em></td>
<td></td>
</tr>
<tr>
<td><strong>Nuclear Features</strong></td>
<td><strong>Nuclear Features</strong></td>
</tr>
<tr>
<td><em>elongated hyperchromatic nuclei</em></td>
<td><em>round vesicular nuclei</em></td>
</tr>
<tr>
<td><em>basally located with maintained polarity</em></td>
<td><em>prominent nucleoli</em></td>
</tr>
<tr>
<td><em>moderately increased mitotic activity</em></td>
<td><em>markedly increased mitotic activity</em></td>
</tr>
<tr>
<td></td>
<td><em>atypical mitoses</em></td>
</tr>
</tbody>
</table>

Gastric Adenoma

Adenocarcinoma

Adenomatous type Gastric Adenoma
Definition of adenocarcinoma

- Japanese:
  diagnosis of carcinoma was based on cytological changes and architectural changes *regardless of presence of invasion*
  - variably sized and enlarged nuclei
  - round nuclei, loss of polarity, prominent nucleoli
  - complex budding or branching of glands, back to back glands
Well differentiated adenocarcinoma with low-grade atypia by Japanese Pathologists

Fig.1 Well-differentiated adenocarcinoma with low-grade atypia without intramucosal and submucosal invasion of biopsy(a) and EMR specimens (b)

Definition of Well-differentiated adenocarcinoma with low grade atypia

<table>
<thead>
<tr>
<th>Structural findings</th>
<th>Low grade Ca</th>
<th>High grade Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density of gland</td>
<td>high (50 %~)</td>
<td>high (70 %~)</td>
</tr>
<tr>
<td>Shape and size of gland</td>
<td>regular~irregular</td>
<td>irregular</td>
</tr>
<tr>
<td>Structural atypia</td>
<td>papillary, villosus branching, budding gland in gland</td>
<td>small and large cribriform pattern gland in gland</td>
</tr>
<tr>
<td>Surface differentiation</td>
<td>+ ~ -</td>
<td>-</td>
</tr>
<tr>
<td>Nuclear findings</td>
<td>oval~round, small</td>
<td>round, irregular</td>
</tr>
<tr>
<td>Shape and size</td>
<td>slight irregular</td>
<td>large</td>
</tr>
<tr>
<td>Atypia</td>
<td>regular~irregular</td>
<td>irregular, pill up</td>
</tr>
<tr>
<td>Arrangement</td>
<td>( + ) ~ ( - )</td>
<td>( - )</td>
</tr>
<tr>
<td>Polarity</td>
<td>irregular, dot-like</td>
<td>irregular, hyperchromatic clear, numerous</td>
</tr>
<tr>
<td>Chromatin pattern</td>
<td>( - )</td>
<td>( - )</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>clear</td>
<td>clear, increase (40 %~)</td>
</tr>
<tr>
<td>N/C ratio</td>
<td>increase (40 %~)</td>
<td>increase (50 %~)</td>
</tr>
<tr>
<td>Proliferative activity</td>
<td>expansion &amp; high LI*</td>
<td>expansion &amp; high LI*</td>
</tr>
<tr>
<td>Expression of p53</td>
<td>30~40 %</td>
<td>60~70 %</td>
</tr>
</tbody>
</table>

*Labeling index.

### Definition of Well–differentiated adenocarcinoma with low grade atypia

**Table 2** Histological diagnostic criteria of tubular carcinoma of GI-tract

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<tr>
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<td>irregular</td>
</tr>
<tr>
<td>Structural atypia</td>
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<td>small and large</td>
</tr>
<tr>
<td></td>
<td>branching, budding</td>
<td>cribriform pattern</td>
</tr>
<tr>
<td></td>
<td>gland in gland</td>
<td>gland in gland</td>
</tr>
<tr>
<td>Surface differentiation</td>
<td>(+) ~ (-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

### Definition of Well–differentiated adenocarcinoma with low grade atypia

<table>
<thead>
<tr>
<th>Nuclear findings</th>
<th>oval ~ round, small</th>
<th>round, irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape and size</td>
<td>slight irregular</td>
<td>large</td>
</tr>
<tr>
<td>Atypia</td>
<td>(+)</td>
<td>(+++)</td>
</tr>
<tr>
<td>Arrangement</td>
<td>regular ~ irregular</td>
<td>irregular, piling up</td>
</tr>
<tr>
<td>Polarity</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Chromatin pattern</td>
<td>irregular, dot-like</td>
<td>irregular, hyperchromatic</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>clear</td>
<td>clear, numerous</td>
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<tr>
<td>N/C ratio</td>
<td>increase (40% ~)</td>
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<td>Proliferative activity</td>
<td>expansion &amp; high Li^®</td>
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</tr>
<tr>
<td>Expression of p53</td>
<td>30 ~ 40%</td>
<td>60 ~ 70%</td>
</tr>
</tbody>
</table>

*Labeling index.*
Well differentiated adenocarcinoma with Low Grade Atypia

Well differentiated adenocarcinoma High Grade Atypica
Well differentiated adenocarcinoma High Grade Atypica

Definition of Invasion

- Japanese definition of invasion: demarcation from and compression of the normal surrounding tissue
  - equated to invasion
  - very well differentiated adenocarcinoma with low grade atypia
Definition of adenocarcinoma

- Western:
  - diagnosis of carcinoma was based on invasion
    - infiltration of the lamina propria muscularis mucosae by neoplastic epithelium
Lamina Propria Invasion by Signet Ring cell Carcinoma

Irregular Malignant Glands in Fibrotic Lamina Propria
Lamina Propria Invasion or Not?
Lamina Propria Invasion or Still in Basement Membrane?

Lamina Propria Invasion or Atypical Fused glands?
Definition of Invasion

- Still Dilemmas
  - Benign looking glands with muscularis mucosae or submucosal invasion
  - true invasion or pseudoinvasion
    - chronic ulcer or gastritis cystica

S07–21*** F/51
Stomach, Antrum, PW
Depressive lesion
Depressive adenoma with low-grade dysplasia

Muscularis Mucosae Invasion or Not?
Depressive adenoma with low-grade dysplasia: with ulceration

Muscularis Mucosae Invasion or Not?

S07–17*** M/65
Stomach, Antrum, LC
Sharply elevated + flat lesion
Flat adenoma with low-grade dysplasia

Submucosal Invasion of Benign-looking adenomatous glands?
S07–22*** M/56
Stomach, midbody, LC
Elevated Lesion

Submucosal Invasion or adenomatous changes in gastritic cystica profunda?
To overcome Problems I

- Define diagnostic criteria of adenocarcinoma and definition of invasion: Consensus
- Heterogeneity of lesion
  - Standardized Sampling
  - Adequacy of Specimen
- Need GI pathologists
  - In view of the experience of dysplasia in Barrett’s esophagus
Management of GED in view of Barrett’s dysplasia

- Four quadrant biopsy in Barrett’s: define sample number according to size
- Consensus criteria for grading dysplasia in Barrett’s by Reid: define consensus criteria for GED
- Need specialist to confirm high-grade dysplasia in Barrett’s esophagus: need GI pathologists


<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Follow-Up Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two EGDs with biopsy</td>
<td>3 yr</td>
</tr>
<tr>
<td>Low grade</td>
<td>Highest grade on repeat</td>
<td>1 yr until no dysplasia, Focal—every 3 mo</td>
</tr>
<tr>
<td>High grade</td>
<td>Repeat EGD with biopsy to rule out cancer/document high-grade dysplasia, expert pathologist confirmation</td>
<td>Multifocal—intervention, Mucosal irregularity—EMR</td>
</tr>
</tbody>
</table>

High grade: Repeat EGD with biopsy to rule out cancer/document high-grade dysplasia, expert pathologist confirmation
To overcome Problems III

MOST IMPORTANT !!!

Endoscopic resection of gastric epithelial lesion

- ESD/EMR Criteria
- Handling of EMR Specimen
Treatment Strategies of Gastric Cancer


Endoscopic resection techniques of gastric epithelial neoplasia


Endoscopic mucosal resection (EMR)  Endoscopic submucosal dissection (ESD)
### EMR Indication

<table>
<thead>
<tr>
<th>Histology</th>
<th>Mucosal cancer</th>
<th>Submucosal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UL(-)</td>
<td>UL(+)</td>
</tr>
<tr>
<td>Differentiated</td>
<td>20 ≤ 30</td>
<td>30 ≤ 30&lt;</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Guideline criteria for EMR**
- **Surgery**

### ESD Indication

<table>
<thead>
<tr>
<th>Histology</th>
<th>Mucosal cancer</th>
<th>Submucosal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UL(-)</td>
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<tr>
<td>Differentiated</td>
<td>20 ≤ 30</td>
<td>30 ≤ 30&lt;</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Guideline criteria for EMR**
- **Surgery**
- **Extended criteria for ESD**
- **Consider surgery**
EMR/ESD Indication based on the following data

Table 1. Early gastric cancer with no risk of lymph node metastasis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramucosal cancer</td>
<td>0/1230; 0%</td>
<td>0–0.3%</td>
</tr>
<tr>
<td>Differentiated adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irrespective of ulcer findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor less than 3 cm in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intramucosal cancer</td>
<td>0/929; 0%</td>
<td>0–0.4%</td>
</tr>
<tr>
<td>Differentiated adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without ulcer findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irrespective of tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated intramucosal cancer</td>
<td>0/141; 0%</td>
<td>0–2.6%</td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without ulcer findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor less than 2 cm in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute submucosal penetration (SM 1)</td>
<td>0/145; 0%</td>
<td>0–2.5%</td>
</tr>
<tr>
<td>Differentiated adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor less than 3 cm in size</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EMR/ESD Report

S04–66** 정00 F/67 960*****

Stomach, antrum, ESD:

Adenocarcinoma, tubular–well differentiated (tub1), intestinal, EGC type 0–lic, 2x0.5cm in size
1) confind to mucosa
   (muscularis mucosae invasion without penetration)
2) no definite evidence of lymphovascular tumor emboli
3) status of resection margins: LM(+)/VM(–)

S08–9918 PNUH 48/F Antrum