Standard endoscopic treatment for gastric cancer

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Topics

• Brief history of gastric ESD in Korea
• Indications of ESD in Korea
• Outcomes of ESD for EGC
• How to teach and learn ESD?
History of gastric ESD in Korea

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The first report on EMR for EGC in Korea

EMR for adenocarcinoma: 19 cases

- operation(+) 7 cases
- operation(-) 12 cases
  - 4 resection margin(+)
  - 1 incomplete resection
  - 2 F/U GFS, recur

- Surgical specimen
- F/U gastroscopy

- cancer(+) 5 cases
- cancer(-) 2 cases
- cancdr(+) 4 cases
- cancer(-) 8 cases

- Depth of invasion:
  - m: 3
  - sm: 2

- Burning effect:
  - condition: for 3~13 mo
  - LC, burning
  - COPD, MM, effect: 2

- Age:
  - group A
  - group B
  - group C
  - group D

Lee JH. Korean J Gastrointest Endosc 1996;16:928-934
Early personal experience of gastric ESD (2005)
ESD for EGC in Korea
- From Nov 2011 – Dec 2014

• Number of ESD for EGC cases: 23,828
• Age: 64.9 +/- 9.9 years (median: 66)  
• Male: female = 74.2% : 25.8%  
• Hospital stay: 5.0 days  
• Medical cost in 2014: 1,510,000 won (1,305 US dollars)  
• Surgery within 3 months after ESD: 6.6%
Treatment of gastric cancer at SMC

In 2015, there was a MERS outbreak.
Indications of ESD in Korea

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Indications are different from criteria

**Indication**
- Pre-treatment
- Selection of ESD candidates

**Criteria**
- Post-treatment
- Additional surgery after ESD
# Absolute and expanded indications
*
- **Traditional classification**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Depth</th>
<th>M cancer</th>
<th>SM cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No ulceration</td>
<td>Ulcerated</td>
</tr>
<tr>
<td>Differentiated</td>
<td></td>
<td>≤ 20 mm</td>
<td>&gt; 20 mm</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B1</td>
<td>B2</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>C</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>

- **A** absolute indication for ER
- **B** expanded indications for ER
- **C** expanded indications for ER
- **D** surgery (gastrectomy + lymph node dissection)
Absolute indication EGC by pre-treatment diagnostic groups

Pre-Tx AI EGC 396

ESD 355
- LGD 1
- HGD 4
- AI EGC 229
- BAI EGC 120

AGC 1
- ESD 1
- Surgery 53

Operation 41
- LGD 1
- AI EGC 29
- BAI EGC 11

Reason for surgery (multiple)
- Suspicious lymphadenopathy on CT (18)
- Multiple lesions (6)
- Patient’s wish (18)
- Difficult location (3)
- Suspicious SM invasion on EUS (2)

* BAI: beyond absolute indications

Lee JH. Surg Endosc 2016;30:3987-93
Standard indications of ESD in Korea

• ESD candidates are usually selected by the absolute indications.

• After ESD, expanded criteria is applied to determine whether the resection was curative.

• There are controversies about the safety of ESD for expanded indication cases.
Statement 1. Endoscopic resection is recommended for well or moderately differentiated tubular or papillary early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size \( \leq 2\text{cm} \), endoscopically mucosal cancer, and no ulcer in the tumor.

(evidence: moderate, recommendation: strong for)
Do you think total gastrectomy was necessary for a 45 years old lady with 1 cm signet ring cell carcinoma?

- Signet ring cell carcinoma, 1cm, limited in the lamina propria layer
What would you recommend for a 40 years old woman with a small flat signet ring cell carcinoma?
SRC. 10x6mm, lamina propria, clear resection margins, no lymphatic invasion
ESD for expanded indication

• ESD for expanded indication cases can be selectively performed in the individual cases.

• Flat small signet ring cell carcinomas are frequently treated by ESD in Korea.
Statement 2. Endoscopic resection could be performed for well or moderately differentiated tubular early gastric cancer or papillary early gastric cancers with the following endoscopic findings: endoscopically estimated tumor size >2 cm, endoscopically mucosal cancer, and no ulcer in the tumor or endoscopically estimated tumor size ≤3 cm, endoscopically mucosal cancer, and ulcer in the tumor. (evidence: moderate, recommendation: weak for)
Outcomes of ESD for EGC

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Outcome of endoscopic treatment of EGC with differentiated-type histology

1. ITT analysis (both curative and non-curative resection cases)
   • Comparison with surgery (propensity score matched cohort)

2. PP analysis
   1) Curative-resection cases: single-arm long-term data
   2) Non-curative resection cases: comparison between surgery group and observation group
Differentiated type EGC (2002-2012) (n = 3595)

Excluded:
1) LNM on CT or EUS (n=6)
2) Previous gastric cancer (n=20)
3) Cancer of other origin (n=150)
4) Follow up < 2 years (n=856)

EGC meeting indication treated with curative intent (n = 2563)

Endoscopic resection (n = 1290)

Surgery (n = 1273)

Propensity score matching

Endoscopic resection (n = 611)

Surgery (n = 611)

ITT analysis: comparison with surgery - Propensity score matching, differentiated type EGC

Pyo JH. Am J Gastroenterol 2016
Endoscopic resection

Overall survival

- Endoscopic resection
- Surgery

Log rank $P=0.827$

Disease free survival

Log rank $P<0.001$

Disease specific survival

Log rank $P=0.891$

Recurrence free survival

Log rank $P<0.001$

Pyo JH. Am J Gastroenterol 2016
PP analysis (1): single-arm follow-up
- Differentiated, curative (n=1,306)

- EGCs treated by ESD at Samsung Medical Center
- 1,838 patients with 1,889 differentiated-type EGCs
- November 2003 – May 2011
- Censoring date: May 2014
- Differentiated-type EGC
  - Well or moderately differentiated or papillary EGC
  - According to the quantitatively predominant histologic type
  - Differentiated-type EGC > 50%

Min BH. Endoscopy 2015
PP analysis (1): single-arm follow-up
- Differentiated, curative (n=1,306)

- Median follow-up: 61 months (range 17-122)
- Local recurrence: 0.08% (1/1,306)
- Metachronous recurrence: 3.6% (47/1,306)
  - Definition of metachronous recurrence: at least 12 months after ER
- Extragastric recurrence: 0.15% (2/1,306)
- 5-year overall survival
  - Absolute indication: 97.3%
  - Expanded indication: 96.4%
Overall-survival
- 1,306 curative ESDs from December 2003 to May 2011

Min BH. Endoscopy 2015
Two extragastric recurrences (0.15%)

Fig. 4 Two cases of extragastric recurrence after curative endoscopic submucosal dissection (ESD) for early gastric cancer. a–e Patient #1 in Table 3 (Present study): the cancer met the absolute indication and was treated with curative ESD, and was located at the angle. a Esophagogastroduodenoscopy (EGD) appearance of lesion before ESD. b EGD view 61 months after ESD. c 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) image 61 months after ESD; hypermetabolic lesions are seen in perigastric lymph nodes. d Histological appearance of ESD specimen (hematoxylin and eosin [H&E], × 200). e Histological appearance of lymph node with cancer cell infiltration (H&E, × 200). f–j Patient #2 in Table 3 (Present study): the cancer met the expanded indication and was treated with curative ESD, and was located at the antrum. f EGD appearance of lesion before ESD. g EGD view 48 months after ESD. h 18F-FDG PET-CT image 48 months after ESD; hypermetabolic lesions are seen in lymph nodes around the common hepatic artery. i Histological appearance of ESD specimen (H&E, × 200). j Histological appearance of lymph node with cancer cell infiltration (H&E, × 200).
Extragastric recurrence after curative endoscopic resection in Korea

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Rate of extragastric recurrence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsung Medical Center</td>
<td>0.15% (2/1,306)</td>
<td>Min BH. Endoscopy 2015</td>
</tr>
<tr>
<td>Asan Medical Center</td>
<td>0.14% (5/3,588)</td>
<td>Lee S. Gastric Cancer 2017</td>
</tr>
<tr>
<td>Severance Hospital</td>
<td>0.15% (2/1347)</td>
<td>Hahn KY. Gastrointest Endosc 2016</td>
</tr>
<tr>
<td>Seoul National University</td>
<td>0.50% (2/404)</td>
<td>Choi KS. Radiology 2016</td>
</tr>
</tbody>
</table>
7 more extragastric recurrences after the publication
#7. M/D, 16mm, SM 400um
- Enlarged lymph node at CT, 17 months after ESD
#7. M/D, 16mm, SM 400\textmu m

- Enlarged lymph node at CT, 17 months after ESD
#7. M/D, 16mm, SM 400um
- Enlarged lymph node at CT, 17 months after ESD

- Stomach, subtotal gastrectomy: Status ESD
- Gastric location: cannot be determined (no residual tumor)
- Lymph node metastasis: metastasis to 1 out of 22 regional lymph nodes (pN1) (perinodal extension: present)
  
  (1/22: "LN#6" for frozen section-1, 1/1; "3,5", 0/3; "4,6", 0/6; "5", 0/0; "6", 0/3; "7", 0/2; "9", 0/2; "8a", 0/2; "11p", 0/2; "12a", 0/1; "4sb", 0/0; "1", 0/0)
PP analysis (2): non-curative resection
- Comparison between surgery and observation group

Noncurative resection 341

Lateral margin positive 67 (19.6%)

Risk of lymph node metastasis 274 (80.4%)

- Surgery 194 (70.8%)
  - Lymph node 11 (5.6%)
  - Local residual 10 (5.2%)

- Observation 80 (29.2%)
  - Patients’ refusal: 64
  - High surgical risk: 8 (severe comorbidities)
  - Concomitant advanced cancer in other organs: 8

Kim ER. Br J Surg 2015
Predictors of LN metastasis (5.7%)

Table 2  Comparison of clinicopathological characteristics according to the presence of lymph node metastasis among patients undergoing rescue surgery

<table>
<thead>
<tr>
<th></th>
<th>No LN metastasis (n = 183)</th>
<th>LN metastasis (n = 11)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(s.d.)</td>
<td>62.4(8.4)</td>
<td>68.6(8.7)</td>
<td>0.019†</td>
</tr>
<tr>
<td>Median (range)</td>
<td>63.0 (44–84)</td>
<td>68.1 (57–80)</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>142 : 41</td>
<td>8 : 3</td>
<td>0.715</td>
</tr>
<tr>
<td>Tumour site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum, angle</td>
<td>119 (65.0)</td>
<td>9 (82)</td>
<td>0.338</td>
</tr>
<tr>
<td>Body, fundus, cardia</td>
<td>64 (35.0)</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td>Mean(s.d.) tumour size (cm)</td>
<td>2.1(1.1)</td>
<td>2.6(1.2)</td>
<td>0.113†</td>
</tr>
<tr>
<td>Tumour depth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>19 (10.4)</td>
<td>0 (0)</td>
<td>0.295‡</td>
</tr>
<tr>
<td>SM1</td>
<td>30 (16.4)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>SM invasion depth ≥ 500 μm</td>
<td>134 (73.2)</td>
<td>10 (91)</td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td>0.128</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>37 (20.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>146 (79.8)</td>
<td>11 (100)</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>No</td>
<td>76 (41.5)</td>
<td>5 (45)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (58.5)</td>
<td>6 (55)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise. LN, lymph node; SM1, submucosal invasion depth less than 500 μm from muscularis mucosa layer; SM, submucosal. *χ² test, except †Student’s t test. ‡Mucosa or SM1 versus SM invasion depth of 500 μm or more.
Overall survival

- Median duration of follow-up after ER: 60.5 months (6-141)

![Graph showing overall survival over time after endoscopic resection. The graph compares 'Rescue surgery' with 'No treatment'. The number of patients at risk is given for each group at different time points: Rescue surgery: 194, 193, 169, 98, 53; No treatment: 80, 77, 62, 39, 16.](Image)
Survival benefit of additional surgery
- Additional surgery: 127, follow-up: 67

Additional surgery group
Observation group

Eom BW. Gastrointest Endosc 2017;85:155-63
Is surgery necessary for mucosal cancer with lymphovascular invasion?

Table 3. Lymph node metastasis rate according to criteria in EGC patients with lymphovascular invasion

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Ulceration</th>
<th>Differentiated (%)</th>
<th>Undifferentiated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td>Ulcer (−)</td>
<td>≤ 2 cm</td>
<td>&gt; 2 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0/28 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulcer (+)</td>
<td>≤ 3 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/2 (50.0)</td>
<td></td>
</tr>
<tr>
<td>SM1</td>
<td></td>
<td>≤ 3 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/61 (11.5)</td>
<td></td>
</tr>
</tbody>
</table>

SM1 < 500 μm from the muscularis mucosae
How to teach and learn ESD?

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Must knows before starting ESD

- Indications and skills for careful endoscopic evaluation for candidate lesions
- Advantages and disadvantages of each instrument
- Strategies for technically successful ESD
- How to manage complications

- Side by side hands-on training
IT knife and needle-type knife

- Mucosectom
- Flush knife
- Dual knife
- ClutchCutter
- B knife
- Flex knife
- Hook knife
- SAFE knife
- Needle knife
- IT knife
- TT knife
- IT knife2
- SB knife Jr.

Timeline:
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
ESD knives with water-jet function

http://www.finemedix.com
H-type ESD knife
- IT-type function + needle type function
ESD using H type ESD knife

Benign ulcer

EGC

I-type tip

O-type tip

W/D tubular adenocarcinoma 10mm in lamina propria, RM (-), L/V (-/-)
병소 경계 5mm 바깥에 marking proximal 부위에 추가 marking

충분한 접각화 주사 후 ①, ②, ③의 순서로 marking, 5mm 바깥쪽 접막을 충분히 cutting, muscularis mucosae가 완전히 cutting 되어 접막과 종이 충분히 보존 되도록
Location matters.

M/D, 8x8mm, MM, RM (-), L/V (-/-)
A large loop approach
Most perforations can be treated endoscopically without surgery
- Primary closure of perforation

Tubular adenocarcinoma (M/D), in lamina propria, RM (-)
When the resection is big and close to the cardia or pylorus, short-term oral steroid can be used.
The hospital stay for gastric ESD is usually 4 days.
For the beginners, hands on training using a pig stomach model is very useful.
Side by side hands-on training
- Changing the role of the main operator and the first assistant
The first ESD of a young fellow endoscopist
Tele-mentoring using Facetime is a very useful tool for ESD beginners.

International mentoring is also possible. If you want some real-time comments from me, send me an e-mail (stomachlee@gmail.com).
Unforgettable case

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ESD for EGC in an surgical ICU
ESD for EGC in a patient on ECMO due to arrest by dilated cardiomyopathy
ESD for EGC in a patients on ECMO
- Tubular adenocarcinoma, M/D, 16x7mm, MM, L/V/N (---/-/-)
Take home message

• ESD is widely performed for EGCs in the absolute indication in Korea. Annually, its more than 7,000 cases.

• We are still very careful about expanded indication cases. It’s done usually for flat SRCs less than 1 cm.

• Starting the role of the first assistant is the beginning of learning ESD techniques.