

# Different Managements for Esophageal Epithelial Neoplasms between the Japanese, Singaporean, and Korean Endoscopists

**Background/Aims:** There are controversies for the management of esophageal neoplasia due to its variety among countries. In this study, we tried to uncover the different managements on esophageal neoplasia between Korea, Singapore, and Japan. **Materials and Methods:** We administered ten questionnaires to Korean, Japanese, and Singaporean endoscopists. The questionnaire consisted of endoscopic images from ten different esophageal neoplasms. **Results:** For Barrett esophagus (BE) with adenocarcinoma ( $P=0.013$ ) and well-differentiated-type squamous cell carcinoma ( $P=0.007$ ), all (100%) of the Japanese endoscopists selected endoscopic resection as treatment, whereas 25~40% of the Korean and Singaporean endoscopists selected surgical resection. For BE with low grade dysplasia ( $P=0.002$ ) and flat-type squamous dysplasia ( $P<0.001$ ), observation without endoscopic treatment was preferred in Japan, whereas endoscopic treatment was preferred in Korea and Singapore. Similar findings between three countries were; (i) medication for BE, (ii) endoscopic treatment for BE with high grade dysplasia and elevated-type squamous dysplasia, and (iii) operation for moderately-differentiated or poorly-differentiated typed SCC. **Conclusions:** Our survey addresses different managements on esophageal neoplasia between Korea, Singapore, and Japan. More advanced or aggressive treatments are preferred in Korea and Singapore than in Japan for the management of BE with LGD, flat-type squamous dysplasia, BE with adenocarcinoma, and WD-typed SCC. (The Korean Journal of *Helicobacter* and Upper Gastrointestinal Research 2011;11: 59-64)

**Key Words:** Esophageal neoplasms; Neoplasms; Barrett esophagus

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## INTRODUCTION

Apart from the different incidences of squamous cell carcinoma (SCC) and esophageal adenocarcinoma among the countries,<sup>1</sup> there is a large discrepancy in the diagnostic criterion

for dysplasia and cancer.<sup>2,3</sup> According to the World Health Organization criteria, esophageal cancer is diagnosed when the tumor invades the lamina propria mucosa or further. If the tumor is located within the epithelium, it is diagnosed as low grade dysplasia (LGD) or high grade dysplasia (HGD), depending on the thickness of basaloid type neoplastic cells in the

epithelium. However, in Japan, the term intramucosal cancer is commonly used instead of dysplasia when the tumor is limited in the epithelium, since diagnosis is established both on cytologic and structural criteria.<sup>2,3</sup>

Due to recent advances in endoscopic techniques, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are used for the managements of early esophageal cancers and their precursor lesions. Different from standard EMR method, ESD is a time-consuming procedure that needs special devices to dissect submucosal layer beneath the gastrointestinal (GI) lesions. ESD is consisted of five main procedures; (i) marking around the lesion, (ii) pre-cutting, (iii) mucosal incision, (iv) submucosal dissection, and (v) hemostatic procedure. Although endoscopic resection allows evaluation of tumor infiltration depth, vascular invasion, and cell type of the lesion by obtaining a specimen for histological examination with minor morbidity, it is not yet preferred in some countries.<sup>4</sup>

Because of such differences among countries, managements for esophageal neoplasia might be different among endoscopists practicing in different countries. In this study, we tried to compare and contrast different endoscopic management of esophageal lesions between Korea, Singapore, and Japan.

## MATERIALS AND METHODS

### 1. Questionnaire

All questions were presented in one page and the survey took approximately 5~10 minutes to complete. All survey results were anonymous. The questionnaire included questions about each participant's background; name of the hospital and years of GI endoscopic practice.

Ten endoscopic scenarios were prepared as follows: (i) short-segment Barrett esophagus (BE), (ii) long-segment BE, (iii) BE with LGD, (iv) BE with HGD, (v) BE with adenocarcinoma, (vi) elevated-type squamous dysplasia, (vii) flat-type squamous dysplasia, (viii) SCC of well-differentiated (WD) type, (ix) SCC of moderately-differentiated (MD) type, and (x) SCC of poorly-differentiated (PD) type. Each scenario included 1 or 2 endoscopic images showing the site of the biopsy. Other provided informations included location of the lesion and histological result of the biopsied specimen. Additional information for cancerous lesions included findings of chest CT scan, PET-CT scan, and endoscopic ultrasonographic findings.

The institutional review boards of Konkuk University

Medical Center approved this survey study (KUH 1010252).

### 2. Study subjects

GI endoscopists working at Konkuk University Medical Center, Kyoto Second Red Cross Hospital, Gifu University Hospital, and University of Singapore constituted potential survey subjects. Ten questionnaires were sent in one powerpoint slide with an answer sheet. Participants were asked to choose one of the following five answers for each question; (i) observation with medication (proton pump inhibitor, etc), (ii) endoscopic ablation (argon plasma coagulation, photodynamic therapy, etc), (iii) endoscopic resection (EMR, ESD, etc), (iv) surgical resection, and (v) chemotherapy and/or radiotherapy.

### 3. Statistical analysis

For categorical variables, the counts (n) and the percentages (%) are provided. The comparisons of the categorical variables between the institutions were performed using Pearson's chi test or Fisher's exact test, as appropriate. Differences in normally distributed continuous variables (years of GI practice) were analyzed separately using ANOVA. To compare differences between two groups, t-tests were performed. Median years of GI practice were presented with range [minimum - maximum]. A *P* value less than 0.05 was considered significant.

**Table 1.** Questions and Most Frequent Answers for Each Questionnaire

Questions	Frequent answers
Q1. Short segment BE	Medication 100%
Q2. Long segment BE	Medication 95.1%
Q3. BE with LGD	Medication 70.7%
Q4. BE with HGD	EMR/ESD 87.8%
Q5. BE with adenocarcinoma	EMR/ESD 87.8%
Q6. Squamous dysplasia, elevated type	EMR/ESD 92.7%
Q7. Squamous dysplasia, flat type	EMR/ESD 51.2%
Q8. SCC, WD type	EMR/ESD 85.4%
Q9. SCC, MD type	Operation 51.2%
Q10. SCC, PD type	Operation 61.0%

BE, Barrett esophagus; LGD, low grade dysplasia; HGD, high grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SCC, squamous cell carcinoma; WD, well-differentiated; MD, moderately-differentiated; PD, poorly-differentiated.

## RESULTS

A total of 41 endoscopists (24 Japanese, 12 Korean, and 5 Singaporean endoscopists) completed answering ten questions. The most frequent answers for each questionnaires are summarized in Table 1. The years of GI practice was not different among three countries ( $P=0.689$ ) (Table 2).

### 1. Treatment for BE

All and 95.1% of the participants selected medication as a treatment for short-segment BE and long-segment BE, re-

spectively (Table 1). With regard to BE with LGD, some Korean (66.7%) and Singaporean (40%) endoscopists selected endoscopic ablation or endoscopic resection as a treatment, which was a significantly different finding from the Japanese endoscopists ( $P=0.002$ ) (Fig. 1A). For BE with HGD, most of the participants (87.8%) selected endoscopic resection as a treatment (Table 1), and there was no difference among three countries ( $P=0.081$ ). For BE with adenocarcinoma, some Korean (33.3%) and Singaporean (20%) endoscopists selected surgical resection as a treatment, whereas all of the Japanese endoscopists selected endoscopic resection ( $P=0.013$ ) (Fig. 1B).

**Table 2.** Differences between Korea, Singapore, and Japan

	Korean endoscopists (n=12)	Singaporean endoscopists (n=5)	Japanese endoscopists (n=24)	<i>P</i> value
Years of GI endoscopy (median [range])	6.5 [1~30]	11.0 [5~17]	7.5 [1~20]	0.689
BE with LGD (%)				0.002
Observation	3 (25)	3 (60)	23 (95.8)	
Endoscopic ablation	3 (25)	1 (20)	1 (4.2)	
Endoscopic resection	5 (41.7)	1 (20)	0 (0)	
Surgical resection	1 (8.3)	0 (0)	0 (0)	
BE with HGD (%)				0.081
Observation	0 (0)	0 (0)	1 (4.2)	
Endoscopic ablation	3 (25)	0 (0)	0 (0)	
Endoscopic resection	8 (66.7)	5 (100)	23 (95.8)	
Surgical resection	1 (8.3)	0 (0)	0 (0)	
BE with adenocarcinoma (%)				0.013
Endoscopic resection	8 (66.7)	4 (80)	24 (100)	
Surgical resection	4 (33.3)	1 (20)	0 (0)	
Elevated-type squamous dysplasia (%)				0.682
Observation	0 (0)	0 (0)	1 (4.2)	
Endoscopic ablation	0 (0)	0 (0)	2 (8.3)	
Endoscopic resection	12 (100)	5 (100)	21 (87.5)	
Flat-type squamous dysplasia (%)				<0.001
Observation	0 (0)	1 (20)	17 (70.8)	
Endoscopic ablation	2 (16.7)	0 (0)	0 (0)	
Endoscopic resection	10 (83.3)	4 (80)	7 (29.2)	
WD-type SCC (%)				0.007
Endoscopic resection	8 (66.7)	3 (60)	24 (100)	
Surgical resection	4 (33.3)	2 (40)	0 (0)	
MD-type SCC (%)				0.800
Endoscopic resection	6 (50)	2 (40)	10 (41.7)	
Surgical resection	6 (50)	3 (60)	14 (58.3)	
PD-type SCC (%)				0.051
Endoscopic resection	1 (8.3)	1 (20)	13 (54.2)	
Surgical resection	10 (83.4)	4 (80)	11 (45.8)	
Chemotherapy and/or radiotherapy	1 (8.3)	0 (0)	0 (0)	

GI, gastrointestinal; BE, Barrett esophagus; LGD, low grade dysplasia; HGD, high grade dysplasia; WD, well-differentiated; SCC, squamous cell carcinoma; MD, moderately-differentiated; PD, poorly-differentiated.

**2. Treatment for squamous dysplasia**

Most of the participants (92.7%) selected endoscopic resection as a treatment for the elevated-type squamous dysplasia, and there was no difference among three countries ( $P=0.682$ ). For flat-type squamous dysplasia, endoscopic resection was preferred in Korea (83.3%) and Singapore (80%), but not in Japan (29.2%). Most of the Japanese endoscopists preferred observation without endoscopic treatment ( $P<0.001$ ) (Fig. 1C).

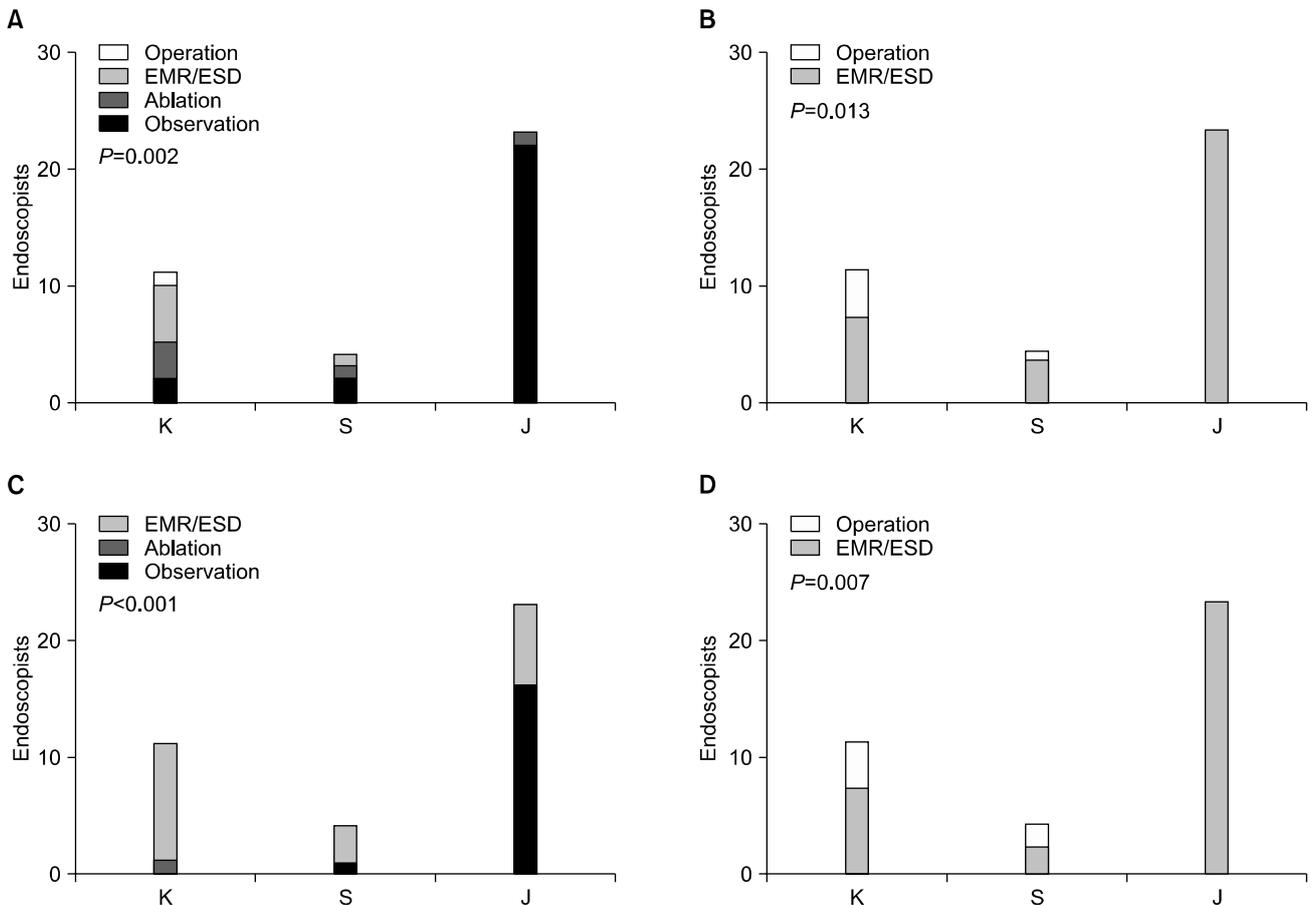
**3. Treatment for SCC**

For early-staged SCC, either endoscopic resection or surgical resection was preferred as a treatment (Table 2). For WD-type SCC, 85.4% of the participants selected endoscopic resection as a treatment (Table 1). Notably, all the Japanese endoscopists (100%) selected endoscopic resection, whereas some Korean (33.3%) and Singaporean (40%) endoscopists selected surgical resection ( $P=0.007$ ) (Fig. 1D).

For MD-type SCC, surgical resection (51.2%) and endoscopic resection (43.9%) were the most common answers, and there was no difference among three countries ( $P=0.800$ ). For PD-type SCC, surgical resection was the most answer (61%) (Table 1).

**DISCUSSION**

To the best of our knowledge, this is the first comparison study between Korea, Singapore, and Japan on the managements for BE, esophageal dysplasia, and early-type esophageal cancer. It is interesting that several significant differences were noticed among three countries for the management of (i) BE with LGD, (ii) BE with adenocarcinoma, (iii) flat-type squamous dysplasia, and (iv) WD-type SCC. We assume that different diagnostic criteria on dysplasia and cancer, and abundant Japanese literatures on ESD have led to such discrepancy between Japan and other two countries; Singapore and Korea.



**Fig. 1.** Different managements between Korea, Singapore, and Japan for BE with LGD (A), BE with adenocarcinoma (B), flat-type squamous dysplasia (C), and WD-type SCC (D). K, Korea; S, Singapore; J, Japan.

It is interesting that all of the Japanese endoscopists preferred endoscopic resection for BE with adenocarcinoma and WD-type SCC, whereas 25~40% of the Korean and Singaporean endoscopists preferred surgical resection. The goal of endoscopic treatment is to completely remove the esophageal lesions with less morbidity. Therefore, the degree of differentiation and the presence of vascular or lymphatic invasion which are related to the risk of lymph node metastasis, should be considered before endoscopic resection. It is known that lymph node metastasis is very rare in m1 (epithelium) and m2 (lamina propria) cancers.<sup>5-7</sup> Recent Japanese expanded indication recommends ESD for m3 (cancers reaching muscularis mucosa) and sm1 (upper 1/3 layer of submucosa) cancers,<sup>8</sup> but it should be taken seriously because of high potential lymph node involvement. The risk of nodal metastases is low when infiltration is less than 200  $\mu$ m in esophageal SCC,<sup>9</sup> whereas a submucosal infiltration micrometric cutoff of 500  $\mu$ m has been proposed in esophageal adenocarcinoma due to its lower risk of nodal metastases.<sup>10,11</sup> Taken as a whole, these Japanese studies might have led our Japanese participants to select endoscopic resection instead of surgery in BE with adenocarcinoma and WD-type SCC.

Another interesting finding in this study is that, for BE with LGD and flat-type squamous dysplasia, medication was preferred in Japan, whereas endoscopic treatment was preferred in Korea and Singapore. Such differences might be due to different definitions for dysplasia in Japan. Dysplasia is diagnosed for non-invasive neoplastic proliferation in Western criteria, but in Japan, there is a resistance to use the term HGD, because it is consisted of severe dysplasia and carcinoma in situ (CIS).<sup>2,3,12</sup> Japanese pathologists use the terms intraepithelial carcinoma or CIS for squamous esophageal lesions, instead of distinguishing invasion and non-invasion for glandular lesions.<sup>5</sup> In summary, we assume that there is a tendency among Japanese endoscopists to consider dysplasia as less severe form than those of HGD diagnosed in other countries.

Limitations of our study are: (i) that the number of participants is small and (ii) that we could not provide variable cases for each histopathology. For example, near half of the Japanese endoscopists preferred endoscopic resection for PD-type SCC, but we could not show from which size or from which depth, the operation could be preferred instead of endoscopic resection in PD-type SCC. A large-sized study with various SCC cases of each cell-type will verify this issue.

In conclusion, this study addresses different managements for esophageal epithelial neoplasia between Korea, Singapore, and Japan. One-step advanced or aggressive treatment is preferred in Korea and Singapore than in Japan with regard to BE with LGD, flat-type squamous dysplasia, BE with adenocarcinoma, and WD-typed SCC. For BE with adenocarcinoma and WD-type SCC, endoscopic resection is preferred in Japan, whereas operations are preferred in among Korean and Singaporean endoscopists. For BE with LGD and flat-type squamous dysplasia, medication was preferred in Japan, whereas endoscopic treatment was preferred in Korea and Singapore. We assume that such discrepancy comes from abundant Japanese literatures on ESD and different diagnostic criteria for dysplasia and cancer in Japan comparable to Singapore and Korea.

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