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Long-term outcome of early gastric cancer after endoscopic submucosal dissection: Expanded indication is comparable to absolute indication

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ABSTRACT

Background: Endoscopic submucosal dissection has become widely used for early gastric cancer with an expanded indication, although there is no strong consensus. We aimed to compare the clinical and long-term oncological outcome after endoscopic submucosal dissection according to indication.
Methods: Retrospective review of 1152 patients with 1175 lesions who had undergone endoscopic submucosal dissection for early gastric cancer at tertiary educational hospital in Korea, between March 2005 and November 2011. Of these, 366 and 565 lesions were included in the absolute and expanded indication groups, respectively.
Results: En bloc resection rates were not significantly different between the absolute and expanded indication groups. The complete resection rate was higher in the absolute indication group versus the expanded indication group (94.8% vs. 89.9%, respectively; $P = 0.008$). In the expanded indication group, complete resection rate was higher in the differentiated versus undifferentiated tumour subgroups (92.9% vs. 78.4%, respectively; $P < 0.001$). Recurrence rates were 7.7% in the absolute indication group vs. 9.3% in the expanded indication group ($P = 0.524$). Disease-free survival was not significantly different between the two indication groups ($P = 0.634$).
Conclusions: Endoscopic submucosal dissection for early gastric cancer with expanded indication is a feasible approach to disease management. Periodic endoscopic follow-up is necessary to detect cancer recurrence.

1. Introduction

Since the introduction of endoscopic mucosal resection (EMR) in the early 1990s, endoscopic resection has been a preferential treatment instead of gastrectomy for early gastric cancer (EGC) confined to the mucosa without lymph node metastasis because of minimal invasiveness [1–6]. However, EMR, the first developed method of endoscopic resection, is limited in that it is inadequate for en bloc resection of gastric lesions larger than 2 cm in diameter [7]. Endoscopic submucosal dissection (ESD) was developed for the purpose of en bloc resection, regardless of tumour size and location [8]. According to current guidelines, the absolute indication (AI) for endoscopic resection is a differentiated-type adenocarcinoma without ulcerative findings that is 2 cm or less in diameter, with tumour invasion confined to the mucosa [9]. These criteria, however, are so strict that unnecessary surgeries are likely performed [10]. A study by Gotoda et al. on 5265 patients who had undergone gastrectomy with lymph node dissection for EGC proposed criteria suggesting a low risk of lymph node metastasis [11]. Based on these observations, expanded indication (EI) for ESD was suggested [9]. Although ESD has become widely used according to EI [12–18], there is no strong consensus regarding EI due to concerns of increasing risk of lymph node metastasis [19–22]. To evaluate the practicality of ESD following the expanded criteria, we analyzed the clinical and long-term oncological outcome after ESD for EGC, comparing AI versus EI.

2. Patients and methods

2.1. Patients

Consecutive clinical data of 1152 patients with 1175 lesions who had undergone ESD for EGC between March 2005 and November 2011 were prospectively collected at our tertiary educational hospital in Seoul, Korea. ESD for EGC was performed based on EI. Although all lesions were considered to meet the expanded indication through endoscopy and biopsy before ESD, 241 were revealed to be outside of EI after histopathological examination. These 241 lesions that did not satisfy AI or EI were excluded from the study.

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In addition, three lesions were also excluded because they were in a remnant stomach. The remaining 931 lesions were enrolled and reviewed retrospectively. We divided lesions into either AI or EI groups. The AI group included 366 lesions of differentiated intramucosal adenocarcinoma which were elevated and smaller than 2 cm diameter, or were depressed and smaller than 1 cm without ulceration. The EI group comprised 565 lesions, which were categorised based on the criteria proposed by Gotoda et al, as following: (a) differentiated intramucosal adenocarcinoma smaller than 3 cm diameter, without lymphatic-vascular invasion, irrespective of ulcer findings; (b) differentiated intramucosal adenocarcinoma without lymphatic-vascular invasion and negative for ulceration, irrespective of tumour size; (c) undifferentiated intramucosal cancer smaller than 3 cm, without lymphatic-vascular invasion and ulcer findings; and (d) differentiated adenocarcinoma smaller than 3 cm with minimal submucosal invasion (SM1, <500 μm), without lymphatic-vascular invasion [11]. These 931 lesions were analyzed for procedural results. Of them, 265 lesions which underwent ESD within the last year were inappropriate for long-term survival analysis. In addition, we excluded 172 lesions for long-term survival analysis for the following reasons: (a) 16 lesions which underwent surgery directly after the ESD because of non-curative resection, (b) 143 lesions whose follow-up periods were less than 1 year, and (c) 13 lesions which did not receive two or more follow-up EGDs with biopsies, or which did not receive follow-up abdominal computed tomography (CT) scan. The remaining 494 lesions were enrolled for long-term survival analysis. The Institutional Review Board of our hospital approved this study.

2.2. ESD technique

All ESDs were performed with a standard single-channel endoscope (GIF-Q260J or GIF-H260Z, Olympus Optical Co. Ltd., Tokyo, Japan). The typical procedure sequence comprised marking, mucosal incision, and submucosal dissection with simultaneous hemostasis. After making several marking dots outside the lesion circumferentially using a needle knife (KD-10Q-1-A, Olympus Optical Co. Ltd., Tokyo, Japan) or a needle knife papillotome (MTW Endoscopy, Wesel, Germany), a saline solution containing epinephrine (0.01 mg/mL) mixed with 0.8% indigo carmine was injected into the submucosal layer using a 21-gauge needle to lift the lesion off of the muscle layer. A circumferential incision was made in the mucosa using a needle knife and an insulated-tip knife (KD-610L, Olympus Optical Co. Ltd., Tokyo, Japan). The submucosal layer was dissected directly with various knives, until complete removal was achieved. Endoscopic hemostasis was performed with hemoclips or hemostatic forceps whenever bleeding or exposed vessels were observed.

2.3. Gross and histopathologic evaluation

Tumour location and macroscopic types were endoscopically evaluated, and classified by the Japanese Gastric Cancer Association Classification [23]. Tumour size and presence of ulcerative change were also investigated by endoscopy. Invasion depth, lymphatic and vascular involvement, and tumour involvement at the lateral and vertical margins were histopathologically assessed. En bloc resection was defined as tumour removal in a single piece without fragmentation. Complete resection of en bloc resected tumours was defined as all lateral and vertical margins being tumour-free on histologic examination. Complete resection of piecemeal resected tumours was defined as entire tumour removal, including sufficient tumour-free margins, ascertained after perfect reconstruction of all pieces. En bloc complete resection denotes removal of the tumours meeting the en bloc resection and complete resection criteria.

2.4. Complications

Bleeding was defined as the occurrence of clinical symptoms such as melena or haematemesis after ESD. All suspected bleeding events were confirmed by performing emergency endoscopy. A diagnosis of perforation required the direct endoscopic observation of mesenteric fat or the presence of free air on an abdominal radiography or CT scan.

2.5. Follow up

All patients underwent an esophagogastroduodenoscopy (EGD) at 1 month after ESD to confirm healing of the artificial ulcer and to check for residual tumours. After that, EGD was scheduled at 3, 6, 12, 18, and 24 months after ESD to check for local or metachronous lesions. After 24 months, EGD was performed annually. Additionally, abdominal CT scans were done every 6 months for the first year and annually thereafter, to detect lymph node or distant metastasis.

Tumour recurrences found during follow-up EGD were classified into five groups as follows: residual disease, local recurrence, synchronous lesion, metachronous lesion, and distant metastasis. Residual disease was defined as cancer detected at the resection site on the first or second follow-up EGD within 12 months after ESD. Local recurrence was defined as recurrent cancer at the resection site after 12 months post-ESD with two negative prior follow-up EGDs. When cancer was detected at a gastric site other than the primary resection area on the follow-up EGD within 6 months after ESD, cancer was regarded as a synchronous lesion. Cancer detected at sites other than the primary resection area at 6 months or later after ESD was regarded as a metachronous lesion. Distant metastasis was defined as a post-ESD recurred tumour that was detected in an extra-gastric area by follow-up imaging studies. Disease-free survival duration was defined as the length of time after ESD in which no disease was found on follow-up EGDs or CT scans. Recurred lesions included only cancer, not adenoma.

2.6. Statistical analysis

Statistical tests to compare the measured results included Student t-test, χ^2 test, Fisher's exact test, and the Mann–Whitney U test. The Kaplan–Meier method, Log-rank test, and Cox regression analysis were used for survival analysis. Continuous variables of descriptive statistics quantity were presented as mean ± standard deviation. In addition, estimated disease-free survival was expressed as mean duration ± standard error. $P < 0.05$ was regarded as a significant difference between group comparisons. All statistical analyses were performed by using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinicopathological characteristics

Table 1 shows patient and tumour characteristics according to the ESD indication. Mean age was higher in the AI versus the EI group (64 vs. 62 years, respectively; $P = 0.004$). The percentage of males was also higher in AI group than in EI group (78.2% vs. 69.9%, respectively, $P = 0.006$). Tumour locations were not different between the two groups. Due to differences of indication criteria between the AI and EI groups, tumour characteristics including macroscopic appearance, size, presence of ulcer, and differentiation varied considerably according to the indication. Flat- or depressed-type cancer was more frequent in the EI group (87.8%) than the AI group (45.1%), and this difference was highly significant ($P < 0.001$). In the EI group, 24.1% of the tumours were larger than 2 cm, and 8.0% of the tumours showed ulcerative change. All of the AI lesions