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# Long-Term Outcome of Extended Endoscopic Submucosal Dissection for Early Gastric Cancer with Differentiated Histology

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Endoscopic mucosal resection was introduced in the 1990s, and endoscopic submucosal dissection (ESD) in 2003. Currently, ESD is becoming the main procedure for the resection of early gastric cancer (EGC) and is leading to the development of extended indications for endoscopic resection. Many reports showed that the endoscopic and oncologic outcome of endoscopic treatment in the extended indication group was acceptable in terms of curability and safety. Especially, ESD showed better results to remove extended indication EGCs with relatively high resection rate and low local recurrence rate. However, more long-term follow-up data are needed for clinical application of the extended criteria of ESD due to the risk of lymph node metastasis. We should also keep in mind that accurate diagnosis, characterization of the lesion, and proper appreciation of technical aspects are most essential in therapeutic endoscopy.

**Key Words:** Endoscopic submucosal dissection; Early gastric cancer; Extended indication; Long-term outcome

## INTRODUCTION

Gastric cancer is the most common malignancy in Korea. In recent years, mortalities associated with gastric cancer have decreased markedly in some Asian countries due to health-care policies that introduced screening tests for early detection of gastric cancer. Since curative treatment is possible when tumors are resectable, screening modalities that detect gastric cancers when they are still resectable can increase long-term survival rates. Although surgical resection is the standard method of treatment, patients diagnosed with early gastric cancer (EGC) can be resected endoscopically and early diagnosis, allowing endoscopic resection, is therefore important.

Endoscopic mucosal resection (EMR) is widely accepted as a standard treatment of EGC, with nominal risk of lymph node (LN) metastasis, because it is minimally invasive, safe,

and convenient.<sup>1,2</sup> According to current guidelines, absolute indications for endoscopic resection include differentiated EGCs less than 20 mm in diameter and small ( $\leq 10$  mm), depressed EGCs without ulceration or scarring;<sup>3,4</sup> moreover, these lesions must be confined to the mucosa, with no lymphatic or vascular involvement. These criteria, however, have been considered too strict, leading to unnecessary surgery,<sup>5</sup> and *en bloc* resection of specimens larger than 20 mm is difficult by EMR.

Endoscopic submucosal dissection (ESD) has shown advantages over conventional EMR for the removal of larger or ulcerated EGC lesions in an *en bloc* manner<sup>6-8</sup> as well as for preventing residual disease and local recurrence.<sup>1,5,8</sup> These findings have led to the development of extended indications for endoscopic resection,<sup>1,5,9,10</sup> indicated for differentiated cancer with no lymphatic or vascular involvement, including: 1) mucosal cancers without ulcerative findings, regardless of tumor size; 2) mucosal cancers with ulcerative findings  $\leq 30$  mm; and 3) minute ( $\leq 500$   $\mu$ m from the muscularis mucosae) submucosal invasive cancers  $\leq 30$  mm. The number of patients receiving ESD for EGC has continuously increased because of expansion of criteria.<sup>11</sup> Until now, several studies showed the positive results about the ESD in extended indication with similar recurrence rate and disease free survival rate with absolute indication.<sup>10,12-14</sup>

However, some reports showed LN metastasis in EGC of ex-

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tended indication, especially in submucosal invasive EGC,<sup>13,15,16</sup> so we could not perform the endoscopic resection by force according to the indication. On the other hand, some patients who have gastric cancer which is not included absolute and extended indication need endoscopic resection due to clinical situations. Therefore, we should select the proper treatment methods according to the state of cancer and condition of patients, based on the precise results which have been reported by clinical practices. In this article, we tried to determine the long-term follow-up results of endoscopic resection in differentiated EGC for the better management of patients.

## OUTCOME OF EXTENDED INDICATION IN EGC

Some studies showed that ESD is acceptable using the extended indication with acceptable recurrence rate and disease-free survival which were not different from absolute indication.<sup>10,12-14</sup> In the report by Isomoto et al.,<sup>17</sup> ESD in extended indication of EGC showed 94.7% of complete resection and 97.1% of 5-year survival rate, and these results were similar to those of surgical resection with LN dissection. Choi et al.<sup>18</sup> also reported that EMR was comparable to surgery in terms of the risk of death (18.8% vs. 14.8%) and recurrence (1.2% vs. 1.1%) with lower medical costs and shorter duration of hospital stay. Sanomura et al.<sup>19</sup> reported that complete resection was achieved for 93.2% of the submucosal cancer (sm1,  $\leq 500 \mu\text{m}$ ) that met the extended criteria and there was no LN metastasis.

Disease-specific survival did not differ significantly between patients who were simply followed up after ESD and those who were treated by additional surgical resection.<sup>19</sup> In 1,370 cases of endoscopic resection of EGC in absolute and extended indication, the complete resection rate was higher (95.9% vs. 88.4%) and the complication rate was lower (6.8% vs. 9.8%) in the absolute than in the extended indication group; however, there was no between group difference in local recurrence rate (0.9% vs. 1.1%) at a median follow-up of 32 months.<sup>13</sup> In this report, the 5-year overall survival rate was 95.8%; 95.3% in the absolute indication group, 96.8% in the extended indication group. The overall 3-year disease-specific local recurrence-free rate was 98.8%; 99.0% in the absolute indication group and 98.5% in the extended indication groups. In another recent study which compared absolute and extended indication, recurrent rates were 7.7% in the absolute indication group and 9.3% in the extended indication group. Disease-free survival was not significantly different between the two indication groups.<sup>12</sup>

A prospective comparative study was reported in Japan<sup>10</sup> concerning the clinical outcomes of absolute and expanded indication of EMR and ESD. A total of 589 EGC lesions were

divided to either the guideline group or the extended group. *En bloc*, complete and curative resections were achieved in 98.6%, 93.0%, and 95.1%; and 88.5%, 97.1%, and 91.1% of the guideline and expanded criteria lesions, respectively, and the differences between the two groups were significant. However, the overall survival was equally adequate in both groups, and the disease-specific survival rates were 100% in both groups.

## LIMITATIONS OF EXTENDED INDICATION

In endoscopic treatment, the most important thing is to exclude the possibility of LN metastasis, which usually depends on the endoscopic findings such as the feature which can predict the invasion depth, size of tumor, and the existence of ulceration on the tumor.

A previous study reported that there was no LN metastases in patients with minute submucosal cancers  $\leq 30 \text{ mm}$  in size without lymphovascular invasion<sup>9</sup> and, based on this finding, it was suggested that the criteria for ESD for EGC could be extended.<sup>1,5,10,11</sup> However, recent studies have reported positive LN metastasis in pathologic reviews of surgical specimens in less than 3 cm sized EGCs.<sup>13,15,16</sup> Kang et al.<sup>15</sup> reported that LN metastasis was noted in 15.0% of submucosal cancer (sm1,  $\leq 500 \mu\text{m}$ ) without lymphovascular invasion and measuring  $\leq 3 \text{ cm}$  in size, and An et al.<sup>16</sup> revealed 1.7% of LN metastasis in submucosal cancer (sm1,  $\leq 500 \mu\text{m}$ ) EGCs which were less than 2 cm. In another study, among 119 cases of submucosal cancer (sm1,  $\leq 500 \mu\text{m}$ ), 2.5 cm sized one metastatic LN was found on surgically resected specimen.<sup>13</sup> Therefore, in submucosal cancer (sm1,  $\leq 500 \mu\text{m}$ ) in extended indication, we should decide carefully to perform endoscopic treatment due to the possibility of LN metastasis.

In a recent study, none of well differentiated mucosa-confined cancers smaller than 3 cm in diameter had associated LN metastasis, regardless of the presence of ulceration, and the probability of LN involvement significantly increases in EGC containing an ulcer (3.4%) compared to EGC without an ulcer (0.5%).<sup>9</sup> However, establishing ulceration on EGC by definition (ulcers measuring 5 mm or larger in diameter and are on exposed submucosa) is another problem, especially in real endoscopic examination, because of the change of ulceration by life cycle of a malignant ulcer and the interobserver variation in defining an ulcer in EGC. To overcome these factors, education to reduce the interobserver variation by sharing the endoscopic findings of ulceration which are diagnosed in pathologic data is needed.

## RESULTS OF NONCURATIVE, ENDOSCOPICALLY RESECTED, DIFFERENTIATED EGC

Following endoscopic treatment, meticulous pathological evaluation of the resected specimen is used to stratify patient management. Patients with lesions that meet the guidelines or extended criteria are closely followed, whereas those who have undergone noncurative resection are considered for additional treatment such as surgery or a follow-up endoscopic procedure.<sup>20</sup> The surgical outcomes of EGC are known to be excellent;<sup>21</sup> however, partial or total gastrectomy is also associated with short- and long-term morbidity and mortality.<sup>22,23</sup> In clinical practice, some patients who undergo noncurative endoscopic resection are contraindicated for additional treatment due to individual factors, such as comorbid disease, old age, or patient refusal. A recent report showed that the death rate of patients who undergo noncurative endoscopic resection was 25.2%, the median survival time was 42 months (interquartile range, 30 to 66), and the overall 3- and 5-year survival rates were 82.9% and 77.1%. In addition, the 3- and 5-year survival rates of the patients with lymphovascular invasion were 61.9% and 42.4%, respectively, and the rates of patients without lymphovascular invasion were 86.1% and 81.8%, respectively.<sup>24</sup>

## CONCLUSIONS

Endoscopic removal has become the method of choice for indicated patients with EGCs. Moreover, the ESD method is superior to EMR because of the higher en bloc and complete resection rates, despite having longer procedure time and higher complication rate.<sup>6,25-29</sup> The advance of instruments and techniques allows to extend the indication for endoscopic resection as well as to avoid unnecessary surgery.<sup>10,30</sup> The above reports showed that the endoscopic and oncologic outcomes of endoscopic treatment in the extended indication group was acceptable in terms of curability and safety. Especially, ESD showed better results to remove extended indication EGCs with relatively high resection rate and low local recurrence rate. However, more long-term follow-up data are needed for clinical application of the extended criteria of ESD due to the risk of LN metastasis. We should also keep in mind that accurate diagnosis, characterization of the lesion, and proper appreciation of technical aspects are most essential in therapeutic endoscopy.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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