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Endoscopic Resection for Early Gastric Cancer beyond Absolute Indication with Emphasis on Controversial Issues

Yang Won Min and Jun Haeng Lee

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Endoscopic resection is the established treatment for early gastric cancer in selected patients with negligible risk of lymph node metastasis ('absolute indication'). Based on clinical observations and large pathological databases, expanding indications for endoscopic resection beyond absolute indication has been tried in Japan and Korea. However, controversies exist regarding the safety of treating early gastric cancer beyond absolute indication in terms of pathological evaluation of the resected specimen, definition of expanded indication, discrepancy between pre-endoscopic resection and post-endoscopic resection diagnoses of gastric neoplasm, and the best strategy for cases with non-curative resection. In this brief review, current evidence and clinical experience regarding issues of endoscopic resection beyond absolute indication will be summarized.

Key Words: Stomach neoplasm; Endoscopic gastrointestinal surgical procedures

Introduction

Gastric cancer is one of the most common malignancies in Korea and many other countries.[1] Because screening endoscopy or barium gastrography is quite commonly performed in Korea[2] and Japan,[3] the proportion of early gastric cancer (EGC) at diagnosis is rapidly increasing. At the same time, instruments and techniques of endoscopic resection (ER) for EGC have been developed. ER is an established treatment modality for EGC with negligible risk of lymph node (LN) metastasis.

The original technique of ER was endoscopic mucosal resection (EMR), and the treatment outcome of EMR has been reported to be acceptable.[4-8] However, tumors larger than 2 cm in diameter are difficult to cut in one piece using EMR; therefore, the rate of local recurrence is somewhat high. In the era of EMR, the indications for endoscopic treatment were rather limited ('guideline indication' in Japan and 'absolute indication' [AI] in Korea). To overcome the limitations of EMR, the technique of endoscopic submucosal dissection (ESD) was developed in the late 1990s. The major advantage of ESD is that larger tumors can be removed endoscopically in one piece; therefore, the rate of local recurrence can be minimized.[9] Using the ESD technique for EGC patients with a low risk of LN metastasis, identified from a large surgical database,[10] many patients with EGC beyond AI have been treated using ESD. However, data on the long-term outcome is still limited.

Controversies exist regarding the safety of treating EGC beyond AI. Some issues related to optimal evaluation of the endoscopically resected EGC specimen are unsolved. No consensus has been reached on the definition of expanded indication (EI), and the ambiguity of the histological category of 'differentiated type' and 'undifferentiated type' is worrisome in countries outside Japan. Additionally, discrepancies between pre-ER and post-ER diagnoses of gastric neoplasm have not been addressed adequately.

Correspondence to: Jun Haeng Lee
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3409, Fax: +82-2-3410-6983
E-mail: stomachlee@gmail.com
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The best strategy for cases with non-curative resection, which is quite common in ER for EGC beyond AI, has not yet been established.

Pathological Considerations for Endoscopic Resection of Early Gastric Cancer Beyond Absolute Indication

1. Pathological basis for the indications for endoscopic treatment of early gastric cancer

Pathological evaluation of endoscopically resected EGC within AI occasionally reveals some worrisome findings, such as size larger than 2 to 3 cm, minute submucosal invasion, and areas of poorly differentiated adenocarcinoma or signet ring cell carcinoma. Standard treatment for cases beyond AI in pathological result is surgical gastrectomy with LN dissection. However, many patients with EGC beyond AI do not recur after ER without surgery. Close observation for selected patients with endoscopically resected EGC beyond AI may be a relevant option. In addition, some patients with EGC beyond AI may be candidates for ER.

Supporting data for ER beyond AI comes from a pathological database. From surgical data involving 5,265 patients who underwent gastrectomy for EGC, Gotoda et al.[10] determined 4 groups with a low risk of LN metastasis. According to their results, no LN metastasis was found in 1,230 differentiated intramucosal adenocarcinomas less than 3 cm in size irrespective of ulcer findings but without lymphovascular invasion, in 929 differentiated intramucosal adenocarcinomas without lymphovascular invasion and ulcer findings irrespective of tumor size, in 141 undifferentiated intramucosal cancers less than 2 cm in size without lymphovascular invasion and ulcer, and in 145 differentiated adenocarcinomas with minute submucosal penetration less than 3 cm in size without lymphovascular invasion. These results led to the development of the concept of ('EI') for ER for EGC.[11]

2. Concerns for micrometastasis

Recently, LN micrometastasis has been a focus of interest in various malignant neoplasms. LN micrometastasis is defined as the presence of a single or small cluster of gastric tumor cells identified by immunohistochemistry (IHC) in pN0 LNs determined by hematoxylin-eosin (H&E) staining.[12] The incidence of LN micrometastasis ranges from 10% to 36% in patients with pN0 gastric cancer.[12] Maehara et al.[13] reported a high incidence (23.5%) of LN micrometastasis by IHC using CAM 5.2 monoclonal antibodies from 34 node-negative EGC patients. However, whether LN micrometastasis has clinical significance in patients with gastric cancer is presently controversial.[12,14]

In a study of 300 gastric cancer patients with pT1N0 tumor, Morgagni et al.[15] reported no significant differences in the 10-year overall survival rates among patients with or without LN micrometastasis. In contrast, Cao et al.,[16] in a study of 160 gastric cancer patients with pT1N0 tumors, reported that LN micrometastasis was one of the independent prognostic factors in pN0 EGC patients. In this context, caution is needed to expand the indications for ER for EGC based on the surgical database of LN assessments by conventional HE staining. Therefore, the feasibility of ER for EI-EGC needs to be determined from outcome data.

3. Evaluation of submucosal invasion depth and lymphovascular emboli

One of the most important factors in the evaluation of endoscopically resected EGC is the depth of invasion. In mucosal cancers, the determination of invasion depth does not influence the clinical management plan. In submucosal cancer, however, depth of invasion is very important because surgery is usually recommended for cases with submucosal invasion greater than 500 μm. The thickness of the submucosa is variable, and many differences occur between specimens obtained from ER versus surgery. Cho et al.[17] demonstrated that the thickness of the submucosa significantly changed by being stretched before pinning it. Therefore, the handling process for ER specimens should be standardized, and objective measuring methods for submucosal invasion, complementing depth of tumor invasion, would make current submucosal invasion criterion more reliable.

In contrast to the low risk of LN metastasis reported by Gotoda et al.[10] and Hirasawa et al.,[18] a significant LN metastasis rate (15%) was shown in minute submucosal cancers without lymphovascular invasion and measuring ≤3 cm in size.[19] If this discrepancy stems from the differences between Korean and Japanese pathologic criteria or methods, a criterion of submucosal invasion less than 500 μm should be challenged, and methods need to be standardized. Moreover, this cut-off value (500 μm) was not obtained from ER specimens but from surgically resected gastric specimens.

The presence of lymphovascular emboli is one of the most important risk factors for predicting LN metastasis. Therefore, surgery is usually recommended if evidence for lymphovascular emboli exists in the endoscopically resected specimen. However, criteria for the diagnosis of lymphovascular emboli are inconsistent

and controversial. Park et al.[20] defined lymphovascular emboli as the presence of tumor cells within a space according to the following criteria: (1) red cells or lymphocytes surrounding the tumor cells, (2) an endothelial cell lining, and (3) attachment to the vascular wall. They also developed a new index for predicting LN metastasis.[21] A nodal prediction index, based on variables extracted from univariate analysis and defined as nodal prediction index=(2.128×lymphovascular tumor emboli)+(1.083×submucosal invasion width ≥0.75 cm)+(0.507×submucosal invasion depth ≥ 1,000 μm)+(0.515×infiltrative growth pattern), has the potential to standardize the method of evaluating endoscopically resected tumors with submucosal invasion.

4. Histological heterogeneity

To expand the indications for ER for submucosal invading EGC, the histological heterogeneity of gastric cancer is an important issue to be addressed. In a retrospective study comparing the clinicopathologic features of node-positive (n=35) and node-negative (n=221) submucosal invading differentiated gastric cancers, histological heterogeneity was an independent risk factor for LN metastasis (odds ratio 3.88, 95% CI 1.60~9.38, P=0.0026).[22] Hanaoka et al.[23] evaluated the risk of LN metastasis in 4 types of gastric cancer with submucosal invasion (differentiated type, differentiated-type-predominant mixed type, undifferentiated-type-predominant mixed type, and undifferentiated type). Among them, undifferentiated-type-predominant mixed histologic type was an independent risk factor for LN metastasis. Therefore, ESD could be indicated for gastric cancer with a proportion of undifferentiated component below 50% when it is considered for submucosal invading cancer. However, this remains to be evaluated in large-scale prospective studies.

Issues to Be Addressed Regarding Endoscopic Resection beyond Absolute Indication

1. Definition of expanded indication

No consensus exists regarding the definition of EI. Two major issues are (1) the terminology of differentiated cancer, and (2) whether undifferentiated cancers can be included in the EI.

According to the World Health Organization classification, gastric cancers are histologically classified as (1) papillary adenocarcinoma, (2) tubular adenocarcinoma (including well differentiated, moderately differentiated, and poorly differentiated adenocarcinoma), (3) signet ring cell carcinoma, and (4) other rare subtypes. In Japan, however, all gastric cancers are traditionally divided into differentiated and undifferentiated gastric cancers.[24] Literature from Japan uses this terminology ('differentiated' vs. 'undifferentiated') to describe the indications for endoscopic resection for gastric cancer. This has created great confusion in Korea, where the term 'differentiated carcinoma' is not routinely used. Instead, Korean physicians consider that 'differentiated carcinoma' in Japan is similar to 'well-differentiated and moderately differentiated adenocarcinoma' in Korea. However, no direct comparison exists between them. We do not know whether 'differentiated carcinoma' in Japan is exactly the same as 'well-differentiated and moderately differentiated adenocarcinoma' in Korea. This problem makes the direct comparison of data between the 2 countries difficult.

The most commonly used definition of EI is differentiated cancer with no lymphovascular involvement and (1) mucosal cancers without ulcerative findings, regardless of tumor size; (2) mucosal cancers with ulcerative findings ≤30 mm; or (3) minute (<500 μm from the muscularis mucosae) submucosal invasive cancers ≤30 mm.[25] In the original review by Soetikno et al.,[11] gastric cancers were divided into intestinal and diffuse. Only EGCs with intestinal type histology were included in the EI. EGCs with diffuse type histology were not considered as appropriate for EMR. In some recent Japanese clinical studies, however, small undifferentiated type cancers were also considered as EI.[26] This is also true for some reviews by Japanese authors.[27]

In Korea, the situation is very confusing. Some Korean doctors think that poorly differentiated adenocarcinoma or signet ring cell carcinoma cannot be considered as EI. Other Korean doctors agree with the Japanese doctors that undifferentiated cancers can be included in EI. Until now, most Korean endoscopic studies regarding EI did not include poorly differentiated adenocarcinoma or signet ring cell carcinoma. ESD for poorly differentiated adenocarcinoma and that for signet ring cell carcinoma were handled separately. Jee et al.,[28] from Seoul National University Bundang Hospital, reported that LN metastasis occurred in 2.8% (5 patients) of surgically treated EGC within EI for ER. However, 4 out of 5 cases with LN positive EGC were poorly differentiated adenocarcinoma or signet ring cell carcinoma. Some Korean doctors think poorly differentiated adenocarcinoma or signet ring cell carcinoma may be included in the EI. In a recent clinical guideline for the treatment of gastric cancer in Korea, small undifferentiated mucosal cancer is considered as an EI for ER.[29] To prevent further confusion, it is urgent to clearly define EI in Korea.

2. Poorly differentiated adenocarcinoma and signet ring cell carcinoma

The risk of LN metastasis is known to increase in EGC with undifferentiated type histology due to lymphovascular invasion.[30] However, we have identified EGC with undifferentiated type histology as a group with a low risk of LN metastasis.[10] In addition, Hirasawa et al.[18] reported that from the analysis of 3,843 patients who underwent gastrectomy with LN dissection for solitary EGC with undifferentiated type histology, none of the 310 intramucosal cancers 2 cm or less in size without lymphovascular invasion and ulcer findings were associated with LN metastases. Therefore, Japanese gastric cancer treatment guidelines 2010 (ver. 3) state that ER for EGC with undifferentiated type histology with these characteristics is regarded as an EI, and that ESD, not EMR, should be employed.[31]

A few reports exist on the outcomes of ER for EGC with undifferentiated type histology.[32-34] However, the data were limited regarding long-term outcomes. Recently, Abe et al.[35] presented the short-term and long-term outcomes of ESD carried out to treat 97 patients with EGC with undifferentiated type histology diagnosed on preoperative biopsy. En bloc and R0 resection rates were excellent at 99.0% and 90.7%, respectively, but curative resection was achieved in only 63.9%. The major reasons for noncurative resection were submucosal invasion (54.3%) and tumor size >2 cm (40%). The 5-year overall mortality rate after curative resection was 7.0%, but no patient died of gastric cancer. Accordingly, additional treatment seems not necessary for EGC with undifferentiated type histology when resection is curative. In cases of noncurative resection, additional surgery should be performed. In addition, considering the relatively high noncurative resection rate and considerable number of patients not receiving additional surgery, great caution is needed when deciding to perform ESD for EGC with undifferentiated type histology.

To improve the curative resection rate, accurate determination of depth and extent of tumor is pursued. Unfortunately, this can be difficult. The accuracy of depth diagnosis by endoscopic ultrasound in EGC patients with undifferentiated type histology has been known to be worse than that in EGC patients with differentiated type histology.[36] EGC with undifferentiated type histology can extend along the proliferative zone in the middle layer of the mucosa, leaving normal ducts covering the superficial epithelium.[37] In this situation, even magnifying endoscopy with narrow band imaging is not very useful.[38] At first, therefore, EGC with undifferentiated type histology in tumors smaller than 20 cm needs to be considered for ESD, and when ESD is carried out, marks should be placed farther away from the endoscopically determined margins than in EGC with differentiated type histology. Nevertheless, more data are necessary to confirm the feasibility of ESD for EGC with undifferentiated type histology.

3. Discrepancy between pre- and post-treatment diagnoses

A histologic discrepancy may exist between pre- and post-treatment diagnoses, making it difficult to know whether a lesion is compatible with EI prior to ER. Therefore, the strict meaning of EI, rather than an indication, may be criteria for determining if a curative resection is achieved after evaluating the resected specimen. Despite advanced techniques and development of new diagnostic methods, the precise pre-treatment evaluation of gastric neoplasm is somewhat limited. In a recent Korean single-center retrospective study, 80/236 (33.9%) biopsy-proven, low-grade gastric adenomas/dysplasias (category 3 of the Vienna classification) turned out as invasive carcinoma (category 5) in 71 (30.1%) and high-grade gastric adenomas/dysplasias (category 4) in 9 (3.8%) after resection.[39] In a Japanese multicenter retrospective study, among 468 biopsy-proven gastric noninvasive neoplasias (equivalent to category 3 or 4.1 of the Vienna classification), 205 (43.8%) were diagnosed with adenocarcinoma after ESD.[40] However, most studies presenting the clinical outcomes of ER for EGC were based on the post-treatment diagnoses.

To analyze the discrepancy between pre- and post-treatment diagnoses of gastric neoplasm, we performed a retrospective study involving a total of 2,056 patients with gastric adenoma or cancer who underwent a curative ER or surgery at Samsung Medical Center in 2012. According to our results, about one third of pre-treatment AI-EGC (131/396) was shifted to post-treatment beyond AI-EGC, and 42.8% of the changes (56/131) were beyond EI for ESD. This observation suggests that applying EI in selecting the treatment method for EGC could be risky. Moreover, among the post-treatment beyond AI-EGC patients (n=876), 185 patients initially received ESD and 73 patients (40%) were identified as not satisfying EI. Considering the discrepancy between pre- and post-treatment diagnoses of gastric neoplasms and the significant number of patients not receiving additional surgery, applying EI in selecting ESD for EGC could be risky.

4. Optimal strategy for noncurative resection after endoscopic resection

ER is classified as either curative or noncurative. Resections are deemed curative when the tumor is completely removed and

lymphatic or distant metastasis is not risky. Noncurative resections are defined as tumors that are not completely removed or do not satisfy the AI or EI. In a retrospective study involving a total of 713 EGC cases treated by ESD, tumor size was significantly associated with resectability of ESD ($P<0.05$), and piecemeal resection was the sole significant contributor to noncurative resection ($P<0.001$).[41] In a recent study by Park et al.,[42] the en bloc complete resection rate was lower in EI-EGC than in AI-EGC (83.2% vs. 89.1%, respectively, P=0.013). In cases of EGC with undifferentiated type histology, the curative resection rate seems to drop more (63.9%).[35] Noncurative resection after ER for EGC can be attributed to local recurrence or distant metastasis. Accordingly, it is important to establish the best strategy when curative resection is not achieved after ER in expanding indications for ER for EGC. Ryu et al.[43] presented data from 43 patients who underwent surgery after ER. The surgical specimens showed residual cancer in 17 patients (39.5%) and LN metastasis in 4 patients (9.3%). In a retrospective study involving 19 cases undergoing gastrectomy after ESD based on pathological results (13 incomplete resections and 6 lymphatic invasions), LN metastasis was revealed in 7.7% of cases with incomplete resection and 50% of cases with lymphatic invasion.[44] An interesting new approach to noncurative resection is early additional ESD. It is too soon to draw a conclusion regarding this approach, but early clinical results have been excellent.[45]

Recently, 3 studies regarding the outcomes of noncurative ER for EGC were reported in abstract form at the 63rd Congress of the Korean Society of Gastrointestinal Endoscopy in Seoul, South Korea (November 23, 2013). Han et al.[46] reported no local recurrence during follow-up in 14/45 cases receiving additional endoscopic treatment for only lateral margin positivity, while there were 3 (6.8%) LN metastases in 44/90 cases receiving additional surgery for high risk factors of LN metastasis. Kim et al.[47] reported the long-term outcomes of 97 patients without additional treatment. Extragastric recurrence occurred in 3 cases, and all initially had both lymphovascular invasion and deep submucosal invasion. Yang et al.[48] identified the risk factors for LN metastasis and residual tumor. Venous invasion and lower-third location of tumor were independent risk factors for LN metastasis, and tumor involvement of the lateral resection margin was an independent risk factor for residual tumor. Accordingly, surgery is a reasonable approach in cases at high risk of LN metastasis, such as lymphovascular and deep submucosal invasions. Endoscopic treatment could be considered as another salvage modality in cases at low risk of LN metastasis, particularly in those with only lateral margin positivity.

Outcome of Endoscopic Resection for Expanded Indication - Early Gastric Cancer

1. Immediate technical outcome

In a retrospective study of EGC that fulfilled EI, en bloc resection was achieved in 94.9% (559/589), and 550 of 581 lesions (94.7%) were deemed to have undergone curative resection.[41] Perforation rate was higher in EI-EGC than in AI-EGC (6.3% vs. 2.0%, $P<0.05$). Ahn et al.[25] have shown excellent en bloc resection rates by ESD, higher than 95% both in AI- and EI-EGC. The complete resection rate was higher in AI-EGC than in EI-EGC (97.9% vs. 91.1%, $P<0.001$). The complication rate was marginally elevated in EI-EGC than in AI-EGC (9.8% vs. 6.8%, P=0.054), and median procedure time was longer in EI-EGC than in AI-EGC (35 min vs. 23 min, $P<0.001$). Park et al.[42] have shown excellent en bloc resection rates by ESD both in AI- and EI-EGC (92.9% and 89.9%, respectively). However, complete resection and en bloc complete resection rates were higher in AI-EGC than in EI-EGC (complete resection rates were 94.8% vs. 89.9%, respectively, P=0.008; en bloc complete resection rates were 89.1% vs. 83.2%, respectively, P=0.013). Bleeding and perforation rates did not differ between AI- and EI-EGC.

Although these results could support the contention that experienced operators can achieve excellent short-term outcomes in the treatment of lesions that are technically more challenging, it is true that the short-term outcomes of EI-EGC were slightly worse compared to those of AI-EGC. Technical invasiveness appears to increase procedure time and the risk of complications.

2. Long-term clinical outcome

Favorable outcomes of ER have been reported in patients meeting EI for ER for EGC.[49] In Japan, Isomoto et al.[41] and Gotoda et al.[50] compared outcomes of ESD for EGC between AI and EI. They reported no significant difference in the overall survival rates between AI- and EI-EGC. In Korean retrospective studies by Choi et al.[51] and Ahn et al.,[25] the overall and disease-specific survival rates did not differ between AI- and EI-EGC. Lee et al.[52] and Park et al.[42] also reported similar disease-free survival rates between AI- and EI-EGC. However, these studies did not have long follow-up periods, with median follow-up ranging from 26 to 44.1 months. Recently, Kosaka et al.[53] presented the long-term outcomes of ESD for EGC in 438 patients who were followed for at least 5 years after treatment, although follow-up of more than half of the patients was based on a questionnaire survey. In their study, the 5-year survival

rate was 83.1%, and no significant differences were seen between AI and EI. However, given few reports on the long-term outcomes of ER for EI-EGC, confirmation of more long-term outcomes under EI is warranted for establishing appropriate indications for ER for EGC.

Conclusions

Expanding indications for ER for EGC based on the surgical database needs to be carefully approached. The clinical significance of LN micrometastasis remains to be elucidated, and differences between specimens obtained from ER and surgery should be considered. To expand the range of ER for EGC, further efforts are needed to make ESD easier and safer, which could be achieved through technological advances, and the best strategy needs to be established for noncurative resection after ER. Surgery seems like a reasonable approach in cases at high risk for LN metastasis, and endoscopic treatment could be considered another method in cases at low risk for LN metastasis, particularly with only lateral margin positivity. Standardization of the pathologic diagnosis and handling process of ER specimens is also necessary for more reliable ER for EGC under EI. In cases of EGC with undifferentiated type histology, ESD needs to be considered for tumors smaller than 2 cm, and when ESD is carried out, adequate safety margins should be achieved. However, as 'differentiated and undifferentiated' is highly confusing, it would be better to avoid using these terms. Considering significant discrepancies between pre- and post-treatment diagnoses of EGC, applying EI for selecting ESD for EGC could be risky. Finally, given few reports on the long-term outcomes of ER for EGC in EI, confirmation of more long-term outcomes under EI is warranted for establishing appropriate indications for ER for EGC.

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