EDITORIAL

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Expanding Indications of Endoscopic Submucosal Dissection for Early Gastric Cancer: Hope or Hype?

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See "Clinical Outcomes of the Endoscopic Submucosal Dissection of Early Gastric Cancer Are Comparable between Absolute and New Expanded Criteria" by Keun Young Shin, et al. on page 181, Vol. 9. No. 2, 2015

Endoscopic submucosal dissection (ESD) has been established as one of the treatment options for selected cases of early gastric cancer (EGC). It is generally agreed that lesions within absolute indications (AI)—so-called "conventional indications" in Korea and "guideline indications" in Japan—can be safely resected by ESD, and the long-term outcome is comparable with surgery. Some lesions beyond AIs also can be histologically completely resected by endoscopy, so many researchers are trying to develop wider indications of endoscopic treatment of EGC. There are some literatures suggesting that ESD may be appropriate not only for AI but also for expanded indication (EI). However, due to the limitations of the study design, there are concerns on the EI of ESD. Some examples are (1) unclear definition of EI and handling of undifferentiated type cancer, (2) diagnostic discrepancies in pre- and post-endoscopic resections, (3) selection bias of retrospective analyses, and (4) scanty data on the long-term outcomes.

First of all, a standard definition of EI is urgently needed. By the recently published clinical practice guideline for gastric cancer in Korea, expanded indications include (1) well or moderately differentiated adenocarcinoma in the mucosal layer without an ulcer regardless of the size, (2) well or moderately differentiated adenocarcinoma measuring less than 3 cm in the mucosal layer with ulcer, (3) small (less than 2 cm) intramucosal cancer with undifferentiated histology, and (4) well or moderately differentiated adenocarcinoma with minute submucosal invasion (500 or less micrometer, SM1).[1] However, there is no consensus whether undifferentiated type EGCs (i.e., poorly differentiated adenocarcinomas and signet-ring cell carcinomas) should be included in EI of ESD. Data on clinical outcomes of ESD for undifferentiated type EGCs indicate that optimal curative resection would be difficult to guarantee, given the overall unpredictability of tumor depth and extent. In addition, there is little long-term outcome data to support endoscopic treatment of undifferentiated type EGC at this time.[2-4] There are some cases with histological heterogeneity. In order to avoid confusions regarding histological type, we propose that the long-term outcome of ESD for differentiated type EGCs, undifferentiated type EGCs, and EGCs with mixed histology need to be separately reported.

The second limitation can be named as "indication/criteria issue." We choose ESD candidates using some kind of indications. After ESD, we evaluate the resected specimen using some kind of criteria. The contents of indications and criteria may be the same. However, indications are something before ESD, and criteria are something after ESD. The "indication/criteria issue" is related with the problem of pre- and post-resection diagnostic discrepancies. Recent clinical analysis from Samsung Medical Center has shown that about one-third of preresection AI-EGC was shifted to postresection beyond AI-EGC, and 42.8% of the changes were beyond EI for ESD.[5] Another report from National Cancer Center demonstrated that 13.7% were out-of-indication at the pathological evaluation of resected specimen in preresection AI group, and 35.3% were postresection out-of-indication in the clinically EI group.[6] Until now, most data on ESD for EI-EGC are based on postresection diagnostic groups. This means a lot of cases in reports on ESD for EI-EGC were originally considered as AI-EGCs before ESD. If we do not consider this bias carefully, patients can be exposed to unnecessary risks.

Long-term follow-up data likewise are generally troublesome.

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According to various observational cohort studies, outcomes of ESD in EGC were similar whether AI or EI were applied.[7-9] Neither overall nor disease-free survival rates routinely differed in groups classified by indications. On the other hand, most investigations have clearly been plagued by less than adequate durations of follow-up. Although some 5-year follow-up data have been analyzed, yielding little survival differences between groups, evidence supporting favorable long-term oncologic outcomes is meager. Furthermore, greater care should be devoted to subject selection, inasmuch as most patients of EI groups were surgically treated as well. Prospective randomized clinical trials for EI-EGCs are strongly required for the definitive comparison between ESD and surgery.

In this issue, Shin *et al*.[10] examined clinical outcomes after ESD for EI of EGC, drawing from a regional multicenter database in Korea. Various objective data on short- and long-term results were reported (including overall and disease-free survival rates), and putative risk factors impacting curative resection were analyzed. Consequently, they found that curative, *en bloc*, and complete resection rates did not differ by group. Also, similar 3-year overall and disease-free survival rates were recorded for AI and EI patient groups (99.0% vs 98.6% and 98.1% vs 97.1%, respectively), corroborating other publications. Based on both short- and long-term outcomes, ESD was deemed effective in treating EI of EGC.

These authors are to be congratulated for coordinating their multicenter, collaborative effort. This large-scale study serves to strengthen existing long-term follow-up data. However, the lingering question is how well this study population reflects all instances of EI for EGC. As conceded, issues with definitions (e.g., ulceration) and patient selection may have skewed allocation of subjects to the EI group. This particular flaw is a global failing of research aimed at indications of ESD. Then again, follow-up duration was not adequate for decisive long-term outcome assessment. Finally and importantly, it is important to note that analysis of postresection pathology does not always equate with feasibility of ESD in EGC lesions. As far as diagnostic discrepancies before and after ESD, one might speculate that reanalysis of data using preresection criteria could supplant postresection indications.

In conclusion, this effort by Shin *et al*. adds to the body of retrospective evidence supporting expanded clinical application of ESD. Long-term patient outcomes in EGC were not influenced by indications and were favorable, in agreement with other small-scale investigations. It is nonetheless critical that issues of key definitions, selection bias, discrepant pathologic diagnoses, and limited follow-up periods be addressed to ensure the clinical safety of ESD use for EI of EGC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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