COMMENTARY
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# Endoscopic Resection of Early Gastric Cancer with Undifferentiated-Type Histology

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See "Therapeutic Outcomes of Endoscopic Resection of Early Gastric Cancer with Undifferentiated-Type Histology: A Korean ESD Registry Database Analysis" by Chang Seok Bang, Jae Myung Park, Gwang Ho Baik, et al., on page 569-577.

Endoscopic resection (ER) has become a standard local therapy for early gastric cancer (EGC) without risk of lymph node metastasis (LNM). Although the indications for ER have been expanded to include undifferentiated-type histology, the usefulness of ER for undifferentiated EGC is still controversial, likely because of its more aggressive behavior than differentiated-type gastric cancer.[1-3]

Thus, a precise histological diagnosis before ER is important, especially for undifferentiated-type EGC. If differentiated histology on prior biopsy is changed to undifferentiated-type histology after ER, the treatment strategy can also be changed.[4] Most studies on the therapeutic outcomes of ER focused on histology after ER. However, in the clinical field, the final pathology after ER may unexpectedly be reported as undifferentiated-type histology.

Approximately 15% to 20% of patients with undifferentiated-type EGC diagnosed after ER exhibit differentiated histology on biopsy prior to ER.[4,5] Undifferentiated-type EGC exhibiting a differentiated histology on biopsy is more aggressive and is associated with a lower curative resection (CR) rate than undifferentiated-type EGC, consistent with the biopsy pathology.[4-6] These reasons likely explain why Bang et al. (in this issue of *Clinical Endoscopy*) analyzed therapeutic outcomes of ER after dividing enrolled EGC into lesions with the expanded and beyond the expanded indications.[7] According to their results, the histological type of 46.1% of the lesions on biopsy was other than undifferentiated-type histology.[7] The histological findings varied from atypical cells to differentiated histology. The CR rate after ER was lower than that of lesions with the expanded indications, consistent with previous reports. This result is probably to be expected because the criteria for CR are stricter for undifferentiated-type EGC than for other histologies. Thus, when precise histological diagnosis prior to ER is required, magnifying endoscopy (ME) with narrow-band imaging (NBI) can be helpful. In addition, the actual biopsy site may be more important than the number of biopsies.[8] A previous study featuring histopathological mapping of undifferentiated-type EGC, which showed differentiated histology on biopsy, found that the zone of transition from differentiated to undifferentiated histology was frequently located at one or two peripheral sites of the lesion.[4,8] Thus, biopsy of several peripheral regions may assist in the diagnosis of undifferentiated-type histology prior to ER.[4,8]

ER is performed with reference to the Japanese classification, that is, differentiated or undifferentiated-type histology. Poorly differentiated adenocarcinoma (PDA) and signet-ring cell carcinoma (SRC) are included within the undifferentiated-type histology. PDA is associated with higher LNM rates than other histological types of EGC, whereas SRC has a

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lower LNM rate than other histological types of EGC.[9-12] Thus, biological behaviors such as LNM differ between PDA and SRC, despite both being categorized as undifferentiated types of EGC.

However, when ER is performed according to current indications, the clinical outcomes of PDA and SRC do not differ significantly.[13,14] Bang et al. also showed no significant differences between PDA and SRC in terms of immediate and long-term outcomes.[7] According to previous studies, the pattern of non-CR differs between PDA and SRC. Non-CR is associated with vertical margin involvement in PDA but lateral margin involvement in SRC.[13,14] In the study of Bang et al., the proportion of vertical margin involvement was higher in PDA, while that of lateral margin involvement was higher in SRC, albeit not significantly.[7] Furthermore, PDA showed significantly more submucosal invasion than SRC.[7] Thus, the main considerations prior to ER can differ between PDA and SRC; prediction of tumor depth is important in PDA, whereas the extent of the lesion is important in SRC.[8] To predict the extent of SRC, intramucosal spreading of cancer cells can be considered.[15] The intramucosal spreading pattern of SRC can be categorized as expanding (epithelial spread) or infiltrative (subepithelial spread).[15] Moreover, infiltrative spread was greater in cases with lateral margin involvement and more prevalent than expanding spread in cases surrounded by atrophy and intestinal metaplasia.[15] Therefore, larger ER safety margins may be necessary in cases of SRC with surrounding mucosa exhibiting atrophy or/and intestinal metaplasia, which can spread subepithelially to the margins.[15] Predictions of tumor extension using ME with NBI is inaccurate in SRC, unlike in differentiated EGC.[16,17] However, ME with NBI taking into consideration the pathologic growth pattern could facilitate the exact prediction of tumor extension in undifferentiated-type EGC.[18] Thus, for CR of undifferentiated-type EGC by ER, it is important to consider the biological characteristics of cancer cells, not simply to perform advanced endoscopy techniques such as ME with NBI. After ER, if the tumor size is within the present expanded criteria for CR, it can be sufficient for good clinical outcomes. In fact, one study investigated whether the risk of LNM or lymphovascular invasion (LVI) was increased when the difference in tumor size was >1 mm in comparison with the ER size criteria.[19] The result showed that the risk of LNM or LVI was not increased when there was a >10-mm tumor size difference from the ER size criteria in the ulcer-negative intramucosal cancer with undifferentiated-type histology.[19]

Bang et al. stated that previous studies on the therapeutic outcomes of ER in undifferentiated-type EGC focused on post-ER histology, or included lesions that met only the expanded indications or criteria, which might have overestimated the therapeutic outcomes.[7] Thus, Bang et al. categorized the lesions according to pre/post ER and the expanded indications/criteria.[7] The present analysis may be helpful by describing real-world experience of the therapeutic outcomes of ER in undifferentiated-type EGC, although the results were not different from those of previous reports. However, it had better have provided readers more useful information, not analyzing simply therapeutic outcomes according to pre-/post ER and the expanded indication/criteria. The CR rate is low after ER in undifferentiated-type EGC according to many studies, including that by Bang et al.[7] However, long-term therapeutic outcomes are acceptable if CR is performed. Nevertheless, the biological characteristics of undifferentiated-type EGC differ from those of differentiated EGC. Thus, the decision to perform ER in cases of undifferentiated-type EGC must be made carefully and in accordance with strict criteria based on the unique biological features of undifferentiated-type EGC.

## Conflicts of Interest

The author has no financial conflicts of interest.

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