EDITORIAL

The international emergence of endoscopic submucosal dissection for early gastric cancer

Every endoscopic procedure has a cognitive and a technical component. What makes endoscopic submucosal dissection (ESD) challenging is that it requires constant data interpretation and decision making (from detecting a dysplastic lesion to defining the margins for resection, selecting the right tools, identifying and avoiding exposed vessels, and then determining the right plane for submucosal dissection). ESD is also labor intensive and demands a high level of technical expertise. In this issue of *Gastrointestinal Endoscopy*, 2 significant challenges to performing gastric ESD are addressed: (1) how to accurately determine the depth of invasion (T stage) for an early gastric cancer (EGC) and (2) what factors can be used to predict the time required to complete a gastric ESD.

FOUNDATION FOR ESD IN THE TREATMENT OF EGC

ESD was developed in Japan in response to the inadequacy of EMR for the oncologic resection of large EGCs that were confined to the surface epithelium (Tis), mucosa (T1a lesions), or the upper portion of the submucosa (early T1b lesions, referred to as sm1 lesions in Japan).[1,2] ESD is more than an extension of EMR because it uses specialized endoscopic knives and tools that make the procedure more akin to endoscopic microsurgery than to advanced endoscopic polypectomy. Although ESD has been performed for more than a decade in Japan, this procedure has been slow to spread to other parts of the world because of its steep learning curve, long procedure time, increased risks to the patient, lack of commensurate reimbursement, and the need for specialized tools, which have only recently passed 510(k) premarketing evaluation by the U.S. Food and Drug Administration, making them available for commercial use in the United States.[3] However, in the past few years, international interest and experience with ESD has rapidly increased. A search of PubMed for "gastric ESD" found more than 80 articles published in 2010 alone.

By reviewing large databases, criteria for performing ESD for EGC were first established in Japan to select patients who were at low risk of lymph node (LN) metastasis.[4,5] The extended criteria for ESD for EGC include (1) differentiated mucosal cancer, without ulceration, of any size; (2) differentiated mucosal cancer, with ulceration, 3 cm or less in size; and (3) differentiated submucosal cancer (sm1, ≤500 μm of submucosal invasion), 3 cm or less in size.[1] In addition to these criteria, lesions must be without lymphovascular invasion on final pathology after ESD; otherwise, gastrectomy with LN dissection is indicated. When these criteria are met, the risk of LN metastasis has been estimated to be as low as 0%.[5] Criticism of these criteria center on differences in what Western and Japanese pathologists would interpret as being high-grade dysplasia as opposed to mucosally based gastric carcinoma.[6] A Korean study published in *GIE* in 2010, using Western pathological criteria, found an LN metastasis rate of 1.4% to 1.6% for mucosally based EGCs, and an LN metastasis rate of 15.0% for early submucosal EGCs that fit the extended criteria for ESD.[7] Although these data call into question whether superficial submucosal (early T1b or sm1) gastric carcinomas should be treated by ESD, they do support the role of ESD in the treatment of epithelial (Tis) and mucosal (T1a) EGCs. In fact, ESD is likely to play an increasingly important role in the worldwide management of dysplastic lesions and mucosally based cancers throughout the GI tract.[8] As such, the 2 articles featured in this issue of *GIE* by Choi et al[9] and Ahn et al[10] are timely and relevant.

> In experienced hands, lesions appropriate for ESD can be identified and staged and ESD can be performed in a time-efficient manner, particularly in the stomach for early gastric cancer.

DETERMINING THE DEPTH OF INVASION OF EGC AND A WESTERN PARADIGM FOR GASTRIC ESD

Choi et al[9] conducted a 2-part validation study that first used 111 cases of pathologically proven EGC (62 mucosal and 49 submucosal cancers) to identify endoscopic surface criteria that might differentiate mucosal from submucosal EGCs. Subsequently, endoscopic images from 2105

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consecutive patients with EGC who underwent either surgical or endoscopic resection were retrospectively reviewed by 2 blinded expert endoscopists, and predictions about the depth of invasion were made by using the endoscopic criteria derived from the pilot analysis. Features attributed to mucosally based EGCs included a smooth surface protrusion, shallow and even depression, erosion with slight marginal elevation, flat or superficially spreading lesions, and a size less than 3 cm for Paris type 0-I lesions.[11] Features attributed to submucosal EGC included an irregular or nodular surface with or without abnormal converging folds, subepithelium-like protrusion, deep ulceration with marked marginal elevation, and irregular protrusion for Paris type 0-I lesions.[11] Endoscopies were performed with a high-definition endoscope and included chromoendoscopy, by using indigo carmine, but without the assistance of optical magnification.

For mucosal EGCs (termed T1m by the authors), these criteria had a sensitivity of 85.5%, a specificity of 73.9%, a positive predictive value (PPV) of 82.0%, and a negative predictive value (NPV) of 78.5%. For submucosal EGCs (designated T1sm), the sensitivity was 72.6%, the specificity was 81.9%, the PPV 71.9%, and the NPV was 82.4%. EGCs were incorrectly staged in 22% of cases (8.5% were overstaged and 13.5% were understaged). On multivariate analysis, a flat or depressed type, between 1 and 3 cm in size, and submucosal invasion were associated with worse diagnostic accuracy.

A study published in *GIE* in 2007[12] assessing the accuracy of EUS, which variably used conventional radial echoendoscopes or 20-MHz miniprobes, found the accuracy of EUS to be 92.1% for diagnosing T1a lesions (overestimation of 0% and underestimation of 7.9%). However, the accuracy of EUS in identifying T1b lesions was only 57.3% (overestimation of 33.3% and underestimation of 9.4%).[12] These data were supported by another study by Choi et al,[13] the same investigators responsible for the previously mentioned study in this issue of *GIE*, that compared T staging of EGCs by using an EUS miniprobe with that determined by the surface characteristics identified on conventional high-resolution or high-definition endoscopy (CE). The PPV for T1m lesions was 80.3% by using EUS, 83.2% by using CE, and 83.9% when both EUS and CE were in agreement. The PPV for T1sm lesions was 38.5% by using EUS and 60.0% by using CE.[13]

Taken together with the data from the current study by Choi et al,[9] an EGC that appears to be mucosally based by CE and/or by EUS is likely to be a mucosal, T1a lesion. Although far from perfect, endoscopic characteristics appear to be to more reliable than EUS in predicting superficial submucosal, early T1b, lesions. Because EUS and CE techniques are imperfect, even in expert hands, for T staging of EGCs, ESD still fills an important role by providing an intact specimen for definitive pathological diagnosis and T staging. Goto et al[14] found that patients who underwent ESD but later required gastrectomy and LN dissection fared no worse compared with (historical data on) patients who underwent gastrectomy and LN dissection without initial endoscopic resection.

At present, in North America and in most European countries, there are no established guidelines concerning the screening for or resection of EGCs,[15] which is likely because of the different incidences of EGC in these countries compared with those found in Asian and certain South American countries.[16] In the absence of further data and ensuing guidelines, it seems reasonable to adopt a practice pattern for ESD in the management of EGC analogous to that being used for dysplastic Barrett's esophagus.[17] In this model, a detailed high-definition endoscopic assessment (in conjunction with biopsies guided by enhanced optical imaging modalities, such as narrow-band imaging or chromoendoscopy) would be the first step. For highly dysplastic lesions, consideration may be given to performing EUS for T staging and evaluation for LN metastasis, but if high-quality EUS imaging is not obtainable, T staging by CE should be sufficient. For mucosally based lesions that fit into the extended criteria,[1] EMR or ESD would then be offered for both diagnostic and curative intent. Although the role of ESD for EGC has yet to be firmly established in Western countries, ESD may still fill an important role by enabling en bloc resection of lesions with focal high-grade dysplasia or large adenomas that are not amenable to EMR. Furthermore, ESD also offers an endoscopic alternative in patients at increased risk of surgical resection. Given the recent concerning data on LN metastasis in early submucosal EGCs, the appropriateness of ESD in these lesions is questionable.

EFFICIENCY OF GASTRIC ESD

The other article featured in this issue of *GIE*, by Ahn et al,[10] retrospectively reviewed the results of 916 ESDs performed for EGC in 889 patients. ESD was done with the patients under conscious sedation by 4 Korean endoscopists, who each had performed more than 50 ESDs and 100 EMRs before this study. A needle-knife (MTW Endoskopie, Wesel, Germany) was used for circumferential incision, and the insulated-tip knife (Olympus, Tokyo, Japan) was the primary tool used in submucosal dissection. Procedure time was defined as the time from circumferential marking to the completion of hemostasis, which was performed after ESD was completed. On multivariate analysis, lesion size larger than 20 mm, location in the proximal stomach, presence of submucosal fibrosis, and perforation were independent predictors of longer procedure time, defined as a procedure of 38 minutes or longer. The median ESD time for even the most difficult lesions was generally less than 1 hour: 45.0 minutes (interquartile range [IQR] 33.5-65.0 minutes) for the lesions 41 mm or larger, 45.0 minutes (IQR 33.0-64.5 minutes) for lesions in the upper stomach, 43.0 minutes (IQR 29.0-59.8 minutes)