Gastric Extremely Well-Differentiated Intestinal-Type Adenocarcinoma: A Challenging Lesion to Achieve Complete Endoscopic Resection

Citation
Kang, K., K.-M. Kim, J. Kim, P.-L. Rhee, J. Lee, B.-H. Min, J. Rhee, R. Kushima, and G. Lauwers. 2012. Gastric extremely well-differentiated intestinal-type adenocarcinoma: a challenging lesion to achieve complete endoscopic resection. Endoscopy 44(10): 949–952.

Published Version
doi:10.1055/s-0032-1310161

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:12601544

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Gastric extremely well-differentiated intestinal-type adenocarcinoma: a challenging lesion to achieve complete endoscopic resection

Authors
K. J. Kang1,*, K.-M. Kim2,*, J. J. Kim1, P.-L. Rhee1, J. H. Lee1, B.-H. Min1, J. C. Rhee1, R. Kushima3, G. Y. Lauwers4

Institutions
1 Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
2 Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
3 Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan
4 Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts, USA

Introduction
Extremely well-differentiated tubular adenocarcinomas (EWDAs) of the stomach are characterized by surface maturation and their mimicking of intestinal metaplasia. Endoscopically, intramucosal EWDAs are frequently ill defined with indistinct borders due to the pallor of the neoplastic mucosa and the lack of contrast against the background atrophic and metaplastic mucosa. We evaluated the effectiveness of endoscopic resection for EWDAs after endoscopic submucosal dissection (ESD).

Among 872 patients with early gastric cancer, 17 EWDAs were identified (1.9%). Endoscopically, the flat or depressed type was significantly more common among EWDAs (88.2%) than among early gastric cancers of other histologies (37.8%; \( P<0.01 \)). The discrepancy between endoscopically estimated tumor size and tumor size as confirmed in pathology reports was significantly greater among EWDAs (18.4±22.0 mm) than among others (5.8±7.5 mm). Involvement of the lateral resection margin was more common (29.4% vs. 2.5%; \( P<0.05 \)), and complete resection was achieved less often in EWDAs (47.1% vs. 80.4%; \( P=0.01 \)) compared to the others.

EWDAs are associated with higher rates of incomplete resection after ESD, especially along the lateral margins. Pathologists should alert endoscopists when this diagnosis is made, with its associated risks; and endoscopists should pay particular attention to the extent of these tumors during resection.

Patients and methods
This retrospective, single-center study was performed after approval by the institutional review board at the Samsung Medical Center. From January 2009 to December 2010, 872 patients were enrolled who had been diagnosed with early gastric cancer and treated with ESD by three experienced endoscopists. The indication for ESD was based on the diagnosis of early gastric cancer with no risk of regional lymph node metastasis following published criteria [4,5]. All ESD procedures were conducted using a single-channel endoscope (Olympus GIF-Q260J; Olympus Corporation, Tokyo, Japan) with a high-frequency generator and an automatically controlled system (Endocut mode, Erbobot ICC200; Erbe Elektromedizin GmbH, Tübingen, Germany) as previously described [6]. To highlight the boundaries of the tumor, a mixture of 0.9% normal saline, 1:10000 epinephrine, and 0.4% indigo carmine (ENI solution) was sprayed on the mucosa. Marking dots were added circumferentially at least 5 mm lateral to the lesion. After the circumferential incision, ENI solution was injected into the submucosa.

* These authors contributed equally to this work.
Gastric EWDAs are reported as very rare, comprising 0.1% of gastric adenocarcinomas (EWDAs) versus early gastric cancers of other histologies. The rate of complete resection was significantly lower in EWDAs (47.1%) than in others (80.4%) \( (P=0.01) \). There were seven EWDAs with incomplete resection (positive lateral margins \( n=5 \), positive vertical margin \( n=1 \), and undetermined margins \( n=1 \) ) after ESD. The average follow-up period was 14.6 ± 8.8 months, and there was no recurrence in the patients who underwent argon plasma coagulation ablation \( n=1 \), additional ESD \( n=3 \), or surgery \( n=3 \).

Figure 1 illustrates an example of an EWDA that was initially evaluated as having negative resection margins. This 1.5-cm type Ic early gastric cancer lesion was found in the gastric angle. The resection was uncomplicated, and the pathologic evaluation revealed an EWDA 2.6 × 1.9 cm in size. Although the resection margins were negative, the clearances were narrow, and therefore an additional ESD to obtain wider safety margins was performed. Unexpectedly, microscopic evaluation of the additional specimen demonstrated a residual EWDA \( (0.8 \times 0.3 \text{ cm in size}) \) limited to the lamina propria, with wide and clear resection margins (Fig. 2).

Discussion

In this series, we investigated the differences in the effectiveness of endoscopic resection between EWDAs and non-EWDAs after ESD. We showed that the rate of complete resection was significantly lower in EWDAs than in other neoplasms. In particular, the rate of positive lateral margins was much higher in EWDAs (18.4 ± 22.0 mm) than for others (5.8 ± 7.5 mm) \( (P<0.05) \).

Table 1 Clinical and pathologic characteristics of 872 patients undergoing endoscopic submucosal dissection for early gastric cancer: extremely well-differentiated tubular adenocarcinomas (EWDAs) versus early gastric cancers of other histologies

|                      | EWDA cancer, \( n=17 \) | Non-EWDA cancer, \( n=855 \) | \( P \) value |
|----------------------|-------------------------|-----------------------------|-------------|
| Mean age, years, mean ± SD | 55.3 ± 13.5             | 62.8 ± 9.7                  | 0.04        |
| Male sex, n (%)      | 13 (76.5)               | 678 (79.3)                  | 0.77        |
| Location, n (%)      |                         |                             | 0.40        |
| Upper                | 1 (5.9)                 | 66 (7.7)                    |             |
| Mid                  | 6 (35.3)                | 161 (18.8)                  |             |
| Lower                | 10 (58.8)               | 628 (73.4)                  |             |
| Macroscopic appearance, n (%) |             |                             | <0.01       |
| Elevated             | 2 (11.8)                | 532 (62.2)                  |             |
| Flat or depressed    | 15 (88.2)               | 323 (37.8)                  |             |
| Endoscopic size, mm, mean ± SD | 11.0 ± 5.9             | 14.8 ± 7.4                  | <0.02       |
| Pathologic size, mm, mean ± SD | 29.0 ± 24.6          | 15.8 ± 11.0                 | <0.04       |
| Histological type, n (%) |                        |                             | <0.05       |
| Differentiated       | 17 (100)                | 834 (97.5)                  |             |
| Undifferentiated     | 0                       | 21 (2.5)                    |             |
| Invasion depth, n (%) |                         |                             | n.s.        |
| Mucosa               | 14 (82.4)               | 708 (82.8)                  |             |
| Submucosa            | 3 (17.6)                | 147 (17.2)                  |             |
| Lymphatic invasion present, n (%) | 2 (11.8)               | 62 (7.3)                    | 0.87        |
| Venous invasion present, n (%) | 0                      | 5 (0.6)                     | n.s.        |
| En bloc resection, n (%) | 15 (88.2)               | 831 (97.2)                  | 0.09        |
| Lateral margin positive, n (%) | 5 (29.4)               | 21 (2.5)                    | <0.01       |
| Vertical margin positive, n (%) | 1 (5.9)                | 20 (2.3)                    | 0.03        |
| Margins indeterminable, n (%) | 1 (5.9)                | 9 (1.1)                     | 0.18        |
| Complete resection, n (%) | 8 (47.1)                | 687 (80.4)                  | 0.01        |

SD, standard deviation; n.s., not significant.

1 Due to electrosurgery effect.
EWDA cancer was 1.9%. The design of the study (i.e., restricted to early gastric cancers manageable by ESD) may explain the relatively high incidence of this subtype. Endoh et al. were the first to report these diagnostically challenging well-differentiated adenocarcinomas that mimic the complete type of intestinal metaplasia and display a WHYX architectural pattern [3]. Microscopically, it is difficult to discriminate EWDA from regenerative or inflammatory changes of metaplastic epithelium [3]. Endoscopically, most EWDA in our series demonstrated limited color contrast against the surrounding mucosa and/or a slight depression. These subtle mucosal changes may explain the high positive rate of lateral resection margins in EWDA in spite of thorough chromoendoscopic evaluations. In this study, the en bloc resection rate was 88.2% in EWDA and 97.2% in non-EWDA cancers. With regard to non-EWDA cancers, the en bloc resection rate in our series was similar to that in a previous report [10]. In EWDA, the incomplete resection rate in our series (52.9%) was higher than the incomplete resection rate of non-EWDA after ESD in the previous study, because of higher rates of lateral resection margin involvement after the ESD procedure. Despite our findings, endoscopic resection should remain the first therapeutic option because these neoplasms generally demonstrate slow tumor growth and a low ability to infiltrate submucosa [11, 12]. In practice, the completeness of resection can be difficult to predict for EWDA because the lesional spread can be wider than estimated endoscopically [13, 14]. However, a pre-ESD biopsy diagnosis of EWDA is critical information that should help to guide the endoscopist to achieving complete resection.
In conclusion, this study represents the first attempt to investigate the effectiveness of ESD for gastric EWDAs. Compared to ESD for non-EWDAs, the complete resection rate was significantly lower, and we conclude that the higher rate of positive lateral resection margins results from the difficulties in determining the tumor boundaries of EWDAs endoscopically. Consequently, pathologists have an important role to play in guiding therapy by informing the endoscopists when a diagnosis of EWDA is made on preoperative biopsies. Endoscopists should then pay particular attention to the extent of these tumors and make every attempt to perform a wide excision when performing an ESD in order to achieve satisfactory lateral clearances.

Competing interests: None

References
1 Endoh Y, Watanabe HJ. Intestinal-type adenocarcinoma in the fundic gland area of the stomach. Stomach Intest 1994; 28: 1009–1023
2 Koike M, Takizawa T, Iwasaki Y. Pathological aspect of early gastric carcinoma, handling of the endoscopically mucosectomized specimen and problem in the pathological diagnosis. Stomach Intest 1993; 28: 127–138
3 Endoh Y, Tamura G, Motoyama T et al. Well-differentiated adenocarcinoma mimicking complete-type intestinal metaplasia in the stomach. Hum Pathol 1999; 30: 826–832
4 Gotoda T, Yanagisawa A, Sasaki M et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225
5 Ohkawa M, Hosokawa K, Boku N et al. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001; 33: 221–226
6 Kim JJ, Lee JH, Jung HY et al. EMR for early gastric cancer in Korea: a multicenter retrospective study. Gastrointest Endosc 2007; 66: 693–700
7 Kim KM, Park CK. Pathology of endoscopic submucosal dissection: how do we interpret? Korean J Gastroenterol 2010; 56: 214–219
8 Endoh Y, Watanabe H, Hitomi J. Intestinal-type adenocarcinoma in the fundic gland area of the stomach. Stomach Intest 1994; 20: 1009–1023
9 Niimi C, Goto H, Ohmiya N et al. Usefulness of p53 and Ki-67 immunohistochemical analysis for preoperative diagnosis of extremely well-differentiated gastric adenocarcinoma. Am J Clin Pathol 2002; 118: 683–692
10 Chung IK, Lee JH, Lee SH et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc 2009; 69: 1228–1235
11 Watanabe H, Kato N, Fuchigami T, Sato T. Natural history of gastric carcinoma from analysis of microcarcinoma. Stomach Intest 1992; 27: 59–67
12 Kaizaki Y, Hosokawa O, Miyanglo T et al. Natural history of gastric low-grade differentiated carcinoma. Stomach Intest 2010; 45: 801–810
13 Tada M, Murakami A, Karita M et al. Endoscopic resection of early gastric cancer. Endoscopy 1993; 25: 445–450
14 Kwon CW, Park CH, Cho JH et al. Follow-up result of endoscopic mucosal resection for gastric adenoma and early gastric cancer. Korean J Med 2006; 71: 483–490