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

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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.

Introduction

Extremely well-differentiated tubular adenocarcinomas (EWDAs) (also reported in the Japanese literature as “WHYX lesions”) of the stomach demonstrate low-grade cytological atypia difficult to differentiate from complete-type intestinal metaplasia and considerable structural atypia with interconnecting neoplastic tubules [1,2]. Endoscopically, EWDAs present ill-defined peripheral borders that are paler in color than the background atrophic and metaplastic gastric mucosa [3]. Because of these characteristics, we assumed that the rate of incomplete resection will be high after endoscopic submucosal dissection (ESD), especially with regard to the lateral margins. The aim of this study was to investigate the rate of completeness of excision of EWDAs after ESD.

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, Erbotom ICC200; Erbe Elektromedizin GmbH, Tübingen, Germany) as previously described [6]. To highlight the boundaries of the tumor, a mixture of 0.9% normal saline, 1:10 000 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

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	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	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 electrocautery effect.

again and the submucosal plane was dissected using an electro-surgical knife. En bloc resection was defined as removal of the tumor as a single piece without fragmentation. Negative resection margins (lateral and vertical) were defined as such after microscopic examination. Complete resection was defined as meeting all of the following criteria: (i) en bloc resection, (ii) tumor-free lateral and vertical resection margins, (iii) absence of lymphovascular invasion, and (iv) submucosal tumor invasion of less than 500 μm.

ESD specimens were pinned to cork mats and fixed in 10% neutral-buffered formalin, and the resection margins were marked by different colored inks. After fixation, the specimens were serially sectioned at 2-mm intervals and completely embedded. All specimens were reviewed by one gastrointestinal pathologist (K. M.K.), as described elsewhere [7]. A diagnosis of EWDA was made when branching tubules formed interconnecting and anastomosing structures, making the shapes of the letters W, H, Y, or X at low-power view, and lacked overt back-to-back arrangement of glands [3, 8]. The neoplastic glands showed low-grade cytologic atypia and mimicked complete intestinal metaplasia. The endoscopically estimated tumor size ("endoscopic tumor size") was determined by evaluating medical records, and the final tumor size ("pathologic tumor size") was determined by reviewing the pathology reports. "Size discrepancy" was defined as the difference between the endoscopic tumor size and the final pathologic tumor size.

Results

Among the 872 patients who underwent an ESD, 17 had EWDA (1.9%) and 855 non-EWDAs (▶ **Table 1**). Endoscopically, the flat or depressed type was significantly more common among EWDA (88.2%) than among other histologic subtypes (37.8%;

$P < 0.01$). The discrepancy (mean ± SD) between pathologic tumor size and endoscopic tumor size was significantly greater for EWDA (18.4 ± 22.0 mm) than for others (5.8 ± 7.5 mm) ($P < 0.05$).

The rate of complete resection was significantly lower in EWDA (47.1%) than in others (80.4%) ($P = 0.01$). There were seven EWDA 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 IIc 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 × 0.3 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 EWDA and non-EWDA after ESD. We showed that the rate of complete resection was significantly lower in EWDA than in other neoplasms. In particular, the rate of positive lateral margins was much higher in EWDA. Gastric EWDA are reported as very rare, comprising 0.1% of gastric adenocarcinomas [9]. However, in our series, the incidence of

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

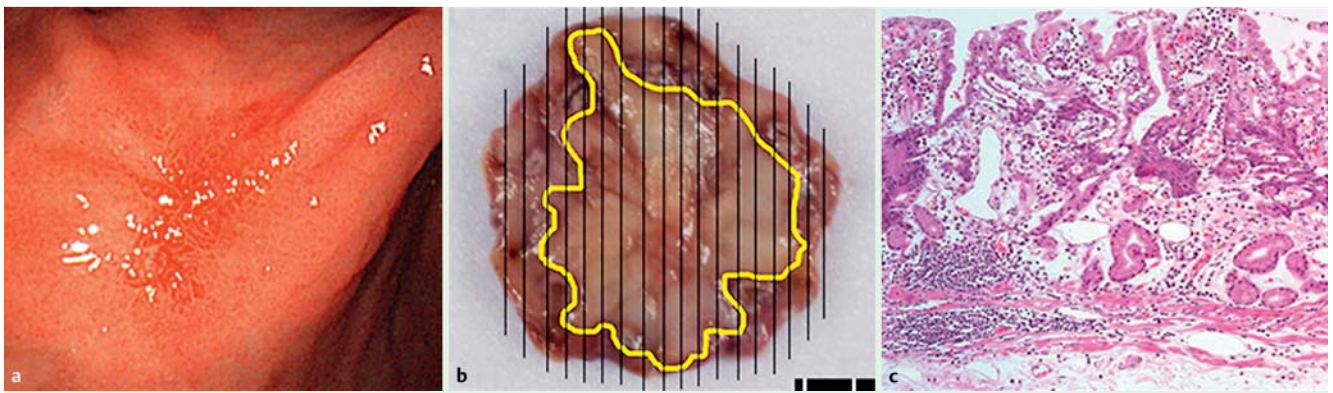


Fig. 1 **a** Endoscopic appearance of a gastric carcinoma. **b** Tumor topography on the primary endoscopic submucosal dissection. The yellow line illustrates the boundary of the neoplasm. The proximal, anterior, and posterior sites of the specimen were located at the 12 o'clock, 9 o'clock, and 3 o'clock positions, respectively (safety margins: 0.1 cm distally, 0.2 cm proximally, 0.6 cm anteriorly, and 0.2 cm posteriorly). **c** Pathologic findings. Extremely well-differentiated tubular adenocarcinoma confined to the lamina propria of the gastric mucosa (H&E, $\times 20$). The neoplastic tubules show branching, tortuous, anastomosing structures associated with cryptitis.

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 is 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.

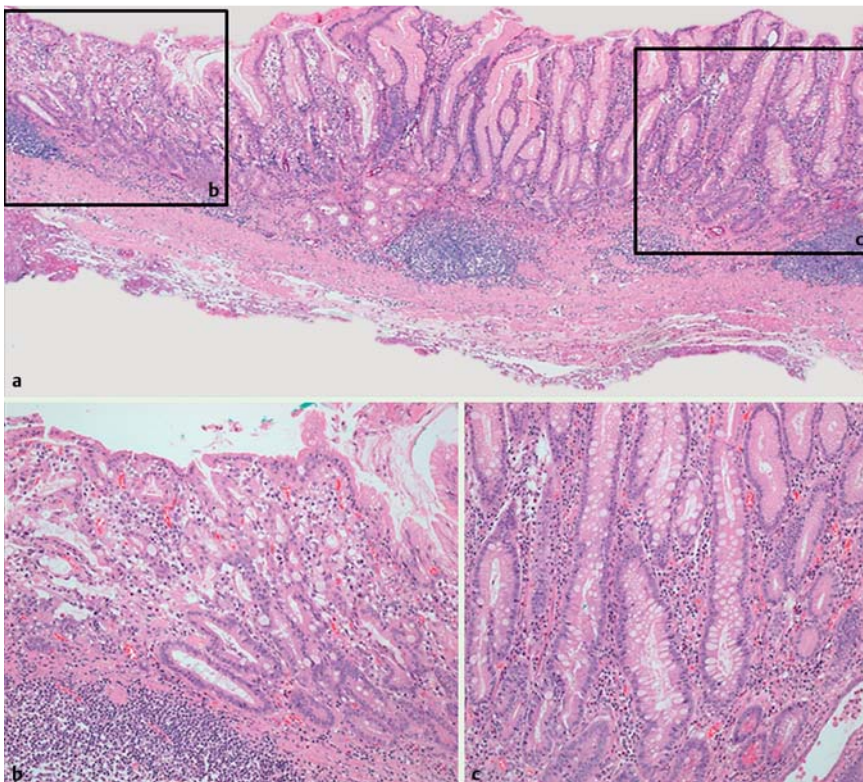


Fig. 2 Pathologic findings of the second endoscopic submucosal specimen (same patient as in **Fig. 1**). **a** The residual neoplasm was limited to the lamina propria and did not involve the resection margins (H&E, $\times 4$). **b, c** Higher magnification views of extremely well-differentiated tubular adenocarcinoma (**b**) and adjacent complete intestinal metaplasia (**c**) (H&E, $\times 20$).

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

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