EDITORIAL

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Metachronous Gastric Cancer: Another Hurdle for Successful Endoscopic Treatment for Early Gastric Cancer?

Moon Won Lee and Gwang Ha Kim

Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan, Korea

See "Clinical Outcomes of Metachronous Gastric Cancer after Endoscopic Resection for Early Gastric Cancer" by Jue Lie Kim, et al. on page 190, Vol. 14, No. 2, 2020

Endoscopic submucosal dissection (ESD) has been widely used as a curative treatment for early gastric cancers (EGCs). ESD has historically high *en bloc* and curative resection rates for EGCs, regardless of their size and location. ESD is a minimal invasive procedure compared to surgical gastrectomy, and is an advantageous approach due to preservation of the entire stomach. Despite these advantages, there is a concerning rate of newly developed gastric cancers in the preserved stomach after ESD. Metachronous gastric cancer (MGC) is defined as a newly developed gastric cancer occurring at a previously uninvolved site 1 year or more after index ESD.

In this issue of *Gut and Liver*, Kim *et al*.[1] evaluated the clinical outcomes of MGC after ESD for EGCs between the re-ESD and surgery groups. During the mean follow-up period of 66 months, MGC occurred in 117 of 1,302 patients (9%) who had undergone ESD for EGCs; of patients with MGC, 90 underwent re-ESD and 22 underwent surgery. In multivariate analysis, a low body mass index, multiplicity of index cancers, diffuse or mixed-type Lauren classification, submucosal or deeper invasion, and upper stomach location were factors associated with surgery for MGC. Interestingly, the surgical group showed a significantly shorter overall survival rate than the re-ESD group.

Risk factors associated with development of MGC include male sex, old age, current smoking, severe atrophy, intestinal metaplasia, persistent *Helicobacter pylori* infection, pepsinogen (PG) I/II ratio ≤3, differentiated-type histology, and multiple initial gastric cancers.[2-9] Male sex, old age, and current smoking are also potential risk factors for gastric cancer in the general population. According to Correa's hypothesis, intestinal-type gastric cancer may develop as chronic *H. pylori* infection evolves over time to chronic gastritis, atrophy, intestinal metaplasia and dysplasia. Because ESD is an organ-sparing treatment, gastric mucosa with histologic changes remains after ESD for EGCs. Therefore, risk factors for MGC are like to those for intestinal-type gastric cancer. Some studies suggest that *H. pylori* eradication may not always reduce the development of MGC after ESD, especially in cases of multiple initial gastric cancers;[9] severe atrophy with intestinal metaplasia represents the "point of no return" at which the development of gastric cancer can no longer be prevented by *H. pylori* eradication alone. On the contrary, many studies suggest that persistent *H. pylori* infection is a risk factor for MGC, and a recent meta-analysis shows that *H. pylori* eradication can effectively reduce rates of MGC.[10] Therefore, *H. pylori* eradication is strongly recommended for prevention of MGC after ESD for EGCs. Serum PG I/II ratio can also be used as a predictive indicator of the development of MGC after ESD, as it is a reliable marker in the diagnosis of more extensive atrophy.[8]

Because gastric atrophy progresses from the antrum to the lower body, MGC is usually located at the lower third of the stomach and appears as a small, differentiated-type intramucosal cancer <20 mm in size.[6,11] Most patients with MGC already have marked atrophy and intestinal metaplasia in the background gastric mucosa. Because *H. pylori* eradication decreases inflammation caused by *H. pylori* infection, it can become even more difficult to detect early MGC and its margins. Therefore,

Correspondence to: Gwang Ha Kim
Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7869, Fax: +82-51-244-8180, E-mail: doc0224@pusan.ac.kr
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Table 1. Incidence and Risk Factors of Metachronous Gastric Cancers Occurring after Endoscopic Resection for Early Gastric Cancers

Study (year)	Subject no.	Mean follow-up period (yr)	Incidence of metachronous cancer (%)	Risk factors
Abe *et al*. (2015)[2]	1,526	6.8	15.6	Multiple initial cancers
				Male sex
Sugimoto *et al.* (2015)[3]	155	4.2	14.8	Intestinal metaplasia
				Neutrophil infiltration
Mori *et al*. (2016)[4]	594	4.5	13.3	Male sex
				Severe atrophy
				Multiple initial cancers
Ami *et al*. (2017)[5]	539	8.7	13.0	Old age (>60 yr)
				Current smoking
Cho *et al*. (2017)[6]	2,334	3.5	3.3	Aging
Chung *et al*. (2017)[7]	185	5.6	13.0	Old age (>70 yr)
				Persistent *Helicobacter pylori* infection
Kwon *et al*. (2017)[8]	590	4.0	10.8	Persistent *H. pylori* infection
				Serum pepsinogen I/II ratio ≤3
Okada *et al*. (2019)[9]	384	4.1	15.6	Aging
				Differentiated-type histology
				Multiple initial cancers

more time and biopsies of suspicious lesions are needed during surveillance endoscopy to identify MGC.

The incidence of MGC following ESD for EGCs has been reported to be 3.3% to 15.6%, according to the follow-up duration (Table 1). The mean annual incidence of MGC after ESD is approximately 2.5% to 3.5% and linearly increases;[11] a 10-year cumulative incidence of MGC may increase up to 22.7%.[2] Thus, clinicians should perform annual surveillance endoscopy for at least 10 years after ESD, paying special attention to the lower third of the stomach.

MGC can be treated similarly to an initial EGC. Because MGC is usually a small, differentiated-type, mucosal cancer, it can be treated by ESD. Long-term treatment outcomes of ESD for MGC are excellent when curative resection is achieved. Previous studies have reported that curative resection rates for MGC are 89% to 99%, and the 5-year and 10-year disease-specific survival rates in patients with MGC after curative ESD are 99% and 93%, respectively.[2,4,6] Surgical treatment is necessary for MGC with beyond the extended criteria of ESD for EGCs.

In summary, patients who have undergone ESD for EGCs experiences a high incidence of MGC that increases linearly for at least 10 years. Although *H. pylori* eradication can decrease the incidence of MGC, it does not completely reduce the risk for MGC. Surveillance endoscopy should be used to identify MGC; risk stratification and tailored follow-up intervals should be developed according to the patient's risk factors for MGC. Currently, a minimum of annual surveillance endoscopy is recommended for detecting MGC after ESD for EGCs.

CONFLICTS OF INTEREST

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

ORCID

Moon Won Lee https://orcid.org/0000-0002-8411-6398
Gwang Ha Kim https://orcid.org/0000-0001-9721-5734

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