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Metachronous Gastric Cancer Following Curative Endoscopic Resection of Early Gastric Cancer

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This review article summarizes knowledge about metachronous gastric cancer (MGC) occurring after curative endoscopic resection (ER) of early gastric cancer (EGC), treatment outcomes of patients who developed MGC, and efficacy of *Helicobacter pylori* eradication to prevent MGC. The incidence of MGC following curative ER increases over time and is higher than in patients undergoing gastrectomy. Increasing age and multifocal EGC are independent risk factors for developing MGC. An MGC following curative ER is usually a small (<20 mm) and differentiated intramucosal cancer. Most MGC lesions are found at an early stage on semiannual or annual surveillance endoscopy and are successfully treated by further ER, with excellent long-term outcomes. Eradication of *H. pylori* may reduce the risk of MGC following ER of EGC, but further prospective studies with long-term outcomes are required. Surveillance endoscopy following gastric ER should be continued indefinitely, due to the risk of MGC even after successful *H. pylori* eradication. Risk stratification and tailored endoscopic surveillance schedules need to be developed. **Clin Endosc 2018;51:253-259**

Key Words: Metachronous gastric cancer; Endoscopic resection; Endoscopic mucosal resection; *Helicobacter pylori*; Surveillance endoscopy

INTRODUCTION

Approximately one million new gastric cancer cases occurred in 2012, making it the fifth most common malignancy and the third leading cause of cancer death worldwide.¹ Development of screening esophagogastroduodenoscopy (EGD) programs has led to the detection of gastric cancer at earlier stages, and approximately half of all gastric cancers in Japan are detected at a stage when they are confined to the mucosa or submucosa.²

Increasing numbers of early gastric cancer (EGC) cases have been treated with endoscopic resection (ER), as curative

resection was defined based on large retrospective cohort in surgery cases and the development of endoscopic submucosal dissection (ESD) has allowed for high *en bloc* and curative resection rates of EGC, regardless of size and location.³⁻⁶ Several retrospective studies have shown excellent long-term outcomes in EGC patients undergoing curative gastric ESD.⁷⁻¹⁶ In addition, ESD preserves stomach function and maintains quality of life in those patients who achieve curative ER.¹⁷

A drawback of ER for EGC is the risk of developing metachronous gastric cancer (MGC) in the remaining native stomach. As the popularity of this technique increases, it is vitally important to characterize risk factors and long-term outcomes for those patients who develop MGC. This review article summarizes the definition, incidence, clinical characteristics, and outcomes of MGC.

DEFINITION OF MGC

Gastric cancer detected on surveillance EGD following cu-

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rative ER may be a *de novo* lesion, a previously invisible pre-clinical lesion, or a missed lesion. Determining which of these possibilities is the case can be extremely difficult. General consensus, based on previous publications, is that gastric cancers detected within 1 year after ER should be regarded as a missed synchronous gastric cancer.¹⁸⁻²¹ Thus, MGC is generally defined as a gastric cancer located distant from the original EGC over 1 year following index ESD.

INCIDENCE OF METACHRONOUS GASTRIC CANCER FOLLOWING ENDOSCOPIC RESECTION

Studies have reported an incidence of MGC following ER for EGC ranging from 2.7% to 15.6% (Table 1).^{20,22-30} In these studies, all MGCs were detected on surveillance EGD, and no study reported detection of EGC by barium contrast or computed tomography. ESD was preferred over endoscopic mucosal resection (EMR) in these series.

Kobayashi et al. reported that MGCs developed in 30 of 234 patients during a median follow-up of 5.0 years.²⁸ They also demonstrated that a Kaplan-Meier curve of cumulative incidence of MGC stopped increasing after 10 years of follow-up.²⁸ In contrast, Kato et al. and Min et al. reported that the cumulative incidence curve revealed a linear increase in much larger cohorts.^{24,29} We also demonstrated that 5-year, 7-year, and 10-year cumulative incidence of MGC (adjusted for risk of death from other causes) on surveillance endoscopy was 9.5%, 13.1%, and 22.7%, respectively, with a median follow up of 82.2 months.³⁰

Following gastrectomy, the cumulative incidence of MGC is 0.9%–3.0%.³¹⁻³⁴ The incidence of MGC in patients undergoing ER is much higher. This difference is explained by the organ-sparing nature of ER, as while maintaining luminal continuity offers an improved quality of life, the remaining gastric mucosa continues to be at risk of MGC.

RISK FACTORS ASSOCIATED WITH MGC

Although methods used to analyze risk factors for MGC vary among studies, older age, multiple initial EGCs and persistent *Helicobacter pylori* infection are considered to be common risk factors (Table 2).^{25,28-30,35-37} As older age is a greater potential risk factor for gastric cancer and multifocal lesions tend to develop in gastric mucosa with high risk field changes, these factors are unsurprising. Persistence of *H. pylori* infection as a risk factor is less straightforward. Persistence should be positively correlated with recurrence risk; however, Lim et al. reported that the absence of *H. pylori* infection is an independent risk factor for metachronous neoplasms, including dysplasia.³⁸ One possible explanation for this divergent finding is that long-term *H. pylori* infection may result in severe atrophic gastritis with intestinal metaplasia, such that *H. pylori* is no longer detectable. Long-term infection might have had more effect on metachronous tumorigenesis than newly developed *H. pylori* infections that can be easily detected.³⁹

Table 1. Incidence of Metachronous Gastric Cancer following Endoscopic Resection

Study	Methods of endoscopic resection	Rate of MGC	Follow up period (yr)			Annual incidence of MGC
Kim et al. (2007) ²²	EMR ^{a)}	2.70%	11/379	1.9	Median	-
Lee et al. (2011) ²³	ESD	3.30% ^{b)}	15/458	2.2	Median	-
Kato et al. (2013) ²⁴	ESD	5.20%	65/1258	2.2	Mean	3.50%
Hahn et al. (2016) ²⁵	ESD	4.30%	58/1347	2.4	Median	2.48%
Nakajima et al. (2006) ²⁶	EMR and ESD	8.20%	52/633	4.4	Mean	-
Nasu et al. (2005) ²⁷	EMR	14%	20/143	4.8	Median	Approximately 4%
Kobayashi et al. (2010) ²⁸	EMR and ESD	12.80%	30/234	5	Median	-
Min et al. (2015) ²⁹	ESD	3.60%	47/1306	5	Median	-
Abe et al. (2015) ³⁰	ESD	15.60%	238/1527	6.6	Median	-
Arima et al. (1999) ²⁰	EMR	7.90%	6/76	7	- ^{c)}	-

MGC, metachronous gastric cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

^{a)}Only R0 resection in patients with intramucosal cancer was included.

^{b)}Synchronous lesion was included for analysis.

^{c)}All patients were followed up for 7 year.

CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES OF MGC

According to recent publications, MGCs are commonly characterized as small, differentiated intramucosal cancers <20 mm in size.²⁶⁻²⁸ MGCs often develop when the initial lesion is a differentiated EGC. This suggests that this type of cancer tends to develop in gastric mucosa during field cancerization.^{40,41}

Regular endoscopic surveillance detects MGC at an early stage, allowing for repeat curative ESD resection in the majority of cases, according to absolute or expanded indications based on the Japanese Gastric Cancer Treatment Guidelines.^{5,23-25,29,30} Kato et al. reported that only 4 of 175 synchronous or metachronous cancers invaded the submucosa or deeper layers.²⁴ Our study showed that 215 of 238 patients with MGC underwent ER (mostly ESD), and the *en bloc* resection, R0 resection, and curative resection rates were 99.3%, 94.3%, and 88.8%, respectively.³⁰

In addition, excellent long-term outcomes have been shown by Kato et al. in his multicenter, retrospective cohort study, in which no patients died of gastric cancer during a mean follow-up period of 26.8 months.²⁴ Our study showed a 5-year disease-specific survival rate of 99.2% in patients undergoing curative gastric ESD; of the 238 patients who developed MGC, only 7 died of MGC during a median follow-up of 82.2 months. The patients who died from MGC were lost to follow-up, and did not undergo the surveillance endoscopy that may have detected their cancers at an earlier and more treatable stage. Five of the patients died from MGC more than 5 years after their index ESD.³⁰ These studies support the clin-

ical validity of an organ-preserving strategy with surveillance endoscopy and repeated ESD.

Treatment outcomes for gastric cancer are generally evaluated with 5-year overall and disease-specific survival. A limited 5-year follow-up may be reasonable for patients undergoing gastrectomy, as a majority of postoperative lymph node or distant recurrences occur within 5 years, and the risk of MGC development is much lower than in those treated with ER.⁴² On the other hand, indefinite endoscopic surveillance is required to detect and remove MGCs in patients treated endoscopically.

H. PYLORI ERADICATION FOLLOWING ER

H. pylori infection is characterized by progression through the following stages: chronic active gastritis, atrophy, intestinal metaplasia, and dysplasia, followed by the development of gastric adenocarcinoma. *H. pylori* infection is considered one of the most important risk factors for gastric cancer.⁴³⁻⁴⁷ In 1994, the International Agency for Research on Cancer, a subsidiary of the World Health Organization, categorized *H. pylori* as a group 1 carcinogen for gastric cancer.⁴⁸ Uemura et al. concluded that gastric cancer develops in persons infected with *H. pylori*, but not in uninfected persons.⁴⁹ Take et al. showed that *H. pylori* eradication has preventative effects on the occurrence of initial gastric cancer.⁵⁰ In addition, persistent *H. pylori* infection was considered to a risk factor for MGC after ER in a number of retrospective studies, as shown in Table 2.^{36,37}

Thus, it would seem reasonable to assume that *H. pylori*

Table 2. Intervals of Surveillance Endoscopy and Risk Factors of Metachronous Gastric Cancer following Endoscopic Resection

Study	Intervals of Surveillance endoscopy for MGC	Risk factors of metachronous gastric cancers
Lee et al. (2011) ²³	Biannual then annual	-
Kato et al. (2013) ²⁴	Annual or biannual	-
Hahn et al. (2016) ²⁵	Annual or biannual	Older age, intestinal metaplasia, ESD criteria
Nakajima et al. (2006) ²⁶	Annual	-
Nasu et al. (2005) ²⁷	Annual	-
Kobayashi et al. (2010) ²⁸	Annual	Multiple initial EGC, male, same third of the stomach
Min et al. (2015) ²⁹	Annual or biannual	Multiple initial EGC, well differentiated adenocarcinoma of initial EGC
Abe et al. (2015) ³⁰	Annual or biannual	Multiple initial EGC, male
Arima et al. (1999) ²⁰	-	Multiple initial EGC
Maehata et al. (2012) ³⁵	Annual or biannual	Follow-up period over 5 years, severe gastric mucosal atrophy
Kwon et al. (2014) ³⁶	Annual	Age ≥60 years old, persistent <i>Helicobacter pylori</i> infection
Kim et al. (2014) ³⁷	Annual	Age ≥65 years old, persistent <i>H.pylori</i> infection, family history of gastric cancer

MGC, metachronous gastric cancer; ESD, endoscopic submucosal dissection; EGC, early gastric cancer.

eradication would have a potential prophylactic effect on MGC following ER.⁵¹ However, two recent large, prospective randomized trials have shown contradictory results. Fukase et al. reported that the cumulative incidence of MGC was 6.5% during a 3-year follow-up, and patients receiving *H. pylori* eradication treatment showed significantly lower MGC rates than patients without eradication therapy (3.5% vs. 9.6%, $p=0.003$).⁵² On the other hand, Choi et al. concluded that the cumulative incidence of MGC was comparable in patients with and without *H. pylori* eradication treatment during a 3-year follow-up (2.3% vs. 3.9%, $p=0.24$).⁵³ Other retrospective studies showed similarly controversial conclusions (Table 3),^{35-37,54-58} but meta-analyses by Jung et al. and Yoon et al. concluded that *H. pylori* eradication could play a preventative role by reducing the occurrence of MGC in patients who have undergone ER.^{59,60}

Therefore, *H. pylori* eradication should be considered as preventative of MGC after ER. It should be noted that the definitions of MGC were not consistent among the studies and that some previous studies did not distinguish MGC from synchronous gastric cancer. In addition, the median follow-up periods were less than 5 years in a majority of previous publications and the timing of *H. pylori* eradication could affect the results. Further prospective studies in the ESD era with long follow-up periods might help clarify the preventative effect of *H. pylori* eradication for MGC occurrence.

CLINICAL CHARACTERISTICS AND RISK FACTORS OF MGC FOLLOWING *H. PYLORI* ERADICATION

MGCs following successful *H. pylori* eradication were mainly characterized as small, differentiated EGCs. Mori et al. showed that MGCs were 15 mm in median tumor size, and were commonly located at the middle or lower third of the stomach.⁶¹ Of these, 97% of MGCs were differentiated EGCs and 90% of these were confined to the mucosa. Curative ESD resection was done for all MGCs according to the Japanese Gastric Cancer Treatment Guidelines, except for one differentiated T1b (submucosal invasion to 80 μm) cancer 4 mm in size with lymphatic involvement.⁶¹ Regular endoscopic surveillance would probably play a significant role in early detection. MGCs following *H. pylori* eradication were sometimes covered by non-neoplastic epithelium.

This histological alteration made it more difficult to detect MGC and delineate its margin, even with magnified narrow-band imaging.^{62,63} Yamamoto et al. reported that the average diameter of an MGC following successful eradication was smaller and the Ki-67 index was lower than in cases with persistent *H. pylori* infection.⁶⁴

Moribata et al. analyzed endoscopic mucosal background features associated with MGC in patients who underwent *H. pylori* eradication therapy and concluded the absence of intestinal metaplasia prior to ESD was a negative predictor of MGC after ESD, and the emergence of map-like redness

Table 3. Incidence of Metachronous Gastric Cancer following Successful *Helicobacter pylori* Eradication

Study	Design	Number ^{a)}	Follow up Period (yr)		Incidence	Effect	Results
Uemura et al. (1997) ⁵¹	NR	65/67	-	-	0.0/9.0%	Effective	$p=0.011$
Fukase et al. (2008) ⁵²	RCT	255/250	2.9/2.9 ^{a)}	Median	3.5/9.6%	Effective	$p=0.003$ ^{b)} , OR=0.34
Shiotani et al. (2008) ⁵⁴	Single arm	-/80	2.8	Median	11.3%		
Maehata et al. (2012) ³⁵	Retrospective	177/91	3	Median	8.5/14.3%	Non-effective	$p=0.262$
Choi et al. (2014) ⁵³	RCT	439/441	3	Median	2.3/3.9%	Non-effective	$p=0.15$
Seo et al. (2013) ⁵⁵	Retrospective	61/13	2.3	Mean	9.8/23.1%	Non-effective	$p=0.189$, OR=0.36
Chon et al. (2013) ⁵⁶	Retrospective	85/44	2.2	Median	4.7/11.4%	Effective	$p=0.008$, HR=0.143
Kwon et al. (2014) ³⁶	Retrospective	214/69	3.4	Median	4.7/14.5%	Effective	$p=0.009$
Kim et al. (2014) ³⁷	Retrospective	49/107	5.3/4.6 ^{a)}	Median	4.1/15.0%	Effective	$p=0.006$
Bae et al. (2014) ⁵⁷	Retrospective	485/182	5 ^{c)}	Median	7.0/13.2%	Effective	$p=0.02$, HR=1.9
					14.7/29.7/1,000 pt yr		
Jung et al. (2015) ⁵⁸	Retrospective	506/169	3.3 ^{c)}	Median	4.2/5.9%	Non-effective	$p=0.29$, HR=0.67
Mori et al. (2016) ⁶¹	Single arm	-/594	4.5	Median	29.9/1,000 pt yr		

NR, non-randomized; RCT, randomized controlled trial; OR, odds ratio; HR, hazard ratio.

^{a)}Eradicated group/Persistent infection group.

^{b)}Modified intention to treat analysis.

^{c)}Including gastric dysplasia, including *Helicobacter pylori* non-infection group.

after *H. pylori* eradication was a positive predictor for MGC after ESD.⁶⁵ Mori et al. and Shiotani et al. supported this conclusion and showed that widespread gastric mucosal atrophy and multiple gastric cancers before successful *H. pylori* eradication were risk factors for MGC occurrence following *H. pylori* eradication.^{54,61}

SURVEILLANCE INTERVAL AND PERIOD

There are some established guidelines for surveillance interval in patients undergoing curative ER. The National Comprehensive Cancer Network guidelines state that even for Tis or T1 with N0 lesions achieving R0 with ER or surgery, all patients should be followed up systematically, and follow-up should include a complete history and physical examination every 3 to 6 months for 1 to 2 years, every 6 to 12 months for 3 to 5 years, and annually thereafter all patients.⁶⁶ The Japanese gastric cancer treatment guidelines recommend annual or biannual endoscopy after curative ESD for patients with EGC who meet expanded indications criteria.⁵

Given that most of the MGCs were found in early stages and were successfully treated with ER in many previous reports, annual or biannual endoscopic surveillance may be reasonable. As the individual risk of MGC can vary greatly among patients, risk stratification and tailored follow-up schedules should be considered, similar to surveillance colonoscopy after endoscopic polyp removal.⁶⁷ In addition, we are performing a prospective study to evaluate epigenetic cancer risk prediction of MGC after *H. pylori* eradication. We hope that these results will provide more detailed data on the stratification of risk factors for MGC following *H. pylori* eradication.⁶⁸ Further prospective studies are warranted to determine appropriate surveillance intervals. Regarding the surveillance period, as the cumulative incidence of MGC linearly increased and some patients died of MGC more than 5 years after treatment, endoscopic surveillance should be performed indefinitely.³⁰ In addition, Mori et al. reported that the 5-year cumulative incidence of MGC even after successful *H. pylori* eradication was 15.0% during a 4.5-year median follow-up period.⁶¹ This multicenter, prospective study also showed that 11% of MGCs (10 of 94) were detected more than 5 years after successful *H. pylori* eradication.⁶¹ Therefore, continuous surveillance endoscopy should be performed to identify MGC in patients who have undergone ER for EGC, regardless of success or failure of *H. pylori* eradication.

CONCLUSIONS

EGC patients who undergo ER are at significant risk of developing MGC, but with annual or biannual surveillance EGD, MGC can be detected at an early stage when it is amenable to curative ESD resection. *H. pylori* eradication may reduce the incidence of MGC, but does not completely eradicate risk. Surveillance endoscopy should be continued indefinitely as cumulative incidence of MGC linearly increases. As we gain understanding of MGC, we hope that tailored surveillance intervals are developed, similar to those used to predict colonoscopy surveillance intervals based on the characteristics of the polyps removed. ESD for EGC preserves the quality of life by retaining the native stomach; however, the native stomach is at high risk for developing other gastric cancers. These patients should undergo life-long endoscopic surveillance for detection of MGC at an early and treatable stage.

Conflicts of Interest

The authors have no financial conflicts of interest.

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