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Review Article

Optimal Surveillance of Metachronous Gastric Lesion after Endoscopic Resection of Early Gastric Cancer

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Endoscopic resection (ER)–a minimal invasive procedure, compared to surgical gastrectomy, with the advantage of preserving the entire stomach and maintaining the patient's quality of life–is a widely used curative treatment for early gastric cancers (EGCs). Despite its advantages, such as the preservation of the whole stomach, a large area of the gastric mucosa with histologic changes such as atrophy and intestinal metaplasia remains after ER, and so does the risk of metachronous gastric cancers (MGCs). Therefore, regular surveillance endoscopy after curative ER of EGCs is important so that MGCs are detected early and so minimally invasive ER remains a treatment option. To date, the optimal interval for surveillance endoscopy after curative ER of EGCs has not been established. Therefore, this review summarizes the results of the published studies on this topic with the aim of establishing the optimal surveillance interval for early identification of MGCs. Based on my review, the median timing of MGC occurrence is within 3 years, and reports suggest biannual endoscopy during the first 3 years; however, the evidence suggests that individual patient characteristics may influence the risk of MGCs. Therefore, stratified endoscopic strategies for surveillance based on patient characteristics, such as age, family history of gastric cancer, synchronous gastric lesions, and corpus intestinal metaplasia, should be applied.
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Key Words: Gastric cancer; Endoscopic resection; Metachronous neoplasms; Surveillance

INTRODUCTION

Gastric cancer is the fifth most common malignant neoplasm and the fourth leading cause of cancer death globally.[1] The diagnosis of early gastric cancers (EGCs) has been increasing because of the widespread use of endoscopy, especially during health check-ups, and advances in the development of endoscopy equipment, such as high-definition endoscopy and image-enhanced endoscopy.[2] Endoscopic resection (ER), particularly endoscopic submucosal dissection (ESD), is a widely used curative treatment for EGCs. ESD has histopathologically high *en bloc,* complete, and curative resection rates for EGCs regardless of their size and location.[3] ER is a minimally invasive procedure compared to surgical gastrectomy, offering the advantage of preserving the entire stomach while maintaining the patient's quality of life. Despite these advantages, a large area of gastric mucosa, especially with atrophy and intestinal metaplasia, remains after ER. Thus, the occurrence of metachronous gastric cancers (MGCs) remains an important concern after curative ER for EGCs. However, considering that EGCs develop most commonly in the middle to lower third of the stomach, when distal gastrectomy is performed for EGCs, this high-risk area for gastric cancer is entirely resected, leaving only the lower-risk portion of the stomach intact. Accordingly, ER for EGCs only resolves a particular lesion and does not influence the overall cancer risk in the whole stomach; therefore, life-long regular surveillance endoscopy is needed in these patients who have undergone ER as they remain at a high risk of gastric cancer.

The cumulative incidence of MGCs is 3.3% to 15.6%, and it increases linearly over time.[3] The 10-year cumulative incidence of MGCs is reported to be 22.7%,[4] with a mean

annual incidence of 2.5% to 3.5%.[5,6] A recent meta-analysis demonstrated that the risk of MGCs is five times higher after ER than after subtotal gastrectomy (9.3% vs 1.2%; odds ratio [OR], 4.73; 95% confidence interval [CI], 2.87 to 7.80).[7] Approximately 83% to 96% of MGCs can be treated with repeated ER alone, but some lesions require surgical resection for curative treatment.[5,8,9] Previous studies have shown that the proportion of MGCs beyond the curative ER criteria is 3.8% to 40.4%.[10,11] Furthermore, a Japanese multicenter prospective cohort study demonstrated 10 (0.1%) gastric cancer-related deaths at 5 years among 7,242 patients who underwent curative gastric ER; of them, six deaths were caused by MGCs.[12] Therefore, it is important to detect MGCs early enough to be cured by ER to preserve the whole stomach and maintain the quality of life in these patients. This finding indicates the importance of regular surveillance endoscopy after curative ER for EGCs.

In terms of the optimal examination interval for these patients, the Korean Society of Gastrointestinal Endoscopy and Japan Gastroenterological Endoscopy Society guidelines recommend annual or biannual endoscopy,[13,14] whereas the European Society of Gastrointestinal Endoscopy guidelines recommend endoscopy at 3 to 6 months and then annually after curative ER for EGCs.[15] However, the optimal surveillance interval after curative ER for EGCs remains controversial. Because the data for optimal surveillance for MGCs in a remnant stomach are inadequate, this review summarizes the results of published studies on this topic to establish the optimal surveillance interval for patients with a whole stomach after ER for EGCs for early identification of MGCs.

DEFINITION AND RISK FACTORS FOR MGCs

A new gastric cancer detected on surveillance endoscopy after curative ER for EGCs may be a previously invisible preclinical lesion, missed lesion, or *de novo* lesion.[5] However, it is difficult to determine which of these possibilities are applicable. Based on previous reports, gastric cancers detected within 1 year of ER are defined as missed or synchronous gastric cancers.[5] In contrast, MGCs are newly developed gastric cancers occurring at a previously uninvolved site 1 year or more after the index ER (Fig. 1).[3,5]

The known risk factors associated with development of MGCs are old age, male sex, current smoking, persistent *Helicobacter pylori* infection, pepsinogen I/II ratio ≤3, severe atrophy, intestinal metaplasia, differentiated-type histology, and multiple initial gastric cancers.[4,5,9,11,16-18] Of them, old age, male sex, and current smoking status are also important risk factors for gastric cancer in the general population. Per Correa's hypothesis, differentiated-type gastric cancer can develop as a result of chronic *H. pylori* infection gradually progressing to chronic gastritis, atrophy, intestinal metaplasia, and dysplasia over time.[19]

As ER is an organ-sparing treatment modality, gastric mucosa with histological changes such as atrophy and intestinal metaplasia remains after ER for EGCs. Accordingly, the risk factors for MGCs are similar to those for differentiated-type gastric cancer. Persistent *H. pylori* infection is an important risk factor for MGCs.[20] However, *H. pylori* eradication cannot effectively reduce the development of MGCs after ER in cases with severe atrophy and intestinal metaplasia, especially in those with multiple initial gastric cancers;[18] severe atrophy and intestinal metaplasia indicates the "point of no return" at which *H. pylori* eradication alone is no longer sufficient to prevent the development of gastric cancer. Nevertheless, recent meta-analyses have suggested that *H. pylori* eradication provides protection against MGCs, and this quantitative benefit seems greater than that in asymptomatic individuals.[20,21] In a recent meta-analysis including 17 studies with 8,995 individuals, *H. pylori* eradication was associated with 54% lower odds of MGC development (relative risk, 0.46; 95% CI, 0.35 to 0.60); that is, *H. pylori* eradication significantly decreases the risk of MGCs by 54%.[21] Therefore, *H. pylori* eradication is strongly recommended to prevent the development of MGCs after ER.

ENDOSCOPIC FEATURES OF MGCs

As atrophy progresses from the gastric antrum to the lower body, MGCs are usually located in the lower third

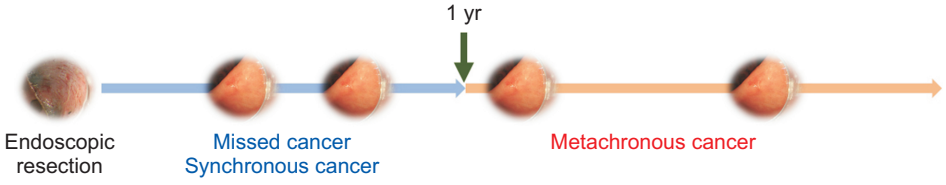

Fig. 1. Definition of metachronous gastric cancer. Metachronous gastric cancers are defined as newly-developed gastric cancers occurring at a previously uninvolved site 1 year or more after index endoscopic resection. When gastric cancers are detected within 1 year after endoscopic resection, they are defined as missed or synchronous gastric cancers.

of the stomach and exhibit small, differentiated-type intramucosal cancers of <20 mm in size.[4] In most patients with MGCs, severe atrophy and intestinal metaplasia occur in the background gastric mucosa. Additionally, these patients usually undergo *H. pylori* eradication to prevent the occurrence of MGCs after ER. As *H. pylori* eradication reduces the inflammatory changes caused by *H. pylori* infection, it becomes more difficult to detect MGCs early and delineate their margins. As an epithelium with low-grade atypia usually covers the gastric cancer tissue after *H. pylori* eradication,[22] MGCs often have a gastritis-like appearance.[23]

The quality of endoscopy is a key factor in the detection of MGCs at an early stage.[24] According to a previous meta-analysis, the missing rate of gastric cancers by diagnostic endoscopy is 9.4% (95% CI, 5.7% to 13.1%).[25] The main reasons for missing gastric cancers include the inability to detect lesions; detecting lesions, but not performing biopsies; an insufficient number of biopsies or poor quality of biopsy specimens; lack of follow-up endoscopy; endoscopy performed by trainees; technical limitations such as blind spots during endoscopy; presence of marked gastric atrophy/intestinal metaplasia; and the presence of gastric ulcers or adenoma.[25] In particular, the missing rate of synchronous lesions in patients subjected to ER is 32.3% (95% CI, 6.7% to 57.8%).[25] The primary reasons for missing synchronous lesions are adenoma as the initial lesion, shorter gastric examination time (<10 minutes), endoscopist inexperience (<500 esophagogastroduodenoscopies), older age (>65 years), and multiple lesions at initial endoscopy.[8,26,27] Therefore, sufficient examination time, adequate biopsies of suspicious lesions, and endoscopist experience are essential during surveillance endoscopy for MGCs.

APPROPRIATE SURVEILLANCE INTERVAL FOR DETECTING MGCs

In 2006, Nakajima *et al.*[28] reported that the cumulative 3-year incidence of MGCs in 633 patients was 5.9%, with an average time to discovery of MGCs of 3.1 years, and almost all MGCs (96.2%) were curatively treated with repeated ER. Accordingly, the authors suggested that annual endoscopic surveillance is both practical and efficient for detecting MGCs. A multicenter cohort study by the Osaka University ESD study group also reported the effectiveness of scheduled endoscopic surveillance (mainly biannual for 3 years) in 1,258 patients; the mean annual incidence rate of MGCs after ESD was 3.5%, and almost all MGCs were treatable by ER.[8]

Min *et al.*[29] reported that the incidence of MGCs was 3.6% in 1,497 patients, and the median timing of the occurrence of MGCs was 30 months (range, 13 to 75 months). All MGCs were curatively treated, including 28 with ESD and 19 with surgical resection. The cumulative incidence curve of MGCs increased linearly during the 5-year period, and extragastric recurrence occurred in 0.15% of patients at least 4 years after curative ESD. Therefore, the authors suggested that annual or biannual surveillance endoscopy and abdominal computed tomography may be necessary for at least 5 years after curative ESD. Cho *et al.*[30] also reported that the 5- and 10-year cumulative incidences of MGCs were 4.7% and 11.3% in 2,334 patients, respectively, and the median timing of the occurrence of MGCs was 26 months (range, 19 to 50 months). All metachronous lesions were initially treated with ER, and curative resection was achieved in 89.6% of patients. Therefore, the authors recommend that surveillance endoscopy should be suggested for at least 10 years.

In study of Hahn *et al.*[31] including 1,347 patients who underwent curative ESD for EGCs, the proportion of recurrence as adenocarcinomas in the long-surveillance interval (>12 months) group was higher than that in the short-surveillance interval (≤12 months) group (60.9% vs 31.9%, p=0.033). Approximately 87.2% of the recurrent tumors were identified within 3 years of the initial ESD, and the rate of MGCs declined sharply after 3 years. The size of recurrent cancer was larger in the long-surveillance interval group compared to the short-surveillance interval group (18.1±10.1 mm vs 8.9±4.2 mm, p=0.010). In addition, more patients in the long-surveillance interval group underwent additional gastrectomy for recurrent cancers than those in the short-surveillance interval group (46.2% vs 7.1%, p=0.033).

In a recent Korean study, 521 patients who underwent gastric ESD for high-grade dysplasia or EGCs were classified into annual (n=254) or biannual surveillance groups (n=267).[32] During the mean follow-up period of 5.3 years, there was no significant difference in the detection rate of MGCs between the two groups (7.1% vs 16.9%, p=0.219). However, the detection rate of MGCs was significantly higher in the biannual group than in the annual group during the first 3 years (6.4% vs 2.4%, p=0.026). This difference was more prominent in patients with moderate-to-severe atrophy. Almost all MGCs were treated with additional ER or surgical resection and were classified as stage IA. Only one patient in the annual group was diagnosed with stage IIIA advanced gastric cancer.

In a recent Japanese study, 216 patients with MGCs were classified into short-interval (≤7 months, n=43) and regular-interval (8 to 13 months, n=173) groups based on the surveillance endoscopy interval, and propensity score

matching was used to adjust for possible confounding factors.[33] Although none of the patients in the short-interval group had MGCs beyond the curative ESD criteria, 27 patients in the regular-interval group had MGCs beyond the curative ESD criteria. Furthermore, the regular-interval group had a significantly higher proportion of MGCs beyond the curative ESD criteria compared to the short-interval group (11.5% vs 0%, p=0.028). Therefore, the authors suggested a potential advantage of conducting biannual surveillance endoscopy in the early post-ESD period. However, in a recent study by Choe *et al.*,[10] which included 61 patients with metachronous gastric neoplasia, there was no difference in the cumulative incidence of MGCs between the annual and biannual groups, regardless of the primary lesion histology, and all MGCs were resected endoscopically and did not require surgical resection in either the annual or biannual surveillance groups. Similarly, in a recent meta-analysis, endoscopic treatment was possible in 83.2% of MGCs, and the proportion of patients undergoing endoscopic treatment was comparable for those with annual surveillance and those with more frequent surveillance.[7]

In a multicenter cross-sectional study including 1,085 patients who underwent ER for EGCs, the multivariate logistic analysis demonstrated that current *H. pylori* infection (OR, 2.18; 95% CI, 1.50 to 3.16) and a surveillance interval of >1.5 years (OR, 1.96; 95% CI, 1.35 to 2.84) were independent risk factors for pT1b or deeper gastric cancer.[34] The rate of pT1b or deeper gastric cancer increased progressively increasing surveillance intervals and surpassed 30% when the interval was >2.5 years. Furthermore, the 5-year disease-specific survival rate for patients with a surveillance interval of >1.5 years was significantly lower than that for those with a surveillance interval of ≤1.5 years (93.7% vs 98.3%, p<0.001). The authors suggested that EGD within at ≤1.5 years and *H. pylori* eradication therapy are important for reducing the incidence of invasive gastric cancer during surveillance endoscopy.

In a post-hoc analysis of a non-randomized confirmatory trial of an expanded indication for ESD for differentiated-type EGCs in Japan (surveillance endoscopy was performed annually after ESD), the cumulative incidence of MGCs at 5 years was 12.7% (95% CI, 9.3% to 16.7%) and the annual incidence of MGCs was 3.1% (95% CI, 2.3% to 3.9%).[35] Of the 61 MGCs, gastrectomy was performed for three MGCs in three patients, and ESD for 58 MGCs in 45 patients. Finally, 85.2% of MGCs met the pathologic criteria of curative ESD. In a recent Chinese population-based prospective study including 375,800 individuals, repeated endoscopy at an interval of <2 years, especially within 1 year, for individuals with intestinal metaplasia or low-grade intraepithelial neoplasia, significantly improved the detection of EGCs compared with repeated screening after 2 years (p-trend=0.02).[36] These population-based results also support the necessity for annual surveillance endoscopy after curative ER for EGCs. A representative case showing the importance of regular surveillance endoscopy after curative ESD for EGCs is shown in Fig. 2.

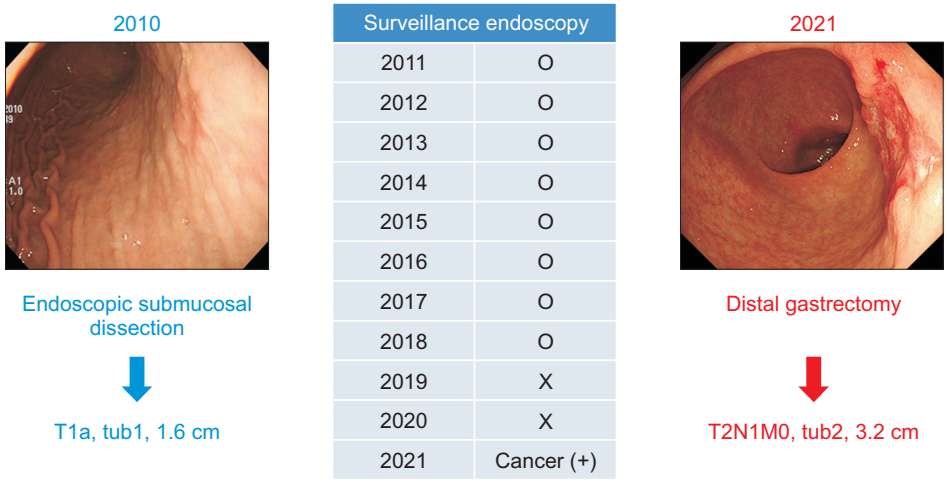

Fig. 2. A representative case showing the importance of regular surveillance endoscopy after curative endoscopic resection of early gastric cancer. A 72-year-old male patient underwent endoscopic submucosal dissection for an early gastric cancer located at the posterior wall of gastric midbody in 2010. Curative resection was achieved: a well-differentiated adenocarcinoma limited to the lamina propria mucosae without lymphovascular invasion. Since then, the patient underwent annual surveillance endoscopy till 2018, then no endoscopy for 2 years. In 2021, an advanced gastric cancer occurred at the posterior wall of gastric lower body, and the patient underwent distal gastrectomy. The final histopathology showed a moderately differentiated adenocarcinoma which invaded the muscularis propria, with lymph node metastasis. Informed consent was obtained from the patient to publish these images.

COST-EFFECTIVENESS AND INDIVIDUALIZED SURVEILLANCE INTERVAL

Cost-effectiveness is another important issue in determining an appropriate surveillance interval. For example, although biannual endoscopy increases the detection rate of early MGCs and prevents gastrectomy, compared with annual endoscopy, the examination costs are doubled. In Japan, the cost of ESD procedures for gastric cancer is 1,250 USD, while the cost for laparoscopic gastrectomy is 4,400 to 5,000 USD.[33] This means that an economic benefit is expected when at least one in four patients with MGCs avoids gastrectomy by shortening the interval by half. Ozeki *et al.*[33] suggested that surgical gastrectomy could be avoided in approximately one in six patients with MGCs by performing surveillance endoscopy biannually instead of annually. Therefore, a strategy that shortens the interval by half would not be cost-effective. In addition to cost-effectiveness, biannual endoscopy is a burden to endoscopists, and an excessive workload can interfere with accurate examination during endoscopy. The risks of endoscopic procedures, particularly sedation-related adverse events, cannot be ignored.[37,38] Therefore, it is reasonable to determine the surveillance interval according to the estimated risk of further development of MGCs, especially in patients with severe atrophy and intestinal metaplasia.

To determine the individualized surveillance intervals, it is reasonable to stratify patients who will benefit from short-interval endoscopy from those who will not. According to a recent meta-analysis, older age, male sex, family history of gastric cancer, synchronous lesions, severe gastric mucosal atrophy, intestinal metaplasia in the corpus, persistent *H. pylori* infection, and a lower pepsinogen I/II ratio are predictors of MGCs.[7] However, because MGCs occur at different post-ESD periods, it would be ideal to determine surveillance intervals according to the risk factors. Although MGCs are defined as cancers located distant from the original cancer more than 1 year after ESD, it is assumed that MGCs observed in the early post-ESD period are undetected lesions that may have already been present at the time of the initial ESD. Accordingly, regular-interval endoscopy in the early post-ESD period poses the risk that a patient may develop MGCs beyond the curative ESD criteria. In a Japanese study, more than half of the MGCs beyond these criteria were detected in the early post-ESD period (<5 years).[33] In a Korean study, patients in the long-interval group (>1 year) had required gastrectomy more often than those in the short-interval group (≤1 year),[31] and in a recent Japanese multicenter retrospective study, current *H. pylori* infection and surveillance interval >1.5 years were risk factors for the occurrence of pT1b or deeper gastric cancer.[34] Accordingly, short-interval endoscopy or at least annual endoscopy would be effective during the early post-ESD period.

Recently, a risk-prediction model based on the risk of metachronous gastric lesions (MGLs) according to patient characteristics and stomach state was introduced to stratify individual MGL risks and define the appropriate surveillance interval.[39] The authors developed a prediction risk score model for the occurrence of MGLs after ESD and validated the prediction model using a retrospective, single-center cohort. Unlike previous studies, in this study, an MGL was defined as any lesion identified after the first endoscopic surveillance (6 months after ESD) in a different region of the stomach from the index lesion. This model includes six clinical parameters (age, sex, family history of gastric cancer, *H. pylori* infection status, synchronous gastric lesions, and corpus intestinal metaplasia) based on a recent meta-analysis.[7] Each parameter was scored based on the numerical value of the OR: 1 point for positive family history, older age, male sex, and presence of synchronous gastric lesions; 2 points for persistent *H. pylori* infection; and 3 points for corpus intestinal metaplasia (Table 1).[39] The area under the receiver operating characteristic curve of this model for predicting MGLs at 3 years was 0.704 (95% CI, 0.603 to 0.806). At 3 years, a cutoff score of <2 represented maximal sensitivity and negative predictive values (both 100%), and a cutoff score of <3 demonstrated a sensitivity of 85.2% and a negative predictive value of 94.4%. Overall, 15% of the patients were assigned to the low-risk group (score 0–1 point), and none of the patients in the low-risk group developed MGLs. In the intermediate-risk group (score of 2 points), 94% of the patients did not develop MGLs. Based on these results, the authors recommended that after the first annual surveillance, follow-up endoscopy should be performed 3 years later for the low-risk group, 2 years later for the intermediate-risk group, and annually for the high-risk group. Notably, they recommended annual endoscopy for patients with

Table 1. A Prediction Risk Score Model for Predicting the Occurrence of Metachronous Gastric Lesions

Parameter	Odds ratio (95% CI)	Points
Family history of gastric cancer	1.88 (1.03–3.41)	1
Age (>65 yr)	1.02 (0.24–4.43)	1
Male sex	1.43 (1.22–1.66)	1
Synchronous gastric lesions	1.72 (1.30–2.28)	1
Persistent *H. pylori* infection	2.08 (1.60–2.72)	2
Corpus intestinal metaplasia	3.15 (1.67–5.96)	3

H. pylori, *Helicobacter pylori*; CI, confidence interval.
Adapted from Rei A, *et al.* Endoscopy 2023;55:909-917, with permission from Georg Thieme Verlag KG.[39]

synchronous gastric lesions, even in the low- and intermediate-risk groups, as this was found to be a significant predictor of MGLs in their cohort.

SURVEILLANCE AFTER ER OF UNDIFFERENTIATED-TYPE GASTRIC CANCER

Almost all studies on MGCs have focused on patients who underwent ESD for differentiated-type EGCs. Undifferentiated-type EGCs are reported to arise from native gastric epithelial cells and occur more commonly in young women; conversely, differentiated-type EGCs mainly arise from atrophic gastritis and intestinal metaplasia.[40,41] In a study comparing the incidence of MGCs in undifferentiated-type (n=175) and differentiated-type (n=350) EGCs, the cumulative incidence of MGCs in the undifferentiated-type group at 3, 5, and 7 years was 1.1%, 3.5%, and 4.5%, respectively.[42] The annual incidence of MGCs in the undifferentiated-type group was 0.9%, which was significantly lower than that in the differentiated-type group (5.3%). In the univariate analysis, older age (relative risk, 6.90) and severe mucosal atrophy (relative risk, 6.12) were significant risk factors for MGCs in the undifferentiated-type group; however, this significance disappeared in the multivariate analysis. MGCs occurring in the undifferentiated-type group had undifferentiated-type histology in all cases and a higher rate of submucosal or deeper invasion. The curative resection rate of ESD for MGCs was significantly lower in the undifferentiated-type group than in the differentiated-type group (42.9% vs 96.7%, p<0.001). Therefore, routine surveillance endoscopy should be conducted for the early detection of MGCs after ESD for undifferentiated-type EGCs.

In a study involving 198 patients with curative ESD for undifferentiated-type EGCs, which was a post-hoc analysis of a prospective multicenter trial on ESD for undifferentiated-type EGCs, the 5-year cumulative incidence of MGCs was 1.0% (95% CI, 0.2% to 3.3%), and the median time to MGC occurrence was 4.5 years (range, 3.1 to 5.4 years).[43] Of the four MGCs, two were histologically differentiated-type EGCs and two were undifferentiated-type EGCs; three patients achieved curative resection with ESD. As surveillance endoscopy was performed biannually for the first 3 years and annually thereafter in this study, surveillance endoscopy with a similar interval as that of differentiated-type EGCs is recommended for undifferentiated-type EGCs.

Table 2. Recommendations for Surveillance Endoscopy to Detect Metachronous Gastric Cancers after Curative Endoscopic Resection

Risk factors for metachronous gastric cancers
- Old age
- Male sex
- Persistent *Helicobacter pylori* infection
- Severe atrophy/intestinal metaplasia
- Multiple initial gastric cancers
- Differentiated-type histology
Endoscopic features of metachronous gastric cancers
- Located at the lower third of the stomach
- Small size (<20 mm)
- Differentiated-type histology
- Mucosal cancer
- Gastritis-like appearance after *H. pylori* eradication
Endoscopy interval
- Annual or biannual
- Biannual endoscopy may be needed in high-risk patients during early 3 yr
How long
- Indefinitely (at least 10 yr)

CONCLUSIONS

Curative ER preserves the entire stomach and maintains the quality of life of patients with EGCs. Considering that ER is a local treatment for a particular cancer lesion in the stomach and that background precancerous changes, such as severe atrophy and intestinal metaplasia, are still present, the occurrence of MGCs after ER of EGCs is inevitable. Therefore, it is important to prevent patients who achieve curative ER for EGCs from undergoing surgical gastrectomy for MGCs. Accordingly, surveillance endoscopy should be performed in all patients to detect MGCs at an endoscopically-treatable stage.

Based on previous reports, annual surveillance endoscopies have long been necessary. Considering the median time of MGC occurrence is within 3 years in most studies, biannual endoscopy is suggested during the first 3 years, especially in patients with a high risk of MGCs. Recommendations for surveillance endoscopy to detect MGCs after curative ER of EGCs are summarized in Table 2. In summary, instead of applying a uniform surveillance endoscopy strategy for every patient, application of strategies based on patient characteristics, such as age, family history of gastric cancer, synchronous gastric lesions, and corpus intestinal metaplasia, are more appropriate. These strategies should ensure a balance between early detection and burden on the health system.

CONFLICTS OF INTEREST

G.H.K. is an editorial board member of the journal but

was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: G.H.K. Data acquisition: D.C.J. Data analysis and interpretation: D.C.J., G.H.K. Drafting of the manuscript: D.C.J., G.H.K. Obtained funding: G.H.K. Approval of final manuscript: D.C.J., G.H.K.

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