Endoscopic surveillance strategy after endoscopic resection for early gastric cancer

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INTRODUCTION

Gastric cancer is the second most common cause of death from cancer worldwide\(^1\), and more than half of the world's gastric cancer cases arise in Eastern Asia. Early gastric cancer (EGC) is typically small and asymptomatic and has a good prognosis\(^4\), but advanced gastric cancer has a higher mortality rate.\(^5\) Therefore, early detection and treatment could contribute to improved prognosis for patients with gastric cancer. Screening with endoscopy and biopsy sampling is important for patients with premalignant lesions and may lead to early cancer detection\(^6\). In Japan, a mass-screening program for gastric cancer is conducted on a nationwide scale because of the high prevalence of gastric cancer. Such a screening program may help to detect EGC that is treated by endo-

Abstract

Early detection of early gastric cancer (EGC) is important to improve the prognosis of patients with gastric cancer. Recent advances in endoscopic modalities and treatment devices, such as image-enhanced endoscopy and high-frequency generators, may make endoscopic treatment, such as endoscopic submucosal dissection, a therapeutic option for early gastric cancer (EGC). Consequently, short-term outcomes of endoscopic resection (ER) for EGC have improved. Therefore, surveillance with endoscopy after ER for EGC is becoming more important, but how to perform endoscopic surveillance after ER has not been established, even though the follow-up strategy for more advanced gastric cancer has been outlined. In this review, we discuss clinical problems in surveillance after ER for EGC.

Core tip: Recent advances in endoscopic modalities and treatment devices may make endoscopic treatment, such as endoscopic submucosal dissection, a therapeutic option for early gastric cancer (EGC). Consequently, short-term outcomes of endoscopic resection (ER) for EGC have improved. Therefore, surveillance with endoscopy after ER for EGC is becoming more important, but how to perform endoscopic surveillance after ER has not been established, even though the follow-up strategy for more advanced gastric cancer has been outlined. In this review, we discuss clinical problems in surveillance after ER for EGC.

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Key words: Early gastric cancer; Endoscopic resection; Synchronous gastric cancer; Metachronous gastric cancer; Surveillance
Synchronous cancer is also classified as
n based on Japanese gastric
Stomach carcinogenesis is generally considered to origi
HELICOBACTER PYLORI
INFECTION
WITH
GASTRIC CANCER RISK IN PATIENTS
development after ER.
synchronous and metachronous multiple gastric cancer
treatment guidelines
with non-curative resectio
also been detected and diagnosed before the initial
comitant cancer is defined as multiple cancers that had
fied as “concomitant cancer” or “missed cancer”. Con
cancers develop. Moreover, synchronous cancer is classi
nous cancer according to the time at which the multiple
surgical resection (ER).
Japanese guidelines classify EGC into the following
two groups, as proposed by Gotoda et al[8], when con-
considering the indication of ER for EGC: the “guideline
group”, the “expanded guideline group” and the “non-
curative group”. Based on the tumor characteristics, the
guideline group is defined as mucosal differentiated
cancer with the largest diameter measuring < 20 mm. In
Japan, ER is definitely indicated for this group. If the le-
son meets Japanese guideline criteria and R0 resection is
achieved, it is classified as a curative tumor, which does
not require need further intense follow-up because it has
a negligible risk for lymph node or distant metastasis[9-11].
Moreover, with the advancement of endoscopy and high-frequency generators, endoscopic submucosal
dissection (ESD) has been developed. Consequently, the short-term outcomes of ER for EGC have im-
proved[12,13].
However, patients who have undergone ER for EGC are considered at high risk for having other gastric
cancer lesions. The incidence of local recurrence is de-
creasing because of ESD, which enables the evaluation of the horizontal and vertical margins of the resected
specimen. Therefore, the risk of secondary gastric neo-
plasms developing during the follow-up period after ER
has become a serious problem. In this review, we discuss
clinical problems in developing a secondary gastric can-
cer after ER in patients with EGC, except for patients with non-curative resection based on Japanese gastric
cancer treatment guidelines[14], with the goal of targeting synchronous and metachronous multiple gastric cancer
development after ER.

DEFINITIONS OF SYNCHRONOUS AND
METACHRONOUS MULTIPLE GASTRIC
CANCER DEVELOPMENT

Even patients after curative ER for EGC have higher
risks of multiple cancer development than patients with
atrophic gastritis or intestinal metaplasia without past
EGC. The doubling time of EGC is relatively long, rang-
ing from 1.6 to 9.5 years[21]. Therefore, some occult le-
isons in the stomach might be observed when detecting
a first EGC. Moreover, detecting secondary cancer after
initial ER depends on how often the surveillance endos-
copy is performed, which can include a lead-time bias.
It is difficult to determine whether a secondary cancer is
synchronous and metachronous gastric cancer. Until now,
there have not been strict definitions of these lesions af-
ter ER.

In this review, we define multiple gastric cancer de-
velopment as synchronous (within 1 year) or metachro-
nous cancer according to the time at which the multiple
cancers develop. Moreover, synchronous cancer is classi-
fied as “concomitant cancer” or “missed cancer”. Con-
comitant cancer is defined as multiple cancers that had
already been detected and diagnosed before the initial
ESD. In recent reports, there is a consensus that cancers
detected within 1 year after the initial ER should be re-
garded as ‘missed’ synchronous cancers[22,23]. We define
missed cancer as cancer that is detected within 1 year,
except for concomitant cancer (Figure 1).

CONCOMITANT AND MISSED
SYNCHRONOUS GASTRIC CANCER
AFTER ER

There are many reports about synchronous gastric can-
cer in surgically resected stomachs, with an incidence
ranging from 4.8% to 14.6%(24-27) (Table 1). In addition,
endoscopy and magnifying endoscopy. Therefore, we should pay special attention to the possibility of missed cancers, not only initially detected lesions at the first evaluation, and the first surveillance EGD should be performed soon after the ESD so as not to miss cancers.

### METACHRONOUS GASTRIC CANCER AFTER ER

In reports conducted on patients with surgically resected stomachs in the remnant stomach after surgery for gastric cancer, the rate of metachronous gastric cancer ranges from 1.8% to 5%[9,19,28,29]. Therefore, the remnant stomach is at high risk for developing metachronous gastric cancer. ER contributes to preserving the stomach compared with surgically resected stomach and maximizing quality of life. Therefore, patients with EGC resected by ER are considered at higher risk for developing metachronous gastric cancer than surgically resected patients because the former have more remnant stomach and tend to survive longer. The metachronous cancer rate after ER ranges from 2.7% to 14% (Table 3). Nakajima et al[9] reported that metachronous gastric cancer had an overall incidence of 8.2% (52 out of 633 patients) and that the annual incidence was constant (cumulative 3-year incidence 5.9%). The average time to detect a first metachronous gastric cancer after ER was 3.1 ± 1.7 years (range, 1.8-6.6 years)[9]. We also found that the cumulative incidence curve revealed a linear increase. The cumulative incidence rates of metachronous cancers at 2, 3, 4 and 5 years were 3.7%, 6.9%, 10% and 16%, respectively. Based on these data, the metachronous gastric cancer incidence curve, except for synchronous cancer, seems to increase linearly by 3%-3.5%[9,19,33].

### LOCAL RECURRENCE AFTER ER

Conventional endoscopic mucosal resection (EMR) techniques are associated with the risk of local recurrence because it is difficult to achieve en bloc resection, in particular with larger lesions. Until recently, EMR was widely accepted as a useful, standard treatment for gastrointestinal tract neoplasms, but ESD has been replaced by ESD because en bloc resection of specimens larger than 20 mm is difficult to perform with EMR. Local recurrence

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**Table 1 Incidence of synchronous gastric cancers in the surgically resected stomach**

| Ref.          | Overall | Missed lesion |
|---------------|---------|---------------|
| Noguchi et al[21], 1985 | 6.50%   | 468/7220      |
| Ezaki et al[22], 1987 | 14.60%  | 75/512        |
| Honyo et al[23], 1989 | 4.80%   | 40/839        |
| Mitsudomi et al[24], 1989 | 8.30%  | 83/997        |
| Kosaka et al[25], 1990 | 5.80%   | 49/852        |
| Kodera et al[26], 1995 | 5.70%   | 160/2790      |
| Kodama et al[27], 1996 | 6.80%   | 107/1458      |
| Fujita et al[28], 2009 | 8.70%   | 266/3042      |
| Lee et al[29], 2010 | 5.20%   | 51/986        |
| Total         | 6.90%   | 1299/18696    |

1Including 14 adenomas; 2Including 5 adenomas. NA: Not available.

**Table 2 Incidence of synchronous gastric cancers in the endoscopically resected stomach within 1 yr of the initial endoscopic resection**

| Ref.          | Overall | Missed lesion |
|---------------|---------|---------------|
| Arima et al[30], 1999 | 6.60%   | 5/76          |
| Nasa et al[31], 2005 | 11%     | 16/143        |
| Nakajima et al[32], 2006 | 9.20%  | 58/633        |
| Kobayashi et al[33], 2010 | 19.20%  | 45/234        |
| Han et al[34], 2011 | 4%      | 7/176         |
| Kato et al[35], 2013 | 8.70%   | 110/1288      |
| Kim et al[36], 2013 | 2%      | 12/602        |
| Total         | 8.10%   | 253/3122      |

**Table 3 Metachronous cancer rate after endoscopic resection**

| Ref.          | Rate   | Follow up period (yr) |
|---------------|--------|-----------------------|
| Arima et al[30], 1999 | 7.90%  | 6/76                  |
| Nasa et al[31], 2005 | 14%    | 20/143                |
| Nakajima et al[32], 2006 | 8.40%  | 53/633                |
| Kim et al[33], 2007 | 2.70%  | 13/479                |
| Kobayashi et al[34], 2010 | 12.80% | 30/234                |
| Lee et al[35], 2011 | 3.30%  | 15/458                |
| Kato et al[36], 2013 | 5.20%  | 65/1258               |
| Total         | 6.70%  | 202/3281              |

1All patients were followed up for 7 yr.
Table 4 Local recurrence rate after endoscopic resection

| Ref.       | Local recurrence rate | EMR | ESD | Curative | Not curative | Curative | Not curative |
|------------|-----------------------|-----|-----|----------|--------------|----------|--------------|
| Oka et al[43], 2006 | 2.90% | 4.40% | 0%  | 0%       |              |          |              |
| Kim et al[46], 2007 | 6.0% (24/399) | 15% (10/68) |     |          |              |          |              |
| Park et al[44], 2010 | 18% (9/50, not en bloc: 18) | 3.7% (7/189, not en bloc: 25) |     |          |              |          |              |
| Lee et al[45], 2011 | NA | NA | 0.7% (2/276, not en bloc: 3) |          |              |          |              |
| Kato et al[47], 2013 | NA | NA | 0% (0/182, not en bloc: 22) |          |              |          |              |
| Tanabe et al[48], 2013 | 4.2% (15/359) | 0.2% (1/421) |     |          |              |          |              |

“Not curative” includes piecemeal resection or marginal positive resection. 1Including 34 lesions treated by ESD (6.6%); 2Guideline group; 3Expanded guideline group; 4For lesions meeting the JGCA criteria, the local recurrence rates were 2.9% in the EAM group and 0% in the ESD group; 5Treated by endoscopic aspiration mucosectomy (EAM). EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; NA: Not available.

strongly depends on whether the initial lesion is completely resected. With piecemeal resection or marginal-positive resection (not curative), local recurrence ranges from 4.4% to 18% (Table 4). Using ESD, en bloc marginal-negative resection can be performed with larger specimens. Developing local recurrence after complete en bloc resection in mucosal gastric cancers occurs rarely. In fact, our study revealed that local recurrence was seen in only 0.40% of patients (5/1258)[19]. This rate was quite low, but not zero. Park et al[11] also reported complete en bloc resection in one patient who developed local recurrence after complete resection by ESD. It is speculated that it is difficult to detect a very small concomitant lesion or precancerous lesion near the initial ESD site at initial evaluation or that detection depends on the status of the resected specimen reviewed by pathologists or each pathologist’s experience. To evaluate resected specimens properly, the ER specimen should be cut parallel to the closest margin direction. When the negative margin is obvious, the specimens are step-sectioned along the minor axis of the specimen to obtain more information. The Japanese Gastric Cancer Association recommended that a section width of 2 mm allows for a more accurate diagnosis. We should remember that complete resection does not exclude the possibility of local recurrence in cases where R0 resection is achieved.

INTERVENTION FOR SECONDARY CANCER AFTER ER OF GASTRIC CANCER

In a study by our group, 169 of 175 secondary cancers (97%) after ESD were treated by re-ESD[19]. Among these cancers, 164 lesions were diagnosed as fitting the guideline or expanded guideline group and were followed up without additional treatment. Of the remaining five lesions, two were diagnosed as mucosal undifferentiated adenocarcinomas, and three were diagnosed as submucosal cancers after ESD; these patients then underwent additional gastrectomies. In addition, six lesions were treated by gastrectomy. Of these cases, four were pathologically diagnosed as belonging to the guideline or expanded guideline group after gastrectomy, and the remaining two were pathologically diagnosed as non-curative. Altogether, seven lesions were diagnosed as non-curative: three were intramucosal undifferentiated cancers, and four were massively invading cancers. Nakajima et al[50] concluded that frequent follow-up examinations negatively affect a patient’s quality of life and result in an increase in overall medical expenses. Similarly, we also found that almost all secondary cancers after ESD were treatable by re-ESD[19]. Nakajima et al[50] reported that almost all first metachronous gastric cancers (96.2%) were treated curatively with re-ER. Considering those re-ER rates for metachronous cancer (96.2%, 97%), most metachronous secondary cancers can be non-surgically treated after the follow-up endoscopy.

HANDLING OF GASTRIC HIGH- AND LOW-GRADE INTRAEPITHELIAL NEOPLASMS

Gastric intraepithelial neoplasia, also called dysplasia or adenoma, is considered to be a precancerous lesion with a variable clinical course. The natural course of gastric intraepithelial neoplasia remains unclear. In particular, it is difficult to differentiate dysplasia/adenoma and adenocarcinoma using biopsy specimens because of the inaccuracy of obtaining a biopsy specimen from a malignant region of an adenoma[48,51,52]. Previous prospective long-term follow-up studies indicated that the gastric cancer-developing incidence in low-grade intraepithelial neoplasms (LGIN) is approximately 10%[38]. This low risk of malignant transformation compared to high-grade intraepithelial neoplasia (HGIN) may be due to the slowly progressive natural course of LGIN and supports a follow-up strategy. Once developing HGIN is diagnosed from biopsy specimens, 90% of them are ultimately diagnosed as adenocarcinoma after ER[36]. Generally, it is recommended that category 4 lesions (based on the Vienna classification: high-grade dysplasia and intramucosal cancer) be resected because they have a high potential for progression to adenocarcinoma[38]. Our current knowledge based on initial endoscopic intervention - not follow-up - indicates that over 40% of LGINs are diagnosed as adenocarcinoma after ER. Considering the high incidence of adenocarcinoma in HGIN, it could be recommended that ER be considered an indication for HGIN detected as a secondary lesion after ER. We are currently evaluating whether ESD is a valid strategy for gastric intraepithelial neoplasms with regard to safety and cost-effectiveness (UMIN Clinical Trials Registry: http://www.umin.ac.jp/ctr/, number UMIN000007476).
H. PYLORI ERADICATION

Extensive epidemiologic studies have shown that H. pylori infection is a major risk factor for developing gastric cancer[37]. According to most retrospective case-control and prospective epidemiologic studies, the risk of developing gastric cancer is two- to six-fold higher in patients with H. pylori infection than in patients without H. pylori infection[38]. Furthermore, some of the trials eradicating H. pylori have shown that successful eradication reduces the frequency of gastric cancer in high-risk populations, but H. pylori eradication may not completely abolish the risk for gastric carcinogenesis[39]. Therefore, H. pylori eradication might reduce secondary cancer after ER. Fukase et al[33] prospectively reported that prophylactic eradication of H. pylori after ER of EGC reduced secondary metachronous cancer by approximately one-third (OR = 0.353). Therefore, it is highly recommended that H. pylori be eradicated after ER for EGC. Based on Fukase's report, as of 2010, Japanese health insurance is allowed to cover H. pylori eradication therapy after ER for EGC. However, some retrospective cohort studies report no difference in the rate of metachronous cancer between patients who undergo successful H. pylori eradication and those who do not receive eradication treatment[19,40,41]. Therefore, because of the short 3-year observation of Fukase's report, whether H. pylori eradication reduces metachronous recurrence after ER for EGC is considered controversial. We speculate that the requirement for H. pylori eradication depends on how many high-risk patients have synchronous or metachronous recurrence. Therefore, it is important to conduct annual surveillance endoscopies after ER in patients with or without successful eradication, though patients with successful eradication will require longer surveillance until it is clear how long and how often surveillance endoscopy needs to be performed.

SURVEILLANCE STRATEGY FOR SECONDARY CANCER AFTER ER OF GASTRIC CANCER

There are no randomized trials to guide surveillance strategies after curative EGC resection. The 2013 consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) suggest the same follow-up strategy that is used for more advanced disease, regardless of treatment type (NCCN Guideline version 2, 2013, http://www.nccn.org/professionals/physician_gls/ E_guidelines.asp). The guidelines state that even for Tis or T1 with N0 lesions achieving R0, all patients should be followed up systematically, and follow-up should include a complete history and physical examination every 3 to 6 mo for 1 to 2 years, every 6 to 12 mo for 3 to 5 years and annually thereafter, along with other advanced stages. However, it is important to consider the curability of the initial ER. In Japan, ER is definitely indicated for guideline groups according to Japanese guideline criteria[44]. If the lesions meet the Japanese guideline criteria and R0 resection is achieved, the lesion is classified as a curative group and does not require further intense follow-up because it has a negligible risk for lymph node or distant metastasis[41].

Therefore, we recommend the following surveillance strategies: (1) an endoscopist who has performed at least 500 esophagogastroduodenoscopies should perform the preoperative screening; (2) intensive (every 6 mo) surveillance is preferred in the first year after ER to detect missed concomitant invasive cancers; and (3) annual surveillance should be performed for at least 5 years after the ER. From the viewpoint of avoiding gastrectomy and preserving most of the stomach and quality of life, it might not be important to strictly define the difference between synchronous and metachronous gastric cancer.

At this time, it is unclear whether the developing metachronous cancer is self-limiting or permanent. In report by Kobayashi et al[30], which included a follow-up longer than 10 years, showed that the metachronous recurrence curve reached a plateau and that the risk was not continuous after 10 years. In the future, the validity of our recommendations should be confirmed with a prospective study, and it is necessary to evaluate whether metachronous cancer is self-limiting.

CONCLUSION

It has not yet been established how endoscopic surveillance after curative ER should be performed. The rate of synchronous multiple gastric cancers among patients treated by ER is < 20%. After 1 year, the metachronous gastric cancer incidence increases linearly at an approximate rate of 3% per year. However, approximately 96% of patients with developing metachronous cancer were treated curatively with re-ER. Considered together with the population of ESD and advances in endoscopy, local recurrence or missed cancer may be negligible. Therefore, it might not be necessary to perform intensive endoscopy surveillance within 1 year to detect local recurrence. Surveillance endoscopies can permit the endoscopic treatment of cancers that may have been missed or that develop later.

In conclusion, skilled endoscopists should perform preoperative screening before initial ESD. We recommend that intensive (every 6 mo) surveillance be performed in the first year after ER to detect missed concomitant invasive cancers, and then annual surveillance should be performed for at least 5 years. In the future, it should be clarified whether longer surveillance is necessary.

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