Pattern of extragastric recurrence and the role of abdominal computed tomography in surveillance after endoscopic resection of early gastric cancer: Korean experiences

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Abstract

Background Although extragastric recurrence after endoscopic resection of early gastric cancer is rare, it is important because of its potentially fatal outcomes. We investigated the patterns of extragastric recurrence after endoscopic resection and evaluated the role of abdominal computed tomography in surveillance.

Methods Between July 1994 and June 2014, 4915 patients underwent endoscopic resection of early gastric cancer. Because of follow-up periods of less than 6 months and consecutive surgery within 1 year, 810 patients were excluded. Thus, 4105 patients were retrospectively reviewed.

Results The median follow-up period was 37 months (interquartile range 20–59.6 months). The overall incidence of extragastric recurrence was 0.37% ($n = 15$). In patients who underwent curative resection, the incidence was 0.14% ($n = 5$). There were three recurrences in the absolute indication group, six in the expanded indication group, and six in the beyond expanded indication group. The median time to extragastric recurrence was 17 months (interquartile range 16.5–43.2 months). Of the 15 extragastric recurrences, 11 were in the regional lymph nodes and 4 were in the liver, adrenal gland, and peritoneum. Sixty percent (9/15) of the extragastric recurrences occurred without intragastric lesions. Eleven recurrences

were detected by abdominal computed tomography, and eight patients underwent curative surgery.

Conclusions After endoscopic resection of early gastric cancer, regional lymph node recurrence is the predominant extragastric recurrence pattern, which can be detected via abdominal computed tomography and cured by rescue surgery. Abdominal computed tomography should be considered as a surveillance method, especially in patients with an expanded indication.

Keywords Early gastric cancer · Endoscopic resection · Extragastric recurrence · Surveillance · Abdominal CT

Introduction

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosa or submucosa, irrespective of lymph node metastasis [1]. Complete cure can almost always be achieved by conventional gastrectomy with lymph node dissection [2]. Concurrently, endoscopic resection such as endoscopic submucosal dissection (ESD) is also accepted as a standard treatment for EGC with a negligible risk of lymph node metastasis because it is minimally invasive and safe and provides good postoperative quality of life [2–4]. A number of studies have reported a favorable prognosis after curative resection of EGC by endoscopic resection [5–8]. Although the 5-year overall survival and 5-year disease-specific survival rates of patients with EGC after curative therapy are more than 97% and 99% respectively [7–9], there have been several reports of EGC recurrence after curative treatment, which can lead to unfavorable outcomes [8, 10, 11]. After curative endoscopic resection, the recurrence rate ranges from 4.5% to 16%. The commonest recurrence pattern is

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metachronous recurrence in the remnant stomach, followed by local recurrence at the primary resection site and, rarely, extragastric recurrence [6, 7, 9, 12]. After curative resection, the 2010 Japanese gastric cancer treatment guidelines recommend follow-up with annual or biannual endoscopy for tumors of absolute and expanded indications, and abdominal ultrasonography or computed tomography (CT) scans for tumors of expanded indication [2]. Scheduled endoscopic surveillance effectively detects almost all intragastric recurrences, which can again be treated with endoscopic resection [13–15]. However, the role of CT in surveillance after endoscopic resection is unclear. In the present study, we investigated the incidence and clinical course of extragastric recurrence of EGC after endoscopic resection and evaluated the role of abdominal CT as a surveillance method.

Patients and methods

Patients

All patients in whom EGC was diagnosed after treatment with endoscopic resection, including endoscopic mucosal resection and ESD, between January 1994 and June 2014 in the Department of Gastroenterology, Asan Medical Center, were retrospectively enrolled and analyzed. Patients were excluded from the study if any of the following criteria applied: (1) the follow-up period was less than 6 months; (2) they underwent consecutive gastrectomy and lymph node dissection within 1 year because of noncurative resection, synchronous EGC, or the physician's recommendation; (3) there was no adenocarcinoma in the resected specimen; or (4) the indication and curability of the specimen was not evaluable (Fig. 1). In patients with multiple EGCs, the most advanced lesion was considered in the analysis.

Definitions

Curative resection for EGCs with an absolute indication was to be performed when all of the following conditions were achieved: en bloc resection; negative horizontal and vertical margins; no lymphovascular invasion; and differentiated intramucosal tumor of 2 cm or smaller without ulcerative findings. Curative resection for an expanded indication was classified into four discrete groups, which included the following: category I (differentiated intramucosal tumor larger than 2 cm without ulcerative findings); category II (differentiated intramucosal tumor of 3 cm or smaller with ulcerative findings); category III (undifferentiated intramucosal tumor of 2 cm or smaller without ulcerative findings); and category IV

(differentiated tumor of 3 cm or smaller with submucosal invasion of less than 500 μm). These expanded indication patients also needed to fulfill the requirements for en bloc resection, negative horizontal and vertical margins, and no lymphovascular invasion [2].

The endoscopic procedures of our institution have been described previously [5]. Briefly, they are as follows: use of dots to mark the outside of the lesion; the injection of saline solution containing epinephrine and indigo carmine into the submucosal layer; and removal of the lesion with a snare in endoscopic mucosal resection, or a circumferential incision into the mucosa and submucosal dissection with various electronic knives in ESD.

Histological examination

For histological examination, the resected specimen was stretched, pinned to a polystyrene plate, and totally immersed in 10% neutral buffered formalin. After fixation, the specimen was grossly examined to identify the lesion and closest resection margin. After application of black ink to all lateral and deep resection margins, the entire specimen was sectioned into 2-mm-thick slices parallel to an imaginary line drawn from the edge of the tumor to the closest resection margin. Each sliced tissue specimen was then embedded in paraffin, and 5- μm sections were cut from each paraffin block and stained with hematoxylin and eosin. All of the lesions were classified as a gastrointestinal epithelial neoplasia in accordance with the Vienna classification (i.e. low-grade adenoma/dysplasia for category 3 lesions, high-grade adenoma/dysplasia or noninvasive carcinoma for category 4 lesions, and intramucosal carcinoma or submucosal carcinoma or beyond for category 5 lesions [16]. The histological type of the tumors was classified with the World Health Organization classification of tumors [17]. Lymphovascular invasion was defined as the observable spread of tumor cells through the lymphatic vessels (e.g., carcinoma cells floating within the endothelia-lined space).

Follow-up after endoscopic resection

Patients were followed up with an endoscopic examination and abdominal CT. Both procedures were performed every 6 months for the first 2 years and then annually for the next 3 years. Extragastric recurrence was defined as regional recurrence in perigastric lymph nodes and distant recurrence in the liver, lung, bone, brain, distant lymph nodes, and peritoneum, irrespective of intragastric lesions. Recurrence in the extragastric field was detected by abdominal CT and confirmed with tissue taken by ultrasonography-guided or endoscopic-ultrasonography-guided

Fig. 1 Flowchart for the enrolled patients who underwent endoscopic resection for early gastric cancer (EGC): incidence and pattern of extragastric recurrence

biopsy or rescue surgery. In some cases, recurrence was presumed on the basis of CT findings.

Overall survival was estimated by the Kaplan–Meier method and compared with the log-rank test. This analysis was performed with the statistical software package IBM SPSS for Windows (version 21.0; IBM, Armonk, NY, USA). This study was approved by the Institutional Review Board of Asan Medical Center (2015-1073). Before endoscopic resection, all patients provided oral and written informed consent for the procedure.

Results

Study patients

Between July 1994 and June 2014, 4915 EGC patients underwent endoscopic resection of their tumor at Asan Medical Center. On the basis of our exclusion criteria, 810 patients were excluded from the study. Thus, 4105 patients were analyzed. The median follow-up period for all study patients was 37 months (interquartile range 20–59.6 months). With use of the indication criteria for endoscopic resection, the patients were divided into three groups: 2402 patients (58.5%) in the absolute indication group, 1410 patients (34.3%) in the expanded indication

group, and 293 patients (7.1%) in the beyond expanded indication group (Fig. 1).

Treatment outcomes of endoscopic resection in accordance with the indication criteria

Overall, curative resection was achieved in 3588 patients (87.4%): 2286 patients (95.2%) in the absolute indication group and 1302 patients (92.3%) in the expanded indication group (Fig. 1). In the subgroup analysis of the expanded indication group based on the four indication categories of the Japanese gastric cancer treatment guidelines, primary EGCs were classified as follows: category I (differentiated intramucosal tumor larger than 2 cm without ulcers), 1025 patients (72.8%); category II (differentiated intramucosal tumor of 3 cm or smaller with ulcers), 99 patients (7%); category III (undifferentiated intramucosal tumor of 2 cm or smaller without ulcers), 128 patients (9.1%); and category IV (differentiated tumor of 3 cm or smaller with submucosal invasion less than 500 μ m without ulcers), 158 patients (11.1%). The curative resection rates were 91.7% in category I, 98% in category II, 96.9% in category III, and 88.6% in category IV.

The overall extragastric recurrence rate after endoscopic resection of EGC was 0.37% ($n = 15$) (Table 1). When the analysis was confined to patients in which

Table 1 Clinical and endoscopic characteristics of the patients with extragastric recurrence

	Absolute indication			Expanded indication			Beyond expanded indication									
	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient	Patient
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Sex/age (years)	Female/ 75	Male/ 70	Male/ 55	Male/ 55	Female/ 74	Male/ 62	Female/ 60	Male/ 60	Female/ 60	Female/ 83	Female/ 72	Male/ 77	Male/ 55	Male/ 61	Male/ 84	
Tumor size (mm)	15	14	10	30	24	25	29	25	25	60, 69	34	47	34	35	32	
Tumor depth	M	M	M1	SM1	SM1	M3	M3	M1	M2	SM2	SM1	SM1	SM3	SM1	SM3	
Histological type	WD	WD	WD	MD	MD	WD	MD	WD	MD	MD	MD	MD	WD	MD	MD	
Resection margin (deep/ lateral)	-/-	-/+	+/+	-/-	-/-	-/-	+/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	
Lymphovascular invasion	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	
Ulcer	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	
Curability	CR	NCR	NCR	CR	CR	CR	NCR	NCR	NCR	NCR	NCR	NCR	NCR	NCR	NCR	
Location	Antrum	Antrum	LB	HB	Antrum	Angle	Angle	Antrum	Angle	Antrum	Angle	Antrum	GEJ	Antrum	LB	
Endoscopic resection	ESD	EMR	EMR	ESD	ESD	ESD	EMR	EMR	ESD	ESD	ESD	ESD	ESD	ESD	ESD	
En bloc	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Recurrence type	RI	RI	DI	RO	RO	RO	RO	RI	DI	RO	RO	RO	RI	DO	DO	
Time to recurrence (months)	24.7	54.6	84.5	9	17	19	28	17.7	36.4	37	10	9	18.5	21	41	
Detection of recurrence	EGD	EGD	EGD/ CT	CT	CT	CT	CT	EGD	EGD/ CT	CT	CT	CT	EGD	CT	CT	

CR curative resection, CT computed tomography, DI distant recurrence with intragastric lesion, DO distant recurrence without intragastric lesion, EGD esophagogastroduodenoscopy, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, GEJ gastroesophageal junction, HB high body, LB low body, M mucosal layer, M1 epithelium, M2 lamina propria, M3 muscularis mucosae, MD moderately differentiated, NCR noncurative resection, SM1 submucosal invasion less than 500 µm, SM2 submucosal invasion less than 1000 µm, SM3 submucosal invasion more than 1000 µm, RI regional lymph node recurrence with intragastric lesion, RO regional lymph node recurrence without intragastric lesion, WD well differentiated

Table 2 Extragastric recurrence patterns and detection methods according to the recurrence pattern after endoscopic resection of early gastric cancer

Detection methods	Pattern of recurrence			
	Regional LN recurrence ($n = 11$)		Distant recurrence ($n = 4$)	
	Without intragastric lesion	With intragastric lesion	Without intragastric lesion	With intragastric lesion
EGD alone	0	4 (26.7%)	0	0
CT alone	7 (46.7%)	0	2 (13.3%)	0
Both EGD and CT	0	0	0	2 (13.3%)

CT computed tomography, EGD esophagogastrroduodenoscopy, LN lymph node

curative resection was achieved, the extragastric recurrence rate was 0.14% ($n = 5$). In the absolute indication group, three extragastric recurrences (0.12%) were detected: one (0.04%) after curative resection and two (1.72%) after noncurative resection. In the expanded indication group, six extragastric recurrences (0.43%) were detected: four (0.31%) after curative resection and two (1.85%) after noncurative resection. Four noncurative resections across both indication groups were due to a failure of en bloc resection. Among them, one patient in the absolute indication group had a positive lateral resection margin but, in the first follow-up endoscopy, the biopsy from the endoscopic resection site showed no remnant malignant cells. All of these patients were followed up closely without additional surgery. The other six recurrences were detected in patients in the beyond expanded indication group (2.05%). Additional surgery was recommended to these patients, but some of them chose surveillance instead of additional surgery. The median time to extragastric recurrence after endoscopic resection was 17 months (interquartile range 16.5–41.2 months; Fig. 1).

Overall, death from any cause occurred in 312 patients (7.9%): 170 deaths (7.1%) in the absolute indication group, 107 deaths (7.6%) in the expanded indication group, and 35 deaths (11.9%) in the beyond expanded indication group. Death related to gastric cancer occurred in eight patients overall (0.2%): two deaths in the absolute indication group (0.08%), one death in the expanded indication group (0.07%), and five deaths in the beyond expanded indication group (1.71%). All of these patients died because of gastric cancer progression after extragastric recurrence with or without intragastric recurrence (Table 2). The 5-year overall survival rate was 94%, and the 5-year disease-specific survival rate was 99.6%. When subdivided according to indication, the 5-year overall survival rates were 95.2% in the absolute indication group, 93.5% in the expanded indication group, and 85.8% in the beyond expanded indication group (Fig. 2).

Clinical and endoscopic characteristics of the patients with extragastric recurrence

The clinical and endoscopic characteristics of the patients with extragastric recurrence are presented in Table 1. The time to recurrence from endoscopic resection ranged from 9 to 84.5 months. All primary lesions had a differentiated histological type. In more than half of the patients, the tumor invaded the submucosal layer, and one fifth showed lymphovascular invasion. Of the 15 extragastric recurrences, 11 were in the regional lymph nodes and 4 were in the liver, adrenal gland, and peritoneum. In the absolute indication group, all extragastric recurrences were accompanied by metachronous intragastric lesions and were initially detected via endoscopy. In the expanded indication group, four of the six extragastric recurrences developed in the regional lymph nodes and the adrenal gland without intragastric lesions and could be detected only by abdominal CT. Two extragastric recurrences with intragastric lesions were found by endoscopy. In the beyond expanded indication group, five of the six extragastric recurrences did not have concurrent intragastric lesions and consisted of three regional lymph node recurrences and two distant recurrences, which were found by abdominal CT (Table 2).

Treatment outcomes in the patients with extragastric recurrence

Six patients who had regional lymph node recurrences with or without intragastric lesions in the absolute and expanded indication groups were treated with curative surgery. In the absolute indication group, one patient, who had metachronous advanced gastric cancer with regional lymph node metastasis and underwent rescue surgery with post-operative chemotherapy, died of secondary mesenteric recurrence encasing the superior mesenteric artery. In the expanded indication group, one patient with regional lymph node recurrence without an intragastric lesion refused rescue surgery and started chemotherapy. After three cycles of chemotherapy, he refused further treatment

Fig. 2 Kaplan–Meier survival curves for overall survival of early gastric cancer (EGC) patients after endoscopic resection: **a** overall survival of all EGC patients treated with endoscopic resection;

b overall survival of EGC patients treated with endoscopic resection according to the indication

because of chemotherapy intolerance. At 68 months after recurrence, the number of regional lymph nodes with recurrent tumors was increasing. In the beyond expanded indication group, one patient with regional recurrence without an intragastric lesion 37 months after endoscopic resection underwent curative surgery and was alive 19 months after the recurrence. All patients with extragastric recurrence involving distant organs across each indication group, irrespective of intragastric lesions, died of gastric cancer progression. Two patients with regional lymph node recurrence with intragastric lesions as advanced gastric cancer died of another recurrence even after curative surgery and adjuvant chemotherapy (Table 3).

Discussion

Endoscopic resection for the treatment of EGC has been performed for more than 20 years. With the accumulation of experience and technical advances, its indication has widened. From the early days of endoscopic resection for treatment of EGC, lymph node metastasis has been a concern; however, several large studies determined that curative resection of EGC meeting the absolute and expanded indications carries a negligible risk of lymph node metastasis [4, 5, 18]. Extragastric recurrence has been reported as a rare experience or in small case series from several large centers. In the present study, although more than 4000 patients received a diagnosis of EGC and underwent endoscopic resection, extragastric recurrence

occurred in 15 patients (0.37%) and in just 5 patients who underwent curative resection (0.14%). A previous Korean study by Min et al. [8] reported two extragastric recurrences among 1306 patients in the absolute and expanded indication groups who underwent curative endoscopic resection (0.15%). In large-scale studies from Japan, similar results have been found. Oda et al. [19] detected three cases of extragastric recurrence in 2999 patients from six institutions who underwent curative endoscopic resection for primary EGC meeting the absolute and expanded indications (0.1%). More recently, Suzuki et al. [9] reported two cases of extragastric recurrence in 1537 patients (0.13%) who underwent curative ESD for EGCs that met the absolute and expanded indications and had a median follow-up period of 83.3 months. Consistent with the findings from these large-scale studies from both Korea and Japan, our current study confirmed the rarity of extragastric recurrence after curative endoscopic resection of EGCs meeting expanded indications.

Regional lymph node recurrence is the predominant pattern of extragastric recurrence after endoscopic resection. In the present study, of the 15 extragastric recurrences, 11 were in the regional lymph nodes and 4 were in the liver, adrenal gland, and peritoneum. A recent study from Korea [8] analyzing extragastric recurrence after curative endoscopic resection reported eight extragastric recurrences in a single center and from a literature review; seven of these were regional lymph node recurrences, as in the present study. In the previously mentioned Japanese studies [9, 19], three cases among five extragastric recurrences were regional lymph node recurrence and two cases

Table 3 Treatment outcomes among the study patients with extragastric recurrence

Patient	Indication	Curability	Recurrence type	Treatment for recurrence	Outcome
1	Absolute	CR	Regional LN recurrence with metachronous AGC	STG	Dead (56.2 months)
2	Absolute	NCR	Regional LN recurrence with metachronous EGC	STG	Alive (108.7 months)
3	Absolute	NCR	Distant recurrence with metachronous EGC (liver, lung)	Refusal	Dead (3.6 months)
4	Expanded	CR	Regional LN recurrence	TG + CTx	Alive (34 months)
5	Expanded	CR	Regional LN recurrence	TG + CTx	Alive (79 months)
6	Expanded	CR	Regional LN recurrence	CTx	Alive (68 months)
7	Expanded	NCR	Regional LN recurrence	STG	Alive (135 months)
8	Expanded	NCR	Regional LN recurrence with metachronous EGC	STG	Alive (164.6 months)
9	Expanded	CR	Distant and regional LN recurrence with metachronous EGC (left adrenal gland)	CTx	Dead (34.8 months)
10	Beyond expanded	NCR	Regional LN recurrence	STG	Alive (19 months)
11	Beyond expanded	NCR	Regional LN recurrence	CTx	Dead (33 months)
12	Beyond expanded	NCR	Regional LN recurrence	Refusal	Dead (9 months)
13	Beyond expanded	NCR	Regional LN recurrence with locally recurred AGC	TG + CTx	Dead (31.7 months)
14	Beyond expanded	NCR	Distant and regional LN recurrence (liver)	CTx	Dead (11 months)
15	Beyond expanded	NCR	Distant and regional LN recurrence (peritoneal seeding)	Refusal	Dead (3 months)

AGC advanced gastric cancer, CR curative resection, CTx chemotherapy, EGC early gastric cancer, LN lymph node, NCR noncurative resection, STG subtotal gastrectomy, TG total gastrectomy

were a distant lymph node metastasis with local recurrence. After curative surgery for EGC, in contrast, the commonest recurrence pattern was distant recurrence through hematogenous spread to other organs such as the liver, followed by locoregional recurrence in the regional lymph nodes and anastomotic sites and peritoneal recurrence [20–22]. This difference in the pattern of recurrence requires distinct therapeutic approaches and leads to different outcomes. There is no curative treatment for hematogenous or peritoneal recurrence; therefore, palliative chemotherapy is given in the hope of improving survival. However, gastric cancer tends to progress with unfavorable outcomes. In cases of regional lymph node recurrence, surgical resection with curative intent is possible. In the current study, six patients with regional lymph node recurrences were treated with curative surgery; one in the absolute indication group, four in the expanded indication group, and one in the beyond expanded indication

group. When the recurrence is confined to the regional lymph nodes and detected early, with a small number of affected nodes, surgical resection can be an effective and curative treatment. When patients with EGC are left untreated, several studies have reported that approximately 25–64% of the cancers progress to the advanced stage and half of the patients die of gastric cancer progression within 5 years of diagnosis [23, 24]. The disease course might be similar in cases of extragastric recurrence. For the same T category, more regional lymph nodes being involved leads to a lower 5-year survival rate [25]. If regional lymph node recurrence is detected early with a small number of affected nodes, patients have a higher chance of cure. With a curative operation, a greater than 96% 5-year survival rate can be achieved in EGC with lymph node metastasis at stages such as T1N1 [25]. Even after noncurative endoscopic resection of EGC, additional radical gastrectomy with lymph node dissection showed a 5-year overall

survival rate of 94.3–94.7%, which is significantly greater (by about 10 percentage points) than that seen after no treatment [26–28]. For extragastric recurrences involving only regional lymph nodes, some case reports and studies showed good prognosis after curative surgery [8, 19]. Therefore, surveillance for early detection of extragastric recurrence and curative surgery in cases of regional lymph node recurrence should be recommended after endoscopic treatment of EGC.

Although the value of postoperative surveillance remains controversial [29–31], major guidelines recommend regular and systematic follow-up with endoscopy and cross-sectional imaging, and many cancer centers have established their own follow-up protocols after curative treatment that include these methods [2, 32, 33]. The role of endoscopy in surveillance after endoscopic resection has been proven in several studies, but its role is limited to the detection of intragastric recurrence [13–15]. In the present study, all the extragastric recurrences with intragastric lesions were initially detected by endoscopy. However, the role of CT after endoscopic resection is not clear. After surgical resection of gastric cancer, use of abdominal CT has not been shown to improve long-term survival [30, 31, 34]. In colorectal cancer, several randomized clinical trials and meta-analyses have reported that intensive follow-ups that included CT after curative resection increased the rate of curative surgery for recurrence compared with minimal follow-ups [35, 36]. In hepatocellular carcinoma, surveillance with high-quality cross-sectional imaging is also recommended after primary resection. This is because hepatocellular carcinoma tends to recur locally rather than at distant sites; therefore, earlier identification can provide an opportunity for curative treatment that prolongs survival [37, 38]. In EGC, some studies have evaluated the role of CT in surveillance for intramucosal gastric cancer after curative endoscopic resection, reporting that CT had a minor or nonexistent role in detecting local or metachronous gastric recurrence [13, 15]. However, these reports included only patients with intragastric recurrence and thus could not define the role of abdominal CT in extragastric recurrence. In the current study, follow-up was performed with endoscopy and abdominal CT, and 73.3% (11/15) of extragastric recurrences were detected via abdominal CT. In the absolute indication group, all extragastric recurrences arose with metachronous intragastric lesions and were initially detected via endoscopy. Therefore, surveillance with esophagogastroduodenoscopy may be enough for this group. In the expanded and the beyond expanded indication groups, 66.7% (4/6) and 83.3% (5/6) of extragastric recurrences were not accompanied by intragastric recurrence and were found only by abdominal CT. With this diagnostic method, it was possible to find extragastric recurrences that did not have intragastric

lesions, and patients had an increased chance of survival with additional curative surgery and/or chemotherapy. Nevertheless, the beyond expanded indication group had poorer survival with distant recurrences. Additional surgery after endoscopic resection should be recommended instead of surveillance in the beyond expanded indication group.

PET/CT has been evaluated in a few studies as another surveillance method for gastric cancer patients who have undergone gastrectomy [39, 40]. A large study found that PET/CT could be a useful imaging modality for the follow-up of gastric cancer patients, particularly advanced gastric cancer patients, but was limited in its ability to detect local and peritoneal metastasis [40]. Also, a recent study compared PET/CT with CT in gastric cancer diagnosis and reported that PET/CT had diagnostic effectiveness in the identification of regional metastatic nodes but not distant abdominal metastases [41]. However, there have been very few studies on the role of PET/CT as a surveillance method after surgical or endoscopic resection of EGC. In the current study, we did not evaluate the performance of PET/CT in the surveillance of EGC patients after endoscopic resection. Further studies are thus needed in this regard.

A number of studies have reported the outcome of endoscopic resection for EGC. Recent reports from Korea and Japan included large populations of EGC patients and longer follow-up periods [8, 9, 19, 28]. In terms of extragastric recurrence, all of the studies to date have reported a low incidence and a common pattern. In the expanded indication population in which curative resection was achieved, the rate of extragastric recurrence was much lower and the predominant pattern was regional lymph node recurrence that could be resolved with rescue surgery. Thus, surveillance after endoscopic resection was reasonable and appropriate under this condition. However, in the beyond expanded indication population described thus far, endoscopic resection was noncurative and the rate of distant metastasis was higher, leading to a poorer prognosis and requiring additional surgery after endoscopic resection. Unlike previous studies, here we evaluated extragastric recurrence in patients with curative and noncurative resections. Moreover, we examined the correlation between intragastric recurrence and extragastric recurrence, and identified the proportion of patients in our cohort with extragastric recurrence without intragastric recurrence (60%). This result emphasizes the important role of CT in the surveillance of gastric cancer patients.

The current study had some noteworthy limitations associated with its retrospective design. First, patients lost to follow-up within 6 months of endoscopic resection were excluded from the analysis of extragastric recurrence. Thus, its incidence might have been underestimated. Second, the median follow-up period may not have been long enough to

encounter slowly emerging extragastric recurrences, such as those detected more than 5 years after endoscopic resection. Third, our study series included extragastric recurrences accompanied by metachronous EGC or advanced gastric cancer and it was not possible to tell whether these recurrences originated from the primary EGC or the metachronous intragastric lesion. However, because we aimed to analyze all possible extragastric recurrences, we included these types of extragastric recurrence, making the analysis more comprehensive. Notwithstanding these limitations, our study also had several strengths. First, it included the largest population of patients with EGC reported to date. Second, the rate of standardized follow-up was high (92.8%, 4105/4423). Third, the endoscopic procedure and reports of pathologic findings were performed in accordance with a standardized format.

Our current large-scale retrospective cohort study showed the rarity of extragastric recurrence after endoscopic resection of EGC as well as the feasibility of endoscopic resection of EGC meeting the absolute and expanded indications. Regional lymph node recurrence was confirmed as the predominant type of extragastric recurrence. In the absolute indication group, as extragastric recurrences occurred with metachronous intragastric recurrences, abdominal CT had a limited role in detecting recurrences. In the expanded indication group, however, as the proportion of patients with extragastric recurrence without intragastric recurrence was higher than that with intragastric lesions, abdominal CT performed well in the detection of recurrence. Furthermore, patients with regional lymph node recurrences could potentially be cured by rescue surgery. Therefore, the value of abdominal CT should be emphasized as an important part of the surveillance strategy after endoscopic resection of EGC that meets the expanded indication criteria.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the Institutional Review Board of Asan Medical Center and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for their being included in the study.

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