

Case Control Study

Clinical features of second primary cancers arising in early gastric cancer patients after endoscopic resection

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Abstract

AIM: To investigate the incidence and distribution of second primary cancers (SPCs) in early gastric cancer (EGC) patients who underwent endoscopic resection (ER), compared to advanced gastric cancer (AGC) patients who underwent surgery.

METHODS: The medical records of 1021 gastric cancer (GC) patients were retrospectively reviewed from January 2006 to December 2010. The characteristics and incidence of SPCs were investigated in those with EGC that underwent curative ER (the EGC group) and those with AGC who underwent curative surgical resection (the AGC group).

RESULTS: We ultimately enrolled 184 patients in the EGC group and 229 patients in the AGC group. A total of 38 of the 413 (9.2%) GC patients had SPCs; the rate was identical in both groups. Of these 38 patients, 18 had synchronous and 20 had metachronous cancers. The most common SPC was lung cancer (18.4%), followed by colorectal cancer (13.2%) and esophageal cancer (13.2%). No significant risk factors were identified for the development of SPCs.

CONCLUSION: Endoscopists should provide close surveillance and establish follow-up programs to ensure SPC detection in GC patients undergoing curative

resection regardless of their clinical characteristics.

Key words: Second primary cancers; Early gastric cancer; Endoscopic resection; Advanced gastric cancer

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Core tip: In this study, we investigate the incidence and distribution of second primary cancers (SPCs) in early gastric cancer (EGC) patients who underwent endoscopic resection (ER) compared to advanced gastric cancer patients who underwent surgery. Although SPCs developed rather commonly in gastric cancer patients, no significant risk factors were identified for their development. Therefore, endoscopists should perform close surveillance and establish follow-up programs for SPC detection after use of ER to treat EGC.

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INTRODUCTION

Worldwide, gastric cancer (GC) is the fourth most common cancer and the second-leading cause of cancer-related death, and is especially prevalent in the Asia-Pacific region including Korea^[1]. Recently, the outcomes of GC patients have significantly improved, attributable to the introduction of periodic cancer screening programs and advances in early-detection techniques, surgical procedures, and multimodal treatments^[2-5]. In practice, annual mortality from GC is continuously decreasing in Korea^[6]. Also, implementation of a population-based mass-screening program has increased the detection rate of early gastric cancers (EGCs) from 33% in 1999 to 60% in 2012^[7]. Along with this increase, endoscopic resection (ER), including both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has become a widely accepted standard technique for treatment of EGC in Korea and Japan, associated with a nominal risk of lymph node metastasis. The technique is minimally invasive, safe, and convenient^[8-10]. To date, several reports have described excellent short- and long-term outcomes in patients who have undergone curative ER of EGC; the 5-year survival rate is 96.8%^[9,11,12].

Such improved outcomes are associated with increases in the risk of development of second primary cancers (SPCs) at different locations throughout the body^[13]. The risk of developing an SPC in cancer patients is considerably higher than in the general population^[14]. As SPCs may have adverse effects

on the overall prognosis of GC, early detection and proper management of SPCs in patients who have undergone curative resection of GC is especially important^[13]. To date, few studies have explored the incidence or clinical features of SPCs in GC patients; those that have, studied heterogeneous groups of GC patients^[13,15-18]. Further, although ER is now widely performed in EGC patients, no study has yet analyzed the clinical features of SPCs in EGC patients who have undergone ER. Apart from showing that ER is appropriate for treatment of very early-stage EGC, it is important to emphasize that long-term and regular endoscopic surveillance must be conducted to detect local recurrence or the development of metachronous GC. In addition, surveillance of SPCs may be an important responsibility of endoscopists, especially in patients with endoscopically resectable EGCs. Therefore, in the present study, we excluded GC patients who underwent non-curative resection (in whom SPCs are of relatively low importance), to focus on GC patients with very early-stage EGC, who require particular attention from endoscopists. We compared the incidence of, clinical features of, and risk factors for, SPC between two groups: EGC patients who underwent curative ER, and AGC patients who underwent curative surgical resection. We also attempted to identify risk factors that may have contributed to the development of SPCs in EGC patients who underwent ER.

MATERIALS AND METHODS

Study population

Between January 2006 and December 2010, 1021 patients with GC were diagnosed and managed at the Kyung Hee University Hospital, Seoul, Korea, and we retrospectively analyzed their data. All patients underwent surgical or endoscopic GC resection. EGC patients underwent EMR or ESD according to individual indications. AGC patients underwent either partial or total gastrectomy, with lymph node dissection, depending on tumor location. Patients who had a previous history of malignancy, died within 1 year after diagnosis of GC, or required further therapy including chemotherapy, radiation therapy, or additional surgery were excluded. EGC patients who did not undergo curative ER of EGC, or who exhibited an undifferentiated histology, were also excluded. Curative ER for EGC was defined as R0 resection followed by pathological confirmation that resected specimens were included in the conventional indication^[10] of EMR or the expanded indication^[19] of ESD for EGC. R0 resection was defined as lateral tumor-free margin ≥ 2 mm and vertical tumor-free margin ≥ 0.5 mm on histologic examination after ER. Surgery was recommended to any patient who did not fulfill the criteria of curative ER upon pathological assessment following ER.

Clinical characteristics, including age, gender, history of smoking, alcohol consumption, the GC cell type, diagnosis of early or advanced GC, and *Helicobacter pylori* (*H. pylori*) infection were assessed. *H. pylori* infection was determined using either a rapid urease test, a ¹³C-urea breath test, or histology. All patients with GC underwent preoperative esophagogastroduodenoscopy. The standard preoperative or preprocedural workup for GC included a complete physical examination, routine blood testing including measurement of tumor markers, chest X-ray, computed tomography (CT) of the chest and abdomen, and whole-body positron emission tomography (PET)-CT. On regular follow-up examinations after treatment, blood tests, a chest X-ray, abdominal CT, and endoscopy of the gastrointestinal (GI) tract were performed. The study was approved by the Institutional Review Board of Kyung Hee University Hospital (KMC IRB 1217-03).

Endoscopic resection

All ER procedures were performed by a single experienced endoscopist (Jang JY) who had performed more than 1500 procedures. ER involved performance of both ESD and EMR. All EGC patients who underwent ER met the conventional or expanded criteria for EMR or ESD^[10,19]. EMR was performed to treat lesions < 10 mm in diameter. ESD was performed for lesions ≥ 10 mm and for lesions that exhibited a high probability of piecemeal resection. EMR-P (precutting) was used on the lesion to avoid any incomplete resection of the transverse cutting. Lesions were marked externally using argon plasma coagulation (ERBE, Tubingen, Germany). To lift the lesion, a mixture of glycerin, epinephrine, and indigo carmine was locally injected into the external side of the marking. Once the lesion was lifted, incisions were made into its external side using a needle knife (KD-V451M, Olympus Medical Systems Co., Ltd., Tokyo, Japan) or an insulated tipped (IT) knife 2 (KD-611L, Olympus Medical Systems Co., Ltd., Tokyo, Japan). VIO 300D (ERBE, Tubingen, Germany) was used as the electrosurgical unit. In cases of EMR-P, after performing circumferential mucosal incision, a snare (SD-210U-15, 25, Olympus Medical Systems Co., Ltd., Tokyo, Japan) was mounted along the incision groove to subsequently dissect the lesion. In patients treated *via* ESD, a standard ESD method was used to achieve tumor resection. A typical sequence featured marking, incision, and submucosal dissection with simultaneous hemostasis. After placing an IT knife 2 into the incision site, resection was completed *via* submucosal dissection performed parallel to the proper muscle layer.

Second primary cancers

The diagnostic criteria of Warren and Gates^[20] were used to diagnose SPCs: (1) a tumor must be unequivocally malignant upon histological evaluation; (2) each cancer must be geographically separate

and distinct; and (3) the possibility that the second cancer represents a metastasis must be excluded. If necessary, immunohistochemical stains were used to differentiate SPCs from the metastasis of primary gastric cancer. SPCs were categorized into two groups depending on time of detection: synchronous cancer and metachronous cancer. Synchronous cancer was defined as a cancer diagnosed at the same time as the first primary cancer or within the following year, and metachronous cancer was defined as a cancer developing more than 1 year later. All GCs and SPCs were confirmed pathologically and/or radiologically.

Statistical analysis

Between-group comparisons of clinical features were performed using the two-tailed χ^2 test and the independent samples *t*-test. Logistic regression analysis was used to define risk factors for SPC. Statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, United States). A *P* value < 0.05 was considered to be statistically significant.

RESULTS

Clinical characteristics of the patients

Of the 1021 GC patients reviewed, we enrolled 413 patients who underwent curative endoscopic or surgical resection. A total of 314 EGC subjects were excluded because of surgery (249), a previous history of malignancy (9), loss to follow-up (8), performance of non-curative ER (34), or undifferentiated histology (14). Also, 294 AGC subjects were excluded because they required additional therapy after surgery (267), died within 1 year after diagnosis of GC (15), or had a previous history of malignancy (12). Finally, we evaluated 184 EGC patients who underwent curative ER (the EGC group) and 229 AGC patients who underwent curative surgical resection (the AGC group) (Figure 1). Table 1 shows the clinical characteristics of both groups. No differences existed in the age and gender distribution between the groups (*P* = 0.263 and *P* = 0.159, respectively). The incidence of cigarette smoking (59.8% vs 47.6%, *P* = 0.014) and alcohol consumption (52.7% vs 40.6%, *P* = 0.014) was higher in the EGC group than in the AGC group. The prevalence of *H. pylori* infection was higher in the AGC group (57.1% vs 66.8%, *P* = 0.042). All patients in the EGC group exhibited a differentiated histology. There were no significant differences between the two groups with regard to the mean follow-up period (36.9 ± 14.9 mo vs 37.4 ± 16.7 mo, *P* = 0.679).

Characteristics of SPCs

SPCs were identified in 9.2% of the patients in the EGC group and 9.2% of the patients in the AGC group. Notably, the overall incidence of SPC did not differ between the two groups (*P* = 0.981). Synchronous

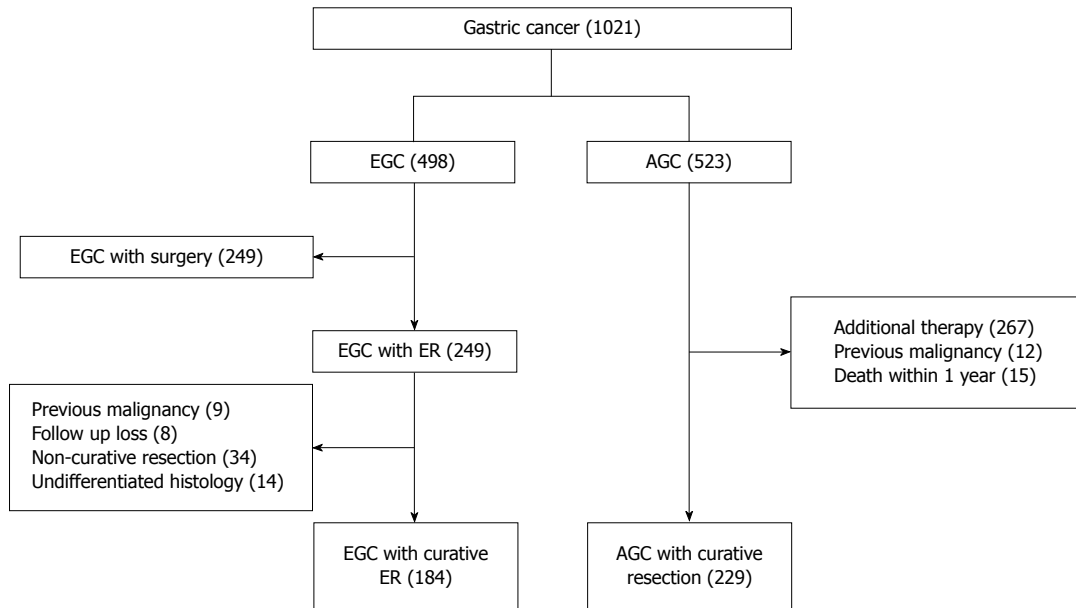


Figure 1 Flow chart of patients included in the analysis.

Table 1 Characteristics of the early gastric cancer and advanced gastric cancer groups *n* (%)

	Overall (<i>n</i> = 413)	EGC group (<i>n</i> = 184)	AGC group (<i>n</i> = 229)	<i>P</i> value
Mean age (mean ± SD, yr)	61.3 ± 11.6	62.1 ± 10.2	60.8 ± 12.6	0.263
Gender				
Male	293 (70.9)	137 (74.5)	156 (68.1)	0.159
Female	120 (29.1)	47 (25.5)	73 (31.9)	
Smoking	229 (55.4)	110 (59.8)	109 (47.6)	0.014
Alcohol	190 (46.0)	97 (52.7)	93 (40.6)	0.014
<i>H. pylori</i> infection	258 (62.5)	105 (57.1)	153 (66.8)	0.042
Histology				
Differentiated	262 (63.4)	184 (100)	78 (34.1)	< 0.001
Undifferentiated	151 (36.6)	0	151 (65.9)	
Follow-up duration (mean ± SD, months)	37.2 ± 15.9	36.9 ± 14.9	37.4 ± 16.7	0.697

EGC: Early gastric cancer; AGC: Advanced gastric cancer; SD: Standard deviation; *H. pylori*: *Helicobacter pylori*.

Table 2 Incidence of second primary cancers in gastric cancer patients *n* (%)

	Overall (<i>n</i> = 413)	EGC group (<i>n</i> = 184)	AGC group (<i>n</i> = 229)	<i>P</i> value
Second primary cancer	38 (9.2)	17 (9.2)	21 (9.2)	0.981
Synchronous cancer	18 (4.4)	8 (4.3)	10 (4.4)	0.993
Metachronous cancer	20 (4.8)	9 (4.9)	11 (4.8)	0.967

EGC: Early gastric cancer; AGC: Advanced gastric cancer.

cancers were diagnosed in 4.3% of the patients in the EGC group and 4.4% of the patients in the AGC group. Metachronous cancers were diagnosed in 4.9% of the patients in the EGC group and 4.8% of the patients in the AGC group. There were no differences in the

overall incidence of synchronous and metachronous cancers between the two groups ($P = 0.994$ and $P = 0.967$, respectively) (Table 2).

The majority of SPCs in both groups were solid cancers (94.1% in the EGC group and 95.2% in the AGC group) (Figure 2). Table 3 shows the number of patients with various types of SPCs and GCs. The most common site of SPC occurrence in the EGC group was the lung (17.6%), followed by the colorectum (11.8%), esophagus (11.8%), and urogenital area (11.8%). The most frequent sites of SPC occurrence in the AGC group were the lung (19.0%), followed by the colorectum (14.3%) and esophagus (14.3%). Both groups exhibited one patient that developed hematologic malignancies: non-Hodgkin lymphoma in the EGC group and multiple myeloma in the AGC group (Table 2 and Figure 2).

Risk factors for SPCs in EGC patients who underwent curative ER

Logistic regression analyses of risk factors showed that age, gender, smoking, alcohol consumption, and *H. pylori* infection were not significantly associated with incidence of synchronous cancer. In contrast, smoking, *H. pylori* infection, and being of male gender all tended to be associated with a higher incidence of metachronous cancer. Alcohol consumption, on the other hand, tended to be associated with a lower incidence of metachronous cancer. However, these data were not statistically significant (Table 4).

DISCUSSION

In Korea, the National Cancer Screening Program facilitates biennial gastroscopy or upper GI barium

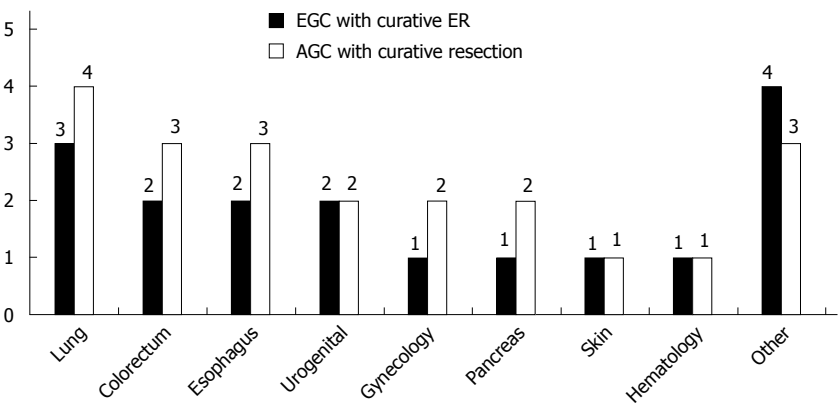


Figure 2 Site distribution of second primary cancers according to gastric cancer group. EGC: Early gastric cancer; AGC: Advanced gastric cancer.

Table 3 Distribution of second primary cancers according to gastric cancer group n (%)			
Location	Overall (n = 38)	EGC group (n = 17)	AGC group (n = 21)
Lung	7 (18.4)	3 (17.6)	4 (19.0)
Colorectal	5 (13.2)	2 (11.8)	3 (14.3)
Esophagus	5 (13.2)	2 (11.8)	3 (14.3)
Urogenital	4 (10.5)	2 (11.8)	2 (9.5)
Gynecologic	3 (7.9)	1 (5.9)	2 (9.5)
Pancreas	3 (7.9)	1 (5.9)	2 (9.5)
Skin	2 (5.3)	1 (5.9)	1 (4.8)
Hematology	2 (5.3)	1 (5.9)	1 (4.8)
Others	7 (18.3)	4 (23.4)	3 (14.3)

EGC: Early gastric cancer; AGC: Advanced gastric cancer.

studies for anyone in the population over 40 years old. With such efforts, the overall proportion of early-stage GC occurrence has been progressively rising^[3,4]. Kim *et al*^[21] participated in the Korean National Cancer Screening Program conducted from 2007 to 2010, analyzed the results of 34416 gastroscopies, and found that 74.0% of diagnosed GCs were EGCs. Due to the fact that the skills and techniques of endoscopists have evolved and developed, ER is the preferred method for treating EGC when appropriately indicated. This treatment not only preserves the stomach, warranting a better quality of life^[22], but is also associated with a good prognosis when considering a 5-year survival rate of 96.8%^[9]. Consequently, GC patients who are cured through ER or surgery are more vulnerable to the development of SPCs during their lifetime than those who have not curative resection, which may potentially have adverse effects on their overall health. To improve the outcomes of GC patients, timely identification of SPCs is considered an important clinical issue. However, previous studies have focused on the occurrence of metachronous GC after ER of EGC, prevention of metachronous GC, or prediction of the risk thereof^[23,24]. Therefore, our present study of SPCs in EGC patients who underwent ER is both timely and important.

In the present study, the incidence of SPCs in

Table 4 Logistic regression analysis of risk factors in the early gastric cancer group				
	Synchronous cancer		Metachronous cancer	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (> 60 yr)	0.676 (0.082-5.580)	0.589	1.151 (0.278-4.768)	0.846
Sex (male)	0.992 (0.193-5.104)	0.992	1.488 (0.356-6.214)	0.586
Smoking	0.392 (0.091-1.696)	0.210	1.307 (0.316-5.408)	0.712
Alcohol	0.501 (0.116-2.165)	0.355	0.418 (0.101-1.726)	0.228
H. pylori infection	1.294 (0.299-5.594)	0.730	1.553 (0.376-6.421)	0.543

EGC: Early gastric cancer; OR: Odds ratio; CI: Confidence interval; H. pylori: *Helicobacter pylori*.

patients who underwent ER for EGC and surgery for AGC was 9.2% in both groups. This incidence is somewhat higher than those of previous studies, in which the figure ranged from 2% to 8%^[13,15-17]. One reason for the discrepancy may be that all patients enrolled in the present study underwent curative endoscopic or surgical resection. Because the survival rate of early-stage GC patients is good, SPCs are more frequently detected in such patients. Previous studies have also found as much^[15,17,25]. Therefore, the high incidence of SPCs noted in the present study is attributable to the fact that the prognoses of our enrolled patients were expected to be excellent. We have confirmed that long-term survival may contribute to the development of SPCs. Thus, GC patients who have undergone curative resection require particularly careful monitoring for the development of SPCs. Another possible reason for the higher incidence of SPCs noted here is that the evaluation protocol of our center dictates that all GC patients undergo extensive pretreatment work-up including colonoscopy, a chest X-ray, chest and/or abdominal CT, or PET-CT. Patients were also closely monitored through a regular follow-up protocol, contributing to an increase in the detection rates of metachronous cancers.

We compared two groups, EGC and AGC patients who underwent curative resection of primary GC. Some authors have sought to show that genetic

differences contribute to variation in the prognoses of EGC and AGC patients^[26-28]. Several genetic changes in AGC patients may contribute to the development of SPCs. However, our results suggest the possibility that it makes no genetic difference contributing the development of SPC between EGC and AGC, because the SPC incidence after complete resection of the tumor was identical in the two groups.

In the present study, lung cancer (18.4%) was the most common cancer noted in GC patients with SPCs, followed by colorectal cancer (13.2%) and esophageal cancer (13.2%); these figures are similar to those of previous reports^[13,15,17]. Interestingly, more than 25% of SPCs occurred in the GI tract, including the esophagus and colorectum. Development of multiple primary cancers of the digestive tract has been associated with microsatellite instability^[29,30]. It is well known that hereditary non-polyposis colorectal cancer patients tend to develop GC^[31]. Taking the results of previous studies and those of the present study together, it is possible that multiple malignancies in the digestive tract share a common carcinogenic process. Therefore, the high incidence of other GI tract cancers developing in GC patients suggests the need for careful endoscopic evaluation of the whole digestive tract in GC patients. Next, it is possible that the high proportion of smokers (55.4%) in the present study affected the distribution and prevalence of SPCs. Cigarette smoking is a major risk factor for many cancers, especially those of the aerodigestive tract, such as lung and esophageal cancer^[32]. An association between cigarette smoking and the development of GC and colorectal cancer has also been reported^[33,34]. However, in the present study, such detection may have been in large part attributable to the performance of routine pre-operative colonoscopy, and post-operative endoscopic surveillance for GC; these tests detect colorectal and esophageal cancer, respectively. Although no mechanism underlying the association between GC and SPCs has yet been established, careful screening for lung and digestive tract cancers should follow a diagnosis of GC.

We also analyzed risk factors for SPCs in EGC patients who underwent ER. Although previous studies have reported that age, smoking, differentiated histology, and being male are all risk factors of SPC development^[13,16,25], no statistically meaningful risk factors were found in the present study. This may be attributable to our small sample size and short-term follow-up. However, it is conceivable that the characteristics of very early-stage differentiated EGC patients with SPCs differ from those of later-stage or undifferentiated GC patients. This means that clinicians should pay particular attention to SPC development in all EGC patients undergoing ER, regardless of their characteristics.

Our study had some limitations. First, the work

was retrospective in nature and conducted in a single center. Second, our sample size may have been inadequate to allow evaluation of the precise prevalence and distribution of SPCs in EGC patients with ER. However, as we enrolled GC patients who underwent only curative endoscopic or surgical resection, we maintained group homogeneity in terms of analysis of SPC diagnosis. Third, the prevalence of *H. pylori* infection in our patients (62.5%) was low compared to that of previous studies^[35]. This may be attributable to missed histories of *H. pylori* eradication and/or acid suppression therapy, as well as our small sample size. Lastly, because our follow-up period was relatively short, we have likely underestimated the prevalence of SPCs. However, previous studies found that many metachronous primary cancers developed within 3 or 5 years^[15,36]. Therefore, our results are reliable, at least to some extent. Despite these limitations, it is very important that we investigated SPCs developing in very early-stage EGC patients who underwent ER.

In conclusion, SPCs developed rather commonly in GC patients and early detection of SPCs is essential to improve the prognosis and longevity of such patients. Thus, clinicians should consider, at the time of diagnosis of or surveillance for GC, that multiple primary cancers may develop later. In particular, endoscopists should perform close surveillance and establish follow-up programs for SPC detection, as well as cancer recurrence and metachronous GC detection, after use of ER to treat EGC.

COMMENTS

Background

Worldwide, gastric cancer (GC) is the fourth most common cancer and the second-leading cause of cancer-related death, and is especially prevalent in the Asia-Pacific region including Korea. In practice, annual mortality from GC is continuously decreasing in Korea.

Research frontiers

To date, several reports have described excellent short- and long-term outcomes in patients who have undergone curative endoscopic resection (ER) of early gastric cancer (EGC); the 5-year survival rate is 96.8%.

Innovations and breakthroughs

The authors also attempted to identify risk factors that may have contributed to the development of second primary cancers (SPCs) in EGC patients who underwent ER.

Applications

SPCs developed rather commonly in GC patients and early detection of SPCs is essential to improve the prognosis and longevity of such patients.

Peer-review

The manuscript submitted by Kim *et al* evaluates a set of gastric cancer patient data in regards to early and advanced stage gastric cancer and second primary cancer development incidence and location.

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