

Retrospective Study

Clinicopathologic factors and molecular markers related to lymph node metastasis in early gastric cancer

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Abstract

AIM: To analyze predictive factors for lymph node metastasis in early gastric cancer.

METHODS: We analyzed 1104 patients with early gastric cancer (EGC) who underwent a gastrectomy with lymph-node dissection from May 2003 through July 2011. The clinicopathologic factors and molecular markers were assessed as predictors for lymph node metastasis. Molecular markers such as microsatellite instability, human mutL homolog 1, p53, epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) were included. The χ^2 test and logistic regression analysis were used to determine clinicopathologic parameters.

RESULTS: Lymph node metastasis was observed in 104 (9.4%) of 1104 patients. Among 104 cases of lymph node positive patients, 24 patients (3.8%) were mucosal cancers and 80 patients (16.7%) were submucosal. According to histologic evaluation, the number of lymph node metastasis found was 4 (1.7%) for well differentiated tubular adenocarcinoma, 45 (11.3%) for moderately differentiated tubular adenocarcinoma, 36 (14.8%) for poorly differentiated tubular adenocarcinoma, and 19 (8.4%) for signet ring cell carcinoma. Of 690 EGC cases, 77 cases (11.2%) showed EGFR overexpression. HER2 overexpression was present in 110 cases (27.1%) of 406 EGC patients. With multivariate analysis, female gender (OR = 2.281, $P = 0.009$), presence of lymphovascular invasion (OR = 10.950, $P < 0.0001$), diameter (≥ 20 mm, OR = 3.173, $P = 0.01$), and EGFR overexpression (OR = 2.185, $P = 0.044$) were independent risk factors for lymph node involvement.

CONCLUSION: Female gender, tumor size, lymphovascular invasion and EGFR overexpression were predictive risk factors for lymph node metastasis in EGC.

Key words: Receptor; Epidermal growth factor; Stomach neoplasms; Carcinoma; Neoplasm metastasis; Lymph node

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Core tip: We analyzed the factors related lymph node metastasis in early gastric cancer. The factors were not only clinicopathologic finding but also molecular biomarkers. It is unique because of the first study about biomarker related with metastatic lymph node in early gastric cancer.

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INTRODUCTION

Early gastric cancer (EGC) is defined as cancer invasion confined to the mucosa or submucosa, irrespective of lymph node metastasis^[1,2]. Radical gastrectomy with lymph node dissection is the procedure of choice for EGC. Because the prognosis of patients with EGC has improved, the treatment strategies for EGC now include the improvement of quality of life.

Recently, endoscopic mucosal resection (EMR) has been widely accepted as an alternative treatment to open surgery for early gastric cancer without lymph node metastasis (LNM)^[3,4]. EMR preserves gastric function and maintains a high quality of life, while extensive surgery carries a significant risk of morbidity and mortality. However, the indications for EMR are limited to EGC with elevated lesions < 2 cm in diameter and differentiated mucosal cancer without ulceration^[4]. An endoscopic technique has included endoscopic submucosal dissection (ESD) that can be used to remove a larger amount of tumor *en bloc* with a negative safety margin^[5]. In order to apply endoscopic techniques such as EMR/ESD to treat EGC, the absence of lymph node metastasis must be confirmed. Identifying patients at high risk for LNM is important for the application of a minimally-invasive endoscopic technique.

Several molecular markers have been reported to be useful predictors for prognosis of gastric cancer. Microsatellite instability (MSI) is a form of genomic instability that is associated with defective DNA mismatch repair in tumors^[6]. In gastric cancer, the frequency of a microsatellite instability-high (MSI-H) phenotype was reported to range from 8.2% to 37%^[7,8]. Several studies have shown that MSI in gastric cancers was an independent predictive factor of lower LNM and improved survival^[9]. In addition, MSI was directly associated with the function of a mismatch repair gene such as human mutL homolog 1 (hMLH1)^[10]. A study showed that hMLH1 methylation plays a probable role in the advanced stages of tumor

progression^[11]. In addition, mutation of the *p53* gene is one of the most frequent genetic abnormalities associated with gastric cancer; it is associated with lymph node metastasis in EGC^[12]. Moreover, epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) overexpression were associated with disease recurrence and poor prognosis in gastric cancer patients^[13,14]. Thus, the aim of this study was to identify the clinicopathologic factors and molecular markers related lymph node metastasis and to identify high risk patients for minimal invasive therapy.

MATERIALS AND METHODS

Patients

A retrospective review identified 1104 patients with EGC who underwent a radical gastrectomy with regional lymph-node dissection from May 2003 through July 2011 at Seoul National University Bundang Hospital (Seoul, South Korea). This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1308-214-101). Patients were excluded if they had a recurrence or multifocal gastric cancer. The Histologic type was classified according to the World Health Organization classification for gastric cancer. Undifferentiated gastric carcinoma included poorly differentiated tubular adenocarcinoma (PD) and signet ring cell carcinoma (SRC). Well-differentiated (WD) and moderately-differentiated tubular adenocarcinoma (MD) were classified as the differentiated type. The relationship between the various clinicopathologic factors, molecular markers and lymph node metastasis were analyzed to identify the risk factors that were predictive of lymph node metastasis. These factors included: age (< 60 years or ≥ 60 years), sex, tumor size, location (upper third, middle third, or lower third), gross type of lesion (elevated, depressed, flat, or mixed), depth of invasion, lymphatic-vascular involvement, and histological type. Molecular markers such as MSI, hMLH1, p53, EGFR and HER2 were analyzed.

The Japanese classification of gastric carcinoma was used to designate the gross type of tumor: type I (protruded), type II a (superficial elevated), type II b (flat), type II c (superficial depressed), and type III (excavated)^[15]. Type I, type II a, and a combination of these two types with II b were classified as the elevated type. Type II b was defined as a flat type. Type II c and III lesions, as well as the combined lesions, were defined as the depressed type. Both the elevated and depressed types, such as type II a and II c, were classified as mixed types.

Microsatellite instability analysis

DNA was obtained from formalin-fixed, paraffin-embedded surgical sections. DNA was extracted from harvested tumor cells by standard proteinase-K digestion and phenol/chloroform extraction. Normal DNA was extracted from the surrounding normal tissue. Five microsatellite markers originally recommended by a NCI

Table 1 Baseline characteristics of patients with early gastric cancer (*n* = 1104)

Characteristics	Value
Age (yr)	
< 60	546 (49.5)
≥ 60	558 (50.5)
mean ± SD	58.49 ± 11.63
Gender	
Male	709 (64.2)
Female	395 (35.8)
Size of tumor (mm)	
< 20 mm	397 (34.3)
≥ 20 mm	725 (65.7)
mean ± SD	27.8 ± 17.8
Location	
Upper third	125 (11.3)
Middle third	325 (29.4)
Lower third	654 (59.2)
Macroscopic type	
Elevated (I, IIa, I + IIa, IIa + IIb)	86 (7.8)
Flat (IIb)	81 (7.3)
Depressed (IIc, III, IIb + III)	815 (73.8)
Mixed	122 (11.1)
Depth of invasion	
Mucosa	625 (56.6)
Submucosa	
Sm 1	150 (13.6)
Sm 2	157 (14.2)
Sm 3	172 (15.6)
Ulcer	
Absent	958 (86.8)
Present	146 (13.2)
Lymphovascular invasion	
Absent	955 (86.5)
Present	149 (13.5)
Histological type	
Well differentiated	236 (21.4)
Moderate differentiated	398 (36.1)
Poorly differentiated	243 (22.0)
Signet ring cell	227 (20.6)
Lymph-node metastasis	
Negative	1000 (90.6)
Positive	104 (9.4)

Data are expressed as absolute numbers (percentage) or mean ± SD. Sm1: Upper third; Sm2: Middle third; Sm3: Lower third.

workshop on MSI (BAT-25, BAT-26, D2S123, D5S346 and D17S250) were used to analyze paired normal and tumor DNA for MSI. According to the guidelines of the international workshop of NCI, tumors were classified as MSI-H when at least 2 of the 5 markers displayed novel bands, MSI-low (MSI-L) when additional alleles were found with one of the five markers, and microsatellite stable (MSS) when all microsatellite markers examined displayed identical patterns in both tumor and normal tissue.

Immunohistochemistry

Core tissue biopsy specimens (2 mm in greatest dimension) were obtained from individual paraffin-embedded tumors (donor blocks) and arranged in new recipient blocks (tissue microarray blocks), using a trephine apparatus (Superbiochips Laboratories, Seoul, South Korea). Three

separate core samples per tumor were obtained to counter the effects of tumor heterogeneity. Sections (4 mm) were cut from each tissue microarray block, deparaffinized, and dehydrated. Immunohistochemical staining for hMLH1, p53, EGFR, HER-2 was performed as previously described^{16,17}. Immunohistochemical expression of HER-2 was scored using DAKO-Hercep Test kits as follows: score 0, no membrane staining at all or membrane staining in < 10% of tumor cells; score 1+, faint/barely perceptible partial membrane staining in > 10% of tumor cells; score 2+, weak to moderate staining of entire membrane in > 10% of tumor cells; and score 3+, strong staining of entire membrane in > 10% of tumor cells. Scores of 0 and 1+ were considered negative for HER-2 overexpression, and scores of 2+ and 3+ were considered positive. EGFR immunopositivity was scored by using the instructions supplied with the EGFR PharmDx kits; scores of 2+ and 3+ indicated overexpression.

Statistical analysis

To identify the predictive factors of lymph node metastasis, the data were analyzed by using Pearson's χ^2 test and an unpaired Student's *t*-test. Multivariate logistic regression analysis was then performed to evaluate the risk factors for LNM. *P* < 0.05 was considered to be statistically significant. Statistical calculations were performed using IBM SPSS (version 19).

RESULTS

Of the 1104 patients with EGC evaluation, the mean age was 58.5 years (range: 25–86 years). This study included 709 men and 395 women. The mean tumor size was 27.8 mm. Mucosal cancers were 625 (56.6%) and submucosal cancers were 479 (43.4%). According histologic classification, WD was 236 (21.4%), MD was 398 (36.1%), PD was 243 (22.0%), and SRCC was 227 (20.6%). In 104 of 1104 (9.4%) patients, pathologic specimens contained LNM (Table 1).

With molecular marker analysis, 909 (90.1%) of 1,009 EGCs showed MSS. MSI-L was observed in 3.1% and MSI-H was observed in 6.8% of EGCs. Of 764 patients, 48 (6.3%) were deemed to have loss of hMLH1, while 716 (93.7%) had expression of hMLH1. Loss of p53 was seen in 651 (62.2%) of 716 patients. Of 690 EGC cases, 77 cases (11.2%) showed EGFR overexpression. In addition, HER2 overexpression was found in 110 cases (27.1%) of 406 EGC patients (Table 2).

The respective rate of LNM was 3.8% among lesions confined to the mucosa and 16.7% among those infiltrating the submucosa (sm1 cancer, 7.3%; sm2 cancer, 21.6%; sm3 cancer, 20.3%). According to histologic evaluation, the number of lymph node metastasis found was 4 (1.7%) for WD cancer, 45 (11.3%) for MD cancer, 36 (14.8%) for PD cancer, and 19 (8.4%) for SRC cancer. Lymph node metastasis was more frequent in MD than SRC cancers.

With univariate analysis, lymph node metastasis was

Table 2 Molecular markers of patients with early gastric cancer *n* (%)

Molecular markers	Value
Microsatellite instability	
MSS	909 (90.1)
MSI-L	31 (3.1)
MSI-H	69 (6.8)
hMLH1	
Loss	48 (6.3)
Expression	716 (93.7)
p53	
Negative	651 (62.2)
Positive	396 (37.8)
EGFR overexpression	
Negative	613 (88.8)
Positive	77 (11.2)
HER2 overexpression	
Negative	296 (72.9)
Positive	110 (27.1)

MSS: Microsatellite stable; MSI-L: Microsatellite instability-low; MSI-H: Microsatellite instability-high; hMLH1: Human mutL homolog 1; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2.

associated with age (≥ 60 years), female gender, tumor size (≥ 20 mm), macroscopic type, depth of invasion, lymphovascular invasion, and histological type (Table 3). Among molecular markers, EGFR overexpression was significantly associated with lymph node metastasis in early gastric cancer (Table 4). Of these factors, female gender, large tumor size (≥ 20 mm), lymphovascular invasion, and EGFR overexpression were independently associated with lymph node metastasis by multivariate logistic regression analysis (Table 5).

DISCUSSION

Gastric cancer is the second leading cause of cancer-related deaths worldwide^[18], and the highest mortality rates of AGC have been reported in East Asia including Japan and South Korea^[19,20]. In contrast, EGC has a good prognosis with surgical treatment^[21]. In South Korea, the proportion of EGC increased to 47.4% of all diagnosed gastric cancers in 2004^[22]. This was attributed to widely-performed upper gastrointestinal endoscopy screening programs. Because the prognosis of patients with EGC has improved with radical gastrectomy, the treatment strategies for EGC now include the improvement of quality of life. Endoscopic resection such as EMR/ESD can be applied to EGC without lymph node metastasis instead of a radical gastrectomy^[3,4].

Preoperative evaluation of for lymph node metastasis is the most important consideration, when deciding on a treatment strategy for EGC^[23]. A number of researchers have attempted to identify factors predictive of LNM in EGC. The size of the primary tumor, histologic type, lymphatic or venous invasion, and depth of invasion are known to be associated with regional lymph node metastases in EGC^[24-27]. In addition, multi-

Table 3 Univariate analysis of potential risk factors for lymph node metastasis *n* (%)

Factor for lymph node metastasis	Presence (<i>n</i> = 104)	Absence (<i>n</i> = 1000)	<i>P</i> value
Age (yr)			0.049
< 60	61 (58.7)	485 (48.5)	
≥ 60	43 (41.3)	515 (51.5)	
Gender			0.003
Male	53 (51.0)	656 (65.6)	
Female	51 (49.0)	344 (34.4)	
Size of tumor (mm)			< 0.0001
< 20 mm	9 (8.7)	370 (37.0)	
≥ 20 mm	95 (91.3)	630 (63.0)	
Location			0.389
Upper third	9 (8.7)	116 (11.6)	
Middle third	36 (34.6)	289 (28.9)	
Lower third	59 (56.7)	595 (59.5)	
Macroscopic type			< 0.0001
Elevated	7 (6.7)	78 (7.8)	
Flat	1 (1.0)	80 (8)	
Depressed	72 (69.2)	743 (74.3)	
Mixed	24 (23.1)	98 (9.8)	
Depth of invasion			< 0.0001
Mucosa	24 (23.1)	601 (60.1)	
Submucosa	80 (77.0)	399 (39.9)	
Sm1	11 (10.6)	139 (13.9)	
Sm2	34 (32.7)	123 (12.3)	
Sm3	35 (33.7)	137 (13.7)	
Ulceration			0.222
Absent	86 (9.0)	872 (91.0)	
Present	18 (12.1)	128 (85.9)	
Lymphovascular invasion			< 0.0001
Absent	44 (42.3)	911 (91.1)	
Present	60 (57.7)	89 (8.9)	
Histological type			< 0.0001
Well differentiated	4 (3.8)	232 (23.2)	
Moderate differentiated	45 (43.3)	352 (35.2)	
Poorly differentiated	36 (34.6)	208 (20.8)	
Signet ring cell	19 (18.3)	208 (20.8)	

Sm1: Upper third; Sm2: Middle third; Sm3: Lower third.

detector computerized tomography (MDCT) and/or endoscopic ultrasound (EUS) were generally employed to detect metastatic lymphadenopathy. However, the overall diagnostic accuracy of MDCT imaging for LNM in EGC has been reported to range from 37% to 70%, whereas that of EUS was reported to range from 39% to 90%^[28-30]. Reported sensitivity and specificity of EUS to detect LNM in gastric cancer varies widely: sensitivity from 59.5% to 97.2% and specificity from 40.0% to 100%^[1]. Using MDCT, studies showed a sensitivity of 84.2% and a specificity of 84.0%^[1]. Preoperational accuracy of LNM staging using EUS or CT was inadequate for the prediction of the pathological N stage in order to determine the treatment plan.

Not only clinicopathologic factors but also molecular markers can be predictors for lymph node metastasis in gastric cancer patients^[13,14]. The human epidermal growth factor receptor (HER) consists of four transmembrane tyrosine kinase receptors, which have a similar structure, are named ErbB1 (HER1, also known as EGFR), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4)^[31].

Table 4 Univariate analysis of predictive molecular markers for lymph node metastasis *n* (%)

Lymph node metastasis	Presence	Absence	<i>P</i> value
Microsatellite instability			0.412
MSS	89 (90.8)	820 (90.0)	
MSI-L	1 (1.0)	30 (3.3)	
MSI-H	8 (8.2)	61 (6.7)	
hMLH1			0.703
Negative	5 (7.4)	43 (6.2)	
Positive	63 (92.6)	653 (93.8)	
p53			0.773
Negative	59 (60.8)	592 (62.3)	
Positive	38 (39.2)	358 (37.7)	
EGFR overexpression			0.001
Negative	55 (77.5)	558 (90.1)	
Positive	16 (22.5)	61 (9.9)	
HER2 overexpression			0.084
Negative	33 (84.6)	263 (71.7)	
Positive	6 (15.4)	104 (28.3)	

MSS: Microsatellite stable; MSI-L: Microsatellite instability-low; MSI-H: Microsatellite instability-high; hMLH1: Human mutL homolog 1; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2.

Table 5 Multivariate analysis of potential risk characteristics for lymph node metastasis

Characteristics	Odds ratio	95%CI	<i>P</i> value
Gender (female)	2.281	1.228-4.235	0.009
Lymphovascular invasion	10.950	5.418-22.134	< 0.0001
Diameter (\geq 20 mm)	3.173	1.324-7.603	0.010
EGFR	2.185	1.020-4.683	0.044

EGFR: Epidermal growth factor receptor.

Alterations in the expression of receptor tyrosine kinases pathways including EGFR, HER2 were proven to be critical factors for cancer cell survival^[32]. EGFR expression correlated with disease recurrence and poorer survival in gastric cancer patients^[13,14]. Furthermore, HER2 has predictive ability for estimating overall survival in gastric cancer patients and may be useful for determining their prognosis^[14]. However, EGFR positivity, but not HER2 positivity, was associated with poor patient outcomes after a curative resection of stage II/III gastric cancer^[33]. In our study, EGFR overexpression was an independent risk factor for lymph node metastasis in EGC patients. However, HER2 overexpression was not associated with lymph node metastasis. Previous studies have reported EGFR or HER2 overexpression in gastric cancer regardless of stage. Only a handful of studies were limited to early gastric cancer for EGFR or HER2 overexpression.

In this study, the clinicopathologic risk factors for lymph node metastasis were found to be female gender, the presence of lymph-vascular involvement, and tumor size > 2 cm. Lymph-vascular involvement and tumor size were consistent to those reported by previous studies. Interestingly, female gender was an independent predictive factor for LNM; this was a unique finding

compared to a previous report. Male to female gender ratio was 1:1.08 among young patients (age < 40 years) and 2.5:1 in older patients (age > 40 years)^[34]. Age-standardized and cumulative incidence rates of gastric cancer in males are approximately double those of females. This predominance of gastric cancer in males is related to a 10-to-15 year delay in female gastric cancer. The prevalence of gastric cancer in females is similar to that of males only after menopause^[35]. This finding suggested that sex hormones (estrogens) protect woman from gastric cancer. In previous studies in South Korea, the incidence of lymph node metastasis in female EGC was higher than in male EGC and female gender is a predictive risk factor for lymph node metastasis^[36,37]. However, this gender difference of lymph node metastasis in EGC was not shown in other populations. It is extremely difficult to generalize risk factors in all populations.

Some studies have reported a lower rate of LNM and better prognosis in EGC with SRC histology than cancer with PD^[38,39]. Previous studies have reported a rate of LNM with SRC histology to range from 5.7% to 15%^[23,38,40]. Our study found that the rate of LNM with SRC histology was lower than PD cancer and even MD (18.3% *vs* 34.6% and 18.3% *vs* 43.3%). However, the frequency of LNM in mucosal cancer with SRC histology was much higher than mucosal cancer with differentiated histology (0.0% in WD, 2.9% in MD, 10.6% in PD, and 9.6% in SRC). Based on our study, mucosal EGC with SRC histology still had a higher risk of LNM than differentiated EGC. We suggest that the application of EMR/ESD in EGC with SRC was inadequate (Table 6).

This study had some limitations. First, it was a retrospective study based on medical records in a single center. Because of its retrospective nature, we could not collect additional data such as family history, comorbidity, or life style. Second, we analyzed pathologic findings based on postoperative examination of the resected specimen. At the time of endoscopy, the endoscopist subjectively estimated tumor size and reported gross findings and the presence of ulceration; this may have caused a discrepancy between endoscopic findings and pathologic findings. Considering that the preoperative clinical decision was made by endoscopic findings, it may be difficult to apply our pathologic characteristics to determine treatment plans. However, endoscopic resection criteria including tumor size, presence of ulceration and gross finding were based on pathologic evaluation of a surgical specimen that was fixed in formalin^[41]. In addition, endoscopic findings had an inter-observer variability. Third, not all surgical specimens underwent immunohistochemical staining. Finally, there is the problem of selection bias. To perform immunohistochemical staining on all the postoperative specimens in EGC is not cost effective. However, EGFR overexpression correlated with LNM and a poorer prognosis; therefore, EGFR targeted therapy may be considered as adjuvant therapy postoperatively for high risk

Table 6 Lymph node metastasis by depth of invasion and histological type *n* (%)

	Lymph node metastasis		Total
	Presence (<i>n</i> = 104)	Absence (<i>n</i> = 1000)	
Well differentiated			
Mucosa	0 (0.0)	176 (17.6)	176 (0.0)
Submucosa	4 (3.8)	56 (5.6)	60 (6.7)
Moderate differentiated			
Mucosa	3 (0.0)	165 (1.8)	168 (1.8)
Submucosa	42 (40.4)	187 (18.7)	229 (18.3)
Poorly differentiated			
Mucosa	11 (10.6)	112 (11.2)	123 (8.9)
Submucosa	25 (24.0)	96 (9.6)	121 (20.7)
Signet ring cell			
Mucosa	10 (9.6)	147 (14.7)	157 (6.4)
Submucosa	9 (8.7)	61 (6.1)	70 (12.9)

patients with lymph node metastasis in EGC. Despite of these limitations, our study has significance because we analyzed not only clinicopathologic factors but also molecular markers for a high risk of LNM in EGC patients.

Female gender, tumor size, and lymphovascular invasion were predictive risk factors for LNM in EGC. In addition, EGFR overexpression was identified as an independent prognostic factor with multivariate analysis; thus, suggesting that EGFR overexpression is likely to be one of the potential risk factor for LNM in EGC.

COMMENTS

Background

Endoscopic resection can be an alternative treatment to a radical gastrectomy for early gastric cancer without lymph node metastasis. The possible presence of lymph node metastasis is critical for the selection of the appropriate treatment strategy for early gastric cancer.

Research frontiers

This study to determine the predictive factors for lymph node metastasis in early gastric cancer (EGC). This is significant because the first research showed the biomarkers were related with lymph node metastasis in early gastric cancer.

Innovations and breakthroughs

In this study, epidermal growth factor receptor (EGFR) overexpression is one of the potential risk factors for lymph node metastasis in EGC.

Applications

The results suggest that patients who had EGFR overexpression in EGC were considered as high risk group for lymph node metastasis. Physicians pay attention to decide the treatment strategy.

Terminology

Microsatellite instability is the condition of genetic hypermutability that results from impaired DNA mismatch repair. The EGFR is the cell-surface receptor for members of the epidermal growth factor-family of extracellular protein ligands. Human epidermal growth factor receptor 2 is a member of the EGFR/ERBB family.

Peer review

This study analyzed 1104 patients with early gastric cancer who underwent a gastrectomy with lymph-node dissection. The goal was to assess predictive factors for lymph node metastasis in early gastric cancer. This is a general look at a specific tumor work up. The data suggest that EGFR overexpression is likely to be one of the potential risk factors for lymph node metastasis in EGC. This information may be value in helping the management of these subjects.

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