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Extragastric recurrence in patients who underwent surgical resection of stage I gastric cancer

Incidence, risk factors, and value of abdominal computed tomography as a postoperative surveillance method

Su Jin Kim, PhD, MD[a], Tae Un Kim, MD[b,*], Cheol Woong Choi, PhD, MD[a], Dae Gon Ryu, PhD, MD[a]

Abstract

Extragastric recurrence after radical resection of stage I gastric cancer is very rare. We investigated the incidence of extragastric recurrence and risk factors in patients who underwent surgical resection of stage I gastric cancer and evaluated the value of abdominal CT as a surveillance tool. This retrospective study enrolled 914 patients with stage I gastric cancer who underwent surgical resection at a single tertiary hospital. We investigated extragastric recurrence during the follow-up period, and disease-free survival (DFS) was assessed. Over a median follow-up period of 39 months, the overall incidence of extragastric recurrence was 2.2% (20/914). Risk factors for extragastric recurrence included deep submucosal invasion (SM2-3), muscularis propria invasion, and lymph node metastasis (hazard ratio [HR]=10.37, 28.101, and 6.843; *P* = .028, .002, and .001, respectively). Based on the number of risk factors, patients were stratified into 3 subgroups: low-risk (pT1aN0, pT1b(SM1)N0, 496/914), moderate-risk (pT1aN1, pT1b(SM1)N1, pT1b(SM2-3)N0, pT2N0, 369/914), and high-risk (pT1b(SM2-3)N1, 49/914). DFS was significantly longer in the low-risk group, followed by the moderate-risk and high-risk groups. We propose that postoperative CT surveillance should be omitted for stage 1A cases involving the mucosa and SM1 because of the extreme rarity of extragastric recurrence.

Abbreviations: AJCC = American Joint Committee on Cancer, B = bone, CI = confidence interval, CT = computed tomography, DFS = disease-free survival, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, HR = hazard ratio, LN = lymph node, LNM = lymph node metastasis, NCCN = National Comprehensive Cancer Network, OS = overall survival, P = peritoneum, SM = submucosa, WHO = World Health Organization.

Keywords: computed tomography, extragastric recurrence, gastric cancer, surgical resection

1. Introduction

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide.[1] Although the 5-year overall survival (OS) rate is 62%–71% in patients treated with surgery, a significant proportion of patients relapse after resection.[2,3] Populations from East Asia present a higher incidence of gastric cancer than those from other parts of the world. Over the past several decades, nationwide screening programs conducted in Japan and South Korea have contributed to an increase in early-stage gastric cancer detection rates.[4] As the proportion of early-stage gastric cancer cases increased, the overall long-term survival of patients with gastric cancer improved.

Patients with stage I gastric cancer generally have excellent prognosis after curative (R0) resection. The 5-year survival rates for stage IA and IB tumors treated with surgery were reported to be 94% and 88%, respectively.[5] However, recurrence still occurs in a certain proportion of patients with stage I gastric cancer who have received curative resection. Hence, identifying the relevant risk factors for extragastric recurrence in patients

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The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Pusan National University Yangsan Hospital (IRB no. 05-2022-139).

[a] Department of Internal Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea, [b] Department of Radiology, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea.

**Correspondence: Tae Un Kim, Department of Radiology, Medical Research Institute, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Beomeo-ri Mulgeum-eup, Yangsan-si, Gyeongsangnam-do 50612, Republic of Korea (e-mail: pmcac@hanmail.net).*

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with stage I gastric cancer is crucial for predicting prognosis and future management strategies.

Various methods, such as assessment of tumor markers and imaging studies, have been used to detect extragastric recurrence. Among them, abdominal computed tomography (CT) has been the most popular imaging modality for diagnosing recurrent gastric cancer under many professional guidelines.[6–9] However, there is no consensus regarding postoperative CT surveillance for gastric cancer. In particular, routine abdominal CT without specific indications may have limited value and impose unnecessary costs and burdens on patients such as radiation exposure, which has a low incidence of recurrence.

Recently, there have been several reports regarding the role of CT surveillance based on the risk of extragastric recurrence in early gastric cancer (EGC) after endoscopic submucosal dissection (ESD) or surgical resection.[10–15] Unlike stage I gastric cancer, EGC is a heterogeneous group composed of various stages because it is defined as gastric cancer limited to the mucosa or submucosa, irrespective of the presence of lymph node metastasis (LNM). As TNM staging is the most important prognostic factor for gastric cancer, postoperative follow-up strategies are based on this system. Therefore, it is necessary to verify the efficiency of follow-up CT only for patients with stage I gastric cancer based on TNM staging after surgical resection.

However, to our knowledge, no study has examined the efficiency of routine abdominal CT as part of the postoperative surveillance protocol for patients with stage I gastric cancer. Therefore, this study aimed to investigate the incidence of extragastric recurrence, risk factors, and value of abdominal CT as a surveillance method in patients who have undergone curative resection of stage I gastric cancer.

2. Methods

2.1. Patients

Between March 2009 and December 2016, 981 patients with stage I gastric cancer who underwent surgical resection were enrolled in this study. The standard operation for gastric cancer was total or subtotal gastrectomy with D1 + β or more lymph node dissection. Among these patients, 43 were excluded for the following reasons: having another concurrent malignancy (n=21); having recurrent cancer or remnant stomach cancer (n=6); having a follow-up period <1 year (n=16). The remaining 914 patients were included (Fig. 1).

The following clinicopathological variables were collected: age and sex of the patients, type of surgery (total or subtotal gastrectomy), and pathological information of gastric cancer (multiplicity, size, location, World Health Organization [WHO] histological subtype, Lauren classification, pathologic T [pT] stage, and pathologic N [pN] stage). The depth of invasion was categorized as mucosal or submucosal. Submucosal invasion was divided into submucosa (SM) 1 (submucosal invasion ≤500 μm from the muscularis mucosae) and SM2-3 (submucosal invasion >500 μm from the muscularis mucosae) types. When multiple synchronous cancers were present, cancer with the deepest invasion depth or largest size was selected for analysis. Tumor location was categorized as the upper, middle, or lower third of the stomach, according to the center of the tumor. The histological classification of stage I gastric cancer was performed using the WHO and Lauren classifications. The WHO histological subtype is subdivided as differentiated (tubular adenocarcinoma or papillary adenocarcinoma) or undifferentiated (poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma) types.[16,17] When the tumor had a mixed histological type, it was classified according to its predominant component (≥50%). The Lauren classification is subdivided into diffuse, intestinal, and mixed types.[16] Pathological staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system.

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB no.: 05-2022-139), and written informed consent was obtained from all patients.

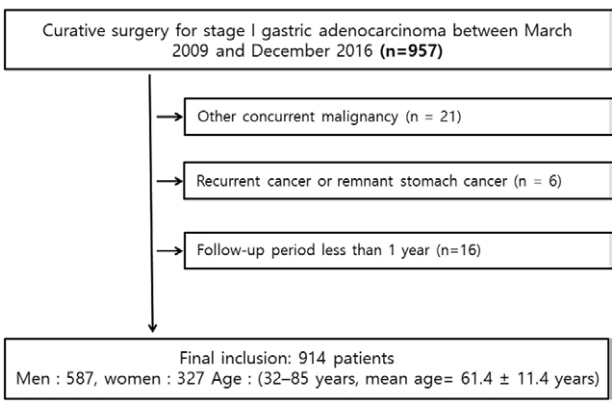

Figure 1. Flow diagram of the study population.

2.2. Follow-up assessments

Regular follow-up included physical examinations, serological tests, assessment of tumor markers, and abdominal CT scans. Abdominal CT and gastroscopy were performed every 6 months for the first 2 years and annually for the next 3 years. These were also implemented when a recurrence was suspected.

Extragastric recurrence was defined as regional recurrence in the perigastric lymph nodes and distant metastases irrespective of intragastric lesions. Recurrence in the extragastric field was detected on abdominal CT findings. When recurrence was suspected on abdominal CT, ultrasonography-guided or endoscopic-ultrasonography-guided biopsies were performed for confirmation. Bone scintigraphy, chest CT, or positron emission tomography-CT was performed for suspected metastasis to the bone, pleura, and/or other sites. Disease-free survival (DFS) was calculated from the date of surgery to the date when the first follow-up image showing evidence of extragastric recurrence (event) or the last follow-up image without evidence of tumor recurrence (censored) was obtained. As this study aimed to assess the role of imaging surveillance, we focused on extragastric recurrence that was identifiable on imaging examinations but not through death.

2.3. Statistical analysis

Continuous variables are presented as means ± standard deviations or medians with the 25th and 75th percentiles. Categorical variables are expressed as counts with percentages. Univariate and multivariate analyses for DFS were performed using Cox regression analysis with a stepwise backward method. Parameters with a P value <.05 on univariable analysis were included in multivariable analysis. DFS rates were estimated using the Kaplan–Meier method with log-rank analysis. The Bonferroni correction was used to assess differences among the 3 groups, and a P value <.05/6 was considered statistically significant. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 914 patients who underwent curative gastrectomy are summarized in Table 1. The mean age was 61.4 years, and 64.2% of patients (n=587) were male. Subtotal gastrectomy was performed in 88.3% of patients. The mean tumor size was 2.8 cm. In terms of the WHO histological subtypes, differentiated tumors were observed in 54.3% of patients while undifferentiated tumors were observed in 45.7%. Regarding the Lauren classification, 46.7% of patients had intestinal-type tumors while the remaining tumors were either diffuse or of the mixed type. Most tumors were in the lower third of the stomach (n=536, 58.6%). Patients were divided into 4 groups based on pathologic T stage (pT1a, pT1b(SM1), pT1b(SM2-3), and pT2); there were 424 (46.4%), 89 (9.7%), 289 (31.6%), and 112 (12.2%) patients in each group, respectively. Regarding the pathologic N stage, there were 849 (92.9%) and 65 (7.1%) patients in the pN0 and pN1 groups, respectively. Based on the current 8th AJCC staging system, most of the patients had stage IA tumors (n=737, 80.6%).

3.2. Extragastric recurrence after curative resection

The median follow-up duration was 39 (interquartile range, 38–48) months. Extragastric recurrences were detected in 2.2% (20/914) of the patients. The estimated median DFS was 37 (95% CI, 20.0–40.9) months. The lymph nodes and liver were the 2 most common organs involved in extragastric recurrence (Table 2). All involved lymph nodes were distant metastases. Confirmation of extragastric recurrence was based on pathological results in 5 patients and follow-up imaging in 15 patients. Patients with extragastric recurrence received palliative chemotherapy (n=15), supportive care (n=3), or unknown treatment because of follow-up loss (n=2).

3.3. Prediction of extragastric recurrence

The results of the univariable and multivariable Cox regression analyses are summarized in Table 3. In univariable analysis, large size (HR, 1.148; 95% CI, 1.009–1.306; P = .036), SM2-3 invasion (HR, 17.36; 95% CI, 2.256–133.554; P = .006), muscularis propria invasion (HR, 24.133; 95% CI, 2.962–196.624; P = .003), and LNM (HR, 7.154; 95% CI, 2.851–17.949; P = .001)

Table 1

Clinicopathologic characteristics of patients.

Characteristic	
Age (years)*	61.4 ± 11.4
Male	587 (64.2)
Type of surgery	
Subtotal gastrectomy	807 (88.3)
Total gastrectomy	107 (11.7)
Tumor location	
Upper third	108 (11.8)
Middle third	270 (29.5)
Lower third	536 (58.6)
Size (cm)**	2.8 (1.8, 4.2)
Lesion number	
Single	878 (96.1)
Multiple	36 (3.9)
WHO histological subtype	
Differentiated	496 (54.3)
Undifferentiated	418 (45.7)
Lauren classification	
Intestinal	427 (46.7)
Diffuse	400 (43.8)
Mixed	87 (9.5)
Pathologic T stage	
pT1a	424 (46.4)
pT1b, SM1	89 (9.7)
pT1b, SM2-3	289 (31.6)
pT2	112 (12.2)
Pathologic N stage	
pN0	849 (92.9)
pN1	65 (7.1)
Pathologic Stage	
Stage IA	737 (80.6)
Stage IB	177 (19.4)

Unless indicated, data are numbers of patients, and numbers in parentheses are percentages.

* Data are mean ± standard deviation.

** Data are median (interquartile range).

Table 2

Clincopathologic characteristics of the patients with extragastric recurrence.

Patient	Sex/age (y)	TNM	WHO/Lauren	Size(cm)	Involvedorgan	Recur time (mo)
1	M/81	T1b(SM2-3)N1	Undifferentiated/Diffuse	2	Liver	60
2	M/69	T1b(SM2-3)N0	Undifferentiated/ Diffuse	2	P	38
3	M/77	T1aN1	Differentiated/ Intestinal	1.7	Liver, B	32
4	M/38	T2N0	Differentiated/ Diffuse	6	Liver	36
5	F/72	T2N0	Undifferentiated/ Intestinal	3	P	22
6	F/47	T2N0	Undifferentiated/ Diffuse	2	P, rectum	44
7	M/77	T1b(SM2-3)N0	Differentiated/ Intestinal	2.7	LN	39
8	M/67	T1b(SM2-3)N1	Differentiated/ Intestinal	5	P, LN	43
9	M/60	T1b(SM2-3)N0	Undifferentiated/ Intestinal	1.7	Bone	47
10	F/59	T2N0	Differentiated/ Diffuse	7	LN	19
11	M/69	T1b(SM2-3)N0	Differentiated/ Intestinal	3	LN	41
12	M/77	T1b(SM2-3)N1	Differentiated/ Intestinal	5	Liver	17
13	M/80	T1b(SM2-3)N0	Differentiated/ Intestinal	4.3	LN, Ureter	50
14	M/80	T1b(SM2-3)N0	Differentiated/ Intestinal	3.9	Liver	28
15	F/63	T2N0	Undifferentiated/ Intestinal	15	LN, Pleura, B	11
16	F/47	T1b(SM2-3)N1	Undifferentiated/ Diffuse	6	LN	34
17	M/63	T1b(SM2-3)N1	Undifferentiated/ Diffuse	5	Liver	32
18	M/44	T1b(SM2-3)N1	Undifferentiated/ Diffuse	5	LN	25
19	M/67	T2N0	Undifferentiated/ Diffuse	4	Duodenum	38
20	M/79	T2N0	Undifferentiated/ Intestinal	2	LN, liver	52

B = bone, LN = lymph node, P = peritoneum.

were associated with shorter DFS. In multivariate analysis, SM2-3 invasion (HR, 10.37; 95% CI, 1.283–83.841; P = .028), muscularis propria invasion (HR, 28.101; 95% CI, 3.424–230.653; P = .002), and LNM (HR, 6.843; 95% CI, 2.239–20.901; P = .001) were independent predictors of shorter DFS.

Kaplan–Meier survival curves based on tumor depth and LNM are presented in Figure 2. Patients with mucosal and SM1 invasion showed a longer DFS than those with muscularis propria invasion (P < .0001; Fig. 2A) or SM2-3 invasion (P < .0001; Fig. 2A). DFS (P = .4953, Fig. 2A) did not differ significantly between patients with muscularis propria invasion and those with SM2-3 invasion. Patients with LNM had a significantly shorter DFS than those without LNM (P < .0001; Fig. 2B).

Based on the number of risk factors for extragastric recurrence, the 914 patients with stage I gastric cancer were stratified into 3 subgroups: the low-risk (pT1aN0, pT1b(SM1)N0, 496/914), moderate-risk (pT1aN1, pT1b(SM1)N1, pT1b(SM2-3)N0, pT2N0, 369/914), and high-risk groups (pT1b(SM2-3)N1, 49/914). Figure 3 shows that the low-risk group had the longest DFS, which was followed by the moderate-risk group and the high-risk group. There was no extragastric recurrence in patients in the low-risk group (n=496).

4. Discussion

It is controversial whether there might be a survival benefit for regular CT surveillance to detect the recurrence of EGC in recent years. Several retrospective studies have failed to demonstrate an improvement in survival with intensive postoperative surveillance[8,18,19] However, some studies have shown that asymptomatic patients who receive active surveillance have longer postrecurrence and overall survival than do symptomatic patients who are given symptom-driven follow-up.[20–22] There was no randomized clinical trial to examine the efficacy of surveillance programs and schedules after curative gastrectomy to improve the OS rates. Nevertheless, regular and systematic follow-up with cross-sectional imaging modalities is recommended by major guidelines, and many cancer centers have established their own follow-up protocols that include these methods.[23–25]

Therefore, follow-up surveillance CT programs for stage I gastric cancer differ according to major guidelines. The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology guidelines recommend abdominal CT based on symptoms to assess recurrence in patients with Stage I disease.[23,24] In contrast, the Japanese Society for Gastric Cancer advocates a more intensive follow-up CT examination for patients with stage I gastric cancer. They recommended the use of imaging tests every 6 to 12 months for the first 2 years and then annually for up to 5 years for these patients.[25]

Although CT is an effective modality to diagnose extragastric recurrence, it inevitably requires radiation exposure, medical costs, and potential adverse reactions associated with iodinated contrast media.[6,26,27] In particular, cumulative radiation from CT significantly increases the incidence and mortality of cancer.[28,29] Kim et al reported a significant increase in the risk of subsequent primary malignancies from 9 or more CT scans.[30] Therefore, it is necessary to obtain minimal CT images while maintaining the benefits of regular CT surveillance.

As expected, patients with stage I gastric cancer typically have an excellent prognosis, and there is a low risk of relapses or distant metastases.[31] Yago et al reported that the 5-year DFS rates for stage IA and IB gastric cancer were 99.0% and 97.0%, respectively.[32] Consistent with the findings of previous studies, our study confirmed the rarity of extragastric recurrence after curative resection of stage I gastric cancer. During the median follow-up period of 39 months after gastrectomy, extragastric recurrence occurred in 2.18% (20/914) of the patients. In addition, 4786 CT examinations were performed to detect only 20 cases of extragastric recurrence. Therefore, considering the very low incidence of extragastric recurrence in patients with stage I gastric cancer and the increasing risk of radiation exposure, intense surveillance via abdominal CT may not be clinically appropriate for all patients.

All extragastric recurrences in our study were distant metastases. Several recent studies have also reported that the most

Table 3

Predictors of extragastric recurrence after surgical resection of stage I gastric cancer.

	Univariate analysis		Multivariate analysis	
Characteristics	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age	1.03 (0.99, 1.08)	.137	…	…
Sex				
M	1	Reference	…	…
F	1.64 (0.59, 4.50)	.341	…	…
Type of surgery				
Subtotal gastrectomy	1	Reference	…	…
Total gastrectomy	0.71 (0.16, 3.07)	.646	…	…
Tumor location				
Upper third	1	Reference	…	…
Middle third	0.98 (0.37, 2.62)	.970	…	…
Lower third	0.78 (0.18, 3.50)	.749	…	…
Size	1.15 (1.01, 1.30)	**.036**	1.05 (0.90, 1.22)	.539
Lesion number				
Single	1	Reference	…	…
Multiple	2.55 (0.59, 10.98)	.210	…	…
WHO histological subtype	1.30 (0.54, 3.15)	.556	…	…
Differentiated	1	Reference	…	…
Undifferentiated				
Lauren classification	1	Reference	…	…
Intestinal	0.91 (0.38, 2.20)	.834	…	…
Diffuse	…	…	…	…
Mixed				
Pathologic T Stage	1	Reference	1	Reference
pT1a	…	…	…	…
pT1b, SM1	17.36 (2.26, 133.55)	**.006**	10.37 (1.28, 83.84)	**.028**
pT1b, SM2-3	24.13 (2.96, 196.62)	**.003**	28.10 (3.42, 230.65)	**.002**
pT2				
Pathologic N stage	1	Reference		Reference
pN0	17.15 (2.85, 17.95)	**<.001**	1	**.001**
pN1			16.84 (2.24, 20.90)	

P values < .05 are indicated in bold.
CI = confidence interval.

common recurrence patterns in patients with gastric cancer are hematogenous spread to other organs, such as the liver, and peritoneal metastasis.[33,34] Therefore, palliative chemotherapy is the primary treatment after relapse. Considering the appropriate risk-benefit balance in a CT surveillance program for patients with stage I gastric cancer after radical surgery, it is essential to establish optimal risk stratification and CT surveillance strategies.

Our study showed that SM2-3 invasion, muscularis propria invasion, and LNM were significantly associated with extragastric recurrence in our patients. These results were consistent with those of previous studies, which also showed that T and N stages were significant independent prognostic factors for gastric cancer.[35,36] We classified patients with stage I gastric cancer into the low-, moderate-, and high-risk groups according to the risk of extragastric recurrence, and each group had a statistically significantly different risk of extragastric recurrence. Notably, no extragastric recurrence was observed in patients in the low-risk group (pT1aN0 and pT1b(SM1)N0) (n=496). According to the risk scoring system for predicting extragastric recurrence of EGC after radical surgical resection presented by Seo et al,[14] postoperative CT surveillance should be avoided in the low-risk group. Among the variables used in the risk scoring system in this study, the 2 with the highest scores were beyond the ESD indications and LNM, which is substantially similar to the results of our study. According to a study by Bae et al,[15] patients with pT1aN0 gastric cancer demonstrated significantly lower risks of extragastric recurrence (2 of 2196 patients), suggesting that postoperative imaging surveillance for extragastric recurrence may be spared. This was consistent with our study results, except that pT1b (SM1)N0 gastric cancer was included in the low-risk group in our study. Based on our observations and those of previous studies, routine abdominal CT surveillance may be unnecessary for patients with stage 1A gastric cancer involving mucosal and SM1 invasion. This strategy may be feasible for patients who received endoscopic resection for early gastric cancer with negligible lymph node metastasis risk.

This study had several limitations. First, selection bias was inevitable because of its retrospective nature. We enrolled all consecutive patients to reduce selection bias. Second, our institution had a routine postoperative surveillance protocol that was adhered to for most patients; however, the follow-up intervals for CT may have varied slightly between clinicians. Third, the median follow-up period may not have been long enough to detect late recurrences more than 5 years after gastrectomy. Approximately 80% of these recurrences are experienced in

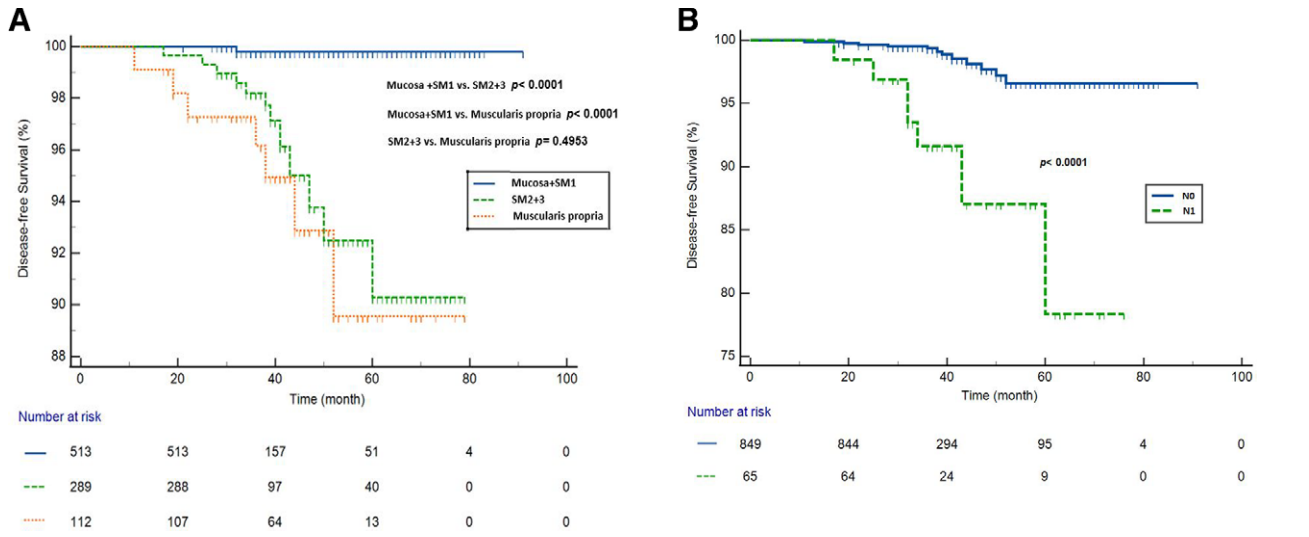

Figure 2. Kaplan–Meier survival curves based on tumor depth and lymph node metastasis (LNM) in the stage I gastric cancer. (A) Patients with mucosal and SM1 invasion showed significantly longer disease-free survival (DFS) than those with muscularis propria invasion ($P < .0001$) or SM2-3 invasion ($P < .0001$). DFS was not significantly different between patients with muscularis propria invasion and those with SM2-3 invasion ($P = .4953$); (B) Patients with LNM had significantly shorter DFS than those without LNM ($P < .0001$).

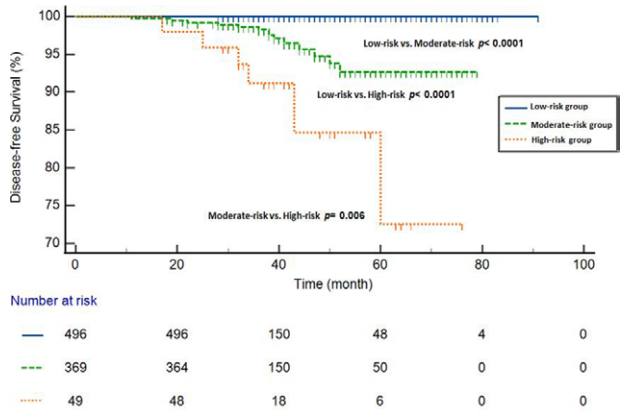

Figure 3. Disease-free survival (DFS) curves of low-, moderate-, and high-risk patients with stage I gastric cancer based on the number of risk factors for predicting extragastric recurrence. DFS differed significantly among the 3 subgroups of patients with stage I gastric cancer according to the Kaplan–Meier method and log-rank tests.

the first 2 years and, thus, our study could cover a high-risk period. Fourth, although the study population was large, the number of extragastric recurrences was relatively small, which may have affected the statistical power. Finally, we did not perform an external validation of patients from other institutions. Therefore, an external validation study with a larger study population is required to generalize the results.

5. Conclusions

In conclusion, SM2-3 invasion, muscularis propria invasion, and LNM are significant factors for predicting extragastric recurrence after surgical resection of stage I gastric cancer. Based on the follow-up data of our patients, we suggest that postsurgical CT surveillance should be avoided for stage 1A gastric cancer cases involving mucosal and SM1 invasion given that extragastric recurrence is extremely rare. This stratified CT surveillance program may contribute to risk-based, personalized management that can minimize risks such as radiation exposure from routine CT follow-up programs.

Author contributions

Conceptualization, SJK; methodology, SJK; formal analysis, TUK; investigation, TUK; resources, CWC; data curation, DGR; writing—original draft preparation, TUK; writing—review and editing, SJK; supervision, TUK. All authors have read and agreed to the published version of the manuscript.

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