J Gastric Cancer. 2020 Sep;20(3):328-336
https://doi.org/10.5230/jgc.2020.20.e30
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Original Article

Check for updates

Prognostic Factors in Stage IB Gastric Cancer after Surgical Resection

Byunghyuk Yu [1,*], **Ji Yeon Park** [1,2], **Ki Bum Park** [1,2], **Oh Kyoung Kwon** [1,2], **Seung Soo Lee** [2,3], **Ho Young Chung** [2,3]

[1]Gastric Cancer Center, Kyungpook National University Chilgok Hospital, Daegu, Korea
[2]Department of Surgery, School of Medicine, Kyungpook National University, Daegu, Korea
[3]Department of Surgery, Kyungpook National University Hospital, Daegu, Korea

OPEN ACCESS

Received: May 14, 2020
Revised: Aug 8, 2020
Accepted: Sep 8, 2020

Correspondence to
Ji Yeon Park
Gastric Cancer Center, Kyungpook National University Chilgok Hospital, 807 Hoguk-ro, Daegu 41404, Korea.
E-mail: jybark99@hanmail.net

*Current Address: Department of Critical Care Medicine, Samsung Medical Center, Seoul, Korea

ORCID iDs
Byunghyuk Yu
https://orcid.org/0000-0001-8502-9352
Ji Yeon Park
https://orcid.org/0000-0002-6178-7906
Ki Bum Park
https://orcid.org/0000-0001-5404-5667
Oh Kyoung Kwon
https://orcid.org/0000-0002-3614-8563
Seung Soo Lee
https://orcid.org/0000-0003-4398-6300
Ho Young Chung
https://orcid.org/0000-0001-7264-0865

ABSTRACT

Purpose: The standard treatment for stage IB gastric cancer is curative surgery alone, but some patients show poor survival with disease recurrence after curative surgery. The aim of this study was to identify prognostic factors of recurrence and long-term survival in patients with stage IB gastric cancer after surgery.
Materials and Methods: We retrospectively reviewed data from 253 patients with stage IB gastric cancer who underwent gastrectomy between 2011 and 2016 at Kyungpook National University Chilgok Hospital and analyzed the clinicopathological characteristics associated with recurrence and survival.
Results: Fourteen patients experienced recurrence with a mean follow-up of 54.1 months. Two of these patients had locoregional recurrence and 12 patients had systemic recurrence. The median interval between the operation day and the day of recurrence was 11 months (range 4–56 months). Multivariate analysis revealed that lymphatic vessel invasion (LVI) (hazard ratio [HR], 3.851; 95% confidence interval [CI], 1.264–11.732) and the elderly (age≥65) (HR, 3.850; 95% CI, 1.157–12.809) were independent risk factors for recurrence after surgery. The LVI (HR, 3.630; 95% CI, 1.105–11.923) was the independent prognostic factors for disease-specific survival (DSS). The 5-year DSS rates were 96.8% in patients who did not have LVI, and 89.3% in patients who had LVI.
Conclusions: This study shows that LVI was associated with recurrence and poor survival in patients with stage IB gastric cancer after curative gastrectomy. Patients diagnosed with LVI require careful attention for systemic recurrence during the follow-up period.

Keywords: Stomach neoplasm; Prognosis; Gastrectomy; Lymphatic metastasis

INTRODUCTION

Gastric cancer is a major cause of cancer-related death worldwide, but the incidence and mortality have decreased during the last several decades [1]. As the proportion of early gastric cancer has increased in East Asia, particularly in South Korea, because of national cancer screening programs and examinations [2], overall long-term survival of patients with gastric cancer has improved.

jgc Journal of Gastric Cancer

Authors Contributions

Conceptualization: Y.B., P.J.Y.; Data curation: Y.B., P.J.Y., P.K.B., K.O.K.; Formal analysis: Y.B., P.J.Y., L.S.S.; Investigation: Y.B., P.J.Y., P.K.B., K.O.K., C.H.Y.; Methodology: Y.B., P.J.Y.; Resources: P.J.Y., P.K.B., K.O.K.; Supervision: P.J.Y.; Validation: P.J.Y., P.K.B., K.O.K., L.S.S., C.H.Y.; Visualization: Y.B., P.J.Y.; Writing - original draft: Y.B., P.J.Y.; Writing - review& editing: Y.B., P.J.Y., P.K.B., K.O.K., L.S.S., C.H.Y.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

The standard treatment for stage I gastric cancer is curative resection alone without adjuvant chemotherapy according to the Korean and Japanese treatment guidelines [3,4], but a certain proportion of patients with stage I gastric cancer develop a recurrence after gastrectomy and lymph node dissection. Stage I gastric cancer is divided into stage IA and stage IB according to the 7th edition of the American Joint Committee on Cancer (AJCC), and stage IB results in relatively poorer survival outcomes than stage IA [5,6].

Some studies have reported prognostic factors for stage IB gastric cancer. Old age, histologically undifferentiated-type tubular adenocarcinoma, and venous invasion are independent risk factors for recurrence and prognosis in these studies [7-9]. However, these studies were based on the 6th edition of the AJCC staging system in which gastric cancer invading serosa without regional lymph node metastasis (T3N0) or invading mucosa/submucosa with 3–6 metastatic regional lymph nodes (T1N2) was included in stage IB, but it is classified as stage II gastric cancer in the AJCC 7th edition and also in the subsequent 8th edition [10-12].

The aim of this study was to identify the risk factors associated with recurrence and the prognosis for long-term survival in patients with stage IB gastric cancer based on the AJCC 8th edition after curative gastrectomy.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the prospectively established gastric cancer database of 2,827 patients with primary gastric cancer who underwent curative gastrectomy at Kyungpook National University Chilgok Hospital between January 2011 and December 2016. All patients underwent gastrointestinal endoscopy and abdominal computed tomography (CT) before surgery, and clinical staging was performed by endoscopy and abdominal CT reading. CT reading was mainly performed by radiologists and once again by surgeons before surgery. The positron emission tomography (PET)/CT was performed when CT reading suspected distant metastasis such as peritoneal seeding or paraaortic metastatic lymph nodes. All patients had undergone gastrectomy and D1+ or D2 lymph node dissection, and 263 patients (9.3%) were pathologically diagnosed with stage IB gastric cancer according to the AJCC 8th edition. Among these patients, 1 patient had synchronous colon cancer, 6 patients underwent neoadjuvant or adjuvant chemotherapy due to clinical trials, 2 patients were not followed up within 6 months after surgery, and 1 patient died due to postoperative bleeding within 1 month after surgery. These 10 patients were excluded and the remaining 253 patients were included in this study. This study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUCH 2018-07-017).

Follow-up and diagnosis of disease recurrence

Patients who underwent gastrectomy visited the outpatient clinic every 3 months for the first year after surgery, every 6 months for the next 2 years, and annually thereafter. These patients underwent hematological tests, physical examinations, and a chest X-ray at every visit. Chest and abdominal CT scans were performed every 6 months for 3 years, and annually thereafter, and a gastroscopic examination was performed annually for 5 years. These tests were performed annually 5 years after the operation, if desired by the patients. Recurrence was diagnosed based on a CT scan or gastroscopy. When the diagnosis was uncertain, PET/CT was also performed.

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer

Histological evaluation

The depth of the tumor and lymph node metastasis were evaluated according to the AJCC staging manual 8th edition. The histological type of the tumors was determined according to the World Health Organization classification. Well-differentiated tubular adenocarcinoma, moderately differentiated tubular adenocarcinoma, and papillary adenocarcinoma were classified as differentiated tumors, and the other types, such as poorly differentiated adenocarcinoma and poorly cohesive carcinoma, were classified as undifferentiated tumors. Lymphatic vessel invasion (LVI) was defined as detecting tumor cells within the endothelium lined space or within a smooth muscle cell-lined space on hematoxylin and eosin (H&E) stained tissues. Venous invasion and nerve invasion were also evaluated on H&E-stained specimens.

Statistical analysis

The χ^2 test, Fisher's exact test, and linear by linear association were used to compare categorical variables, and the Student's t-test was used to compare continuous variables. A logistic regression model was used for the multivariate analysis to identify predictors of recurrence. Disease-specific survival (DSS) was defined as the time from surgery to the date of death from gastric cancer or to the last follow up date for patients who were still alive. Recurrence-free survival (RFS) was defined as the time from surgery to the time of recurrence of cancer or death due to any cause. Overall survival (OS) was defined as the time from surgery to the time of death from any cause. The 5-year DSS, RFS and, OS rates were calculated using the Kaplan–Meier method and compared with the log-rank test. Cox's proportional hazard model was used to identify predictors of survival. A P-value<0.05 was considered significant. We performed univariate analysis on variables that showed significant differences according to recurrence after gastrectomy. Significant risk factors identified by univariate analysis (P<0.1) and variables known as prognostic factors in other studies [13] were further assessed by multivariate analysis using backward elimination. The statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the patients was 61.4±11.5 years. In total, 169 patients (66.8%) were male and 84 were female (33.2%). Fifty-seven patients (22.5%) underwent total gastrectomy, 194 patients (76.7%) underwent distal gastrectomy, 1 patient underwent proximal gastrectomy and 1 patient underwent pylorus-preserving gastrectomy. D1+ lymph node dissection was performed in 14 patients (5.5%), and D2 lymph node dissection was performed in 239 patients (94.5%). The pathological stage was classified as T2N0 in 163 patients (62.9%) and T1N1 in 96 patients (37.1%). The mean number of retrieved lymph nodes was 40.3±13.5.

The mean follow-up period was 54.1±18.4 months. Among the patients, 14 (5.5%) experienced recurrence, and the median time to recurrence after surgery was 11 months (range 4–56 months). **Table 1** shows the clinicopathological characteristics of the recurrence group compared to the non-recurrence group. Less than 3% of patients had elevated tumor markers, and none of the patients who had elevated tumor markers experienced a recurrence. The extent of surgery and the extent of lymph node dissection was not different between the 2 groups. Patients in the recurrence group were significantly older (P=0.036) and demonstrated LVI more frequently (P=0.014). The number of retrieved lymph nodes and tumor differentiation were marginally significant between the two groups (P=0.071 and 0.053, respectively).

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer

Table 1. Comparison of clinicopathological characteristics according to recurrence after surgery in patients with stage IB gastric cancer

Variables	Without recurrence (n=239)	With recurrence (n=14)	P-value
Sex			0.152
Male	157 (65.7)	12 (85.7)	
Female	82 (34.3)	2 (14.3)	
Age	61.04±11.44	67.64±10.22	0.036
Elevated CEA	5 (2.2)	0 (0.0)	>0.999
Elevated CA19-9	3 (1.3)	0 (0.0)	>0.999
Elevated CA125	3 (1.3)	0 (0.0)	>0.999
Extent of surgery			0.347
Total gastrectomy	56 (23.4)	1 (7.1)	
Distal gastrectomy	181 (75.7)	13 (92.9)	
Others	2 (0.8)	0 (0.0)	
Extent of lymph node dissection			>0.999
D1+	14 (5.8)	0 (0.0)	
D2	225 (94.2)	14 (100.0)	
Pathologic stage			0.150
T2N0	155 (64.9)	6 (42.9)	
T1N1	84 (35.1)	8 (57.1)	
Depth of tumor invasion			0.115
T1a (mucosa)	13 (5.4)	0 (0.0)	
T1b (submucosa)	71 (29.7)	8 (57.1)	
T2 (muscularis propria)	155 (64.9)	6 (42.9)	
Number of retrieved LNs	40.67±13.50	33.93±13.26	0.071
Tumor size (mm)	3.01±1.45	2.94±1.32	0.847
Histology			0.053
Differentiated	91 (38.2)	9 (64.3)	
Undifferentiated	147 (61.8)	5 (35.7)	
Lymphatic vessel invasion			0.014
Negative	179 (74.9)	6 (42.9)	
Positive	60 (25.1)	8 (57.1)	
Venous invasion			>0.999
Negative	226 (94.6)	14 (100.0)	
Positive	13 (5.4)	0 (0.0)	
Nerve invasion			0.135
Negative	199 (83.3)	14 (100.0)	
Positive	40 (16.7)	0 (0.0)	

Values are presented as number (%) or mean±standard deviation.
CEA = carcinoembryonic antigen; CA 19-9 = cancer antigen 19-9; CA125 = cancer antigen 125; LNs = lymph nodes.

Table 2 shows the clinicopathological characteristics of the patients with a recurrence. Two patients only had a locoregional recurrence, and 12 patients had distant metastasis. Nine patients had liver metastasis, 1 patient had liver and lung metastases, 1 patient had bone metastasis, and 1 patient had peritoneal metastasis. Two patients who had locoregional recurrence underwent completion total gastrectomy and were alive during the follow-up period (55–60 months). Among the patients who had distant metastasis, 10 received systemic chemotherapy. The chemotherapy regimen administration period was selected by medical oncologists considering the pathological findings, type of recurrence, and the patient's general condition. Among these patients, 9 died during the follow-up period.

Multivariate analyses showed that the elderly (HR, 3.850; 95% CI, 1.157–12.809; P=0.028) and LVI (HR, 3.851; 95% CI, 1.264–11.732; P=0.018) were independent risk factors for recurrence after surgery (**Table 3**). And multivariate analyses using Cox's proportional hazard model revealed that LVI (HR, 3.630; 95% CI, 1.105–11.923; P=0.034) was the only independent prognostic factors for DSS (**Table 4**). **Figure 1** shows the DSS and RFS of patients with stage IB gastric cancer according to the presence of LVI; patients with LVI had significantly poorer

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer

Table 2. Clinicopathological characteristics of the patients with recurrence

No.	Sex	Age	Size (mm)	Histology	Tumor depth	Number of metastatic LNs	LVI	VI	NI	Time interval between surgery and recurrence (mon)	Follow up period (mon)	Time interval between recurrence and death (mon)	Recurrence site
1	M	47	25	por	sm	2	1	0	0	47	60	12	Liver
2	M	54	20	mod	sm	1	0	0	0	19	46	26	Liver
3	M	67	50	mod	sm	2	0	0	0	6	41	34	Liver
4	M	55	32	por	mp	0	0	0	0	30	37	7	Peritoneum
5	F	73	15	por	sm	2	1	0	0	11	28	17	Liver
6	M	76	60	por	mp	0	1	0	0	11	21	9	Liver
7	F	59	36	por	sm	1	0	0	0	5	13	7	Bone
8	M	66	25	por	sm	1	1	0	0	4	13	8	Liver, lung
9	M	76	27	mod	mp	0	1	0	0	6	6	0	Liver
10	M	80	17	mod	mp	0	0	0	0	18	32	13	Liver
11	M	68	30	mod	sm	1	1	0	0	11	72	-	Stomach
12	M	76	24	mod	mp	0	1	0	0	5	28	-	Liver
13	M	77	13	mod	sm	2	1	0	0	56	61	4	Liver
14	M	73	37	mod	mp	0	0	0	0	48	59	-	Stomach

LVI = lymphatic vessel invasion; VI = venous invasion; NI = nerve invasion; por = poorly differentiated adenocarcinoma; mod = moderately differentiated adenocarcinoma; sm = submucosa; mp = muscularis propria.

Table 3. Risk factors for recurrence in patients with stage IB gastric cancer after gastrectomy

Variables	Univariate analyses			Multivariate analyses		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<65	Ref.			Ref.		
≥65	3.995	1.217–13.110	0.022	3.850	1.157–12.809	0.028
Histological type						
Undifferentiated	Ref.					
Differentiated	2.400	0.806–7.147	0.116			
LVI						
Negative	Ref.			Ref.		
Positive	3.978	1.327–11.928	0.014	3.851	1.264–11.732	0.018
Pathologic stage						
T2N0	Ref.					
T1N1	2.460	0.826–7.327	0.106			
Number of retrieved LNs						
<30	Ref.					
≥30	0.353	0.117–1.063	0.064			

HR = hazard ratio; CI = confidence interval; LNs = lymph nodes; Ref = reference; LVI = lymphatic vessel invasion.

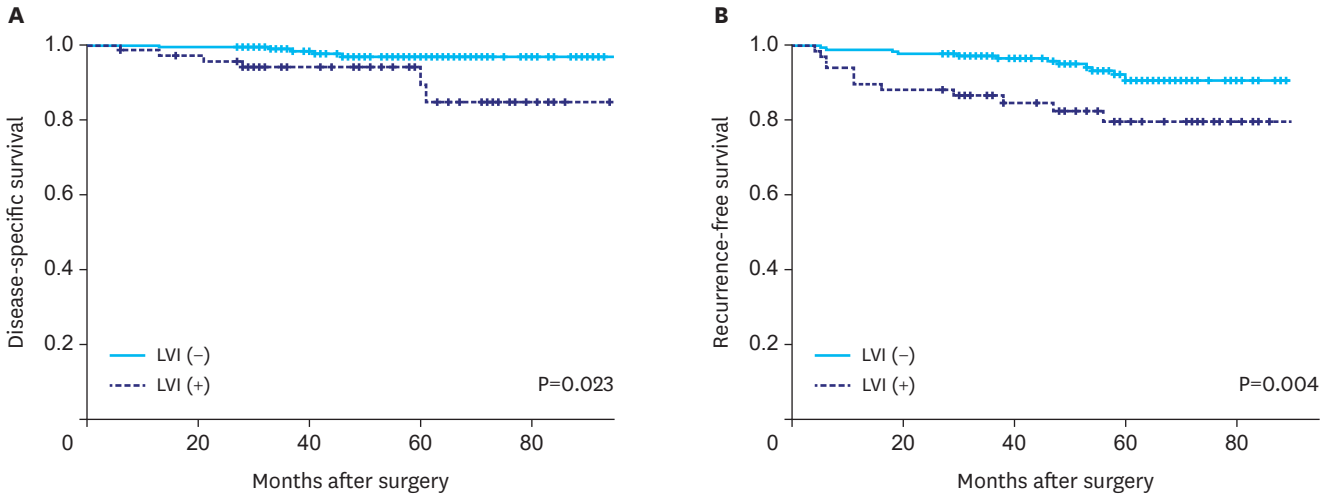
Table 4. Prognostic factors for disease-specific survival in stage IB gastric cancer after gastrectomy

Variables	Univariate analyses			Multivariate analyses		
	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<65	Ref.					
≥65	2.574	0.753–8.800	0.132			
Histological type						
Undifferentiated	Ref.					
Differentiated	1.387	0.423–4.545	0.589			
LVI						
Negative	Ref.			Ref.		
Positive	3.631	1.107–11.909	0.033	3.630	1.105–11.923	0.034
Pathologic stage						
T2N0	Ref.					
T1N1	3.109	0.910–10.628	0.070			
Number of retrieved LNs						
<30	Ref.			Ref.		
≥30	0.353	0.108–1.159	0.086	0.354	0.108–1.162	0.087

HR = hazard ratio; CI = confidence interval; Ref = reference; LNs = lymph nodes; LVI = lymphatic vessel invasion.

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer



No. at risk					
LVI (−)	184	183	142	56	21
LVI (+)	67	63	41	19	4

No. at risk					
LVI (−)	184	180	140	56	21
LVI (+)	67	59	40	16	4

Fig. 1. Disease-specific survival (A) and recurrence-free survival (B) of patients with stage IB gastric cancer according to the presence of LVI (log-rank test, P=0.023 and 0.004, respectively).
LVI = lymphatic vessel invasion.

DSS and RFS than those without LVI (P=0.023 and 0.004, respectively). The 5-year DSS and RFS rates in patients with or without LVI were 89.3%, 79.7% and 96.8%, 90.7%, respectively.

DISCUSSION

Stage I gastric cancer has been reported to have a 5-year survival rate of more than 90% [5], and adjuvant chemotherapy is recommended only in stage II or higher advanced gastric cancer based on several studies, such as the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trial and the capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) trial [14,15]. However, some patients with stage I gastric cancer also experience recurrence, and stage IB gastric cancer patients have a poorer prognosis than those with stage IA gastric cancer [5]. Although the TNM stage is most important for the prognosis of gastric cancer, the prognosis varies in patients with the same stage, and other factors can affect the prognosis.

The 5-year OS of the patients with stage IB gastric cancer was 88.9% in our study, which is similar to that of other studies [5,10]. Patients with stage I gastric cancer are less likely to have a recurrence than those with advanced gastric cancer and the cause of death is often other than the cancer recurrence considering the increasing number of older patients. In our study, 22 of the 253 patients died during the follow-up period, and only 11 (50%) died of cancer recurrence or progression. Therefore, we presented the 5-year DSS instead of 5-year OS to specifically analyze the prognostic factors for cancer-related deaths.

The 2 most common recurrence patterns in patients with gastric cancer are a hematogenous recurrence and peritoneal metastasis. The former tends to occur in early gastric cancer, and the latter tends to occur in advanced gastric cancer [16,17]. In our study, 71.4% of recurred patients had a recurrence in the liver caused by hematogenous metastasis, and only 1 patient

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer

had a peritoneal recurrence. This result is consistent with previous studies in terms of the relationship between cancer stage and the recurrence pattern.

The presence of LVI was an independent risk factor for recurrence and a prognostic factor for DSS [18]. These results are consistent with previous studies which have identified various prognostic factors of early gastric cancer after curative surgery [19,20]. Lee et al. [19] reported that extranodal extension was an independent prognostic factor of poor outcome in patients with stage IB gastric cancer. Park et al. [20] demonstrated that old age (>65 years), male gender, stage IB, LVI, perineural invasion, and an elevated level of carcinoembryonic antigen were independent poor prognostic factors for recurrence-free survival (RFS) in stage I gastric cancer. Among these six risk factors, patients with 2 or more risk factors showed a poorer 5-year RFS than those with less than 2 risk factors. (79% vs. 97%, P<0.001). Aoyama et al. [13] demonstrated that the tumor location was associated with survival in patients with stage IB gastric cancer. Although the tumor location was not included in the analysis in our study, patients with cancer located in the upper third of the stomach are expected to undergo total gastrectomy and the surgical extent did not significantly affect DSS. This difference is probably due to the very low recurrence rate in the study cohort with small sample size. In addition, Aoyama et al. [13] analyzed the prognostic factors of OS unlike the present study using DSS, which might have affected the final results.

LVI is known to be an important prognostic factor for postoperative recurrence and poor prognosis in patients with other cancers [21-23]. Lymphatic invasion was a negative prognostic factor independent of tumor stage in patients with thoracic esophageal squamous cell carcinoma, and lymphatic invasion was a risk factor for lymph node metastasis in T1 tumors and a high risk factor of recurrence in patients without lymph node involvement [21]. LVI was a negative prognostic factor in patients with stage I or IIA non-small cell lung cancer [22]. Yuan et al. [23] analyzed the impact of LVI in stage I/II colorectal cancer, and showed that LVI is significantly associated with poor OS and RFS. In these studies, LVI was an important prognostic factor in relatively early stage cancers with a good prognosis, and these results are consistent with our study.

LVI is a prognostic factor not only for early gastric cancer but also for advanced gastric cancer. Lu et al. [24] reported that age, LVI, and pathological T category are independent risk factors for the prognosis of node-negative gastric cancer. Li et al. [25] demonstrated that the presence of LVI is a risk factor for recurrence of cancer and an independent indicator of a poor outcome in gastric cancer patients following surgery. Hwang et al. [26] reported that the concomitant existence of lymphovascular and perineural invasion has a significant prognostic impact on DFS and OS in patients with stage II or III gastric cancer.

Adjuvant chemotherapy is not recommended for patients with stage IB gastric cancer because of lack of evidence from randomized controlled trials (RCTs). Most previous studies were designed to evaluate adjuvant chemotherapy for advanced gastric cancer. According to the ACTS-GC, patients who have been diagnosed with stage II or III gastric cancer and who underwent surgery and adjuvant chemotherapy (S-1) have better 5-year OS and RFS than patients who underwent surgery alone. In a subgroup analysis, the effect of S-1 adjuvant chemotherapy was better in relatively early gastric cancer than in advanced gastric cancer [27]. Kunisaki et al. [28] found that survival outcomes between stage T2N0 gastric cancer patients with LVI and stage II gastric cancer patients are similar. They suggested that T2N0 gastric cancer patients with LVI may be eligible for adjuvant chemotherapy. However, no

https://doi.org/10.5230/jgc.2020.20.e30

jgc Journal of Gastric Cancer

large-scale RCTs have been reported to demonstrate the efficacy of adjuvant chemotherapy for stage IB gastric cancer. As the proportion of early gastric cancer increases, well-designed prospective RCTs for adjuvant chemotherapy in patients with stage IB gastric cancer based on the risk factors for recurrence and poor prognosis are needed.

This study had some limitations. First, this study was retrospective and was performed at a single institution; therefore, the number of patients who experienced recurrence was very small (n=14, 5.5%). Gathering data from multiple centers would lead to a more concrete conclusion. Second, the mean follow-up period was relatively long (54.1 months), but 32 patients were followed up for less than 36 months. Fifteen patients experienced a postoperative recurrence or death after 36 months, so a longer follow-up is needed.

In conclusion, our data demonstrate that LVI was an independent risk factor for recurrence and poor survival in patients with stage IB gastric cancer. Therefore, patients diagnosed with LVI require careful attention for systemic recurrence during the follow-up period. And in these patients, adjuvant chemotherapy may be a reasonable approach to improve the prognosis. Based on the results of this study, a prospective RCT is required to assess adjuvant chemotherapy in patients with stage IB gastric cancer.

REFERENCES

1. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23:700-713.
PUBMED | CROSSREF
2. Information Committee of Korean Gastric Cancer Association. Korean Gastric Cancer Association Nationwide Survey on Gastric Cancer in 2014. J Gastric Cancer 2016;16:131-140.
PUBMED | CROSSREF
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
PUBMED | CROSSREF
4. Guideline Committee of the Korean Gastric Cancer AssociationDevelopment Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer 2019;19:1-48.
PUBMED | CROSSREF
5. Kwon OK, Kim SW, Chae HD, Ryu SW, Chung HY, Kim SW, et al. Validation of the 7th AJCC/UICC staging system for gastric cancer and a proposal for a new TNM system based on a prognostic score: a retrospective multicenter study. Ann Surg Treat Res 2016;91:295-302.
PUBMED | CROSSREF
6. Edge SB, Byrd DR, Campton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York (NY): Springer-Verlag, 2010.
7. Yokoyama T, Kamada K, Tsurui Y, Kashizuka H, Okano E, Ogawa S, et al. Clinicopathological analysis for recurrence of stage Ib gastric cancer (according to the second English edition of the Japanese classification of gastric carcinoma). Gastric Cancer 2011;14:372-7.
PUBMED | CROSSREF
8. Araki I, Hosoda K, Yamashita K, Katada N, Sakuramoto S, Moriya H, et al. Prognostic impact of venous invasion in stage IB node-negative gastric cancer. Gastric Cancer 2015;18:297-305.
PUBMED | CROSSREF
9. Toyokawa T, Ohira M, Sakurai K, Kubo N, Tanaka H, Muguruma K, et al. The role of adjuvant chemotherapy for patients with stage IB gastric cancer. Anticancer Res 2015;35:4091-4097.
PUBMED
10. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077-9.
PUBMED | CROSSREF
11. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. AJCC Cancer Staging Manual. 6th ed. New York (NY): Springer-Verlag, 2002.

12. Amin MB, Edge SB, Greene FL, Schilsky RL, Gaspar LE, Washington MK, et al. AJCC Cancer Staging Manual. 8th ed. New York (NY): Springer, 2017.
13. Aoyama T, Yoshikawa T, Fujikawa H, Hayashi T, Ogata T, Cho H, et al. Prognostic factors in stage IB gastric cancer. World J Gastroenterol 2014;20:6580-6585.
PUBMED | CROSSREF
14. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-1820.
PUBMED | CROSSREF
15. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1389-1396.
PUBMED | CROSSREF
16. Kim JW, Hwang I, Kim MJ, Jang SJ. Clinicopathological characteristics and predictive markers of early gastric cancer with recurrence. J Korean Med Sci 2009;24:1158-1164.
PUBMED | CROSSREF
17. Moriguchi S, Maehara Y, Korenaga D, Sugimachi K, Nose Y. Risk factors which predict pattern of recurrence after curative surgery for patients with advanced gastric cancer. Surg Oncol 1992;1:341-346.
PUBMED | CROSSREF
18. Kim H, Kim JH, Park JC, Lee YC, Noh SH, Kim H. Lymphovascular invasion is an important predictor of lymph node metastasis in endoscopically resected early gastric cancers. Oncol Rep 2011;25:1589-1595.
PUBMED | CROSSREF
19. Lee IS, Kang HJ, Park YS, Ryu MH, Yook JH, Kang YK, et al. Prognostic impact of extranodal extension in stage 1B gastric carcinomas. Surg Oncol 2018;27:299-305.
PUBMED | CROSSREF
20. Park JH, Ryu MH, Kim HJ, Ryoo BY, Yoo C, Park I, et al. Risk factors for selection of patients at high risk of recurrence or death after complete surgical resection in stage I gastric cancer. Gastric Cancer 2016;19:226-33.
PUBMED | CROSSREF
21. Wang S, Chen X, Fan J, Lu L. Prognostic significance of lymphovascular invasion for thoracic esophageal squamous cell carcinoma. Ann Surg Oncol 2016;23:4101-4109.
PUBMED | CROSSREF
22. Sung SY, Kwak YK, Lee SW, Jo IY, Park JK, Kim KS, et al. Lymphovascular invasion increases the risk of nodal and distant recurrence in node-negative stage I-IIA non-small-cell lung cancer. Oncology 2018;95:156-162.
PUBMED | CROSSREF
23. Yuan H, Dong Q, Zheng B, Hu X, Xu JB, Tu S. Lymphovascular invasion is a high risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. Oncotarget 2017;8:46565-46579.
PUBMED | CROSSREF
24. Lu J, Dai Y, Xie JW, Wang JB, Lin JX, Chen QY, et al. Combination of lymphovascular invasion and the AJCC TNM staging system improves prediction of prognosis in N0 stage gastric cancer: results from a high-volume institution. BMC Cancer 2019;19:216.
PUBMED | CROSSREF
25. Li P, He HQ, Zhu CM, Ling YH, Hu WM, Zhang XK, et al. The prognostic significance of lymphovascular invasion in patients with resectable gastric cancer: a large retrospective study from Southern China. BMC Cancer 2015;15:370.
PUBMED | CROSSREF
26. Hwang JE, Hong JY, Kim JE, Shim HJ, Bae WK, Hwang EC, et al. Prognostic significance of the concomitant existence of lymphovascular and perineural invasion in locally advanced gastric cancer patients who underwent curative gastrectomy and adjuvant chemotherapy. Jpn J Clin Oncol 2015;45:541-546.
PUBMED | CROSSREF
27. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387-4393.
PUBMED | CROSSREF
28. Kunisaki C, Makino H, Kimura J, Takagawa R, Kosaka T, Ono HA, et al. Impact of lymphovascular invasion in patients with stage I gastric cancer. Surgery 2010;147:204-211.
PUBMED | CROSSREF