Adverse prognostic impact of postoperative complications after gastrectomy for patient with stage II/III gastric cancer: Analysis of prospective collected real-world data

Jeong Ho Song

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Woo Jin Hyung

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This certifies that the Master's Thesis of
Jeong Ho Song is approved.

Thesis Supervisor : Woo Jin Hyung

Thesis Committee Member#1 : In Gyu Kwon

Thesis Committee Member#2 : Minkyu Jung

The Graduate School
Yonsei University

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ABSTRACT

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Jeong Ho Song

Department of Medicine
The Graduate School, Yonsei University

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Background: The impact of postoperative complications on the prognosis of gastric cancer patients remains controversial. This study aimed to evaluate the relationship between postoperative complications and long-term survival in a large cohort of patients undergoing gastrectomy for stage II/III gastric cancer.

Methods: A total of 939 patients who underwent curative gastrectomy for stage II/III gastric cancer were identified from prospectively collected real-world data between 2013 and 2015. We divided patients according to the presence of serious complications, specifically, Clavien-Dindo grade III or higher complications or complications causing a hospital stay of 15 days or longer.

Results: Serious complications occurred in 125 (13.3%) patients, of which 86 (9.2%) experienced Clavien-Dindo grade III or higher complications and 39 (5.2%) exhibited complications causing to a hospital stay of 15 days or longer. Patients without serious complications (n=523, 64.3%) completed adjuvant chemotherapy significantly more adequately than patients with serious complications (n=47, 37.6%; $p<0.001$). The 5-year overall survival (OS) rate was 58.1% and the

recurrence-free survival (RFS) rate was 58.1% in patients who had serious complications, which were significantly worse than those of patients without serious complications (73.4% and 74.7%, respectively; $p<0.001$ for OS and RFS). In stage II, once patients completed adjuvant chemotherapy adequately, the OS and RFS of patients with serious complications did not differ from those without serious complications ($p=0.495$, $p=0.936$, respectively). However, in stage III, the patients with serious complications showed a worse OS even after completion of adequate adjuvant chemotherapy ($p=0.013$).

Conclusion: Analysis of prospectively collected real-world data revealed that serious complications after gastrectomy had a negative impact on the prognosis of patients with stage II/III gastric cancer. Serious complications worsen the survival outcomes in association with inadequate adjuvant chemotherapy. Efforts to reduce serious complications, as well as support adequate chemotherapy through proper management of serious complications, will improve the long-term survival of stage II/III gastric cancer patients.

Key words: gastric cancer, postoperative complications, prognosis, real-world data

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I. INTRODUCTION

Over a million new cases of gastric cancer are diagnosed worldwide, making it the fifth most common cancer and the third leading cause of cancer death[1]. Radical surgical resection provides the only definitive chance to cure gastric cancer[2,3]; however, patients that undergo gastrectomy to treat gastric cancer frequently experience postoperative complications. The complication rates following gastrectomy for gastric cancer is reported to be approximately 10–60% of cases[4,5], with 1.3–12.5% of these having major complications[6,7], despite recent advances in surgical techniques and perioperative patient care.

Complications after cancer surgery have detrimental effects on the long-term survival of cancer patients, which has been shown in colorectal cancer[8], head and neck cancer[9], and esophageal cancer[10]. However, few studies have evaluated the impact of postoperative complications on the long-term outcome of gastric cancer patients[5,6,11-13]. Moreover, the prognostic impact of complications after gastrectomy on gastric cancer patients remains controversial.

These conflicting results are derived from the potential under-reporting of postoperative complications and their management in retrospective studies, as well as the selection bias of enrolling relatively physically fit patients in prospective studies. Data from a real-world setting may overcome these drawbacks and clarify the prognostic impact of complications after gastrectomy for gastric cancer patients.

We hypothesized that the effect of complications after gastric cancer surgery on the prognosis of gastric cancer patients could be exactly evaluated with prospectively collected real-world data. This study aimed to investigate the relationship between postoperative complications and long-term survival in a large cohort of patients undergoing gastrectomy for gastric cancer using prospectively collected real-world data.

II. METHODS

1. Patients

A prospectively collected real-world gastric cancer database consisting of 3,363 patients who underwent gastrectomy at Severance Hospital, Department of Surgery at Yonsei University from January 2013 to December 2015 was reviewed retrospectively. A total of 1,009 patients with pathologic stage II/III gastric cancer who underwent curative gastrectomy was identified from the database. Patients who met any of the following criteria were excluded from the analysis: 1) completion total gastrectomy; 2) gastrectomy combined with other cancer surgery; 3) history of preoperative chemotherapy or radiotherapy; 4) mortality or recurrence within 3 months of the operation; and 5) lost to follow-up This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (Protocol 4-2020-0303).

2. Surgery

Seven surgeons performed gastrectomy for gastric cancer. Three of them performed only open surgery, whereas the other four surgeons performed minimally invasive surgery (MIS), including laparoscopic and robotic surgery, as well as open surgery. MIS was usually performed for patients with serosa-negative advanced gastric cancer with or without limited involvement of perigastric lymph nodes. On the other hand, patients with serosa-positive advanced gastric cancer or extensive involvement of perigastric lymph nodes were generally considered for open gastrectomy. The extent of gastric resection (total, distal subtotal, or proximal gastrectomy) was determined based on tumor location. If the tumor was located in the distal area of the stomach and distal gastric resection was possible, distal gastrectomy was performed. If the tumor was located in the proximal area of the stomach, a total gastrectomy was usually performed. Some surgeons performed proximal gastrectomy on patients diagnosed with early gastric cancer. Surgeons removed the greater omentum in

serosa-positive advanced gastric cancer patients and preserved the omentum more than 4 to 5 cm away from the gastroepiploic arcade for serosa-negative gastric cancer patients. D1+ lymphadenectomy was performed for early-stage gastric cancer and D2 lymphadenectomy was performed for advanced gastric cancer. The reconstruction method used for distal subtotal gastrectomy was gastroduodenostomy (Billroth I), gastrojejunostomy (Billroth II), or Roux-en Y gastrojejunostomy. The reconstruction method used for total gastrectomy was Roux-en Y esophagojejunostomy and that of proximal gastrectomy was double tract reconstruction[14]. Tumor stage was defined in accordance with the 8th edition of American Joint Committee on Cancer staging system[15].

3. Perioperative management

At our institution, we established a “standard clinical pathway” for patients undergoing gastrectomy for gastric cancer. We injected prophylactic antibiotics 15 minutes before surgery without administering routine postoperative antibiotics. We only used postoperative antibiotics in cases where gross bowel content contamination occurred during surgery or when symptoms and signs of inflammation, such as fever and leukocytosis, persisted for 3 days or more after surgery. We indwelled a urinary catheter in the operating room after general endotracheal anesthesia and removed it on postoperative day (POD) 1. Nasogastric tube was not inserted routinely, but rather only for those patients with pyloric obstruction. Postoperative pain was primarily managed by patient-controlled anesthesia (PCA), and non-steroidal anti-inflammatory drugs (NSAIDs) were used for patients in need of additional pain control. Intravenous antiemetics were injected every 12 hours only on the day of operation. Mucolytics were administered every 8 hours until POD 2 to support pulmonary toileting. Patients started drinking water on POD 2, having liquid diet (LD) on POD 3, and eating a soft diet (SD) on POD 4. On POD 5, patients were recommended to be discharged if ready.

4. Data collection and classification of postoperative complications

Our institution has a clinical data retrieval program that allows researchers to search and organize patient electronic medical records without manual intervention by the researchers. As such, data accuracy is maximized and missing data are minimized. Using this program, we organized a prospective database of patient demographics, operative outcomes, pathologic features, and survival outcomes. We also extracted all medications, radiologic finding, laboratory results, and body temperature data through this program to confirm whether any complications occurred.

To obtain well-organized patient complication data, six or more surgeons held weekly meetings to confirm postoperative complications, discuss treatment plans, and evaluate treatment efficacy for complications. The list of complications considered is shown in Table 1. We classified complications into surgical and medical categories. The complications included re-admission due to any surgery-related complications within 90 days of surgery. We used the modified Clavien-Dindo classification to grade the severity of complications[16]. Most patients exhibiting a grade II complication in our study were those who were taking medications, such as liver- or pancreas-supporting drugs, antipyretics, and antibiotics to treat elevated hepatic or pancreatic enzymes or fever. Patients with grade I complications did not take any medications but exhibited abnormal chest radiograph findings, such as atelectasis and pleural effusion, or a body temperature above 38℃.

Table 1. Definition of the complications

Type	Definition
Surgical complications	
Fluid collection	Loculated fluid collection confirmed by imaging modality
Intra-abdominal abscess	Collection of pus or infected fluid collection caused by bacteria

Chyle leakage	Diagnosed as the presence of milky fluid in a drain with a triglyceride level ≥110 mg/dl
Intra-abdominal bleeding	Bleeding confirmed by CT scan or abdominal drains
Intra-luminal bleeding	Bleeding confirmed by nasogastric tube drainage or endoscopy
Intestinal obstruction	Defined as mechanical obstruction with an air-fluid level on imaging studies
Ileus	Temporary impairment of gastrointestinal motility following surgery (72 hours) without any stenosis, obstruction, or inflammation
Gastric stasis	Delayed emptying of stomach in the absence of mechanical obstruction confirmed by imaging modality
Anastomotic stenosis	Inability to pass the anastomotic site with endoscope
Anastomotic leakage	Diagnosed when the luminal contents were detected in a drain or a leak was confirmed by imaging modality
Pancreatitis	Elevated amylase of percutaneous drain (3 times the upper normal limit of serum amylase) starting from postoperative day 3 or elevated serum amylase treated by octreotide or camostat mesilate
Remnant stomach ischemia	Insufficient blood flow to remnant stomach confirmed by contrast CT scans
Anemia	Decrease of hemoglobin in blood requiring transfusion or iron supply
Wound complication	Seroma, hematoma, infection, or dehiscence of the wound
Medical complications	
Pulmonary	Acute respiratory failure requiring intervention or atelectasis, pleural effusion, or pneumonia in a chest X-ray or CT scan read by radiologists
Urinary	Voiding difficulty or urinary tract infection
Hepatic	Elevated liver enzymes treated by hepatotonics or cholecystitis confirmed by imaging modality
Cardiac	Hypertension, arrhythmia, angina, or myocardial infarction
Fever	Defined as body temperature above 38℃. If body temperature was less than 38℃, patients were prescribed antipyretics and regarded as having complication grade I or were regarded as having complication grade II if antibiotics were prescribed. Patients with body temperature over 38℃ who recovered without antibiotics or antipyretics were classified as having

complication grade I.

CT indicates computed tomography

5. Adjuvant chemotherapy

After surgery, patients with pathologic stage II/III gastric cancer were referred to a medical oncologist for adjuvant chemotherapy. Medical oncologists recommended patients to receive 5-FU-based adjuvant chemotherapy within 4–8 weeks after surgery. A majority of adjuvant chemotherapy regimens were TS-1 monotherapy or XELOX (capecitabine plus oxaliplatin), which were used to treat patients with stage II or stage III disease, respectively. TS-1 (80–120 mg per day) was administered for 4 weeks, followed by 2 weeks of rest. This 6-week regimen was repeated for eight cycles[17]. The XELOX regimen involved 3-week cycles of oral capecitabine (1,000 mg/m^2 twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle). The XELOX treatment regimen was administered for eight cycles[18].

6. Follow up

We followed up with all patients every 3 months for 1 year after surgery, and then every 6 months thereafter. They underwent abdomino-pelvic computed tomography (CT) scans every 6 months for 5 years after surgery. We performed an upper endoscopy every year. In any case of suspected recurrence, an abdomino-pelvic CT scan and upper endoscopy were performed. Recurrence was confirmed either by radiologic studies, such as CT, positron emission tomography, whole-body bone scan, or endoscopic examination with biopsy, or by surgery.

7. Statistical analysis

The serious complication (SC) group consisted of patients with Clavien-Dindo grade III or higher complications or patients with any

complications causing a hospital stay of 15 days or longer. Patients without complications or who stayed in the hospital for less than 15 days with Clavien-Dindo grade I/II complications were defined as the non-serious complication (non-SC) group. We defined the adequate adjuvant chemotherapy group as patients who completed chemotherapy without omission or delayed initiation, while the inadequate adjuvant chemotherapy group as patients who omitted, delayed in initiation, or not completed the scheduled chemotherapy. Delayed initiation in adjuvant chemotherapy was defined as starting at 8 weeks after surgery[19], and incompletion of adjuvant chemotherapy was defined as discontinued treatment during the scheduled chemotherapy cycles.

Chi-square or Fisher's exact tests for categorical variables and the Mann-Whitney test for continuous variables were used. The Kaplan-Meier method was used to calculate the overall and recurrence-free survival, whereas differences between survival curves were assessed using the log-rank test. In the analysis of overall survival, death by any cause was defined as an event. Recurrence-free survival was defined as time from curative resection until disease recurrence or death by any cause. The hazard ratio (HR) and two-sided 95% confidence intervals (CI) were estimated using a Cox proportional hazards model. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the statistics software Statistic Package for Social Science (SPSS) version 25.0 for Windows (SPSS, Inc., Chicago, IL, USA).

III. RESULTS

1. Patients characteristics

A retrospective review of prospective real-world data revealed 1,009 patients who underwent curative gastrectomy for stage II/III gastric cancer. After 70 patients were excluded from the analyses (completion total gastrectomy [n=28]; combined other cancer surgery [n=17]; history for preoperative chemotherapy or radiotherapy [n=4]; mortality or recurrence within postoperative 3 months [n=17]; and follow-up loss [n=4]), data from 939 patients were included in this study (Table 2).

Table 2. Comparison of Clinicopathologic characteristics according serious complication

	Overall (N=939)	non-SC group (N=814)	SC group (N=125)	P-value
Age, median (IQR), year	60 (52-70)	60 (52-60)	66 (54-74)	0.001
Sex				0.01
Female	348 (37.1%)	312 (38.3%)	36 (28.8%)	
Male	591 (62.9%)	502 (61.7%)	89 (71.2%)	
BMI, median (IQR), kg/m^2	22.9 (20.8-25.0)	22.8 (20.8-25.0)	23.3 (20.6-25.4)	0.477
ASA score				0.021
I	153 (16.3%)	137 (16.8%)	16 (12.8%)	
II	569 (60.6%)	502 (61.7%)	67 (53.6%)	
III	209 (22.3%)	169 (20.8%)	40 (32.0%)	
IV	8 (0.9%)	6 (0.7%)	2 (1.6%)	
Operation				< 0.001

method				
Open	643 (68.5%)	534 (65.6%)	109 (87.2%)	
Laparoscopy	189 (20.1%)	180 (22.1%)	9 (7.2%)	
Robot	107 (11.4%)	100 (12.3%)	7 (5.6%)	
Surgical procedure				0.001
STG	641 (68.3%)	573 (70.4%)	68 (54.4%)	
TG	294 (31.3%)	238 (29.2%)	56 (44.8%)	
PG	4 (0.4%)	3 (0.4%)	1 (0.8%)	
Lymph node dissection				0.129
< D2	105 (11.2%)	86 (11.8%)	9 (7.2%)	
D2	834 (88.8%)	718 (88.2%)	116 (92.8%)	
Combined operation				< 0.001
No	788 (83.9%)	703 (86.4%)	85 (68.0%)	
Yes	151 (16.1%)	111 (13.6%)	40 (32.0%)	
Histology				0.085
Differentiated	305 (32.5%)	256 (31.4%)	49 (39.2%)	
Undifferentiated	634 (67.5%)	558 (68.8%)	776 (60.8%)	
Tumor depth				0.043
T1	56 (6.0%)	52 (6.4%)	4 (3.2%)	
T2	130 (13.8%)	116 (14.3%)	14 (11.2%)	
T3	341 (36.3%)	294 (36.1%)	47 (37.6%)	
T4a	399 (42.5%)	344 (42.3%)	55 (44.0%)	
T4b	13 (1.4%)	8 (1.0%)	5 (4.0%)	

Lymph node metastasis				0.682
N0	226 (24.1 %)	201 (24.7%)	25 (20.0%)	
N1	187 (19.9%)	159 (19.5%)	28 (22.40%)	
N2	241 (25.7%)	208 (25.6%)	33 (26.4%)	
N3	285 (30.4%)	246 (30.2%)	39 (31.2%)	
Pathologic stage[a]				0.097
II	463 (49.3%)	410 (50.4%)	53 (49.6%)	
III	476 (50.7%)	404 (42.4%)	72 (57.6%)	
Complication				
No	198 (21.1%)			
Yes	741 (78.9%)			
CD grade	741 (78.9%)	616 (65.6%)	125 (13.3%)	
I	363 (38.7%)	359 (98.9%)	4 (1.1%)	
II	292 (31.1%)	257 (88.0%)	35 (12.0%)	
III	76 (8.1%)	0	76 (100%)	
IV	10 (1.1%)	0	10 (100%)	

SC indicates serious complications; IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiology score; STG, subtotal gastrectomy; TG, total gastrectomy; PG, proximal gastrectomy; CD, Clavien-Dindo.

[a]Pathologic stages were defined in accordance with the 8th edition of American Joint Committee on Cancer staging system.

Patient clinicopathologic characteristics are summarized in Table 2. The median age was 60 years (interquartile range (IQR), 52–70) and most patients were male (n=591; 62.9%). The median BMI was 22.9 (IQR, 20.8–25.0) with 229 patients (24.4%) exhibiting a BMI of 25 or higher. The 68.5% of all patients (n=643) underwent open gastrectomy. The majority of patients underwent subtotal gastrectomy (n=641; 68.3%). This study consisted of 463 (49.3%) and 476 (50.7%) patients with pathologic stage II and stage III disease,

respectively.

Complications occurred in 741 out of 939 patients (78.9%), of which the number of patients with Clavien-Dindo grade I/II or grade III and higher was 655 (69.8%) or 86 (9.2%), respectively. Details of postoperative complications are shown in Table 3.

Table 3. Type and severity of postoperative complications

Type of complications	Overall (N=741)	CD grade I/II/III/IV	Trivial[a] complications (N=616)	Serious[b] complications (N=125)
Medical complications	**473**	**326/125/18/4**	**446(72.4%)**	**27(21.6%)**
Pulmonary	181	130/29/18/4	157(25.4%)	24(19.2%)
Hepatic	56	0/56/0/0	55(8.9%)	1(0.8%)
Urinary	20	3/17/0/0	19(3.1%)	1(0.8%)
Cardiac	5	0/5/0/0	4(0.6%)	1(0.8%)
Fever	202	191/11/0/0	202(32.8%)	0
Others	9	2/7/0/0	9(1.5%)	0
Surgical complications	**268**	**37/167/58/6**	**170(27.6%)**	**98(78.4%)**
Wound problem	36	23/11/2/0	30(4.9%)	6(4.8%)
Intra-luminal bleeding	2	0/2/0/0	2(0.3%)	0
Intra-abdominal abscess	5	0/1/2/2	0	5(4%)
Fluid collection	14	2/10/2/0	6(1.0%)	8(6.4%)
Chyle leakage	47	4/15/28/0	16(2.6%)	31(24.8%)
Anastomotic leakage	20	0/6/13/1	1(0.2%)	19(15.2%)
Intra-abdominal bleeding	8	0/1/4/3	1(0.2%)	7(5.6%)

Ileus	3	1/2/0/0	2(0.3%)	1(0.8%)
Intestinal obstruction	9	1/5/3/0	3(0.5%)	6(4.8%)
Anastomotic stenosis	6	0/2/4/0	2(0.3%)	4(3.2%)
Pancreatic complication	55	0/55/0/0	48(7.8%)	7(5.6%)
Gastric stasis	5	2/3/0/0	5(0.8%)	0
Remnant stomach ischemia	4	0/4/0/0	3(0.5%)	1(0.8%)
Anemia	54	4/50/0/0	51	3(2.4%)

CD grade indicates Clavien-Dindo grade.
[a]Trivial complications were defined as complications requiring a hospital stay less than 15 days with a Clavien-Dindo grade I/II.
[b]Serious complications were defined as Clavien-Dindo grade III or higher complications or complications causing a hospital stay of 15 days or longer.

The non-SC group consisted of 198 patients who did not experience complications and 616 patients who exhibited complications less than 15 days of hospital stay. The SC group consisted of 86 patients with Clavien-Dindo grade III or higher and 39 patients with any complications causing a hospital stay of 15 days or longer. The SC group was more likely to be characterized by old age, male, and higher American Society of Anesthesiology (ASA) scores than the non-SC group (p=0.001, p=0.04, and p=0.021, respectively). The occurrence of serious complications was associated with tumors located in the upper body of the stomach or advanced tumor, which required total gastrectomy and open surgery rather than MIS (Table 2).

Compared with the non-SC group, patients who stayed in the hospital for 15 days or longer with Clavien-Dindo grade I/II complications were significantly associated with old age, high ASA score, open surgery, and combined operation (p=0.040, p=0.025, p<0.001, and p=0.011, respectively; Table 4).

Table 4. Comparison of clinicopathologic characteristics between the non-SC group and patients with a hospital stay 15 days or longer with a Clavien-Dindo grade I/II.

	Overall (N=853)	non-SC group (N=814)	15 or longer with CD I/II (n=39)	P-value
Age, median (IQR), year	60 (52-70)	60 (52-69)	64 (56-71)	0.040
Sex				0.342
Female	348 (37.1%)	312 (38.3%)	12 (30.8%)	
Male	591 (62.9%)	502 (61.7%)	27 (69.2%)	
BMI, median (IQR), kg/m^2	22.9 (20.8-25.0)	22.8 (20.8-25.0)	22.9 (20.3-25.7)	0.438
ASA score				0.025
I	153 (16.3%)	137 (16.8%)	6 (15.4%)	
II	569 (60.6%)	502 (61.7%)	17 (43.6%)	
III	209 (22.3%)	169 (20.8%)	16 (41.0%)	
IV	8 (0.9%)	6 (0.7%)	0	
Operation method				< 0.001
Open	643 (68.5%)	534 (65.6%)	37 (94.9%)	
Laparoscopy	189 (20.1%)	180 (22.1%)	1 (2.6%)	
Robot	107 (11.4%)	100 (12.3%)	1 (2.6%)	
Surgical procedure				0.456
STG	641 (68.3%)	573 (70.4%)	25 (64.1%)	
TG	294 (31.3%)	238 (29.2%)	14 (35.9%)	
PG	4 (0.4%)	3 (0.4%)	0	
Lymph node				1.000

dissection				
< D2	105 (11.2%)	96 (11.8%)	4 (10.3%)	
D2	834 (88.8%)	718 (88.2%)	35 (89.7%)	
Combined operation				0.011
No	788 (83.9%)	703 (86.4%)	28 (71.8%)	
Yes	151 (16.1%)	111 (13.6%)	11 (28.2%)	
Histology				0.444
Differentiated	305 (32.5%)	256 (31.4%)	10 (25.6%)	
Undifferentiated	634 (67.5%)	558 (68.8%)	29 (74.4%)	
Tumor depth				
T1	56 (6.0%)	52 (6.4%)	2 (5.1%)	0.280
T2	130 (13.8%)	116 (14.3%)	4 (10.3%)	
T3	341 (36.3%)	294 (36.1%)	14 (35.9%)	
T4a	399 (42.5%)	344 (42.3%)	17 (43.6%)	
T4b	13 (1.4%)	8 (1.0%)	2 (5.1%)	
Lymph node metastasis				
N0	226 (24.1 %)	201 (24.7%)	6 (15.4%)	0.580
N1	187 (19.9%)	159 (19.5%)	9 (23.1%)	
N2	241 (25.7%)	208 (25.6%)	12 (30.8%)	
N3	285 (30.4%)	246 (30.2%)	12 (30.8%)	
Pathologic stage[a]				
II	463 (49.3%)	410 (50.4%)	16 (41.0%)	0.254
III	476 (50.7%)	404 (42.4%)	23 (59.0%)	

CD indicated Clavien-Dindo; SC, serious complications; IQR, interquartile range; BMI, body mass index;

ASA, American Society of Anesthesiology score; STG, subtotal gastrectomy; TG, total gastrectomy; PG, proximal gastrectomy.
[a]Pathologic stages were defined in accordance with the 8th edition of American Joint Committee on Cancer staging system.

The clinicopathologic characteristics of patients with Clavien-Dindo grade I/II complications causing a hospital stay of 15 days or longer were similar to those with Clavien-Dindo grade III or higher complications, except for tumor histology (Table 5).

Table 5. Comparison of clinicopathologic characteristics between patients with a hospital stay of 15 days or longer with a Clavien-Dindo grade I/II and those with a Clavien-Dindo grade III or higher.

	Overall (n=125)	15 or longer with CD I/II (n=39)	CD III/IV (n=86)	P-value
Age, median (IQR), year	66 (54-74)	64 (56-71)	67 (54-74)	0.324
Sex				0.743
Female	36 (28.8%)	12 (30.8%)	24 (27.9%)	
Male	89 (71.2%)	27 (69.2%)	62 (72.1%)	
BMI, median (IQR), kg/m^2	23.3 (20.6-25.4)	22.9 (20.3-25.7)	23.5 (21.0-25.2)	0.393
ASA score				0.330
I	16 (12.8%)	6 (15.4%)	10 (11.6%)	
II	67 (53.6%)	17 (43.6%)	50 (58.1%)	
III	40 (32.0%)	16 (41.0%)	24 (27.9%)	
IV	2 (1.6%)	0	2 (2.3%)	
Operation method				0.282
Open	109 (87.2%)	37 (94.9%)	72 (83.7%)	

Laparoscopy	9 (7.2%)	1 (2.6%)	8 (9.3%)	
Robot	7 (5.6%)	1 (2.6%)	6 (7.0%)	
Surgical procedure				0.297
STG	68 (54.4%)	25 (64.1%)	43 (50.0%)	
TG	56 (44.8%)	14 (35.9%)	42 (48.8%)	
PG	1 (0.8%)	0	1 (1.2%)	
Lymph node dissection				0.459
< D2	9 (7.2%)	4 (10.3%)	5 (5.8%)	
D2	116 (92.8%)	35 (89.7%)	81 (94.2%)	
Combined operation				0.540
No	85 (68.0%)	28 (71.8%)	57 (66.3%)	
Yes	40 (32.0%)	11 (28.2%)	29 (33.7%)	
Histology				0.037
Differentiated	49 (39.2%)	10 (25.6%)	39 (45.3%)	
Undifferentiated	76 (60.8%)	29 (74.4%)	47 (54.7%)	
Tumor depth				0.895
T1	4 (3.2%)	2 (5.1%)	2 (2.3%)	
T2	14 (11.2%)	4 (10.3%)	10 (11.6%)	
T3	47 (37.6%)	14 (35.9%)	33 (38.4%)	
T4a	55 (44.0%)	17 (43.6%)	38 (44.2%)	
T4b	5 (4.0%)	2 (5.1%)	3 (3.5%)	
Lymph node metastasis				0.794
N0	25 (20.0%)	6 (15.4%)	19 (22.1%)	

N1	28 (22.4%)	9 (23.1%)	19 (22.1%)	
N2	33 (26.4%)	12 (30.8%)	21 (24.4%)	
N3	39 (31.2%)	12 (30.8%)	27 (31.4%)	
Pathologic stage[a]				0.834
II	53 (42.4%)	16 (41.0%)	37 (43.0%)	
III	72 (57.6%)	23 (59.0%)	49 (57.0%)	

CD indicated Clavien-Dindo; IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiology score; STG, subtotal gastrectomy; TG, total gastrectomy; PG, proximal gastrectomy.
[a]Pathologic stages were defined in accordance with the 8th edition of American Joint Committee on Cancer staging system.

The median hospital stay of patients with Clavien-Dindo grade I/II complications causing a hospital stay of 15 days was 16 days (IQR, 15–22), which was similar to that of patients with Clavien-Dindo grade III or higher complications (median 15; IQR, 10–22). The median stay for the non-SC group was 7 days (IQR, 6–8).

2. Relationship between postoperative complication and adjuvant chemotherapy

Overall, 750 of 939 (79.9%) patients were treated with adjuvant chemotherapy. The SC group was associated with a higher rate of omission (n=41, 32.8%) than the non-SC group (n=148, 18.2%; p<0.001). The SC group also exhibited more instances of delayed initiation, incompletion, and inadequacy of adjuvant chemotherapy (n=8, 9.5%; n=32, 38.1%; n=78, 62.4%) than the non-SC group (n=14, 2.1%, p=0.002; n=135, 20.3%, p<0.001; n=291, 35.7%, p<0.001, respectively) (Table 6).

Table 6. Relationship between postoperative complications and adjuvant chemotherapy.

Adjuvant chemotherapy	Overall	non-SC	SC group	P-value

	(N=939)	group (N=814)	(N=125)	
Omission	939			< 0.001
(-)	750 (79.9%)	666 (81.8%)	84 (67.2%)	
(+)	189 (20.1%)	148 (18.2%)	41 (32.8%)	
Time to AC	750			0.002
≤ 8 weeks	728 (97.1%)	728 (97.1%)	652 (97.9%)	
> 8 weeks (Delay)	22 (2.9%)	22 (2.9%)	14 (2.1%)	
Scheduled cycles of AC	750			< 0.001
Completed	583 (77.7%)	531 (79.7%)	52 (61.9%)	
Not completed	167 (22.3%)	135 (20.3%)	32 (38.1%)	
Adequacy of AC	939			< 0.001
Adequate[a]	570 (60.7%)	523 (64.3%)	47 (37.6%)	
Inadequate[b]	369 (39.3%)	291 (35.7%)	78 (62.4%)	

Abbreviations: AC, adjuvant chemotherapy; SC, serious complications.
[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

Similar findings were noted in stage II and III, respectively (Table 7, 8) , with only marginal differences seen in the number of patients who did not complete their chemotherapy.

Table 7. Relationship between postoperative complications and adjuvant chemotherapy in stage II gastric cancer.

Adjuvant chemotherapy	Overall (N=463)	non-SC group (N=410)	SC group (N=53)	P-value
Omission	463			0.047
(-)	333 (71.9%)	301 (73.4%)	32 (60.4%)	
(+)	130 (28.1%)	109 (26.6%)	21 (39.6%)	
Time to AC	333			0.027

≤ 8 weeks	320 (96.1%)	292 (97.0%)	28 (87.5%)	
> 8 weeks (Delay)	13 (3.9%)	9 (3.0%)	4 (12.5%)	
Scheduled cycles of AC	333			0.078
Completed	268 (80.5%)	246 (81.7%)	22 (68.8%)	
Not completed	65 (19.5%)	55 (18.3%)	10 (31.3%)	
Adequacy of AC	463			0.004
Adequate[a]	261 (56.4%)	241 (58.8%)	20 (37.7%)	
Inadequate[b]	202 (43.6%)	169 (41.2%)	33 (62.3%)	

Abbreviations: AC, adjuvant chemotherapy; SC, serious complications.
[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

Table 8. Relationship between postoperative complications and adjuvant chemotherapy in stage III gastric cancer.

Adjuvant chemotherapy	Overall (N=476)	non-SC group (N=404)	SC group (N=72)	P-value
Omission	476			< 0.001
(-)	417 (87.6%)	365 (90.3%)	52 (72.2%)	
(+)	59 (12.4%)	39 (9.7%)	20 (27.8%)	
Time to AC	417			0.017
≤ 8 weeks	408 (97.8%)	360 (98.6%)	48 (92.3%)	
> 8 weeks (Delay)	9 (2.2%)	5 (1.4%)	4 (7.7%)	
Scheduled cycles of AC	417			0.001
Completed	315 (75.5%)	285 (78.1%)	30 (57.7%)	
Not completed	102 (24.5%)	80 (21.9%)	22 (42.3%)	
Adequacy of AC	476			< 0.001
Adequate[a]	309 (64.9%)	282 (69.8%)	27 (37.5%)	
Inadequate[b]	167 (35.1%)	122 (30.2%)	45 (62.5%)	

Abbreviations: AC, adjuvant chemotherapy; SC, serious complications.

[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

The rate of omission and inadequacy of adjuvant chemotherapy were significantly higher in Clavien-Dindo grade I/II patients who stayed 15 days or longer in the hospital in the SC group compared to the non-SC group (Table 9).

Table 9. Comparison of adequacy of adjuvant chemotherapy between the non-SC group and the patients with a hospital stay of 15 days or longer with Clavien-Dindo I/II in stage II/III gastric cancer.

Adjuvant chemotherapy	Overall (n=853)	Less than 15 with CD I/II or No Cx (n=814)	15 or longer in CD I/II (n=39)	P-value
Omission	853			0.018
(-)	692 (81.1%)	666 (81.8%)	26 (66.7%)	
(+)	161 (18.9%)	148 (18.2%)	13 (33.3%)	
Time to AC	692			0.118
≤ 8 weeks	676 (97.7%)	652 (97.9%)	24 (92.3%)	
> 8 weeks (Delay)	16 (2.3%)	14 (2.1%)	2 (7.7%)	
Scheduled cycles of AC	692			0.077
Completed	548 (79.2%)	531 (79.7%)	17 (65.4%)	
Not completed	144 (20.8%)	135 (20.3%)	9 (34.6%)	
Adequacy of AC	853			0.001
Adequate[a]	538 (63.1%)	523 (64.3%)	15 (38.5%)	
Inadequate[b]	315 (36.9%)	291 (35.7%)	24 (61.5%)	

Abbreviations: AC, adjuvant chemotherapy; CD, Clavien-Dindo.
[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

However, the rate of omission, delayed initiation, incompletion and inadequacy of adjuvant chemotherapy were similar between the Clavien-Dindo

grade I/II patients who stayed 15 days or longer in the hospital and those with Clavien-Dindo grade III or higher complications (Table 10).

Table 10. Relationship between Clavien-Dindo grade and adjuvant chemotherapy in stage II/III gastric cancer patients with serious complications.

Adjuvant chemotherapy	Overall (n=853)	15 or longer in CD I/II (n=39)	CD III or higher (n=86)	P-value
Omission	125			0.932
(-)	84 (67.2%)	26 (66.7%)	58 (67.4%)	
(+)	41 (32.8%)	13 (33.3%)	28 (32.6%)	
Time to AC	84			1.000
≤ 8 weeks	76 (90.5%)	24 (92.3%)	52 (89.7%)	
> 8 weeks (Delay)	8 (9.5%)	2 (7.7%)	6 (10.3%)	
Scheduled cycles of AC	84			0.660
Completed	52 (61.9%)	17 (65.4%)	35 (60.3%)	
Not completed	32 (38.1%)	9 (34.6%)	23 (39.7%)	
Adequacy of AC	125			0.893
Adequate[a]	47 (37.6%)	15 (38.5%)	32 (37.2%)	
Inadequate[b]	78 (62.4%)	24 (61.5%)	54 (62.8%)	

AC indicates adjuvant chemotherapy; CD, Clavien-Dindo.
[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

3. Survival outcomes

The median follow-up duration after surgery was 52 months (ranging between 7–71 months) until the cutoff date of December 31, 2018. During the follow-up period, 245 patients (26.1%) died of which 52 (41.6%) were from the SC group and 193 (23.7%) were from the non-SC group. The HR for death in the SC group, as compared with that in the non-SC group, was 1.92 (95% CI,

1.4-2.6; p<0.001). The 5-year overall survival rate of the SC group was 58.1% (95% CI, 49.2-68.6) and that of the non-SC group was 71.3% (95% CI, 70.0-76.9; log-rank p<0.001). The number of patients that experienced a recurrence was 240 (25.6%), of which 58 (46.4%) were from the SC group and 182 (22.4%) were from the non-SC group. The HR for recurrence in the SC group, as compared to the non-SC group, was 1.75 (95% CI, 1.3-2.4; p=0.001). The 5-year recurrence-free survival rate in the SC group was 58.1% (95% CI, 49.0-69.0) and that in the non-SC group was 74.7% (95% CI, 71.5-77.9; log-rank p<0.001). When we stratified the patients according to pathologic stages, the SC group exhibited worse overall and recurrence-free survival rates than the non-SC group for patients with stages II and III (Fig. 1).

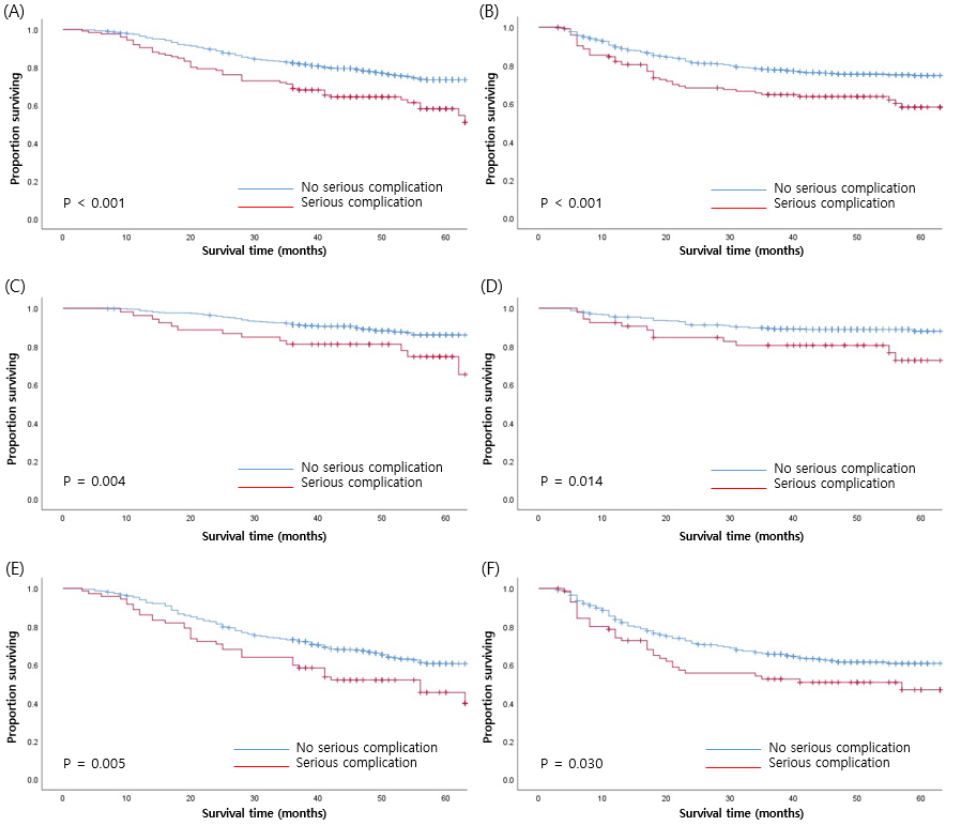

Figure 1. Overall (A, C, E) and recurrence-free survival (B, D, F) in patients with and without serious complication after gastrectomy by pathologic stage. (A, B) Overall stage. (C, D) Pathologic stage II. (E, F) Pathologic stage III.

Survival outcomes based on the presence of serious complications combined with the adequacy of adjuvant chemotherapy were compared after dividing the patients into three groups, namely non-SC patients who received adequate adjuvant chemotherapy (n=523), SC patients who received adequate adjuvant chemotherapy (n=47), and SC patients whose adjuvant chemotherapy was inadequate (n=78). Patients who received inadequate adjuvant chemotherapy in the SC group showed significantly worse overall and recurrence-free survival than non-SC patients who received adequate adjuvant chemotherapy (log-rank $p<0.001$ for both). In stage II, SC patients who received adequate adjuvant chemotherapy had similar overall and recurrence-free survival outcomes to those under adequate adjuvant chemotherapy in the non-SC group (log-rank $p=0.495$ and $p=0.936$, respectively). On the contrary, in stage III, the overall and recurrence-free survival of SC patients under adequate adjuvant chemotherapy were similar to those who did not receive adequate adjuvant chemotherapy in the SC group (log-rank $p=0.426$ and $p=0.551$, respectively). Non-SC patients under adequate adjuvant chemotherapy had significantly higher overall survival than SC patients who received adequate adjuvant chemotherapy (log-rank $p=0.013$) even though the recurrence-free survival did not differ statistically (log-rank $p=0.115$) (Fig. 2).

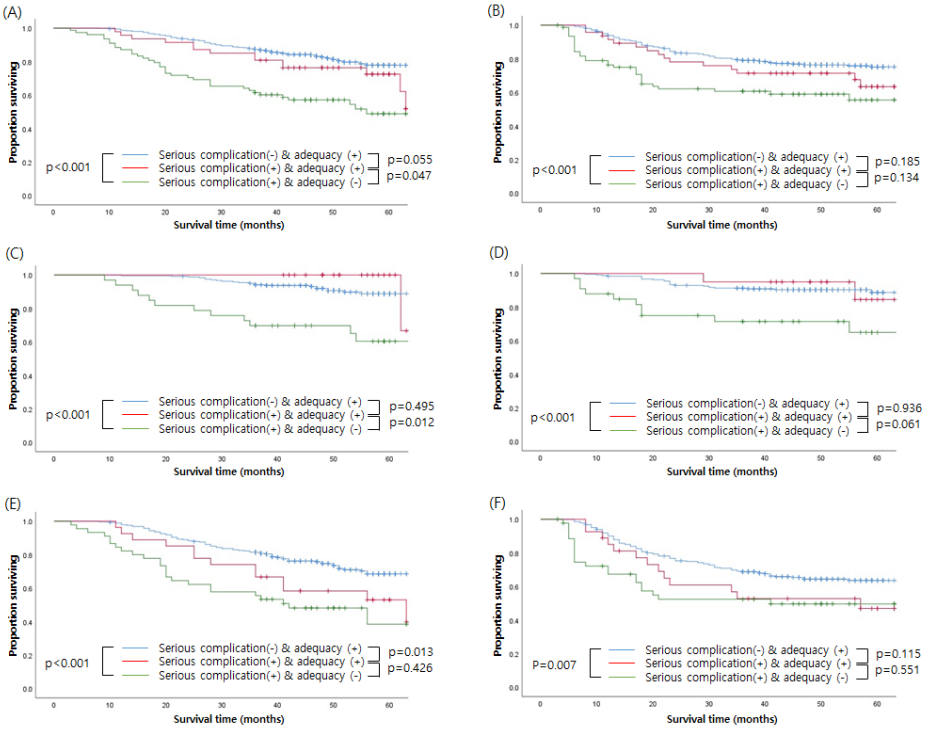

Figure 2. Overall (A, C, E) and recurrence-free survival (B, D, F) according to the presence of serious complications with the function of adequacy of adjuvant chemotherapy by pathologic stage. (A, B) Overall stage. (C, D) Pathologic stage II. (E, F) Pathologic stage III.

Patients with Clavien-Dindo grade I/II complications causing a hospital stay of 15 days exhibited worse overall and recurrence-free survival than the non-SC group (Fig. 3).

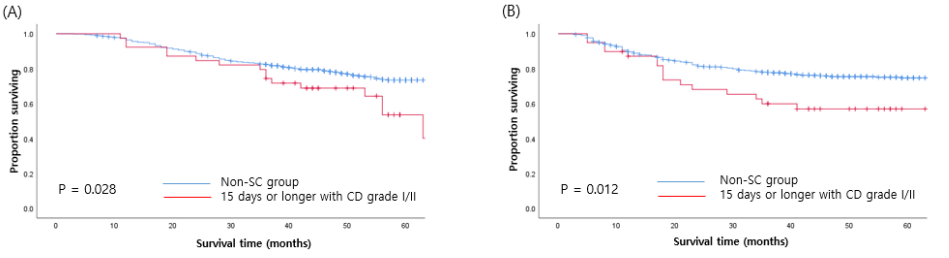

Figure 3. Overall (A) and recurrence-free survival (B) in non-SC group and patients with a hospital stay of 15 days or longer with a Clavien-Dindo grade I/II.

In the SC group, the overall and recurrence-free survival of patients with Clavien-Dindo grade I/II complications causing a hospital stay of 15 days were similar to those of patients with Clavien-Dindo grade III or higher complications (Fig. 4).

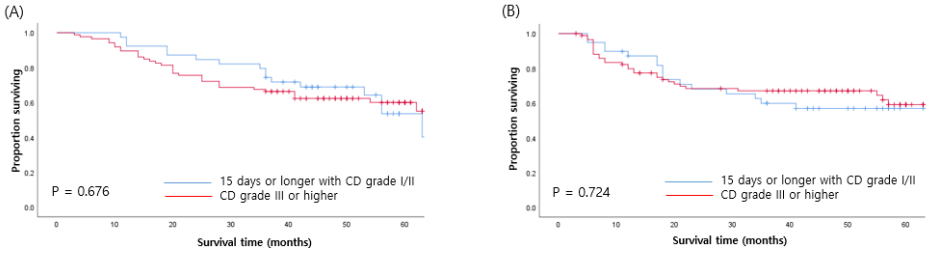

Figure 4. Overall (A) and recurrence-free survival (B) in patients with Clavien-Dindo grade III or higher and those with a hospital stay of 15 days or longer with a Clavien-Dindo grade I/II.

A multivariable analysis of overall survival identified adequate adjuvant chemotherapy (HR, 2.28; 95% CI, 1.7–3.0, p<0.001) as an independent risk factor. In contrast, the presence of serious complications was not a risk factor (HR, 1.27; 95% CI, 0.9-1.7, p=0.146; Table 11). In multivariable analyses for recurrence-free survival, inadequate adjuvant chemotherapy (HR, 1.55; 95% CI, 1.2–2.0) was found to be an independent prognostic factor even though the presence of serious complications showed only a marginal difference (HR 1.38; 95% CI, 1.0-1.9, p=0.06; Table 12).

Table 11. Univariate and multivariate analyses of overall survival rate.

Characteristics	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Age				< 0.001			0.025
≤ 60 years	471	1			1		
> 60 years	468	1.749	1.352-2.262		1.358	1.039-1.775	
Sex				0.723			
Female	348	1					
Male	591	1.048	0.807-1.361				
Operation method				< 0.001			0.064
MIS	296	1			1		
Open	643	1.944	1.422-2.660		1.355	0.982-1.870	
Tumor size				< 0.001			< 0.001
≤ 50 mm	543	1			1		
> 50 mm	396	2.246	1.741-2.897		1.69	1.299-2.199	
Tumor location				0.063			
Lower	483	1					
Middle	248	1.002	0.732-1.370				
Upper/Whole	208	1.395	1.036-1.879				
Histology				0.854			
Differentiated	305	1					
Undifferentiated	634	1.026	0.784-1.342				
LVI				0.001			0.616
(-)	369	1			1		
(+)	570	1.579	1.203-2.072		1.076	0.807-1.434	
Serious complications				< 0.001			0.146
(-)	814	1			1		

(+)	125	1.919	1.413-2.607		1.267	0.921-1.742	
Adjuvant chemotherapy				< 0.001			< 0.001
Adequacy[a]	570	1			1		
Inadequacy[b]	369	2.071	1.611-2.662		2.276	1.748-2.964	
Pathologic stage				< 0.001			< 0.001
II	463	1			1		
III	476	3.364	2.525-4.481		3.216	2.386-4.334	

HR indicates hazard ratio; CI, confidence interval; MIS, minimally invasive surgery; LVI, lymphovascular invasion.

Abbreviations: HR, hazard ratio; CI, confidence interval; MIS, minimally invasive surgery; LVI, lymphovascular invasion.

[a]Adequate AC was defined when AC was completed without omission or delayed initiation.

[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

Table 12. Univariate and multivariate analyses of recurrence-free survival rate.

Characteristics	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Age				0.18			
≤ 60 years	471	1					
> 60 years	468	1.189	0.923-1.532				
Sex				0.493			
Female	348	1					
Male	591	0.913	0.705-1.184				
Operation method				< 0.001			0.144
MIS	296	1			1		
Open	643	1.916	1.403-2.616		1.246	0.901-1.722	
Tumor size				< 0.001			< 0.001
≤ 50 mm	543	1			1		
> 50 mm	396	2.533	1.954-3.283		1.965	1.507-2.562	

Tumor location				0.025			0.294
Lower	483	1			1		
Middle	248	0.881	0.638-1.216		1.039	0.751-1.436	
Upper/Whole	208	1.391	1.032-1.875		1.267	0.937-1.713	
Histology				0.373			
Differentiated	305	1					
Undifferentiated	634	1.134	0.860-1.496				
LVI				< 0.001			0.555
(-)	369	1			1		
(+)	570	1.663	1.260-2.195		1.109	0.825-1.491	
Serious complications				0.001			0.06
(-)	814	1			1		
(+)	125	1.754	1.272-2.420		1.376	0.987-1.919	
Adjuvant chemotherapy				0.019			0.001
Adequacy[a]	570	1			1		
Inadequacy[b]	369	1.358	1.051-1.753		1.554	1.191-2.026	
Pathologic stage				< 0.001			< 0.001
II	463	1			1		
III	476	3.733	2.777-5.019		3.352	2.471-4.547	

HR indicates hazard ratio; CI, confidence interval; MIS, minimally invasive surgery; LVI, lymphovascular invasion.
Abbreviations: HR, hazard ratio; CI, confidence interval; MIS, minimally invasive surgery; LVI, lymphovascular invasion.
[a]Adequate AC was defined when AC was completed without omission or delayed initiation.
[b]Inadequate AC was defined when AC was omitted, delayed in initiation, or not completed the scheduled chemotherapy cycles.

IV. DISCUSSION

In this study based on real-world data, patients with serious complications demonstrated worse survival and a higher rate of disease recurrence than patients without serious complications after curative gastrectomy for stage II/III gastric cancer. A majority of patients with serious complications failed to receive adequate adjuvant therapy. Eventually, patients who experienced serious complications combined with inadequate adjuvant chemotherapy revealed the worst survival rate as well as the highest recurrence rates.

Poor survival of patients with postoperative complications after gastrectomy for stage II/III gastric cancer cannot be considered apart from adjuvant chemotherapy. Randomized controlled studies have established that adjuvant chemotherapy following gastrectomy has survival advantages compared to gastrectomy alone[17,18]. Thus, adequate delivery and completion of adjuvant chemotherapy is necessary to obtain a survival benefit after curative gastrectomy for stage II/III gastric cancer. As shown in this study, the SC group demonstrated a higher proportion of patients who did not receive adequate adjuvant chemotherapy.

Consistent with our results, postoperative complications in gastric cancer patients prompted failure to complete multimodal therapy even in a perioperative chemotherapy setting[20]. Patients are relatively tolerant of perioperative chemotherapy because they receive chemotherapy under a relatively healthy condition compared to a postoperative condition. Therefore, it is difficult to determine the effect of postoperative complications on the survival outcomes of patients who have received preoperative chemotherapy because chemotherapy itself can affect postoperative complications and survival outcomes. Moreover, in the perioperative chemotherapy setting, all patients completed preoperative chemotherapy even though postoperative chemotherapy could be affected by postoperative complications. However, in the adjuvant

setting, patients are affected by the effect of the complication on the whole process of chemotherapy. Thus, adverse effect of complications on chemotherapy would be greater in an adjuvant setting than in a perioperative one.

The prognostic impact of serious complications differed according to pathologic stage in our study. Assessing the impact of serious complications combined with the adequacy of adjuvant chemotherapy on survival outcome is very complex. In this study, the presence of serious complications in stage III patients resulted in poor prognosis regardless of adequacy of chemotherapy. However, the adverse impact of serious complications was not profound in stage II patients. If chemotherapy was delivered adequately, even patients with serious complications in stage II demonstrated similar survival to those who did not experience serious complications. Thus, it is important to treat serious complications befittingly to administer adequate adjuvant chemotherapy.

To consider the timely treatment of complications, we combined the length of stay and the severity of modified Clavien-Dindo complication grade to define serious complications. Most previous studies in gastric cancer used a modified Clavien-Dindo classification system, and grade III or higher was used to express the severity of the complication[6,21,22]. Under this classification, many surgeons expect patients with complications to recover from conservative care without active treatment to avoid a high-grade complication rating. As a result, patients stay longer in the hospital and have poor general conditions, which is most likely adversely affects the delivery of adjuvant chemotherapy and survival outcomes even without serious complications. Furthermore, patients remaining in the hospital for 15 days or longer with Clavien-Dindo grade I/II complications showed similar clinicopathologic characteristics as those with Clavien-Dindo grade III or higher complications. Similar impact on the adequacy of adjuvant chemotherapy and survival outcomes was also observed. Therefore, serious complications are more suitable in determining patient group

according to the severity of postoperative complications.

The adverse effects of serious complications on prognosis in our study are consistent with previous studies[5,11,20,23]. Poor prognosis of patients with serious complications was presumed since host immunosuppression and proinflammatory cytokines induce growth of residual cancer cells[24,25]. In fact, patients who experienced anastomotic leakage, intra-abdominal infectious complications, or inflammatory complications following gastrectomy demonstrated worse survival than those without complications[5,11,26].

This study has several limitations. First, only a relatively small number of patients with serious complications limited to analyze the impact of the type of complications on adjuvant chemotherapy and survival outcomes. It is necessary to identify the effect of each type of complication on prognosis after gastrectomy. Second, the regimens of adjuvant chemotherapy used in this study were not homogeneous, although most of patients received either TS-1 monotherapy or XELOX. Differences in chemotherapy regimen may influence the adequacy of adjuvant chemotherapy because they affect patient compliance. It is difficult to assess the precise relationship between postoperative complications and adequacy of adjuvant chemotherapy with patient prognosis. Another possible limitation is the retrospective nature of this study. To exactly evaluate the prognostic impact of complications together with chemotherapy, a randomized trial would be ideal. However, a randomized clinical trial is not always feasible in complication-related research. Moreover, the patient population selected by the inclusion and exclusion criteria in a prospective study is relatively not vulnerable, resulting in fewer postoperative complications which do not reflect real clinical practice. Therefore, in this study, we used prospectively collected real-world data which reflected real clinical practice.

V. CONCLUSIONS

A prospectively collected real-world data analysis revealed that serious complications after gastrectomy had a negative impact on the prognosis of patients with stage II/III gastric cancer. Serious complications significantly worsened survival outcomes in association with inadequacy of adjuvant chemotherapy. Therefore, efforts should be made to reduce serious complications as well as support adequate chemotherapy in a timely manner through the proper management of serious complications, which will improve the long-term survival of patients with stage II/III gastric cancer.

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ABSTRACT (IN KOREAN)

2/3기 위암 환자에서 위 절제술 후 합병증이 예후에 미치는 부정적인 영향: 전향적으로 수집된 실제 임상 데이터의 분석

<지도교수 형 우 진 >

연세대학교 대학원 의학과

송 정 호

연구적 배경: 위암 환자의 예후에 대한 수술 후 합병증의 영향은 후향적 분석에서 누락 된 데이터와 전향적 연구에서 환자 선택 편견으로 인해 논란의 여지가 있다. 본 연구는 전향적으로 수집된 실제 임상 데이터를 사용하여 2기와 3기 위암에 대해 위 절제술을 받은 환자의 대규모 코호트에서 수술 후 합병증과 장기 생존 사이의 관계를 분석하는 것을 목표로 했다.

방법: 본 연구는 2013년부터 2015년까지 2기와 3기 위암으로 위 절제술을 받은 939명의 환자를 대상으로 하였다. 재원 기간이 15일 이상인 합병증 또는 Clavien-Dindo 3등급 이상을 나타내는 serious 합병증에 따라 환자를 나누었다. 생존 결과를 그룹간에 비교하였다.

Results: serious 합병증 발생률은 13.3%였다. 수술 후 보조 화학 요법의 생략, 지연 또는 중단으로 정의된 보조 화학 요법의 부적절성은 serious 합병증이 없는 환자 (n = 291, 35.7 %; p < 0.001)보다 serious 합병증이 있는 환자 (n = 78, 62.4 %)에서 더 높았다. 수술 후 평균 추적 관찰 시간은 52개월 (7-71) 이었다. serious 합병증이 있는 환자의 5년 전체 생존 (OS) 및 재발 없는 생존 (RFS)은 각각 58.1 % 및 58.1 %였고, serious 합병증이 없는 환자의 5년 OS 및 RFS은 각각 73.4, 74.7 % (p < 0.001 for OS and RFS)였다.

2기에서, 적절한 보조 화학 요법 하에서 심각한 합병증이 있는 환자는 적절한 보조 화학 요법 하에서 심각한 합병증이 없는 환자와 유사한 OS 및 RFS를 가졌다 (각각 p = 0.495, p = 0.936). 3기에서, 적절한 보조 화학 요법 하에서 심각한 합병증이 없는 환자는 적절한 보조 화학 요법 하에서 심각한 합병증이 있는 환자보다 전체 생존율이 더 우수 하였다 (p = 0.013).

Conclusion: 전향적으로 수집된 실제 임상 데이터에 기반한 본 연구는 위 절제술 후 serious 합병증이 2기와 3기 위암 환자의 예후에 부정적인 영향을 미친다는 것을 나타낸다. serious 합병증은 보조 화학 요법의 부적절성에 영향을 미쳐 생존 결과를 악화시킨다. 장기 생존 결과를 높이려면 심각한 합병증을 줄이기 위한 노력이 필요하다. 또한 적절한 화학 요법을 받도록 serious 합병증이 있는 환자를 적시에 치료하는 것이 중요하다.

핵심되는 말: 위암, 수술 후 합병증, 예후, 실제 임상 데이터