J Gastric Cancer. 2020 Sep;20(3):233-244
https://doi.org/10.5230/jgc.2020.20.e20
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Advantages of ypTNM Staging in Post-surgical Prognosis for Initially Unresectable or Stage IV Gastric Cancers

Gyu-Seong Jeong [1], **In-Seob Lee** [1], **Young-Soo Park** [2], **Beom-Su Kim** [1], **Moon-Won Yoo** [1], **Jeong-Hwan Yook** [1], **Byung-Sik Kim** [1]

[1]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received: Jan 1, 2020
Revised: Apr 16, 2020
Accepted: May 1, 2020

Correspondence to
In-Seob Lee
Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: inseoblee77@gmail.com

ORCID iDs
Gyu-Seong Jeong
https://orcid.org/0000-0001-9597-1130
In-Seob Lee
https://orcid.org/0000-0003-3099-0140
Young-Soo Park
https://orcid.org/0000-0001-5389-4245
Beom-Su Kim
https://orcid.org/0000-0002-3656-2086
Moon-Won Yoo
https://orcid.org/0000-0003-0346-9042
Jeong-Hwan Yook
https://orcid.org/0000-0002-7987-5808
Byung-Sik Kim
https://orcid.org/0000-0001-9579-9211

Author Contributions
Conceptualization: J.G.S., L.I.S.; Data curation: J.G.S., L.I.S.; Formal analysis: J.G.S., L.I.S.;

ABSTRACT

Purpose: For unresectable or initially metastatic gastric cancer, conversion surgery (CVS), after systemic chemotherapy, has received attention as a treatment strategy. This study evaluated the prognostic value of ypTNM stage and the oncologic outcomes in patients receiving CVS.
Materials and Methods: A retrospective review of clinicopathologic findings and oncologic outcomes of 116 patients who underwent CVS with curative intent, after combination chemotherapy, between January 2000 and December 2015, has been reported here.
Results: Twenty-six patients (22.4%) underwent combined resection of another organ and 12 patients received para-aortic lymphadenectomy (10.3%). Pathologic complete remission (CR) was confirmed in 11 cases (9.5%). The median overall survival (OS) and disease-free survival (DFS) times were 35.0 and 21.3 months, respectively. In multivariate analysis, ypTNM stage was the sole independent prognostic factor for DFS (P=0.042). Tumors invading an adjacent organ or involving distant lymph nodes showed better survival than those with peritoneal seeding or solid organ metastasis (P=0.084). Kaplan-Meier curves showed that the 3-year OS rate of patients with pathologic CR and those with CR of the primary tumor but residual node metastasis was 81.8% and 80.0%, respectively. OS was 65.8% for stage 1 patients, 49.8% for those at stage 2, and 36.3% for those at stage 3.
Conclusions: The ypTNM staging is a significant prognostic factor in patients who underwent CVS for localized unresectable or stage IV gastric cancers. Patients with locally advanced but unresectable lesions or with tumors with distant nodal metastasis may be good candidates for CVS.

Keywords: Gastric cancer; Conversion surgery; Metastasis; Stage IV; TNM staging

INTRODUCTION

Gastric cancer is the second most common cause of cancer-related mortality in the world [1,2], and surgery is a potentially curative treatment. However, in locally advanced, unresectable, or initially metastatic tumors, palliative chemotherapy is the standard treatment and the role of surgery is very limited, except in cases where bleeding, obstruction, or perforation occurs [3,4]. Combination chemotherapy improves overall survival (OS) of

jgc Journal of Gastric Cancer

Methodology: L.I.S., P.Y.S., K.B.S.,[1] Y.M.W., Y.J.H., K.B.S.[2]; Resources: L.I.S., P.Y.S., K.B.S.,[1] Y.M.W., Y.J.H., K.B.S.[2]; Supervision: L.I.S.; Validation: L.I.S.; Writing - original draft: J.G.S.; Writing - review & editing: L.I.S.

[1]K.B.S., Beom-Su Kim; [2]K.B.S., Byung-Sik Kim.

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

patients with stage IV gastric cancer [5], and the addition of a targeted agent, to conventional chemotherapy, can improve prognosis when compared to chemotherapy alone [6,7]. However, prognosis remains poor, due to cumulative toxicity or chemo-resistance.

Conversion surgery (CVS) refers to the surgical removal, with curative intent, of tumors that are initially unresectable or accompanied by distant metastasis, but respond to combination chemotherapy [8]. Some studies have reported that CVS could improve OS in patients with unresectable or stage IV gastric cancer, and that achieving R0 resection is an important prognostic factor [8-12]. However, as these studies tend to be small in scale and use a variety of definitions of CVS, the clinical value of CVS remains controversial [13-15]. Moreover, there is a lack of analysis of prognostic factors, recurrence patterns, and the usefulness of the staging system for predicting prognosis after curative surgery.

Since the introduction of the staging system by the Union for International Cancer Control/ American Joint Committee on Cancer, the notion of the y-stage has been used in gastric cancer. This refers to TNM staging, applied in cases where neoadjuvant treatment is given before surgery. However, in terms of CVS, data to support the prognostic value of yp-staging has previously been limited.

This study aims to evaluate the oncologic outcomes of CVS in patients with unresectable or stage IV gastric cancers and, for these patients, the prognostic value of ypTNM staging.

MATERIALS AND METHODS

Patients

We reviewed the medical records of patients who underwent surgery with curative intent, after systemic chemotherapy for histologically proven, primary gastric adenocarcinoma. All selected cases were initially diagnosed as locally advanced but unresectable, or stage IV disease, on presentation at the Asan Medical Center, Seoul, Korea between January 2000 and December 2015. We initially identified 143 patients meeting the criteria. From these, we excluded patients who received surgery within 3 months after 1st chemotherapy (n=17) and cases not achieving curative resection (n=10). Finally, a total of 116 patients were included in this study.

Assessment of preoperative staging and curability

The reasons for palliative chemotherapy were classified into 4 categories: 1) distant lymph node metastasis beyond D2 dissection territory (LN), 2) peritoneal seeding (PS), 3) other solid organ metastasis (SO), and 4) invasion to an unresectable adjacent organ, including pancreas head, celiac axis, etc. (OI). The presence of non-curable factors was assessed by enhanced abdominopelvic computed tomography (CT) and positron emission tomography (PET), prior to chemotherapy, and/or exploratory laparoscopy or laparotomy. Patients suspected of having peritoneal metastasis, but without confirmation by exploratory procedure, were so-defined if they showed a minimum of 2 features on imaging examinations: definite seeded mass, multiple nodular lesions, omental infiltration, or the presence of a quantity of ascites. Preoperative curability was evaluated by a multidisciplinary team, including experienced gastrointestinal surgeons, oncologists, and radiologists. In patients with multiple incurable factors, we classified them according to the dominant one.

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

Chemotherapy regimen and the response evaluation

Palliative chemotherapy was administered to all patients, and various regimens were employed, such as docetaxel plus capecitabine with cisplatin (DXP), capecitabine plus cisplatin (XP) and capecitabine plus oxaliplatin (XELOX). Disease progression was regularly evaluated by physical examination, laboratory tests, tumor markers, and radiography. Tumor size was measured by CT every 2–3 cycles of chemotherapy, and response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines [16]. During the follow-up period, if the imaging showed improvement or disappearance of non-curable factors and if curative resection was expected, CVS was performed. All patients received distal or total gastrectomy plus D2 lymph node dissection. If needed, resection of an invaded adjacent organ or para-aortic lymphadenectomy was performed at the same time, to achieve curability. In some cases, where metastasis of the liver or para-aortic area was initially identified but subsequently disappeared, and there was no uptake on PET after chemotherapy, metastatectomy was omitted.

After surgery, the oncologist decided whether to resume adjuvant chemotherapy, considering the patient's general condition and compliance, the operative findings, and ypTNM stage. Recurrence was checked using laboratory test and tumor markers every 3 months, and by CT every 3–6 months.

Follow-up data

Patient medical records were reviewed to identify clinicopathologic characteristics, including age, sex, tumor location, differentiation, reason for palliative chemotherapy, number of incurable factors, yc- and ypTNM stage based on the American Joint Committee on Cancer 8th edition [17], combined organ resection, oncologic outcomes, and recurrence pattern. The data cut-off date was December 2018.

Statistical analysis

SPSS statistical software (version 21.0 for Windows; IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The OS and disease-free survival (DFS) rates were calculated using the Kaplan-Meier method. OS was defined as the time from surgery to death, from any cause, and DFS was defined as the time from the date of CVS to the time of confirmed recurrence or death from any cause. Patients were censored for OS and DFS, if they were recurrence-free and alive, 5 years after the surgery. Patients who were lost to follow-up, without evidence of recurrence before 5 years, were censored for DFS at the date of their last clinic visit. Cox proportional hazards models were used for univariate and multivariate analyses, and outcomes were reported as hazard ratios and 95% confidence intervals. A threshold for statistical significance was set at $P<0.05$.

Ethical approval

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Institutional Review Board of Asan Medical Center (No. 2019-0498), Seoul, Korea. Informed consent was waived according to the retrospective design.

RESULTS

Clinicopathologic and operative findings of patients

There were 82 men and 34 women included in the study and the median age at operation was 53 years.

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

Tumors were located in the lower third of the stomach in 56 cases (48.3%) and 60 cases (51.7%) had an undifferentiated histology. At diagnosis, more than 80% of the patients were clinically suspected to have tumors involving serosa or an adjacent organ, or to have more than 7 accompanying metastatic lymph nodes. Distant nodal metastasis was the most common reason for incurability, followed by OI, PS, and SO. About 90% of the patients had a single, non-curable factor. After palliative chemotherapy, tumors at clinical T4 and N2–N3 stage decreased to 56 (48.3%) and 47 cases (40.6%), respectively. The median interval between initial chemotherapy and surgery was 4.6 months (range: 3.0–40.2). About 60% of the patients received total gastrectomy and 12 patients underwent para-aortic lymphadenectomy. Twenty-six patients (22.4%) underwent combined resection of another organ to achieve curability, most commonly the spleen (**Table 1**).

Table 1. Characteristics of patients who underwent conversion surgery for unresectable or stage IV gastric cancers

Variables	Value (n=116)
Age in years	53 (26–76)
Sex	
Male	82 (70.7)
Female	34 (29.3)
Tumor location	
Lower third	56 (48.3)
Middle third	23 (19.8)
Upper third	9 (7.8)
Entire	28 (24.1)
Differentiation	
Differentiated	56 (48.3)
Undifferentiated	60 (51.7)
cT stage*	
≤T3	18 (15.5)
T4a/b	98 (84.5)
cN stage*	
≤N1	13 (11.2)
≥N2	103 (88.8)
Causes of palliative chemotherapy	
LN	63 (54.3)
PS	20 (17.2)
SO	4 (3.4)
OI	29 (25.0)
No. of incurable factors	
1	102 (87.9)
2	14 (12.1)
ycT stage*	
≤T3	60 (51.7)
T4a/b	56 (48.3)
ycN stage*	
≤N1	69 (59.4)
≥N2	47 (40.6)
Interval between initial chemotherapy and surgery in months	4.6 (3.0–40.2)
Chemotherapy regimen	
Triplet regimen	87 (75.0)
DXP	65 (56.0)
DXP + avastin	17 (14.6)
DXO	4 (3.4)
Doublet regimen	29 (25.0)
XP	9 (7.8)
XP + herceptin	5 (4.3)
XELOX	7 (6.1)
Others	4 (3.4)
Chemotherapy cycle	6.0 (3–13)

(continued to the next page)

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

Table 1. (Continued) Characteristics of patients who underwent conversion surgery for unresectable or stage IV gastric cancers

Variables	Value (n=116)
Operation type	
Distal gastrectomy	47 (40.5)
Total gastrectomy	69 (59.5)
Para-aortic lymphadenectomy	
Yes	12 (10.3)
No	104 (89.7)
Combined organ resection (n=26)	
Spleen	14
Pancreas + spleen	5
Pancreas + spleen + colon	1
Pancreas + spleen + liver	1
Pancreas	1
Spleen + colon + ovary	1
Spleen + liver	1
Liver	1
Colon	1
ypTNM stage	
NRT	11 (9.5)
NRT but residual lymph node	5 (4.3)
1	24 (20.7)
2	36 (31.0)
3	40 (34.5)

Values are presented as median (range) or number (%).
LN = distant lymph node metastasis; PS = peritoneal seeding; SO = solid organ metastasis; OI = invasion to an unresectable adjacent organ; DXP = docetaxel plus capecitabine with cisplatin; DXO = docetaxel, capecitabine, and oxaliplatin; XP = capecitabine plus cisplatin; XELOX = capecitabine plus oxaliplatin; NRT = no residual tumor.
*TNM stage was based on the American Joint Committee on Cancer 8th edition.

Pathologic complete remission (CR) was confirmed in 11 cases (9.5%), and CR of the main tumor with residual metastatic lymph node was observed in 5 patients (4.3%). With regard to ypTNM stage, stage 3 tumor was the most common (34.5%) followed by stage 2 (31.0%) and stage 1 (20.7%).

OS and DFS after CVS

The median follow-up period was 33.9 months from surgery. Seventy-one patients (61.2%) died and sixty-eight patients (58.6%) experienced relapse during the follow-up period. The 3-year and 5-year OS rates were 52.8% and 33.2%, respectively, and the median OS time was 35.0 months (**Fig. 1A**). There was a difference in OS according to incurable factors, and the OI and LN group demonstrated better prognosis compared to PS and SO groups, which was statistically significant (respective 3-year OS rate: 61.7% vs. 54.6% vs. 45.0% vs. 0%, P=0.025) (**Fig. 1B**). The 3-year and 5-year DFS rates were 42.5% and 32.1%, respectively, and the median survival time was 21.3 months (**Fig. 1C**). The DFS curve also showed similar, significant results (3-year DFS rate: 54.6% vs. 45.0% vs. 25.0% vs. 0%, P=0.019) (**Fig. 1D**).

A chemotherapeutic regimen of DXP was the most commonly used (70.6%), followed by XP (12.1%) and XELOX (6.1%). A triplet regimen was followed by 75% of patients, and a doublet regimen by 25%. There was no significant difference in OS and DFS according to chemotherapy regimen (triplet vs. doublet 5-year OS rate 31.7% vs. 34%/5-year DFS rate: 30.4% vs. 33.1%). The median cycle of systemic chemotherapy was 6 (range: 3–13) (**Table 1**). After surgery, a total of 84 patients (72.4%) resumed chemotherapy and the median cycle of chemotherapy was 3 (range: 1–16). There was no significant difference in recurrence rate and survival rate according to the total duration of chemotherapy or whether adjuvant chemotherapy was carried out.

https://doi.org/10.5230/jgc.2020.20.e20

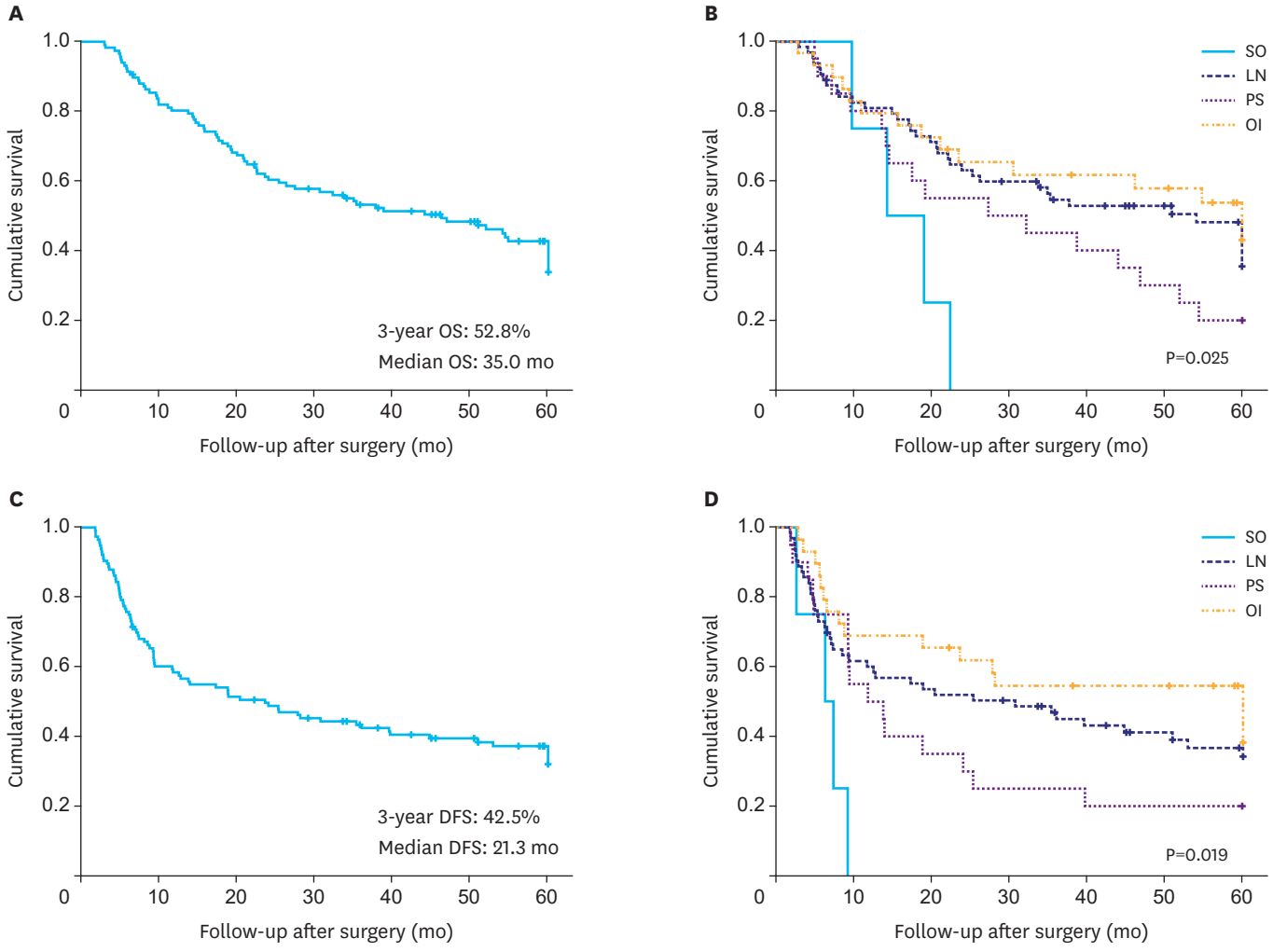

Fig. 1. OS and DFS of patients receiving conversion surgery for unresectable or stage IV gastric cancers. (A) OS of all patients, (B) OS according to the causes for palliative chemotherapy, (C) DFS of all patients, (D) DFS according to the causes of palliative chemotherapy.
OS = overall survival; DFS = disease-free survival; SO = solid organ metastasis; LN = distant lymph node metastasis; PS = peritoneal seeding; OI = invasion to an unresectable adjacent organ.

Prognostic factors and prognosis based on TNM staging after curative CVS

The univariate analysis revealed that tumors involving the entire stomach, undifferentiated histology, total gastrectomy, distant SO, PS, and advanced ypTNM stage were associated with worse DFS in patients receiving CVS. In the multivariate analysis, ypTNM stage was the sole independent prognostic factor for DFS (P=0.042) (**Tables 2** and **3**). An advanced ycT category was related to a shorter OS in the univariate analysis, but its significance was not maintained in the multivariate one.

The Kaplan-Meier curves showed that the 3-year OS rate of patients with pathologic CR and those with a CR of main tumor and residual node metastasis was 81.8% and 80.0%, respectively. OS of patients classified as stage 1 was 65.8%, stage 2 was 49.8%, and stage 3 was 36.3% (**Fig. 2**). The 3-year DFS rate for patients who were classified as CR was the highest with the rate of 81.8%, followed by patients with CR of the primary tumor and residual node metastasis (60.0%), then those classified as stage 2 (44.4%) and stage 3 (21.0%).

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

Table 2. Prognostic factors for OS after conversion surgery in patients with unresectable or stage IV gastric cancers

Variables	Univariate analysis for OS			Multivariable analysis for OS		
	HR	95% CI	P-value	HR	95% CI	P-value
Tumor location			<0.001			0.162
Lower third	1.000			1.000		
Upper third	1.462	0.781–2.737	0.236	0.767	0.329–1.786	
Middle third	1.673	0.692–4.044	0.253	0.947	0.352–2.547	
Entire	3.819	2.134–6.833	<0.001	1.754	0.785–3.922	
Differentiation			0.001			0.154
Differentiated	1.000			1.000		
Undifferentiated	2.217	1.373–3.580		1.512	0.856–2.671	
Causes of palliative chemotherapy			0.037			0.200
OI	1.000			1.000		
LN	1.202	0.658–2.197	0.549	1.120	0.574–2.186	0.739
PS	1.909	0.942–3.869	0.073	0.963	0.437–2.120	0.925
SO	4.183	1.353–12.931	0.013	3.442	1.033–11.470	0.044
ycT stage*			0.025			0.444
≤T3	1.000			1.000		
T4a/b	1.708	1.070–2.729		1.232	0.722–2.100	
Operation type			0.001			0.066
Distal gastrectomy	1.000			1.000		
Total gastrectomy	2.463	1.474–4.117		2.025	0.954–4.298	
ypTNM stage*			0.001			0.146
NRT and NRT N(+)	1.000			1.000		
1	2.631	0.865–8.002	0.088	2.142	0.648–7.076	0.212
2	3.491	1.205–10.112	0.021	3.121	0.978–9.954	0.054
3	5.766	2.024–16.426	0.001	3.389	1.076–10.677	0.037

OS = overall survival; HR = hazard ratio; CI = confidence interval; OI = invasion to an unresectable adjacent organ; LN = distant lymph node metastasis; PS = peritoneal seeding; SO = solid organ metastasis; NRT = no residual tumor; NRT N(+) = no residual tumor with residual metastatic lymph node.
*TNM stage was based on the American Joint Committee on Cancer 8th edition.

Table 3. Prognostic factors for DFS after conversion surgery in patients with unresectable or stage IV gastric cancers

Variables	Univariate analysis for DFS			Multivariate analysis for DFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Tumor location			0.002			0.676
Lower third	1.000			1.000		
Upper third	1.665	0.869–3.190	0.124	0.969	0.411–2.285	0.942
Middle third	1.758	0.723–4.275	0.213	1.118	0.412–3.034	0.827
Entire	3.143	1.751–5.642	<0.001	1.478	0.665–3.284	0.337
Differentiation			0.001			0.289
Differentiated	1.000			1.000		
Undifferentiated	2.328	1.422–3.811		1.351	0.775–2.355	
Causes of palliative chemotherapy			0.021			0.084
OI	1.000			1.000		
LN	1.327	0.741–2.375	0.220	1.310	0.651–2.637	0.449
PS	1.900	0.947–3.811	0.047	1.149	0.501–2.638	0.743
SO	4.781	1.553–14.717	0.004	4.736	1.409–15.924	0.012
Operation type			0.001			0.153
Distal gastrectomy	1.000			1.000		
Total gastrectomy	2.480	1.455–4.229		1.758	0.810–3.815	
ypTNM stage*			0.001			0.042
NRT and NRT N(+)	1.000			1.000		
1	2.692	0.877–8.259	0.083	2.156	0.639–7.276	0.216
2	3.175	1.088–9.260	0.034	2.973	0.922–9.587	0.068
3	6.305	2.211–17.978	0.001	4.264	1.355–13.425	0.013

DFS = disease-free survival; HR = hazard ratio; CI = confidence interval; OI = invasion to an unresectable adjacent organ; LN = distant lymph node metastasis; PS = peritoneal seeding; SO = solid organ metastasis; NRT = no residual tumor; NRT N(+) = no residual tumor with residual metastatic lymph node.
*TNM stage was based on the American Joint Committee on Cancer 8th edition.

https://doi.org/10.5230/jgc.2020.20.e20

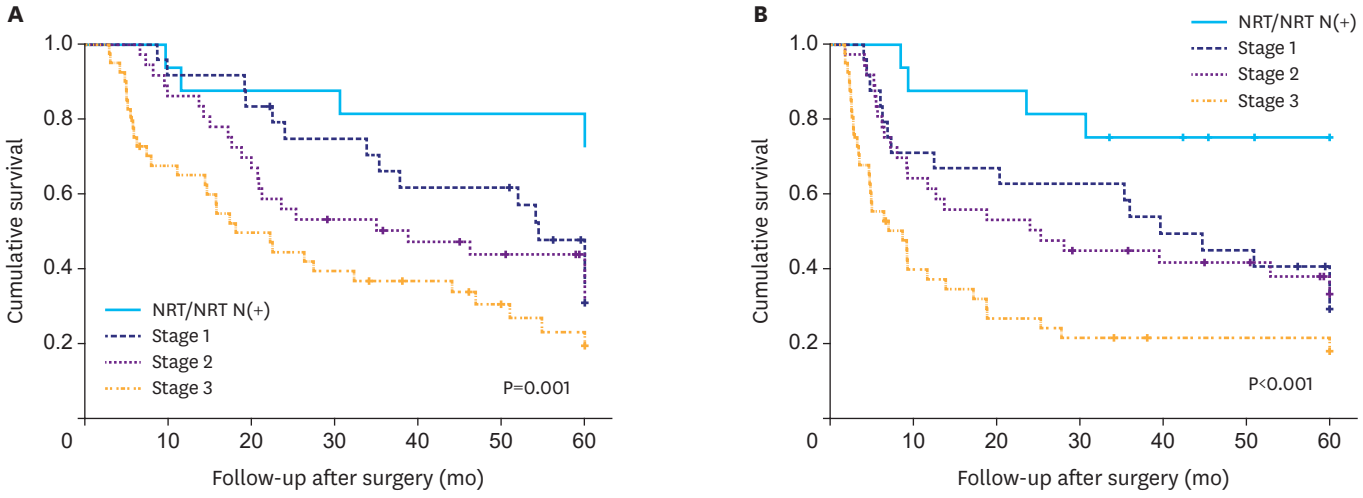

Fig. 2. OS and DFS curves according to ypTNM staging.
OS = overall survival; DFS = disease-free survival; NRT = no residual tumor; NRT N(+) = no residual tumor but with residual metastatic node.

Recurrence pattern after CVS

Recurrence rates in the SO, PS, LN, and OI groups were 100%, 75%, 57.1%, and 44.8%, respectively. Among patients initially diagnosed with PS and OI, PS was the most common site of relapse, while patients initially diagnosed with distant nodal metastasis most frequently developed recurrent lymph node metastasis. In the SO group, all recurrences occurred in the liver (**Fig. 3**).

DISCUSSION

The REGATTA clinical trial established that gastrectomy, followed by chemotherapy, provides no additional survival benefit over chemotherapy alone, in advanced gastric cancer with a single non-curable factor and, therefore, the role of surgery is limited in stage IV cancer [18]. Nevertheless, recent studies, focusing on the feasibility and oncologic outcomes of

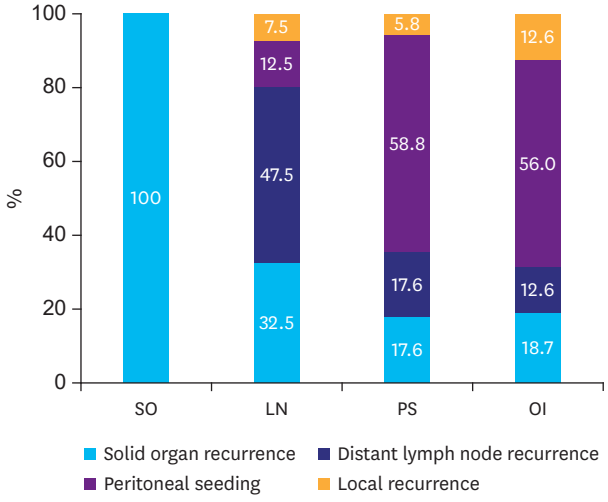

Fig. 3. Recurrence patterns in patients receiving conversion surgery for unresectable or stage IV gastric cancers.
SO = solid organ metastasis; LN = distant lymph node metastasis; PS = peritoneal seeding; OI = invasion to an unresectable adjacent organ.

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

CVS, have shown promising results. With the help of new chemotherapeutic drugs, an increasing number of patients with distant metastasis undergo surgery after palliative chemotherapy. However, because most studies are small-scale and retrospective, including patient populations not achieving R0 resection [9,19-22], prognostic factors for patients receiving curative CVS remain to be determined. Reports on prognostic factors have included N stage [9], lesion length [19], number of non-curative factors [8], and pathologic response [23] as well as curative resection. To the best of our knowledge, this is the first study to report ypTNM staging to be a prognostic factor for outcomes of CVS.

Cisplatin-based and 5-fluorouracil-based regimens have been widely used as standard palliative treatments. Previously, a phase II study conducted in our institution demonstrated that 74% of the patients with unresectable, locally advanced or limited, intra-abdominal, metastatic gastric cancer underwent surgery, and 63% of them achieved R0 resection after receiving DXP, suggesting that surgery with DXP might offer a curative option for these types of cancer [24]. This is why the DXP regimen was frequently used in the current study.

Previous studies demonstrated that CVS could offer a 5-year OS which ranged from 34.4% to 49%, with a median survival time between 19.2 and 62 months, which is similar to our findings. However, we had an R0 resection rate of 92%, which is higher than that reported in other studies. We excluded patients receiving surgery within 3 months after initial chemotherapy because many of them required urgent operations, due to impending or actual perforation or bleeding, which could disturb curative intervention and optimal timing. Moreover, resectability was not confirmed by exploratory procedures for some tumors suspected of having direct invasion to the pancreas head, so the potential for preoperative overstaging might affect the R0 rate.

Peritoneal carcinomatosis is the most common route of tumor metastasis in stage IV gastric cancer, and its prognosis is worse than that for other metastases [25,26]. We also found that the prognosis for patients with PS was worse than for patients classified as OI or LN, in the univariate analysis; however, the multivariate analysis did not identify any significant relationship between these factors and prognosis. We also found that the prognosis of SO was significantly worse than other metastases. The 4 patients classified as SO had metastases confined to the liver, before surgery. Among them, three patients received CVS after hepatic lesions disappeared on CT and/or PET during the follow-up period. As the disappearance of hepatic metastases was regarded as CR, we performed only radical gastrectomy with lymphadenectomy, while the one patient with remaining hepatic lesions received gastrectomy plus left hemihepatectomy. All 4 patients experienced relapse in the liver.

Patients classified as OI and LN had better outcomes, with the 3-year OS exceeding 50% and a DFS of 45% or higher. Although we removed para-aortic lymph nodes in 12 patients, there was no difference in survival between those who received lymphadenectomy and those who did not. Because the number of patients in the SO group was too small for meaningful analysis, we re-analyzed prognostic factors for the three other groups and ypTNM staging remained as a significant prognostic factor for DFS (P=0.043). Therefore, patients with locally advanced but unresectable lesions, or with tumors with distant nodal metastasis, could be good candidates for CVS.

The TNM classification system is used to direct treatment and to predict prognosis, as well as to stage tumors. The total number of unresectable or stage IV gastric cancers reaching

https://doi.org/10.5230/jgc.2020.20.e20

jgc Journal of Gastric Cancer

curative surgery, after chemotherapy, is so small that the value of a staging system for prognosis after CVS has not been fully realized. Two previous studies reported that pN3 stage and preoperative T4b disease were prognostic factors for relatively worse outcomes, but there was no direct relationship with TNM staging [9,27]. Another study demonstrated that pT stage was the prognostic factor for OS, in a univariate analysis, but it failed to maintain significance in a multivariate one [10].

This current study revealed that ypTNM classification was the sole prognostic factor for DFS and, although it did not reach a statistical significance for OS, might also be a potential candidate as a predictive factor for OS. We also demonstrated that the survival period of patients with complete resolution of their main tumor was longer than that of other groups, showing a significant survival difference.

Our study had some limitations. First, this study was retrospective and based on data from a single institution. Second, there was the potential for selection bias because not all patients underwent surgical exploration when determining curability, and imaging studies were used to inform treatment decisions in OI and PS groups. Finally, in some cases with accompanying metastasis in the liver or para-aortic area, we regarded radiologic disappearance of metastatic lesions as CR and metastatectomy was not performed at the same time. A prospective multicenter study could help provide more objective results. However, the present study is valuable because it demonstrates that ypTNM staging is useful in making a prognosis for patients receiving CVS for unresectable or stage IV gastric adenocarcinomas.

REFERENCES

1. Ferro A, Peleteiro B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, et al. Worldwide trends in gastric cancer mortality (1980–2011), with predictions to 2015, and incidence by subtype. Eur J Cancer 2014;50:1330-1344.
PUBMED | CROSSREF
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30.
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 Association (KGCA), Development 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. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903-2909.
PUBMED | CROSSREF
6. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-697.
PUBMED | CROSSREF
7. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-1235.
PUBMED | CROSSREF
8. Fukuchi M, Ishiguro T, Ogata K, Suzuki O, Kumagai Y, Ishibashi K, et al. Prognostic role of conversion surgery for unresectable gastric cancer. Ann Surg Oncol 2015;22:3618-3624.
PUBMED | CROSSREF

9. Han DS, Suh YS, Kong SH, Lee HJ, Im SA, Bang YJ, et al. Outcomes of surgery aiming at curative resection in good responder to induction chemotherapy for gastric cancer with distant metastases. J Surg Oncol 2013;107:511-516.
PUBMED | CROSSREF
10. Beom SH, Choi YY, Baek SE, Li SX, Lim JS, Son T, et al. Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy. BMC Cancer 2018;18:1116.
PUBMED | CROSSREF
11. Ishigami S, Natsugoe S, Nakajo A, Matsumoto M, Uenosono Y, Arigami T, et al. Salvage gastrectomy following a combination of biweekly paclitaxel and S-1 for stage IV gastric cancer. J Gastrointest Surg 2008;12:1370-1375.
PUBMED | CROSSREF
12. Yabusaki H, Nashimoto A, Matsuki A, Aizawa M. Significance of surgical treatment in multimodal therapy for stage IV highly advanced gastric cancer. Hepatogastroenterology 2013;60:377-381.
PUBMED
13. Okabe H, Ueda S, Obama K, Hosogi H, Sakai Y. Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. Ann Surg Oncol 2009;16:3227-3236.
PUBMED | CROSSREF
14. Satoh S, Hasegawa S, Ozaki N, Okabe H, Watanabe G, Nagayama S, et al. Retrospective analysis of 45 consecutive patients with advanced gastric cancer treated with neoadjuvant chemotherapy using an S-1/CDDP combination. Gastric Cancer 2006;9:129-135.
PUBMED | CROSSREF
15. Suzuki T, Tanabe K, Taomoto J, Yamamoto H, Tokumoto N, Yoshida K, et al. Preliminary trial of adjuvant surgery for advanced gastric cancer. Oncol Lett 2010;1:743-747.
PUBMED | CROSSREF
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.
PUBMED | CROSSREF
17. Amin MB, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, et al. AJCC cancer staging manual. 8th ed. New York: Springer International Publishing, 2017.
18. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016;17:309-318.
PUBMED | CROSSREF
19. Kanda T, Yajima K, Kosugi S, Ishikawa T, Ajioka Y, Hatakeyama K. Gastrectomy as a secondary surgery for stage IV gastric cancer patients who underwent S-1-based chemotherapy: a multi-institute retrospective study. Gastric Cancer 2012;15:235-244.
PUBMED | CROSSREF
20. Kim SW. The result of conversion surgery in gastric cancer patients with peritoneal seeding. J Gastric Cancer 2014;14:266-270.
PUBMED | CROSSREF
21. Nakajima T, Ota K, Ishihara S, Oyama S, Nishi M, Ohashi Y, et al. Combined intensive chemotherapy and radical surgery for incurable gastric cancer. Ann Surg Oncol 1997;4:203-208.
PUBMED | CROSSREF
22. Satoh S, Okabe H, Teramukai S, Hasegawa S, Ozaki N, Ueda S, et al. Phase II trial of combined treatment consisting of preoperative S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV gastric cancer. Gastric Cancer 2012;15:61-69.
PUBMED | CROSSREF
23. Sato Y, Ohnuma H, Nobuoka T, Hirakawa M, Sagawa T, Fujikawa K, et al. Conversion therapy for inoperable advanced gastric cancer patients by docetaxel, cisplatin, and S-1 (DCS) chemotherapy: a multi-institutional retrospective study. Gastric Cancer 2017;20:517-526.
PUBMED | CROSSREF
24. Sym SJ, Chang HM, Ryu MH, Lee JL, Kim TW, Yook JH, et al. Neoadjuvant docetaxel, capecitabine and cisplatin (DXP) in patients with unresectable locally advanced or metastatic gastric cancer. Ann Surg Oncol 2010;17:1024-1032.
PUBMED | CROSSREF
25. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004;22:2395-2403.
PUBMED | CROSSREF

jgc Journal of Gastric Cancer

26. Kim JG, Ryoo BY, Park YH, Kim BS, Kim TY, Im YH, et al. Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. Cancer Chemother Pharmacol 2008;61:301-307.
PUBMED | CROSSREF

27. Fukuchi M, Ishiguro T, Ogata K, Kimura A, Kumagai Y, Ishibashi K, et al. Risk factors for recurrence after curative conversion surgery for unresectable gastric cancer. Anticancer Res 2015;35:6183-6187.
PUBMED