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Clinical Outcomes and the Role of Adjuvant Concurrent Chemoradiation Therapy in D2-resected LN-positive Young Patients (≤45 Years) With Gastric Cancer

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Abstract. *Background/Aim: This study aimed to investigate the clinical outcomes and role of adjuvant concurrent chemo-radiation therapy (CCRT) compared to adjuvant chemotherapy alone in young patients with gastric cancer (GC) defined as those ≤45 years old versus older patients. Patients and Methods: Data were collected from December 2004 to January 2013 on patients with pathologically confirmed, regional lymph node metastasis of GC who had undergone curative D2 resection. Results: During the study period, a total of 1,633 patients (341 young and 1,292 older GC) was investigated. Female sex and diffuse type were more frequent among the younger group, but, lymphatic and venous invasion were less frequent. During the follow-up, there was no difference in recurrence-free survival (RFS; p=0.81), but RFS was significantly higher in young patients with stage II GC (p=0.02). In the younger group, adjusted RFS did not differ according to adjuvant treatment (p=0.98), but the RFS was significantly higher in the older group treated with CCRT than with chemotherapy alone after adjustment for significant prognostic factors (p=0.008). Conclusion: Although young patients with GC had different characteristics, their clinical outcomes did not differ from those of the older patients. In the present study performed in curatively D2-resected GC, there was no benefit from adjuvant CCRT over chemotherapy alone among young patients, unlike among the older patients.*

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Gastric cancer (GC) is the fifth most common malignant tumor type and the third most common cause of cancer-related death worldwide (1). Although overall the incidence of GC appears to have been decreasing, its incidence among young patients, defined as ≤35 or ≤45 years, has been reported to be increasing in recent articles (2, 3).

In studies of young patients with GC, it is repeatedly reported that its occurrence is higher among females, diffuse type of Lauren's classification is more frequent, and stage is higher among young patients than among older ones (4-6). Additionally, in a recent study from a single institution in Korea, one of the countries with the highest incidence of GC, about 15% of all patients were young, defined as age 45 years or younger (7). Although the prognoses and treatment outcomes among young patients with GC are still controversial, it is generally accepted that the clinical and genetic characteristics of GC in young patients are distinct from those in older patients (4-6). Thus, there is the question about the need for modifying GC management between younger and older patients.

In managing GC, treatment outcomes are improving with D2 resection and adjuvant chemotherapy as a standard treatment based on the results of randomized clinical trials

(8-12). The role of adjuvant radiotherapy (RT) combined with chemotherapy, however, remains uncertain in D2-resected GC despite the positive outcomes from the Intergroup (INT)-0116 trial and meta-analysis of randomized trials (13-16). Our Institution reported the outcomes of the adjuvant chemoradiation therapy in stomach cancer (ARTIST) randomized phase III trial, which compared adjuvant concurrent chemo-RT (CCRT) with chemotherapy alone (CA) in D2-resected GC (17), and we found beneficial effects in the subgroup with lymph node (LN) metastasis, although we failed to confirm the superiority of RT combination over CA in patients overall.

Based on the results from the INT-0116 and ARTIST trials, adjuvant CCRT might be beneficial in GC, especially in patients with LN metastasis, but no research has yet evaluated the effects of CCRT in young patients with GC, who have clearly distinct clinical and genetic characteristics from those of older patients. Based on this background, we performed the present study to compare the treatment outcomes according to adjuvant CCRT or CA after D2-resectin young and old GC patients with LN metastasis.

Patients and Methods

Patients. This study was approved by the Samsung Medical Center Institutional Review Board (SMC-IRB 2018-04-069) and was exempted from the requirement of written informed consent. A separate, previously published article compared the effects of CCRT in all patients using the same patient group as this study, and a detailed description of the patients enrolled in this study is provided in that (18). Briefly, this study enrolled patients with pathologically confirmed M0 gastric adenocarcinoma with LN metastasis who underwent curative D2 and R0 resection without neoadjuvant chemotherapy or RT at the Samsung Medical Center from December 2004 to January 2013. Patients who had comorbid malignancies within 1 year before or after the operation, for whom we had no information on treatment, who were lost to follow-up or in whom recurrence was detected within 2 months after the operation were excluded. For this study, we defined young patients as those age 45 years or younger on the date of surgery and defined all others as older patients.

Adjuvant treatment. The ARTIST study was conducted during the period of this study, and we recommended participation to eligible patients. Patients who agreed to participate in the ARTIST trial received six cycles of capecitabine and cisplatin (XP) or two cycles of XP followed by 45 Gy of external beam RT in 25 fractions with capecitabine and then two additional cycles of XP based on random assignment (17). When patients refused to participate in the ARTIST study or participation was not indicated, we recommended one cycle of fluorouracil and leucovorin (FL) followed by 45 Gy of external beam RT in 25 fractions with FL according to the INT-0116 protocol (14). As adjuvant CA, we also recommended S-1 based on the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer trial or capecitabine and oxaliplatin (XELOX) based on the CLASSIC trial after the beneficial effects of adjuvant chemotherapy in randomized trials had been published (8, 10). Adjuvant CCRT or CA was the patient's choice based on a full explanation by their physician.

Radiation therapy. Detailed explanation of adjuvant RT for GC was given in a previous publication (19). Briefly, we used anterior-posterior parallel opposing fields and an X-ray simulator (Ximatron; Varian, Palo Alto, CA, USA) until June 2007 and then used Acuity (Varian) until September 2007. The RT target was defined as the tumor bed in T4 disease and regional LN area (group 2 including left gastric, common hepatic, celiac, and splenic, and group 3; hepaticoduodenal ligament, retropancreatic, and para-aortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal artery). When the surgical resection margins were less than 3 cm, the anastomosis site and duodenal stump were also involved in the target. With an additional 1.5 cm lateral and 2.0 cm supero-inferior block margin from the described target volume, we determined the treated volume. In January 2008, we began applying CT simulation for GC at our Institution, and through February 2008, we did not change our treatment technique from the anterior-posterior parallel opposing fields or our target definition from the 2D era. In March 2008, we began 3D conformal RT technique for the adjuvant GC RT. The clinical target volume was defined the same as the previous target including regional LN area with 5 mm margin, and the beam margin was designed with an additional 1.5 cm lateral and 2.0 cm supero-inferior block margin.

Follow-up. Four to six weeks after surgery, the medical oncologist determined adjuvant treatment with or without RT with patient informed consent. During the chemotherapy and/or CCRT, follow-up was every four weeks for chemotherapy and/or every week with the radiation oncologist. Regular follow-up was continued every 3 months in the first year, every 6 months over the next 2 years, then every year after completion of adjuvant treatment. Disease recurrence was confirmed by histological examination if possible or by radiological examination including computed tomography (CT), magnetic resonance imaging, with/without positron-emission tomography CT.

Locoregional recurrence (LRR) was defined as any site of recurrence at the anastomosis site, remnant stomach, tumor bed, duodenal stump, or regional LNs within the RT field or hypothetical RT field of the non-RT group. Radiation oncologists who specialized in gastrointestinal tumors including stomach cancer (J.I.Y. and D.H.L.) reviewed the recurrence sites and the medical records to determine whether the recurrence was LRR according to the criteria described above, and all other recurrences were defined as distant metastases (DM). LRR was considered an event in this study only if it occurred without any other recurrence or if diagnosed within 2 weeks from detecting any other recurrences after the operation.

Statistical analysis. Chi-square test or Fisher's exact test were used to compare the categorical variables between groups and two-sample *t*-test or the Wilcoxon rank-sum test were used to compare the continuous variables. Recurrence-free survival (RFS) was calculated from the date of operation to the date of recurrence detection or last follow-up, and the log-rank test was used for statistical comparison of the survival curves, which were estimated using the Kaplan–Meier product limit. Multivariable analysis with forward stepwise selection was used to compare the RFS between the groups. In the multivariable analysis, we analyzed the variables for which the *p*-vaIue was 0.1 in the univariable analysis and adjuvant treatment, except for the number of metastatic LNs, which had strong association with the pN stage and age. The Kaplan–

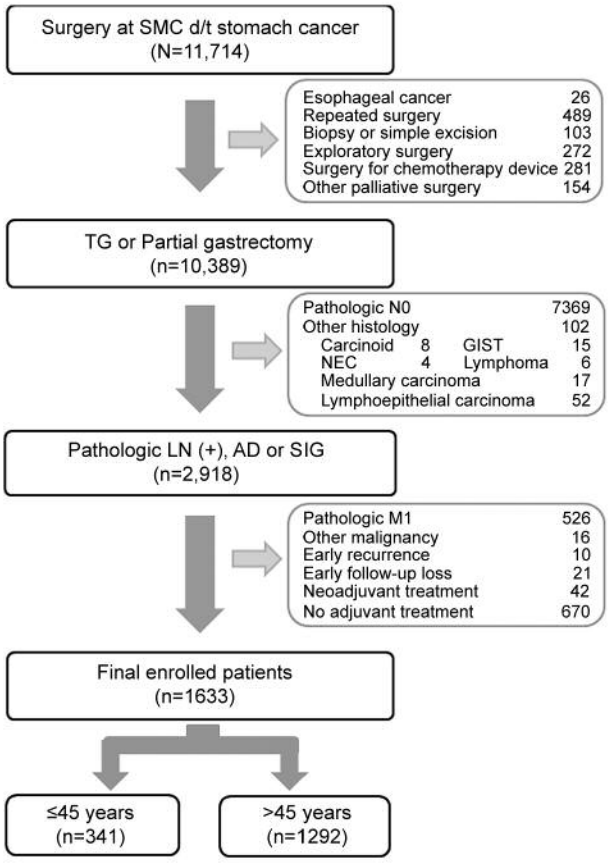

Figure 1. *Flow diagram of patient inclusion in the present study. SMC: Samsung Medical Center; TG: total gastrectomy; GIST: gastrointestinal stromal tumor; NEC: neuroendocrine carcinoma; LN: lymph node; AD: adenocarcinoma; SIG: signet ring cell carcinoma.*

Meier RFS curves were also compared according to adjuvant treatment in the young *versus* older patients after inverse probability treatment weighting using the factors that showed statistical significance in the multivariable analysis in both groups. All statistical analyses were performed using SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Institute, Cary, NC, USA), or R 3.4.0 (Vienna, Austria; http://www.R-project.org/), and *p*-values of less than 0.05 were considered statistically significant.

Table I. *Baseline characteristics of the patients with gastric cancer.*

Parameter	Young (n=341)	Old (n=1,292)	*p*-Value
Age, years			<0.001
Median (range)	40 (28-45)	59 (46-84)	
Gender, n (%)			<0.001
Male	167 (49.0)	889 (68.8)	
Female	174 (51.0)	403 (31.2)	
Type of surgery (%)			0.70
Total gastrectomy	116 (34.0)	455 (35.2)	
Subtotal gastrectomy	225 (66.0)	837 (64.8)	
Lauren classification			<0.001
Intestinal	53 (15.5)	497 (38.5)	
Diffuse	232 (68.0)	583 (45.1)	
Mixed	2 (0.6)	13 (1.0)	
Unclassified	54 (3.3)	199 (15.4)	
pT stage, n (%)			0.02
1	71 (20.8)	185 (14.3)	
2	138 (40.5)	560 (43.3)	
3	84 (24.6)	381 (29.5)	
4	48 (14.1)	166 (12.8)	
pN stage, n (%)			0.60
1	108 (31.7)	448 (34.7)	
2	112 (32.8)	388 (30.0)	
3a	84 (24.6)	330 (25.5)	
3b	37 (10.9)	126 (9.8)	
Number of dissected LNs			0.39
Median (range)	43 (16-111)	44 (15-142)	
Number of LN metastases			0.88
Median (range)	4 (1-48)	4 (1-54)	
Lymphatic invasion			0.007
Yes	233 (68.3)	979 (75.8)	
No	108 (31.7)	313 (24.2)	
Venous invasion			0.004
Yes	37 (10.9)	221 (17.1)	
No	304 (89.1)	1071 (82.9)	
Perineural invasion			0.08
Yes	174 (51.0)	588 (45.5)	
No	167 (49.0)	704 (54.5)	
EBV*			0.34
Positive	10 (6.1)	58 (8.7)	
Negative	153 (93.9)	606 (91.3)	
Adjuvant treatment			<0.001
Chemotherapy alone	107 (31.4)	617 (47.8)	
CCRT	234 (68.6)	675 (52.2)	

LN, Lymph node; EBV, Epstein-Barr virus, CCRT, concurrent chemoradiation therapy. *This analysis was performed only for patients with EBV immunohistochemistry results (young: n=163; old: n=664).

Results

Enrolled patients. Among the 11,714 patients who underwent surgery and were registered in the Samsung Medical Center registry for GC during the study period, a total of 1,633 patients who satisfied the study criteria were enrolled in this study, 341 aged 45 years or younger and 1,292 over this age. We reported the details of the patients we excluded in previous studies in Figure 1.

Baseline characteristics. Table I displays the baseline characteristic of the 1,633 patients with GC we enrolled in the present study, 341 (20.9%) young and 1,292 (79.1%) old. There were significantly more females (51.0% *vs*. 31.2%, $p<0.001$), and patients with diffuse-type cancer according to Lauren's classification (68.0% *vs*. 45.1%, $p<0.001$) in the young group. There was no outstanding difference in

Table II. *Patterns of failure between the two groups of patients with gastric cancer according to the adjuvant treatment.*

Site of recurrence	Young (n=341)			Old (n=1,292)		
	CCRT	CA	*p*-Value	CCRT	CA	*p*-Value
LRR, n (%)						
Total	12/234 (5.1)	7/107 (6.5)	0.62	42/675 (6.2)	48/617 (7.8)	0.28
Stage I	0/21 (0.0)	0/14 (0.0)	-	0/55 (0.0)	1/56 (1.8)	1.00
Stage II	4/97 (4.1)	0/48 (0.0)	0.30	7/259 (2.7)	14/311 (4.5)	0.37
Stage III*	8/116 (6.9)	7/45 (15.6)	0.12	35/361 (9.7)	33/250 (13.2)	0.19
DM, n (%)						
Total	56/234 (23.9)	16/107 (15.0)	0.06	141/675 (20.9)	118/617 (19.1)	0.45
Stage I	0/21 (0.0)	1/14 (7.1)	0.40	0/55 (0.0)	1/56 (1.8)	1.00
Stage II	5/97 (5.2)	1/48 (2.1)	0.66	21/259 (8.1)	39/311 (12.5)	0.10
Stage III	51/116 (44.0)	14/45 (31.1)	0.21	120/361 (33.2)	78/250 (31.2)	0.66
Recurrence, n (%)						
Total	66/234 (28.2)	22/107 (20.6)	0.14	170/675 (25.2)	161/617 (26.1)	0.75
Stage I	0/21 (0.0)	1/14 (7.1)	0.40	0/55 (0.0)	2/56 (3.6)	0.50
Stage II	9/97 (9.3)	1/48 (2.1)	0.16	27/259 (10.4)	52/311 (16.7)	0.04
Stage III	57/116 (49.1)	20/45 (44.4)	0.73	143/361 (39.6)	107/250 (42.8)	0.45

CCRT: Concurrent chemoradiation therapy; CA: chemotherapy alone; LRR: locoregional recurrence; DM: distant metastasis. The seventh edition of the American Joint Committee on Cancer staging system was used.

pathologicaI staging between the two groups, although there was a statistically significant difference in the pT stage (p=0.02), with pT1 and pT4 being slightly higher in young patients with GC. The rates of lymphatic (68.3% *vs.* 75.8%, p=0.007) and venous (10.9% *vs.* 17.1%, p=0.004) invasion were significantly lower in the young group, and the proportion of those who received adjuvant CCRT was also higher in the young group (68.6% *vs.* 52.2%, p<0.001).

Baseline characteristics of CCRT and CA subgroups. In the young group, there was no noticeable difference in characteristics between the CCRT and CA subgroups, although there was a tendency for more LN metastases in the CCRT group (median=4 *vs.* 3, p=0.04). In contrast, there were significant differences in several factors between the two subgroups among the older patients, including age (median=58 *vs.* 62 years, p<0.001), number of metastatic LNs (median=5 *vs.* 3, p<0.001), and higher pN stage (p<0.001); there were also more LNs dissected in the CCRT subgroup (median= 45 *vs.* 43, p=0.004).

Recurrence and survival outcomes. The median follow-up periods for the young and older patients were 68.8 (range=8.5-133.3), and 64.6 (range=3.9-141.7) months. During the follow-up, we detected recurrence in 88 (25.8%) young patients and 331 (25.6%) older patients (p=0.95). There were no significant differences between the two groups in either LRR or DM; we detected LRR in 19 (5.6%) young patients and 90 (7.0%) older patients (p=0.40) and DM in 72 (21.1%) young and 259 (20.0%) older patients (p=0.65).

Failure patterns according to adjuvant treatment. Table II shows the results of the patterns of failure according to the adjuvant treatment and stage in D2-resected patients with LN metastasis. As shown, the overall LRR did not differ significantly between the CCRT and CA subgroups in either the old or young group, at approximately 5 to 8%, and DM and overall recurrence were also similar between the subgroups in both GC groups; however, the frequency of DM was marginally higher in the CCRT subgroup than in the CA group among the young patients (p=0.06). There were no significant differences in failure patterns between young and old patients according to adjuvant treatment by stage, except for stage II in the older group: Among the older patients, overall recurrence was significantly lower in the CCRT subgroup than in the CA subgroup in those with stage II (p=0.04).

Survival outcomes. Overall, there was no difference in RFS between the young and old patients (p=0.81), and by stage, there was no significant difference in RFS between the two groups in stage I and stage III; in contrast, RFS was significantly higher in the young patients than in the older patients in those with stage II GC (p=0.02). Figure 2 shows the Kaplan–Meier RFS curves for all patients and by stage according to age.

Recurrence-free survival according to the adjuvant treatment. In the young group, Kaplan–Meier survival curves for RFS were marginally lower in the CCRT subgroup than in the CA subgroup (Figure 3A, p=0.18), although RFS was

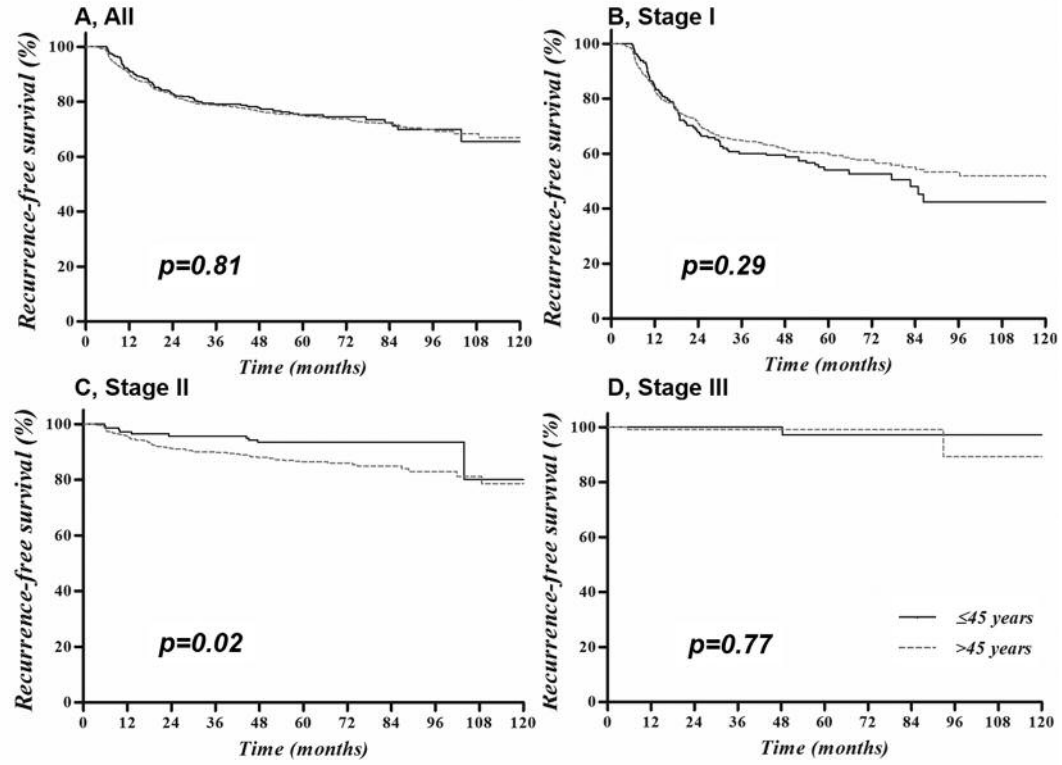

Figure 2. *Kaplan–Meier curve of recurrence-free survival (RFS) in all patients with gastric cancer (GC) (A) and by stage according to age (B-D). There was no difference in RFS between the young and old GC patients overall, but RFS was significantly higher in those with stage II in the young group (p=0.02).*

not statistically significant superior for the CA subgroup than for the CCRT subgroup by stage. RFS was marginally worse in the CCRT subgroup than CA subgroup in the group with stage II disease (p=0.11).

Table III illustrates the probable prognostic factor resulting from the univariable and multivariable analyses of RFS in the young GC group, and type of operation (p=0.001), pT stage (p<0.0001), pN stage (p<0.0001), lymphatic invasion (p=0.03), vascular invasion (p=0.005), perineural invasion (p<0.0001), and number of metastatic LNs (p<0.0001) were significant prognostic factors of RFS. In the multivariable analysis, pT/pN stage, and perineural invasion were significant prognostic factors of RFS, and the RFS curves adjusted with these prognostic factors were not different according to adjuvant treatment in the young group (Figure 3B, p=0.98).

Among the older patients, RFS was not significantly different between the CCRT and CA subgroups (Figure 3C, p=0.48); however, there was a tendency for superior outcomes in the CCRT subgroup than CA subgroup by stage, especially in patients with stage II disease (p=0.02).

Table IV illustrates the results of univariable and multivariable analyses for probable prognostic factors of RFS in the older group. In the univariable analysis, total gastrectomy (p<0.0001), higher pT stage (p<0.0001), higher pN stage (p<0.0001), vascular invasion (p<0.0001), and perineural invasion (p<0.0001) were significant categorical predictors of poor RFS, and increased age (p=0.005) and higher number of metastatic LNs (p<0.0001) were significant poor prognostic factors among continuous variables. In the multivariable analysis, pT/pN stage, type of operation, and vascular invasion were significant prognostic factors of RFS, and CCRT led to significantly higher RFS curves adjusted with these prognostic factors in the older group (Figure 3D, p=0.008).

Discussion

There is growing evidence that young patients with GC have different genetic and clinicopathological characteristics from those for general GC, which typically occurs after 60 years of age (4-6, 20). It is known that GC in the young is more common in women, and it is more often diagnosed as an advanced disease of diffuse type by Lauren's classification than it is among older patients. There are some reports that the prognosis is poorer for young patients than older patients,

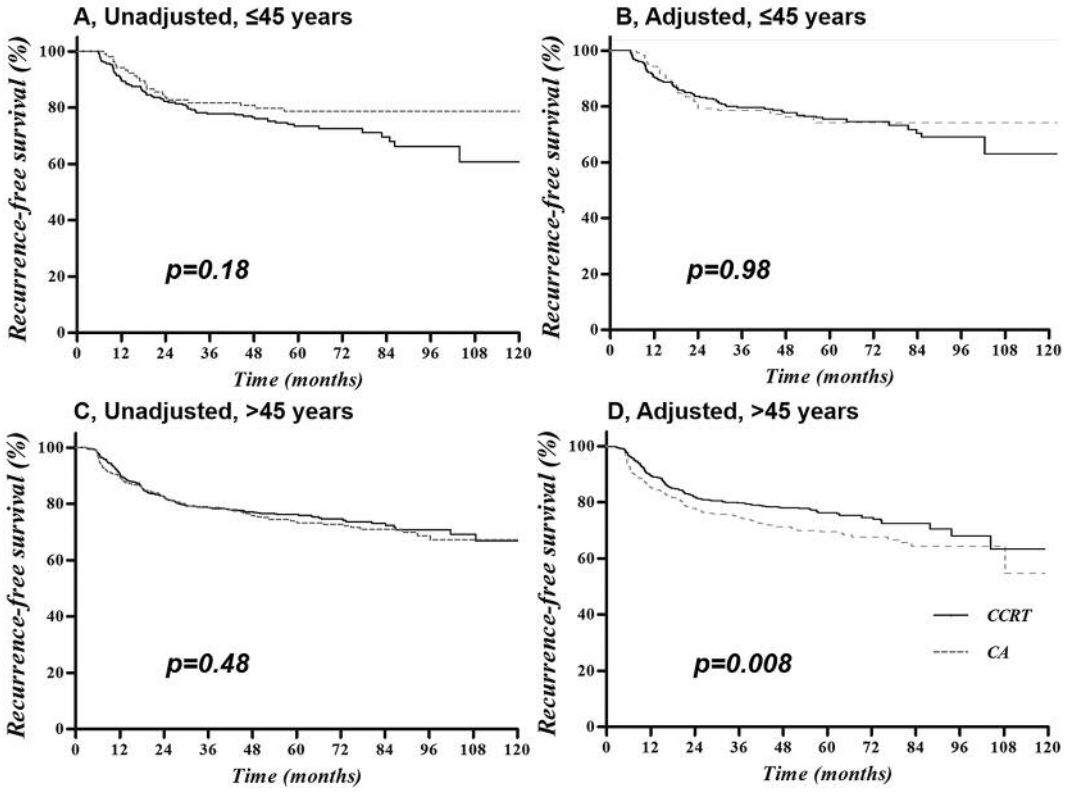

Figure 3. *Kaplan–Meier curve of recurrence-free survival (RFS) according to age and adjuvant treatment without (A and C) and with (B and D) after adjusting for significant predictors. After adjustment, adjuvant concurrent chemoradiation therapy (CCRT) led to significantly higher RFS in the older group with gastric cancer (D), but there was no significant difference in RFS by adjuvant treatment in the young group (B).*

but some have also found no difference between young and old patients matched by stage (4-6).

In the present study, which we performed with a relatively large cohort of patients with LN metastasis undergoing D2 resection of GC at a single institution, we found results similar to those of previous studies; for instance, the rates of female patients and diffuse Lauren's classification were significantly higher in the young group. Interestingly, the rates of lymphatic and venous invasion, which are well recognized prognostic factors of GC, were significantly lower in the young group. The characteristic association of these factors with GC in young patients suggests the possibility of different recurrence patterns and the need for different subsequent adjuvant strategies in these patients.

Commonly in oncology, new classification methods are being proposed for stomach cancer based on molecular/gene expression (21, 22), and it has been shown that these classifications are more representative of tumor aggressiveness and treatment outcomes than the conventional WHO classification, which is largely based on microscopic morphology.

By molecular classification of GC, The Cancer Genome Atlas (TCGA) Research Network has classified GC into four major subtypes: Epstein–Barr virus-infected, microsatellite instability, genomically stable, and chromosomally unstable tumors (21). In addition, Lee *et al*. proposed another classification with four molecular subtypes in the patients of the Asian Cancer Research Group that better predicted GC (22). In that study, more than 80% of the mesenchymal-like type were diffuse, and the patients with this type were significantly younger than were patients with other types. This subtype also showed the worst prognosis, with the highest recurrence frequency, especially of peritoneal seeding with malignant ascites.

In one recent study, the authors evaluated the unique characteristics in terms of genetic alteration among young *versus* old patients with diffuse type GC (20). In that study, they observed high frequency of somatic cadherin 1 (*CDH1*) and transforming growth factor beta receptor 1 (*TGFBR1*) alterations with fewer somatic Ras homolog gene family, member A (*RHOA*) and tumor protein p53 (*TP53*) mutations in Korean patients. Additionally, these genetic characteristics were associated with the aggressiveness of GC in young

Table III. *Univariable and multivariable analysis of probable prognostic factors in recurrence-free survival in the young group with gastric cancer.*

Variable	Univariable			Multivariable		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (years)						
Increase	0.982	0.944-1.022	0.38			
Gender						
Female	1	-				
Male	0.925	0.609-1.407	0.72			
Type of operation						
Subtotal gastrectomy	1	-		1		
Total gastrectomy	1.958	1.288-2.978	0.001	1.310	0.852-2.014	0.22
Lauren classification				0.48		
Diffuse	1					
Intestinal	1.077	0.614-1.889	0.80			
Mixed	0.666	0.344-1.288	0.23			
Unclassified	0.844	0.051-14.109	0.91			
Dissected LNs						
Increase	1.008	0.995-1.021	0.21			
Metastatic LNs						
Increase	1.075	1.566-1.095	<0.0001			
pT stage			<0.0001			
1	1			1		
2	4.066	1.217-13.586	0.02	2.307	0.673-7.903	0.183
3	14.623	4.511-47.405	<0.0001	5.367	1.556-18.512	0.008
4	19.206	5.785-63.764	<0.0001	7.869	2.261-27.385	0.001
pN stage			<0.0001			
1	1			1		
2	2.063	0.927-4.592	0.08	1.423	0.730-3.652	0.23
3a	7.027	3.401-14.521	<0.0001	4.651	2.223-9.731	<0.001
3b	9.488	4.365-20.627	<0.0001	5.012	2.262-11.105	<0.001
Lymphatic invasion						
No	1			1		
Yes	11.738	1.055-2.862	0.03	11.195	0.911-1.568	0.20
Venous invasion						
No	1			1		
Yes	2.124	1.235-3.653	0.005	0.930	0.703-1.231	0.61
Perineural invasion						
No	1			1		
Yes	3.796	2.317-6.219	<0.0001	2.084	1.238-3.507	0.006
Adjuvant treatment						
CA	1			1		
CCRT	11.394	0.860-2.259	0.18	0.993	0.603-1.634	0.98

HR: Hazard ratio; CI: confidence interval; LN: lymph node; CCRT: concurrent chemoradiation therapy; CA: chemotherapy alone.

patients, with the *CDH1* alteration tended to be more frequent in patients with DM than in those without metastasis. It is also known that CDH1 germline mutation is associated with shorter survival in hereditary diffuse gastric cancer (23).

Despite the clear clinicopathological differences between young and older patients with GC that we discussed above, there was no noticeable difference in recurrence rate or significant difference in recurrence patterns between the two groups. Additionally, by stage, the other clinical outcomes for young patients with D2-resected GC with LN metastasis were neither better nor worse than those for older patients. Nevertheless, there is still the need and the possibility to improve clinical outcomes by modifying adjuvant treatments because of the large clinicopathological and genetic differences between young and old patients.

In this study, we focused on the treatment effects on young and old patients with GC, particularly with adjuvant CCRT. In general, there were no differences in recurrence rates or patterns with and without adjuvant CCRT in both

Table IV. *Univariable and multivariable analysis of probable prognostic factors in recurrence-free survival (RFS) in old gastric cancer group.*

Variable	Univariable			Multivariable		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (years)						
Increase	1.018	1.005-1.032	0.005			
Gender						
Female	1	-				
Male	0.872	0.778-1.237	0.87			
Type of operation						
Subtotal gastrectomy	1	-		1		
Total gastrectomy	1.908	1.537-2.367	<0.0001	1.315	1.053-1.641	0.02
Lauren classification				0.09		
Diffuse	1	-		1		
Intestinal	0.765	0.603-0.970	0.03	1.022	0.797-1.310	0.86
Mixed	1.200	0.445-3.233	0.72	2.643	0.967-7.223	0.06
Unclassified	0.753	0.540-1.049	0.09	0.911	0.647-1.281	0.51
No of dissected LN						
Increase	1.006	0.999-1.013	0.08			
No of metastatic LN						
Increase	1.075	1.065-1.086	<0.0001			
pT stage			<0.0001			
1	1			1		
2	3.246	1.741-6.050	0.0002	2.690	1.439-5.029	0.002
3	7.768	4.202-14.361	<0.0001	4.885	2.615-9.172	<0.0001
4	12.148	6.471-22.805	<0.0001	6.497	3.803-13.719	<0.0001
pN stage				<0.0001		
1	1			1		
2	2.270	1.603-3.215	<0.0001	1.926	1.357-2.732	0.0002
3a	3.637	2.600-5.087	<0.0001	2.698	1.912-3.807	<0.0001
3b	9.606	6.713-13.745	<0.0001	6.497	4.453-9.478	<0.0001
Lymphatic invasion						
No	1					
Yes	1.046	0.812-1.347	0.73			
Venous invasion						
No	1			1		
Yes	1.757	1.364-2.263	<0.0001	1.302	1.004-1.690	0.05
Perineural invasion						
No	1			1		
Yes	2.017	1.619-2.514	<0.0001	1.186	0.935-1.503	0.16
Adjuvant treatment						
CA	1			1		
CCRT	0.924	0.745-1.147	0.47	0.742	0.597-0.929	0.008

HR: Hazard ratio; CI: confidence interval; LN: lymph node; CCRT: concurrent chemoradiation therapy; CA: chemotherapy alone.

groups. By stage, the recurrence rate with adjuvant CCRT tended to be lower among the older patients but not in the young group. Most of all, the difference in RFS adjusted by pT and pN stages was statistically significant with and without adjuvant CCRT in the older group but not among the younger patients. There was a strong possibility that the benefit of adjuvant CCRT was less among young patients than among older patients in D2-resected GC with LN metastasis.

This study has several limitations. Firstly, it was not free from selection bias because of the retrospective study design. It was difficult to determine the true effects of adjuvant CCRT because of the differences in characteristics between the CCRT and CA subgroups, although the prognostic factors were adjusted in analysis. Secondly, we performed this study at a single tertiary referral institution in Korea, although one that is highly experienced in managing GC. Thirdly, the adjuvant treatment policy changed during the study period. Fourthly, the number of young patients with GC was relatively small compared to the number of older patients. Finally, we did not perform genetic analysis, and it was not possible to analyze the reason for the little effect of adjuvant

CCRT in the young patients. The ARTIST-II trial, which we are performing in the same patient population to evaluate the effects of adjuvant CCRT in D2-resected GC with pathologically confirmed LN metastasis and which is a multicenter phase III randomized study, may resolve these limitations and provide more reliable information on this aspect.

In conclusion, among patients with D2-resected GC with LN metastasis, there were more females, more with diffuse-type tumors by Lauren's classification, and less lymphatic and venous invasion among the young patients. There was also no difference in RFS with or without adjuvant CCRT in these patients, in contrast with the older patients. Additional prospective studies are needed including the ARTIST-II study and studies that analyze genetic differences and RT effects.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

JIY and DHL have participated in the study design, analysis and interpretation of the data and drafting the manuscript. JIY, HSK and SA conducted the statistical analysis of the clinical data. All Authors have contributed to the manuscript's critical revision for important intellectual content. All Authors have given final approval of the version to be published, and agreed to be accountable for all aspects of the work in replying to all questions related to the accuracy or integrity of any part of the article.

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