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Original Article

Survival analysis according to lymph nodes dissection and adjuvant therapy types in gastric cancer: A retrospective multicenter cohort study

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ABSTRACT

Aim: While the main treatment of gastric cancer (GC) is surgery, controversy continues regarding appropriate lymph nodes dissection (LND) types and optimal adjuvant therapy after surgery. Therefore, we aim to analyze the survival outcomes of different treatment sequences in GC.
Materials and methods: In total, 234 GC patients who developed recurrence after D1 or D2 LND, R0 gastrectomy were retrospectively investigated. Patients treated with following different treatment sequences were compared for time to recurrence (TTR) and overall survival (OS) of patients with recurrence: D1-LND followed by chemoradiotherapy (CRT) or chemotherapy (CT); D2-LND followed by CRT or CT. RFS and OS estimated by Kaplan-Meier method and long-rank test was used to assess hazard ratio.
Results: In the whole group; there were 161 men (68.8%) and mean age was 57.9 (±1.69) years. In 4 arms, 94.8% of patients had positive lymph nodes, 42.7% of patients had pT4 stage tumor, and intestinal-type GC was present in 95 patients (40.6%). The median TTR were 14.0 (11.5–16.5), 7.0 (5.8–8.2), 13.0 (10.5–15.5), and 13.0 (10.8–15.2) months, for D1-LND + CRT; D1-LND + CT; D2-LND + CRT; and D2-LND + CT groups, respectively (HR; 95%CI:2086; 1133–3,839, P = 0,018 for D1-LND + CT group after adjusted for pN stage, PNI, and LVI). The median OS of the patients with recurrence was 29.0 months (26.8–31.2). While higher pT and pN stage, PNI and LVI positivity, undifferentiated and diffuse + mixed histological types presented with worse overall survival, treatment choices were not effect on OS.
Conclusion: RT is not necessary after D2-LND but it is still a major part of adjuvant treatment after D1-LND. D2-LND may not be require to cure GC when appropriate adjuvant treatment is given after D1-LND.

1. Introduction

After the Intergroup 0116 trial showed that adjuvant radiotherapy (RT) with 5-fluoropyrimidine (5-FU) significantly improved overall survival (OS) of patients with gastric cancer (GC), adjuvant chemoradiotherapy (CRT) was introduced into our clinical practice after curative surgery.[1,2] On the other hand, since most of the patients included in the Intergroup 0116 study underwent suboptimal lymph node dissection (LND), this made it questionable whether RT are required after optimal surgical procedure in GC. Although RT is a standard treatment for patients who have not achieved R0

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resection and have undergone dissection under 15 lymph nodes, there is a controversial area as to whether to exclude RT in patients undergoing optimal surgery with R0 resection/D1 LND due to a lack of randomized trials. Thus, postoperative CRT remains the recommended standard of care following D1 LND.

Dissection of at least 15 lymph nodes along with adequate resection margin has been recommended by experts as the main part of the backbone treatment of resectable GC for greater survival advantage, however, it is not clear whether an extended LND named as D2 dissection is required. While the debate between D1 and D2 lymph nodes dissection continues, the question arises as to which adjuvant treatment is better. Since the recurrence pattern after surgery is different between D1 or D2 dissection, adjuvant treatments options was questioned over time. The phase III CLASSIC trial showed that postoperative CT with oxaliplatin (P) and capecitabine (X) after D2 LND presented significant 3-year DFS benefit with a ratio 74% compared to only surgery (59%, $P < 0.001$).[3] Since D2 dissection introduces lower loco-regional recurrence rates, the ARTIST trial was designed to answer whether adjuvant RT can be omitted for this group. Although postoperative CRT did not significantly reduce the recurrence after D2 LND compared to chemotherapy (CT) alone (the 3-year disease-free survival: 74% vs. 78%, $P = 0.09$, respectively), survival benefit was provided with CRT for the some subgroup of patients.[4,5] Therefore, CT alone can be an option for patients undergoing D2 LND, but some subgroup of patients who may benefit from CRT need to be clarified. In this regard, we evaluated the patients who underwent R0 gastrectomy with D1 or D2 dissection, and treated with CRT or CT. Then we compared the survival analysis according to the following treatment choices; D1-LND followed by CRT or CT, D2-LND followed by CRT or CT.

2. Materials and Methods

2.1. Study design

The multicenter retrospective observational cohort study was conducted with 274 GC patients who developed recurrence after curative surgery with adjuvant CT or CRT according to primary physician's discretion. This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

Primary aim of the study was to compare the recurrence free survival (RFS), overall survival (OS) of the patients who were treated with different treatment sequences in operated GC; 1. D1 LND followed by CRT; 2. D1 LND followed by CT; 3. D2 LND followed by CRT; 4. D2 LND followed by CT, then to select the subgroup of patients who may benefit from additional radiotherapy to chemotherapy.

The secondary aim was to clarify the recurrence pattern of different treatment choices.

2.2. Patients and treatments

In this retrospective analysis, the data of 1970 patients with GC who underwent curative gastrectomy and who were treated in multi-center between January 2008 and January 2018 were screened. Patients who were out of follow-up, who had neo-adjuvant therapy, had positive peritoneal washing, were initially metastatic, and underwent R1/R2 resection were excluded. All patients received adjuvant CT or CRT. Patients who developed recurrence after curative intent surgery and adjuvant therapy were included in the analysis. Gastric resection including the regional lymphatics with perigastric lymph nodes named as D1 dissection or D2 dissection those along the named vessels of celiac axis. Patients with dissection under 15 lymph nodes were categorized as D0 dissection and excluded. The following information of patients and tumor were recorded: age, gender, tumor location, and tumor characteristics, including pathological type, histopathological differentiation, Lauren's classification, presence of lymphovascular invasion (LVI), and perineural invasion (PNI), and lymph nodes ratio (LNR; number of metastatic lymph nodes/number of all removed lymph nodes). Lauren' s classification was evaluated in two groups: intestinal type and diffuse type/mixed types. All cases were staged according to the 8th edition of American Joint Committee on Cancer (AJCC) TNM staging. Additionaly, lymph nodes ratio (metastatic lymph nodes/removed lymph nodes) were noted, and divided into two group according to median value. All patients were treated with the adjuvant CT or CRT with 5-fluorouracil (5-FU) based chemotherapy (with or without platinum, taxane, etc …) according to physician's discretion.

We divided the whole patient cohort into 4 groups;

1. D1 LND followed by CRT
2. D1 LND followed by CT
3. D2 LND followed by CRT
4. D2 LND followed by CT

Local recurrence was defined as recurrence in the gastric bed, or anastomotic recurrence, regional recurrence was defined as upper abdominal retroperitoneal lymph nodes.

2.3. Statistics

All results were presented as the rate for categorical values or mean/median for continuous variables. To detect significant differences between qualitative variables, Chi-square and/or Fischer-exact test for rates, and *t*-test for continuous variables were used. Quantitative variables were described as means with standard deviation [SD], while qualitative variables were presented as frequencies with proportions. Time to recurrence (TTR) and OS of the patients with recurrence estimated by Kaplan-Meier method and long-rank test was used for the univariate analysis. Cox proportional hazard regression analysis was used to determine the effect of variables on survival. P value of less than or equal to 0.05 was considered as statistically significant and statistical analyses were carried out using the statistical software package SPSS 22.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Study population and treatments

In total, 234 gastric cancer patients who developed recurrence after curative intent surgery were included in the study. In whole group; there were 161 men (68.8%) and median age was 58 (29–82) years old years. In 4 arms, 94.8% of patients had positive lymph nodes and 42.7% of patients had pT4 stage tumor. Intestinal-type GC was present in 95 patients (40.6%), and 100 patients (42.7%) had diffuse-type + mixed GC. Patient baseline characteristics were shown in Table 1.

All patients received CT or CRT after optimal surgery. Number of the patients who were treated with CRT or CT followed by D1 LND were 86 (31.4%) and 14 (5.1%), respectively. Number of the patients who were treated with CRT or CT followed by D2 LND were 102 (37.2%) and 32 (11.7%), respectively. The treatment choices were summarized in Table 2.

Table 1
Patient and tumor baseline characteristics according to treatment modalities.

Characteristic	D1 LND + CRT	D1 LND + CT	D2 LND + CRT	D2 LND + CT
	N (%)	N (%)	N (%)	N (%)
Age, years				
Median	59.0	58.5	56.5	58.5
Range	39–82	34–76	29–80	36–76
Gender				
Female	21 (28.8)	3 (21.4)	36 (35.3)	13 (40.6)
Male	65 (75.6)	11 (78.6)	66 (64.7)	19 (59.4)
Tumor site				
Cardia-fundus	17 (21.3)	5 (35.7)	26 (26.0)	7 (23.3)
Antrum-korpus	52 (65.0)	8 (57.1)	67 (67.0)	17 (56.7)
Pylorus	11 (13.8)	1 (7.1)	7 (7.0)	6 (20.0)
Lauren classification				
Intestinal	37 (62.7)	7 (58.3)	37 (39.8)	14 (45.2)
Diffuse + mixed	22 (37.3)	5 (41.7)	56 (60.2)	17 (54.8)
Histological grade				
Differentiated	39 (48.8)	6 (46.2)	36 (37.1)	14 (43.8)
Undifferentiated	41 (51.2)	7 (53.8)	61 (62.8)	18 (56.3)
pT stage				
T1-2	23 (27.1)	4 (28.6)	15 (14.7)	4 (12.5)
T3	36 (42.4)	4 (28.6)	38 (37.3)	9 (28.1)
T4a-b	26 (30.6)	6 (42.9)	49 (48.0)	19 (59.4)
pN stage				
N0	4 (4.7)	1 (7.1)	4 (3.9)	2 (6.3)
N1	6 (7.1)	1 (7.1)	11 (10.8)	2 (6.3)
N2	34 (40.0)	5 (35.7)	17 (16.7)	4 (12.5)
N3a	29 (34.1)	4 (28.7)	46 (45.1)	15 (46.9)
N3b	12 (14.1)	3 (21.4)	24 (23.5)	8 (28.1)
LVI				
+	54 (68.4)	9 (64.3)	71 (74.0)	24 (75.0)
–	25 (31.6)	5 (35.7)	25 (26.0)	8 (25.0)
PNI				
+	57 (73.1)	11 (78.6)	66 (68.8)	22 (68.8)
-	21 (26.9)	3 (21.4)	30 (31.3)	10 (31.3)

LND, Lymph nodes dissection; CRT, chemoradiotherapy; CT: chemotherapy; LVI, lymphovascular invasion; PNI, perineural invasion.

Table 2
Distribution of patients regarding to adjuvant treatment modalities.

Treatment modalities	5-FU/X N (%)	XP/5-FU-P N (%)	CF/CX N (%)	ECF/DCF N (%)
D1+CRT	43 (50)	4 (4.7)	36 (41.9)	3 (3.5)
D1+CT	5 (38.5)	2 (15.4)	5 (38.5)	1 (7.7)
D2+CRT	44 (43.2)	7 (6.9)	48 (47.1)	3 (3.0)
D2+CT	7 (31.6)	10 (32.3)	14 (45.2)	–

LND, Lymph nodes dissection; CRT, chemoradiotherapy; CT: chemotherapy; 5-FU, 5-fluorouracil; X, capecitabine; P, oxaliplatin; P, cisplatin; E, antracycline; D, taxanes.

3.2. Analysis of the recurrence free survival according to treatment choices and clinicopathological features

The median TTR of all patients was 13 months (10.8–15.2). It was 14.0 (11.5–16.5), 7.0 (5.8–8.2), 13.0 (10.5–15.5), and 13.0 (10.8–15.2), for D1 LND + CRT, D1 LND + CT, D2 LND + CRT, and D2 LND + CT groups, respectively. The Hazard ratio (HR) of the patients treated with D1 LND after CT was higher for TTR compared with the other groups as was shown in Table 3 (HR; 95%Confidence interval [CI]: 1.805; 1.022–3.189, P = 0.04). Among the clinicopathological features, high pathologic lymph node stages, presence of LVI and PNI were poor RFS markers (Table 3). After adjusted for these parameters, HR increased further in the group treated with D1 LND after CT in multivariate analysis (HR; 95%CI: 2086; 1133–3,839, P = 0,018) (Fig. 1).

3.3. Subgroup analysis for recurrence free survival

3.3.1. Addition of platinum to 5-FU/X

The patients were divided into two groups: treated with 5-fluoruracil (5-FU)/capesitabine (X) and cisplatin plus 5-fluorouracil (CF) or oxaliplatin plus capacitabine (XP) for both arm treated with CRT and CT alone. We demostrated that addition of platinum to 5-FU/X had no effect on the improvement of TTR for those group treated with D1 followed by CRT (HR; 95%CI: 1.405; 0.888–2.224, P = 0.146) or CT (HR; 95%CI: 0.938; 0.262–3.354, P = 0.922), and for patients underwent D2 LND followed by CRT (HR:95%CI: 1.102; 0.739–1.642, P = 0.635) or CT (HR; 95%CI: 1.654; 0.669–4.088, P = 0.276).

3.3.2. Intestinale and diffuse type

The patients were divided into two groups: Intestinal and diffuse + mixed histological types. There were no differences in terms of TTR between intestinal and diffuse + mixed histological types among treatment groups: The patients treated with D1 followed by CRT (HR; 95%CI: 0.65; 0.381–1.120, P = 0.12) or CT (HR; 95%CI: 2.300; 0.613–8.637, P = 0.22), and for patients underwent D2 LND followed by CRT (HR:95%CI: 1.234; 0.807–1.885, P = 0.332) or CT (HR; 95%CI: 0.840; 0.394–1.791, P = 0.652).

3.3.3. Lymph nodes ratio (LNR)

Since most of the patients had lymph nodes involvement, we

Table 3
Time to recurrence and overall survival of the patients with recurrence according to treatment modalities and patient and tumor characteristics.

	TTR	P value	OS	P value
	HR; 95%CI		HR; 95%CI	
Gender	1.139; 0.877–1.480	0.329	0.957; 0.676–1.353	0.80
Treatments				
D1 LND + CRT	1 (ref)		1 (ref)	
D1 LND + CT	*1.805; 1.022-3.189*	*0.04*	1.144; 0.518–2.526	0.74
D2 LND + CRT	1.090; 0.813–1.462	0.56	1.359; 0.946–1.952	0.10
D2 LND + CT	1.109; 0.737–1.669	0.62	0.918; 0.524–1.606	0.76
pT stage				
1–2	1 (ref)		1 (ref)	
3	0.944; 0.679–1.311	0.73	0.942; 0.611–1.451	0.79
4	1.125; 0.812–1.558	0.48	*1.589; 1.047-2.411*	*0.029*
pN stage				
0	1 (ref)		1 (ref)	
1	1.101; 0.617–1.966	0.75	1.928; 0.903–4.117	0.09
2	1.196; 0.731–1.957	0.48	1.494; 0.760–2.938	0.24
3a	1.162; 0.724–1.865	0.54	1.833; 0.954–3.521	0.07
3b	*2.005; 1.194-3.366*	*0.009*	*3.609; 1.805-7.213*	*<0.001*
LVI	*1.309; 0.998-1.718*	*0.052*	*1.944; 1.311-2.883*	*0.001*
PNI	*1.337; 1.017–1.758*	*0.037*	*1.936; 1.292-2.901*	*0.001*
Tumor site	-	0.29	-	0.49
Lauren classification	1.011; 0.776–1.317	0.94	1.369; 0.973–1.926	0.07
Histological grade	0.969; 0.757–1.241	0.80	*1.564; 1.130-2.166*	*0.007*

LND, Lymph nodes dissection; CRT, chemoradiotherapy; CT: chemotherapy; LVI, lymphovascular invasion; PNI, perineural invasion; TTR, time to recurrence; OS, overall survival; HR, hazard ratio; CI, confidence interval.

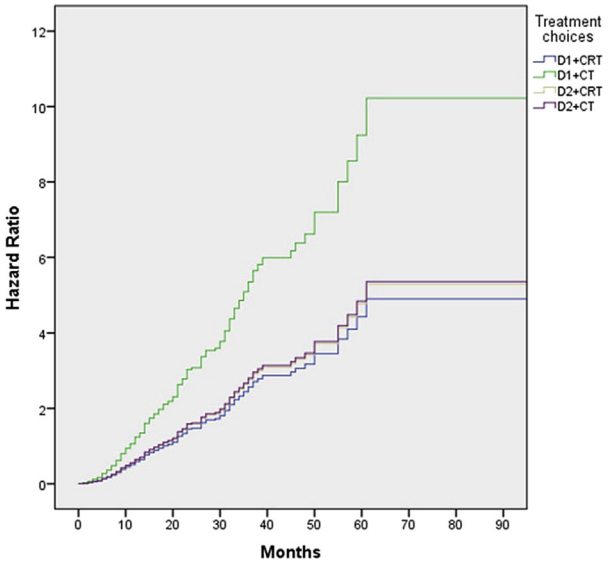

Fig. 1. Cox regression curve of the patients treated with different modalities after adjusted for, lymph nodes stage, LVI, and PNI for time to recurrence. HR; 95%CI: 2086; 1133–3,839, P = 0,018. LND, Lymph nodes dissection; CRT, chemoradiotherapy; CT: chemotherapy.

assessed LNR Patients were divided into two groups according to median LNR of 0.375. Patients who had lower LNR presented with longer TTR (HR; 95%CI: 1.348; 1.026–1.770, P = 0.032). However, among treatment modalities, there was no survival benefit with low LNR, there was no group providing survival improvement according to LNR. Hazard ratio of the patients with low LNR were 1.307 (0.826–2.069), 0.472 (0.145–1.534), 1.335 (0.890–2.003), and 1.887 (0.818–4.352), respectively and all p values < 0.05.

3.4. Analysis of the overall survival according to treatment choices and clinicopathological features

The median OS of patients with recurrence was 29.0 months (26.8–31.2) for patients who developed recurrence after optimal surgery and adjuvant treatment. 144 (%61.5) patients died during follow up. While higher pT and pN stage, PNI and LVI positivity, undifferentiated and diffuse + mixed histological types presented with poor overall survival, treatment choices did not affect on overall survival (Table 3).

3.5. Pattern of recurrence

Local recurrence were 16.3% (n = 14), 28.6% (n = 4), 21.6% (n = 22), and 18.8 (n = 6), in those D1-LND + CRT; D1-LND + CT; D2-LND + CRT; and D2-LND + CT groups, respectively (p = 0.66). These rates were 29.1% (n = 25), 50% (n = 7), 34.3% (n = 35), and 34.4% (n = 11), respectively (p = 0.473) for including loco-regional recurrence. Although the loco-regional recurrence rate was higher in D1-LND + CT group, it was not statistically significant.

4. Discussion

While cornerstone curative treatment of GC is gastrectomy with at least 15 lypmh node dissection and R0 resection, controversy continues regarding the appropriate LND types and optimal adjuvant treatment after D1-LND or D2-LND. Therefore, we would like to analyze the survival outcomes of treatment sequences as D1-LND followed by CRT or CT, D2-LND followed by CRT or CT in GC. Overall, the present study demostrated that addition of radiotherapy to chemotherapy did not improve survival in patient undergoing D2-LND compared with CT alone. On the other hand, CRT provided a survival benefit with longer TTR compared with CT alone in patients undergoing D1-LND (14.0 [11.5–16.5] vs.7.0 [5.8–8.2] months, for CRT and CT, respectively, HR; 95%CI: 1.805; 1.022–3.189, P = 0.04).

Baseline tumor and patient characteristics were balanced among four groups, however the pN3 ratio was higher in patients undergoing D2-LND. Among the patient and tumor characteristics, higher pN stage, and PNI, LVI were associated with poor TTR in patients treated with adjuvant therapy in univariate analysis. Among the treatment modalities, patients who underwent D1 LND followed by CT group also showed the worst TTR after adjusted for

pN stage, PNI, and LVI, in multivariate analysis compared to the other groups (HR; 95%CI: 2086; 1133–3,839, P = 0,018). On the other hand, there was no differences among four treatment modalities in term of overall survival. As expected, the higher pT stage and pN stage, positive PNI and LVI, and undifferentiated tumor histology were associated with poor overall survival.

Whereas gastrectomy with extended lymph node dissection (LND), called D2 LND, is a standard surgical procedure in East Asia, it should be performed by experienced surgeons because of higher complication rates.[6] D2 LND without adjuvant treatment was associated with lower loco-regional recurrence compared with D1 dissection, however did not have a positive effect on OS according to studies from the Western region.[7,8] In contrast, when the D2 LND was performed by experienced surgeons in high-volume centers, lower postoperative complications and trend towards OS benefit was shown in the West.[9,10] Therefore, it was considered a procedure that could be recommended but was not essential for the goal of cure in the West. In this study, among the four treatment modalities, only D1 LND followed by CT group showed a higher hazard ratio for TTR. Patients who undergoing D1 LND and treated with CRT presented similar survival outcomes to those in D2 LND groups. Therefore, we found that two types of lymph nodes dissection can be recommended when appropriate adjuvant treatment is given.

The phase III ARTIST trial was designed to compare adjuvant CT using XP or XP plus RT in patients undergoing D2 LND.[5] The long term survival analysis of the phase III ARTIST trial demonstrated that 5 year-DFS was similar in both groups (73% vs. 75%, respectively, P = 0.48) and the hazard ratio can not be reduced with adding RT to CT for OS (1.130; 0.78–1.65, P = 0.53) with a median time to recurrence as 9.7 and 7.2 months, respectively (P = 0.08).[4] In our study, we also demonstrated that RT added to CT did not provide a survival benefit in patients undergoing D2 LND. We also demonstrated that, the addition of platinum to 5-FU/X did not improve time to recurrence in the patient treated with CRT. This, can be related with inadequate number of patents in the CT arms. Therefore, we need to more satisfying number of patient to make sub-group analyses in this regard. Subgroup analysis of ARTIST trial showed a survival benefit in the subgroup of patients treated with CRT in node-positive disease or higher lymph node ratio (LNR), and intestinal type of GC (3-year DFS rates were 83% and 94%, CT group and CRT group, respectively, P = 0.01).[4,11] Since most of the patients included in the present analysis were node positive with a ratio 94.8, we were unable to evaluate the in this respect, however we demonstrated that lower LNR was associated with longer TTR. On the other hand, after adjusted for treatment modalities, LNR did not affect survival and did not predict the benefit of any treatments. In addition, we did not show any survival benefit with RT added to CT for intestinal GC in all treatment modalities (for all $p > 0.05$).

While adjuvan CRT is standard of care for D1 LND, there is no phase III randomized trial to compare effect of CRT and CT on survival.[12] In the present study, we showed that CRT provided better TTR than CT alone following D1 LND, after adjusted for pN stage, PNI and LVI positivity, in multivariate analyses, even though satisfying surgical prodecure with R0 resection and at least 15 LND was performed. Additionally, this benefit was independent of platinum addition to 5-FU/X, diffuse/intestinal histological type, and LNR. Although the rate of recurrences including local recurrence were lower in those treated with RT, there was numerical trend toward an increase in to CT arm in the present study, but it was not statistically significant.

The limitations of the study are retrospective and multicenter design because it is difficult to achieve the standardization in terms of surgical procedures and radiotherapy applications. Additionaly, there were fewer patients in CT arms compared to CRT arms. On the other hand, we screened a very high number of patients, such as 1970, and included 234 patients who developed recurrence after optimal curative intent surgical intervention and adjuvant therapy. We evaluated the effect of both dissection types and adjuvant treatment modalities on survival. Therefore, we concluded that D2 LND, which is a complicated surgery, may not be necessary to achievecure when appropriate adjuvant therapy is given. In addition, we demonstrated that adjuvant RT is needed for D1 LND but not for D2 LND regardless of pN stage, LVI-PNI and subtype of GC even if optimal resection margin and LND procedure were obtained. Therefore, we showed that more aggressive treatment approaches with surgery or radiotherapy do not reduces recurrence and dead from GC, and we need new adjuvant treatment modalities to obtain better survival benefit. Additionally to support these findings, we need a randomized clinical trial with a large patient cohort.

5. Conclusions

RT is not necessary after D2 LND but it is still a major part of adjuvant treatment after D1 LND. D2-LND may not be required to cure GC when appropriate adjuvant treatment is given after D1 LND.

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