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ORIGINAL ARTICLE

Benefit of adjuvant chemoradiotherapy in patients with pathologically lymph node-positive and locally advanced gastric cancer

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Abstract

Objective This study aimed to compare the effectiveness of adjuvant chemoradiotherapy (CRT) and adjuvant chemotherapy (ChT) for T3–4/N+ gastric cancer (GC) following D2/R0 dissection, and identify the specific subgroups that could benefit from adjuvant CRT.

Methods All eligible patients were divided into the CRT group and ChT group. We assessed the survival outcomes and patterns of recurrence for each group, and determined the prognostic factors for survival by performing Cox proportional risk regression analyses.

Results A total of 192 gastric cancer patients were included in the study. The estimated 3-year and 5-year disease-free survival (DFS) probabilities in the CRT and ChT groups were 52.9% *vs.* 36.7% (P = 0.024) and 41.2% *vs.* 31.1% (P = 0.148), respectively, and the estimated 3-year and 5-year overall survival (OS) probabilities were 82.4% *vs.* 70.0% (P = 0.044) and 52.0% *vs.* 35.6% (P = 0.022). Patients in the CRT group had a lower risk of locoregional recurrence than those in the ChT group (20.6% *vs.* 34.4%; P = 0.031). The subset analyses revealed that patients with stage N1–2 disease were more likely to benefit from adjuvant CRT than from adjuvant ChT (DFS: 53.1% *vs.* 36.4%; P = 0.039; OS: 53.1% *vs.* 38.6%; P = 0.036).

Conclusion For locally advanced gastric cancer patients with LN+, adjuvant CRT showed superior survival benefits compared with adjuvant ChT alone. Patients with N1–2 achieved better survival from adjuvant CRT.

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Key words: locally advanced gastric cancer; adjuvant chemoradiotherapy; adjuvant radiotherapy; lymph node-positive; survival and prognosis

Gastric cancer (GC) is the fifth most common malignant tumor in the world and one of the major causes of cancer-related deaths. Surgical resection is the main treatment paradigm of non-metastatic GC. Currently, radical D2 resection has become the globally recognized standard surgery, especially in Asian countries. However, a high rate of locoregional recurrence and distant metastasis occurred after surgery [1–2]. Therefore, adjuvant treatment is the key to improving survival outcomes after gastrectomy.

Two phase III clinical studies, the CLASSIC trial from Korea and the Japanese ACTS-GC trial, established the value of postoperative adjuvant chemotherapy (ChT) and recommended the routine use of adjuvant ChT in GC patients who underwent D2-dissection in East Asia. However, the overall survival (OS) of patients with node-positive (N2–3) disease has not improved in the ACTS-GC trial, and fewer T3 and T4 lesions had been reported in patients in the CLASSIC trial (comprising 44% of patients) [3–4]. Therefore, adjuvant ChT alone appeared to have a limited clinical value.

The ARTIST trial was a large phase III randomized clinical study that evaluated the issues described above [5]. This study did not determine the superiority of adjuvant ChT over adjuvant chemoradiotherapy (CRT). However, an unplanned subgroup analysis of node-positive patients reported significant disease-free survival (DFS). Approximately 60% of the enrolled patients had an early-

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stage disease (stages Ib/IIa), of which over 20% had T1 or T2 lesions [6].

Although the results of previous studies were not satisfactory, radiotherapy (RT) is still considered a promising therapeutic modality. Numerous studies have demonstrated that a considerable percentage of relapses following radical surgery occurred in the tumor bed or the anastomotic or regional lymph node, which provided further rationale for the utilization of adjuvant RT [7–9]. In China, most patients with gastric cancer are usually diagnosed in the later stages, with a resulting poor prognosis. Adjuvant CRT has been considered as the best option for patients with a higher risk of locoregional recurrence. In recent years, some randomized controlled trials have confirmed the clinical efficacy of postoperative CRT for certain gastric cancer patients [10–11]. The National Comprehensive Cancer Network guidelines indicated that GC patients with pathological T3–4 Nx or TxN+ stage should receive postoperative adjuvant RT. This study therefore aimed to compare the effectiveness of adjuvant CRT and adjuvant ChT for T3-4/N+ GC following D2/R0 dissection, and identify the specific subgroups that could benefit more from adjuvant CRT.

Materials and methods

This was a retrospective cohort study conducted in patients with locally advanced GC, who were surgically treated at the Affiliated Hospital of Qingdao University between June 2010 and June 2014. Patients (1) aged between 18 and 75 years, who underwent R0 resection and D2 lymphadenectomy; (2) with pathologically confirmed stage T3-4N+M0 adenocarcinoma of the stomach or gastroesophageal junction according to the 7th edition of the American Joint Committee on Cancer staging system; and (3) who received systemic postoperative adjuvant CRT or ChT were included in the study. Patients (1) who had undergone palliative surgery; (2) who underwent R1 dissection confirmed as positive surgical resection margins; (3) with incomplete function of important organs such as the heart, liver, kidney, and bone marrow; (4) who had other malignant tumors; and (5) who lacked detailed medical records including surgical records, pathology data, and adjuvant therapy regimens were excluded. Informed consent was signed by each patient included in the study. The research was approved by the ethics committee of the Affiliated Hospital of Qingdao University.

All eligible patients agreed to undergo total/subtotal gastrectomy with D2 lymph node dissection without a routine splenectomy or caudal pancreatectomy. Total gastrectomy was defined as the total resection of the stomach, while subtotal gastrectomy was defined as resection of the proximal or distal two-thirds of the stomach.

RT was administered using intensity-modulated radiation therapy using a 6-MV linear accelerator. The clinical target volume (CTV) included the tumor bed, areas of anastomosis, and regional lymph nodes. The tumor bed was delineated based on preoperative imaging and the intraoperative description provided by the surgeon. For cancer in the lower one-third of the stomach, RT was administered in the duodenal stump; for tumors in the esophagogastric junction + upper one-third of the stomach, RT was performed after conducting esophageal and intestinal anastomosis. Regional lymph nodes included in the CTV such as the perigastric, hepatoduodenal, or hepatic portal; pancreaticoduodenal; splenic hilum or splenic artery and para-aortic LNs; and the specific CTV-node (CTV-n) varied according to the location of the tumors. The planning target volume was determined by expanding a margin of 0.5–1.0 cm based on the CTV, after considering breathing movements or positioning errors.

In the CRT group, the patients were treated with one to two cycles of ChT followed by CRT (45 Gy of radiation at 1.8 Gy per day, 5 days per week, for 5 weeks with concurrent ChT) and four or five subsequent cycles of ChT after surgery. Concurrent ChT regimens included oral capecitabine (625 mg/m^2 twice daily for 14 consecutive days followed by a 7-day rest period, for 21 days) or oral S-1 (40 mg/m^2 twice daily for 14 consecutive days followed by a 7-day rest period, for 21 days). In the ChT alone group, the patients were given six to eight cycles of ChT. The ChT regimens primarily included a combination of treatments using 5-fluorouracil or oral fluorouracil derivatives along with platinum, epirubicin, or taxanes.

After systemic treatments, all patients were followed up every 3 months for the first 2 years, at 6-month intervals until 5 years, and then annually thereafter. The follow-up consisted of history and physical examination, laboratory tests (serum tumor biomarkers, blood count, hepatic function, and renal function), computed tomography scans of the chest, gastrointestinal tract ultrasonography, and a yearly gastroscopy.

Recurrence was diagnosed by histological biopsy, cytological examination, or radiographic evidence based on the patient's reviewed or follow-up receipt in the medical record. Only sites of first recurrence and metastasis were recorded and analyzed. Recurrences that occurred at the remnant stomach, anastomosis, duodenal stump, tumor bed, and regional lymph nodes were considered as locoregional recurrences. Recurrences that occurred inside the abdominal cavity were defined as abdominal metastases. Distant metastasis referred to the spread of cancer to some sites outside the abdominal cavity such as the liver and supraclavicular lymph nodes.

The study aimed to compare the 3-year and 5-year DFS as well as the OS of patients who received adjuvant CRT and ChT after D2 resection. Finally, the subgroups who benefited more from adjuvant CRT were identified.

All statistical analyses were carried out using SPSS statistical software for Windows, version 24.0 (SPSS, Chicago, IL, USA), and the χ^2 test or t-test/Wilcoxon rank sum test were performed to detect the differences in the baseline characteristics and the significance differences in the 3-year and 5-year DFS and OS between the two arms. All survival outcomes were compared using the log-rank test and were plotted using Kaplan-Meier survival curves. The Cox proportional risk regression model was used for assessing the prognostic factors for survival by univariate and multivariate analyses. A P value of < 0.05 was regarded as significant, and all P-values were two sided.

Results

Study population and clinicopathological characteristics

A total of 192 GC patients were recruited in the study between June 2010 and June 2014. The baseline characteristics are summarized in Table 1. The investigated baseline characteristics of the two arms were balanced and comparable.

Treatment delivery and safety

Patients who underwent adjuvant CRT were provided a median radiotherapy dose of 45 Gy (range: 45.0–50.0 Gy). In the CRT and ChT groups, 81.4% (83/102) and 70.0% (63/90) of the patients finished the planned ChT, respectively (P = 0.065); primary CRT regimens delivered in both groups consisted of XELOX, SOX, and FOLFOX. The most common adverse events were gastrointestinal reaction (asthenia/anorexia, nausea/vomiting, and abdominal pain/diarrhea) and hematological toxicity (leukocyte/neutropenia and hepatic insufficiency). Neither treatment-related death nor grade 3/4 adverse events occurred in either group.

Survival prognostic factors

On the evaluation date, the median follow-up time of the entire group was 54 months (range: 6–109 months). A total of 126 patients died (63 deaths in both groups), and 127 had recurrence (63 patients in the CRT arm and 64 patients in the ChT arm). The estimated 3-year and 5-year DFS probabilities of the CRT and ChT arms were 52.9% *vs.* 36.7% (P = 0.024) and 41.2% *vs.* 31.1% (P = 0.148), respectively (Fig. 1). The estimated OS probability was 82.4% *vs.* 70.0% (P = 0.044) and 52.0% *vs.* 35.6% (P = 0.022) in the same consecutive order (Fig. 2). Tables 2 and 3 list the results of the univariate and multivariate analyses for DFS and OS, respectively. Adjuvant CRT, nodal status, and tumor diameter were regarded as independent prognostic factors for DFS and OS in the univariate and multivariate analyses. Additionally, the Cox proportional hazard regression model showed that tumor location, histopathology, and differentiation were also important survival prognostic factors.

Table 1 The baseline patient characteristics in the adjuvant CRT and adjuvant ChT groups

Characteristics	CRT group		ChT group		P value
	n = 102	%	n = 90	%	
Gender					
Male	78	76.5	66	73.3	0.616
Female	24	23.5	24	26.7	
Age (years)					
≤ 60	79	77.5	56	62.2	0.021
> 60	23	22.5	34	37.8	
Tumor location					
GEJ + upper 1/3	13	12.7	7	7.8	0.461
Middle 1/3	25	24.5	29	32.2	
Lower 1/3	60	58.8	49	54.4	
Multiple/diffuse	4	3.9	5	5.6	
Histopathology					
Adenocarcinoma	92	90.2	78	86.7	0.518
Mucinous adenocarcinoma	6	5.9	5	5.6	
SRC adenocarcinoma	4	3.9	7	7.8	
Differatiantion					
Mid-low	24	23.5	16	17.8	0.327
Low	78	76.5	74	82.2	
Diameter (cm)					
Mean (SD)	5.71	(2.59)	5.51	(2.41)	0.581
Median (range)	5.25	(1.5-15.0)	5.00	(1.5-14.0)	
Tumor depth					
T3	65	63.7	49	54.4	0.191
T4	37	36.3	41	45.6	
No. resected nodes					
< 16	28	27.5	19	21.1	0.308
≥ 16	74	72.5	71	78.9	
N stage					
N1	17	16.7	17	18.9	0.913
N2	32	31.4	27	30.0	
N3a	44	43.1	36	40.0	
N3b	9	8.8	10	11.1	
Operation type					
Proximal	8	7.8	6	6.7	0.556
Distal	63	61.8	50	55.6	
Total	31	30.4	34	37.8	
Chemotherapy regimen					
Single	4	3.9	5	5.6	0.133
Doublet	89	87.3	83	92.2	
Triplet	9	8.8	2	2.2	

CRT, chemoradiotherapy; ChT, chemotherapy; GEJ, gastroesophageal junction; SRC, signet ring cell; SD, standard deviation

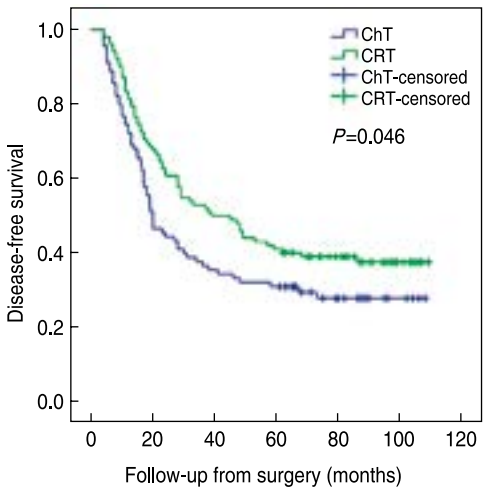

Fig. 1 DFS curves of patients in the two groups. ChT, chemotherapy; CRT, chemoradiotherapy; DFS, Disease-free Survival

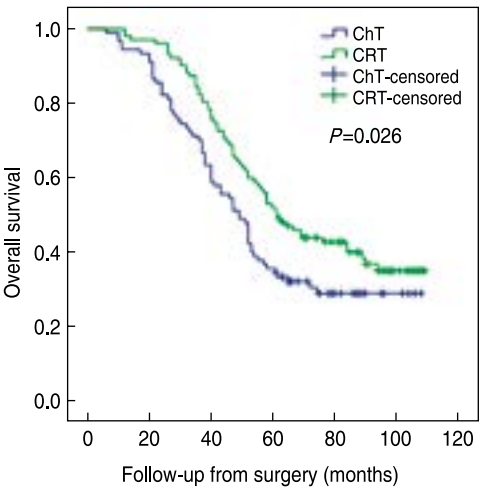

Fig. 2 OS curves of patients in the two groups. ChT, chemotherapy; CRT, chemoradiotherapy; OS, Overall Survival

Table 2 Univariate and multivariate analysis of clinical characteristics in relation to DFS

Prognostic factors	*n*	Univariate analysis			multivariate analysis		
		HR	95%CI	*P*	HR	95%CI	*P*
Gender							
Male	144	Ref.			Ref.		
Female	48	0.865	0.574–1.303	0.488	0.835	0.549–1.270	0.399
Age (years)							
≤ 60	135	Ref.			Ref.		
> 60	57	1.128	0.773–1.645	0.533	0.906	0.610–1.346	0.626
Tumor location							
GEJ + upper 1/3	20	Ref.			Ref.		
Middle 1/3	54	0.460	0.254–0.831	0.010	0.365	0.198–0.675	0.001
Lower 1/3	109	0.628	0.370–1.064	0.084	0.546	0.316–0.942	0.030
Multiple/diffuse	9	0.582	0.229–1.477	0.254	0.477	0.184–1.234	0.127
Histopathology							
Adenocarcinoma	170	Ref.			Ref.		
Mucinous adenocarcinoma	11	2.162	1.126–4.151	0.020	3.048	1.529–6.077	0.002
SRC adenocarcinoma	11	0.883	0.388–2.008	0.766	1.400	0.578–3.389	0.456
Differatiantion							
Mid-low	40	Ref.			Ref.		
Low	152	1.534	0.968–2.430	0.069	1.712	1.042–2.815	0.034
Diameter (cm)							
≤ 6	137	Ref.			Ref.		
> 6	55	1.739	1.204–2.512	0.003	1.750	1.182–2.592	0.005
N stage							
N1–2	93	Ref.			Ref.		
N3a–3b	99	1.889	1.322–2.698	< 0.001	1.890	1.305–2.736	0.001
Group							
ChT	90	Ref.			Ref.		
CRT	102	0.705	0.497–0.999	0.049	0.610	0.422–0.882	0.009

DFS, disease free survival; CRT, chemoradiotherapy; ChT, chemotherapy; GEJ, gastroesophageal junction; SRC, signet ring cell; HR, hazard ratio; CI, confidence interval; Ref, reference

Recurrence pattern

We collected the patients' imaging data and endoscopy results during the follow-up period, and then compared the patterns of recurrence between the two treatment groups (Table 4). There was no significant difference in the total recurrence rate (61.8% in the CRT group *vs.*

Table 3 Univariate and multivariate analysis of clinical characteristics in relation to OS

Prognostic factors	*n*	Univariate analysis			Multivariate analysis		
		HR	95%CI	*P*	HR	95%CI	*P*
Gender							
Male	144	Ref.			Ref.		
Female	48	0.865	0.574–1.304	0.490	0.837	0.551–1.273	0.406
Age							
≤60	135	Ref.			Ref.		
>60	57	1.159	0.794–1.691	0.445	0.924	0.624–1.370	0.695
Tumor location							
GEJ+upper 1/3	20	Ref.			Ref.		
Middle 1/3	54	0.460	0.253–0.834	0.011	0.372	0.201–0.686	0.002
Lower 1/3	109	0.596	0.351–1.010	0.055	0.529	0.307–0.914	0.022
Multiple/diffuse	9	0.606	0.239–1.539	0.292	0.503	0.194–1.302	0.157
Histopathology							
Adenocarcinoma	170	Ref.			Ref.		
Mucinous adenocarcinoma	11	2.170	1.130–4.169	0.020	2.444	1.242–4.810	0.010
SRC adenocarcinoma	11	0.864	0.380–1.966	0.728	1.368	0.572–3.271	0.481
Differatiantion							
Mid-low	40	Ref.			Ref.		
Low	152	1.548	0.968–2.474	0.068	1.589	0.971–2.600	0.066
Diameter (cm)							
≤ 6	137	Ref.			Ref.		
> 6	55	1.887	1.304–2.732	0.001	1.881	1.266–2.795	0.002
N stage							
N1–2	93	Ref.			Ref.		
N3a–3b	99	1.910	1.335–2.735	< 0.001	1.836	1.270–2.654	0.001
Group							
ChT	90	Ref.			Ref.		
CRT	102	0.674	0.475–0.958	0.028	0.587	0.407–0.848	0.004

OS, overall survival; CRT, chemoradiotherapy; ChT, chemotherapy; GEJ, gastroesophageal junction; SRC, signet ring cell; HR, hazard ratio; CI, confidence interval; Ref, reference

71.1% in the ChT group; $P = 0.172$), peritoneal seeding (24.5% in the CRT group *vs.* 27.8% in the ChT group; $P = 0.607$), and distant metastasis (21.6% in the CRT group *vs.* 24.4% in the ChT group; $P = 0.636$) between the two groups. However, patients in the CRT group had a lower risk of locoregional recurrence than those in the ChT group (20.6% *vs.* 34.4%; $P = 0.031$). In addition, patients with N3 stage had higher rates of total recurrence than those with N1–2 stage (76.8% *vs.* 54.8%; $P = 0.001$).

Subgroup analysis

The results of the subgroup analysis for DFS and OS are shown as a forest plot in Fig. 3 and Fig. 4. Patients in most subsets showed improvements in DFS and OS after undergoing adjuvant CRT. In patients with N1–2 stage disease, a tumor diameter of >6 cm, mucinous adenocarcinomas and SRC, and low differentiation, the adjuvant CRT proved to be a significant beneficial factor (all $P < 0.05$). We further mapped the survival curves of DFS and OS based on the different lymph node states; the patients with pathologically N3a–3b (pN3a–3b) had a higher risk of recurrence and mortality than those with pN1–2 (DFS, $P < 0.001$; OS, $P < 0.001$) (Fig. 5a; Fig. 6a). Patients with pN1-2 were more likely to benefit from adjuvant CRT compared with adjuvant ChT (DFS: 53.1% vs. 36.4%; P=0.039; OS: 53.1% *vs.* 38.6%; $P = 0.036$) (Fig. 5b; Fig. 6b). However, no significant survival advantage from adjuvant CRT was observed in patients with N3a–3b stage disease (DFS: 24.5% *vs.* 21.7%; $P = 0.383$; OS: 24.5% *vs.* 21.7%; $P = 0.254$) (Fig. 5c; Fig. 6c). Due to the small

Table 4 Recurrence patterns

Relapse status	CRT group, *n* (%)		ChT group, *n* (%)	
	N1–2	N3	N1–2	N3
	n = 49	*n* = 53	*n* = 44	*n* = 46
No relapse	26 (53.1)	13 (24.5)	16 (36.4)	10 (21.7)
Relapse	23 (46.9)	40 (75.5)	28 (63.6)	36 (78.3)
Local/regional	7 (14.3)	14 (26.4)	12 (27.3)	19 (41.3)
Peritoneal	10 (20.4)	15 (28.3)	11 (25.0)	14 (30.4)
Distant	6 (12.2)	16 (30.2)	10 (22.7)	12 (26.1)
CRT	0.674	0.475–0.958	0.587	0.407–0.848

ChT, chemotherapy; CRT, chemoradiotherapy; Some people have multiple sites of relapse at the same time

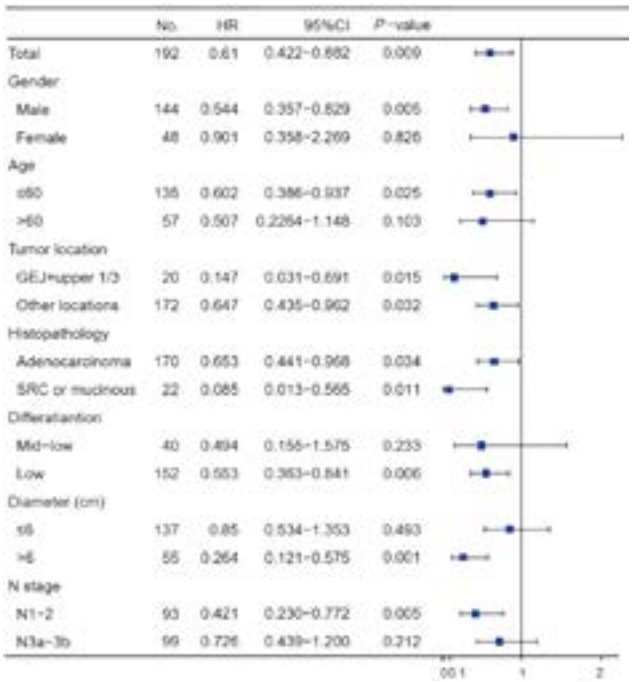

Fig. 3 Forest plot of subgroup analysis for DFS. HR < 1 favors adjuvant CRT and HR > 1 favors adjuvant ChT. ChT, chemotherapy; CRT, chemoradiotherapy; GEJ, gastroesophageal junction; SRC, signet ring cell; CI, confidence interval; HR, hazard ratio; DFS, disease-free survival

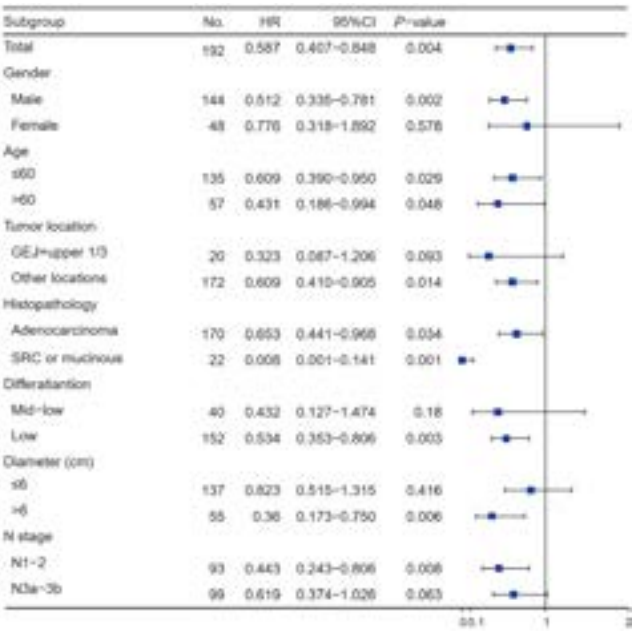

Fig. 4 Forest plot of subgroup analysis for OS. HR < 1 favors adjuvant CRT and HR > 1 favors adjuvant ChT. ChT, chemotherapy; CRT, chemoradiotherapy; GEJ, gastroesophageal junction; SRC, signet ring cell; CI, confidence interval; HR, hazard ratio; OS, overall survival

number of patients and uneven distribution in the other subgroups (55 patients with tumor diameters of >6 cm, 22 patients with mucinous adenocarcinomas and SRC, and 152 patients with low differentiation), the survival results of those subgroups should be interpreted dialectically, but the survival curves were not shown. Further clinical studies are warranted to characterize the effectiveness of combined CRT for these subgroups of patients.

Discussion

There remains a lack of consensus regarding the choice of adjuvant therapy for GC patients who underwent radical resection, especially in countries where D2 dissection is the standard surgery. Extended D2 resection provides more accurate staging and is associated with reduced locoregional recurrence and GC-related mortality risk, compared with D1 resection [12]. The research results from the ACTS-GC and the CLASSIC trials established the importance of postoperative adjuvant ChT in GC patients who underwent D2 resection. However, it remains

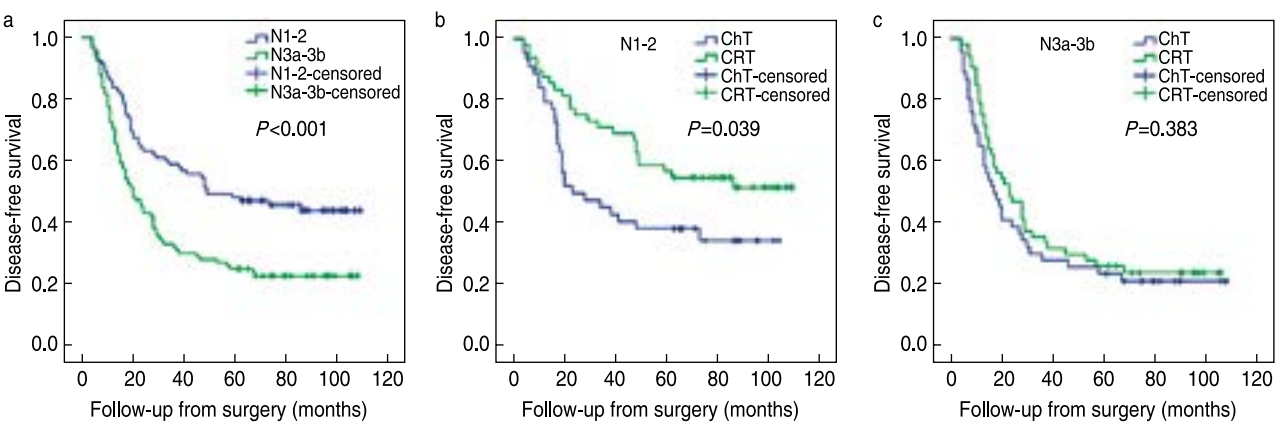

Fig. 5 Survival curves showed significant survival difference (DFS) in different LN stage (a).ChT, chemotherapy; CRT, chemoradiotherapy; DFS, disease-free survival. The patients with N1-2 stage disease (b) benifited from CRT, but the patients with N3a-3b stage disease (c) not

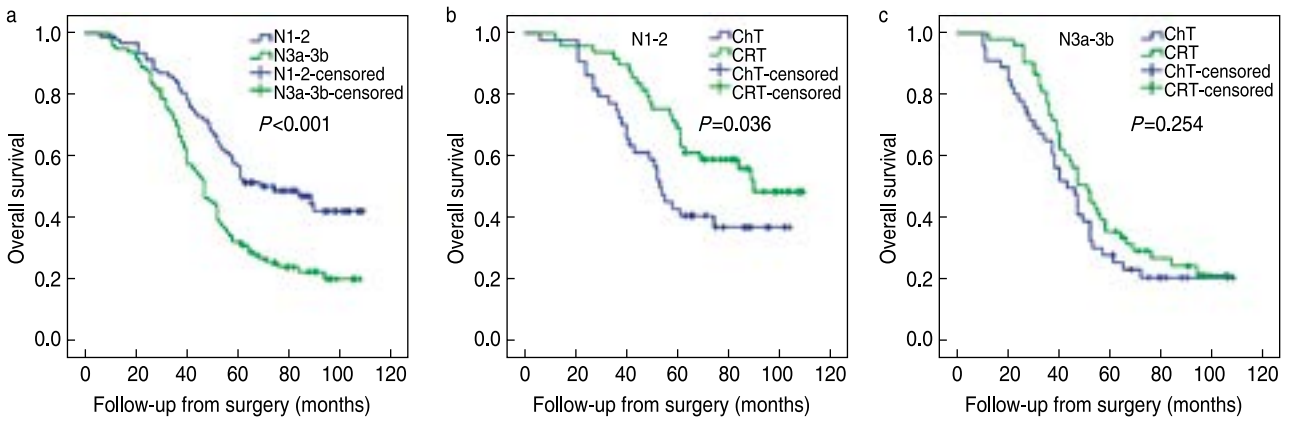

Fig. 6 Survival curves showed significant survival difference (OS) in different LN stage (a). ChT, chemotherapy; CRT, chemoradiotherapy; OS, overall survival. The patients with N1-2 stage disease (b) benifited from CRT, but the patients with N3a-3b stage disease (c) not

controversial whether the addition of RT provides further survival benefits. The ARTIST study was the first clinical study to assess the effectiveness of postoperative CRT in GC patients who underwent D2 resection. The results showed that the addition of RT to XP CRT did not significantly reduce the percentage of relapses. However, the subgroups with positive lymph nodes and intestinal type were more likely to benefit from the addition of RT. This finding indicated that it is important to explore the predominant population of adjuvant CRT cases. Therefore, we carried out a retrospective study to compare the role of adjuvant CRT and adjuvant ChT in locally advanced GC patients with positive lymph nodes who underwent D2 gastrectomy.

In this study, we only included GC patients with pathological T3–4 and pN+ stages, which was consistent with China's actual situation, because most patients in China are usually diagnosed in the later stages of the disease. Our patients mainly received doublet or triplet ChT regimens using 5-fluorouracil or oral fluorouracil derivatives, which was similar to those used in previous studies and has been shown to be well-tolerated. However, the consistency of the ChT regimens still needs to be determined using a series of clinical trials in the future. Our study demonstrated that patients with locally advanced cancer who received adjuvant CRT had significant improvements in their 3-year and 5-year DFS and OS, respectively. Although no significant difference was observed in the 5-year DFS, our results should be interpreted with caution due to the small number of relapses occurring after 3 years and the possible lower statistical efficiency. Our results did not show an improvement in the 5-year OS of patients who underwent adjuvant CRT or adjuvant ChT (5 year OS: 52.0% *vs.* 35.6%) compared with those reported in the ARTIST study (5 year OS: 75.0% *vs.* 73.0%). This could be due to the fact that 60% of the patients from each group in the ARTIST study had stage IB and II disease; therefore, they had better survival prognosis than those with late-stage disease. By contrast, our patients were usually in the later stages of the disease and, therefore, had a worse prognosis owing to the more prominent negative survival effect of advanced stage.

Subgroup analysis identified that patients with the N1–2 stage disease and poorly differentiated, larger tumor sizes (> 6 cm) showed a significantly prolonged survival after adjuvant CRT. Lymph node staging was an independent prognostic factor, which could predict distant metastasis and survival [13–14]. Kim *et al* [15] and a subgroup analysis of the ARTIST trial revealed an improvement in the DFS in pN+ patients who received CRT. In our cohort, all patients were pathologically lymph node positive and showed a significant improvement in the 3-year DFS (52.9% in the CRT arm *vs.* 36.7% in the ChT arm; P = 0.024), which was consistent with the reports of previous studies. In addition, those patients who received adjuvant CRT showed a significant improvement in their 3-year and 5-year OS. RT was reported to be the most effective locoregional therapeutic modality in patients with a high risk of relapse after surgery [16]. In our study, the CRT arm (20.6%) had lower rates of locoregional relapse than the ChT arm (34.4%; P = 0.031). This result indicated that RT might improve patient's survival through the process of locoregional control. However, patients with stage pN3 did not benefit from RT because of the high incidence of distant metastasis and peritoneal dissemination [17-19]. After further stratifying the lymph node staging into separate subgroups, we found that adjuvant CRT prolonged the survival of patients with stage pN1-pN2 disease, while no significant survival difference was shown between the two treatment strategies for patients with the pN3 classification.

In our study, tumor size showed a unique predictive value; patients with tumor size > 6 cm had superior

survival rates after receiving CRT. Maruyama Index (MI) was a quantitative standard for assessing the adequacy of lymph node dissection in gastric cancer; an MI of < 5 was considered a strong independent predictor of better disease-free survival and OS in gastric cancer patients, and tumor size was one of the seven variables [20–21]. Tumor size was consequentially considered as an essential prognostic factor in some solid tumors such as breast, lung, and liver cancer; however, for patients with lymph node metastasis, a tumor size stage system showed a significant improvement in predictive accuracy in the subgroup survival analysis [22]. Tumor size was associated with the degree of invasion and lymph node metastases in GC. We hypothesized that larger tumors were more likely to undergo micrometastases after surgery and that RT improved locoregional control by facilitating the clearance of the subclinical lesions.

The patients with the major forms of carcinoma had superior survival outcomes from adjuvant CRT based on our subset analysis, including adenocarcinoma, mucinous adenocarcinoma, and signet ring cell (SRC) carcinoma. However, there might be some bias due to the limited number of patients with mucinous adenocarcinomas and SRC types in our study ($n = 22$). In addition, Charalampakis et al. reported that tumors with a higher percentage of SRC were more likely to be resistant to RT [23]. Hence, further studies are warranted to solve this contradiction.

There were several limitations in the study. First, the sample size of the study was small. Second, it was difficult to avoid bias due to the retrospective nature of the study. Third, it was difficult to select a standard adjuvant ChT regimen, although the final distribution of ChT treatments was balanced in the two groups. Finally, due to the uneven distribution of patients in different subgroups, after combining these cases to perform a series of subgroup analyses, the results of these analyses should be cautiously interpreted. To confirm our findings, multi-center, prospective, large sample clinical trials should be conducted to obtain more rigorous results.

Conclusion

Our study showed the value of adjuvant CRT in locally advanced GC patients treated with D2 resection. For locally advanced GC patients with positive lymph nodes, the addition of adjuvant CRT showed superior clinical benefits in both OS and DFS, compared with adjuvant ChT alone. Using a subgroup analysis, we identified that high-risk patients are suitable for CRT; however, the results and significance of such subgroup analysis need to be confirmed because of the uneven distribution of patients among some subgroups, as well as the lower test efficiency. Further prospective clinical trials are needed to verify the efficacy and to characterize the predominant population of patients treated with adjuvant CRT.

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Ethics approval and consent to participate

The research was approved by the ethics committee of Affiliated Hospital of Qingdao University. Informed consent was signed by each patient included in the study.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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