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FULL PAPER

Adjuvant chemoradiotherapy versus adjuvant chemotherapy for R1 resected gastric cancer: a retrospective cohort study

^{1,2}MENG-LONG ZHOU, ^{1,2}GUI-CHAO LI, ^{1,2}WANG YANG, ^{1,2}WEI-JUAN DENG, ^{1,2}RAN HU, ^{1,2}YAN WANG, ^{2,3}ZI-WEN LONG, ^{2,3}XIAO-WEN LIU, ^{2,3}YA-NONG WANG and ^{1,2}ZHEN ZHANG

¹Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, PR China

²Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, PR China

³Department of Gastric Surgery, Fudan University Shanghai Cancer Center, Shanghai, PR China

Address correspondence to:

Prof. Zhen Zhang

E-mail: zhen_zhang@fudan.edu.cn

Prof. Ya-nong Wang

E-mail: dr_wangyn@163.com

Meng-long Zhou and Gui-chao Li have contributed equally to this study and should be considered as co-first authors.

Objective: The aim of this study was to compare the effects of adjuvant chemoradiotherapy (CRT) and adjuvant chemotherapy (ChT) on the survival of locally advanced gastric cancer (LAGC) patients treated with R1 resection.

Methods: The patients with LAGC and microscopically positive margins after a potentially curative gastrectomy in Fudan University Shanghai Cancer Centre were retrospectively identified. The patients who were referred to our hospital for adjuvant CRT after an R1 resection elsewhere were also included. The patients were divided into either the CRT group or ChT group according to the treatment strategy. We, then, examined the patient survival results and patterns of recurrence for each group.

Results: There were 114 LAGC patients treated with an R1 resection identified (CRT, $n = 33$; ChT, $n = 81$). The baseline characteristics between the two groups were not different. The estimated 3year recurrence-free

survival and overall survival in the CRT and ChT groups were 45.1% vs 31.8% ($p = 0.09$) and 49.6% vs 39.4% ($p = 0.20$), respectively. The results indicated that only nodal status was an independent prognostic factor (hazard ratio 4.04, 95% confidence interval 2.06–7.93). The risk of locoregional recurrence was increased in the ChT group. The subgroup analysis revealed that patients with pN0–2 GC showed a better recurrence-free survival due to adjuvant CRT (hazard ratio 0.19, 95% confidence interval 0.04–0.90; $p = 0.022$).

Conclusion: Adjuvant CRT improves locoregional control and may benefit patients with pN0–2 GC after R1 resection. The nodal status may be the most important predictor for patient selection.

Advances in knowledge: Nodal status may be the most important predictor for patient selection. Compared with adjuvant ChT, LAGC patients with pN0–2 disease may further benefit from additional radiotherapy after R1 resection.

INTRODUCTION

Although the global incidence of gastric cancer (GC) is declining, it remains more prevalent in Asia than in the West.¹ R0 resection is currently considered the standard approach for curing the disease. However, performing a radical surgery with tumour-negative resection margins in locally advanced gastric cancer (LAGC) frequently poses a challenge. A microscopically tumour-positive resection margin is defined as an R1 resection, which occurs in 2–22% of patients and is considered a poor prognostic factor.^{2–5}

There are no clear treatment guidelines after an R1 resection. However, there are two main strategies for this situation. The first option is surgical reintervention. The value of this option is still under debate due to the risks of a second operation or a more extensive primary resection.^{4,6,7} An alternative strategy is the administration of adjuvant chemoradiotherapy (CRT). Adjuvant CRT reduces locoregional recurrence after R0 resections and is considered to be an appropriate intensified local treatment for R1 GC resection.

There are currently no randomised controlled trials examining the role of adjuvant CRT after R1 GC resection, and published randomized trials on adjuvant CRT have invariably enrolled patients with a radical (R0) resection.^{8,9} The available evidence includes several retrospective studies involving patients with an R1 resection.^{10–14} However, the majority of these studies were from western countries and compared surgery plus adjuvant CRT with surgery alone. Thus, it is unsurprising that the survival of patients in the CRT group were superior to the patients receiving surgery alone because surgery has already been proven to be insufficient for LAGC patients.^{15,16}

In Asian countries, adjuvant chemotherapy (ChT) is widely applied as a standard strategy.^{17,18} However, we do not know if the addition of RT to adjuvant ChT further benefits patients with R1 resection. We conducted the current study with the aim of comparing the survival of patients who had undergone an R1 GC resection followed by adjuvant CRT or ChT at Fudan University Shanghai Cancer Centre (FUSCC) due to the limited data available on this subject.

METHODS AND MATERIALS

Patient enrolment

The patients who were surgically treated in FUSCC or referred for adjuvant CRT after surgical treatment in other hospitals between first January, 2006 and 31 December, 2015 were retrospectively identified. We excluded patients in whom gross residual tumour was left behind after surgery (R2 resection). Additionally, patients with positive peritoneal washing cytology were also excluded from the study. All patients in the study signed informed consent forms before the treatment. The study was approved by the ethics committee of FUSCC.

Histopathology

All resected tumours were staged according to the pathological classification of the American Joint Committee on Cancer seventh edition. An R1 resection was defined as the presence of tumour cells in the resection margins on standard microscopic examination or additional immunohistochemical staining with the anti cytokeratin monoclonal antibody CAM 5.2.

Treatment

All patients underwent a total or subtotal gastrectomy and D1/D2 lymphadenectomy according to the Japanese Research Society for Gastric Cancer guidelines. A routine splenectomy or pancreatic tail resection was not performed. The patients in the CRT group received one or two courses of ChT post-operatively, which was 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 to five additional subsequent courses of ChT. The patients in the ChT group received six to eight courses of ChT. The ChT regimens mostly consisted of combination therapies involving 5-FU or oral fluorouracil derivatives as the backbone with the addition of oxaliplatin and epirubicin. The ChT regimens can be subdivided based on the number of combined drugs. The triple-drug regimens include EOF (epirubicin + oxaliplatin + 5 FU) and EOX (epirubicin + oxaliplatin + capecitabine). The double-drug regimens include SOX (S1 + oxaliplatin), XELOX

(capecitabine + oxaliplatin) and OF (oxaliplatin + 5 FU). The single-drug regimens were oral fluorouracil derivatives such as capecitabine and S1. The courses or dosage of ChT was reduced for the elderly cases or patients exhibiting obvious adverse effects.

RT was targeted to the preoperative tumour extension, tumour bed, anastomosis site, and regional lymph nodes. The planning target volume margins were added by individually considering uncertainties. The remnant stomach was not routinely included within the radiation field after 2008 due to the results of a study from Korea.¹⁹ Fluorouracil-based ChT was concurrently used with RT and consisted of a continuous intravenous infusion of 225 mg m⁻² of 5-FU for 120 h each week (*n* = 5), 625 mg m⁻² capecitabine b.i.d. during RT (*n* = 11) or 40 mg m⁻² S1 b.i.d. daily during RT (*n* = 13). The remaining patients (*n* = 4) received RT without concurrent ChT after consideration of the toxicities and tolerance of treatment.

Follow-up and definition of recurrence

Patients were followed-up every 3 months for the first 2 years, every 6 months until 5 years and then annually, thereafter. The follow-up examinations included a complete history and physical examination, serum tumour biomarkers, CT scans of the chest, abdomen and pelvis and endoscopy every year. Overall survival (OS) was calculated from surgery until death of any cause (event) or last follow-up contact (censored). Recurrence-free survival (RFS) was calculated from surgery until recurrence (event) or the day of last follow-up without recurrence (censored).

Disease recurrence was documented by biopsy or cytology reports or by clinical evidence of radiographic studies. The recurrences were categorized as local recurrence (LR), regional recurrence (RR), peritoneal metastasis (PM) or distant metastasis (DM). The recurrences within the potential radiation field were considered a locoregional recurrence. LR was defined as any recurrence at the site of anastomosis, remnant stomach, duodenal stump or tumour bed. An RR was defined as recurrence occurring at regional lymph nodes within the RT field or hypothetical RT field of the ChT group. A radiologist specialized in gastrointestinal radiology reviewed the radiological findings and confirmed the sites of LR. Recurrence inside the peritoneal cavity was considered PM. DM was defined as liver metastasis or metastasis to extra abdominal sites.

Statistical analysis

Continuous variables were reported as mean ($\pm$ standard deviation) or median (with range), as appropriate, and categorical variables were reported as number and percentage. Variables were compared using the χ^2 test or t test/Wilcoxon rank sum test, as appropriate. All survival curves were plotted using the Kaplan–Meier method and were compared using the log-rank test. The Cox proportional hazards model was used to perform both the univariate and multivariate analyses of prognostic factors for RFS. All *p*-values were two sided, and a *p*-value less than 0.05 is regarded as statistically significant. All statistical analyses were performed using R (v. 3.4.3; R Project for Statistical Computing, Vienna, Austria).

Figure 1. Patient inclusion in the (a) CRT group ($n = 33$), and (b) ChT group ($n = 81$) (2006–2015). ChT, chemotherapy; CRT, chemoradiotherapy; LAGC, locally advanced gastric cancer.

RESULTS

Study population and patient characteristics

All patients included in this study were treated between first January, 2006 and 31 December, 2015. There were 33 and 81 patients who met the inclusion criteria and were included as the CRT and ChT groups, respectively. Two detailed flow diagrams of patient inclusion are shown in [Figure 1a](#) (CRT group) and [1b](#) (ChT group). The patients' clinicopathological characteristics and the regimens and courses of ChT are summarized in [Table 1](#). The baseline features including tumour and nodal stage were balanced between groups.

Survival, prognostic factors and treatment effects

At the time of analysis, the median patient follow-up in the CRT group and ChT group were 30 and 24 months, respectively. A total of 44 deaths occurred (11 deaths in the CRT group and 33 deaths in the ChT group), and 57 patients experienced recurrence (15 patients in the CRT group and 42 patients in the ChT group). The estimated 3year RFS and OS in the CRT and ChT groups were 45.1 vs 31.8% ($p = 0.09$, [Figure 2](#)) and 49.6 vs 39.4% ($p = 0.20$, [Figure 3](#)), respectively.

The results of univariate and multivariate analyses for RFS are listed in [Table 2](#). Although no significant difference was observed,

the trend indicated that adjuvant CRT may be a better prognostic factor for RFS compared to adjuvant ChT [univariate Cox hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.33–1.09; multivariate Cox HR 0.62; 95% CI 0.33–1.16].

Recurrence pattern

We collected patient histories and physical examinations, CT scans and endoscopy results. We then compared the results with the radiotherapy plans for patients in the CRT group. There were significant differences between the two groups in the patterns of recurrence ([Table 3](#)). Overall, recurrences occurred in 57 patients with 91 recurrent sites during the follow-up period. The ChT group showed an increased risk of local (14.8% vs 3.0%) and regional (17.3% vs 6.1%) recurrence compared with the CRT group. The rates of peritoneal (32.1% in the CRT group vs 27.3% in the ChT group) and distant (24.7% in the CRT group vs 21.2% in the ChT group) metastasis were similar between the two groups.

Subgroup analysis

Subgroup analyses were performed to identify patient populations who may benefit from adjuvant CRT, and the results are shown in [Figure 4](#). The calculated HRs and 95% CIs showed the potential benefit from the addition of RT to adjuvant ChT could

Table 1. Patient characteristics of CRT and ChT groups

	CRT group		ChT group		
Characteristics	No.	%	No.	%	<i>p</i>
Total	33		81		
Sex					
Male	27	81.8	54	66.7	0.165
Female	6	18.2	27	33.3	
Age					
≤60	24	72.7	50	61.7	0.368
>60	9	27.3	31	38.3	
Location					
GEJ + upper 1/3	7	21.2	9	11.1	0.278
Middle 1/3	5	15.2	16	19.8	
Lower 1/3	9	27.3	15	18.5	
Multiple	12	36.4	41	50.6	
Gastrectomy					
Proximal	5	15.2	8	9.9	0.244
Distal	12	36.4	20	24.7	
Total	16	48.5	53	65.4	
Borrmann's type					
Type II	1	3.0	9	11.1	0.323
Type III	24	72.7	50	61.7	
Type IV	8	24.2	22	27.2	
Diameter (cm)					
≤5	18	54.5	41	50.6	0.862
>5	15	45.5	40	49.4	
Differentiation					
Poor	20	60.6	49	60.5	1.000
Well-moderate	13	39.4	32	39.5	
Nodes harvested					
<16	6	18.2	9	11.1	0.479
≥16	27	81.8	72	88.9	
Tumour stage					
T3	12	36.4	23	28.4	0.540
T4	21	63.6	58	71.6	
Nodal status					
N0	7	21.2	15	18.5	0.858
N1	3	9.1	6	7.4	
N2	3	9.1	12	14.8	
N3	20	60.6	48	59.3	
ChT courses					
Mean (SD)	3.8	(1.7)	4.4	(2.2)	0.186

(Continued)

Table 1. (Continued)

	CRT group		ChT group		
Characteristics	No.	%	No.	%	<i>p</i>
Total	33		81		
Median (range)	4	(1-6)	5	(1-8)	
Unknown	5		9		
ChT regimens					
Triple drugs	9	27.3	19	23.5	0.878
Double drugs	15	45.5	42	51.9	
Single drug	4	12.1	11	13.6	
Unknown	5	15.2	9	11.1	

CRT, chemoradiotherapy; ChT, chemotherapy; GEJ, gastroesophageal junction; SD, standard deviation.

not be excluded in patients with pN0-2 GC (HR 0.19, 95% CI 0.04–0.90).

DISCUSSION

The management of positive margins after GC resection remains a clinical dilemma. A second surgery or a more extensive primary resection could be options. However, the concomitant risk should not be neglected. Another choice is adjuvant CRT, which is recommended by the NCCN guidelines for GC. Although adjuvant ChT is prevalent in Asia, it is unknown if the addition of RT provides further benefit after an R1 GC resection. Thus, we performed the current study comparing the efficacy of adjuvant CRT with adjuvant ChT after an R1 resection.

Figure 2. RFS curves of patients in the CRT and ChT groups. ChT, chemotherapy; CRT, chemoradiotherapy; RFS, recurrence-free survival.

Figure 3. OS curves of patients in the CRT and ChT groups. ChT, chemotherapy; CRT, chemoradiotherapy; OS, overall survival.

The baseline characteristics were balanced in the current study cohort. The extension of tumours was relatively broad, which can be manifested by the multiple tumour sites and diameters. Additionally, 60% of patients had pN3 stage GC. This finding was consistent with the report that R1 resection occurs in patients with more aggressive tumour biology.⁵

The tumour stage and nodal status showed their prognostic impact in the univariate analysis. Nodal status remained the only independent prognostic factor in our cohort. Our data failed to indicate that adjuvant CRT has a significant advantages compared to adjuvant ChT with respect to RFS and OS. However, a trend emerged in the univariate and multivariate analyses (Table 2). It is possible that a larger cohort could reveal the improved efficacy of adjuvant CRT.

The statistically insignificant difference in benefits in our study was inconsistent with previous reports comparing adjuvant CRT with surgery alone after an R1 GC resection. In addition to the difference regarding treatment strategy, there are also other important disparities in our study. The study conducted by Stiekema et al¹⁴ included a relatively large sample size and enrolled 40 patients in the CRT group and 369 patients in the no-CRT group. However, only 10% patients in the no-CRT group were treated with adjuvant ChT. Second, patients with more than 15 evaluated lymph nodes only accounted for

30% of cases in the CRT and 36% of cases in the no-CRT group. Third, the proportions of patients with pN3 disease in each group were no more than 38%. Thus, the patients in this cohort had the “CRT beneficial” features such as insufficient lymphadenectomy and less severe nodal metastasis. In contrast, patients in our cohort received more D2 dissection (81.8 and 88.9% of patients in the CRT and ChT group, respectively, harvested more than 16 lymph nodes), and the nodal metastasis was more severe (60% of patients were pN3 in both groups).

In Asian countries using adjuvant ChT as a standard strategy for LAGC patients, the role of RT is still under investigation, and the importance of patient selection has been gradually realized. The subgroup analysis of the ARTIST trial indicated that patients with metastatic nodes (pN+) and intestinal type of Lauren’s classification may benefit from the addition of RT to adjuvant ChT.²⁰ A meta-analysis showed that the improved locoregional control caused by RT does not improve survival because the risk of metastasis does not decrease.²¹ Moreover, patients with pN + disease may be further divided, as several studies indicate the patients with pN3 disease cannot benefit from RT due to the high rate of DM and peritoneal dissemination.^{22–24}

Similar to adjuvant CRT for R0 resected patients, the identification of R1 resected patients who may benefit from RT is critical.

Table 2. Univariate and multivariate analysis of prognostic factors for RFS

Variable	N	No. of events	3 years RFS (%)	Univariate analysis			Multivariate analysis		
				HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Sex									
Male	81	42	35.3	Ref.			Ref.		
Female	33	15	39.8	1.11	0.62–2.01	0.713	1.51	0.79–2.90	0.214
Age									
≤60	74	41	32.4	Ref.			Ref.		
>60	40	16	46.2	0.66	0.37–1.18	0.158	0.71	0.39–1.31	0.278
Location									
GEJ + upper 1/3	16	10	17.1	Ref.			Ref.		
Middle 1/3	21	10	39.2	0.59	0.25–1.43	0.246	0.55	0.22–1.37	0.197
Lower 1/3	24	11	41.8	0.73	0.31–1.73	0.475	0.62	0.25–1.53	0.300
Multiple	53	26	38.3	0.92	0.44–1.91	0.818	0.76	0.34–1.67	0.490
Differatiation									
Poor	69	33	40.0	Ref.			Ref.		
Well-moderate	45	24	30.0	1.19	0.70–2.02	0.516	1.38	0.81–2.37	0.239
Tumour stage									
T3	35	11	45.8	Ref.			Ref.		
T4	79	46	29.6	2.25	1.16–4.34	0.016	1.68	0.86–3.30	0.132
Nodal status									
N0-2	46	13	55.8	Ref.			Ref.		
N3	68	44	22.5	3.88	2.08–7.24	<0.001	4.04	2.06–7.93	0.001
Treatment									
ChT	81	42	31.9	Ref.			Ref.		
CRT	33	15	45.1	0.60	0.33–1.09	0.090	0.62	0.33–1.16	0.136

ChT, chemotherapy; CI, confidence interval; CRT, chemoradiotherapy; GEJ, gastroesophageal junction; HR, hazard ratio, Ref,reference.

Our subgroup analysis showed the patients with pN0-2 disease could benefit from adjuvant CRT. Furthermore, the patterns of recurrence showed a high rate of PM and DM of pN3 patients

in both groups. However, the rate of LR and RR was lower in the CRT group than in the ChT group. In the pN3 group, the patients with locoregional recurrence were always accompanied by PM

Table 3. Patterns of recurrence

	CRT Group (N = 33)				ChT Group (N = 81)			
	N0-2 (N = 13)		N3 (N = 20)		N0-2 (N = 33)		N3 (N = 48)	
	No.	%	No.	%	No.	%	No.	%
Recurrent pts								
Total	2	15.4	13	65.0	13	33.3	29	60.4
Recurrent sites								
LR	0	0	1	5.0	5	15.2	7	14.6
RR	0	0	2	10.0	4	12.1	10	20.8
PM	1	7.7	8	40.0	5	15.2	21	43.8
DM	1	7.7	6	30.0	3	9.1	17	35.4

ChT, chemotherapy; CRT, chemoradiotherapy; DM, distant metastasis; LR, local recurrence; PM, peritoneal metastasis; Pts, patients; RR, regional recurrence.

Figure 4. Forest plot of subgroup analysis for RFS. HR<1 favours adjuvant CRT and HR>1 favours adjuvant ChT. ChT, chemotherapy; CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; RFS, recurrence-free survival.

or DM. Thus, our findings may verify the efficacy of adjuvant therapy on locoregional control and indicates that the patients with pN0-2 disease after R1 resection may benefit from adjuvant CRT.

This result is consistent with the conclusions made by Raziee et al⁵ in their meta-analysis. Margin status is an important consideration in patient survival, but it loses prognostic significance in patients with advanced disease because of the more dominant negative survival effect of advanced stage compared to margin status. The patients with advanced cancers such as pN3 GC are more likely to die of carcinomatosis or disseminated disease than anastomotic recurrence. The benefit of

locoregional control brought by adjuvant RT may not transfer to increased survival. Thus, lymph node status may be one of the most important predictors of whether a patient will benefit from adjuvant CRT or not.

There are several limitations to the current study. First, as a retrospective analysis with a relatively small sample size, the statistical power of tests may be too low to show the survival difference. The numbers of patients with N0, -1 or -2 in the CRT group were only 7, 3 and 3, respectively. Although the prognosis of these patients may be substantially different, we combined these cases to perform the subgroup analysis (N0-2 vs N3) due to the small numbers. Thus, the findings should be cautiously interpreted. Theoretically, a randomised trial is the preferred method, but it is highly unlikely that such a trial will ever be performed. Second, referral bias may exist in this study as a proportion of patients enrolled in the CRT group underwent resections elsewhere and were referred for post-operative treatment in our centre. The quality control of surgery is unfeasible, but surgery itself can have a major impact on survival. Third, there is loss to follow up in our study, but the rate is no more than 10% in each group.

CONCLUSION

The role of adjuvant CRT in patients with R1 GC resection remains unclear. Due to the retrospective design and insufficient sample size, we could not reach a firm conclusion. However, this study showed the trend of potential benefit and the advantage of adjuvant CRT in the subgroups of patients. Thus, the addition of RT can further improve locoregional control, and we proposed the hypothesis that patients with pN0-2 stage might be the most suitable candidates for additional RT. Further validation from larger cohorts is necessary.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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