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FULL PAPER

Identification of patients with lymph node metastasis from gastric cancer who may benefit from adjuvant chemoradiotherapy after D2 dissection—do N3 patients benefit from additional radiation?

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Objective: The role of adjuvant chemoradiotherapy (CRT) in locally advanced gastric cancer (LAGC) after D2 dissection is controversial. Subgroup analysis of the ARTIST trial indicated that patients with lymph node metastasis might benefit from additional radiation. The present study compared adjuvant CRT with adjuvant chemotherapy (CT) for the treatment of lymph node metastasis and suggested patient-selection guidelines.

Methods: Patients with LAGC and positive lymph nodes who underwent D2, R0 gastrectomy in our hospital were retrospectively investigated. Patients were divided into two balanced groups by the use of propensity-score matching: CRT group ($n = 138$) received adjuvant CRT with fluorouracil-based regimens and radiation (45–50.4 Gy), and the CT group ($n = 138$) received adjuvant CT alone.

Results: Of the 276 patients, 147 patients died (69 patients in the CRT group and 78 patients in the CT group), and

151 patients experienced recurrence (65 patients in the CRT group and 86 patients in the CT group). The estimated 3-year disease-free survival (DFS) and overall survival in the CRT and CT groups were 51.5% vs 41.3% ($p = 0.05$) and 52.0% vs 50.1% ($p = 0.35$), respectively. The risk of local regional recurrence was increased in the CT group compared with the CRT group (16.7% vs 8.7%, $p = 0.04$, respectively). In the subgroup analysis, patients with N1–2 stage were associated with better survival from CRT (hazard ratio = 0.44, $p = 0.01$).

Conclusion: Adjuvant CRT may improve the 3-year DFS and local control in patients with LAGC after D2 dissection. Investigation of stratification factors for patient selection is warranted.

Advances in knowledge: Patients with N1–2 stage rather than those with N3 stage benefit most from additional radiation after D2 dissection.

INTRODUCTION

Gastric cancer is the fifth most common malignant cancer and the third leading cause of cancer-related death in the world.¹ In the past decades, the mortality of gastric cancer decreased remarkably owing to advances in surgical procedures and multimodality treatments consisting of chemotherapy (CT) and radiotherapy. However, in patients with locally advanced gastric cancer (LAGC), differences in the morbidity and mortality among different areas have led to various management strategies worldwide. In Europe, perioperative CT combined with radical surgery is standard therapy, whereas in Japan, D2 gastrectomy followed by adjuvant CT is recommended.^{2,3} In the USA, radical surgery followed by post-operative chemoradiotherapy (CRT) has been recommended since the Intergroup (INT) 0116 trial reported a distinct survival benefit from CRT.^{4–6} However, a the Phase III trial

known as the ARTIST trial, which compared adjuvant CT alone with adjuvant CRT in patients undergoing D2 dissection, failed to show improvements in 5-year disease-free survival (DFS); therefore, adjuvant CRT is controversial in patients undergoing D2 dissection.^{7,8} Nevertheless, subgroup analyses in the ARTIST trial revealed that patients with lymph node metastasis and intestinal type by Lauren classification might benefit from additional radiation,⁸ underscoring the importance of defining the indications for selective CRT. A follow-up ARTIST II trial in which all patients had positive lymph nodes is under way.⁸ In this article, we retrospectively analysed patients with gastric cancer who received adjuvant CRT after D2 lymph node dissection for pathologically confirmed lymph node metastasis in comparison with those who received adjuvant CT alone and discussed potential stratification factors for patient selection. To

minimize confounding factors, propensity score matching was used in this study.

METHODS AND MATERIALS

Inclusion criteria

We retrospectively identified consecutive patients who were treated in our hospital between January 2004 and October 2011. The inclusion criteria were as follows: (1) patients who had undergone radical gastrectomy (R0 resection) with D2 lymph node dissection, at least 15 lymph nodes dissected; (2) those who had histologically confirmed gastric adenocarcinoma and lymph node positivity, with no clinical evidence of distant metastasis (M0), according to the International Union Against Cancer tumour–node–metastasis classification;⁹ (3) those with adequate function of major organs, including cardiac, hepatic and renal functions; and (4) those with no history of any other cancer or previous radiotherapy or CT or coexisting malignancies. All patients in the study signed informed consent forms.

TREATMENT DELIVERY

Surgery

The surgical requirement for eligibility was radical, with *en bloc* resection of the tumour with negative margins proved by pathology (R0 resection). All patients had undergone D2 lymph node dissection with resections of all perigastric lymph nodes (right and left cardiac nodes, nodes along the lesser curvature, short gastric, left gastroepiploic and the right gastroepiploic vessels, suprapyloric nodes and infrapyloric nodes), and nodes along the root left gastric artery, common hepatic artery, around the celiac axis, at the splenic hilum or along the splenic artery, depending on the location of the primary tumour.

Radiotherapy

Radiotherapy was delivered by a linear accelerator-based 6-MV photons using either three-dimensional CRT or intensive modulation radiotherapy. Patients were treated with a total dose of 45–50.4 Gy, with 1.8-Gy daily fractions administered over 5–6 weeks. The clinical target volume included the tumour bed, anastomotic stoma and regional draining lymph nodes. The tumour bed was defined by pre- and post-operative computer tomography imaging, barium radiography and surgical clips. Regional lymph nodes included perigastric, para-oesophageal, paracardial, celiac, splenic, hepatoduodenal or hepatic portal and pancreaticoduodenal depending on the location of the tumour.¹⁰ The planning target volume margin was 0.5–1.0 cm, and it was optimized to ensure 45 Gy to be >95% of the planning target volume. The V_{15} of the kidney was <40% and the V_{30} of the liver was <60%. The spinal cord received <45 Gy. The breath-hold technique was applied in patients with respiratory motion >1 cm under fluoroscopic imaging.

Concurrent chemotherapy

Concurrent CT regimens were as follows: 5-fluorouracil 225 mg/m²/d weekly intravenously or capecitabine 625 mg/m²/d bid d1–5 weekly.

Adjuvant chemotherapy

All eligible patients received 4–6 cycles of fluorouracil-based regimens after surgery. In the CRT group, CT was delivered in 1–2 cycles before and 4–5 cycles after CRT.

Follow-up

Patients were followed up every 3 months for the first 2 years, then every 6 months until 5 years and yearly thereafter. Follow-up examinations included a complete history and physical examination, serum tumour biomarkers, CT scans of the chest, abdomen and pelvis each time as well as endoscopy every year. We calculated overall survival (OS), DFS and failure patterns of different management strategies. Local regional recurrence included recurrence at anatomic sites, a duodenal stump, tumour bed, residual stomach and regional lymph nodes, which were included in the clinical target volume in the radiotherapy plan. Distant metastasis was defined as any metastasis to distant lymph nodes outside the radiation field, distant organs or sites except for the peritoneum. Toxicities were assessed using the Common Terminology Criteria for Adverse Effect 4.0.

Statistical analysis

All statistical analyses were performed using SPSS® v. 22.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The Kaplan–Meier method was used to analyse OS and DFS, and the log-rank test was used to detect differences. χ^2 tests were used to detect differences in clinical factors and failure patterns between the two groups. A Cox proportional hazards model was used to detect the potential effective factors for survival in the subgroup analysis. All *p*-values were two sided, and a *p*-value of <0.05 was regarded as statistically significant. The propensity score was calculated by using a logistic regression model with a caliper of 0.01.

RESULTS

Study population and patient characteristics

A total of 436 patients treated between January 2004 and October 2011 met our criteria. After adjustment for age, T-stage, N-stage, American Joint Committee on Cancer stage and tumour differentiation, 276 patients were successfully matched. Half of the patients (138 patients) received adjuvant CRT after radical surgery and were considered as the CRT group, and the other half received adjuvant CT alone and was defined as the CT group. Baseline characteristics are listed in Table 1. Most of the matched patients were at Stage III (>70%) and more than half of these patients were at N3 stage.

Treatment delivery

Patients in the CRT group received a median dose of 45 Gy (range 45.0–50.4 Gy) of radiation. In the CRT and CT groups, 72.4% and 74.6% of patients, respectively, completed the entire treatment regimen as planned (*p* > 0.05). Reason for unfinished treatment mainly lied in toxic effects, accounting for 84.2% and 82.8% in CRT and CT groups.

Safety

The most common Grade III–IV toxicities were leucopenia/granulocytopenia, accounting for 33.3% and 26.1% in CRT and CT groups. Haematological toxicity was higher in the CRT group than in the CT group (34.7% vs 26.1%, respectively). No treatment-related death occurred. Details of the toxicities are listed in Table 2.

Efficacy

The median follow-up time was 36 months (range 4–88 months). A total of 147 deaths occurred (69 deaths in the CRT group and

Table 1. Baseline characteristics

Characteristics	Chemoradiotherapy (<i>n</i> = 138)		Chemotherapy (<i>n</i> = 138)		<i>p</i> -value
	Number	%	Number	%	
Age					
Mean	53.4		55.3		0.87
Range	19–77		28–82		
Gender					
Male	96	69.6	93	67.4	0.70
Female	42	30.4	45	32.6	
Tumour location					
Proximal	26	18.8	36	26.1	0.08
Gastric body	23	16.7	27	19.6	
Distal	89	64.5	75	54.3	
Stage					
IB	3	2.2	3	2.2	0.90
IIA	4	2.9	7	5.1	
IIB	5	3.6	3	2.2	
IIIA	21	15.2	18	13.0	
IIIB	40	29.0	42	30.4	
IIIC	65	47.1	65	47.1	
T stage					
T1	6	4.4	7	5.1	0.99
T2	4	2.9	4	2.9	
T3	14	10.1	14	10.1	
T4	114	82.6	113	81.9	
N stage					
N1	26	18.8	23	16.7	0.77
N2	36	26.1	41	29.7	
N3	76	55.1	74	53.6	
Number of dissected lymph nodes					
Median	22		23		0.06
Range	15–49		15–59		
Number of involved lymph nodes					
Median	6		6		0.07
Range	1–38		1–36		
Differentiation					
Low	122	88.4	118	85.5	0.48
Mid–high	16	11.6	20	14.5	

78 deaths in the CT group), and 151 patients experienced recurrence (65 patients in the CRT group and 86 patients in the CT group). The estimated 3-year DFS and OS in the CRT and CT groups was 51.5% vs 41.3% ($p = 0.05$, [Figure 1](#)) and 52.0% vs 50.1% ($p = 0.35$, [Figure 2](#)), respectively.

Patterns of recurrence

We collected patient histories and physical examinations, CT scans as well as endoscopies and compared them with radiotherapy plans. Recurrence occurred in 151 patients during the follow-up period. There were significant differences between the two groups

Table 2. Grade III–IV toxic effects

Toxicity	Chemoradiotherapy <i>n</i> (%)	Chemotherapy <i>n</i> (%)
Leucopenia/granulocytopenia	46 (33.3)	36 (26.1)
Anorexia	9 (6.5)	8 (5.8)
Nausea	13 (9.4)	13 (9.4)
Vomiting	7 (5.1)	5 (3.6)
Anaemia	1 (0.7)	0 (0.0)
Thrombocytopenia	2 (1.5)	0 (0.0)
Liver dysfunction	1 (0.7)	1 (0.7)
Diarrhoea	3 (2.2)	2 (1.4)

in the patterns of recurrence (Table 3). The CT group showed an increased risk of local regional recurrence compared with the CRT group (16.7% vs 8.7%, $p = 0.04$), while there were no statistically significant differences in other sites between the two groups. None of the patients with N1–2 stage experienced local regional recurrence after receiving additional radiation, while there was no obvious difference between those in the N3 subgroups.

Subgroup analysis

Table 4 shows the results of the subgroup analysis including the hazard ratios and 95% confidence intervals of DFS for the different treatments within the selected stratification factors. Adjuvant CRT was identified as a factor associated with treatment benefit in most subsets. Among these subsets, patients with N1–2 stage showed the greatest benefit from adjuvant CRT (hazard ratio = 0.44, $p = 0.01$). Kaplan–Meier survival curve of DFS based on different lymph node status (Figure 3) also discovered robust survival benefit in patients with N1–2 stage

($p < 0.01$), while there was little difference between N3 subgroups ($p = 0.81$).

DISCUSSION

The foundation of adjuvant CRT was laid by the landmark INT 0116 trial published in 2001.⁵ In this trial, 556 patients were randomly assigned to surgery plus adjuvant CRT or surgery alone groups, and a significant OS benefit (40% vs 22%) and a decrease in local recurrence rate (19% vs 29%) were observed in the CRT group compared with the surgery-only group, and these effects were maintained during the long follow-up of 11 years.⁶ However, the ARTIST trial^{7,8} failed to demonstrate any significant differences in DFS between CT and CRT groups after D2 dissection, thus leading to controversies regarding the role of radiation after D2 dissection in patients with LAGC. The aforementioned trials differed in the study design, patient selection and treatment delivery; therefore, it is difficult to compare them intrinsically.

Figure 1. Disease-free survival (DFS) curve for chemoradiotherapy (CRT) group and chemotherapy (CT) group. The estimated 3-year DFS in the CRT and CT groups was 51.5% vs 41.3% ($p = 0.05$).

Figure 2. Overall survival (OS) curve for chemoradiotherapy (CRT) group and chemotherapy (CT) group. The estimated 3-year OS in the CRT and CT group was 52.0% vs 50.1% ($p = 0.35$).

Table 3. Patterns of recurrence^a

Failure patterns	Chemoradiotherapy			Chemotherapy			
	N1–2 (<i>n</i> = 62), <i>n</i> (%)	N3 (<i>n</i> = 76), <i>n</i> (%)	Total (<i>n</i> = 138), <i>n</i> (%)	N1–2 (<i>n</i> = 64), <i>n</i> (%)	N3 (<i>n</i> = 74), <i>n</i> (%)	Total (<i>n</i> = 138), <i>n</i> (%)	<i>p</i> -value ^{<i>b</i>}
Relapse status							
No relapse	46 (74.2)	27 (35.5)	73 (52.9)	30 (47.9)	22 (29.7)	52 (37.7)	0.01
Relapse	16 (25.8)	49 (64.5)	65 (46.1)	34 (53.1)	52 (70.3)	86 (62.3)	0.01
Local/ regional	0 (0.00)	12 (15.8)	12 (8.7)	8 (12.5)	15 (20.3)	23 (16.7)	0.04
Peritoneum	12 (19.4)	16 (21.1)	28 (20.2)	15 (23.4)	22 (29.7)	37 (26.8)	0.20
Distant	10 (16.1)	21 (27.6)	31 (23.9)	16 (25.0)	24 (32.4)	40 (29.0)	0.22

^aGenerally, patients with N3 stage had increased risk of recurrence in both groups.

The reduction of local/regional recurrence in patients with N3 was limited by additional radiation (15.8% vs 20.3%, respectively), while in the N1–2 groups, the reduction is obvious (0.0% vs 12.5%, respectively).

^b*p*-value was detected between chemoradiotherapy and chemotherapy groups.

Lacking sufficient evidence from large randomized trials, adjuvant CRT after D2 dissection remained undefined; however, subgroup analysis in the ARTIST trial indicated that patients with lymph node metastasis and intestinal-type tumours could benefit from additional radiation. Under these circumstances, the goal is to detect patients who will derive benefit from adjuvant CRT. The potential stratification factors consisted of two aspects: clinical factors and pathological/histological factors.

Table 4. Subgroup analysis of disease-free survival

Factor	<i>n</i>	HR ^a	95% CI ^b	<i>p</i> -value
Gender				
Female	87	0.93	0.52–1.64	0.80
Male	189	0.66	0.45–0.98	0.04
Age				
≤60	182	0.73	0.49–1.09	0.12
>60	94	0.72	0.41–1.26	0.25
N stage				
N1–2	126	0.44	0.24–0.79	0.01
N3	150	0.95	0.65–1.41	0.81
Tumour site				
Proximal	62	0.74	0.38–1.45	0.38
Middle	70	0.94	0.49–1.82	0.86
Distal	219	0.82	0.56–1.19	0.29
Differentiation				
Low	243	0.79	0.56–1.15	0.18
Mid–high	50	0.90	0.42–1.95	0.79

^aHR, hazard ratio; HR <1 favours adjuvant chemoradiotherapy.

^bCI, confidence interval.

Regarding clinical factors, the quality of surgery is crucial. Radiation oncologists cannot evaluate the quality of D2 dissection based on operation notes or post-operative pathology reports. More than 15 dissected lymph nodes have been used for the evaluation of D2 dissection; however, it does not reflect the extent of dissection.^{11–13} Some patients who underwent the so-called “D2” dissection were actually D1 or D1 plus, with a loco-regional recurrence rate of up to 41% according to the long-term results of a Dutch trial.¹³ According to Morgan et al,¹⁴ hospitals with cancer programme recognition have a higher probability to dissect 15 or more lymph nodes than their counterparts (45.5% vs 34.8%, respectively), which indicates variation in the surgical quality between hospitals. The uncertainty of operation highlights the importance of adjuvant CRT.

Lauren classification and lymph node status are essential among pathological/histological factors. Patients with intestinal type according to Lauren’s classification are more likely to benefit from CRT than those with diffuse-type tumours in the subgroup

Figure 3. Disease-free survival curve based on different lymph node status. There is robust survival benefit in patients with N1–2 stage (*p* < 0.01), while for those with N3 stage, there was no obvious difference (*p* = 0.81).

analyses of the INT 0116 and ARTIST trials.^{6,8} Unfortunately, because of the limitations of the retrospective study, we were unable to retest the pathological samples to evaluate Lauren classification status. Future studies will take this into consideration. The results of the ARTIST trial⁸ and the study by Ejaz et al¹⁵ indicated that patients with positive lymph nodes at surgery are prone to show better survival benefits from adjuvant CRT, underscoring the importance of evaluating lymph node status.

Our study is desired to focus on patients with lymph node metastasis after D2 dissection. In our study, adjuvant CRT significantly improved local control compared with CT alone. Although the statistic analysis of DFS resulted in a borderline *p*-value of 0.05, there was an obvious favour of CRT according to the Kaplan–Meier survival curve. No differences in OS were observed between the two groups, which might be due to the high risk of peritoneal and distant metastasis as well as an inadequate follow-up period. According to current studies, the local recurrence rate after D2 dissection varies from 13% to 24.2%^{7,8,16,17} for patients receiving CT only and from 7% to 15.6%^{8,16} in those treated by CRT. In our study, we observed an increased risk of local regional recurrence in the CT group compared with that in the CRT group (16.7% vs 8.7%, *p* = 0.04) and this difference in the recurrence patterns highlighted the importance of CRT even after D2 dissection.

Although higher Grade III–IV haematological toxicities was observed in the CRT group (34.7% vs 26.1%) was observed in the CRT group, there was no difference in treatment completion, and we believe that this is related to a more frequent follow-up during concurrent CRT.

In the subgroup analysis, we discovered that patients with N1–2 stage seemed to benefit most from additional radiation, while the benefit for N3 stage was limited. Previous studies indicated that patients with lymph node metastasis could benefit from

adjuvant CRT. Subgroup analysis of the ARTIST trial revealed an improved DFS after radiation for patients with positive lymph nodes.⁸ However, since approximately 90% of the patients who were node positive were at the N1–2 stage, this survival benefit most likely owed to these patients, and the therapeutic effect on N3 stage remained unclear. The study of Ejaz et al¹⁵ using propensity score matching also showed to be in favour of CRT for patients with positive lymph nodes. Unfortunately, in their study, not all the patients received D2 dissection, and patients were divided into node positive or node negative without specific N stages. According to lymph node status-based failure patterns in our study, additional radiation could significantly reduce local regional recurrence in patients with N1–2 stage (0% vs 12.5%, respectively); however, the benefit was reduced to approximately 5% in patients with N3 stage (15.8% vs 20.3%). In addition, in patients with more than seven lymph node metastases (N3 stage), the probability of local/regional recurrence, peritoneal and distant metastases were comparable between the CRT and CT groups (*p* > 0.05), leading to a limited survival benefit from additional radiation among these patients. Therefore, precedence should be given to optimizing CT among these patients.

The role of adjuvant CRT after D2 dissection in patients with LAGC remains unclear. Although limited by retrospective design and non-randomized data, we could not draw a firm conclusion from our study; but, this study showed the advantage of adjuvant CRT after D2 dissection, and proposed the hypothesis that patients with N1–2 stage might be the most suitable candidates for additional radiation. Further validation from randomized controlled trials such as the ARTIST II trial is necessary.

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