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ORIGINAL ARTICLE

Prospective Study

Efficacy and toxicity of capecitabine combined with intensity-modulated radiotherapy after D1/D2 lymph node dissection in patients with gastric cancer

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Abstract

BACKGROUND

Adjuvant chemoradiotherapy (ACRT) with oral capecitabine and intensity-modulated radiotherapy (IMRT) were well tolerated in a phase I study in patients who had undergone partial or total gastrectomy for locally advanced gastric cancer (GC). This phase II study aimed to further determine the efficacy and toxicity of this combination after radical resection and D1/D2 lymph node

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dissection (LND) for patients with locally advanced GC.

AIM

To further determine the efficacy and toxicity of this combination after radical resection and D1/D2 LND for patients with locally advanced GC.

METHODS

Forty patients (median age, 53 years; range, 24-71 years) with pathologically confirmed adenocarcinoma who underwent D1/D2 LND were included in this study. The patients received ACRT comprising IMRT (total irradiation dose: 45 Gy delivered in daily 1.8-Gy fractions on 5 d a week over 5 wk) and capecitabine chemotherapy (dose: 800 mg/m² twice daily throughout the duration of radiotherapy). The primary study endpoint was disease-free survival (DFS), and the secondary endpoints were overall survival (OS), toxic effects, and treatment compliance.

RESULTS

The 3-year DFS and OS were 66.2% and 75%, respectively. The median time to recurrence was 19.5 mo (range, 6.1-68 mo). Peritoneal implantation (n = 10) was the most common recurrence pattern, and the lung was the most common site of extra-abdominal metastases (n = 5). Nine patients developed grade 3 or 4 toxicities during ACRT. Two patients discontinued ACRT, while eleven underwent ACRT without receiving the entire course of capecitabine. There were no treatment-related deaths.

CONCLUSION

The ACRT protocol described herein showed acceptable safety and efficacy for patients with locally advanced GC who received radical gastrectomy and D1/2 LND.

Key Words: Gastric cancer; Radiotherapy; Chemoradiotherapy; Clinical trial; Phase II

Core Tip: In our previous phase I study, we found that an adjuvant chemoradiotherapy (ACRT) regimen of 45 Gy radiotherapy concurrent with oral capecitabine was well tolerated in patients with locally advanced gastric cancer who had received partial or total gastrectomy. The maximum tolerated and recommended dose of capecitabine was 800 mg/m² twice daily with oral administration. We performed this phase II study to further assess the efficacy and toxicity of this ACRT regimen as an adjuvant therapy after radical resection and D1/D2 lymph node dissection for patients with locally advanced gastric cancer.

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INTRODUCTION

The Intergroup trial (INT0116) demonstrated a major survival benefit of using a combination of conventional radiotherapy (RT) and fluorouracil (5-FU) chemotherapy on the 3-year disease-free survival (DFS) in patients with locally advanced gastric cancer (GC) after radical surgery (R0) and D0/D1 lymph node dissection (LND)[1]. However, more than half of the patients developed grade 3/4 hematologic toxicity and one-third developed gastrointestinal (GI) toxicity, which may affect the prognosis. Thus, it is important to combine advanced radiation techniques with a low-toxicity

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chemotherapy regimen to improve compliance to adjuvant chemoradiotherapy (ACRT) among postoperative GC patients who show poor tolerability for adjuvant treatment because of partial or total loss of the stomach.

Capecitabine, which belongs to fluoropyrimidines, has been widely used for chemotherapy and concurrent with radiotherapy in GC[2,3]. It is comparable to 5-FU and has a safer side effect profile and convenient oral administration[3,4]. High tumor response rates (26%-34%) have been reported with capecitabine monotherapy in phase II studies[5-7], and the drug has been found to be more efficacious when used in combination with platinum-based drugs in some phase III trials in patients with advanced GC[4-8].

Modern intensity-modulated radiotherapy (IMRT) planning systems have made it possible to deliver radiation doses more accurately to the planning target volume (PTV) and spare critical normal tissues to a substantial degree. IMRT has also been confirmed to be superior to two- or three-dimensional RT.

In our previous phase I study, we found that the ACRT regimen of 45 Gy radiotherapy concurrent with oral capecitabine was well tolerated in patients with locally advanced GC who had received partial or total gastrectomy. The maximum tolerated and recommended dose of capecitabine was 800 mg/m^2 twice daily with oral administration[9]. We performed this phase II study to further assess the efficacy and toxicity of this ACRT regimen as an adjuvant therapy after radical resection and D1/D2 LND for locally advanced GC patients.

MATERIALS AND METHODS

Eligibility

Participants were recruited if they met the following inclusion criteria: received partial (proximal or distal subtotal gastrectomy) or total gastrectomy with D1/D2 LND; had not received neoadjuvant anti-cancer treatment; postoperative pathologic diagnosis of adenocarcinoma; pathologic classification of T3-4N0 or any TN+M0 according to the 7th edition of the American Joint Committee on Cancer TNM classification; age ≤ 75 years and good performance (Eastern Cooperative Oncology Group performance status ≤ 1); no prior or concurrent history of malignant disease (except non-melanoma skin cancers or *in situ* carcinoma of the cervix); no prior abdominal radiation; and leukocyte count ≥ 3.5 × 10^9/L, neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, hemoglobin level ≥ 10.0 g/L, and normal alanine aminotransferase/aspartate aminotransferase and creatinine level.

All patients entering the trial received physical examinations, computed tomography (CT) scans of the chest/abdomen/pelvis, a complete blood count, and biochemical profile before treatment began. A complete blood count and biochemical profile were conducted every 1 and 2 wk, respectively. Adverse events terms and grade were coded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The follow-up interval for patients was once every 3 mo for the first 2 years and every 6 mo thereafter. Permission to conduct the study was obtained from the institutional ethics committees, and the study was registered at clinicaltrials.gov (NCT01674959). All patients provided signed informed consent.

Surgery

All patients were recommended D2 LND, which requires resection of all perigastric LNs, left gastric artery, common hepatic artery, celiac artery, proximal splenic artery, and proper hepatic artery, depending on the primary tumor location.

Radiotherapy

The prescription dose and fraction were 45 Gy in daily 1.8 Gy (5 d a week over 5 wk) by IMRT techniques. To enable visualization of the small intestine, patients needed to fast for 4 h before CT simulation, and take an oral positive contrast (300 mL) 30 min before the simulation. A normalized meal (300 mL of ready-to-eat canned porridge) was given to the patients 15 min before CT simulation and each treatment daily to decrease heterogeneity in gastric filling. The patients were placed in the supine position with thermoplastic immobilization masks; intravenous contrast was recommended but no 4D-CT planning or motion management was required during IMRT with 6-MV photon beam.

Clinical target volume (CTV) for each patient was contoured in accordance with recommendations from the Japanese Gastric Cancer Association depending on the extension and location of the primary tumor and the LN region involved status[10]. The CTV generally covered anastomoses, duodenal stump, tumor bed (only for stage T4b, if present), and regional LNs (Table 1). The remnant stomach was not routinely included in the target volume. The PTV typically includes the CTV plus a 5-7 mm margin in the radial direction and a 10 mm margin in the superior-inferior direction. Dose limitations for an organ at risk (OAR) were as follows: volume percentage receiving over 30 Gy (V30) < 40% for the liver, V20 < 30% or a mean dose of < 20 Gy for both kidneys, and V30 < 30% for the heart; the maximal dose for the spinal cord planning OAR volume was < 40 Gy. The maximal dose was less than the prescribed dose for the small intestine and colon. An experienced physicist did the IMRT plans design using a five-to-seven–field, coplanar, sliding window technique using the Pinnacle system, version 8.0.

Chemotherapy

Oral capecitabine was delivered twice daily (after breakfast and after dinner) at a dose of 800 mg/m^2 from the beginning to end of the radiation period based on the results of a previous phase I study[9]. Adjuvant chemotherapy (ACT) was required for a maximum of 6 mo and was conducted before or after ACRT depending on the performance status, clinical comorbidities, and toxicity profile of the patient; however, the regimens were open.

Statistical analyses

The primary endpoint of our phase II study was DFS, which was defined as the length of time after surgery ends that the patient's disease progresses or dies from any cause. The secondary endpoints were overall survival (OS), toxic effects, and treatment compliance. We hypothesized that the 3-year DFS rate would improve from 50% to 70% based on the results of INT0116. The use of Fleming's design ($P1$ = 0.50 and $P2$ = 0.70, setting α = 0.05 [two-sided], 80% power) revealed that 37 study participants were needed. At least 40 patients were required for this study with assumption of a 10% dropout rate.

The first site of recurrence was recorded to analyze treatment failure patterns. Locoregional recurrence was defined as reappearance of cancer at the anastomosis site, remnant stomach, duodenal stump, tumor bed, or regional LNs within the radiation field. Outside radiation field LNs region relapse, peritoneal implantation, liver metastasis or any other extra-abdominal site metastasis were regarded as distant metastases. Survival analysis were assessed with Kaplan–Meier curves using SPSS for Windows, version 20.0 (IBM SPSS Inc., Armonk, NY, United States).

RESULTS

Patient characteristics

From October 2011 to June 2013, 40 patients were recruited for the study. The patients' general characteristics are shown in Table 2. The median age was 53 years (range, 24-71 years). Thirty-seven (92.5%) patients had positive LNs. The median number of positive LNs was 7 (range, 1-26 nodes), and the median number of LNs resected was 24 (range, 15-56 nodes). D2 LND was performed in 22 (55%) patients. The median interval between surgery and ACRT was 5.5 mo (1.4-8 mo).

The patients received the following ACT regimens based on docetaxel and/or oxaliplatin and 5-FU analogues, with a median of six cycles (range, 3–10 cycles) before or after ACRT: oxaliplatin/cisplatin and S-1 (n = 18, 45%); docetaxel, oxaliplatin, and capecitabine/S-1/5-FU (n = 13, 32.5%); oxaliplatin and capecitabine (n = 6, 15%); and oxaliplatin, 5-FU, and leucovorin (n = 3, 7.5%).

Toxicities and treatment compliance

During ACRT, nine patients (22.5%) developed grade 3-4 toxicities and there were no treatment-related deaths. The most common grade 3-4 toxicities were leukopenia (5 patients, 12.5%), vomiting (4 patients, 10%), nausea (3, 7.5%), esophagitis (3, 7.5%), and thrombocytopenia (3, 7.5%).

Two patients discontinued ACRT due to disease progression (total dose, 25.2 Gy) and serious fatigue (total dose, 5.4 Gy). The remaining 38 patients (95%) received 45 Gy as planned, including 3 patients who developed grade 3 thrombocytopenia (2

Table 1 Clinical target volume for elective nodal regions according to the Japanese Gastric Cancer Association guidelines

Tumor location	CTV for elective nodal regions
Upper 1/3rd or gastroesophageal junction	110, 1-3, 7, 9-11
Middle 1/3rd	1-3, 5-13, 14[1], 16a
Lower 1/3rd	3, 5-9, 11p, 12-13, 14[1], 16a

[1]No. 14 was included in the clinical target volume (CTV) only when the surface or parenchyma of the pancreas was involved by the tumor. 110: Paraesophageal lymph nodes (LNs) in the lower thorax; 1: Right paracardial LNs; 2: Left paracardial LNs; 3: LNs along the lesser curvature; 5: Suprapyloric LNs; 6: Infrapyloric LNs; 7: LNs along the left gastric artery; 8: LNs along the common hepatic artery; 9: LNs around the celiac artery; 10: LNs at the splenic hilum; 11: LNs along the splenic artery (11p: LNs along the proximal splenic artery); 12: LNs in the hepatoduodenal ligament; 13: LNs on the posterior surface of the pancreatic head; 14: LNs along the root of the mesentery; 16a: LNs around the abdominal aorta (above the level of the inferior border of the left renal vein). CTV: Clinical target volume.

cases) and grade 3 vomiting (1 case) but finally completed RT (not with capecitabine) after a break. Besides the treatment discontinuation mentioned above, an additional 8 patients did not finish the whole course of capecitabine because of the reasons below: leukopenia (maximum grade, 3), 2 patients; thrombocytopenia (maximum grade, 3), 2 patients; anemia (maximum grade, 2), 1 patient; gastritis (maximum grade, 3), 1 patient; vomiting (maximum grade, 3), 1 patient; and anorexia (maximum grade, 3), 1 patient. The overall toxicities are showed in Table 3.

Survival and relapse

In total, 19 patients died during the follow-up period (median 80 mo; range, 8.4-96 mo): 18 died of disease and 1 of gastrorrhagia. The 3-year DFS, the primary endpoint of this study, was 66.2 (95% confidence interval [CI]: 58.6-73.8). The survival outcomes of OS, locoregional recurrence-free survival (RFS), and distant metastasis-free survival are listed in Figure 1 and Table 4. During the follow-up period, the following recurrence patterns were observed in the 18 patients (45%, 18/40): peritoneal implantation (n = 10, 25%), hematogenous spread (n = 8, 20%), and locoregional recurrence (n = 7, 17.5%). A single recurrence pattern was noted in 13 patients and multiple recurrence patterns were observed in 5 patients. Among the 7 patients with locoregional recurrence, 4 showed recurrences at the regional LNs, 3 at the anastomosis, and 1 at the gastric stump. The most common site of extra-abdominal metastases was the lung, which was noted in 5 (12.5%) patients. The median time to first recurrence was 19.5 mo (range, 6.1-68 mo). The median time from first recurrence to death was 5.9 mo (range, 0.5-60 mo).

DISCUSSION

Our results suggest that ACRT with 45 Gy IMRT and concurrent oral capecitabine at a dose of 800 mg/m^2 twice daily had an acceptable efficacy and toxicity profile in patients with locally advanced GC after radical gastrectomy and D1/2 LND. The 3-year DFS was 66.2%, which did not reach the primary hypothesis endpoint of our phase II study.

The role of ACRT in patients with locally advanced GC remains debatable. The benefits or drawbacks of this scenario mainly depend on whether a D1 or D2 lymphadenectomy has been performed. The INT0116 study was the first trial to prove the benefit of ACRT in patients after radical gastrectomy and D0/1 LND; it showed that the 3-year OS and DFS increased from 41% to 50% and 31% to 48%, respectively [1]. Even after 10 years of follow-up, ACRT was associated with superior DFS and OS [11]. Dikken *et al*[12] suggested that the addition of ACRT after D1 LND has a major impact on local recurrence in GC. Zhang *et al*[13] suggested that patients with D1 or D1 plus LND benefit from adjuvant RT, and adjuvant RT may be beneficial for some patients with D2 LND. Yu *et al*[14] re-analyzed the ARTIST study and concluded that adjuvant RT after D2 resection in GC reduces locoregional recurrence risk, especially in group 3 LNs, and improves locoregional RFS Patients with positive LN benefited more from the adjuvant RT than the other subgroup[14]. The National Comprehensive Cancer Network (NCCN) guideline recommends ACRT as an adjuvant treatment in patients with less than D2 LND.

Table 2 Patient characteristics

Characteristic	*n*	%
Age in yr, median (range)	53 (24-71)	
Men	28	70.0
Tumor size in cm, median (range)	5.0 (2-20)	
Location of primary tumor		
Upper 1/3rd of stomach	8	20
Middle 1/3rd of stomach	8	20
Lower 1/3rd of stomach	14	35
≥ 2 sites involved	10	25
Surgery type		
Partial gastrectomy	36	90
Total gastrectomy	4	10
Positive LNs, median (range)	7 (1-26)	
LNs resected, median (range)	24 (15-56)	
LN ratio, median (range)	0.27 (0-0.86)	
Extent of dissection		
D1	18	45
D2	22	55
Lauren type		
Intestinal type	12	30
Diffuse type	16	40
Mixed type	12	30
Tumor differentiation		
Good	1	2.5
Moderate	8	20
Poor	31	77.5
Lymphatic/vascular invasion		
Absent	16	40
Present	24	60
Perineural invasion		
Absent	30	75
Present	10	25
Signet ring cells		
Absent	29	72.5
Present	11	27.5
Tumor deposit		
Absent	34	85
Present	6	15
Stage (AJCC 7th)		
IIa	2	5
IIb	6	15
IIIa	11	27.5

IIIb	11	27.5
IIIc	10	25
Stage (AJCC 6th)		
Ib	2	5
II	14	35
IIIa	10	25
IIIb	2	5
IV	12	30

AJCC: American Joint Committee on Cancer; LN: Lymph node.

Table 3 Overall toxicities at the recommended dose, *n* = 40

Toxicity	Grade 1-2, *n* (%)	Grade 3-4, *n* (%)
Nausea	22 (45)	3 (7.5)
Vomiting	15 (37.5)	4 (10)
Anorexia	27 (67.5)	2 (5)
Esophagitis	6 (15)	3 (7.5)
Diarrhea	5 (12.5)	0
Abdominal pain	1 (2.5)	1 (2.5)
Gastritis	9 (22.5)	2 (5)
Fatigue	21 (52.5)	1 (2.5)
Weight loss	8 (20)	0
HFS	14 (35)	0
Leukopenia	27 (67.5)	5 (12.5)
Neutropenia	7 (17.5)	1 (2.5)
Anemia	3 (7.5)	0
Thrombocytopenia	17 (42.5)	3 (7.5)
ALT/AST	2 (5)	0

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HFS: Hand foot syndrome.

Table 4 Survival outcomes

Time	DFS (95%CI)	OS (95%CI)	LRFS (95%CI)	DMFS (95%CI)
3 yr	66.2 (58.6-73.8)	75 (68.2-81.8)	80.8 (74.2-88.6)	72.4 (64.9-79.9)
5 yr	55.2 (47.1-63.3)	58.9 (51.0-66.8)	80.8 (74.2-88.6)	60.4 (52.1-68.7)
7 yr[1]	52.3 (44.1-60.5)	48.2 (39.5-56.9)	80.8 (74.2-88.6)	57.2 (48.8-65.6)

[1]Estimated survival. CI: Confidence interval; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; LRFS: Locoregional recurrence-free survival; OS: Overall survival.

In China, D2 LND is considered a routine surgical procedure for locally advanced GC, because it is the most widely accepted surgical procedure in Asian and European countries[15]. However, given the many differences between centers or institutions in terms of hospital volume, patient populations, surgical practices and training, postoperative nursing experience, and pathological identification and examination of LNs, it is difficult to standardize and generalize D2 LND, even in our specialized cancer

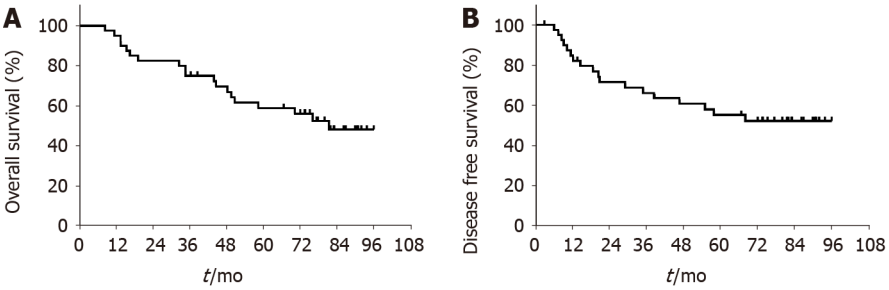

Figure 1 Overall survival rates and disease-free survival rates according to the Kaplan-Meier technique. A: Overall survival rates; B: Disease-free survival rates.

hospital. In our previous retrospective study of 297 patients with locally advanced GC who received radical surgery alone, the median number of LNs resected was 18 (range, 4-68 nodes) with a 27.6% 5-year locoregional recurrence rate[16]. In our phase I trial (performed between 2007 and 2009), D2 LND was performed in only 16.7% (3/18) of patients with GC, with a median of 19 LNs (range, 5-35) examined in our hospital. The median number of LNs resected in this study (performed between 2011and 2013) reached up to 24 nodes (range, 5-56 nodes). In a large observational study conducted in patients who underwent radical resection for GC, the survival benefits were significantly associated with an increase in the number of LNs resected, even when as many as 40 LNs were examined[17]. According to published reports[18,19], the greater number of LNs resected in our study may have provided better locoregional control and possibly a survival advantage, although this number was still much smaller than that reported in studies conducted in Japan and Korea (D2 LND with a median of more than 40 LNs examined)[2,3]. Furthermore, although patients un-derwent a very high-quality D2 LND, the ARTIST trial (ACRT Trial of Capecitabine Plus Cisplatin for Gastric Cancer) demonstrated that DFS could be further improved by ACRT in LN-positive GC. A randomized trial published in 2013 showed RFS benefit (median time 36 mo *vs* 50 mo, P = 0.029, 95%CI: 1.03-1.78) in ACRT group after D2 LND, which did not provide the resected LN number[20]. Thus, it is reasonable that ACRT could be considered as an adjuvant treatment for patients with LN metastasis or those who did not undergo a high-quality D2 LND.

In the past decade, capecitabine has been widely used in GI cancer, as it has a much safer side effect profile and does not require invasive delivery[21,22]. Oral capecitabine was not inferior to infusional 5-FU in randomized control trials for patients with advanced GC[4]. Therefore, capecitabine has been considered as a standard chemotherapy regimen for the treatment of advanced GC worldwide. The NCCN guidelines also suggest that infusional 5-FU can be replaced by oral capecitabine in GC. Our previous study determined that the maximum tolerated dose and recommended dose of capecitabine was 800 mg/m^2 twice daily when administered concurrently with IMRT for GC as adjuvant therapy[9], which is similar to the dose used in the ACRT group concurrent with RT in the ARTIST trial[2]. Lee *et al*[23] evaluated the efficacy and toxicity of ACRT using FP (5-FU+cisplatin) chemotherapy and capecitabine combined with RT for advanced GC; in their study, capecitabine was administered at a dose of 825 mg/m^2 twice daily throughout the duration of RT. Jansen *et al*[24] evaluated the dose escalation of capecitabine monotherapy concurrently with postoperative RT in GC, and recommended a capecitabine dose of 1000 mg/m^2 twice daily on each treatment day during the RT period.

The investigation of issues related to the sequence of ACT or ACRT is important since poor compliance to adjuvant treatment after gastrectomy is the main problem that may affect patient prognosis. Theoretically, for patients with high-risk pathological features (*e.g.*, poorly differentiated cancer, lymphovascular invasion, or multiple LN metastasis) leading to a higher probability of distant failure, more cycles of ACT may be administered soon after surgery to avoid more cancer cell micrometastasis; however, excessive chemotherapy before RT would reduce patient tolerance to ACRT. Soyfer *et al*[25] reported an association between total RT treatment time, and to some extent, the time of the initiation of RT for local control and distant metastases. McMillan *et al*[26] reported that prolonged intervals between surgery and RT initiation were not associated with inferior OS in GC, while prolonged RT treatment duration were. In the studies reported by Jansen *et al*[24,27,28], RT started one 21-d cycle of ACT after surgery, which means that patients might tolerate ACRT well compared to the tolerance observed in those who received several cycles of combination chemotherapy

before RT. With recent randomized evidence reinforcing the benefit of ACRT in node-positive GC[11,29], it is desirable to explore issues related to the proper sequence of ACT and ACRT, since poor compliance to adjuvant treatment after gastrectomy is the main problem that may impact patient prognosis. Based on our clinical experience, compliance to ACRT would be better if it started after no more than four cycles (21 d/cycle) of ACT for patients with many adverse prognostic factors. Furthermore, monotherapy administered as concurrent chemotherapy during RT, rather than as part of a combination chemotherapy regimen, would also improve patient compliance to ACRT. Thus, in our opinion, the adjuvant treatment design of the ACRT arm in the ARTIST trial seems reasonable (two cycles of capecitabine plus cisplatin followed by capecitabine-based ACRT and then two additional cycles of capecitabine plus cisplatin)[2].

The most commonly observed grade 3/4 hematologic and GI toxicities in this study were leukopenia (12.5%) and vomiting (10%), which were much less frequent than those in INT 0116 (54% and 32% of the patients developed grade 3/4 hematologic and GI toxicity) and CALGB 80801 study (about 50% and 16% of the patients developed grade 3/4 hematologic and GI toxicity)[1,30]. The exclusion of the remnant stomach from the target volume and the use of IMRT technology and capecitabine monotherapy (noninferior efficacy and lower GI toxicity than 5-FU) may account for the relatively lower rate of severe toxicities. Nam *et al*[31] demonstrated that the exclusion of the remnant stomach from the radiation field could significantly reduce acute side effects without compromising long-term survival rates. After the long-term follow-up of ARTIST study which CTV did not include remnant stomach, local recurrence in the remnant stomach was seen in only 2% of all patients, and this result was similar to Nam *et al*[14]. Several studies have found that IMRT was superior to two- or three-dimensional RT, providing a more conformal and homogeneous dose to the PTV and accordingly minimizing the probability of toxicity[32-34].We had previously determined that tomotherapy is a better option for adjuvant treatment of GC due to its superior bowel and bone marrow dose sparing, dose conformity, and dose homogeneity[6,7,35,36]. Given this evidence, this study showed acceptable safety and comparable compliance with the treatment course. Our study showed that 95% (38/40) and 72.5% (29/40) of patients completed RT and concurrent capecitabine monotherapy, respectively.

The 3-year DFS of the ACRT arm in INT 0116 was used in the power calculation for the present phase II study, as this is the only randomized trial evaluating the effect of ACRT in GC patients with an LND level less than D2. However, the final 3-year DFS in our study was 66.2%, which did not meet the primary endpoint (3-year DFS = 70%). This could be attributable to the maximum number of positive LNs found (as high as 7) and the fact that only 55% of our patients had D2 LND. Despite previous findings, our results are still better than those obtained with ACRT treatment by Janson *et al*[27,28]. The 2-year OS of their phase II trials evaluating capecitabine/cisplatin chemotherapy with concurrent RT after D0/1/2 LND (18%-22% of patients had D2 LND) was 45%-61%[37]. National Cancer Data Base analysis showed that patients with adjuvant RT 5-year OS rate was 45%. While our study showed a 3-year OS of 75% and 5-year OS of 58.9%. The higher incidence of D2 LND performed during radical gastrectomy in this study may have contributed to our better prognosis. Subgroup analysis of the ARTIST trial showed that the significant 3-year DFS effect of ACRT in node-positive disease improved from 72% to 78%, which may be due to the very high-quality D2 LND (median number of LNs dissected was 40) and relatively lower rate of metastatic LNs (median number was 3)[2].

This study had several limitations that warrant emphasis. Due to the poor patient recruitment for this study, we did not limit the regimens or cycles of adjuvant chemotherapy administered before or after ACRT. Accordingly, this may have influenced the results for the toxicity profile of ACRT and led to different intervals between surgery and initiation of ACRT. However, patients were presumably recruited postoperatively, yielding a subgroup of patients who had undergone surgery. This is relevant if comparisons are to be made with other treatment strategies where patients are recruited preoperatively.

CONCLUSION

In conclusion, we considered that ACRT with 800 mg/m^2/d oral capecitabine twice daily combined with 45 Gy IMRT was safe and efficacious. The use of advanced techniques such as IMRT or tomotherapy, an appropriate irradiation field, and low-

toxicity single-agent chemotherapy regimens such as capecitabine chemotherapy is highly recommended. A randomized phase III study in our hospital comparing ACT with ACRT for node-positive locally advanced GC after D2 LND is ongoing (NCT 02648841), and its results are highly awaited.

ARTICLE HIGHLIGHTS

Research background

Capecitabine has been widely used for chemotherapy and concurrent with radiotherapy in gastric cancer (GC) treatment, while modern intensity-modulated radiotherapy (IMRT) has also been confirmed to be superior to two- or three-dimensional radiotherapy (RT). In our previous phase I study, we found out adjuvant chemoradiotherapy (ACRT) regimen of IMRT concurrent with oral capecitabine was well tolerated in patients with locally advanced GC who had received partial or total gastrectomy.

Research motivation

We performed this phase II study to further assess the efficacy and toxicity of this ACRT regimen as an adjuvant therapy after radical resection and D1/D2 lymph node dissection (LND) for locally advanced GC patients.

Research objectives

The aim of this study was to evaluate the efficacy and toxicity of IMRT combined with capecitabine after radical resection and D1/D2 LND for patients with locally advanced GC.

Research methods

Forty patients with locally advanced GC, who underwent radical resection and D1/D2 LNDwere included in this study. The patients received ACRT comprising IMRT (total irradiation dose: 45 Gy delivered in daily 1.8-Gy fractions on 5 d a week over 5 wk) and capecitabine chemotherapy (dose: 800 mg/m^2 twice daily throughout the duration of RT). The primary study endpoint was disease-free survival (DFS) and the secondary endpoints were overall survival (OS), toxic effects, and treatment compliance.

Research results

The 3-year DFS and OS were 66.2% and 75%, respectively. Nine patients developed grade 3 or 4 toxicities during ACRT. Two patients discontinued ACRT, while 11 underwent ACRT without receiving the entire course of capecitabine.

Research conclusions

ACRT with oral capecitabine and IMRTwas safe and efficacious.

Research perspectives

The use of IMRT and low-toxicity single-agent chemotherapy regimens such as capecitabine is highly recommended in patients who had undergone partial or total gastrectomy for locally advanced GC. Moreover, to further determine the efficacy of this combination therapy, a randomized phase III study in our hospital is ongoing.

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