Phase II Study of Capecitabine Combined With Intensity-Modulated Radiotherapy After D1/D2 Lymph Node Dissection in Patients with Gastric Cancer

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Research

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Abstract

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

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 days a week over 5 weeks) and capecitabine chemotherapy (dose: 800 mg/m² 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.

Results: The 3-year DFS and OS were 66.2% and 75%, respectively. The median time to recurrence was 19.5 months (range, 6.1–68 months). 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 11 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 local advanced gastric cancer received radical gastrectomy and D1/2 LND.

Trial registration: ClinicalTrials.gov, NCT01674959. Registered August 2012 - Retrospectively registered, http://www.isrctn.com/ISRCTN12345678

Background

The Intergroup trial (INT0116) demonstrated a major survival benefit of using a combination of conventional radiotherapy (RT) and fluorouracil chemotherapy on the 3-year disease-free survival (DFS) in locally advanced gastric cancer patients after radical surgery (R0) and D0/D1 lymph node dissection (LND) [1]. However, over half of the patients developed grade 3/4 hematologic toxicity and one third of the patients developed gastrointestinal toxicity, which may affect the prognosis. Thus, it is important to combine advanced radiation techniques with a low-toxicity chemotherapy regimen to improve compliance to adjuvant chemoradiotherapy (ACRT) among postoperative gastric cancer 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 gastric cancer treatment [2, 3]. It was proved to be comparable to 5FU and a more 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 gastric cancer [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 out ACRT regimen of 45Gy radiotherapy concurrent with oral capecitabine was well tolerated in patients with local advanced gastric cancer who had received partial or total gastrectomy. The maximum tolerated dose 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 local advanced gastric cancer patients.

Methods

Eligibility

Participants were recruited if they met the inclusion following criteria: (1) received partial or total gastrectomy with D1/D2 LND, (2) no neoadjuvant anti-cancer treatment (3) postoperative pathologically diagnosed adenocarcinoma, (4)pathologically classification of T3-4N0 or any TN+M0 according to the 7^{th} edition of the American Joint Committee on Cancer TNM classification, (5) age ≤ 75 years and good performance(Eastern Cooperative Oncology Group performance status ≤ 1)(6) no prior or concurrent history of malignant disease (except non-melanoma skin cancers or in situ carcinoma of the cervix), (7) no prior abdominal radiation, and (8) 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 ALT/AST and CRE level.

All the patients entering the trail received physical examinations, computed tomography (CT) scans of the chest/abdomen/pelvis, complete blood count performed, and biochemical profile before treatment started. Complete blood count performed and biochemical profile were conducted every one and two weeks, respectively. Adverse events terms and grade were coded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Follow up interval of patients were once every 3 months for the first 2 years and every 6 months thereafter. Permission to conduct the study was obtained from institutional ethics committees and was registered at clinicaltrials.gov (NCT01674959). All patients signed informed consent.

Treatment

Surgery

All patients were recommended D2 LND, which requires resection of all the perigastric lymph nodes (PLNs), 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 1.8Gy (5 days a week over 5 weeks) by IMRT techniques. To enable visualization of the small intestine, patients needed to fasted 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 every day to decrease heterogeneity in gastric filling. The patients were placed in a 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 were contoured in accordance with Japanese Gastric Cancer Association (JGCA) recommendation depended 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 10mm margin in the superior-inferior direction. Dose limitations for an organ at risk (OAR) were as follows: V30 (volume percentage receiving over 30 Gy) < 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 < 40 Gy. The maximal dose was less than the prescribed dose for the small intestine and colon. An experienced physicist do 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 the dose of 800 mg/m² from the beginning to the end of the radiation period based on the results of previous phase I study [9]. Adjuvant chemotherapy (ACT) was required for a maximum of 6 months 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 analysis

The primary endpoint of our phase II study was DFS, which was defined as the length of time after surgery ends that the patient disease progress or dead from any cause. The secondary endpoints were overall survival, toxic effects, and treatment compliance. We hypothesized the 3-year DFS rate would improve from 50% to 70%. The use of Fleming's design (p1 = 0·50 and p2 = 0·70, setting α = 0·05 [2-sided], 80% power) revealed that 37 study participants were needed. At least of 40 patients were required for this study with assumption of 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 the Kaplan–Meier curves using the SPSS for Windows program, version 20.0 (IBM SPSS Inc., Armonk, NY, USA).

Results

Patient characteristics

From October 2011 to June 2013, 40 patients were recruited in the study. The patient general characteristics are showed 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 PLNs was 7 (range, 1–26 nodes), and the median number of LNs resected was 24 (range, 5–56 nodes). D2 LND was performed in 22 (55%) patients. The median interval between surgery and ACRT was 5.5 months (1.4–8 months).

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 three patients who developed grade 3 thrombocytopenia (2 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 eight 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.

Survival and relapse

Nineteen patients died during the follow-up period (median 80 months; range, 8.4–96 months): 18 died of disease and one of gastrorrhagia. The 3 years DFS, the primary endpoint of the present study, was 66.2 (95% confidence interval [CI], 58.6-73.8). The survival outcomes of OS, locoregional recurrence-free survival, and distant metastasis-free survival are listed in 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 five patients. Among the seven patients with locoregional recurrence, four showed recurrence at the regional lymph nodes, three at the anastomosis, and one showed recurrence 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 months (range, 6.1–68 months). The median time from first recurrence to death was 5.9 months (range, 0.5–60 months).

Discussion

Our results suggest that ACRT with 45Gy 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 local advanced gastric cancer 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 for local advanced gastric cancer remains debatable. The benefits or drawbacks of this scenario mainly depend on whether a D1 or D2 lymphadenectomy has been performed. The INT-0116 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 suggested that addition of ACRT after D1 LND had a major impact on local recurrence in gastric cancer [12]. Zhang, N.et al 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 [13]. Yu, J. I. et al. re-analyse the ARTIST study and conclude that adjuvant RT after D2 resection in gastric cancer reduced locoregional recurrence risk, especially in group 3 LNs, and improved locoregional recurrence-free survival. 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.

In China, D2 LND is considered a routine surgical procedure for locally advanced gastric cancer 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 hospital. In our previous retrospective study of 297 local advance gastric cancer patients 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 gastric cancer, with a median of 19 LNs (range, 5-35) examined in our hospital. The median number of LNs resected in the present study (performed between 2009 and 2012) reached up to 24 nodes (range, 5–56 nodes). In a large observational study conducted in patients who underwent radical resection for gastric cancer, the survival benefits 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 is still much smaller than those reported in studies conducted in Japan and Korea (D2 LND with a median of more than 40 LNs examined) [2, 3]. Furthermore, although patients underwent 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 positive LN gastric cancer. A randomized trail published in 2013 showed recurrence free survival benefit (median time 36 months vs. 50 months, P = 0.029) 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 gastrointestinal cancer, as it has a much safer side effect profile and does not require invasive delivery [21, 22]. Oral capecitabine was not inferior to in fusional 5-FU in randomized control trials for patients with advanced gastric cancer [4]. Therefore, capecitabine has been considered as a standard chemotherapy regimen for the treatment of advanced gastric cancer worldwide. The NCCN guidelines also suggest that infusional 5-FU can be replaced by oral capecitabine in gastric cancer. 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 gastric cancer 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. evaluated the efficacy and toxicity of ACRT using FP (5-FU+cisplatin) chemotherapy and capecitabine combined with RT for advanced gastric cancer; in their study, capecitabine was administered at a dose of 825 mg/m^2 twice daily throughout the duration of RT [23]. Jansen et al. evaluated the dose escalation of capecitabine monotherapy concurrently with postoperative RT in gastric cancer and recommended a capecitabine dose of 1000 mg/m^2 twice daily on each treatment day during the RT period [24].

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 (such as poorly differentiated cancer, lymphovascular invasion, or multiple lymph nodes 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. reported an association between total RT treatment time and, to some extent, the time of the initiation of RT on local control and distant metastases [25]. McMillan et al. reported that prolonged intervals between surgery and RT initiation were not associated with inferior OS in gastric cancer, while prolonged RT treatment duration was [26]. In the studies reported by Janson et al., RT started one 21-day 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 [24, 27, 28]. With recent randomized evidence reinforcing the benefit of ACRT in node-positive gastric cancer [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 days/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 gastrointestinal 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 gastrointestinal toxicity) and CALGB 80801 study (about 50% and 16% of the patients developed grade 3/4 hematologic and gastrointestinal 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 gastrointestinal toxicity than 5FU) may account for the relatively lower rate of severe toxicities. Nam et al demonstrated that the exclusion of the remnant stomach from the radiation field could significantly reduce acute side effects without compromising long-term survival rates [31].And 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]. RT fields including or excluding the remnant stomach. Several studies have found that IMRT was superior to two-dimensional 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 gastric cancer due to its superior bowel and bone marrow dose sparing, dose conformity, and dose homogeneity [6, 7, 35, 36]. Given these evidences, the present 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 complete 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 gastric cancer 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 max number of PLNs found (as high as 7) and the fact that only 55% of our patients had D2 LND. Despite the 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].According to A National Cancer Data Base Analysis, they find 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 the present 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 lymph nodes dissected was 40) and relatively lower rate of metastatic lymph nodes (median number was 3) [2].

This study has 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.

Conclusions

In conclusion, we considered that ACRT with 800 mg/m^2/d oral capecitabine twice daily combined with 45Gy 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 gastric cancer after D2 LND is ongoing (NCT02648841), and its results are highly awaited.

List Of Abbreviations

ACT: adjuvant chemotherapy

ACRT: adjuvant chemoradiotherapy

CTV: clinical target volume

LND: lymph node dissection

IMRT: intensity-modulated radiotherapy

OAR: organ at risk

OS: overall survival

PTV: plan target volume

DFS: disease free survival

Declarations

Ethics approval and consent to participate

This study was approved by the Independent Ethics Committees of Cancer Institute and Hospital, Chinese Academy of Medical Sciences (Approved number:11-72/507).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

JJ and LY contributed to study concepts and design and were major guarantors of integrity of the entire study. JJ participated in funding acquisition and revised the manuscript. WW, SW, YS, YL, YT, NL, WL, HF, YL, DZ, YC contributed to patients recruitments and clinical studies. HR participated in literature research, data analysis and drafted the manuscript. XW performed the statistical analysis, data analysis and drafted the manuscript All authors have read and agreed to the published version of the manuscript.

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References

1. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001, 345:725-730.
2. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, et al: Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012, 30:268-273.
3. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, et al: Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012, 379:315-321.

4. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, et al: Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009, 20:666-673.
5. Hong YS, Song SY, Lee SI, Chung HC, Choi SH, Noh SH, Park JN, Han JY, Kang JH, Lee KS, Cho JY: A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004, 15:1344-1347.
6. Sakamoto J, Chin K, Kondo K, Kojima H, Terashima M, Yamamura Y, Tsujinaka T, Hyodo I, Koizumi W: Phase II study of a 4-week capecitabine regimen in advanced or recurrent gastric cancer. *Anticancer Drugs* 2006, 17:231-236.
7. Lee JL, Kang YK, Kang HJ, Lee KH, Zang DY, Ryoo BY, Kim JG, Park SR, Kang WK, Shin DB, et al: A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer* 2008, 99:584-590.
8. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008, 358:36-46.
9. Wang X, Jin J, Li YX, Ren H, Fang H, Wang SL, Liu YP, Wang WH, Yu ZH, Song YW, Liu XF: Phase I study of postoperative radiotherapy combined with capecitabine for gastric cancer. *World J Gastroenterol* 2014, 20:1067-1073.
10. Japanese Gastric Cancer A: Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998, 1:10-24.
11. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, Sohn I, Jung SH, Choi MG, Lee JH, et al: Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol* 2015, 33:3130-3136.
12. Dikken JL, Jansen EP, Cats A, Bakker B, Hartgrink HH, Kranenbarg EM, Boot H, Putter H, Peeters KC, van de Velde CJ, Verheij M: Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol* 2010, 28:2430-2436.
13. Zhang N, Fei Q, Gu J, Yin L, He X: Progress of preoperative and postoperative radiotherapy in gastric cancer. *World J Surg Oncol* 2018, 16:187.
14. Yu JI, Lim DH, Ahn YC, Lee J, Kang WK, Park SH, Park JO, Park YS, Lim HY, Kim ST, et al: Effects of adjuvant radiotherapy on completely resected gastric cancer: A radiation oncologist's view of the ARTIST randomized phase III trial. *Radiother Oncol* 2015, 117:171-177.
15. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, et al: Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999, 340:908-914.
16. Wang X, Jin J, Li Y, Wang S, Wang W, Song Y, Liu Y, Liu X, Yu Z: Analysis of recurrence for locally advanced gastric or gastroesophageal cancer patients after receiving curative gastrectomy (>D1)

and its indication for adjuvant chemoradiotherapy. *Chinese Journal of Radiation Oncology Chin J Radiat Oncol* 2011, 20:133-137.

17. Smith DD, Schwarz RR, Schwarz RE: Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol* 2005, 23:7114-7124.
18. Huang ZN, Chen QY, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J, Cao LL, Lin M, et al: Are the indications for postoperative radiotherapy in the NCCN guidelines for patients with gastric adenocarcinoma too broad? A study based on the SEER database. *BMC Cancer* 2018, 18:1064.
19. Datta J, McMillan MT, Ecker BL, Karakousis GC, Mamtani R, Plastaras JP, Giantonio BJ, Drebin JA, Dempsey DT, Fraker DL, Roses RE: Implications of Lymph Node Staging on Selection of Adjuvant Therapy for Gastric Cancer in the United States: A Propensity Score-matched Analysis. *Ann Surg* 2016, 263:298-305.
20. Zhu WG, Xua DF, Pu J, Zong CD, Li T, Tao GZ, Ji FZ, Zhou XL, Han JH, Wang CS, et al: A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. *Radiother Oncol* 2012, 104:361-366.
21. Twelves C, Wong A, Nowacki MP, Abt M, Burris H, 3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, et al: Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005, 352:2696-2704.
22. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, Müller L, Link H, Moehler M, Kettner E, et al: Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012, 13:579-588.
23. Lee HS, Choi Y, Hur WJ, Kim HJ, Kwon HC, Kim SH, Kim JS, Lee JH, Jung GJ, Kim MC: Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. *World J Gastroenterol* 2006, 12:603-607.
24. Jansen EP, Boot H, Saunders MP, Crosby TD, Dubbelman R, Bartelink H, Verheij M, Cats A: A phase I-II study of postoperative capecitabine-based chemoradiotherapy in gastric cancer. *Int J Radiat Oncol Biol Phys* 2007, 69:1424-1428.
25. Soyfer V, Geva R, Michelson M, Inbar M, Shacham-Shmueli E, Corn BW: The impact of overall radiotherapy treatment time and delay in initiation of radiotherapy on local control and distant metastases in gastric cancer. *Radiat Oncol* 2014, 9:81.
26. McMillan MT, Ojerholm E, Roses RE, Plastaras JP, Metz JM, Mamtani R, Karakousis GC, Fraker DL, Drebin JA, Stripp D, et al: Adjuvant Radiation Therapy Treatment Time Impacts Overall Survival in Gastric Cancer. *Int J Radiat Oncol Biol Phys* 2015, 93:326-336.
27. Jansen EP, Boot H, Dubbelman R, Bartelink H, Cats A, Verheij M: Postoperative chemoradiotherapy in gastric cancer -- a Phase I/II dose-finding study of radiotherapy with dose escalation of cisplatin and capecitabine chemotherapy. *Br J Cancer* 2007, 97:712-716.

28. Jansen EPM, Boot H, Dubbelman R, Verheij M, Cats A: Postoperative chemoradiotherapy in gastric cancer–a phase I-II study of radiotherapy with dose escalation of weekly cisplatin and daily capecitabine chemotherapy. *Ann Oncol* 2010, 21:530-534.
29. Kim TH, Park SR, Ryu KW, Kim YW, Bae JM, Lee JH, Choi IJ, Kim YJ, Kim DY: Phase 3 trial of postoperative chemotherapy alone versus chemoradiation therapy in stage III-IV gastric cancer treated with R0 gastrectomy and D2 lymph node dissection. *Int J Radiat Oncol Biol Phys* 2012, 84:e585-592.
30. Fuchs CS, Niedzwiecki D, Mamon HJ, Tepper JE, Ye X, Swanson RS, Enzinger PC, Haller DG, Dragovich T, Alberts SR, et al: Adjuvant Chemoradiotherapy With Epirubicin, Cisplatin, and Fluorouracil Compared With Adjuvant Chemoradiotherapy With Fluorouracil and Leucovorin After Curative Resection of Gastric Cancer: Results From CALGB 80101 (Alliance). *J Clin Oncol* 2017, 35:3671-3677.
31. Nam H, Lim DH, Kim S, Kang WK, Sohn TS, Noh JH, Kim YI, Park CH, Park CK, Ahn YC, Huh SJ: A new suggestion for the radiation target volume after a subtotal gastrectomy in patients with stomach cancer. *Int J Radiat Oncol Biol Phys* 2008, 71:448-455.
32. Trip AK, Nijkamp J, van Tinteren H, Cats A, Boot H, Jansen EP, Verheij M: IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. *Radiother Oncol* 2014, 112:289-294.
33. Minn AY, Hsu A, La T, Kunz P, Fisher GA, Ford JM, Norton JA, Visser B, Goodman KA, Koong AC, Chang DT: Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. *Cancer* 2010, 116:3943-3952.
34. Sharfo AWM, Stieler F, Kupfer O, Heijmen BJM, Dirkx MLP, Breedveld S, Wenz F, Lohr F, Boda-Heggemann J, Buergy D: Automated VMAT planning for postoperative adjuvant treatment of advanced gastric cancer. *Radiat Oncol* 2018, 13:74.
35. Wang X, Tian Y, Tang Y, Hu ZH, Zhang JJ, Fu GS, Ma P, Ren H, Zhang T, Li N, et al: Tomotherapy as an adjuvant treatment for gastroesophageal junction and stomach cancer may reduce bowel and bone marrow toxicity compared to intensity-modulated radiotherapy and volumetric-modulated arc therapy. *Oncotarget* 2017, 8:39727-39735.
36. Onal C, Dölek Y, Akkuş Yıldırım B: Dosimetric comparison of 3-dimensional conformal radiotherapy, volumetric modulated arc therapy, and helical tomotherapy for postoperative gastric cancer patients. *Jpn J Radiol* 2018, 36:30-39.
37. Stumpf PK, Amini A, Jones BL, Koshy M, Sher DJ, Lieu CH, Schefter TE, Goodman KA, Rusthoven CG: Adjuvant radiotherapy improves overall survival in patients with resected gastric adenocarcinoma: A National Cancer Data Base analysis. *Cancer* 2017, 123:3402-3409.

Tables

Table 1. Clinical target volume (CTV) for elective nodal regions according to the JGCA 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*, 16a
Lower 1/3rd	3, 5-9, 11p, 12-13, 14*, 16a

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).

*: No. 14 was included in the CTV only when the surface or parenchyma of the pancreas was involved by the tumor.

JGCA: Japanese Gastric Cancer Association.

Table 2. Patient characteristics

Characteristic	N	%
Age (years), median (range)	53 (24-71)	
Men	28	70.0
Tumor size (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 (5-56)	
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		
Present	24	60
Absent	16	40

Perineural invasion		
Present	10	25
Absent	30	75
Signet ring cells		
Present	11	27.5
Absent	29	72.5
Tumor deposit		
Present	6	15
Absent	34	85
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

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

HFS: hand foot syndrome; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 4. Survival outcomes

Time	DFS (%, 95 CI)	OS (%, 95 CI)	LRFS (%, 95 CI)	DMFS (%, 95 CI)
3 year	66.2 (58.6-73.8)	75 (68.2-81.8)	80.8 (74.2-88.6)	72.4 (64.9-79.9)
5 year	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 year*	52.3 (44.1-60.5)	48.2 (39.5-56.9)	80.8 (74.2-88.6)	57.2 (48.8-65.6)

DMFS: distant metastasis–free survival; DFS: disease-free survival; LRFS: locoregional recurrence–free survival; OS: overall survival.

*Estimated survival.