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ORIGINAL PAPER

# Comparison of two different adjuvant treatment modalities for pN3 gastric cancer patients after D2 lymph node dissection: can we avoid radiotherapy in a subgroup of patients?

**Leyla Kilic · Cetin Ordu · Meltem Ekenel · Ibrahim Yildiz · Serkan Keskin · Fatma Sen · Zeynep Gural · Oktar Asoglu · Ahmet Kizir · Faruk Aykan**

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**Abstract** Adjuvant chemoradiotherapy (CRT) is the standard of care for gastric cancer patients in the USA. However, in countries where D2 lymph node dissection is performed, the effect of radiotherapy on locoregional recurrence is controversial. The aim of this study is to compare the outcomes in pN3 gastric cancer patients following two adjuvant treatment modalities: chemotherapy (CT) and CRT after D2 lymph node dissection. Between 2005 and 2009, 71 gastric cancer patients who underwent D2 lymph node dissection and had pTanyN3M0 stage (according to AJCC 6th edition) were identified. Fifty-three patients were treated with CT and 18 patients received CRT. CRT consisted of bolus fluorouracil (FU) 425 mg/m$^2$ and leucovorin 20 mg/m$^2$ before, after, and during radiotherapy. For the CT arm, treatment protocols consisted of combination therapies involving FU and cisplatin as the backbone. Median overall survival (OS) and disease-free survival (DFS) rates for all patients were 26.3 months (15–37.7 months) and 12.5 months (8–17.1 months). Median OS in CT arm was 26.8 months and it was 34.2 months for CRT arm ($p = 0.74$). DFS rates did not differ statistically either ($p = 0.56$, 12.5 and 15.2 months for CT and CRT, respectively). Locoregional recurrence rates were also similar ($p = 0.63$). Only metastatic/dissected lymph node ratio ($\geq$0.75) was identified as a prognostic factor in both univariate and multivariate analyses for DFS. Comparison of CT versus CRT for N3 stage gastric cancer patients with D2 lymph node dissection did not reveal any statistically significant difference in survival rates and locoregional recurrence.

**Keywords** Gastric cancer · Chemoradiotherapy · Adjuvant · Chemotherapy · D2 lymph node dissection

L. Kilic · M. Ekenel · I. Yildiz · S. Keskin · F. Sen · F. Aykan
Medical Oncology Department, Institute of Oncology, Istanbul University, Capa, Istanbul, Turkey
e-mail: leylahmet@gmail.com

M. Ekenel
e-mail: meltemekenel@yahoo.com

I. Yildiz
e-mail: dr_ibrahim2000@yahoo.com

S. Keskin
e-mail: drkeskin76@hotmail.com

F. Sen
e-mail: fkaragoz_2000@yahoo.com

F. Aykan
e-mail: nfaruk@mac.com

C. Ordu (✉)
Medical Oncology Department, Bilim University Beyoglu, Istanbul, Turkey
e-mail: cetinordu@hotmail.com

Z. Gural
Radiation Oncology Department, Bezmialem Vakif University, Fatih, Istanbul, Turkey
e-mail: morkinos@hotmail.com

O. Asoglu
Department of General Surgery, Istanbul University, Capa, Istanbul, Turkey
e-mail: oktarasoglu@yahoo.com

A. Kizir
Radiation Oncology Department, Institute of Oncology, Istanbul University, Capa, Istanbul, Turkey
e-mail: ahmkizir@istanbul.edu.tr

## Introduction

Gastric cancer, the second most common cause of cancer-related death worldwide, constitutes a significant global health problem. Overall 5-year survival rates ranged from 29 to 37 % in stage II and 13–20 % in stage III patients with minimal change from the late 1960s until now [1, 2]. Complete surgical resection of the tumor with extended lymph node dissection is a potentially curative treatment for localized gastric cancer for less than 40 % of cases [3]. High rate of locoregional and distal recurrences have urged the need for adjuvant and neoadjuvant strategies to improve the outcome of these patients.

The INT-0116 trial (Intergroup 0116), as the largest phase III trial which compares chemoradiotherapy (CRT) versus observation, has demonstrated a clear survival benefit with the addition of CRT [4]. The most recent update of this study with more than 10 years of follow-up underscores the continued strong overall survival (OS) and relapse-free survival (RFS) benefit of postoperative CRT [5]. Recently, the results of the ARTIST trial, which was designed to address the role of postoperative CRT in patients with D2 lymph node resection, were published. This study was unable to show a reduction in the recurrence rate with the incorporation of radiotherapy to chemotherapy (CT) regimen [6]. However, there seemed to be a disease-free survival (DFS) advantage for the subgroup of patients with pathologic lymph node metastasis. This finding has emphasized the importance of planning adjuvant treatment strategies according to involved lymph nodes.

According to American Joint Commission on Cancer (AJCC) 6th edition, N3 status was defined as the presence of more than 15 metastatic lymph nodes after D2 lymph node dissection. This group of patients were defined as having non-metastatic stage IV disease with 5- and 10-year survival rates estimated as 7 and 5 %, respectively [7]. Since most of the prospective randomized trials included limited number of these high risk patients, decision of adding potentially toxic CRT has been compulsive. Thus, the primary objective of this study is to investigate the comparison of two different adjuvant treatment modalities: CT alone versus CRT for patients with TanyN3M0 disease after D2 lymph node resection and to evaluate the outcome in both treatment arms.

## Materials and methods

This is a retrospective study comprising 71 locally advanced gastric cancer patients, treated between January 2005 and December 2009 who had non-metastatic, stage IV (pTanyN3M0) disease according to the criteria of AJCC, 6th edition. When this analysis was planned, valid staging criteria defined N3 nodal status as the presence of more than 15 metastatic lymph nodes after D2 lymph node dissection. However, according to the current staging system, this group of patients is now classified as N3b nodal status, stage IIIB or IIIC disease depending upon the T (tumor) status.

All the patients underwent gastrectomy either total or subtotal with D2 dissection in Istanbul University Medical Faculty, Department of General Surgery by experienced surgical oncologists. This procedure entails the en bloc resection of the tumor and all perigastric lymph nodes with some celiac, splenic or splenic-hilar, hepatic artery, and cardiac lymph nodes depending on the location of the primary tumor. All the patients had histologically confirmed adenocarcinoma of the stomach; gastroesophageal junction and distal esophageal adenocancer patients were excluded from the study. All patients were 18 years or older and had Eastern Cooperative Oncology Group performance status of 0 or 1 with adequate major organ functions involving bone marrow, cardiac, hepatic, and renal function. Patients with secondary malignancies or any sign of peritoneal seeding or distant metastasis were also excluded. Before establishing the treatment strategy, all the patients underwent further staging with chest radiographs and abdominopelvic computed tomography.

The institutional review board approved the present study regarding the collection of clinical and demographic data from patient charts, their statistical evaluation, and publication of the study results. Informed consent including details about diagnostic and treatment modalities with further information regarding possible outcomes and side effects of these interventions has been received from each subject prior to admission for adjuvant treatment.

### Treatment plan

Since there is no sufficient data on adjuvant therapy following D2 lymph node dissection, for long years, adjuvant treatment strategy has been planned on the individual patient data at tumor boards involving radiation, medical, and surgical oncologists. CRT consisted of bolus fluorouracil (FU) 425 mg/m$^2$ and leucovorin (LV) 20 mg/m$^2$ before, after and during radiotherapy. Before radiotherapy through days 1 and 5, FU (FU) 425 mg/m$^2$ and LV 20 mg/m$^2$ were administered. Radiation to a total dose of 45 Gy (1.8 g/day 5 days/week for 5 weeks) began on day 28. FU and LV were given at the first 4 and last 3 days of radiotherapy. Then, 2 additional cycles of FU and LV were given in every 28 days. Radiotherapy was directed to tumor bed, regional nodes, and anastomoses.

For the "chemotherapy-alone" arm, treatment protocols mostly consisted of combination therapies involving FU as the backbone with the addition of cisplatin and epirubicin

(ECF; epirubicin 50 mg/m$^2$, cisplatin 60 mg/m$^2$ on day 1, continuous infusion of FU 200 mg/m$^2$ through days 1–21, q21 days) or docetaxel (modified DCF: docetaxel 60 mg/m$^2$, cisplatin 60 mg/m$^2$, continuous infusion of FU 600 mg/m$^2$ through days 1–5, q21 days) or cisplatin and FU (cisplatin 75 mg/m$^2$ day 1, continuous infusion of FU 750 mg/m$^2$ through days 1–5, q21 days). Six cycles of CT were planned for each patient.

### Statistical analysis

Overall survival was defined as the time elapsed between the date of surgery and disease-related death or the date of last contact with the patient or any family member. DFS was calculated starting from the date of surgery to the date of first locoregional or distant relapse detected by computed tomograpy and/or upper gastrointestinal endoscopy. Patterns of failure were defined as locoregional, if the site of recurrence involved surgical anastomosis, gastric bed or remnant stomach, and peritoneal cavity (including intra-abdominal lymph nodes and peritoneum). Distant relapse was defined as any distant metastasis involving liver, lung, bone, or brain.

Statistical analysis was performed with SPSS 16.0 software. For group comparison of categorical variables, $\chi^2$ tests were used and for comparison of continuous variables such as age, number of lymph nodes, and cycle of CT, Mann–Whitney $U$ test was accomplished. Kaplan–Meier method was used for estimation of survival distribution, and differences in survival were evaluated by the log-rank statistics. Multivariate survival analysis was performed using the Cox's proportional hazards regression model. A $p$ value $<0.05$ was considered significant.

## Results

Between January 2005 and January 2009, a total of 438 gastric carcinoma patients were referred to our clinic following surgery with extended lymph node dissection for adjuvant therapy. Among those patients, 71 patients were diagnosed as non-metastatic stage IV (number of metastatic lymph node $\geq$15) disease. Median age at diagnosis was 53 years (range 25–81). All the patients had undergone curative intent surgery either with total ($n = 56$) or subtotal gastrectomy ($n = 15$). The majority of the patients had T3 primary tumors ($n = 62$, 87.3 %). Other patient, tumor, and treatment characteristics are outlined in Table 1. Fifty-three patients (74.6 %) received only adjuvant CT, while 18 (25.3 %) patients were treated with CRT. All the patients had received planned dose of radiotherapy (45 Gy total), while 83.3 % of patients in CRT group and 75.5 % of patients were able to receive at least 4 cycles of CT ($p = 0.97$) There was no toxicity-related death in both groups. The baseline patient characteristics were well balanced between the treatment groups except for a higher proportion of diffuse type of histology among CRT group and higher prevalence of cisplatin-based treatment among chemotherapy-alone arm.

**Table 1** Comparison of two treatment arms according to demographic and pathological parameters

| | CT ($n = 53$) | CT + RT ($n = 18$) | $p$ |
|---|---|---|---|
| Age (median and range) | 54 (26–81) | 46 (25–68) | 0.1 |
| Gender | | | |
| Female/male | 20/33 | 5/13 | 0.44 |
| Operation | | | |
| Total/subtotal | 39/12 | 17/1 | 0.18 |
| Histology | | | |
| Intestinal/diffuse | 37/16 | 7/11 | 0.02 |
| T stage | | | |
| T2 + T3/T4 | 48/5 | 16/2 | 0.72 |
| Lymph node | | | |
| Dissected LN, median (range) | 34 (18–94) | 21 (13–71) | 0.74 |
| Metastatic/dissected LN | 0.7 (0.23–1) | 0.68 (0.27–1) | 0.64 |
| Vascular invasion | | | |
| Negative/positive | 41/7 | 15/3 | 0.55 |
| PNI | | | |
| Negative/positive | 42/6 | 17/1 | 0.38 |
| Cisplatin | | | |
| Absent/present | 17/36 | 15/3 | <0.01 |
| Mean CT cycle | 4 (1–6) | 4 (1–3) | 0.63 |
| Surgical margin | | | |
| Positive/negative | 15/38 | 4/14 | 0.61 |
| Recurrence pattern | | | |
| Locoregional/distant | 8/22 | 6/4 | 0.08 |

### Outcome

Median overall survival and DFS for all patients were 26.3 months (15–37.7 months) and 12.5 months (8–17.1 months), respectively. In the entire cohort, the 2-year OS and DFS rates were 54.2 % (±8.8) and 19.1 % (±6.1), respectively. The 2-year local control rate was 50.6 % (±12.7). There was no statistically significant difference between the two treatment arms with respect to survival; median OS in CT arm was 26.8 months and it was 34.2 months for CRT arm ($p = 0.74$) (Table 2; Fig. 1). DFS rates did not differ statistically either ($p = 0.56$); it was 12.5 and 15.2 months for CT and CRT arms, respectively. Evaluation of clinical and pathological factors did

not reveal any statistically significant effect on OS. However, the ratio of metastatic to dissected lymph nodes (≥75 %) exhibited a negative impact on DFS in univariate analysis (15.2 vs 8.2 months, $p = 0.04$). In addition, multivariate analysis involving factors such as metastatic lymph node ratio, age, histological subtype, number of CT cycles, and presence of platinum-based CT revealed only metastatic lymph node ratio as an independent variable associated with poor DFS (Table 3; Fig. 2). Cox regression analysis for OS did not point out a significant prognostic factor.

## Patterns of failure

The median follow-up time was 13.8 months (range 6.2–74.1 months). During the follow-up period, 40 patients (56.3 %) developed recurrent or metastatic disease while 20 patients (28.2 %) died because of their tumor. Out of 40 patients who recurred, only 12 (16.9 %) patients had isolated locoregional recurrence within the whole group. Among 11 patients with positive margins, only two had isolated locoregional recurrence. In the CRT arm ($n = 18$), 10 patients (55.5 %) had relapsed disease during the

**Table 2** Univariate analysis of various parameters on overall and DFS

| Variable | OS | | | DFS | | |
|---|---|---|---|---|---|---|
| | Nevent/ntotal | Median OS (months) | *p* | Nevent/ntotal | Median DFS (months) | *p* |
| Age (years) | | | | | | |
| ≤40 | 4/11 | 13.3 | 0.72 | 5/11 | 20.6 | 0.8 |
| >40 | 15/56 | 26.3 | | 26/56 | 15.2 | |
| Gender | | | | | | |
| Female | 8/25 | 18.3 | 0.18 | 13/25 | 12.5 | 0.61 |
| Male | 12/44 | 34.2 | | 27/46 | 13.3 | |
| Histology | | | | | | |
| Intestinal | 9/44 | NR | 0.31 | 22/44 | 15.2 | 0.80 |
| Diffuse | 11/27 | 17.2 | | 18/27 | 9.9 | |
| T stage | | | | | | |
| T2 + T3 | 16/64 | 27.1 | 0.35 | 34/64 | 13.5 | 0.61 |
| T4 | 4/7 | 20.3 | | 6/7 | 9.1 | |
| Vascular invasion | | | | | | |
| Positive | 15/56 | 26.3 | 0.84 | 28/56 | 15.2 | 0.75 |
| Negative | 3/10 | NR | | 8/10 | 12.5 | |
| Perineural invasion | | | | | | |
| Positive | 13/59 | 34.2 | 0.37 | 31/59 | 13.3 | 0.71 |
| Negative | 5/7 | 26.3 | | 5/7 | 15.2 | |
| Margins | | | | | | |
| Positive | 5/19 | 20.3 | 0.61 | 10/19 | 13.5 | 0.12 |
| Negative | 15/52 | 34.2 | | 23/52 | 16.7 | |
| Cisplatin | | | | | | |
| Present | 12/39 | 26.3 | 0.67 | 28/56 | 15.2 | 0.78 |
| Absent | 8/32 | 34.2 | | 8/10 | 12.5 | |
| Metastatic/dissected LN | | | | | | |
| ≤0.75 | 11/38 | 27.1 | 0.24 | 21/38 | 15.2 | 0.04 |
| >0.75 | 7/31 | 34.2 | | 17/31 | 8.6 | |
| Types of treatment | | | | | | |
| CT | 14/53 | 26.8 | 0.74 | 30/53 | 12.5 | 0.56 |
| CT + RT | 6/18 | 34.2 | | 10/18 | 15.2 | |
| Cycle of CT | | | | | | |
| ≤4 | 13/46 | 17.2 | 0.25 | 28/46 | 9.6 | 0.06 |
| >4 | 7/23 | 34.2 | | 12/23 | 20.6 | |

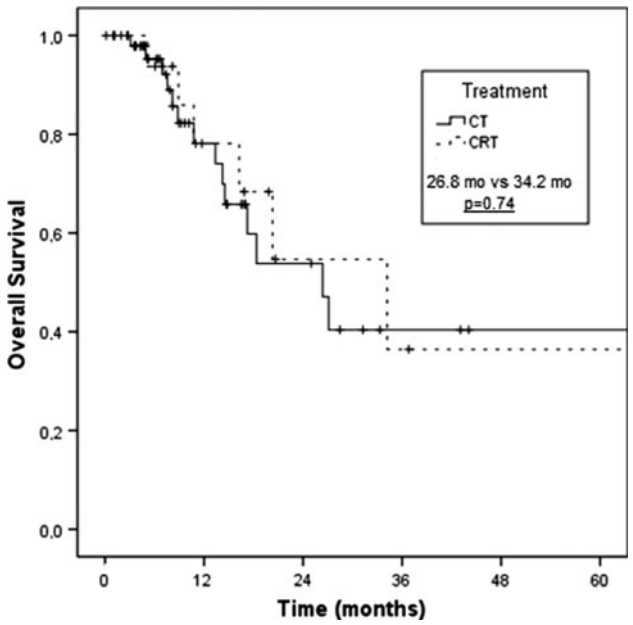


**Fig. 1** Kaplan–Meier survival curve for the effect of two treatment modalities (CT vs CRT) on OS

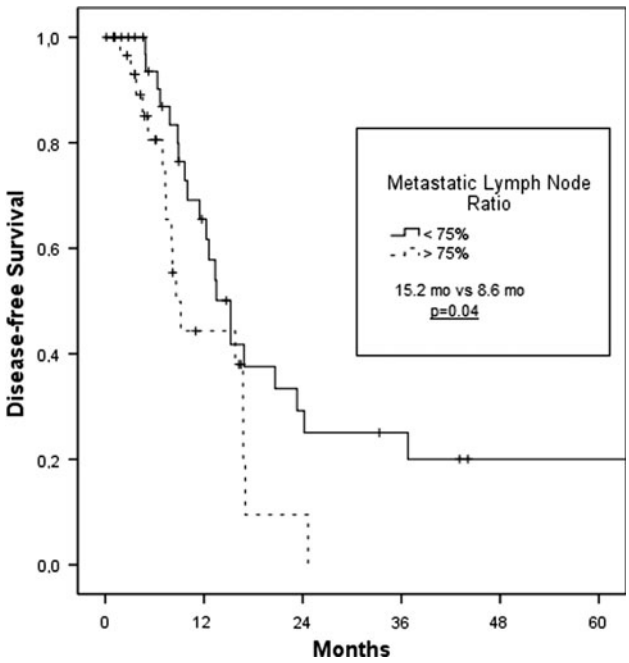


**Fig. 2** Kaplan–Meier survival curve depicting the effect of metastatic lymph node ratio on DFS

**Table 3** Cox regression analysis for DFS of all patients

| | *p* | Hazard ratio | 95 % CI for Exp(B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age >40 versus <40 | 0.88 | 0.93 | 0.39 | 2.24 |
| Diffuse versus intestinal histology | 0.53 | 1.24 | 0.62 | 2.50 |
| Number of CT cycles | 0.13 | 0.54 | 0.25 | 1.19 |
| Metastatic/dissected lymph node ≥0.75 | 0.04 | 2.11 | 1.03 | 4.36 |
| Cisplatin versus no cisplatin | 0.59 | 0.81 | 0.38 | 1.74 |

follow-up period where 4 patients (22.2 %) had isolated locoregional failure and 6 patients (33.3 %) had progression either at only distant site or both. The difference in local recurrence rate between the two treatment arms was not statistically significant ($p = 0.63$) (Table 1). After relapse, 16.9 % of all patients ($n = 12$) received second-line CT while the rest received best supportive care (39.4 %, $n = 28$).

## Discussion

This retrospective study has demonstrated that, for this poor prognostic group with pTanyN3M0 in localized gastric cancer patients, the addition of radiotherapy does not offer survival advantage. Median OS and DFS were 26.8 versus 34.2 months ($p = 0.74$) and 12.5 versus 15.2 months ($p = 0.56$) for CT alone and CRT arms, respectively. For the whole group, the 2-year OS and DFS rates were 54.2 % (±8.8) and 19.1 % (±6.1). In a comparative study between the previous and actual nodal classification of gastric cancer, 5-year survival rates for N3a and N3b patients were reported as 23.1 and 5.4 %, respectively, after only D2 lymph node resection [8]. The relatively high survival rates in our study might be due to short follow-up time or impact of adjuvant treatment following surgery.

There was no significant difference between the two treatment arms with respect to locoregional recurrence rates ($p = 0.63$). A total of 40 patients had relapsed disease, 16.9 % ($n = 12$) had isolated locoregional recurrence while the rest of the patients had distant failures. The pattern of relapse was similar in CRT arms of previous studies concerning patients with D2 lymph node dissections [9, 10]. In the INT-0116 trial, rate of locoregional relapse was significantly higher (67 %), probably reflecting the negative impact of D1 resection accomplished in 90 % of patients. At our institution, we planned the adjuvant treatment strategies based on individual patient data in our tumor boards. Since D2 lymph node dissection is routinely performed by our surgical oncologists and risk of distant metastasis is high in N3 disease, majority of the patients included in this analysis received CT alone as adjuvant treatment (74.6 %, $n = 53$). Although the size of the current study may be too small to draw a definite conclusion, our results encourage the adjustment of adjuvant treatment

modalities according to the presence and/or ratio of nodal involvement in patients undergoing D2 lymph node dissection.

In our study, high ratio of metastatic to dissected lymph node (≥75 %) was identified as a poor prognostic factor for DFS in both univariate and multivariate analyses. Since most of the relapsed patients had received a second-line CT, the effect of different treatments on OS was not statistically significant ($p = 0.2$). In concordance with our data, metastatic lymph node ratio (MLR) was identified as an independent prognostic factor following both D1 and D2 lymph node dissections, previously [11, 12]. Besides, MLR demonstrated further negative influence on survival in N2 stage and yielded better survival information than conventional AJCC node (pN) stage, in another study [13].

Adjuvant treatment for gastric cancer after curative surgery has been under debate in different parts of the world. In the United States, adjuvant CRT has been a standard care for resected gastric cancer patients after the publication of INT-011 study [4]. Updated analysis of this trial with more than 10-year median follow-up has reinforced the persistent benefit of adjuvant CRT [5]. The major limitation for global acceptance of the INT-0116 (or MacDonald's) regimen as an adjuvant treatment modality has been the inadequate lymph node dissection (D0 or D1) in 90 % of patients included in the trial. In Asian and European centers where D2 lymph node dissection is routinely performed, addition of further radiotherapy has been questioned due to the high morbidity rates and poor tolerance. However, another study involving Korean gastric cancer patients with D2 lymph node dissection has advocated CRT as an adjunct to surgery, with acceptable toxicities and good tumor control [9]. But this strategy still has little popularity outside the USA.

The role of adjuvant CT has been questioned in several studies involving both European and Eastern patients. The Spanish multicentric trial randomized 148 stage III gastric cancer patients to either CT with mitomycin and oral tegafur or surgery alone, and the addition of CT resulted a clear 5-year survival benefit (36 vs 52 %, respectively) [14]. Although this unexpectedly high survival advantage was not reproducible in most of the other Western patients, an Italian study performed among 137 node-positive gastric cancer patients was able to demonstrate survival difference with the addition of epirubicin, FU, and LV after curative resection [15]. Similarly, ACTS-GC study which randomized 1,059 patients with stage II–III D2 lymph node dissected gastric cancer either to observation or 1 year S-1 (an oral fluoropyrimidine) monotherapy has reported a significant improvement in 3-year survival from 70.1 to 80.1 % with the addition of S-1 [16]. This markedly longer survival rate is assumed to be related to the inclusion of relatively early-stage disease and high-quality surgery. However, meta-analysis of adjuvant CT studies has yielded conflicting results. When the analysis was restricted to Western patients, overall benefit from CT had been lost (OR 0.96, 95 % CI 0.83–1.12) [17]. Another meta-analysis including Japanese trials has demonstrated an improvement in survival with the addition of CT (HR 0.78, 95 % CI 0.71–0.85) [18].

The major limitation in planning adjuvant treatment for patients with gastric cancer was due to the lack of data comparing CRT versus CT alone after D2 lymph node dissection. To our knowledge, the first prospective trial with this intend was terminated early due to poor patient accrual ($n = 61$) [19]. A total of 61 gastric cancer patients with stage IIIA, IIIB, and IV (without metastasis) were randomized to CRT and 5-fluorouracil/cisplatin (FP) or FP arms; there was no difference in 5-year DFS (76.7 vs 59.1 %, $p = 0.222$) and overall survival rates (70.1 vs 70.0 %, $p = 0.814$), in concordance with our results. Recently, the ARTIST trial compared two different postoperative treatment modalities in 458 completely resected gastric cancer patients, with capecitabine plus cisplatin (XP) versus XP plus radiotherapy with capecitabine [6]. The addition of CRT to XP regimen did not significantly prolong DFS ($p = 0.08$, 3-year DFS rates 78.2 vs 74.2 % for CRT and CT arms, respectively). However, the subgroup of patients with pathologic lymph node metastasis assigned to CRT experienced superior DFS when compared with those who received CT alone ($p = 0.03$). This finding has emerged the establishment of a subsequent trial (ARTIST II) in patients with lymph node metastasis. The most recent study comparing CRT with CT alone investigated the role of intensity-modulated radiotherapy (IMRT) with concomitant CT in gastric cancer patients with D2 lymph node dissection [20]. The experimental arm (IMRT plus CT) was feasible and well tolerated with improvement in RFS; however, this trial also failed to show an OS difference like the previous comparative studies.

The limitations of the current study are mainly due to its retrospective nature: differences in histology between two groups (predominance of diffuse type in CRT group) and heterogeneity of CT regimens. Since all the patients in the CRT arm received FU-based (MacDonald's) regimen, cisplatin combinations constituted the backbone of treatment in CT-only arm. This difference is supposed to cause a therapy-related bias, but uni- and multivariate analyses did not reveal a significant effect of platinum-based CT on OS or DFS.

In conclusion, supporting the previous retrospective and prospective data, the addition of radiotherapy to CT in the adjuvant setting did not significantly effect OS and DFS in TanyN3bM0 patients who underwent D2 node dissection. A longer period of follow-up may be required to observe a survival benefit.

**Conflict of interest** All authors state that the article is novel and original and have made substantial contributions to the information and/or material submitted for publication. All have read and approved the final manuscript and agreed to its submission. No authors have a substantial direct or indirect commercial financial incentive associated with the publication of the article.

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