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Original Article

Capecitabine-cisplatin versus 5-fluorouracil/leucovorin in combination with radiotherapy for adjuvant therapy of lymph node positive locally advanced gastric cancer

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ABSTRACT

Aim of the Study: Although surgery is considered to be curative treatment, recurrence rates are high in gastric cancer. Adjuvant 5-fluorouracil (5-FU) based chemoradiotherapy has been shown to improve the prognosis. We compared tolerability and efficacy of the two different chemotherapy regimens; 5-FU/leucovorin (LV) versus cisplatin with capecitabine (XP) combined with radiotherapy (RT) in the adjuvant therapy of the lymph node positive locally advanced gastric cancer.

Materials and Methods: Totally, 104 patients who underwent curative surgery with lymph node resection were evaluated, respectively. Patients were stratified two group based on the adjuvant chemoradiotherapy regimen. Group 1 ($n = 46$) received XP followed capecitabine with RT (XRT) then XP. Group 2 ($n = 58$) received 5-FU/LV combined with RT postoperatively. Two groups were compared based on clinicopathological parameters. Factors related with disease-free survival (DFS) and overall survival (OS) were analyzed.

Results: Totally, 32 patients had recurrent disease, and there was no difference between two groups. While peritoneal metastasis was more common in XP arm, distant metastasis was commonly seen in 5-FU/LV arm. There was no significant difference between two groups in regard of Grade 3/4 toxicitis; hematologic toxicities were more in 5-FU/LV group than XP arm. In addition, dose modification because of toxicities were more frequent in 5-FU/LV arm ($P = 0.003$). For all groups, lymph node dissection type was related with DFS, surgical margin and recurrence were important for OS.

Conclusion: XP-XRT regimen is well tolerated with lower toxicity compared the standard 5-FU/LV-RT. Although there is no difference with respect to outcome, patients with XP arm without the necessity of intravenous catheter admitted hospital less frequent than bolus5-FU/LV arm.

KEY WORDS: Adjuvant chemoradiotherapy, capecitabine, gastric cancer, lymph node positive, 5-fluorouracil/leucovorin

INTRODUCTION

Gastric cancer is one of the most frequent tumors that lead the mortality because of the cancer worldwide.[1] Surgery with lymph node dissection is the current treatment for the locoregional gastric cancer.[1-3] Although radical surgery with lymph node dissection has been performed widespread, recurrence rates have not been improved by surgery alone. Survival benefit of adjuvant and neoadjuvant treatment strategies has been reported in several studies.[4] Nevertheless, optimal adjuvant therapy regimen is still controversial. Postoperative chemoradiotherapy with 5-fluorouracil/leucovorine (5-FU/LV) has been accepted as standard in the USA after INT0116 trial.[5] In this study, 556 patients with gastric cancer were randomized two groups. One of them was observation and another was chemoradiotherapy group with 5 day cycles of 5-FU/LV intravenous (iv) bolus followed by 45 Gy radiotherapy (RT) with 2nd cycle of chemotherapy (at the beginning of RT 5-FU/LV were given for 4 days and at the end of

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Cite this article as: Ustaalioğlu BB, Bilici A, Tilki M, Surmelioglu A, Erkol B, Figen M, *et al*. Capecitabine-cisplatin versus 5-fluorouracil/leucovorin in combination with radiotherapy for adjuvant therapy of lymph node positive locally advanced gastric cancer. J Can Res Ther 2018;14:S736-41.

Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.183548

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the RT, 5-FU/LV was given for 3 days) and then two cycles of 5-FU/LV every 28 days. Three years overall survival (OS) was longer in the cardiac resynchronization therapy arm (50% vs. 41%, median: 36 months vs. 27 months). Chemotherapy in this trial is considered suboptimal, so new regimens have been investigated. Korean ARTIST trial reported that adjuvant cisplatin with capecitabine (XP) followed capecitabine concomitant RT and additional two cycles of XP could not be prolong disease-free survival (DFS) in gastric cancer patients who underwent D2 dissection.[6] However, in the subgroup analysis, DFS was reported as longer in lymph node metastasis group.

Based on the REAL-2 trial in metastatic gastric cancer, capecitabine has been reported as noninferior in comparison with 5-FU.[7] While ML17032 study was also proved, the XP was equally effective as cisplatin-5-FU.[8] Meta-analysis of these trials revealed that OS was significantly higher in capecitabine compared of 5-FU (hazard ratio: 0.87).[9] Stomatitis and hand-foot syndrome were more common in capecitabine containing arm, but Grade 3/4 neutropenia were more common in 5-FU containing arm.[9] In adjuvant chemotherapy trial of S-1 for gastric cancer (ACTS-GC) trial oral fluoropyrimidine S1 was also reported as survival advantage over surgery after D2 dissection.[10] Bolus 5-FU is known to be more toxic and less effective than infusional or oral 5-FU, so we compared gastric cancer patients who were given 5-FU/LV or XP concomitant with RT in respect to toxicities and effectiveness. Furthermore, cisplatin-5-FU based chemotherapy has been used in stage II and III gastric or esophageal cancer in the adjuvant or neoadjuvant settings with 13–15% of PFS benefit.[11] Capecitabine-oxaliplatin combined with RT was evaluated in 32 gastric cancer, only twenty of them could be completed all cycle (65%).[11] We also added cisplatin to capecitabine in adjuvant settings.

We know that lymph node metastasis is one of the most important poor prognostic factors in gastric cancer and the prognosis of lymph node metastatic gastric cancer remained under the 30% for 5 years despite curative surgery. We hypothesized that gastric cancer prognosis can be improved with more effective postoperative chemotherapy combined with RT. Hence, in here, we analyzed two different adjuvant chemotherapy regimen XP and 5-FU/LV concomitant with RT whether any advantage for survival and tolerability in lymph node-positive gastric cancer.

MATERIALS AND METHODS

Totally, 104 locally advanced gastric cancer who had undergone curative gastrectomy at two center in Istanbul between 2008 and 2014 were evaluated retrospectively. All patients underwent either total or subtotal gastrectomy with regional lymph node dissection to D1, D2, or D3. Lymph node dissections were defined as D1 if only perigastric lymph nodes in the range of 15–25 were removed. D2 dissection involves more than 25 lymph node dissection in addition to perigastric, splenic, celiac, splenic, and hepatic lymph nodes were also removed. If more than 25 lymph nodes with paraaortic lymph nodes were removed, it was defined as D3 dissection. Tumors were staged according to American Joint Committee on cancer tumor-node-metastasis (TNM) classification, 7th edition. The eligibility criteria included histopatologically confirmed gastric cancer with lymph node metastasis and postoperative survival was expected longer than 3 months. Patients with distant metastasis or peritoneal metastasis or patients with comorbidities who were unable to tolerate chemotherapy were excluded from the study.

Patients were classified into two groups according to adjuvant chemoradiotherapy regimen as: XP arm ($n = 46$) received two cycles of XP (capecitabine 2000 mg/m^2/day on days 1–14 and cisplatine 75 mg/m^2 on day 1, every 21 days) followed by 45-Gy RT combined with capecitabine 1650 mg/m^2/day during RT for 5 weeks and additional one or two cycles XP. Adjuvant 5-FU/LV group ($n = 58$) received five cycles 5-FU 425 mg/m^2 and LV 20 mg/m^2 1–5 days iv bolus for 28 day cycles. RT was combined with 2nd cycles 5-FU/LV which continued for 4 days and 3 days at the end of the RT. Radiotherapy was targeted to the tumor bed, regional lymph nodes with 2 cm margin from the proximal and distal surgical resection margin.

Clinicopathological parameters about age, gender, resection type, tumor localization, histopatology, tumor stage, lymphatic invasion, vascular invasion, perineural invasion, resection margin, Lauren and Bormann classification, adjuvant chemotherapy type, toxicity, and survival were obtained from patient's charts after informed consents were taken.

Statistical analysis

Statistical analysis was performed using 13.0 (SPSS Inc., Chicago, IL, USA) software. The clinicopatological differences between two groups were analyzed using the Chi-square test and Fisher's exact. Survival analysis and curves were established according to the Kaplan–Meier method and compared using the log-rank test. DFS was defined as the time from surgery to the last follow-up and the time until relapse was defined as the time since surgery to the first evidence of relapse. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analysis of prognostic factors related to survival were performed by the cyclooxygenase proportional hazards model. Multivariate *P* values were used to characterize the independence of these factors. A 95% of the confidence interval was used to quantify the relationship between survival time and each independent factor. All *P* values were two-sided in tests and $P \leq 0.05$ were considered significant.

RESULTS

Group 1 included 46 patients and group two was 58 patients. Tumors were located equally both upper (42.3) and lower part (42.3%) then the middle of the stomach (15.4%). Median

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age at surgical resection was 57 (range: 30–77), and most of them were male (76%). While 59 patients underwent total gastrectomy (56.7%), others were performed subtotal gastrectomy. Patients were underwent lymph node dissection in order of frequency as 12 D0 (11.5%), 31 D1 (29.8%), 34 D2 (32.7%), 27 D3 (26%). Median number of resected and metastatic lymph nodes was thirty and seven, respectively. Based on the TNM staging, eight (7.2%) patients were classified as stage 2 and 96 (92.8%) as stage 3. Surgical margin was positive in 14 patients (13.8%).

Nearly, 32 (30%) of the patients had a recurrence during median follow-up 13.8 months (range: 3–70 months). Only two patients (6.7%) had local recurrence, on the other hand, 15 peritoneal (46.9%), 15 distant metastases had been diagnosed. The differences between two groups are shown in Table 1. Signet ring histology, lower gastric part localization ulceroinfiltran and infiltran type tumors and D2 dissection were more common in Group 1; on the other hand, upper localization ulcerovegetan tumor type and D1 dissection were more in Group 2. Although recurrence sites were different between two groups ($P = 0.03$), local recurrences were not different ($P = 0.4$). However, peritoneal metastasis was more common in the Group 1 ($P = 0.02$), while distant metastasis was also more common in 5-FU/LV group numerically (64.7% vs. 30.8%) but it was not statistically significant ($P = 0.06$). Table 2 shows the recurrence site for two groups, respectively.

Median OS and 3 years OS times were 40.3 months and 64.9%, respectively. On the other hand, median DFS times and 3 years DFS rates were 24.2 months and 34%, respectively. Figures 1 and 2 show the survival curves of both DFS and OS. There is no differences between median OS or DFS in respect to adjuvant chemotherapy groups ($P = 0.8$ vs. $P = 0.06$, respectively). The 2 years OS rates were 62% in Group 1 and 77% in Group 2. On the other hand, median DFS and 2 years DFS rates were 19.1 and 21% in the Group 1 and 26.7 months and 54% in the Group 2, respectively. While D0 dissection ($P = 0.004$) was related with DFS, positive surgical margin ($P = 0.02$) and the presence of progression ($P < 0.001$) were poor prognostic factor for OS in all patient cohort. When the univariate analysis were performed for two groups respectively, there was no factors found to be related with DFS in the Group 1, but operation type ($P = 0.009$), tumor location ($P = 0.02$), lymph node dissection type ($P = 0.008$), and surgical margin ($P = 0.005$) were found to be related with DFS for Group 2. Upper located tumor, D0 resection, positive surgical margin were poor prognostic factors for DFS in 5-FU/LV group. Positive surgical margin and progression were related with OS for both groups [Table 3]. There was no independent factor related with OS or DFS in the multivariate analysis.

Adjuvant XP was used in 46 (44.2%) of the patients, and 58 of them (55.8%) were treated with 5-FU/LV concomitant with RT. Median total dose of RT was 50.4 Gy with 1.8 Gy per fraction. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0. The most common

Table 1: The clinicopathological factors of two groups

Characteristics	Group 1, *n* (%) 46 (44.2)	Group 2, *n* (%) 58 (55.8)	*P*
Age (years)			
≤50	16 (20.6)	12 (34.7)	0.08
>50	30 (79.4)	46 (65.3)	
Gender			
Female	9 (19.6)	16 (27.6)	0.2
Male	37 (80.4)	42 (72.4)	
Operation type			
Total gastrectomy	25 (54.3)	34 (58.6)	0.6
Subtotal gastrectomy	21 (45.7)	24 (41.4)	
Histopathology			
Adenocarcinoma	21 (45.7)	37 (63.8)	0.03
Signet ring type	19 (41.3)	10 (17.2)	
Mix	5 (10.9)	6 (10.3)	
Musinous	1 (2.2)	5 (8.6)	
Location			
Upper	10 (21.7)	34 (58.6)	0.001
Middle	9 (19.6)	7 (12.1)	
Lower	27 (58.7)	17 (29.3)	
T stage			
T1	1 (2.2)	3 (5.2)	0.08
T2	22 (4.3)	8 (13.8)	
T3	17 (37)	18 (31)	
T4	26 (56.5)	29 (50)	
Lymph node dissection			
D1	9 (19.6)	22 (37.9)	0.02
D2	21 (45.7)	13 (22.4)	
D3	13 (28.3)	14 (24.1)	
D0	3 (6.5)	9 (15.5)	
N stage			
N1	6 (13)	12 (20.7)	0.2
N2	9 (19.6)	17 (29.3)	
N3	31 (64.4)	29 (50)	
Surgical margin			
Negative	40 (87)	50 (86.2)	1
Positive	6 (13)	8 (13.8)	
Stage			
II	3 (6.5)	5 (8.6)	0.4
III	44 (93.5)	53 (91.4)	
LI			
Present	43 (93.5)	52 (89.7)	0.5
Absent	3 (6.5)	6 (10.3)	
VI			
Present	34 (73.9)	43 (74.1)	1
Absent	12 (26.1)	15 (25.9)	
PNI			
Present	37 (80.4)	42 (72.4)	0.2
Absent	9 (19.6)	16 (27.6)	
Borrman			
Ulceroinfiltrative	32 (69.6)	33 (56.9)	<0.01
İnfiltrative	12 (26.2)	4 (6.9)	
Ulcerovegetan	2 (4.3)	18 (31)	
Ulcerous	0 (0)	3 (5.2)	
Grade			
1	0 (0)	1 (1.7)	0.6
2	15 (32.6)	17 (29.3)	
3	31 (67.4)	40 (69)	
Lauren			
Diffuse	21 (45.7)	15 (37.5)	0.1
Mix	13 (28.3)	7 (17.5)	
İntestinal	12 (26)	8 (45)	
Progression			
Present	13 (28.3)	19 (32.8)	0.6
Absent	33 (71.7)	39 (67.2)	
Recurrence site			
Localized	0 (0)	2 (11.8)	0.03
Peritoneum	9 (69.2)	4 (23.5)	
Distant	4 (30.8)	11 (64.7)	

LI=Lymphatic invasion, VI=Vascular invasion, PNI=Perineural invasion

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Grade 3/4 toxicities were neutropenia, hand-foot syndrome, weight loss, gastrointestinal toxicities such as nausea, vomiting, and stomatitis. Grade 3/4 toxicity was detected in 38 patients (36.5%), nine of them was hematologic (23.7%), 16 gastrointestinal which was emesis or mucositis (42.1%) and 13 (34.2%) suffered due to other toxicities like weight loss or hand-foot syndrome. In the XP arm, 18 Grade 3/4 toxicities were detected on the other hand 19 patients were seen toxicities, in other grades, there is no difference between two group significantly in respect to toxicities ($P = 0.1$). Although hematological toxicities were more common in 5-FU/LV (26.3% vs. 11.1%), it was not statistically significant. Only hand-foot syndrome was more common in XP arm ($P = 0.04$). Table 4 shows toxicities between two groups. Dose modifications like delaying chemotherapy or dose reduction were performed in 22 (21.2%) patients due to toxicity. Only two patients (4.3%) in the XP arm could not tolerate the capecitabine during RT and treatment continued as 5-FU/LV. Other two (3.4%) patients in the 2nd group could not tolerate 5-FU/LV bolus so weekly 5-FU/LV were given.

DISCUSSION

Despite adjuvant chemoradiotherapy or chemotherapy has been shown improved survival compared to surgery alone,[4] choice of chemotherapy regimen has still be controversial in locally advanced gastric cancer. Without RT, 8.3–23.3% of the patients had locoregional recurrence, despite D2 lymph node dissection.[12] In the lymph node-positive gastric cancer, prognosis is poor although adjuvant therapy.

Table 2: Recurrence sites between two groups

Recurrence sites	Group 1 (XP/XRT/XP) (%)	Group 2 (5FU/LV) (%)	*P*
Periton	9 (69.2)	4 (23.5)	0.02
Local	0	2 (11.8)	0.4
Distant	4 (30.8)	11 (64.7)	0.06

XP=Capacitabine/cisplatine, 5-FU/LV=5-fluorouracil/leucovorin, XRT=XP followed capecitabine with radiotherapy

Chemoradiotherapy with 5-FU/LV were demonstrated survival advantage compared to surgery alone in the INT-0116 study (3 years OS rates were 50% vs. 41%). In this study, 90% of the patients underwent D0 or D1 dissection. However, 3 years OS was not more than 50% in 3 years although postoperative therapy.[5] In our sense, whether more aggressive chemotherapy than 5-FU/LV combined with RT postoperatively can prolong survival with feasible toxicity in lymph node-positive gastric cancer. Several studies were performed to find the optimal chemotherapy regimen combined RT postoperatively to improve survival with reducing toxicity rate. Capecitabine-based chemoradiotherapy has been well tolerated in rectal and upper gastrointestinal cancer.[13,14] XP also has been used for the first line therapy of the metastatic gastric cancer.[8] Song *et al*. analyzed 13 patients who received adjuvant chemoradiotherapy for gastric cancer with positive surgical margin and they revealed 28% of 5 years DFS rates with peritoneal recurrences of 46%. They used XP as adjuvant chemotherapy part in three patients.[4] One Chinese study included 31 locally advanced gastric cancer were used cisplatin combined with infusional 5-FU followed capecitabine combined with RT as adjuvant therapy with 82.7% of 3 years DFS rate.[15] Half of their patients suffered Grade 3/4 neutropenia without any febrile neutropenia but forth of them could not complete treatment cycle. The adjuvant ARTIST trial, lymph node-positive gastric cancer had been revealed longer survival with XP chemotherapy followed capecitabine-RT.[6,16] Three years DFS rates of lymph node positive diseases were 76% in XP/RT. Different of our trial, in ARTIST trial patients, were randomized as adjuvant XP/XP followed capecitabine with RT (XRT)/XP ($n = 230$) and XP alone ($n = 228$) but we classified patients as XP/XRT/XP and 5-FU/LV-RT. We also used cisplatine 75 mg/m^2 higher than 60 mg/m^2. In their study, 81.7% of the patients in the XP/XRT/XP arm could complete treatment. In our group, 95.7% of the patients completed treatment in XP/XRT/XP arm, but median chemotherapy cycle of us was 5. ARTIST trial included nearly half were stage I or II disease different from us, we

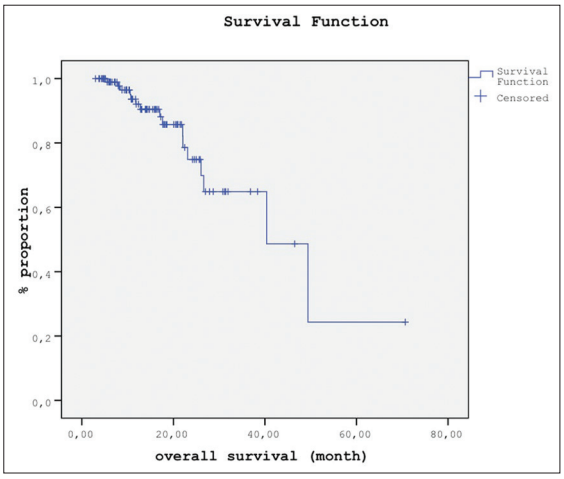

Figure 1: The overall survival curve of all groups

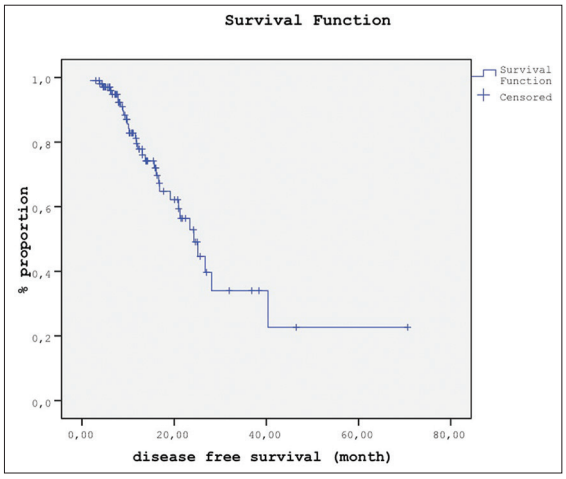

Figure 2: The disease-free survival curve of all groups

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Table 3: The results of the univariate analysis

	P	
	DFS	OS
Surgical margin	0.07	0.02
Progression		<0.001
Lymph node dissection	0.04	0.8
Gender	0.5	0.09
Location	0.09	0.08
Lauren	0.6	0.07
LI	0.09	0.1
VI	0.08	0.5
Adjuvant CT type	0.06	0.8

LI=Lymphatic invasion, VI=Vascular invasion, CT=Chemotherapy, DFS=Disease-free survival, OS=Overall survival

Table 4: The differences of the toxicities between two groups

Grade 3/4 toxicities	Group 1 (*n*=18) (%)	Group 2 (*n*=18) (%)	*P*=0.1
Neutropenia	2 (11.1)	5 (26.3)	0.4
Febrile neutropenia	1 (5.6)	1 (5.3)	
Diarrhea	0 (0)	1 (5.3)	
Hand-foot syndrome	4 (22.2)	0 (0)	0.04
GIS toxicity	8 (44.4)	6 (33.3)	0.7
Mucositis	2 (11.1)	0 (0)	0.2
Weight loss	3 (16.7)	6 (3.6)	0.4

GIS=Gastrointestinal system

included only stage II (7.7%) or III (92.3%) disease. We detected lower Grade 3/4 neutropenia (11.1% vs. 48.4%) but higher rate of hand–foot syndrome (22.2% vs. 3.1%) in XP/XRT/XP arm compared their study group, but they were manageable toxicity. Lower neutropenia and higher hand-foot syndrome rates may be related ethnical differences between East Asia and Turkish population. CALGB 80101 study compared 5-FU/LV plus RT versus postoperative epirubucin-cisplatin-5-FU before and after 5-FU-RT in adjuvant settings of gastric cancer. This trial could not provide noninferiority in respect to OS.[17] Similar the CALGB trial our XP/XRT/XP was not different than 5-FU/LV-based on survival.

Osti *et al*. evaluated the adjuvant chemotherapy included 5-FU (64%) or capecitabine (36%) combined with RT in 55 gastric cancer as adjuvant therapy settings after D2 dissection.[18] They included both stages I or II patients nearly 40%. Three years OS and DFS rates were 59.3% and 60% respectively with 10% of Grade 3 toxicity, mostly with leucopenia. There were no differences between toxicities among capecitabine or 5-FU group. Most recurrences were distant metastasis (33%) on the other hand 9% of local recurrence was reported. Gastric cancer recurrences were seen mostly distant included liver, lung, lymph nodes, or peritoneum.[19] We followed patients for median 13 months, so we reported 3 years DFS or OS rates as 34% and 64.9%.

Major limitation of our study is small sample size and short follow-up time (13.8 months) is the other limitation. Nearly, 30% ($n = 32$) of the patients had recurrence, 13 (28.3%) in the 1st group, and 19 (32.8%) in the 2nd group ($P = 0.6$). Although recurrence sites were different between two groups ($P = 0.03$), local recurrences were not different between two groups ($P = 0.4$). Only two local recurrences but 28 (26%) distant metastasis mostly peritoneum, liver, and others were detected during follow-up. It may be related that both groups were received same dose RT.

Although there is a lack of consensus, in our department D2 dissection is generally preferred. In our study, nearly 60% of our patients underwent D2 or D3 dissection. The CLASSIC trial supported the adjuvant chemotherapy (capecitabine-oxaliplatin) after D2 dissection is more beneficial in compared to observation.[19] ACTS-GC trial also shown that oral fluoropyrimidine monotherapy after D2 dissection improved survival compared to surgery alone.[10] We do not know whether chemoradiotherapy or only chemotherapy are superior postoperative settings after D2 dissection of lymph node-positive gastric cancer. Hence, we prefer chemoradiotherapy after D2 dissection for lymph node-positive gastric cancer in our institute.

CONCLUSION

Postoperative chemoradiotherapy with XP has manageable toxicity in patients with lymph node metastatic gastric cancer. This regimen provides acceptable locoregional and distant metastasis control. In sense of more aggressive therapy is required for lymph node-positive gastric cancer not to be supported in our study. However, there is a need for large and prospective studies in the future for locally advanced gastric cancer with poor prognosis.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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