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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Lymph-node ratio is an important clinical determinant for selecting the appropriate adjuvant chemotherapy regimen for curative D2-resected gastric cancer

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Abstract

Purpose Adjuvant chemotherapy for gastric cancer, particularly stage III, improves survival after curative D2 gastrectomy. We investigated the clinical value of the lymph-node ratio (LNR; number of metastatic lymph nodes/number of lymph nodes examined) for selecting the appropriate adjuvant chemotherapy regimen in patients with D2-resected stage II/III gastric cancer.

Methods We reviewed the data of 819 patients who underwent curative D2 gastrectomy followed by adjuvant chemotherapy. Of them, 353 patients received platinum-based chemotherapy and 466 received TS-1. The patients were categorized into three groups according to their LNR (LNR 1, 0–0.1; LNR 2, > 0.1–0.25; and LNR 3, > 0.25), and their disease-free survival (DFS) was evaluated.

Results The DFS curves of the patients were well separated according to stage and LNR. In multivariate analyses, an LNR > 0.1 was strongly associated with the 3-year DFS (hazard ratio 2.402, 95% confidence interval 1.607–3.590, $P < 0.001$). Platinum-based chemotherapy improved the 3-year DFS compared to TS-1 in patients with LNR 3 group in stage III gastric cancer (platinum vs. TS-1, median DFS 26.87 vs. 16.27 months, $P = 0.028$). An LNR > 0.1 was associated with benefiting from platinum-based adjuvant chemotherapy in stage III gastric cancer patients with lymphovascular invasion (platinum vs. TS-1, median DFS 47.57 vs. 21.77 months, $P = 0.011$).

Conclusions The LNR can be used to select the appropriate adjuvant chemotherapy regimen for patients with D2-resected gastric cancer, particularly in stage III.

Keywords Gastric cancer · Gastrectomy · Lymph node · Adjuvant chemotherapy

Introduction

The only curative treatment strategy for gastric cancer is radical gastrectomy with lymph-node dissection and post-operative adjuvant chemotherapy to prevent recurrence and improve survival (Cunningham et al. 2006; Sakuramoto et al. 2007; Paoletti et al. 2010; Sasako et al. 2011; Bang et al. 2012; Noh et al. 2014). In Asian countries, the most frequently used adjuvant chemotherapy regimens after primary gastrectomy with D2 lymph-node dissection are TS-1 and capecitabine plus oxaliplatin (Xelox) (Sakuramoto et al. 2007; Sasako et al. 2011; Bang et al. 2012; Noh et al. 2014). TS-1 and Xelox improve disease-free survival (DFS) and overall survival (OS) compared to surgery alone in patients with stage II or III gastric cancer. The TS-1 and Xelox regimens after radical D2 gastrectomy show similar efficacies,

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but no comparative randomized controlled trial has been performed.

According to the subgroup analysis, Xelox resulted in an improved OS rate based on an increase in nodal status (N0: hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.32–1.95; N1 or N2: HR 0.67, 95% CI 0.51–0.87). However, the efficacy of TS-1 was somewhat decreased in patients with N2 nodal status (N0: HR 0.317, 95% CI 0.127–0.790; N1: HR 0.608, 95% CI 0.440–0.840; N2: HR 0.839, 95% CI 0.612–1.150) (Sasako et al. 2011; Noh et al. 2014). Recent retrospective and observational studies also suggest that advanced-stage or high-risk patients who undergo radical D2 gastrectomy derive greater benefit from platinum-based adjuvant chemotherapy (Hwang et al. 2017; Kim et al. 2018).

In gastric cancer surgery, examination of at least 16 lymph nodes is recommended for staging purposes, and D2 lymph-node dissection is advocated in Asian countries (Sasako et al. 2011; Costa et al. 2012; Noh et al. 2014). The lymph-node ratio (LNR; number of metastatic lymph nodes/number of lymph nodes examined) is thought to be predictive of recurrence and prognosis in patients with gastric cancer (Nitti et al. 2003; Marchet et al. 2007; Bilici et al. 2010; Xiao et al. 2011; Costa et al. 2012; Wu et al. 2015). Moreover, it is an independent prognostic factor in gastric cancer irrespective of the type of lymphadenectomy (Marchet et al. 2007). High LNR is significantly associated with early recurrence and poor prognosis in patients with gastric cancer (Costa et al. 2012; Kim et al. 2016) and gastric cancer patients with high LNR could greater benefit from platinum-based adjuvant chemotherapy than TS-1.

In this study, we categorized LNR and investigated the clinical prognostic value of LNR in terms of the 3-year DFS and whether the LNR facilitate selection of the most appropriate adjuvant chemotherapy regimen in patients with stage II or III gastric cancer who underwent curative D2 gastrectomy.

Materials and methods

Patient selection

Gastric cancer patients who underwent curative gastrectomy between April 2004 and June 2015 were identified using the database of Chonnam National University Hwasun Hospital. Data from these patients were collected from our institutional database and the survival data were updated at the time of analysis. The Institutional Review Board of Chonnam National University Medical School Research Institution approved the study. The inclusion criteria were as follows: stage II/III gastric adenocarcinoma according to the American Joint Committee on Cancer 7th edition, R0 resection, and D2 lymph-node dissection. Patients with metastatic disease and patients with microscopically (R1) or macroscopically (R2) tumor-positive disease were excluded. Patients who died or were lost to follow-up within 30 days after resection, and patients with missing data on lymph-node status were also excluded. LNR was evaluated as a categorical variable using the cut-off values suggested by Marchet et al. (2007, 2008).

Adjuvant chemotherapy

We administered adjuvant chemotherapy with TS-1 (Taiho Pharmaceutical, Tokyo, Japan), 5-fluorouracil (5-FU) plus cisplatin (FP) or Xelox according to physician judgment and patient preference. The dose of TS-1 was determined based on the body surface area (BSA). Patients received one of the following doses, divided into two, after meals daily: 80 mg for patients with a BSA < 1.25 m^2, 100 mg for those with a BSA of 1.25–1.49 m^2, and 120 mg for those with a BSA ≥ 1.50 m^2. TS-1 was administered for 4 weeks followed by a 2-week rest period. Treatment was continued for 1 year after surgery. The FP regimen was as follows: 5-FU (800 mg/m^2 per day) was administered by continuous intravenous infusion on days 1–5, and cisplatin (80 mg/m^2) was administered by intravenous infusion on day 1. The FP regimen was administered every 4 weeks for six cycles. The Xelox regimen was administered every 3 weeks for eight cycles, and consisted of capecitabine (1000 mg/m^2 twice daily on days 1–14) plus intravenous oxaliplatin (130 mg/m^2 on day 1). The management of adverse events and subsequent dose reductions of the chemotherapeutic agents followed the conventional protocol. Relative dose intensity was defined as the dose received divided by the planned dose for the scheduled total treatment cycles.

Follow-up

Abdomino-pelvic computed tomography (CT) was performed every 3 months during the first 2 years after surgery and every 6 months thereafter until 5 years after surgery to assess tumor recurrence. Physical examination, chest radiography, and measurements of carcinoembryonic antigen and carbohydrate antigen 19-9 tumor makers were performed every 3 months for the first 2 years after surgery, and every 6 months thereafter until 5 years after surgery. If clinical signs or symptoms suggested clinical recurrence or the development of a new gastric cancer, further investigation was performed to determine whether the patient was disease free.

Statistical analyses

DFS was defined as the time from the date of surgery to the date of recurrence or death, whichever occurred first. If neither event had occurred at the time of analysis, the patient was censored. Survival curves were estimated using the Kaplan–Meier method and DFS was compared using the log-rank test. Factors associated with DFS were identified by univariate and multivariate Cox proportional hazard regression models with hazard ratio (HR) and 95% confidence interval (CI). The statistical significance of differences was assessed using the Chi-square test or Fisher's exact test for categorical data and the *t* test or the Mann–Whitney *U* test for continuous data. Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org) software. All *P* values are two-sided, and $P < 0.05$ was considered indicative of statistical significance.

Results

Patient characteristics

The clinicopathological characteristics of the patients are listed in Tables 1 and 2. Compared to the TS-1 group, the platinum-based chemotherapy group (FP + Xelox) had more younger patients (age < 61 years, 60.1% vs. 40.1%), males (72.5% vs. 64.7%), poorly/un-differentiated tumor grades (72.0% vs. 64.4%), stage III gastric cancers (69.4% vs. 40.4%), and lymphovascular invasion positivity (LVI+) (63.5% vs. 53.9%). The platinum-based chemotherapy group included more patients with clinically aggressive cancer. A total of 353 patients received the platinum-based regimen, of whom 132 (37.4%) received Xelox and 221 (62.6%) received FP. All patients in the TS-1 group received TS-1. The median numbers of cycles of Xelox, FP, and TS-1 were eight (range 1–8; mean 7.253 ± 2.230), six (range 1–6; mean 5.37 ± 1.372), and eight (range 1–8; mean 7.127 ± 2.230), respectively.

Among the 466 patients who received TS-1, treatment was continued for at least 3 months in 424 patients (91.0%), at least 6 months in 401 (86.1%), at least 9 months in 375 (80.1%), and 12 months in 355 patients (76.2%). The dose of TS-1 was decreased in 155 of the 466 patients (33.3%) who received TS-1. Of the 355 patients who received TS-1 treatment for 12 months, the dose was decreased in 135 patients (38.0%). The delivered doses were slightly higher than those of the previous clinical trial (Sakuramoto et al. 2007).

101 patients (76.5%) assigned to the XELOX group received eight cycles as planned. 37 patients (28.0%) had capecitabine dose reductions, and 34 (25.8%) needed oxaliplatin dose reductions. The median relative dose intensity was 85% for capecitabine and 95% for oxaliplatin. The delivered dose intensities were similar to those of the previous study (Bang et al. 2012).

173 patients (78.3%) assigned to the FP group received six cycles as planned. 57 patients (25.8%) had 5-FU dose reductions, and 65 (29.4%) needed cisplatin dose reductions. The median relative dose intensity was 91% for 5-FU and 90% for cisplatin.

LNR

A median of 44 (interquartile range [IQR] 33–55) LNs was examined. LN metastasis was found in 78.6% ($n = 644$) of the patients, involving a median of three LNs (IQR 1–7). In LNR 1, a median of 44 LNs (IQR 34–55) were examined, and a median of one (IQR 0–3) was involved. In LNR 2, a median of 43 (IQR 33–55) were examined, and a median of seven (IQR 5–9) were involved. In LNR, 3 a median of 45 (IQR 32–55) were examined, and a median of 16 (IQR 12–24) were involved (Fig. 1). We investigated the clinical prognostic value of the LNR in terms of DFS. LNRs were initially divided into four categories according to Marchet et al. (2007, 2008) to enhance comparability with the previous studies (0, > 0–0.1, > 0.1–025, and > 0.25) (Fig. 2a) (Nitti et al. 2003; Marchet et al. 2007, 2008). However, the 0 and > 0–0.1 groups were merged as they had similar DFS rates; thus, the population was divided into three LNR groups (LNR 1, 0–0.1; LNR 2, > 0.1–0.25; LNR 3, > 0.25) (Fig. 2b). Most patients in the LNR 1 group had stage II gastric cancer (71.0%), whereas most patients in the LNR 2 and LNR 3 groups had stage III gastric cancer (LNR 2, 85.9%; LNR 3, 92.7%; Table 2). The frequency of lymphovascular invasion positivity increased with increasing LNR (LNR 1, 47.2%; LNR 2, 67.7%; LNR 3, 86.4%; $P < 0.001$; Table 2). The frequency of perineural invasion positivity (PNI+) was higher in the LNR 2 and 3 groups than in the LNR 1 group (LNR 1, 65.6%; LNR 2, 75.5%; LNR 3, 77.3%; $P = 0.0059$; Table 2).

Survival analyses

The median follow-up period was 51.6 months (range 1.5–135.1 months) in the entire population. The 3-year DFS rate of the entire population was 71.8%. The 3-year DFS rates of patients who received TS-1 ($n = 466$) and platinum-based chemotherapy ($n = 353$) were 72.3% and 71.0%, respectively. In total, there were 250 recurrences: 116 (14.2%) in the platinum group, 134 (16.4%) in the TS-1 group, 93 (11.4%) in the LNR 1 group, 87 (10.6%) in the LNR 2 group, and 70 (8.5%) in the LNR 3 group. The DFS curves of the entire population were well separated according to LNR and stage (both $P < 0.001$) (Fig. 2b, c). The

Table 1 Baseline characteristics of patients stratified by adjuvant chemotherapy ($n=819$)

Variables	Platinum group ($n=353$)	TS-1 ($n=466$)	P
Ages			
<61, *n* (%)	212 (60.1)	187 (40.1)	<0.001
≥61, *n* (%)	141 (39.9)	279 (59.9)	
Chemotherapy regimen			
Xelox	132 (37.4)	TS-1 (100)	
FP	221 (62.6)		
Sex			
Male, *n* (%)	256 (72.5)	302 (64.8)	0.019
Female, *n* (%)	97 (27.5)	164 (35.2)	
Tumor location			
GEJ, whole stomach	79 (22.4)	97 (20.8)	0.5896
Body, antrum	274 (77.6)	369 (79.2)	
Tumor grade			
Well/moderate differentiated	99 (28.0)	166 (35.6)	0.0218
Poorly/un-differentiated	254 (72.0)	300 (64.4)	
Lauren classification			
Intestinal	167 (47.3)	242 (51.9)	0.1904
Non-intestinal (diffuse or mixed)	186 (52.7)	224 (48.1)	
LNR			
0	41 (11.6)	134 (28.8)	<0.001
>0–0.1	133 (37.7)	181 (38.8)	
>0.1–0.25	122 (34.6)	98 (21.0)	
>0.25	57 (16.1)	53 (11.4)	
AJCC stage			
II	108 (30.6)	278 (59.6)	<0.001
III	245 (69.4)	188 (40.4)	
T stage			
T1	11 (3.1)	26 (5.6)	<0.001
T2	43 (12.2)	77 (16.5)	
T3	128 (36.3)	209 (44.8)	
T4	171 (48.4)	154 (33.0)	
N stage			
N0	41 (11.6)	134 (28.8)	<0.001
N1	73 (20.7)	121 (26.0)	
N2	104 (29.5)	116 (24.9)	
N3	135 (38.2)	95 (20.4)	
LVI+/LVI−	224 (63.5)/129 (36.5)	251 (53.9)/215 (46.1)	0.0059
PNI+/PNI−	254 (72.0)/99 (28.0)	318 (68.2)/148 (31.8)	0.2517

Xelox capecitabine plus oxaliplatin, *FP* 5-fluorouracil/cisplatin, *FU* fluorouracil, *GEJ* gastroesophageal junction, *LNR* lymph-node ratio, *LVI* lymphovascular invasion, *PNI* perineural invasion

median DFS values of LNR 1 and LNR 2 were not reached; however, that of the LNR 3 group was 21.60 months (95% CI 13.59–29.61). The 3-year DFS rate was 83.2% in the LNR 1 group, 63.4% in the LNR 2 group, and 36.8% in the LNR 3 group. The DFS curves were well separated according to LNR irrespective of adjuvant chemotherapy regimen and stage (platinum regimen $P<0.001$, TS-1 $P<0.001$, stage II $P=0.006$, and stage III $P<0.001$) (Fig. 3). There were no differences in DFS between platinum-based chemotherapy and TS-1 in patients in the LNR 1 and 2 groups (LNR 1 platinum vs. TS-1, $P=0.954$; LNR 2 platinum vs. TS-1, $P=0.722$). However, among patients in the LNR 3 group, platinum-based chemotherapy was associated with a trend of an increased DFS (platinum vs. TS-1, median DFS 26.87 months [95% CI 5.85–47.89] vs. 16.53 months [95% CI 10.26–22.81], $P=0.063$) (Fig. 4a). The 3-year DFS rate of patients with LNR 3 group was 47.0% in the platinum group and 23.7% in the TS-1 group (HR 0.642, 95% CI

Table 2 Baseline characteristics of patients stratified by LNR ($n=819$)

Variables	LNR			*P*
	0–0.1 ($n=489$)	>0.1–0.25 ($n=220$)	>0.25 ($n=110$)	
Ages				
<61, *n* (%)	245 (50.1)	108 (49.1)	46 (41.8)	0.2889
≥61, *n* (%)	244 (49.9)	112 (50.9)	64 (58.2)	
Chemotherapy regimen				
Platinum group	174 (35.6)	122 (55.5)	57 (51.8)	<0.001
TS-1	315 (64.4)	98 (44.5)	53 (48.2)	
Sex				
Male, *n* (%)	331 (67.7)	154 (70.0)	73 (66.4)	0.7572
Female, *n* (%)	158 (32.3)	66(30.0)	37 (33.6)	
Tumor location				
GEJ, whole stomach	120 (24.5)	26 (11.8)	30 (27.3)	<0.001
Body, antrum	369 (75.5)	194 (88.2)	80 (72.7)	
Tumor grade				
Well/moderate differentiated	170 (34.8)	68 (30.9)	27 (24.5)	0.1016
Poorly/un-differentiated	319 (65.2)	152 (69.1)	83 (75.5)	
Lauren classification				
Intestinal	250 (51.1)	111 (50.5)	48 (43.6)	0.3595
Non-intestinal (diffuse or mixed)	239 (48.9)	109 (49.5)	62 (56.4)	
AJCC stage				
II	347 (71.0)	31 (14.1)	8 (7.3)	<0.001
III	142 (29.0)	189 (85.9)	102 (92.7)	
T stage				
T1	16 (3.3)	15 (6.8)	6 (5.5)	<0.001
T2	85 (17.4)	24 (10.9)	11 (10.0)	
T3	221 (45.2)	87 (39.5)	29 (26.4)	
T4	167 (34.2)	94 (42.7)	64 (58.2)	
N stage				
N0	175 (35.8)	0 (0)	0 (0)	<0.001
N1	190 (38.9)	3 (1.4)	1 (0.9)	
N2	122 (24.9)	94 (42.7)	4 (3.6)	
N3	2 (0.4)	123 (55.9)	105 (95.5)	
LVI+/LVI−	231 (47.2)/258 (52.8)	149 (67.7)/71 (32.3)	95 (86.4)/15 (13.6)	<0.001
PNI+/PNI−	321 (65.6)/168 (34.4)	166 (75.5)/54 (24.5)	85 (77.3)/25 (22.7)	0.0059

LNR lymph-node ratio, *GEJ* gastroesophageal junction, *LVI* lymphovascular invasion, *PNI* perineural invasion

0.401–1.028, $P=0.065$) (Fig. 4e). In multivariate analyses, an LNR > 0.1, advanced T stage, advanced N stage, and LVI+ were significantly associated with a poor DFS (Table 3); of these, LNR > 0.1 showed the strongest association (HR 2.402, 95% CI 1.607–3.590, $P<0.001$). Platinum-based chemotherapy improved the DFS compared to TS-1 in patients with LNR 3 group in stage III gastric cancer (platinum vs. TS-1, median DFS 26.87 months [95% CI 6.27–47.47] vs. 16.27 months [95% CI 9.76–22.77], $P=0.028$) (Fig. 4b). The 3-year DFS rate of patients with LNR 3 group in stage III gastric cancer was 44.8% in the platinum group and 20.7% in the TS-1 group (HR 0.584, 95% CI 0.359–0.950, $P=0.030$) (Fig. 4e). An LNR > 0.1 was associated with benefitting from platinum-based adjuvant chemotherapy in patients with stage III gastric cancer and LVI+ (platinum vs. TS-1, median DFS 47.57 months [95% CI 15.05–80.08] vs. 21.77 months [95% CI 12.09–31.44], $P=0.011$) (Fig. 4c). The 3-year DFS rate of patients with stage III LVI+ gastric cancer and an LNR > 0.1 was 53.7% in the platinum group and 36.0% in the TS-1 group (HR 0.628, 95% CI 0.438–0.901, $P=0.012$) (Fig. 4e). In T4 cancer, LNR > 0.1 was marginally associated with benefitting from platinum-based adjuvant chemotherapy (platinum vs. TS-1, median DFS 41.80 months [95% CI 24.99–58.61] vs. 21.23 months [95% CI 13.98–28.49], $P=0.069$) (Fig. 4d). The 3-year DFS rate of patients with LNR > 0.1 in T4 cancer

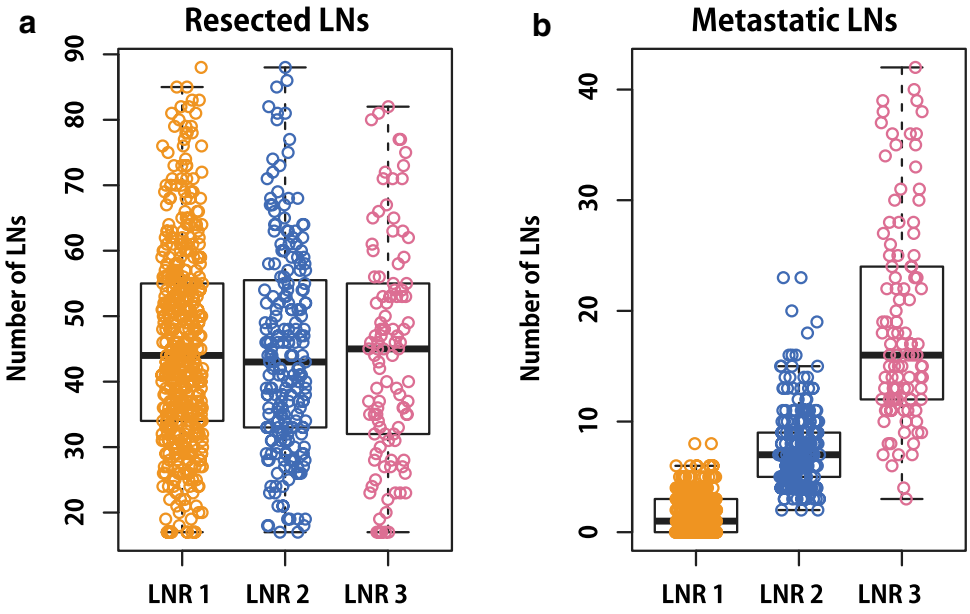

Fig. 1 Resected (**a**) and metastatic (**b**) LNs according to 3 LNR groups. A median of 44 (interquartile range [IQR] 33–55) LNs were examined, involving a median of three LNs (IQR 1–7)

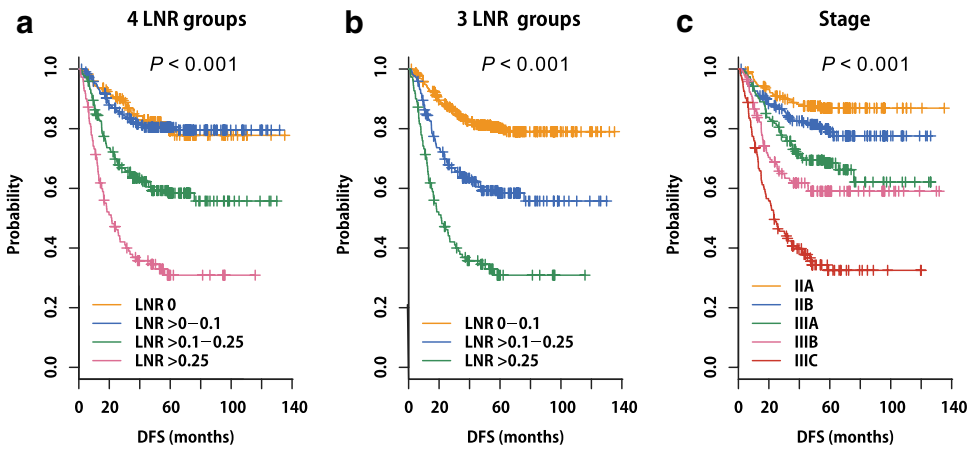

Fig. 2 **a** LNRs were initially divided into four categories (0, 0–0.1, > 0.1–025, and > 0.25). **b** However, the 0 and > 0–0.1 groups were merged as they had similar DFS rates; thus, the population was divided into three LNR groups (LNR 1, 0–0.1; LNR 2, > 0.1–0.25; LNR 3, > 0.25). **c** DFS curves of the entire population were well separated according to stage

was 51.4% in the platinum group and 34.5% in the TS-1 group (HR 0.688, 95% CI 0.459–1.033, $P = 0.071$) (Fig. 4e).

Discussion

The LNR is thought to be predictive of recurrence and prognosis in patients with gastric cancer (Nitti et al. 2003; Marchet et al. 2007; Bilici et al. 2010; Xiao et al. 2011; Costa et al. 2012; Wu et al. 2015). Costa et al. demonstrated that LNR is an independent poor prognostic factor for OS and DFS in patients with gastric cancer underwent gastrectomy and adjuvant chemoradiotherapy (Costa et al. 2012). Another study also showed that LNR is significantly associated with DFS in patients with gastric cancer underwent D2 resection and adjuvant chemoradiotherapy (Kim et al. 2016).

We investigated the clinical prognostic value of LNR in patients who underwent radical gastrectomy with D2 lymph-node dissection and adjuvant chemotherapy for gastric adenocarcinoma. The DFS curves were well separated according to LNR irrespective of adjuvant chemotherapy regimen and stage, especially even in the same stage III (Fig. 3, platinum regimen $P < 0.001$, TS-1 $P < 0.001$, stage II $P = 0.006$, and stage III $P < 0.001$). In multivariate analyses, an LNR > 0.1 was the most significant independent poor prognostic variable for DFS (HR 2.402, 95% CI 1.607–3.590, $P < 0.001$).

Gastric cancer, particularly stage III, frequently recurs, and therefore, postoperative adjuvant treatment is mandatory. The TS-1 and Xelox regimens show similar efficacies after radical D2 gastrectomy. The 3- and 5-year OS rates were 80.1% and 71.7% in the TS-1 trial, and the 3-year DFS and 5-year OS rates were 74% and 78% in the Xelox trial, respectively (Sakuramoto et al. 2007; Sasako et al. 2011; Bang et al. 2012; Noh et al. 2014). However, no prior randomized controlled trial has compared the two regimens. We

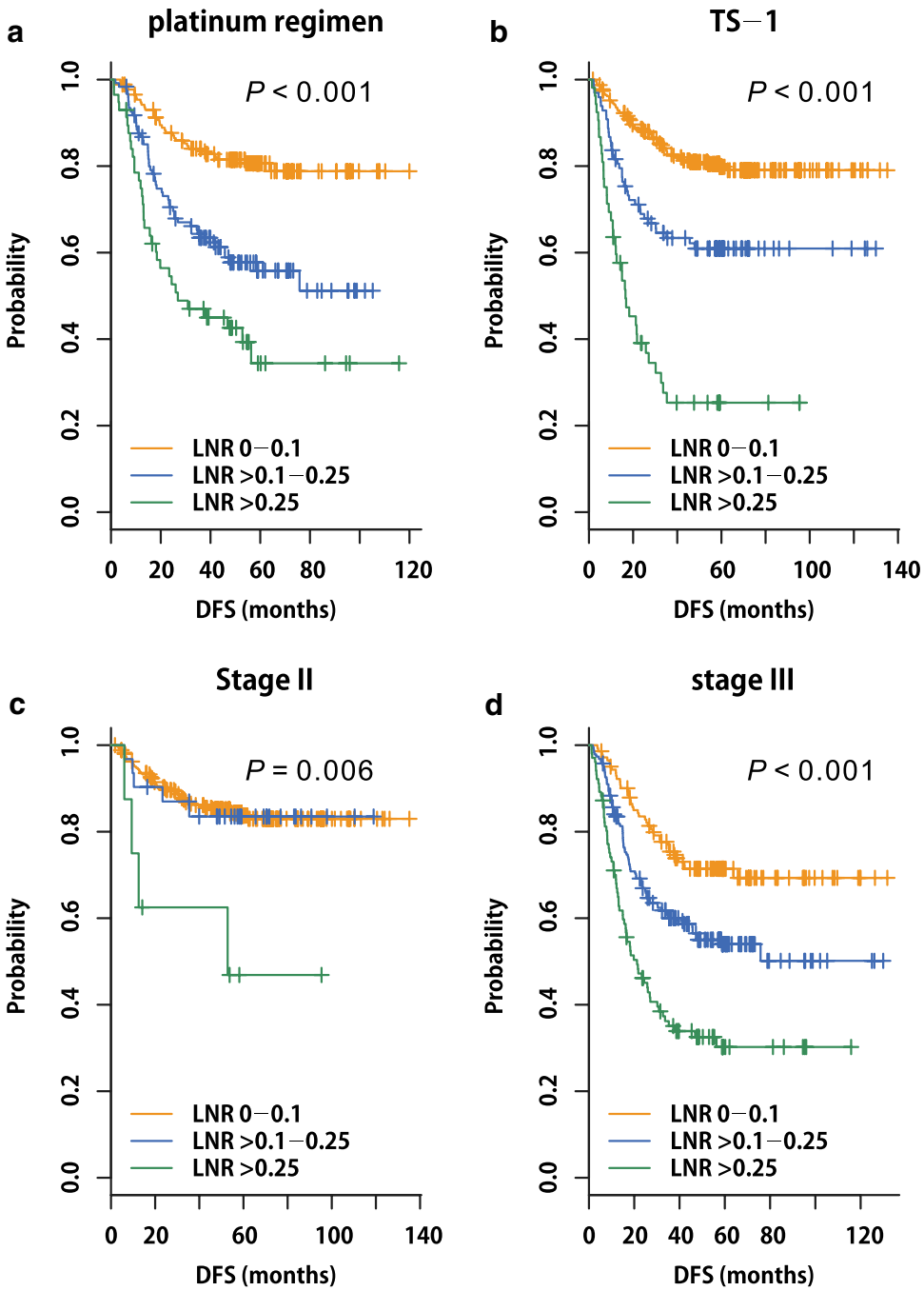

Fig. 3 DFS curves were well separated according to LNR irrespective of adjuvant chemotherapy regimen and stage

report here that patients with LNR 3 group in stage III gastric cancer ($P = 0.030$), and patients with stage III LVI + gastric cancer and an LNR > 0.1 derived the greatest benefit from platinum-based chemotherapy ($P = 0.012$) (Fig. 4e).

Platinum-based chemotherapy improved the DFS of patients with T4 gastric cancer and an LNR > 0.1, albeit not to a significant degree (platinum vs. TS-1, median DFS 41.80 months [95% CI 24.99–58.61] vs. 21.23 months [95% CI 13.98–28.49], $P = 0.069$) (Fig. 4d).

Surgeons are likely to resect a larger number of suspicious LNs during gastrectomy, which increases the likelihood of detecting metastatic LNs despite a lower LNR (Kim et al. 2016). In other words, the LNR is affected by the number of LNs resected. However, in this study, a large number of LNs was resected (median 44, IQR 33–55), and in spite of possibility of lower LNR, multivariate analyses showed that an LNR > 0.1 was independently associated with a poor prognosis (HR 2.402, 95% CI 1.607–3.590, $P < 0.001$). Marchet et al. reported that the LNR is an independent prognostic factor in gastric cancer irrespective of whether ≤ 15 or > 15 lymph nodes are resected (Marchet et al. 2007).

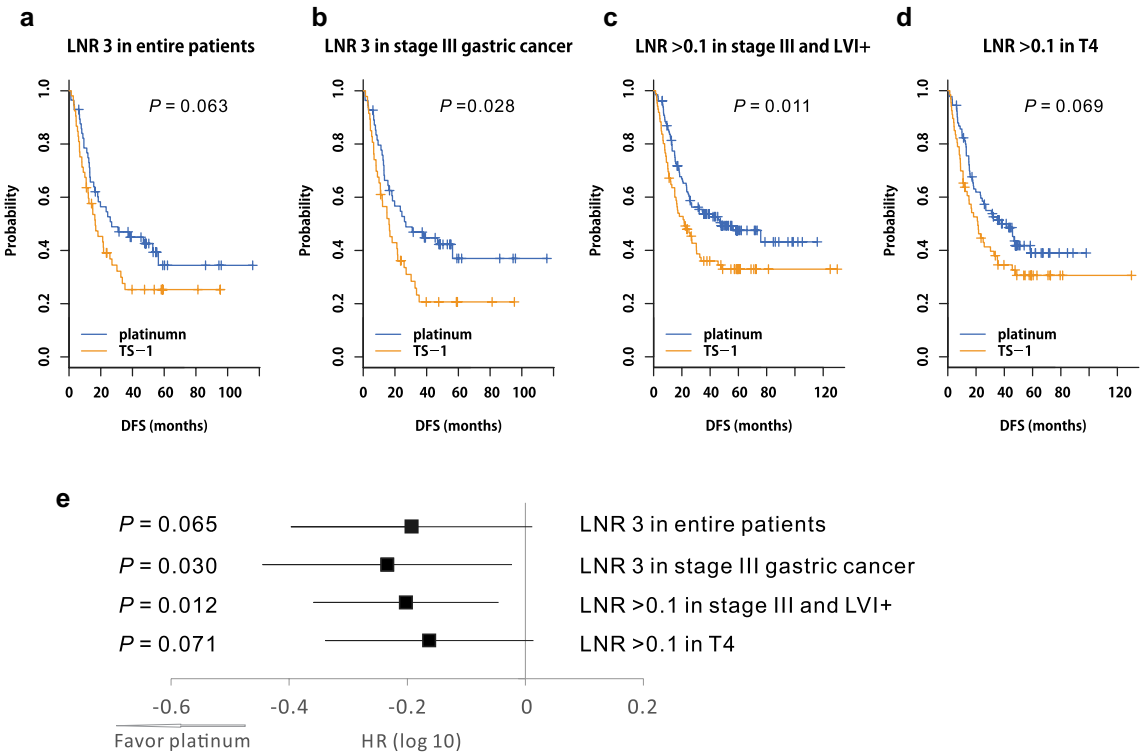

Fig. 4 **a** Platinum-based chemotherapy was associated with a trend of an increased DFS in LNR 3 group of entire patients ($P=0.063$). **b** Platinum-based chemotherapy improved the DFS compared to TS-1 in patients with LNR 3 group in stage III gastric cancer ($P=0.028$). **c** LNR > 0.1 was associated with benefitting from platinum-based adjuvant chemotherapy in patients with stage III gastric cancer and LVI + ($P=0.011$). **d** In T4 cancer, LNR > 0.1 was marginally associated with benefitting from platinum-based adjuvant chemotherapy ($P=0.069$). **e** Cox proportional hazard regression analysis estimating the benefit of platinum-based adjuvant chemotherapy according to LNR subgroups. The solid line represents the 95% CI of the HR

Table 3 Univariate and multivariate analyses of clinicopathological variables for DFS ($n=819$)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥ 62	1.266 (0.986–1.624)	0.063	1.257 (0.963–1.641)	0.093
Male	1.050 (0.804–1.371)	0.72		
Tumor location				
GEJ, whole stomach	1.250 (0.936–1.6668)	0.138		
Lauren classification				
Non-intestinal (diffuse or mixed)	1.158 (0.903–1.486)	0.246		
TS-1	0.864 (0.6674–1.108)	0.25		
LNR (> 0.1)	3.244 (2.508–4.196)	< 0.001	2.402 (1.607–3.590)	< 0.001
T3 + T4	2.448 (1.619–3.701)	< 0.001	2.075 (1.325–3.248)	0.001
N2 + N3	2.757 (2.080–3.653)	< 0.001	1.349 (0.870–2.092)	0.181
LVI+	1.901 (1.450–2.493)	< 0.001	1.516 (1.141–2.013)	0.004
PNI+	1.952 (1.428–2.667)	< 0.001	1.334 (0.950–1.872)	0.096

GEJ gastroesophageal junction, *LNR* lymph-node ratio, *LVI* lymphovascular invasion, *PNI* perineural invasion

A recent multicenter observational study in Korea demonstrated that Xelox is more beneficial than TS-1 for stages IIIB and IIIC, but not stage IIA, IIB, or IIIA, gastric cancer in terms of 3-year DFS (Kim et al. 2018). Therefore, the efficacy of platinum-based adjuvant chemotherapy increases as the number of metastatic LNs increases.

Using genomic and bioinformatics analyses, two recent studies identified adjuvant chemotherapy-resistant

subgroups. One study analyzed the genomic data of The Cancer Genome Atlas Project of gastric cancer and the other analyzed the RNA expression data of the CLASSIC trial (Cancer Genome Atlas Research Network 2014; Sohn et al. 2017; Cheong et al. 2018). The former showed that patients with the chromosomal-instability subtype of gastric cancer derived the greatest benefit from adjuvant chemotherapy, and those with the genomically stable subtype had the least benefit. The latter study also identified a group that did not benefit from adjuvant chemotherapy. In the genomic study of the CLASSIC trial, patients with advanced N stage (N1N2) gastric cancer benefited from adjuvant chemotherapy, whereas those with advanced T-stage (T3T4) cancer did not. The existence of chemotherapy resistance should be considered and a genomic approach could be used in future clinical trials of adjuvant therapies.

This study had some limitations. First, this was a retrospective analysis involving a single institution. We did not report the adverse events of the chemotherapy regimens; however, all regimens are widely used in the clinical setting, and all toxicities were manageable and did not differ from those previously reported. We did not assess OS, but DFS in gastric cancer is an acceptable surrogate endpoint in trials of adjuvant chemotherapy (Deng et al. 2011; Oba et al. 2013). This study enrolled only Korean patients who underwent radical D2 gastrectomy followed by adjuvant chemotherapy. The gastric cancer treatment modalities used in Eastern and Western countries could be different and the effects of radiation and perioperative treatment were not evaluated (Smyth et al. 2016).

In conclusion, LNR is an important clinical prognostic factor for selecting the appropriate adjuvant chemotherapy regimen in patients with D2-resected gastric cancer, particularly in stage III.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board at Chonnam National University Hwasun Hospital in Jeonnam, Korea, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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