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ORIGINAL ARTICLE **CME**

Treatment Outcomes of Stage II or III Gastric Cancer Treated with Adjuvant Chemotherapy with TS-1 or XELOX after Radical Surgery

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ABSTRACT

Introduction: *Capecitabine plus oxaliplatin (XELOX) and tegafur/gimeracil/oteracil (TS-1, also known as 'S-1') are two commonly used adjuvant chemotherapy regimens for gastric cancer in Hong Kong. This study aimed to review the outcomes of patients receiving these two regimens, to investigate important clinical factors that may impact on the risk of disease recurrence, and to explore the roles of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio (PLR) in prognostication after radical surgery.*

Methods: *Patients who received adjuvant treatment (either XELOX or TS-1) for gastric cancer following radical surgical resection from January 2016 to December 2020 at our hospital were included. Patient demographics, overall survival (OS), and disease-free survival (DFS) were analysed.*

Results: *A total of 65 patients were included (XELOX: n = 40; TS-1: n = 25). XELOX appeared to have more favourable OS and DFS, although the result was confounded by older and frailer patients in the TS-1 group. An elevated PLR was associated with inferior OS after surgery (p = 0.036). Cox regression analysis showed that Eastern Cooperative Oncology Group (ECOG) performance status score of 2 and nodal stage of N2 to N3 were two independent factors associated with inferior OS. ECOG performance status score of 2, nodal stage of N2 to N3, and chemotherapy dose intensity <70% were significantly associated with a higher risk of relapse.*

Conclusion: *Poorer ECOG performance status and more advanced nodal stage are independent factors associated with inferior OS and DFS, and lower chemotherapy dose intensity (<70%) resulted in a higher risk of disease relapse. NLR and PLR is a simple clinical marker that may be further explored as a prognostic marker for gastric cancer after radical surgery.*

Key Words: *Blood platelets; Lymphocytes; Neutrophils; Prognosis; Stomach neoplasms*

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Data Availability: All data generated or analysed during the present research are available from the corresponding author on reasonable request.

Ethics Approval: This research has been approved by the Hong Kong East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref. No.: HKECREC-2022-021) and was conducted in compliance with the Declaration of Helsinki. The requirement for patient consent was waived by the Committee due to the retrospective nature of the study.

中文摘要

根治性手術後使用TS-1或XELOX輔助化療治療II期或III期胃癌的治療結果

蘇駿寅、李建忠、王晉彥

簡介：卡培他濱聯合奧沙利鉑（XELOX）及替加氟／吉美嘧啶／氧嗪酸（TS-1，又稱S-1）是香港兩種常用於胃癌的輔助化療方案。本研究旨在回顧接受這兩種方案的病人的結果，調查可能影響疾病復發風險的重要臨床因素，以及研究在根治性手術後嗜中性白血球與淋巴細胞比例（NLR）及血小板與淋巴細胞比例（PLR）在預測方面的角色。

方法：本研究包括於2016年1月至2020年12月期間在本院進行根治性手術切除後接受輔助治療（XELOX或TS-1）的胃癌病人，並分析了有關患者的人口特徵、整體存活及無疾病存活。

結果：本研究共包括65名患者（XELOX：n = 40；TS-1：n = 25）。雖然XELOX的整體存活及無疾病存活似乎較好，但這些結果受TS-1組別中年紀較大及較虛弱的患者影響。血小板與淋巴細胞比例上升與較差的術後整體存活相關（p = 0.036）。Cox迴歸分析顯示美國東岸癌症臨床研究合作組織（ECOG）身體功能狀態評分為2分及癌症分期為N2至N3，是與較差的整體存活相關的兩個獨立因素。ECOG身體功能狀態評分為2分、癌症分期為N2至N3及化療劑量強度<70%與較高復發風險顯著相關。

結論：較差的ECOG身體功能狀態及較晚期的癌症分期是與較差的整體存活及無疾病存活相關的獨立因素，而較低的化療劑量強度<70%造成較高的疾病復發風險。NLR和PLR是簡單的臨床標記，可成為日後的研究方向，以此比例作為根治性手術後胃癌的預後標記。

INTRODUCTION

Gastric cancer was the sixth commonest cancer in Hong Kong, accounting for 3.7% of all new cancer cases in 2019.[1] Although the incidence has been gradually declining, compatible with global trends due to efficacious *Helicobacter pylori* eradication therapy,[2] gastric cancer remains more prevalent in Asian countries than in the West.

Clear surgical resection with D2 lymphadenectomy and chemotherapy is considered the standard of care for resectable locoregionally advanced gastric cancer nowadays,[3] and this has been advocated in several international guidelines.[4,5] Adjuvant chemoradiotherapy (45 Gy over 25 fractions concurrent with 5-fluorouracil and leucovorin) had once been widely adopted, but was later criticised for the inclusion of a high proportion of patients with D1 lymphadenectomy in the study recommending it.[6]

The choice of chemotherapy regimen significantly differs among different parts of the world. In European countries, perioperative chemotherapy, such as the combination of epirubicin, cisplatin, and 5-fluorouracil[7] or 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel,[8] is frequently used, whereas in Hong Kong, clinicians tend to use adjuvant chemotherapy as in most Asian countries. The two most commonly used regimens of adjuvant chemotherapy after radical surgery are capecitabine plus oxaliplatin (XELOX) and tegafur/gimeracil/oteracil (TS-1, also known as 'S-1'). They both demonstrated significant benefits when compared with surgery alone in randomised clinical trials[9,10] conducted in Asian countries. Despite the two regimens having been widely used, there are no prospective randomised clinical trials directly comparing their efficacy.

Regarding the prognostic stratification of patients with resected gastric cancer, several clinical and pathological parameters have long been adopted to predict the recurrence of gastric cancer including age, comorbidities, tumour size, differentiation status, and presence of lymphovascular or perineural invasion.[11-14] In recent years, the clinical utility of the peripheral neutrophil-

to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as systemic inflammatory markers has been addressed. In relation to cancer prognosis, several meta-analyses showed that elevated NLR and PLR correlated with tumour progression and poor survival in a number of gastrointestinal cancers.[15,16] However, what the same observation connotes in the adjuvant setting remains uncertain.

This retrospective study was conducted with three aims: to compare the efficacy of adjuvant XELOX with TS-1 chemotherapy for patients with stage II or III gastric cancer who received radical surgery in our locality; to investigate important clinical factors that may impact on the risk of disease recurrence; and to explore the prognostic value of NLR and PLR as potentially useful and easily available clinical parameters.

METHODS

Patients and Data Collection

Patients who received adjuvant treatment (XELOX: n = 40; TS-1: n = 25) for gastric cancer following radical surgical resection from January 2016 to December 2020 at the Department of Clinical Oncology, Pamela Youde Eastern Hospital, Hong Kong were included in the study. Patients with metastatic disease at presentation (including small-volume peritoneal metastasis) or double primary cancers were excluded. Patients who received adjuvant radiotherapy were also excluded. Relevant clinical and pathological parameters were captured from clinical notes and the Clinical Management System of Hospital Authority.

Treatment

XELOX consists of oral capecitabine (1000 mg/m^2 twice daily on days 1-14 of each cycle) plus intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle) up to 8 cycles. TS-1 is oral chemotherapy (daily dose according to body surface area [BSA]: patients with BSA <1.25 m^2 received 80 mg daily, those BSA ranging from ≤1.25 m^2 to 1.50 m^2 received 100 mg daily, and those with BSA ≥1.50 m^2 received 120 mg daily) given for 4 weeks followed by 2 weeks of rest for a total of 9 cycles.

In practice, patients of an advanced age, borderline Eastern Cooperative Oncology Group (ECOG) performance status and pre-existing neuropathy would be more likely to be given TS-1, as it is a non–self-financed item under the institution.

Doses and schedule modifications were conducted based on patients' ECOG performance status, organ functions, and toxicities by clinicians' decisions. Dose reduction of chemotherapy was conducted in a stepwise manner (75%-85% of the initial dose for 1st dose reduction, then 60%-70% for the 2nd dose reduction). The relative total dose intensity (RTDI) is the ratio of the delivered actual dose intensity (ATDI) to the standard planned dose intensity (PTDI) for a chemotherapy regimen, which is calculated as follows:

$$\text{RTDI (\%)} = \frac{\text{ATDI}}{\text{PTDI}} \times 100$$

$$\text{PTDI (mg/week)} = \frac{\text{Planned total dose (mg)}}{\text{Planned duration of therapy (weeks)}}$$

$$\text{ATDI (mg/week)} = \frac{\text{Actual total dose (mg)}}{\text{Duration of therapy (weeks)}}$$

Follow-up and Assessment

Patients were seen by doctors prior to each cycle of chemotherapy, when tolerance of chemotherapy and results of blood tests would be recorded in the Clinical Management System. Patients who had completed the adjuvant chemotherapy would be followed up at an interval of 3 to 6 months. Computed tomography was performed if there was clinical suspicion of disease relapse. Disease relapse was defined as any radiological and/or histological confirmation of recurrence. Elevated tumour markers alone were not considered as relapse without proof of recurrent disease.

Statistical Analysis

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], United States). Clinical and pathological data were retrospectively reviewed and analysed by descriptive statistics. Pearson's Chi squared test was used for testing any significant correlations and differences between groups.

Treatment outcomes, including disease-free survival (DFS, the time from surgery to disease relapse) and overall survival (OS, the time from diagnosis of disease to death from any cause) were analysed by the Kaplan-Meier method and the difference between groups were tested with the log-rank test. Different clinical parameters were tested for their impact on DFS and OS by Cox regression analysis.

In order to have an accurate assessment of the baseline NLR and PLR of our patients, the complete blood counts right before the administration of first cycle

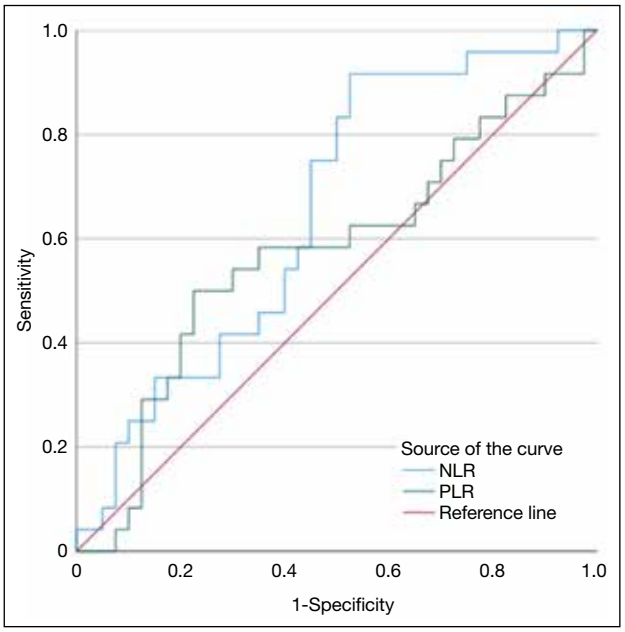

Figure 1. Receiver operating curve (ROC) analysis for optimal cut-off values of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

of chemotherapy were recorded. This is to minimise the effect due to postoperative inflammation and chemotherapy on peripheral blood counts.

Using all-cause mortality as an endpoint for NLR and PLR, the optimal cut-off values were determined by receiver operating curve analysis as shown in Figure 1. The area under the curve of NLR and PLR was 0.653 and 0.575, respectively. The optimal cut-off values determined by the Youden's index for NLR and PLR were 1.9 and 169, respectively.

RESULTS

Patient Characteristics

Sixty-five patients were identified and included in the analysis. Forty patients received XELOX and 25 received TS-1. The median follow-up time for this study was 33.7 months (range, 6.5-78.9).

Patient baseline characteristics are summarised in Table 1. The median age of the entire cohort was 66.0 years. The mean and median age in the XELOX group were 57.7 and 59.0 years respectively, compared to 69.4 and 71.0 years in the TS-1 group. Patients who received TS-1 were significantly older, with 72.0% of them ≥66 years compared to 37.5% in XELOX group (p = 0.007).

Table 1. Patient baseline characteristics of XELOX and TS-1 groups.*

	XELOX group (n = 40)	TS-1 group (n = 25)	p Value (Pearson's Chi squared)
Sex			
Male	25 (62.5%)	15 (60.0%)	0.840
Female	15 (37.5%)	10 (40.0%)	0.840
Age, y			
<66	25 (62.5%)	7 (28.0%)	0.007
≥66	15 (37.5%)	18 (72.0%)	0.007
Mean (median)	57.7 (59.0)	69.4 (71.0)	
ECOG performance status score			
0-1	39 (97.5%)	15 (60.0%)	< 0.001
2	1 (2.5%)	10 (40.0%)	< 0.001
Pretreatment PET			
No	25 (62.5%)	16 (64.0%)	0.903
Yes	15 (37.5%)	9 (36.0%)	0.903
Histology			
Well or moderately differentiated	12 (30.0%)	12 (48.0%)	0.165
Poorly differentiated	27 (67.5%)	13 (52.0%)	0.165
Others	1 (2.5%)	0	0.165
Tumour stage			
T1	2 (5.0%)	0	0.809
T2	6 (15.0%)	2 (8.0%)	0.809
T3	17 (42.5%)	12 (48.0%)	0.809
T4	15 (37.5%)	11 (44.0%)	0.809
Nodal stage			
N0	7 (17.5%)	2 (8.0%)	0.198
N1	6 (15.0%)	9 (36.0%)	0.198
N2	7 (17.5%)	5 (20.0%)	0.198
N3	20 (50.0%)	9 (36.0%)	0.198
Overall stage (AJCC 8th edition)			
IIA	8 (20.0%)	2 (8.0%)	0.380
IIB	6 (15.0%)	8 (32.0%)	0.380
IIIA	7 (17.5%)	5 (20.0%)	0.380
IIIB	12 (30.0%)	5 (20.0%)	0.380
IIIC	7 (17.5%)	5 (20.0%)	0.380
Lymphovascular invasion			
Present	28 (70.0%)	17 (68.0%)	0.822
Absent	9 (22.5%)	5 (20.0%)	0.822
Unknown	3 (7.5%)	3 (12.0%)	0.822
Perineural invasion			
Present	21 (52.5%)	15 (60.0%)	0.571
Absent	16 (40.0%)	7 (28.0%)	0.571
Unknown	3 (7.5%)	3 (12.0%)	0.571
Extent of nodal dissection			
D1	2 (5.0%)	3 (12.0%)	0.240
D1 plus	3 (7.5%)	0	0.240
D2	35 (87.5%)	22 (88.0%)	0.240
Pattern of relapse			
No. of cases	27	22	
Local relapse	1 (2.5%)	2 (8.0%)	0.271
Nodal relapse	9 (22.5%)	6 (24.0%)	0.220
Distant relapse	10 (25.0%)	7 (28.0%)	0.222
Peritoneal relapse	7 (17.5%)	7 (28.0%)	0.339

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography; TS-1 = tegafur/gimeracil/oteracil; XELOX = capecitabine plus oxaliplatin.
* Data are shown as No. (%), unless otherwise specified.

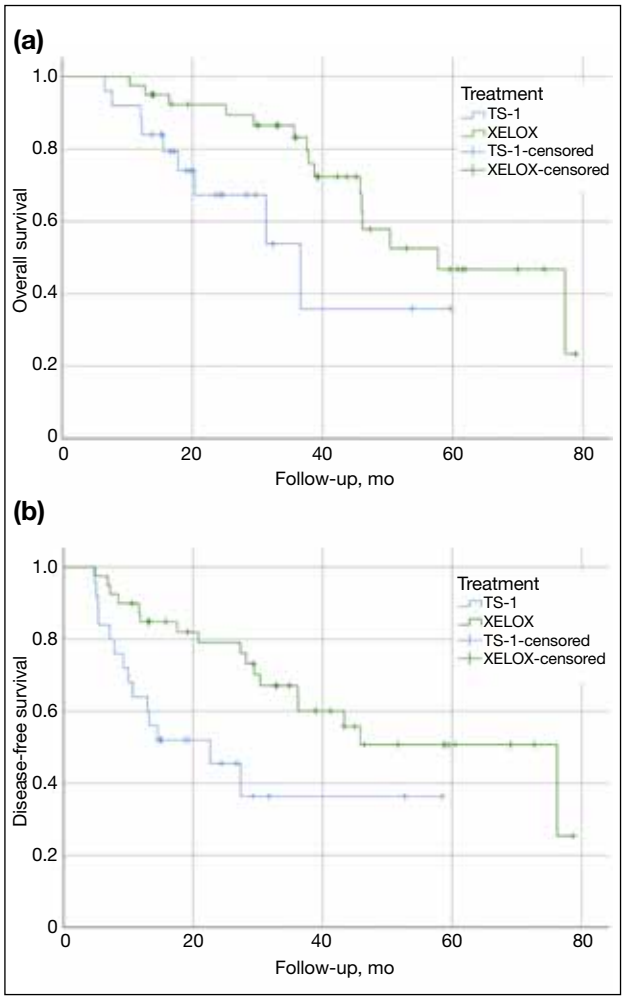

Figure 2. Kaplan-Meier analysis of (a) overall survival (p = 0.037, log-rank test) and (b) disease-free survival (p = 0.012, log-rank test) in all patients with respect to treatment with TS-1 (tegafur/gimeracil/oteracil) or XELOX (capecitabine plus oxaliplatin).

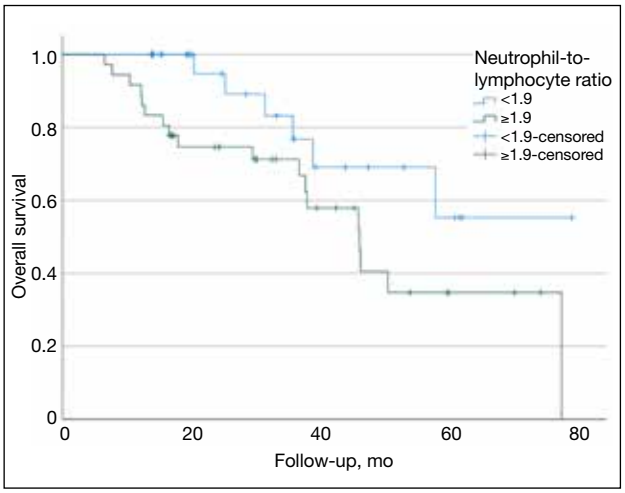

Figure 3. High neutrophil-to-lymphocyte ratio (≥1.9) versus low neutrophil-to lymphocyte-ratio (<1.9) on overall survival (p = 0.051).

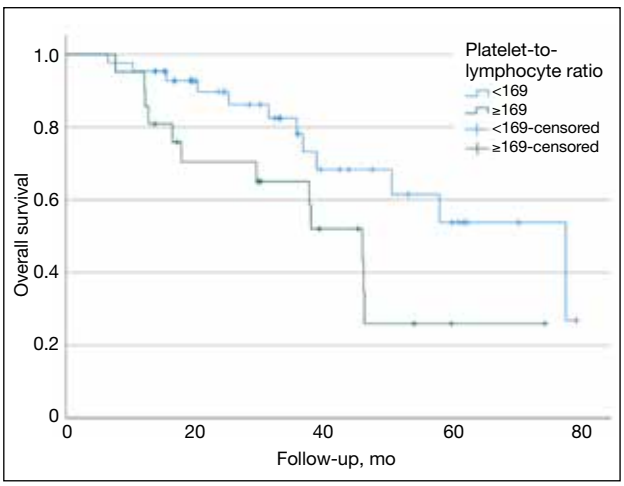

Figure 4. High platelet-to-lymphocyte ratio (≥169) versus low platelet-to-lymphocyte ratio (<169) on overall survival (p = 0.036).

All included patients had an ECOG performance status score of ≤2. There were significantly more patients with ECOG performance status score ≤1 in the XELOX group (97.5%) than in TS-1 group (60.0%) [p < 0.001].

Overall and Disease-Free Survival

The median OS was 38.9 months for the XELOX group and 22.9 months for TS-1 group. The observed OS and DFS in the XELOX group were significantly longer than those in the TS-1 group (Figure 2) [p = 0.037 and 0.012, respectively]. However, it should be interpreted carefully as the baseline patients' characteristics suggested a bias towards prescribing TS-1 in the older age-group and less fit patients. These factors likely confound the survival analysis.

Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio

Overall survival analysis showed that patients with high NLR (≥1.9) before adjuvant chemotherapy had shorter OS than those with low NLR (<1.9), although the difference was marginally significant (p = 0.051; Figure 3). The same analysis also demonstrated that patients with high PLR (≥169) before adjuvant chemotherapy had significantly shorter OS than those with low PLR (<169) [p = 0.036; Figure 4].

In relation to clinical characteristics, patients with elevated NLR correlated with female gender (borderline

Table 2. Clinical characteristics of patients with high and low neutrophil-to-lymphocyte ratio.*

	High NLR (n = 36)	Low NLR (n = 29)	p Value (Pearson's Chi squared
Sex			
Male	26 (72.2%)	14 (48.3%)	0.049
Female	10 (27.8%)	15 (51.7%)	0.049
Age, y			
<66	18 (50.0%)	14 (48.3%)	0.890
≥66	18 (50.0%)	15 (51.7%)	0.890
ECOG performance status score			
0-1	30 (83.3%)	24 (82.8%)	0.951
2	6 (16.7%)	5 (17.2%)	0.951
Histology			
Well or moderately differentiated	11 (30.6%)	13 (44.8%)	0.229
Poorly differentiated	25 (69.4%)	15 (51.7%)	0.229
Others	0	1 (3.5%)	0.229
Overall stage (AJCC 8th edition)			
II	12 (33.3%)	12 (41.4%)	0.303
III	24 (66.7%)	17 (58.6%)	0.303
Lymphovascular invasion			
Present	28 (77.8%)	17 (58.6%)	0.232
Absent	6 (16.7%)	8 (27.6%)	0.232
Unknown	2 (5.6%)	4 (13.8%)	0.232
Perineural invasion			
Present	23 (63.9%)	13 (44.8%)	0.251
Absent	11 (30.6%)	12 (41.4%)	0.251
Unknown	2 (5.6%)	4 (13.8%)	0.251
Treatment received			
XELOX	21 (58.3%)	19 (65.5%)	0.554
TS-1	15 (41.7%)	10 (34.5%)	0.554

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; NLR = neutrophil-to-lymphocyte ratio; TS-1 = tegafur/gimeracil/oteracil; XELOX = capecitabine plus oxaliplatin.
* Data are shown as No. (%), unless otherwise specified.

Table 3. Clinical characteristics of patients with high and low platelet-to-lymphocyte ratio.*†

	High PLR (n = 21)	Low PLR (n = 43)	p Value (Pearson's Chi squared)
Sex			
Male	15 (71.4%)	24 (55.8%)	0.229
Female	6 (28.6%)	19 (44.2%)	0.229
Age, y			
<66	12 (57.1%)	19 (44.2%)	0.330
≥66	9 (42.9%)	24 (55.8%)	0.330
ECOG performance status score			
0-1	17 (81.0%)	36 (83.7%)	0.783
2	4 (19.0%)	7 (16.3%)	0.783
Histology			
Well or moderately differentiated	6 (28.6%)	17 (39.5%)	0.507
Poorly differentiated	15 (71.4%)	25 (58.1%)	0.507
Others	0	1 (2.3%)	0.507
Overall stage (AJCC 8th edition)			
II	3 (14.3%)	20 (46.5%)	0.012
III	18 (85.7%)	23 (53.5%)	0.012
Lymphovascular invasion			
Present	17 (81.0%)	28 (65.1%)	0.412
Absent	3 (14.3%)	10 (23.3%)	0.412
Unknown	1 (4.8%)	5 (11.6%)	0.412
Perineural invasion			
Present	13 (61.9%)	22 (51.2%)	0.587
Absent	7 (33.3%)	16 (37.2%)	0.587
Unknown	1 (4.8%)	5 (11.6%)	0.587
Treatment received			
XELOX	14 (66.7%)	25 (58.1%)	0.512
TS-1	7 (33.3%)	18 (41.9%)	0.512

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; PLR = platelet-to-lymphocyte ratio; TS-1 = tegafur/gimeracil/oteracil; XELOX = capecitabine plus oxaliplatin.
* Data are shown as No. (%), unless otherwise specified.
† Missing data = 1 (one patient has platelet clumped).

p value of 0.049) and elevated PLR was associated with more advanced disease (p = 0.012) [Tables 2 and 3].

Clinical and Pathological Parameters on Overall Survival and Disease-Free Survival

As shown in Table 4, univariate Cox regression analysis showed that ECOG performance status score of 2, nodal stage of N2 to N3, and elevated PLR (≥169) were adverse prognostic factors for OS, while ECOG performance status score of 2, nodal stage of N2 to N3, and RTDI of chemotherapy <70% were adverse factors associated with disease relapse.

Multivariable Cox regression analysis demonstrated that ECOG performance status score of 2 and nodal stage of N2 to N3 were the two independent adverse prognostic factors for OS (Table 4). For DFS, ECOG performance status score of 2, nodal stage of N2 to N3, and RTDI of chemotherapy <70% were the three independent factors associated with disease relapse (Table 5).

DISCUSSION

Our study revealed that the XELOX group had more favourable oncological outcomes (both DFS and OS) than the TS-1 group. However, it should be noted that patients included in the TS-1 group in out centre were older (p = 0.007) and of worse ECOG performance status (p < 0.001). This is largely due to the fact that the institutional guideline recommends TS-1 as the treatment of choice for older patients with anticipated

Table 4. Cox regression analysis on multiple clinical and pathological parameters on overall survival.

Variable	Univariate		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, y (<66, ≥66)	1.166 (0.520-2.612)	0.71		
Sex (male, female)	0.886 (0.375-2.092)	0.783		
ECOG performance status score (0-1, 2)	3.218 (1.143-9.061)	0.027	4.817 (1.509-15.38)	0.008
Histology (differentiated, poorly differentiated)	2.261 (0.836-6.115)	0.108		
Lymphovascular invasion (No, Yes)	0.442 (0.130-1.506)	0.192		
Perineural invasion (No, Yes)	0.676 (0.275-1.661)	0.393		
Tumour stage (T1-T2 vs T3-T4)	1.062 (0.353-3.197)	0.915		
Nodal stage (N0-N1 vs N2-N3)	8.337 (1.952-35.60)	0.004	9.473 (2.114-42.45)	0.003
NLR (<1.9, ≥1.9)	2.437 (0.966-6.147)	0.059		
PLR (<169, ≥169)	2.348 (1.031-5.346)	0.042	1.738 (0.759-3.979)	0.191
Relative total dose intensity (≤70% vs <70%)	1.873 (0.838-4.188)	0.126		

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

Table 5. Cox regression analysis on multiple clinical and pathological parameters on disease-free survival.

Variable	Univariate		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, y (<66, ≥66)	1.416 (0.693-2.894)	0.34		
Sex (male, female)	0.607 (0.278-1.325)	0.21		
ECOG performance status score (0-1, 2)	2.780 (1.157-6.676)	0.022	3.288 (1.297-8.337)	0.012
Histology (differentiated, poorly differentiated)	1.985 (0.850-4.633)	0.113		
Lymphovascular invasion (No, Yes)	0.529 (0.200-1.397)	0.198		
Perineural invasion (No, Yes)	0.531 (0.234-1.206)	0.131		
Tumour stage (T1-T2 vs T3-T4)	1.445 (0.496-4.209)	0.500		
Nodal stage (N0-N1 vs N2-N3)	3.798 (1.454-9.925)	0.006	3.136 (1.180-8.330)	0.022
NLR (<1.9, ≥1.9)	2.129 (0.980-4.627)	0.056		
PLR (<169, ≥169)	1.962 (0.957-4.024)	0.066		
Relative total dose intensity (≤70% vs <70%)	3.383 (1.650-6.935)	0.001	2.936 (1.405-6.138)	0.004

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

poor tolerance to XELOX and that under such circumstances, only the drug costs of TS-1 would be covered by the institution. There has not been any randomised controlled trial comparing the efficacy of the two regimens. Retrospective studies[17-20] did not demonstrate statistically significant differences in DFS between adjuvant TS-1 and XELOX (Table 6). In the subgroup analysis, one study[17] demonstrated the use of XELOX in stage II disease was associated with better OS while another study[18] suggested the same but in stage IIIB/C disease only. Apart from XELOX, combination chemotherapy with more than three agents has shown superior treatment outcomes in recent years. Combination of TS-1 with oxaliplatin[21] or docetaxel[22] is considered a preferred option for high-risk patients and is increasingly recognised as a new standard of care.

In our cohort, elevated PLR is associated with inferior OS after curative surgery and there was a similar trend for NLR despite not reaching statistical significance (p = 0.051). NLR and PLR are important parameters indicating systemic inflammation. It is observed that a chronic inflammatory state confers unfavourable oncological outcomes.[23] Several meta-analyses revealed that elevated NLR and PLR were associated with tumour progression and poor survival in gastrointestinal cancers.[15,16] Microscopically, various inflammatory cytokines and growth factors in the tumour microenvironment are known to dampen hosts' anti-tumour immune response. In tumour models, inflammatory cytokines such as interleukin 6 (IL-6), IL-8 and IL-11 are associated with chemotherapy resistance in gastric cancer through mechanisms such as inhibition of apoptosis pathways, increasing efflux of chemotherapeutic agents, and evasion of DNA damage.[24-26] We therefore postulated that in an adjuvant setting, the persistent inflammatory state after curative surgery possibly led to tumour evasion from immunosurveillance and enhanced chemoresistance

Table 6. Summary of selected retrospective studies comparing XELOX and TS-1 regimens.

	Inclusion criteria	No. of eligible patients	Place of study	Outcomes
Oh et al[17]	• Stage II/III gastric cancer • R0 resection • D2 dissection	1461 (TS-1: n = 825; XELOX: n = 636)	Korea	OS/DFS: No statistically significant difference in DFS OS differs for stages IIA (p = 0.024) and IIB (p = 0.015) Prognostic factor(s): XELOX vs TS-1: HR = 0.47; 95% CI = 0.25-0.89; p = 0.021 in stage II only
Kim et al[18]	• Stage II/III gastric cancer • R0 resection • D2 dissection	1088 (TS-1: n = 846; XELOX: n = 242)	Korea	OS/DFS: No difference in DFS Inferior OS for TS-1 for stages IIIB (65.8% vs 68.6%; p = 0.019) and IIIC (48.4% vs 66.7%; p = 0.002) compared to XELOX
Cho et al[19]	• Stage III gastric cancer • R0 resection • D2 dissection	206 (TS-1: n = 92; XELOX: n = 114)	Korea	OS/DFS: No statistically significant difference in OS and DFS Prognostic factor(s): Nodal stage (HR = 5.639; 95% CI = 1.297-24.522; p = 0.021) and cycle completion (HR = 5.734; 95% CI = 3.007-10.936; p < 0.001) are independent predictors of OS
Lee et al[20]	• Stage II/III gastric cancer • R0 resection • D2 dissection	584 (TS-1: n = 429; XELOX: n = 155)*	Korea	OS/DFS: No statistically significant difference in DFS Prognostic factor(s): Tumour stage (T4 vs T1: HR = 11.667; 95% CI = 1.595-85.351; p = 0.016), nodal stage (N0 vs N3: HR = 2.788; 95% CI = 1.502-5.174; p = 0.001), and completion of chemotherapy (HR = 2.213; 95% CI = 1.618-3.028; p < 0.001) are independent prognostic factors of DFS

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; TS-1 = tegafur/gimeracil/oteracil; XELOX = capecitabine plus oxaliplatin.
* Propensity score–matched.

of micrometastases.[27] NLR and PLR are two readily accessible clinical parameters and may serve as simple prognostic tools in addition to performance status, stage, and age.

Our study revealed that the RTDI is an independent prognostic factor for disease recurrence. Inadequate chemotherapy dose intensity is either attributed to excessive dose reduction or failure to complete scheduled cycles within the planned time interval. It is noteworthy that severe adverse events of chemotherapy (≥ Grade 3) have been shown to be quite uncommon (≤6%) with TS-1 in a large-scale clinical trial,[28] although these patients were generally frailer and older. For elderly patients who may be more vulnerable to chemotherapy toxicity, proper geriatric assessments (such as comorbidity and frailty indices) are needed, as biological age is not a reliable indicator for chemotherapy dose adjustment, and an adaptive dose optimisation approach is recommended based on patients' tolerance of each cycle.

This study has several limitations. First, it is only a single-centre retrospective study in which the small sample size limits its statistical power. Second, there is imbalance between the baseline characteristics of the two groups of patients. Similar to the Korean studies,[17-20] patients in the TS-1 group were generally older and had a worse ECOG performance status. There is a tendency for clinicians to prescribe a more conservative chemotherapy dosage in this group of patients, which may explain the lower dose intensity of TS-1 than XELOX. Propensity score matching should be performed in a larger cohort to reduce the bias due to these confounding variables. Third, a much large sample size is needed to further evaluate the prognostic power of NLR and PLR on OS and DFS in the adjuvant setting. In our cohort, high PLR appeared to correlate with patients with more advanced disease (stage III), which is an important confounding factor.

CONCLUSION

In conclusion, we compared the OS and DFS between adjuvant XELOX and TS-1 in our local gastric cancer patients. Clinical outcomes were statistically better with XELOX- than TS-1–treated patients. However, the results should be viewed with caution because of the limited sample size and obvious imbalance in baseline characteristics. ECOG performance status score of 2

and advanced nodal stage of N2 to N3 are independent adverse prognostic factors associated with poor OS and a higher rate of disease recurrence. NLR and PLR are readily available markers that may be further explored as prognostic markers for gastric cancer after radical surgery. We also speculated that the RTDI of chemotherapy of <70% might affect the risk of disease relapse.

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