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Research Article

Adjuvant Chemotherapy Versus Adjuvant Chemoradiation (CRT) for Gastric Cancer: 16 Years of Local Experience

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ABSTRACT

Background: There is little consensus for the choice of adjuvant therapy for gastric cancer. This study aimed to compare treatment outcomes and toxicities of adjuvant capecitabine-oxaliplatin (XELOX) with adjuvant chemoradiation (CRT).

Methods: Patients with resected gastric cancer stage IIA to IIIC disease treated between January 2004 and July 2018 were analysed retrospectively. Patients were treated with XELOX for eight cycles or CRT. For CRT, 5 cycles of 5-fluorouracil (5FU)/leucovorin with 45 Gy in 25 fractions radiotherapy (RT) concurrent with cycles 2 and 3 were given. Relapse-free survival (RFS) and overall survival (OS) were used to compare the effect of adjuvant chemotherapy and CRT. Acute toxicities and the pattern of relapse were also analysed.

Results: 120 patients were included. 52 patients were treated with XELOX, and 68 patients were treated with CRT. Univariate analysis resulted in a five-year OS of 66% for XELOX, as compared with 48% for CRT (HR 0.706, 95% CI 0.413-1.208, p=0.202). The five-year RFS was 58% for XELOX, and 43% for CRT (HR 0.708, 95% CI 0.424-1.183, p= 0.185). On multivariate analysis, both RFS and OS favored XELOX: RFS HR 0.51 (95% CI 0.29-0.87), p=0.014; OS HR 0.45 (95% CI 0.25-0.81), p=0.007 when XELOX was compared with CRT. Patterns of failure were similar in the two groups, with distant metastases being most common. Acute toxicity grade 3/4 was seen in 42% of patients for XELOX, as compared to 65% of patients for CRT (p=0.015). Neutropenia ≥ grade 3 was more frequent in the CRT group (60% vs 21%; p <0.001).

Background

Gastric cancer is the sixth most common cancer in Hong Kong [1]. Radical gastrectomy is the primary treatment for gastric cancer. However, surgery alone achieves a poor 5-year overall survival rate of 20-35% only [2, 3]. Various adjuvant therapies have been explored in the treatment of gastric cancer. Randomized trials and meta-analyses indicated a significant survival benefit over surgery alone for several approaches, including adjuvant CRT, perioperative chemotherapy, and post-operative chemotherapy [4-14]. Despite all these efforts, there is no universal consensus established and the optimal strategy remains undefined.

In the past, our institute adopted CRT as the adjuvant treatment after radical resection of gastric cancer. But with emerging evidence from various adjuvant chemotherapy trials and wider adoption of D2 dissection, we shifted our practice towards chemotherapy alone [9, 10, 13]. Since March 2012, adjuvant XELOX became our institute's practice. This study aimed to compare patients receiving adjuvant XELOX with CRT regarding the treatment outcomes, toxicity profile, and pattern of failure.

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Methods

In this retrospective study, eligibility criteria included all patients with resected gastric cancer stage IIA to IIIC disease treated with radical intent between January 2004 and July 2018, with Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate major organ function. Patients with R1 and R2 resections were excluded. Patients with metastatic disease detected preoperatively or intra-operatively were excluded. In total 120 patients were included in this study.

I Chemotherapy and Chemoradiation

Patients were treated with either adjuvant CRT or adjuvant chemotherapy. The CRT group received concurrent 5FU/leucovorin chemotherapy (first, fourth, and fifth cycle using 5FU 425mg/m^2 and folinic acid 20mg/m^2 for 5 days; second cycle using 5FU 400mg/m^2 and folinic acid 20mg/m^2 for 4 days, and third cycle using 5FU 400mg/m^2 and folinic acid 20mg/m^2 for 3 days) with radiotherapy 45Gy/25 fractions given concurrently with the 2nd and 3rd cycles of chemotherapy, as per Intergroup 0116. Dose modification was standardized such that a 20% dose reduction was applied if stomatitis or diarrhea was grade two or if the absolute neutrophil count (ANC) was between 0.5 and <1.0; and a 30% dose reduction was applied in patients with grade 3 stomatitis/diarrhea or an ANC of less than 0.5.

All patients received CRT using CT planning. CT images with 3-5 mm slide thickness were acquired from the whole lung to L5. The target volumes including the gastric remnant, anastomosis, porta hepatis, splenic hilum, duodenal stump, and the regional lymph nodes were delineated. The radiation dose was 45 Gy in 25 fractions over 5 weeks. Organs at risk, including the spinal cord, kidneys, liver, and heart were also contoured. Dose-volume histograms (DVHs) of the organs at risk (OAR) were evaluated to ensure that their doses were within tolerance (less than 70% of one functioning kidney exposed to 20 Gy; 60% of the volume of liver exposed to 30 Gy; maximum spinal cord dose 45 Gy; 30% of the volume of whole heart received a dose of 40 Gy). H2 blocker was recommended for patients with subtotal gastrectomy.

Patients treated between March 2012 and July 2018 were treated using XELOX for 8 cycles (capecitabine 2000 mg/m2/day in 2 divided doses per day, on day 1 to 14; and oxaliplatin 130mg/m2 on day 1, every 3 weeks). Dose modification was standardized such that a 25% dose reduction of capecitabine and oxaliplatin was applied in patients with calculated creatinine clearance between 30-50ml/min, grade 3 toxicities, or more than 2 weeks of chemotherapy delay due to any toxicity. A 25% dose reduction to capecitabine alone is applied in patients with grade 2 or above hand-foot syndrome.

Patients were reviewed at regular interval during radiotherapy and chemotherapy period. Patients who underwent CRT were followed up at 2- and 8-weeks post-treatment for toxicity assessment. All patients were followed up every 3-4 months in the first 1-2 years, then every 6 months up to 5 years, then annually. During each visit, a thorough history taking and physical examination were done. Progress imaging and/or endoscopy were arranged upon clinician's discretion.

II Data Analysis

The primary endpoints were relapse-free survival (RFS) and overall survival (OS). The secondary endpoints were acute toxicities and the pattern of relapse. The stages were analysed by both TNM 6th and 7th edition. OS was calculated from the date of definitive surgery until death from any cause, and RFS was calculated from the date of definitive surgery to documented tumor progression or death from any cause. Patients alive at the time of the study report were censored. Survival data was determined by the Kaplan-Meier method, with SPSS V.26.0 (SPSS, Chicago, IL, USA). To compare the difference between 2 groups, Mann-Whitney U test (continuous variables) is used. If categorical variables are analysed, Chi-Square test and Fisher Exact test were used for comparative analyses. Comparison between survival of the two groups were determined using the log-rank test and Cox regression. All p-values were two-sided. Date and site(s) of first relapse were also collected. Toxicities were scored using the Common Toxicity Criteria for Adverse Events (CTCAE v4.0).

III Patient Characteristics

A total of 120 patients were included. All received curative resection. The median age was 60 years (31-79 years) and the male to female ratio was 2:1. 61 patients (51%) had D2 dissection, and 7 patients (6%) had D1 dissection. However, in 52 medical records (43%), the extent of nodal dissection was not specified. 68 patients received adjuvant CRT, and 52 patients received adjuvant XELOX. Most patients had unfavorable prognostic features, including poorly differentiated tumors (63% in CRT arm, 73% in XELOX arm), T3 or 4 primary tumors (86% in CRT arm, 81% in XELOX arm) and nodal involvement (93% in CRT arm, 92% in chemotherapy arm). The patient characteristics were balanced between the two groups, except for T stage (p=0.002 using the TNM 7th edition, and p=0.006 using the TNM 6th edition). Baseline demographic information is summarized in (Table 1).

Table 1: Baseline demographic data.

	XELOX (N=52)	**CRT (N=68)**	**p-value**
Age	62 (range 31-78)	60 (range 31-79)	p =0.506
Sex			p =0.969
Male	35 (67.3%)	46 (67.6%)	
Female	17 (32.7%)	22 (32.4%)	
Surgery type			p = 0.762
Partial gastrectomy	31 (59.6%)	37 (54.4%)	
Total gastrectomy	21 (40.4%)	31 (45.6%)	
Tumor grade			p = 0.124
Well differentiated	0 (0%)	2 (2.9%)	
Mod. Differentiated	14 (26.9%)	18 (26.5%)	
Poorly differentiated	38 (73.1%)	43 (63.2%)	
Not stated	0 (0%)	5 (7.4%)	
Nodal dissection			p = 0.29
D1	2 (3.8%)	5 (7.4%)	
D2	26 (50.0%)	35 (51.5%)	
Not specified	24 (46.2%)	28 (41.2%)	
T stage (6th ed.)			p =0.006
1	5 (9.6%)	2 (2.9%)	
2	17 (32.7%)	42 (61.8%)	

3	28 (53.8%)	21 (30.9%)	
4	2 (3.8%)	3 (4.4%)	
T stage (7th ed.)			*p* =0.002
1	5 (9.6%)	2 (2.9%)	
2	5 (9.6%)	8 (11.8%)	
3	15 (28.8%)	37 (54.4%)	
4a	27 (51.9%)	17 (25.0%)	
4b	0 (0%)	4 (5.9%)	
N stage (6th ed.)			*p* = 0.909
0	4 (7.7%)	4 (5.9%)	
1	24 (46.2%)	35 (51.5%)	
2	15 (28.8%)	17 (25%)	
3	9 (17.3%)	12 (17.6%)	
N stage (7th ed.)			*p* =0.811
0	4 (7.7%)	5 (7.4%)	
1	12 (23.1%)	21 (30.9%)	
2	12 (23.1%)	13 (19.1%)	
3	24 (46.2%)	29 (42.6%)	

Results

I Survival and Relapse

The median follow-up was 3.9 years (0.5 to 16.4). The 3-year OS of the whole cohort is 67.6% and the 5-year OS is 55.4%. The 3-year RFS is 59.1% and the 5-year RFS is 49.6% (Figures 1 & 2). On univariate analysis, the 3-year and 5-year OS of XELOX group is 77.9% and 66.2% respectively; and the 3-year and 5-year OS of the CRT group is 59.7% and 47.6% respectively, HR 0.706 (95%CI 0.413-1.208), *p*=0.202 (Figure 3). The RFS showed a similar trend favouring XELOX: the 3-year and 5-year RFS of the XELOX group is 68.2% and 58.4% respectively; and 52.3% and 43.1% for the CRT group respectively, HR 0.708 (CI 0.424-1.183), *p*=0.185 (Figure 4). On multivariate analysis, after adjusting for age, sex, T and N stage, the XELOX group demonstrated superiority to the CRT group in RFS, with HR 0.51 (95%CI 0.29-0.87), *p*=0.014, and OS with HR 0.45 (95%CI 0.25-0.81), *p*=0.007 (Table 2).

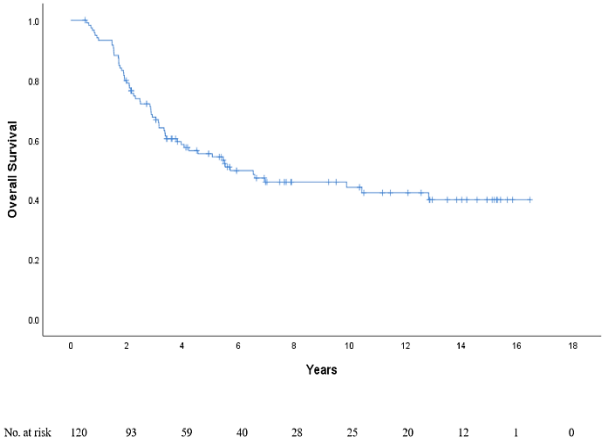

Figure 1: Overall survival of all patients (N= 120). The 3-year OS is 67.6% and the 5-year is OS is 55.4%.

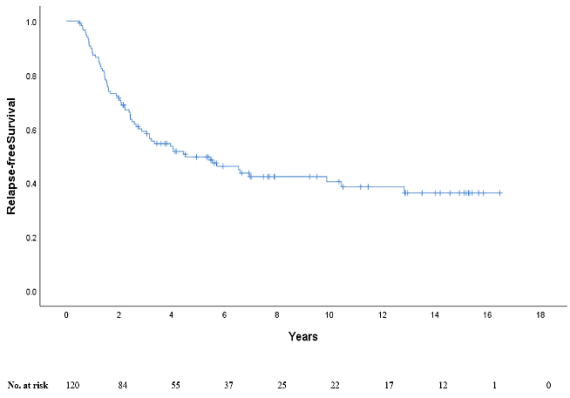

Figure 2: Relapse-free survival of all patients (N=120). The 3-year RFS is 59.1%, and the 5-year RFS is 49.6%.

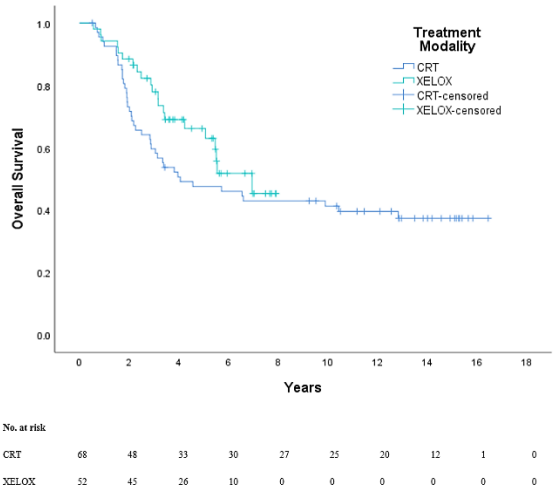

Figure 3: Overall survival of adjuvant XELOX vs adjuvant CRT. The 3-year OS for XELOX and CRT are 77.9% and 59.7% respectively. The 5-year OS for XELOX and CRT are 66.2% and 47.6% respectively. HR 0.706 (95% CI 0.413-1.208), p=0.202.

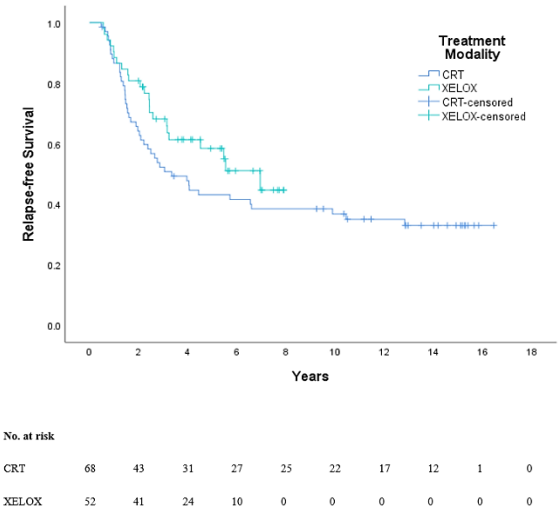

Figure 4: Relapse free survival of adjuvant XELOX and adjuvant CRT. The 3-year RFS for XELOX and CRT are 68.2% and 52.3% respectively. The 5-year RFS for are XELOX and CRT are 58.4% and 43.1% respectively. HR 0.708 (95% CI 0.424-1.183), p=0.185.

Table 2: Multivariate analysis by Cox regression model.

	RFS		**OS**	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age	1.37 (0.80-2.35)		1.27 (0.73-2.22)	
< 60 vs. ≥ 60		0.255		0.403
Gender				
Male vs. Female	1.63 (0.93-2.83)	0.086	1.62 (0.91-2.89)	0.102
T stage (7th Ed)				
T1-2 vs. T4	0.35 (0.15-0.81)	0.014	0.38 (0.17-0.89)	0.026
T3 vs. T4	0.43 (0.23-0.78)	0.005	0.35 (0.19-0.66)	0.001
N stage (7th Ed)				
N0 vs. N3	0.19 (0.05-0.64)	0.008	0.18 (0.05-0.62)	0.007
N1 vs. N3	0.52 (0.27-1.02)	0.057	0.45 (0.22-0.91)	0.027
N2 vs. N3	0.70 (0.37-1.31)	0.263	0.68 (0.35-1.30)	0.244
Treatment modality				
XELOX vs CRT	0.51 (0.29-0.87)	0.014	0.45 (0.25-0.81)	0.007

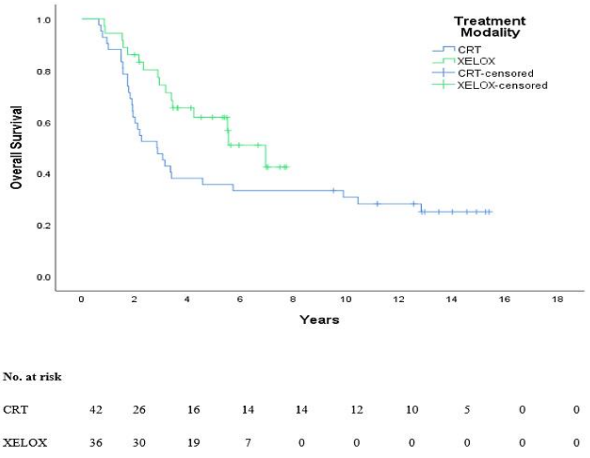

Figure 5: Overall survival of N2 and N3 subgroup (N=78): XELOX vs CRT. The 3-year OS for XELOX and CRT are 74.3% and 47.6% respectively. HR 0.547, (95%CI 0.295-1.015), p=0.05.

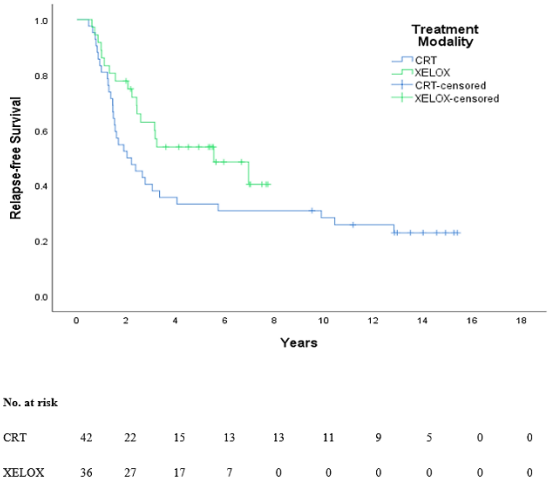

Figure 6: Relapse-free survival of N2 and N3 subgroup (N=78): XELOX vs CRT. The 3-year RFS for XELOX and CRT are 62.9% and 40.5% respectively. HR 0.615, 95%CI 0.341-1.111, p=0.104.

Further exploratory analyses were done to see if patients with different degree of nodal metastases would benefit from XELOX or CRT. In the subgroup with N2/N3 patients (78 patients), adjuvant XELOX trended towards superiority in overall survival compared to CRT with a 3-year OS of 74.3% and 47.6% respectively, HR 0.547(95%CI 0.295-1.015), *p*=0.05. The 3-yr RFS is for XELOX and CRT are 62.9% and 40.5% respectively, with HR 0.615 (95%CI 0.341-1.111), p-value 0.104 (Figures 5 & 6).

Among patients with N0 or N1 (42 patients), there was no difference detected in survival between adjuvant XELOX compared with CRT. The 3-year RFS were 80.2% and 72.0% respectively, HR 0.84 (95%CI 0.293-2.41), *p*=0.790. The 3-year OS were 86.5% and 80.0% respectively, HR 1.116 (95%CI 0.376-3.315), p-value 0.843 (Figures 7 & 8).

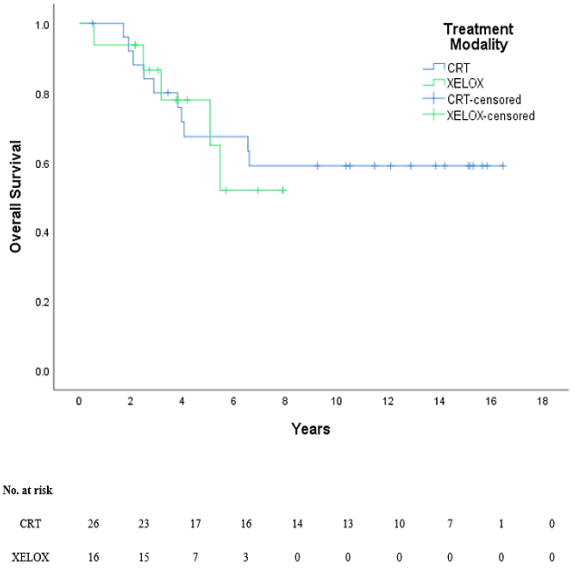

Figure 7: Overall survival of N0/N1 subgroup (N=42): XELOX vs CRT. The 3-year OS for XELOX and CRT are 86.5% and 80.0% respectively. HR 1.116 (95%CI 0.376-3.315), p=0.843.

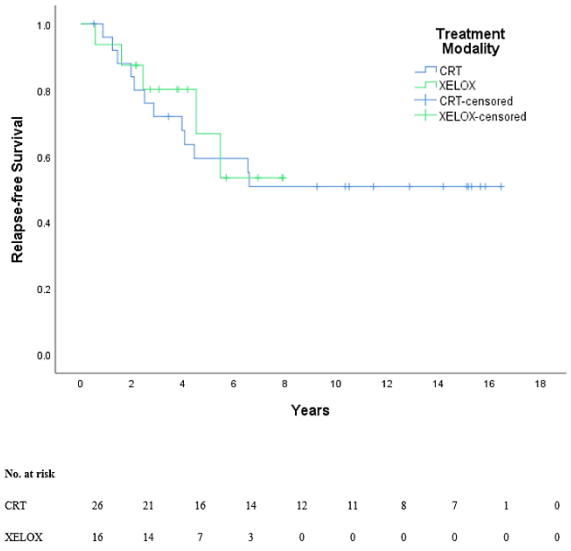

Figure 8: Relapse-free survival of N0/N1 subgroup (N=42): XELOX vs CRT. The 3-year RFS for XELOX and CRT are 80.2% and 72.0% respectively. HR 0.840 (95%CI 0.293-2.41), p=0.746.

II Pattern of Failure

The pattern of disease recurrence was also analysed. By the time of analysis, 35% of patients in the XELOX group and 43% in the CRT group developed recurrence. The majority of recurrences involved distant metastases, with no significant difference detected among the two cohorts (83% for XELOX, 97% for CRT, p=0.150). Recurrences that involved locoregional recurrences were less common, and no significant difference was detected between the two cohorts (44% for XELOX and 52% for CRT, p= 0.627) (Table 3).

Table 3: Patterns of the first site(s) of disease recurrence.

Total number of patients with recurrence	**XELOX N=18**	**CRT N=29**	**p-value (Fisher's exact test)**
Distant recurrence N (%)	15 (83%)	28 (97%)	0.15
Locoregional recurrence N (%)	8 (44%)	15 (52%)	0.627

Table 4: Sites of recurrence among patients with distant failure (N = 43).

Metastatic site	**XELOX N=15 N (%)**	**CRT N=28 N (%)**
Peritoneal / ascites	10 (67%)	15 (54%)
Liver	4 (27%)	8 (29%)
Lung	0 (0%)	5 (18%)
Bone	0 (0%)	5 (18%)
Subcutaneous	3 (20%)	2 (7%)
Miscellaneous	3 (20%)	1 (4%)

Among patients with distant failure, peritoneal metastasis/ascites were the most common in both groups (67% for XELOX, 54% for CRT), followed by liver metastases (27% for XELOX, 29% for CRT). Lung and bone metastases were also seen in 18% of relapses within the CRT group, but these were not detected in the XELOX. Other less common sites of metastases included distant lymph nodes, subcutaneous, pancreas, and colon (Table 4).

III Toxicity

In the adjuvant XELOX cohort, 9 patients (17%) did not complete the planned chemotherapy cycles. 43 patients (83%) required chemotherapy dose adjustment. The median chemotherapy dosage was 75%. In the CRT cohort, 12 patients (18%) did not complete the planned 5 cycles of chemotherapy cycles with bolus 5FU/leucovorin. 55 patients (81%) required chemotherapy dose reduction. The median chemotherapy dosage used in patients was 72% (Table 5). CRT resulted in a slightly higher rate of grade 3 and grade 4 toxicity.

Table 5: Summary of the chemotherapy compliance and dose adjustment information.

	XELOX (N = 52)	**CRT (N = 68)**	**p-value**
Incomplete chemotherapy	9 (17%)	12 (18%)	0.961
Chemotherapy dose reduction	43 (83%)	55 (81%)	0.800

The overall documented rates of grade 3 or greater toxicity were 42% and 65% in the XELOX and CRT cohorts respectively (Table 6); Grade 4 toxicity was 4% and 19% respectively in the two cohorts (Table 7). The most common side effect in CRT treated patients was neutropenia. 60% of patients had Grade 3 and 19% of patients had grade 4 toxicity. This was much higher than patients treated with XELOX (p <0.001 for grade 3 or above). There was no grade 3 or above neuropathy in the XELOX arm. Other grade 3/4 toxicities included anemia, vomiting, and diarrhea. No significant difference was observed between the two cohorts. There were no toxicity-related deaths.

Table 6: Comparing Grade 3 or 4 toxicities between XELOX and CRT.

	XELOX n=52	**CRT n=68**	**p-value**
Anemia	1 (1.9%)	3 (4.4%)	0.632
Thrombocytopenia	3 (5.8%)	0 (0.0%)	0.081
Neutropenia	11 (21.2%)	41 (60.3%)	<0.001
Vomiting	4 (7.7%)	3 (4.4%)	0.465
Diarrhea	5 (9.6%)	6 (8.8%)	1.000
Stomatitis	0 (0.0%)	0 (0.0%)	n/a
Hand-foot syndrome	0 (0.0%)	0 (0.0%)	n/a
Neuropathy	0 (0.0%)	0 (0.0%)	n/a
Others	2 (3.8%)	2 (3.0%)	1.000
Any G3/4 haematological toxicity	12 (23.1%)	41 (60.3%)	<0.001
Any G3/4 GI* toxicity	7 (13.5%)	7 (10.3%)	0.592
Any G3/4 toxicity	22 (42.3%)	44 (64.7%)	0.015

*GI: gastrointestinal

Table 7: Comparing Grade 4 toxicities between XELOX and CRT.

	XELOX n=52	**CRT n=68**	**p-value**
Anemia	1 (1.9%)	0 (0.0%)	0.433
Thrombocytopenia	0 (0.0%)	0 (0.0%)	n/a
Neutropenia	1 (1.9%)	13 (19.1%)	0.003
Vomiting	0 (0.0%)	0 (0.0%)	n/a

Diarrhea	0 (0.0%)	0 (0.0%)	n/a
Stomatitis	0 (0.0%)	0 (0.0%)	n/a
Hand-foot syndrome	0 (0.0%)	0 (0.0%)	n/a
Neuropathy	0 (0.0%)	0 (0.0%)	n/a
Others	0 (0.0%)	1 (1.5%)	1.000
Any G4 haematological toxicity	2 (3.8%)	13 (19.1%)	0.012
Any G4 GI toxicity	0 (0.0%)	0 (0.0%)	n/a
Any G4 toxicities	2 (3.8%)	13 (19.1%)	0.012

Discussion

Gastric cancer is the 4th leading cause of death in Hong Kong [1]. While surgery with R0 resection is the only curative treatment, the 5-year survival rate with surgery alone remains poor at 20-35% [2, 3]. To improve treatment outcomes, a combined modality approach is crucial. Yet, a unified consensus on treatment recommendations is lacking from international guidelines [15, 16].

The North American Intergroup-0116 trial is the landmark study that demonstrated the role of adjuvant chemoradiotherapy in addition to radical gastrectomy. Post-operative bolus 5-FU/leucovorin plus conventionally fractionated radiotherapy (45 Gy in 25 fractions) resulted in improved 3-year OS (50% vs 41%) and 3-year RFS (48% vs 31%) compared with surgery alone [7]. After 10 years of follow-up, the OS and PFS improvement remain significant [8]. This treatment approach is currently the standard therapy in the United States. However, it has not gained worldwide acceptance due to concerns about potential late toxicity and the quality of surgery and radiotherapy within the trial: only 10% of patients received D2 dissection, more than 30% of the radiotherapy plans had significant errors and 30% of patients did not complete CRT. Chang *et al*. have demonstrated that CT planning was a favorable predictor of survival as it enabled optimal coverage of target structures and minimized dose to OAR [17]. Also, whether adjuvant CRT is beneficial for patients with adequate surgery and extended lymphadenectomy remains unresolved. Retrospective data from the D1D2 Dutch trial demonstrated that CRT reduced local recurrence for patients who received D1 dissection but showed no benefit for D2 dissected patients [18].

The overall 3-year OS (67.6%) and 3-year PFS (59.1%) achieved in our CRT cohort appear better than the Intergroup result. This might be explained by the fact that more of our patients (49%) had D2 dissection and the use of CT planning in the whole cohort.

The acceptance of adjuvant chemotherapy in Europe and the United States for patients with resected gastric cancer remains limited due to a perceived lack of benefit and routine use of perioperative chemotherapy or adjuvant CRT. However, a meta-analysis of adjuvant chemotherapy including 17 randomized trials has confirmed a 6% absolute 5-year overall survival benefit for 5-FU-based chemotherapy, compared with surgery alone with a hazard ratio of 0.82, p< 0.001 [6]. In particular, the phase III CLASSIC trial demonstrated survival benefit for post-operative chemotherapy (oxaliplatin and capecitabine) after curative D2 lymph node dissection in patients with stage II-IIIB gastric cancer, with an improved 5-year OS (78% v 69%) and 5-year RFS (68% v 53%) compared with surgery alone [10, 13]. In our XELOX cohort, the 5-year OS was 66.2% and the 5-year PFS was 58.4% respectively. The seeming inferiority of our result may be due to baseline demographic differences in patient cohorts: unlike the CLASSIC trial, we included patients with Stage IIIC disease (TNM 7th T4bN2-3 or T4aN3) and only 50% of our patients had D2 dissection. The remaining 4% patients had D1 dissection, and 46% had unknown status.

Both adjuvant CRT and chemotherapy showed promising results in improving overall survival as compared to surgery alone. Several prospective randomized trials had compared the outcomes of these two approaches. Yet they yielded inconsistent results. Kim *et al.* showed in a prospective phase III trial that adding concurrent RT to adjuvant 5FU/leucovorin in patients treated with R0 gastrectomy and D2 dissection led to significantly better locoregional recurrence-free survival (HR 0.21, p=0.007), but no improvement in disease-free survival (HR 0.76, p=0.29) [19]. The ARTIST trial also compared the effect of adding concurrent radiotherapy to adjuvant capecitabine and cisplatin. The addition of XRT to XP chemotherapy did not significantly reduce RFS (p=0.086), but improved locoregional recurrence, HR 0.49, p= 0.03 [20]. The CRITICS trial explored adding adjuvant RT to the post-operative phase of perioperative chemotherapy (3 cycles of epirubicin, cisplatin/oxaliplatin and capecitabine before and after surgery), which resulted in no improvement in OS (HR: 1.01, 95% CI: 0.84–1.22; p= 0.90) [21]. More recently, a meta-analysis on adjuvant CRT versus adjuvant chemotherapy by Matuschek *et al*. showed that CRT showed no significant improvement of overall survival in comparison to chemotherapy alone (HR=0.93, p= 0.28), but there were improvements for disease-free survival (HR = 0.86; p= 0.023) and locoregional control (odds ratio = 0.56, p= <0.001) favoring CRT [22].

In our multivariate analysis, the RFS HR for XELOX versus CRT was 0.51 (95%CI 0.29-0.87), p=0.014; and the OS HR was 0.45, (95%CI 0.25-0.81), p=0.007, favoring the use of adjuvant XELOX. 65% of patients in our cohort have pN2 or pN3 stage. It is established that the number of involved lymph nodes is one of the most significant prognostic indicators in gastric cancer. We thus postulate that a more intensified adjuvant chemotherapy scheme would be beneficial in this group of patients. Therefore, we performed further exploratory subgroup analysis to see if combination chemotherapy was more useful in heavily nodal positive patients. Among patients with more advanced nodal status (N2/3), the OS for XELOX suggested an improvement compared with CRT, with 3-year OS being 74.3% and 47.6% respectively, (p=0.05, HR 0.547 (95%CI 0.295-1.015)). Regarding RFS, there was also a clear separation of the curves and the 3-yr RFS were 62.9% and 40.5% respectively, however this did not reach statistical significance, with HR 0.615 (95%CI 0.341-1.111), p=0.104 (Figures 5 & 6).

In contrast, among patients with N0/N1 disease, clearly no RFS and OS differences were demonstrated (Figures 7 & 8). Given the heterogeneity of the nodal dissection status of our patients and a significant proportion being unknown, we were unable to conclude whether the degree of dissection influences the results. With that aside, we concluded that XELOX was more efficacious compared to the INT0116 scheme of adjuvant 5FU/leucovorin concurrent with radiotherapy, and this benefit appears more pronounced in the heavily nodal positive patients. Our data on pattern of failure echoed the findings from other studies that the vast majority (80-90%) of recurrences involved distant metastases (either

alone or synchronously with locoregional recurrence). Among these, the majority of failure occurs in the peritoneum [23, 24]. Locoregional recurrences were less common in both of our cohorts (45% and 52%). No difference in locoregional recurrence was seen between the cohorts, which is perhaps due to more than 50% of patients having had D2 dissections. Overall, the predilection of the disease for distant metastases supports the importance of controlling distant metastases by more intensive chemotherapy.

Whether the addition of further CRT in addition to established chemotherapy regimes in node-positive patients would result in superior outcomes would be explored in the ARTIST II study. Retrospective data from the Dutch D1D2 trial demonstrated that CRT reduced local recurrence rates from D1 dissection but showed no benefit for D2 dissected patients [18]. However, other randomized and non-randomized data suggested potential benefits from CRT even after optimal D2 dissection and this is a subject of ongoing debate.

The dosing schedule of chemotherapy agents used in INT 0116 trial was associated with high rates of grade 3 or 4 hematologic and gastrointestinal (GI) toxicities (54% and 33% respectively) [7]. Among the 281 patients assigned to CRT in INT 0116, only 64% completed treatment and 17% discontinued treatment due to toxicity. Three patients (1%) died as a result of CRT-related toxic effects including pulmonary fibrosis, cardiac event, and myelosuppression. Due to concerns regarding toxicity, the dose and schedule of chemotherapy agents used in the INT-0116 trial are no longer recommended by NCCN, which recommends the use of capecitabine or infusional 5FU instead [16]. In our CRT cohort, although we did not have any treatment-related death, the rate of grade 3 or 4 hematologic toxicity was high (60%), among which 19% of patients had grade 4 neutropenia. This was much higher than the XELOX treated group, which only had 23% of patients with grade 3 or 4 hematological toxicities (p=<0.001), among which 2% had grade 4 neutropenia (p=0.003 compared with CRT). The grade 3 or 4 GI toxicity in our CRT cohort was only 10%, which was lower than INT 0116 trial and was comparable to the adjuvant XELOX treated cohort of 15% (p=0.592). From our study, it was clear that the toxicity profile was better for adjuvant XELOX.

Limitations

There were several limitations to this study. Due to the heterogeneity of the operative record, the exact extent of lymphadenectomy was not specified up to 42% of our patients. This hindered data interpretation. Moreover, the follow-up period for our two cohorts was different. Due to the shorter follow up period for adjuvant XELOX cohort, data should be interpreted with caution. Lastly, we did not have any unified protocol for imaging surveillance. This would also impact on the accuracy of reported treatment outcomes.

Conclusion

The PFS and OS appeared to favor XELOX. The toxicity profile for adjuvant XELOX was more favorable. Patterns of failure were similar and distant metastasis was the most common site of initial failure. Adjuvant XELOX should be the treatment of choice.

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