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Real-World Outcomes of FLOT versus CROSS Regimens for Patients with Oesophagogastric Cancers

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Keywords
CROSS · FLOT · Real world · Gastric cancer · Oesophageal cancer

Abstract
Introduction: Treatment of oesophageal (OC), gastro-oesophageal junction (GOJ), and gastric cancer (GC) includes either neoadjuvant Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) for OC or GOJ or perioperative 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for OC, GOJ, and GC adenocarcinomas. This study aims to describe the real-world outcomes of patients with GC, GOJ, and OC treated with FLOT or CROSS and identify variables associated with efficacy through exploratory analysis. We also aimed to evaluate the comparison of FLOT and CROSS for the treatment of OC and GOJ adenocarcinomas. ***Methods:*** This is a retrospective observational study of patients with locally advanced OC, GOJ, or GC treated with FLOT or CROSS between January 2015 and June 2021 in 5 cancer centres across Sydney, Australia. Long-rank test was used to compare survival estimated between subgroups. Hazard ratios for univariate and multivariate analyses were estimated with Cox proportional regression. ***Results:*** The study included 168 patients. The 24-month relapse-free survival (RFS) and overall survival (OS) for FLOT were 59% and 69%, respectively. The median RFS was 29.6 months and median OS was not reached. For CROSS, the 24-month RFS and OS were 55% and 63% with a median RFS and OS of 28.5 and 40.2 months, respectively. There was no difference in OS and RFS between the treatments. FLOT was less tolerable than CROSS with more dose reductions, treatment discontinuation, and clinically relevant grade 3 and 4 toxicity. Neutrophil lymphocyte ratio was associated with survival for both treatments. ***Conclusion:*** Similar efficacy outcomes were seen in this real-world population compared to the clinical trials for FLOT and CROSS.

Introduction

Gastric cancer (GC) and oesophageal cancer (OC) rank fifth and seventh in regards to global incidence of cancer and, respectively, are the third and sixth leading causes of cancer mortality worldwide [1]. These cancers are also associated with high symptom burden causing a reduction

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in quality of life and have significant morbidity [2]. The treatment of upper gastrointestinal malignancy is rapidly evolving and often requires multimodality treatment. For locally advanced OC and gastro-oesophageal junction (GOJ) cancer, perioperative chemotherapy or combination of chemoradiation has become the standard of care [3, 4]. The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) compared combination of neo-adjuvant weekly carboplatin and paclitaxel with radiotherapy versus surgery alone for patients with OC and GOJ, reporting an improvements in median survival of 49.4 (vs. 24 months) months in the treatment arm [3]. Similarly, the perioperative chemotherapy combination of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) given for 4 cycles pre and post-operatively for patients with adenocarcinoma of the OC, GOJ, and GC has reported a median survival of 50 months for the treatment arm [4].

Based on these results, it is uncertain which treatment modality should be utilized for GOJ or distal OC adenocarcinomas. Currently, trials investigating CROSS compared to FLOT are ongoing and are yet to be published. As these treatments are already standard of care in practice, real-world data can be utilized to provide evidence on outcomes for the treatment modalities. In addition, as trials often utilize highly selected patients, it is unclear if the same efficacy and toxicity are observed outside of trial settings.

Consequently, this study aims to describe the real-world outcomes of patients with GC, GOJ, and OC treated with FLOT or CROSS to determine if similar benefits and toxicity are observed outside clinical trial settings. We also aim to evaluate the comparison of FLOT compared to CROSS in OC and GOJ adenocarcinomas and to identify variables associated with efficacy through exploratory analysis.

Materials and Methods

Study Design

This is a retrospective observational study utilizing patient medical records. The study population included patients with histologically confirmed OC, GOJ, or GC that was locally advanced and was treated with at least one cycle of FLOT (5-fluorouracil 2,600 mg/m^2 over 24 h, leucovorin 50 mg, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2 given every 2 weeks for 8 cycles) or CROSS (carboplatin with area under the curve of 2, paclitaxel 50 mg/m^2 weekly with 1.8 Gy over 23 fractions) between January 2015 and June 2021 in five cancer centres across Sydney, Australia. Patients were staged with a combination of endoscopic ultrasound, CT chest-abdomen-pelvis, fluorodeoxyglucose (FDG)-positron emission tomography (PET), and diagnostic laparoscopy. Tumour staging was based on the American Joint Committee on Cancer staging. All patients were discussed at multi-dispensary team meetings to establish expert consensus on management. Patients were excluded if they were found to have metastatic disease prior to starting treatment. Toxicity of treatment was graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Follow up varied between institutions and treatment arms but generally patients who received FLOT were reviewed fortnightly to 4 weekly while on treatment and then 3 to 4 monthly post-completion of treatment. Patients who received CROSS were generally reviewed weekly during treatment and then 3 to 4 monthly post-treatment.

Pre-treatment clinical data were obtained for neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, pre-treatment and post-treatment FDG-PET max standardized uptake values (SUV_{max}) of the primary lesion. Pathological response was assessed with either the Modified Ryan Scheme or the American Joint Committee on Cancer tumour regression grade. The project was approved by the Western Sydney Local Health District Human Research Ethics Committee, 2021/ETH11180.

Statistical Analysis

Demographic and toxicity data were compared using descriptive statistics with χ^2 for categorical variables and the *t* test for continuous variables. Overall survival (OS) was defined from the time of diagnosis to death from any cause. Relapse-free survival (RFS) was defined as the time from diagnosis to disease progression, relapse, or death, whichever came first. The Kaplan-Meier method was used to graphically present survival curves. Long-rank test was used to compare survival estimates between subgroups. Hazard ratios for univariate and multivariate analyses were estimated with Cox proportional regression. A p value of 0.05 was considered statistically significant. All analysis was undertaken with R 4.1.1.

Results

168 patients were included in the study. Table 1 highlights the demographic information of the study population. Median follow-up time for the entire cohort was 21.6 months with a median age of diagnosis of 66 (range 25–83) years. Ninety-five (57%) of patients were treated with CROSS, and 73 (43%) were treated with FLOT. Majority of the patients were male (76%), had a performance status of ECOG 0 (66.7%) and had adenocarcinoma (85%). 23% had GC, 32% had GOJ, and 45% had OC. The CROSS cohort had a higher proportion of patients aged over 70 and ECOG performance status of 1 or above compared with FLOT.

FLOT

The median follow-up for patients who received FLOT was 20.3 months. Patients who received FLOT had 53% GC, 30% GOJ, and 16% OC. No patient with squamous cell carcinoma received FLOT. The median number of cycles received was 5 (range: 1–8) cycles. Sixty-three (86%) patients received 4 cycles of FLOT, 28 (38%) patients received all 8 cycles of FLOT, and 12 (16%) did not require dose reductions throughout their treatment.

Table 1. Characteristics of study cohort

Variable	Total (*N* = 168)	CROSS (*N* = 95)	FLOT (*N* = 73)	*p* value
Age at diagnosis				0.005
<70 years	103 (61.3)	49 (51.6)	54 (74)	
>70 years	65 (38.7)	46 (48.4)	19 (26)	
Sex				1.00
Female	41 (24.4)	23 (24.2)	18 (24.7)	
Male	127 (75.6)	72 (75.8)	55 (75.3)	
ECOG				0.021
0	98 (66.7)	51 (58.6)	47 (78.3)	
1+	49 (33.3)	36 (41.4)	13 (21.7)	
Missing	21 (12.5)	8 (8.4)	13 (17.8)	
BMI				0.806
<25	59 (36.6)	31 (35.2)	28 (38.4)	
>25	102 (63.4)	57 (64.8)	45 (61.6)	
Missing	7 (4.2)	7 (7.4)	0 (0)	
Tumour location				<0.001
GC	39 (23.2)	0 (0)	39 (53.4)	
GOJ	54 (32.1)	32 (33.7)	22 (30.1)	
OC	75 (44.6)	63 (66.3)	12 (16.4)	
Histological subtype				<0.001
Adenocarcinoma	141 (84.9)	68 (73.1)	73 (100)	
SCC	25 (15.1)	25 (26.9)	0 (0)	
Missing	2 (1.2)	2 (2.1)	0 (0)	
NLR				0.260
<2	48 (29.1)	23 (25)	25 (34.2)	
>2	117 (70.9)	69 (75)	48 (65.8)	
Missing	3 (1.8)	3 (3.2)	0 (0)	
PLR				0.654
<200	123 (73.7)	71 (75.5)	52 (71.2)	
>200	44 (26.3)	23 (24.5)	21 (28.8)	
Missing	1 (0.6)	1 (1.1)	0 (0)	
Change in FDG-PET SUV_{max} of primary lesion				1.00
<7	60 (53.6)	37 (53.6)	23 (53.5)	
>7	52 (46.4)	32 (46.4)	20 (46.5)	
Missing	56 (33.3)	26 (27.4)	30 (41.1)	
Pathological response				0.982
Complete	30 (22.2)	17 (23.0)	13 (21.3)	
Non-complete	105 (77.8)	57 (77.0)	48 (78.7)	
Missing	33 (19.6)	21 (22.1)	12 (16.4)	
Pathological stage				<0.001
0	30 (17.9)	17 (17.9)	13 (17.8)	
1	26 (15.5)	24 (25.3)	2 (2.7)	
2	38 (22.6)	14 (14.7)	24 (32.9)	
3	39 (23.2)	19 (20)	20 (27.4)	
4	5 (3.0)	2 (2.1)	3 (4.1)	
No surgery	28 (16.7)	17 (17.9)	11 (15.1)	
Missing	2 (1.2)	2 (2.1)	0 (0)	

Percentages are represented within brackets. BMI, body mass index; PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; GOJ, gastro-oesophageal junction; SCC, squamous cell carcinoma; SUV_{max}, max standardized uptake values.

Twenty-two (30%) patients treated with FLOT had a relapse with a median RFS of 29.6 months (Fig. 1). The 12- and 24-month RFS were 79% and 59%, respectively. Sixteen patients had distant recurrence, and 6 had local or nodal recurrence. Pulmonary and hepatic metastases were the most common sites of recurrence.

Figure 1 demonstrates the OS for patients with adenocarcinoma of OC, GOJ, and GC treated with FLOT. The median survival for the FLOT cohort was not reached. The 12- and 24-month OS were 84% and 69%, respectively. NLR greater than 2 had a significant association with OS, HR: 4.33 (95% CI: 1.28–14.61,

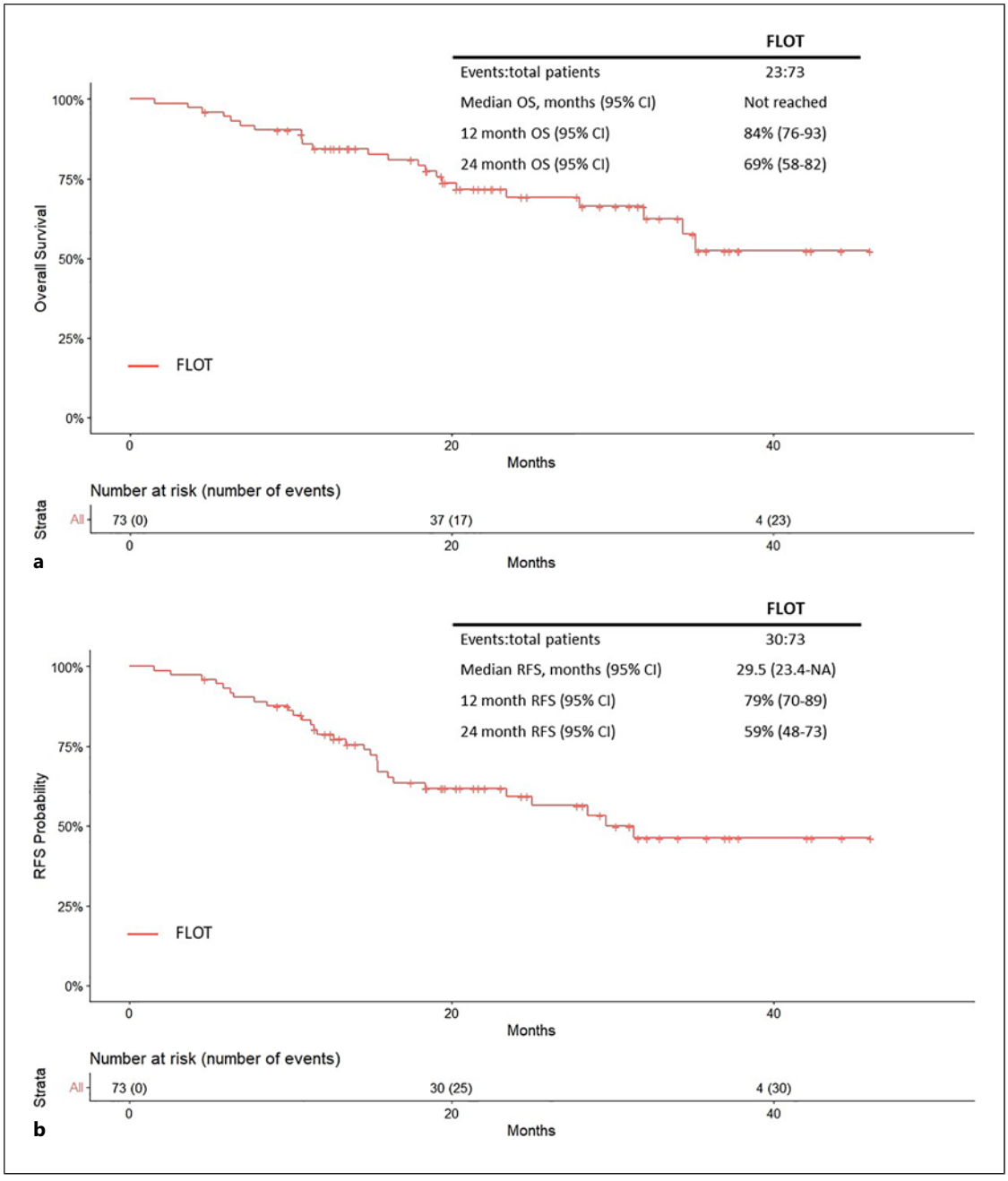

Fig. 1. OS (**a**) and RFS (**b**) for patients with GC, GOJ, and OC adenocarcinomas treated with FLOT.

$p = 0.018$) (Table 2). There was a trend towards improved survival for patients with BMI <25 and female sex (Table 2; online suppl. Fig. S1, S2; for all online suppl. material, see https://doi.org/10.1159/000531536). On univariate analysis, there was no difference in OS and RFS for age groups (less than 70 vs. more than 70), PLR (≥200 vs. < 200), change in FDG-PET SUV of primary lesions, tumour location, and dose reductions (online suppl. material Fig. S3–S13). On multivariable analysis, only BMI greater than 25 was significantly associated with increased risk of death; however, there was wide confidence interval related to the sample size (online suppl. Table 1).

Complete responses were seen in 13 (21%) patients, with 2 being OC, 6 being GOJ, and 5 being GC. No statistically significant difference was seen in complete

Table 2. Univariate Cox proportional hazard for patient who received FLOT

Variable	*N* (%)	HR (univariable)
Age at diagnosis		
<70 years	54 (74.0)	–
>70 years	19 (26.0)	1.79 (0.76–4.24, $p = 0.183$)
Sex		
Female	18 (24.7)	–
Male	55 (75.3)	3.87 (0.91–16.54, $p = 0.068$)
ECOG		
0	47 (78.3)	–
1+	13 (21.7)	1.93 (0.68–5.49, $p = 0.219$)
BMI		
<25	28 (38.4)	–
>25	45 (61.6)	2.50 (0.92–6.77, $p = 0.072$)
Dose reduction		
No	44 (60.3)	–
Yes	29 (39.7)	0.52 (0.21–1.32, $p = 0.170$)
NLR		
<2	25 (34.2)	–
>2	48 (65.8)	4.33 (1.28–14.61, $p = 0.018$)
PLR		
<200	52 (71.2)	–
>200	21 (28.8)	0.97 (0.38–2.48, $p = 0.944$)
Change in FDG-PET SUV		
<7	23 (53.5)	–
>7	20 (46.5)	0.62 (0.22–1.76, $p = 0.372$)
Pathological response		
CR	13 (21.3)	–
nCR	48 (78.7)	1.35 (0.38–4.75, $p = 0.640$)

BMI, body mass index; PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; CR, complete response; nCR, non-complete response; SUV_{max}, max standardized uptake values.

responses and the tumour location. There was no statically significant association between complete response and OS or RFS (online suppl. Fig. S7, S14).

Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study

The median follow-up for the CROSS cohort was 22.8 months. Thirty-two (34%) patients had GOJ and 63 (64%) had OC. Majority of the CROSS cohort had adenocarcinoma (73%). In total, 26 (27%) patients did not receive the full treatment, 22 (23%) had early cessation of chemotherapy, while 4 (4%) patients did not receive the full 41.4 Gy in 23 fractions of radiotherapy. All treatment discontinuation was due to toxicity. The discontinuation rate of chemotherapy was higher at 23% in our cohort versus 9% in the CROSS study, while the discontinuation rate of radiotherapy in our cohort was lower at 4% versus 8% in the CROSS study.

Thirty-nine (41%) of patients who were treated with CROSS had a relapse, and the median RFS was 28.5 months (Fig. 2). The 12- and 24-month RFS were 77% and 55%, respectively. Majority (76%) of relapses were distant (the lung and liver being the most common sites) while 24% had a local recurrence.

Figure 2 demonstrates the OS for patients with OC and GOJ treated with CROSS. Median survival was 40.2 months. The 12-month and 24-month OS were 84% and 63%, respectively. On univariate analysis, ECOG of 1 or above (HR: 2.30 [95% CI: 1.22–4.34, $p = 0.010$] versus ECOG 0) and baseline NLR below 2 (HR: 2.25 [95% CI: 1.00–5.05, $p = 0.050$] versus NLR above 2) were statistically associated with increased risk of death (Table 3). No OS or RFS differences were seen between age groups, sex, BMI, PLR, pathological response, or histological subtype (online suppl. Fig. S15–S27). On multivariate analysis, a decrease in SUV of 7 in the primary lesion on FDG-PET was associated with improved OS, HR: 0.09 (95% CI: 0.01–0.84, $p = 0.035$) (online suppl. Table 2).

There were 17 (23%) patients with complete responses. There was no statistically significant difference in complete responses between tumour location (GOJ vs. oesophagus; $p = 0.595$) or between histological subtypes ($p = 0.326$). There was no statically significant association between complete response and survival or RFS (online suppl. Fig. S19, S26).

CROSS versus FLOT

Figure 3 demonstrates the OS and RFS curves for patients with adenocarcinoma OC or GOJ treated with FLOT ($n = 34$) or CROSS ($n = 70$). There was no statically significant difference in OS and RFS between the treatments. The hazard ratio for death for FLOT compared to CROSS on univariate and multivariate analysis was 0.97 (95% CI: 0.49–1.95 $p > 0.9$) and 1.33 (95% CI: 0.39–4.49, $p = 0.649$), respectively. No subgroups within the cohort had an increased survival benefit from FLOT compared to CROSS. In addition, there was no statistically significant difference in complete pathological response (20% in CROSS, 30% in FLOT) between the treatment arms ($p = 0.462$).

Toxicity

Online supplementary Tables 3 and 4 describe all the toxicities recorded within the cohort. Table 4 describes the number of patients with selected toxicity between treatment arms. Ten (6%) patients in total had at least one grade 4 toxicity, 6 in CROSS, and 4 in FLOT. More patients who received FLOT

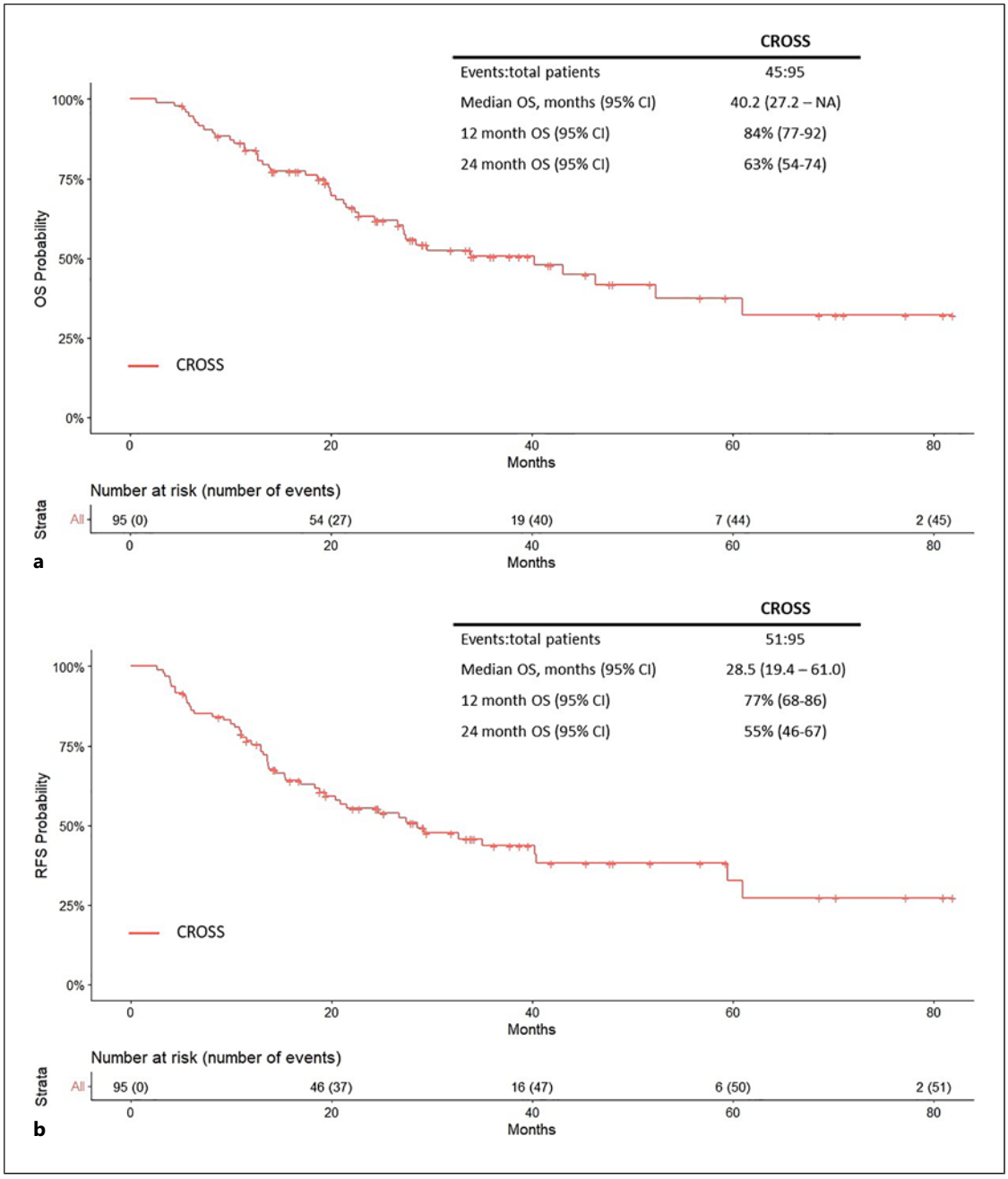

Fig. 2. OS (**a**) and RFS (**b**) for patients with GOJ and OC treated with CROSS.

had grade 2 toxicity compared to those who received CROSS, while more patients who received CROSS had grade 3 toxicity. However, 54% of patients treated with CROSS had grade 3 lymphopenia accounting for the high grade 3 toxicity seen in the CROSS cohort. Fatigue was the most frequently reported toxicity within the study cohort, and it occurred more in the FLOT-treated patients. More diarrhoea and peripheral neuropathy were also seen in the FLOT cohort, while more thrombocytopenia, odynophagia, and oesophagitis were seen in CROSS-treated patients. The rates of grade 3 and 4 neutropenia and febrile neutropenia did not differ between treatment arms.

Table 3. Univariate Cox proportional hazard for patient who received CROSS

Variable	*N* (%)	HR (univariable)
Age at diagnosis		
<70 years	49 (51.6)	–
>70 years	46 (48.4)	1.12 (0.62–2.02, $p = 0.715$)
Sex		
Female	23 (24.2)	–
Male	72 (75.8)	1.08 (0.54–2.19, $p = 0.824$)
ECOG		
0	51 (58.6)	–
1+	36 (41.4)	2.30 (1.22–4.34, $p = 0.010$)
BMI		
<25	31 (35.2)	–
>25	57 (64.8)	0.90 (0.47–1.73, $p = 0.760$)
Histological subtype		
Adenocarcinoma	68 (73.1)	–
SCC	25 (26.9)	1.04 (0.53–2.03, $p = 0.908$)
NLR		
<2	23 (25.0)	–
>2	69 (75.0)	2.25 (1.00–5.05, $p = 0.050$)
PLR		
<200	71 (75.5)	–
>200	23 (24.5)	1.27 (0.66–2.43, $p = 0.471$)
Change in FDG-PET SUV_{max}		
<7	37 (53.6)	–
>7	32 (46.4)	0.56 (0.28–1.12, $p = 0.103$)
Pathological response		
CR	17 (23.0)	–
nCR	57 (77.0)	2.45 (0.86–7.01, $p = 0.094$)

BMI, body mass index; PLR, platelet lymphocyte ratio; NLR, neutrophil lymphocyte ratio; CR, complete response; nCR, non-complete response; SCC, squamous cell carcinoma; SUV_{max}, max standardized uptake values.

Discussion

Our study describes the real-world outcomes of patients treated with FLOT and CROSS. NLR and BMI were associated with survival for FLOT, while ECOG, NLR, and change in SUV on PET of the primary lesion were associated with survival for CROSS. For patients with OC or GOJ adenocarcinoma, there was no survival difference between CROSS and FLOT. FLOT was less tolerable than CROSS with more dose reductions and treatment discontinuation. There were more clinically relevant grade 3 and 4 toxicities for FLOT.

In our study, the median survival was not reached for FLOT and was 40 months for CROSS with 21% (FLOT) and 23% (CROSS) of patients having a complete pathological response. This is comparable to the CROSS trial which reported a similar median survival of 49 months. The trials also reported a similar complete pathological responses in 15% of patients in FLOT and 29% (23% in patients with adenocarcinomas) of patients in the CROSS trial. Our findings suggest that similar benefits are seen in the real-world population of patients treated with CROSS and FLOT compared to their respective trials. Other real-world studies have not reported median survival data for patients treated with FLOT [5, 6]. For FLOT, rates of pCR were variable, with one study reporting 0 and a prospective Italian study reporting rates of 7% [5, 6]. Real-world studies report pCR ranging from 32% to 43% for CROSS, though these include squamous cell carcinoma which is more likely to achieve a pCR [5–8, 9].

Our study showed that CROSS was the more tolerable treatment compared to FLOT with lower proportion of treatment cessation (27% vs. 62%). We reported that 38% of patients received all 8 cycles of FLOT and the majority required dose reductions. Similarly, the FLOT trial reported that 46% of patients completed all 8 cycles of treatment [4]. Given that 86% of patients in our study's FLOT cohort received 4 cycles of FLOT, the low completion of the 8 cycles of FLOT could be accounted for deconditioning post-operatively as well as cumulative toxicities of the treatment. In keeping with this, real-world studies have described increased frequency of grade 3 and 4 gastrointestinal toxicities in the post-operative phase of FLOT treatment [6]. In addition, the perceived increase in toxicity of FLOT could explain the statistically significant difference in our study for the number of patients with ECOG 1 or above and age greater than 70 treated with CROSS compared to FLOT, as they may have been deemed less likely to tolerate FLOT.

We did not find a difference in survival for patients with GOJ and OC adenocarcinomas treated with CROSS or FLOT. Similar findings were reported in the Neo-AEGIS study; however, the trial did include patients who also received the MAGIC protocol in their perioperative chemotherapy group [5]. Currently, there are no published randomized clinical trials directly investigating CROSS compared to FLOT in the treatment of GOJ and OC. However, one real-world study from Turkey reported similar finding to our results with no survival difference between the treatments [7]. We are eagerly awaiting the read out of prospective randomized studies such as ESOPEC (NCT02509286) [10].

We found NLR to be associated with survival for both the CROSS and FLOT cohorts. This is consistent with current evidence in the literature with a number of studies reporting the association in OC, GOJ, and GC with NLR ratio greater than 2 to 5 having reduced survival [8, 11–14]. The underlying biological mechanism of the impact of NLR on survival remains uncertain. A proposed biological

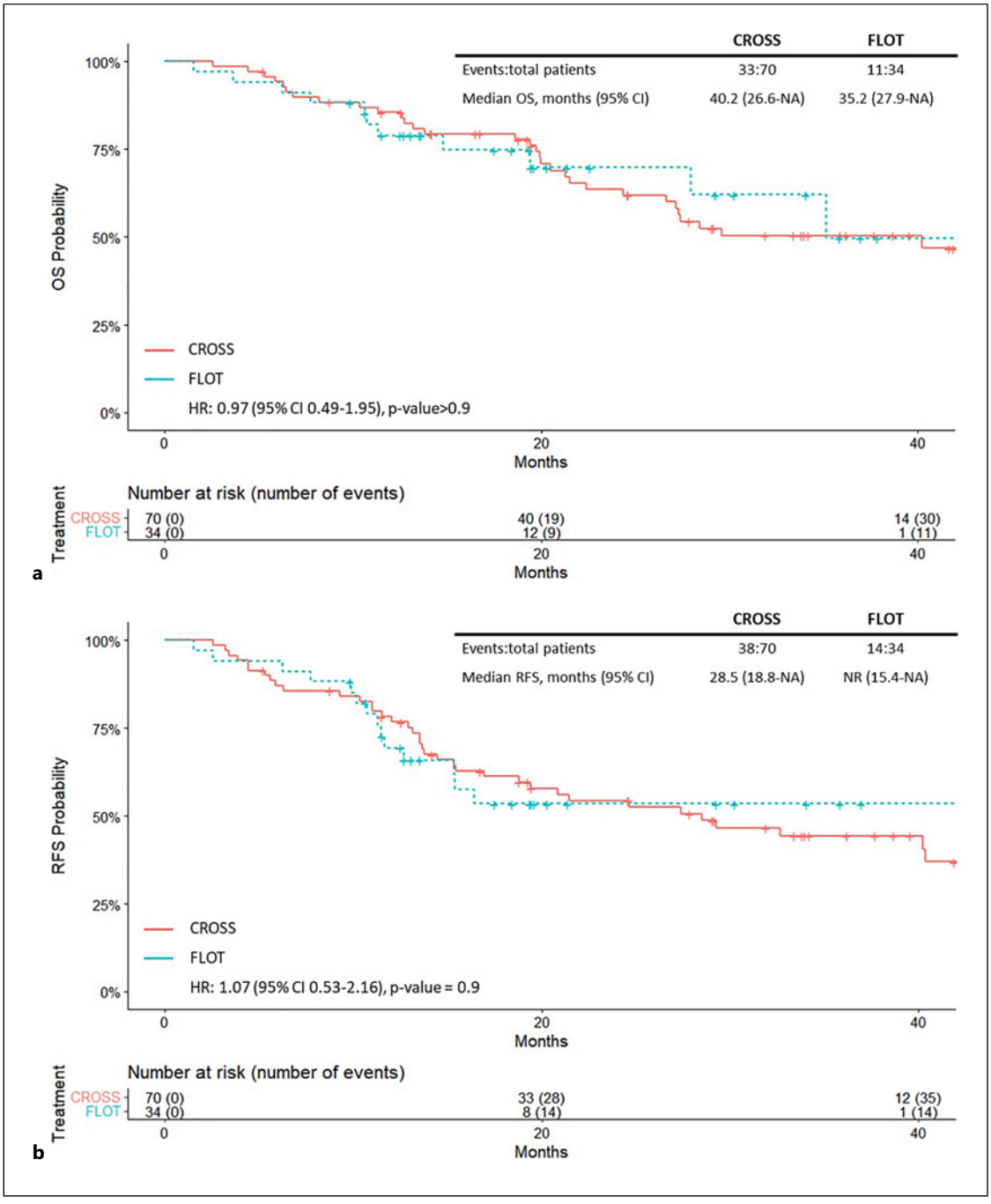

Fig. 3. a OS for patients with GOJ and OC adenocarcinomas treated with FLOT versus CROSS. **b** RFS for patients with GOJ and OC adenocarcinomas treated with FLOT versus CROSS.

mechanism is that neutrophils create a pro-oncogenic environment through the release of cytokines, while lymphocyte through the action of T cells and natural killer cells promote an anti-tumour response [15]. Consequently, having an increased NLR leads to a more oncogenic environment and reduced anti-tumour destruction from lymphocytes [15]. This imbalance can also impact chemotherapy response, with a study reporting reduced pathological complete response in patients with elevated NLR [16].

Our results suggested having a pre-treatment BMI in the overweight range (>25) was associated with reduced survival for patients who received FLOT. This is contrary to what is reported in the literature with a number of

Table 4. Toxicity by grade and selected toxicity between treatment arm

	Overall	CROSS	FLOT	*p* value
	N (%)	*N* (%)	*N* (%)	
Selected grade 1 and 2 toxicity				
Fatigue	90 (53.6)	42 (44.2)	48 (65.8)	0.009
Diarrhoea	38 (22.6)	4 (4.2)	34 (46.6)	<0.001
Peripheral neuropathy	49 (29.2)	3 (3.2)	46 (63.0)	<0.001
Anaemia	56 (33.3)	32 (33.7)	24 (32.9)	1.000
Neutropenia	39 (23.2)	25 (26.3)	14 (19.2)	0.367
Thrombocytopenia	32 (19.0)	24 (25.3)	8 (11.0)	0.032
Odynophagia	16 (9.5)	16 (16.8)	0 (0.0)	0.001
Lymphopenia	58 (34.5)	52 (54.7)	6 (8.2)	<0.001
Oesophagitis	13 (7.7)	13 (13.7)	0 (0.0)	0.003
Selected grade 3 and 4 toxicity				
Fatigue	7 (4.2)	1 (1.1)	6 (8.2)	0.056
Diarrhoea	9 (5.4)	0 (0.0)	9 (12.3)	0.002
Myocardial infarction	1 (0.6)	0 (0.0)	1 (1.4)	0.895
Neutropenia	15 (8.9)	8 (8.4)	7 (9.6)	1.000
Febrile neutropenia	8 (4.8)	4 (4.2)	4 (5.5)	0.986
Lymphopenia	58 (34.5)	52 (54.7)	6 (8.2)	<0.001

studies suggesting a BMI in the overweight range was a predictor of improved survival [14, 17–19]. It is important to note that these studies were in the pre-FLOT era, and the relationship between BMI and FLOT needs to be further explored.

On multivariable analysis, there was an association that a change of 7 in SUV_{max} on FDG-PET of the primary lesion was associated with improved survival for the CROSS-treated patients. Studies reporting on the utility of PET as a predictive marker have reported variable results with some reporting an association with complete pathological response and others showing no association with efficacy outcomes [20–22]. Furthermore, the definition of metabolic response or the change in SUV_{max} has not clearly been established in the literature for OC and GOJ malignancies. Further studies are required to explore the influence on the change in SUV_{max} in predicting OS.

Our study's strength is that it utilizes real-world data which allows the ability to explore efficacy and toxicity outside of trial setting, improving external validity of trial data. The limitations of our study includes its retrospective nature leading to the inability to study important histopathological factors such as statuses of *Helicobacter pylori,* presence of Barrett's oesophagus, mismatch repair protein staining due to missing data. Furthermore, there were statistically significant differences between the demographics of the patients between treatment arms that may confound the results; however, we aimed to account for this by performing multivariate analysis.

Conclusion

Similar efficacy outcomes were seen in this real-world population compared to the clinical trials for FLOT and CROSS. We identified NLR, BMI to be associated with survival for FLOT, while ECOG, NLR, and change in SUV of the primary lesion on PET was associated with survival for CROSS. No survival difference was seen for patients with GOJ and OC adenocarcinomas treated with FLOT or CROSS. Further investigations and strategies are required to improve treatment completion during post-operative phase of FLOT.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The project was approved by the Western Sydney Local Health District Human Research Ethics Committee, 2021/ETH11180. Individual consent from participating subjects was waived due to the low risk and retrospective nature of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained for this project.

Authors Contributions

Conception and design: Adel Shahnam and Mark Wong. Administrative support, provision of study materials or patients, manuscript writing, and final approval of manuscript: all authors. Collection and assembly of data: Adel Shahnam, Udit Nindra, Nicholas McNamee, and Robert Yoon. Data analysis and interpretation: Adel Shahnam, Mark Wong, Weng Ng, Ray Asghari, and Deme Karikios.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Adel Shahnam upon reasonable request.

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