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Cisplatin Substitution with Carboplatin During Radical Chemoradiotherapy for Oesophagogastric Carcinoma: Outcomes from a Tertiary Centre

AVANI ATHAUDA[1], DAVID WATKINS[1], KABIR MOHAMMED[2], IAN CHAU[1], NAUREEN STARLING[1], SHEELA RAO[1], DIANA TAIT[1], KATHARINE AITKEN[1] and DAVID CUNNINGHAM[1]

[1]*Gastrointestinal Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, Surrey, U.K.;*
[2]*Department of Statistics, The Royal Marsden NHS Foundation Trust, Surrey, U.K.*

Abstract. *Background/Aim: Cisplatin-based radical chemoradiotherapy (CRT) is utilised in oesophagogastric (OG) cancer but the toxicity profile of cisplatin limits its use. This study aimed to evaluate the clinical characteristics and outcomes of patients treated with either cisplatin or carboplatin based CRT at our institution. Materials and Methods: This is a retrospective analysis of patients with localised OG cancer undergoing CRT with cisplatin/fluoropyrimidine (CX/F) or carboplatin/fluoropyrimidine (CarboX/F) between January 2001 and December 2014. Results: A total of 91 eligible patients were included. Median age was 65 years (IQR=57-75) for CX/F and 77 years (IQR=69-80) for CarboX/F. Adenocarcinoma histology and Charlson comorbidity index were higher in the CarboX/F group. Endoscopic complete response (CR) was achieved in 64% of CX/F group and 48% of CarboX/F group (p=0.19). The median PFS for CX/F was 31.0 months (95%CI=18.2-NE) vs. 18.7 months for CarboX/F (95%CI=13.5-30.4; HR=1.49, p=0.21). Conclusion: Despite significant differences in baseline clinical characteristics, patients treated with carboplatin CRT demonstrated no significant difference in PFS or endoscopic CR rate, compared to those treated with cisplatin.*

Cancers of the oesophagus or oesophagogastric junction (OGJ) remain an important cause of cancer-related morbidity and mortality worldwide (1) with a significant proportion of patients presenting with locally advanced or advanced disease. Globally, squamous cell carcinoma represents the predominant histological type of oesophageal cancer, but there has been a rapid rise in the incidence of oesophageal adenocarcinoma in western populations over recent years (2). In the UK, rates of oesophageal cancer incidence and mortality are near comparable with 9,000 new cases diagnosed each year and 7,900 deaths each year (3).

The application of multi-modality therapy utilising either neoadjuvant chemotherapy or chemoradiotherapy (CRT) prior to surgical resection has led to increased survival and locoregional control rates for both squamous cell carcinoma and adenocarcinoma (4, 5). In selected patients with localised disease who are deemed unsuitable for surgery, CRT can be utilised as an alternative radical treatment option. The combination of cisplatin and fluoropyrimidine is a standard choice for the chemotherapy component of CRT. Due to its toxicity profile and hydration requirements, cisplatin is not suitable for many patients with renal impairment, hearing impairment, neuropathy or significant cardiac dysfunction. In these circumstances, carboplatin is considered as an alternative platinum compound but there remains a lack of prospective randomised data to support this substitution in oesophagogastric (OG) cancer. Comparative data do, however, exist for this substitution in other cancers which utilise platinum-containing regimens, such as non-small cell lung cancer (NSCLC) and ovarian cancer.

A meta-analysis of randomised controlled trials comparing cisplatin-based regimens to carboplatin-based regimens in advanced NSCLC demonstrated a higher overall response rate to cisplatin, but no survival advantage over carboplatin (6). Toxicity profiles differed between the groups with higher rates of nausea, vomiting and nephrotoxicity with cisplatin compared to higher rates of thrombocytopenia with carboplatin. Furthermore, prospective data from a randomised phase 3 trial comparing chemotherapy regimens containing carboplatin AUC6 *versus* two different doses of cisplatin (80 mg/m^2

Correspondence to: Dr. David Watkins, Gastrointestinal Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, SM2 5PT, Surrey, U.K. Tel: +44 2086613158, Fax: +44 2086439414, e-mail: david.watkins@rmh.nhs.uk

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and 50 mg/m^2) failed to show any differences in survival or patient reported outcomes between the carboplatin and cisplatin 80 mg/m^2 groups (7). Therefore, these two platinum compounds are widely used interchangeably in NSCLC and treatment choice is usually dictated by tolerability and the toxicity profiles of each drug.

Similarly, randomised phase 3 non-inferiority studies in ovarian cancer (8, 9) have shown no survival advantage with cisplatin over carboplatin but improved tolerability, better quality of life and easier administration with carboplatin-containing regimens, thereby leading to the preferred use of carboplatin in this disease.

In this retrospective study we sought to evaluate the clinical characteristics and outcomes of patients with localised OG cancer undergoing radical CRT with either carboplatin or cisplatin-based chemotherapy at our institution.

Materials and Methods

Methods. The Royal Marsden Hospital Electronic Patient Record (EPR) system was searched for patients with OG (oesophagus, oesophagogastric junction (OGJ) or gastric) cancer consecutively treated at the institution over a fourteen-year period between January 2001 and December 2014. Patients with localised OG cancer who received radical chemoradiotherapy utilising cisplatin and fluoropyrimidine or carboplatin and fluoropyrimidine were identified. Patients who received neoadjuvant triplet chemotherapy including epirubicin were excluded from this analysis. All patients required a minimum of three years follow up. A data collection tool was designed and all relevant clinical data including patient demographics, disease characteristics, chemotherapy drugs, radiation doses and outcomes were retrieved from EPR by the authors. The Charlson comorbidity index (CCI) (10), which predicts the 1 year mortality for patients with a range of comorbidities, was calculated for all eligible patients at baseline. For those patients treated with carboplatin in place of cisplatin, the reason for platinum substitution was recorded. Data on frequency of cytopenias during treatment and deterioration in creatinine was collected for each group as a surrogate marker of toxicity. Study approval was sought and obtained from the hospital trust's Committee for Clinical Research.

Statistical analysis. Participant and disease characteristics were analysed using descriptive statistics; for categorical variables, numbers with percentages plus means and standard deviations were presented and for continuous variables, medians along with lower and upper quartiles were presented. Progression-free survival (PFS) was calculated as time from start of chemotherapy treatment to date of progression or death from any cause. Overall survival (OS) was calculated for all patients as time from start of chemotherapy to death from any cause or last follow up. Patients without an event were censored at date of last follow up. Survival estimates and 95% confidence intervals were determined using the Kaplan–Meier method whilst the Cox regression method was used to describe and compare survival hazard rates between the two chemotherapy groups and to adjust for the effect of covariates. Stata v13.1 was used for the analysis.

Results

Patient and disease characteristics. A total of 940 patients with a diagnosis of OG cancer who received some form of systemic platinum chemotherapy for any indication during the study time period were screened, of which 91 patients met the eligibility criteria. Of these, 42 patients received cisplatin/fluoropyrimidine (CX/F) CRT and 49 received carboplatin/fluoropyrimidine (CarboX/F) CRT. All patients received a radical dose of concomitant radiotherapy, most frequently 54 Gy in 30 fractions (range=50-59 Gy in 25-31 fractions). The median age of patients in the CX/F group was 65 years (IQR=57-75) and in the CarboX/F group was 77 years (IQR=69-80). The majority of patients in both groups had an ECOG performance status (PS) of ≥1 at the start of treatment (81% CX/F and 96% CarboX/F). There was a higher proportion of adenocarcinoma histology in the CarboX/F group compared to the CX/F group (59% *vs*. 29%) and the calculated Charlson comorbidity index (CCI) was also higher in the CarboX/F group (CCI>5=57% *vs*. 17%). Baseline demographic, clinical and pathological characteristics are summarised in Table I. The most frequent reasons for implementing platinum substitution with carboplatin were age (33%), hearing impairment (18%), renal impairment (16%) and other comorbidities (16%).

Toxicity. Six patients (14%) in the CX/F group and six patients (12%) in the CarboX/F group experienced an episode of neutropenia during treatment. Eight patients (19%) in the CX/F group experienced an episode of thrombocytopenia compared to 22 (45%) in the CarboX/F group (p=0.009). Nine patients (21%) in the CX/F group required a blood transfusion during the treatment period compared to 22 (45%) in the CarboX/F group. Two patients in the CX/F group and one patient in the CarboX/F group experienced deterioration in creatinine during treatment. Eight patients (19%) in the CX/F group required a dose modification of chemotherapy during treatment compared to 19 patients (39%) in the CarboX/F group. Of these patients, three patients in the CX/F group required a dose modification of cisplatin and 11 patients in the CarboX/F group required a dose modification of carboplatin (p=0.011).

Treatment outcomes

Response. Responses to CRT as assessed by 12-week post-treatment CT imaging and endoscopic biopsy are outlined in Table II. The complete response (CR) at endoscopic biopsy rate was 64% for the CX/F group and 48% for the CarboX/F group (p=0.19).

Survival. The median PFS for the CX/F group was 31.0 months (95%CI=18.2-NE) and for the CarboX/F group was 18.7 months (95%CI=13.5-30.4); adjusting for age,

Table I. *Baseline demographic, clinical and pathological characteristics.*

	CX/F (n=42) No. (%)	CarboX/F (n=49) No. (%)	*p*-Value
Median age at diagnosis (IQR)	65 (57-75)	77 (69-80)	<0.001
Gender			
Male	24(57)	32 (65)	
Female	18 (43)	17 (35)	0.52
PS at start			
0	8 (19)	2 (4)	
1	30 (71)	39 (81)	
2	4 (10)	6 (13)	
3	0 (0)	1 (2)	0.12
Charlson Co-morbidity Index (CCI)			
2-3	12 (29)	5 (10)	
4-5	23 (55)	10 (33)	
>5	7 (17)	16 (57)	<0.001
Primary site			
Oesophagus	34 (81)	32 (65)	
OGJ type I	7 (17)	7 (14)	
OGJ type II	1 (2)	7 (14)	
OGJ type III	0 (0)	2 (4)	
Stomach	0 (0)	1 (2)	0.11
Histology			
Adenocarcinoma	12 (29)	29 (59)	
Squamous	30 (71)	20 (41)	0.003
RT dose			
54Gy	39 (93)	48 (98)	
Other	3 (7)	1 (2)	0.33
Received neoadjuvant chemotherapy	40 (95)	46 (94)	

Table II. *Response to CRT.*

	CX/F No. (%)	CarboX/F No. (%)	*p*-Value
Response post CRT			
CR (endoscopic biopsy)	25 (64)	23 (48)	0.19
PR	4 (10)	4 (8)	
SD	5 (13)	8 (17)	
PD	3 (8)	5 (10)	
Residual disease	2 (5)	8 (17)	
Total	39 (100)	48 (100)	0.42

Table III. *Baseline characteristics of CarboX/F group with hearing/renal impairment as primary reason for platinum substitution.*

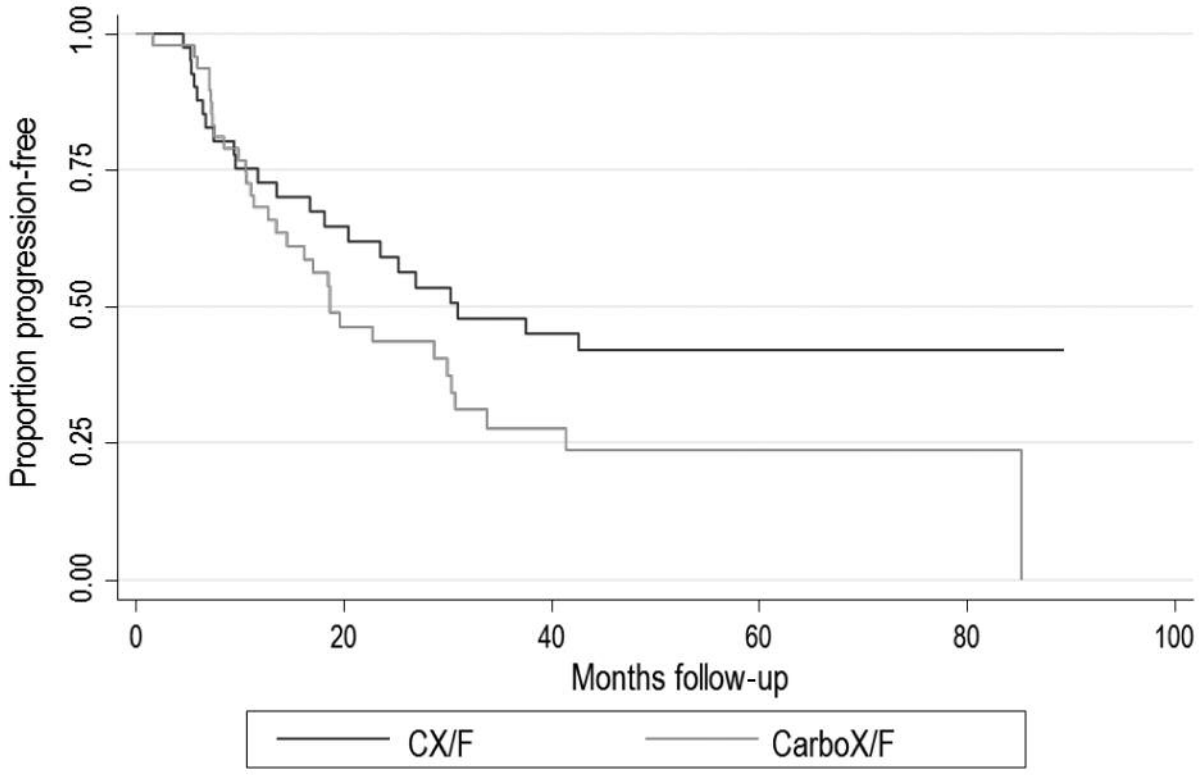
	CX/F (n=42) No. (%)	CarboX/F (renal/ hearing imp) (n=19) No. (%)	*p*-Value
Median age at diagnosis (IQR)	65 (57-75)	75 (66-79)	0.02
Gender			
Male	24 (57)	11 (58)	
Female	18 (43)	8 (42)	0.956
PS at start			
0	8 (19)	1 (5)	
1	30 (71)	17 (89)	
2	4 (10)	1 (5)	0.40
Co-morbidity			
2-3	12 (29)	3 (16)	
4-5	23 (55)	6 (31)	
>5	7 (17)	10 (53)	0.02
Histology			
Adenocarcinoma	12 (29)	10 (53)	
Squamous	30 (71)	9 (47)	0.9

comorbidity and pathology: HR=1.49, p=0.21). Median OS for the CX/F group was not reached (95%CI=63.9-NE) and for the CarboX/F group was 36.3 months (95%CI=24.1-68.5); adjusting for age, comorbidity and pathology: HR 1.92, p=0.09) (Figures 1 and 2). The 3-year PFS rate for the CX/F group was 48% and for the CarboX/F group was 28%. The 5-year OS rate for the CX/F group was 70% and for the CarboX/F group was 38%. Sixty-one patients (45%) had died at last follow up, 72 patients (53%) were alive and 1 patient was lost to follow up. Of the patients who were still alive, 5 were receiving ongoing treatment, 19 had evidence of progressive disease with no further treatment options available and 48 had no evidence of active disease. The median duration of follow up was 53.8 months.

Subgroup analysis. Due to the large discrepancies in age and comorbidity index between the two groups, a further subgroup analysis was performed by comparing those patients who received carboplatin substitution primarily due to isolated hearing or renal impairment (n=19). However, the clinical characteristics of this subgroup did not significantly differ from the overall CarboX/F population. Within this CarboX/F subgroup, the median age at diagnosis was 75 years (IQR=66-79), proportion of patients with a CCI>5 was 53% and the proportion of adenocarcinoma histology was 53% (Table III). The median PFS for this group was 22.8 months (95%CI=16.2-NE; HR=0.75, p=0.12) (Figure 3).

Discussion

The toxicity profile of cisplatin limits its utility in patients with renal impairment, hearing impairment, cardiac dysfunction & neuropathy amongst other comorbidities. In this situation, cisplatin is commonly substituted with carboplatin which has a preferred toxicity profile in this



	Median (95%CI)	IQR in months	HR (95%CI)	HR* (95%CI)
CX/F, n=42	31.0 (18.2-NE)	11.7-Not Reached	*1.00 (ref)*	*1.00 (ref)*
CarboX/F, n=48	18.7 (13.5-30.4)	10.6-41.4	1.54 (0.89-2.67), p=0.12	1.49 (0.79-2.81), p=0.21

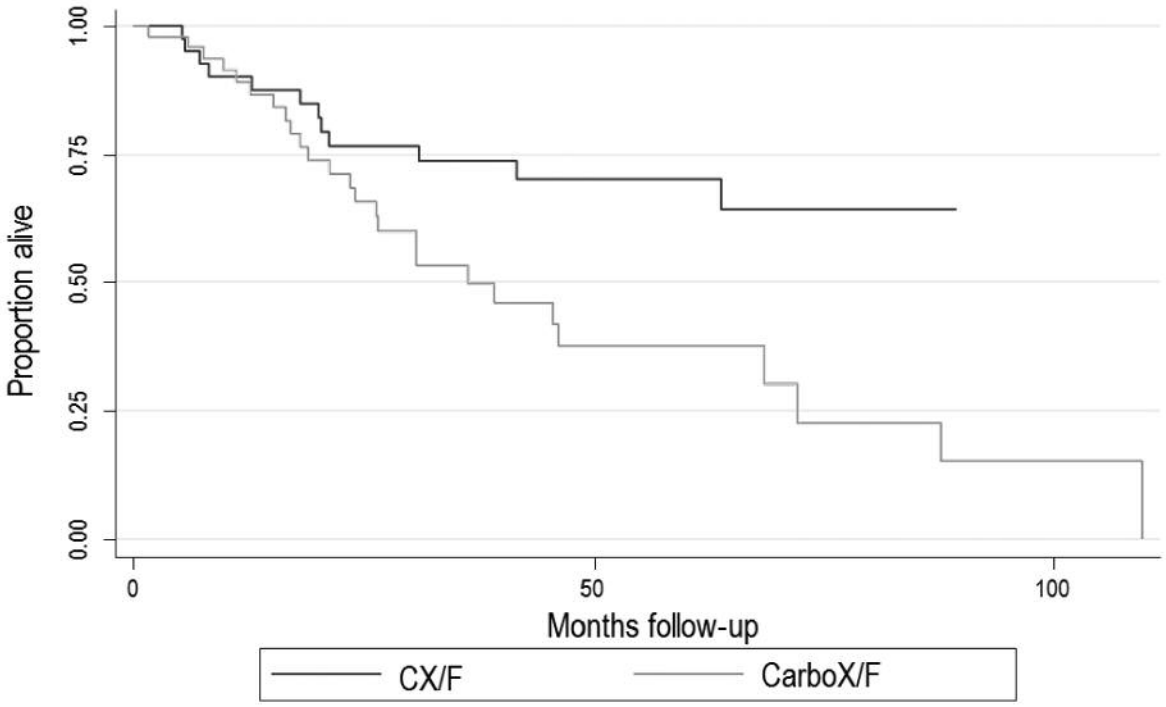
*Adjusting for age at diagnosis, co-morbidity (CCI) and histology

Figure 1. *Progression-free survival (PFS) for CX/F versus CarboX/F.*

clinical setting. Although survival outcomes with platinum substitution are comparable in other tumour types, this has not been prospectively analysed in OG cancer and there is little published data. To our knowledge, we present the first data to describe the clinical characteristics and comparative outcomes for patients with localised OG cancer undergoing radical CRT with either CarboX/F or CX/F.

Within our institution, patients with locally advanced OG cancer who underwent radical CRT with carboplatin substitution were significantly older than those who received cisplatin (median age 77 years *vs*. 65 years). In addition, patients who received carboplatin had higher Charlson comorbidity index scores as well as a higher proportion with adenocarcinoma histology. The differences in patient characteristics were more significant than we had anticipated but can be understood as the presence of renal impairment, hearing impairment & cardiac dysfunction will be associated with an older, frailer patient population. This group represents a clinically challenging population of patients who are often deemed unsuitable for cisplatin. In addition, this patient group is often excluded from clinical trials (involving cisplatin) due to stringent eligibility criteria meaning there is an absence of prospective data on which to base treatment recommendations.

As the majority of cancers in the developed world are diagnosed in patients aged 70 years and over, it is now recognised that cancer is predominantly a disease of older people. However, outcomes remain poorer in these patients and there is a disparity in treatment options compared to younger patients. In recognition of this, the European



	Median (95%CI)	IQR in months	HR (95%CI)	HR* (95%CI)
CX/F, n=42	Not Reached (63.9-NE)	31.0-Not Reached	*1.00 (ref)*	*1.00 (ref)*
CarboX/F, n=49	36.3 (24.1-68.5)	19.0-72.1	2.40 (1.20-4.80), p=0.01	1.92 (0.88-4.16), p=0.09

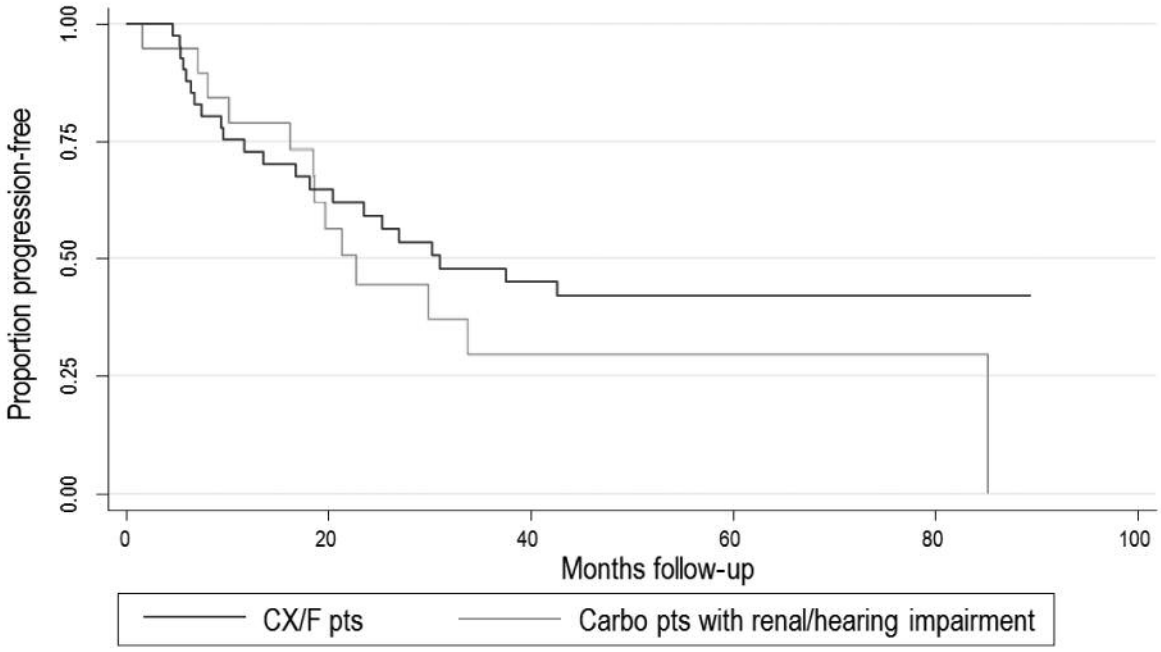
*Adjusting for age at diagnosis, co-morbidity (CCI) and histology

Figure 2. *Overall survival (OS) for CX/F versus CarboX/F.*

Organisation for Research and Treatment of Cancer (EORTC) established the Cancer in the Elderly Taskforce with the aim of improving research and clinical trial access for older patients in order to determine the optimal standards of care in the geriatric population. This recognition will help to develop prospective data to guide treatment decisions in older patients who are often excluded from clinical trials due to comorbidity or frailty. An integrated oncogeriatric approach in the assessment and optimisation of older patients with comorbidity has emerged as a top priority for the geriatric oncology community. Thus, the incorporation of comorbidity and functional assessments (such as the timed up and go test) in guiding management decisions and determining the best treatment options on an individual patient basis is becoming more commonplace (11).

In spite of the differences in the baseline clinical characteristics of the two groups in our cohort, endoscopic CR rates following completion of CRT showed no significant difference between the CX/F and CarboX/F groups despite a higher proportion of adenocarcinoma histology in the carboplatin group. In addition, there was no significant difference in PFS between the two groups after adjusting for age, comorbidity and histology. Although OS appears to be longer in the cisplatin group, this must be interpreted with caution given the differing patient characteristics at baseline.

Recent studies have shown that the utilisation of alternative non-cisplatin based chemotherapy regimens can produce favourable and comparable outcomes to cisplatin-based regimens. The CROSS study assessed carboplatin in combination with low dose paclitaxel in a neoadjuvant CRT approach for operable oesophageal and OGJ tumours (5). Pathological CR and survival rates were comparable to trials using CX regimes. The PRODIGE5/ACCORD17 study used FOLFOX (fluorouracil, leucovorin and oxaliplatin) in



	Median (95%CI)	IQR in months	HR (95%CI)
Renal/hearing impairment, n=19	41.7 (26.4-68.5)	26.4-68.5	*1.00 (ref)*
CX/F, n=42	Not Reached (63.9-NE)	31.1-Not Reached	0.41 (0.18-0.93), p=0.03

Figure 3. *Progression-free survival (PFS) for CX/F vs. CarboX/F renal/hearing impairment only.*

definitive CRT for oesophageal cancer with comparable survival outcomes but reduced toxicity and increased ease of administration compared to CX (12). In addition, platinum substitution of cisplatin with carboplatin, specifically, has also recently been written into trial protocols. In SCOPE- 1 (13), cisplatin was substituted with carboplatin if GFR was below 40 ml/min and in the currently recruiting SCOPE-2 study [NCT02741856], platinum substitution is allowed for hearing impairment or neuropathy. In allowing cisplatin substitution within these protocols, these studies allow an increased population of trial participants and the results will be more clinically relevant to real-life practice.

Conclusion

Our findings showed that, despite treating an older population with increased comorbidity, outcomes of patients with localised OG cancer treated at our institution with carboplatin substitution are not significantly worse than for those patients treated with cisplatin. These findings lend support to the selective use of carboplatin substitution in localised OG cancer.

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