I. REPORT CHECKLIST

The following checklist must be completed and submitted with the project report. By checking an item, *the student and advisor(s) agree that the work has been done appropriately*.

__X__1. If the research report **will be** or has been submitted for publication in a journal, provide the name of the journal here: American Journal of Health-System Pharmacy

__X__2. Project title is concise and clear; lists advisers, course no. & date submitted

__X__3. Abstract is no more than 250 words and retains headings

__X__4. Introduction provides a definition of the topic under study, the importance of the topic, and the issue addressed by the study and is no more than two (2) pages.

__X__5. There is NO literature review section

__X__6. Purpose(s) of project is clearly and concisely stated

__X__7. Methods section uses headings and represents a summary of the methods used. (Actual methods used should be described if they were modified from the proposal.)

__X__8. Data analysis described is appropriate and responds to the purpose.

__X__9. Appropriate tables are included in the results section.

__X__10. Text of results section interprets the findings reported in the tables, not repeating them.

__X__11. The discussion section includes a description of the most important findings, and relates findings to the literature.

__X__12. The final section of the discussion is the limitations section.

__X__13. The conclusions respond to the purpose statement.

__X__14. Reference list uses style from DI class (PhPr 861c) or is specific to journal.

__X__15. Data collection/recording form(s) and/or questionnaire(s)are included in the appendix.

__X__16. Information is placed in the appropriate section—introduction, methods, results, etc.

__X__17. Report does not exceed 15 pages excluding tables & figures & appendices.

Date report submitted: April 17, 2017

Student (1): Merta Cushing

Student (2): Thao Truong

TITLE PAGE

Title of project:

Efficacy and toxicity of capecitabine/oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) in adjuvant and metastatic treatment of colorectal cancer in patients at the Southern Arizona Veteran Affairs Health Care System

Course title: PhPr 896B

Date: April 17, 2017

Faculty advisor(s): Russell Crawford, BPharm, BCOP
Megan Banaszynski, PharmD

Student(s): Merta Cushing
Thao Truong
PharmD Candidates, Class of 2017

ABSTRACT

Specific Aims

To determine the efficacy and toxicity of fluorouracil/leucovorin/oxaliplatin (FOLFOX) versus capecitabine/oxaliplatin (XELOX) in the treatment of colorectal cancer (CRC) in the adjuvant (aCRC) and metastatic (mCRC) setting in Veterans at the Southern Arizona Veteran Affairs Health Care System (SAVAHCS).

Methods

A retrospective chart review was conducted to collect efficacy and toxicity data. Subjects were included based on age, treatment setting and regimen in the preset 5-year period, and appropriate diagnosis via International Classification of Diseases-Revision 9 (ICD-9) codes. Efficacy was measured via 1-year disease-free survival (DFS) for aCRC, progression-free survival (PFS) for mCRC, and overall survival (OS) for both settings.

Main Results

A total of 79 subjects were initially enrolled with 51 and 54 all-male subjects included in the efficacy and toxicity analysis, respectively. Mean range of age was 63-72 years old. Subjects were divided into four groups: FOLFOX aCRC (17) and mCRC (19), XELOX aCRC (10) and mCRC (8). No difference was found in 1-year DFS and OS between aCRC groups, and PFS between mCRC groups; a higher incidence of 1-year OS with FOLFOX in the mCRC setting was noted ($p = 0.03$). No difference was found in toxicity between FOLFOX and XELOX, except a higher incidence of hand-foot syndrome in XELOX ($p = 0.0007$).

Conclusions

Efficacy between FOLFOX and XELOX in aCRC and mCRC is similar, while toxicity is slightly more prevalent in XELOX due to increased hand-foot syndrome incidence. These findings agreed with the results reported by prospective clinical trials.

INTRODUCTION

Colorectal cancer (CRC) develops in the colon or rectum as part of the large intestine. Adenocarcinomas make up more than 95% of all CRC diagnoses.[1] Non-modifiable risk factors for CRC include age, genetics, and family history, while modifiable risk factors include physical inactivity, obesity, low-fiber high-fat diet, smoking, and moderate-to-heavy alcohol use.[1]

CRC is the third most commonly occurring cancer, and the third leading cause of cancer-related deaths in the United States.[1] The highest incidences occur in developed regions such as North America, Europe, Australia, and New Zealand while lower incidences are observed in developing areas such as Central America, Africa, and South Central Asia.[1] Approximately 783,000 new patients are diagnosed every year worldwide and approximately 30% of patients present with metastatic CRC (mCRC) upon diagnosis.[1,2] Patients with early stage CRC have a 5-year survival rate of 88-91%, and those with regional metastasis to lymph nodes and tissues have a 5-year survival rate of 70%.[1]

Patients diagnosed with early stage CRC are considered potentially curable. Surgery is the gold standard with removal of the primary tumor along with adjacent mesenteric and regional lymph nodes. Chemotherapy can be utilized after resection to eradicate micro-metastatic disease and improve disease-free survival (DFS) in the setting of adjuvant CRC (aCRC), particularly with stage III disease. A 5-fluorouracil-based (5-FU) chemotherapy regimen is the standard of care, which can be substituted with oral capecitabine, the pro-drug of 5-FU.[1] Both of these drugs are classified as antimetabolites thereby inhibiting DNA synthesis.[3] The drug 5-FU is often administered with leucovorin, also known as folinic acid, in order to enhance the efficacy of 5-FU.[2]

Common chemotherapy regimens for aCRC include 5-FU/leucovorin/oxaliplatin, also known as FOLFOX, and capecitabine/oxaliplatin, also known as XELOX or CAPOX; typically, these regimens are given for a total of 6 months following surgical resection. A 5-FU-based

regimen is also the standard treatment for mCRC and a double combination is preferred to single agents.[3,4,5]

Some of the most common side effects seen with 5-FU/capecitabine chemotherapy include myelosuppression, diarrhea, and hand-foot syndrome. Hand-foot syndrome may present as mild grade with symptoms of numbness, tingling, erythema, and discomfort of hands/feet; this may progress into a higher grade leading to ulceration, blistering, and severe pain of the hands/feet. Oxaliplatin is an alkylating agent commonly administered in combination with 5-FU-based chemotherapy for CRC patients. The most common adverse effects associated with oxaliplatin include hypersensitivity reactions and neurotoxicity (acute and chronic). Acute oxaliplatin neurotoxicity is described as a transient sensory disturbance with onset of hours to days after infusion; it may present as paresthesias, dysesthesias, or hypoesthesias of hands/throat, which can be exacerbated by cold. Chronic oxaliplatin neurotoxicity presents as persistent sensory peripheral neuropathy that is associated with cumulative doses.[5]

Despite current knowledge regarding specific therapeutic treatments for CRC including XELOX and FOLFOX, there is a lack of studies established among the Veteran population. By assessing the efficacy and toxicity of 5-FU-based regimens in one Veteran population, treatment and management of future patients may be improved.

The purpose of this retrospective cohort study is to examine the differences in efficacy and toxicity of FOLFOX versus XELOX in the aCRC and mCRC treatment setting in the Veteran population at the Southern Arizona Veteran Affairs Health Care System (SAVAHCS).

METHODS

Design:

This study used a retrospective chart review with a retrospective cohort design. It was approved by the SAVAHCS Human Subjects Protection Program Institutional Review Board.

Subjects:

Subjects included in this study were Veterans receiving first-line treatment with FOLFOX

or XELOX for CRC at SAVAHCS between October 1, 2010 and September 30, 2015, with International Classification of Diseases-Revision 9 (ICD-9) codes 153.0, 153.1, 153.2, 153.3, 153.4, 153.6, 153.7, 153.8, 153.9, 154.0, and 154.1. The inclusion criteria were expanded to include several additional ICD-9 codes due to the variability in coding between different providers at SAVAHCS; this ensured that more subjects who had CRC and were treated with FOLFOX or XELOX were captured for this study. Subjects were between 18-89 years old, and had received at least one dose of either study regimen for the toxicity analysis, and completed at least one cycle for the efficacy analysis.

Treatment:

The independent (treatment) variables for this study were the study regimens FOLFOX and XELOX, and treatment setting of adjuvant (aCRC) versus metastatic (mCRC). These variables were collected from electronic medical records and used to divide subjects into the following study groups: FOLFOX aCRC, FOLFOX mCRC, XELOX aCRC, XELOX mCRC.

Measures:

Data were collected using a data extraction form. This data extraction form is a spreadsheet that included the independent, dependent, disease-specific, and demographic variables. These variables were adapted from previous phase 3 prospective studies. The independent variables collected were: treatment regimen (FOLFOX or XELOX), and treatment setting (aCRC or mCRC).

The dependent variables for this study were the efficacy and toxicity of FOLFOX and XELOX. Efficacy was measured via 1-year disease-free survival (DFS) in aCRC, 1-year progression-free survival (PFS) in mCRC, and 1-year overall survival (OS) in both aCRC and mCRC. DFS was defined as the length of time (1 year in this study) after completion of treatment during which the patient survived without signs or symptoms of aCRC; PFS was defined as the length of time (1 year) after end of treatment that the patient survived without progression of mCRC; OS was defined as the length of time (1 year) at start of treatment during

which the patient was still alive. Toxicity was measured via presence of dose reductions or modifications due to toxicity, presence of treatment change due to toxicity, presence and treatment of side effects such as nausea, vomiting, diarrhea, stomatitis, hand-foot syndrome, neutropenia, and neuropathy.

The disease-specific variables were comorbidities, disease stage, and number of doses and cycles received. The demographic variables were age at time of diagnosis, age at beginning of treatment with study regimens, sex, and race.

The data extraction form is attached in Appendix A; the data dictionary utilized in the data extraction form is attached in Appendix B.

Data Collection:

Data was collected through chart reviews using SAVAHCS's electronic health record system.

Data analysis:

The following continuous variables were analyzed by calculating summary means and standard deviations then using a t-test to compare groups: age at time of diagnosis, age at beginning of treatment with study regimens, and number of doses and cycles received. The following categorical variables were analyzed by calculating frequencies and percentages then using a Fisher's exact test (when more than 20% of values were less than 5) or Chi square test (when less than or equal to 20% of values were less than 5) to compare groups: comorbidities, 1-year DFS, 1-year PFS, 1-year OS, presence of dose reductions or modifications due to toxicity, presence of treatment change due to toxicity, number of subjects who experienced side effects, and presence of side effects like nausea, vomiting, diarrhea, stomatitis, hand-foot syndrome, neutropenia, and neuropathy. Incidences of additional side effects were also analyzed; those were cold sensitivity, mouth sores, taste changes, mucositis, appetite loss, and anaphylaxis. The a priori alpha level was set at 0.05.

RESULTS

Figure 1 shows the flow diagram for inclusion of subjects in this study. A list of 79 subjects was initially created based on age of 18 years or older, treatment orders of FOLFOX or XELOX, and diagnosis of aCRC or mCRC through ICD-9 codes. Of the 79 subjects, 25 were excluded after not meeting the inclusion criteria; **Figure 1** describes the reasons for exclusion. A total of 51 subjects were included in the efficacy analysis, and 54 in the toxicity analysis.

The demographic characteristics of the 54 included subjects are shown in **Table 1.** Subjects were divided into one of four groups: 17 in FOLFOX aCRC, 19 in FOLFOX mCRC, 10 in XELOX aCRC, and 8 in XELOX mCRC. There were no statistically significant differences (all calculated p-values were >/= 0.05) in demographic characteristics between groups. The mean age range between groups was 63 to 72 years old, and all subjects were male.

Table 2 shows the results for the efficacy analysis between the four study groups. A total of 51 of the 54 subjects were included in the efficacy analysis due to completion of at least 1 cycle of treatment. There was no significant difference in 1-year DFS between FOLFOX and XELOX in subjects with aCRC (FOLFOX = 88%, XELOX = 78%; p = 0.60). Similarly, there was no difference in 1-year PFS between the two regimens in mCRC (FOLFOX = 22%, XELOX = 0%; p = 0.28). More subjects who received FOLFOX in the mCRC setting met the 1-year OS measure versus XELOX (FOLFOX = 78%, XELOX = 25%; p = 0.03).

Table 3 shows the results of the toxicity analysis between FOLFOX and XELOX. This analysis did not differentiate between aCRC and mCRC since regimen side effects and toxicities are not expected to differ based on the treatment setting. There were no statistically significant differences between the two regimens in regards to dose reductions or modifications and treatment change due to toxicity. In addition, no differences were noted in the various side effects experienced in the two regimens with the exception of hand-foot syndrome; subjects who received XELOX showed a significantly higher incidence of hand-foot syndrome versus those who received FOLFOX (FOLFOX = 0%, XELOX = 33%; p = 0.0007). Nausea, neuropathy, cold

sensitivity, and diarrhea were the most common side effects experienced in both regimens, and the most commonly treated with medications like ondansetron/prochlorperazine, gabapentin, and loperamide/diphenoxylate-atropine (**Table 4**), respectively. Only 36 of the 45 subjects were treated for their side effects.

DISCUSSION

The efficacy analysis of this study showed that there were no differences in 1-year DFS for aCRC and 1-year PFS for mCRC between FOLFOX and XELOX (**Table 2**). This was expected since efficacy between the two regimens has not been shown to be different in prospective trials conducted by Pectasides[6] et al. and Cassidy[7] et al. which evaluated DFS and PFS for longer than 1 year. The 1-year OS was not different among groups except in mCRC, where significantly more subjects met this measure in the FOLFOX group versus the XELOX group. Although OS was not shown to be different between the regimens in literature, several reasons could indicate why this difference was noted in this study. First, the small number of subjects included this study may have skewed the results. Second, due to the nature of practice at SAVAHCS, oftentimes XELOX is reserved for patients who may not be able to tolerate IV infusions. Typically these patients have further metastatic disease and other comorbidities that deem them unsuitable candidates for IV regimens like FOLFOX. As such, those who typically receive XELOX have a worse prognosis than their counterparts who receive FOLFOX. Although this study did not differentiate between prognosis levels of those who received XELOX versus FOLFOX in the mCRC setting, the reasons above could have resulted in less subjects meeting the 1-year OS measure in the XELOX mCRC group. In addition, this study showed that the number of subjects who met the 1-year OS in all 4 groups (**Table 2**) was often higher than the number of subjects who met the 1-year DFS or 1-year PFS. One reason for this could be due to the preset definitions of these measures: the 1-year period for DFS and PFS started after completion of treatment with the study regimens, while the 1-year period for OS started at the beginning of treatment. This difference in definition may account for 3-6 months (typical

treatment duration for subjects in this study) where the 1-year OS was met chronologically while the 1-year DFS and PFS hadn't. In studies conducted by Pectasides[6], Haller[8], Cassidy[7], and Porschen[9], OS was not limited to 1 year; therefore, differences between DFS, PFS, and OS were apparent.

The toxicity analysis of this study showed that overall there were no differences in incidence of side effects between the two regimens with the exception of hand-foot syndrome (**Table 3**). Hand-foot syndrome was significantly more apparent in the XELOX group versus FOLFOX. This finding coincides with published literature by Haller[8], Cassidy[7], and Porschen[9]. The most common side effects were nausea, neuropathy, cold sensitivity, and diarrhea all of which were also the most often treated. These side effects were also commonly found in the literature by the authors listed above. Neuropathy and cold sensitivity are most likely attributed to oxaliplatin which is an integral part of both FOLFOX and XELOX; as a result, it's expected that there would be no significant differences in the incidence of this side effects between the two regimens. The most common treatment for cold sensitivity, neuropathy, and hand-foot syndrome found in this study was dose reduction or modification and treatment change. Although there were no significant differences between dose reductions/modifications or treatment changes between the regimens, there were slightly more subjects whose XELOX regimen was adjusted due to toxicity mainly related to diarrhea, hand-foot syndrome, and neuropathy. Oncology pharmacists at SAVAHCS are generally responsible for monitoring side effects and providing supportive care. Medications with different mechanisms of action were frequently utilized in treating side effects in this study (**Table 4**). This multi-modal approach often resolved side effects more effectively than 1-drug regimens.

The findings of this study were generally similar to those reported in published prospective clinical trials. There were no major differences in efficacy, and there was increased incidence of hand-foot syndrome in XELOX as expected. This indicates that CRC treatment regimens seem to be adequate and do not need optimization based on the results of this study.

However, one implication can be made for practice at SAVAHCS in regards to treatment and prevention of side effects. Although 80% of reported side effects were treated (**Table 3**), efforts can be made to provide further treatment for the most common side effects like nausea (76% treated) and neuropathy (45% treated). Treating these side effects could improve quality of life and allow for less dose reductions/modifications and treatment changes. In addition, due to the small number of subjects included and short duration of this study, further research is needed to more accurately examine efficacy and toxicity of these regimens in the Veteran population. A longitudinal approach is recommended in order to increase the DFS, PFS, and OS periods to more than 1 year.

There were several limitations to this study. First, this a retrospective chart review and as such, the accuracy of the data collected is limited by the vigilance of the healthcare providers at SAVAHCS who are ultimately responsible for recording treatments and their efficacy and toxicity. The number of subjects included in this study is fairly small as compared to published clinical trials; therefore, differences may be more or less apparent in a bigger sample size. Although there were no differences in subject characteristics, this study did not consider the presence of other oncological diagnoses and comorbidities that may have affected the outcomes of the efficacy and toxicity analyses. The limited 1-year observation of DFS, PFS, and OS may not have truly described the efficacy differences between the two regimens since most patients diagnosed with CRC tend to survive for more than 1 year as seen in literature. In addition, since this study was conducted in one VA health facility where all subjects included were older males, the results may not be generalizable to other VA and non-VA health centers, younger subjects, and females.

CONCLUSIONS

There were no statistically significant differences in the efficacy (1-year DFS, 1-year PFS) of FOLFOX versus XELOX in the aCRC and mCRC settings. More subjects with mCRC met the 1-year OS in the FOLFOX group which may be attributed to small sample size and

worse prognosis in the XELOX group. There were no statistically significant differences in the toxicity of FOLFOX versus XELOX with the exception of hand-foot syndrome which was more common in the XELOX group. This finding was expected as it has been noted in published clinical trials.

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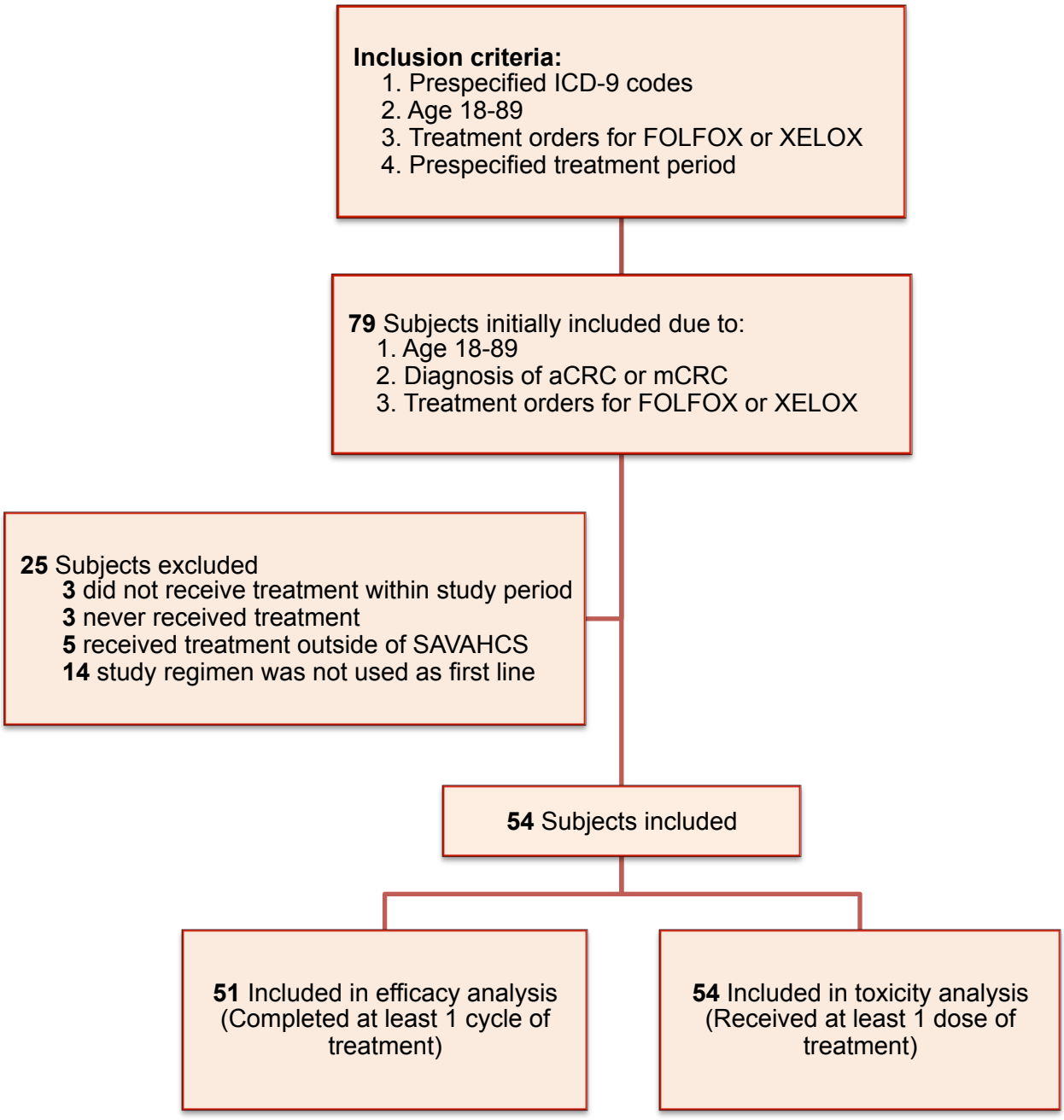

Figure 1. Flowchart of subjects included in efficacy and toxicity analyses. Study period ranged from October 1, 2010 to September 30, 2015. ICD-9 codes included were 153.0, 153.1, 153.2, 153.3, 153.4, 153.6, 153.7, 153.8, 153.9, 154.0, and 154.1. ICD-9 = International Classification of Diseases-Revision 9; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin; aCRC = adjuvant colorectal cancer; mCRC = metastatic colorectal cancer; SAVAHCS = Southern Arizona Veteran Affairs Health Care System.

Table 1. Characteristics of study subjects

	FOLFOX		XELOX	
	aCRC	**mCRC**	**aCRC**	**mCRC**
Number of subjects (N)	17	19	10	8
% Male	100%	100%	100%	100%
Age (years) at diagnosis (Mean, SD)	67 (7.9)	65 (9.7)	63 (12.6)	71 (8.2)
Age (years) at treatment (Mean, SD)	68 (8.0)	66 (9.7)	64 (12.6)	72 (8.2)
Race (N, %)				
White	16 (94%)	14 (74%)	6 (60%)	8 (100%)
Hispanic	1 (6%)	2 (10%)	2 (20%)	0
Other	0	3 (16%)	2 (20%)	0
Comorbidities (N, %)				
One or more comorbidity	15 (88%)	16 (84%)	8 (80%)	5 (62%)
Hypertension	10 (59%)	14 (74%)	6 (60%)	3 (38%)
Hyperlipidemia	9 (53%)	9 (47%)	6 (60%)	3 (38%)
Diabetes	3 (18%)	8 (42%)	4 (40%)	0
Depression	3 (18%)	5 (26%)	3 (30%)	1 (13%)
Chronic kidney disease	3 (18%)	4 (21%)	2 (20%)	2 (25%)
Other*	11 (65%)	9 (47%)	8 (80%)	3 (38%)
Stage of CRC (N, %)				
II	2 (12%)	0	3 (30%)	0
III	15 (88%)	0	7 (70%)	0
IV	0	19 (100%)	0	8 (100%)
Treatments received				
# of Cycles (Mean, SD)	4.7 (1.9)	4.1 (2.4)	5.6 (2.6)	3.1 (2.2)
# of Doses (Mean, SD)	9 (4)	8 (5)	78 (36)	44 (31)

There were no statistically significant differences (p >/= 0.05) in groups with regards to the following characteristics: number of subjects, sex, age at diagnosis and treatment, race (white versus non-white), comorbidities (0 versus 1+ comorbidity), number of cycles and doses received. P-values were not calculated for the remaining characteristics since statistical difference was unlikely. FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin; aCRC = adjuvant colorectal cancer; mCRC = metastatic colorectal cancer; SD = standard deviation.

*Other comorbidities: Hypothyroidism, chronic obstructive pulmonary disease, heart failure, atrial fibrillation, benign prostatic hypertrophy, asthma

Table 2. Efficacy of FOLFOX versus XELOX in the aCRC and mCRC setting

	FOLFOX	XELOX	P-value
aCRC (N)	**16**	**9**	--
1-year DFS (N, %)	14 (88%)	7 (78%)	0.60
1-year OS (N, %)	16 (100%)	9 (100%)	1.00
mCRC (N)	**18**	**8**	--
1-year PFS (N, %)	4 (22%)	0	0.28
1-year OS (N, %)	14 (78%)	2 (25%)	0.03*
Combined aCRC + mCRC (N)	**34**	**17**	--
1-year DFS/PFS (N, %)	18 (53%)	7 (41%)	0.56
1-year OS (N, %)	30 (88%)	11 (65%)	0.07

*P-value of 0.03 showed that the number of subjects who met 1-year OS in mCRC was significantly higher in FOLFOX than in XELOX.
FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin; aCRC = adjuvant colorectal cancer; mCRC = metastatic colorectal cancer; DFS = disease-free survival; PFS = progression-free survival; OS = overall survival.

Table 3. Toxicity of FOLFOX versus XELOX in aCRC and mCRC combined

	FOLFOX	XELOX	Total	Treated
Number of subjects (N)	36	18	54	--
Dose reduction/modification (N, %)	6 (17%)	4 (22%)	10	--
Treatment change (N, %)	8 (22%)	6 (33%)	14	--
Side effects (N, %)				
One or more side effects	30 (83%)	15 (83%)	45	36 (80%)
Nausea	13 (36%)	8 (44%)	21	16 (76%)
Neuropathy	13 (36%)	7 (39%)	20	9 (45%)
Cold sensitivity	14 (39%)	4 (22%)	18	3 (17%)
Diarrhea	8 (22%)	6 (33%)	14	12 (86%)
Appetite loss	5 (14%)	4 (22%)	9	7 (78%)
Neutropenia	7 (19%)	1 (6%)	8	5 (63%)
Hand-foot syndrome*	0	6 (33%)	6	2 (33%)
Vomiting	2 (6%)	3 (17%)	5	4 (80%)
Other**	7 (19%)	1 (6%)	8	3 (38%)

*P-value of 0.0007 showed that the number of subjects who experienced hand-foot syndrome was significantly higher in XELOX versus FOLFOX. P-values for all other side effects were not statistically significant.
**Other side effects included mouth sores, mucositis, taste changes, and anaphylaxis.
FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin.

Table 4. Medications used to treat side effects

Side Effect	Medication	Instances used
Nausea/vomiting	Prochlorperazine	12
	Ondansetron	9
	Olanzapine	1
Neuropathy/cold sensitivity	Gabapentin	9
Diarrhea	Diphenoxylate/atropine	9
	Loperamide	7
Appetite loss	Megestrol	4
	Dexamethasone	2
	Mirtazapine	1
Neutropenia	Filgrastim	5
Mouth sores/mucositis	Miracle mouth wash	3
Anaphylaxis	Diphenhydramine	1
	Prednisone	1

APPENDICES

Appendix A. Data collection form

Demographic Variables	Disease-specific Variables	Efficacy-related Variables	Toxicity-related Variables
Patient unique ID	Comorbidities	1-year DFS: -Time at remission -Time at recurrence	Presence of dose reductions or modifications due to toxicity
Age	Diagnosis of aCRC or mCRC	1-year PFS: -Time at end of treatment -Time at progression	Presence of treatment change due to toxicity
Age at time of diagnosis	Disease stage	1-year OS: -Time at beginning of treatment with study regimens	Presence of side effects: nausea, vomiting, diarrhea, stomatitis, hand-foot syndrome, neutropenia, neuropathy
Age at beginning of treatment with study regimens	Treatment regimen (FOLFOX or XELOX)		Type of treatment of side effects
Sex	Number of doses and cycles received		
Race			

FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; XELOX = capecitabine, oxaliplatin; aCRC = adjuvant colorectal cancer; mCRC = metastatic colorectal cancer; DFS = disease-free survival; PFS = progression-free survival; OS = overall survival.

Appendix B. Data dictionary used in data collection form

Key	Comorbidities	Key	Side Effects	Key	Treatment of Side Effects
1	HTN	**1**	Nausea	**1**	Ondansetron
2	HLD	**2**	Vomiting	**2**	Prochlorperazine
3	COPD	**3**	Diarrhea	**3**	Loperamide
4	HF	**4**	Stomatitis	**4**	Filgrastim
5	DM	**5**	Hand-foot syndrome	**5**	Gabapentin
6	Afib	**6**	Neutropenia	**6**	Diphenoxylate-atropine
7	Hypothyroidism	**7**	Neuropathy	**7**	Miracle mouth wash
8	CKD	**8**	Cold sensitivity	**8**	Megestrol
9	BPH	**9**	Mouth sores	**9**	Dexamethasone
10	Depression	**10**	Taste changes	**10**	Diphenhydramine/prednisone
11	Asthma	**11**	Mucositis	**11**	Mirtazapine
12	Angina	**12**	Appetite loss	**12**	Olanzapine
		13	Anaphylaxis		

HTN = hypertension; HLD = hyperlipidemia; COPD = chronic obstructive pulmonary disease; HF = heart failure; DM = diabetes mellitus; Afib = atrial fibrillation; CKD = chronic kidney disease; BPH = benign prostatic hypertrophy.