Relative Dose Intensity and Myelotoxicity of FOLFOX4 chemotherapy among colorectal cancer patients at Tikur Anbessa Hospital

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SUMMARY PAGE

PROJECT TITLE

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ACRONYMS

CRC	Colorectal Cancer
HDI	High development index
ASIR	Age standardized Ratio
FAP	Familial adenomatous polyposis
HNPCC	Hereditary non-polyposis colorectal cancer
5-FU	5-fluorouracil
FOLFOX	5-FU and Oxaloplatin
LV	Leucovorin
HIV	Human Immunodeficiency Virus
G-CSF	Granulocyte Colony Stimulating Factor
RDI	Relative Dose Intensity
TASH	Tikur Anbessa Hospital
FOLFIRI	Irinotecan with flour pyrimidine
RNA	Ribonucleic Acid
DNA	Di Ribonucleic Acid
TS	Thymidylate Synthase
IV	Intravenous
DPD	Dihydropyrimidine dehydrogenase
BSA	Body surface Area
CI	Continuous infusion
FOLFIRI	5-FU with Irinotecan
MMR	Mismatch Repair
DI	Dose intensity
NCCN	National Comprehensive Cancer Network
MGF	Myeloid growth factors
DLTs	Dose-limiting toxicities
OPDs	Outpatient Departments
RT	Radiotherapy
RFT	Renal Function Test
LFT	Liver Function test
CAPOX	Capecitabine with Oxaliplatin
ECOG	European Cooperative Group
BMI	Body Mass Index

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Summary (Abstract

Background: Colorectal cancer (CRC) is a major global health problem and public health issue. Despite the improved outcome with cytotoxic treatment of CRC, outcomes are affected by adverse treatment effects and their sequel, often resulting in low Relative dose intensity (RDI), considerable, mortality, morbidity and costs. However, there are no previous studies conducted in our clinical practice setting describing the Relative dose intensity of FOLFOX4 or its predicters.

Objective: Our main objective of the study was to determine FOLFOX4 regimen RDI and its predicters, describe incidence of dose delay and dose limiting neutropenia.

Methods: We conducted a retrospective medical record review on 82 CRC patients treated at Tikur Anbessa hospital between May 2019 and July 2020 with FOLFOX4. RDI was calculated with Excel 2019 and entered in to SPSS 26.0 for summary statistics. Reason for delay were assessed through all the 12 cycles. Dose delay were categorized as > 7 days, 7 to 18 days, and more than 18 days. To identify predicters, sensitivity analyses was performed by categorizing RDI based on 25^{th} and 75^{th} percentile and covariates were entered in to multinomial logistic regression model for multivariate analysis.

Results: We identified 82 patients receiving FOLFOX chemotherapy as first line treatment. The mean age was 45 years, and 42.7% were female. The average RDI was 48.6 %. The proportion of patients receiving average RDI less than 85% is 92.7% (N=76). Among stage II and III subgroups, the patients receiving RDI > 70%, are 22.2% and 19% respectively. Myelosuppression in particular Grade II to IV neutropoenias were dose delaying reason in 61.3% of the cases, while non cytopenia related dose delays were observed in 31.7%(n=26) of the patients. Dose schedule modification resulting in treatment prolongation more than 18 days were affecting 38.3% (N=239) of the cycles. The odds of receiving RDI less than 35% increases by 66%, for each decrease in the cycle number for nadir neutropenia count compared to above 60%; AOR=0.44(CI: 0.22, 0.89) at statistically significant p-value=0.02.

Conclusion: Overall FOLFOX chemotherapy RDI was low. Dose limiting myelotoxicity were the main reason for dose modification and were observed at higher rate affecting majority of cycles, and patients. Cycle number for nadir neutropenia independently predicted the risk of falling in to 25^{th} RDI percentile compared 75^{th} percentile, on the sensitivity analysis.

Keywords: RDI, FOLFOX, Dose delay, Neutropenia, Myelotoxicity

Chapter 1: Introduction

1.1 Background

Colorectal cancer (CRC) is a major global problem and public health issue accounting for about 1 in 10 cancer cases and deaths. In 2018, over 1.8 million new colorectal cancer cases and 881,000 deaths were estimated to occur. CRC is the third most common cancer but the second in terms of mortality. (1) Globally the distribution varies greatly because of presumed difference in the adoption of the risk factors, westernized life styles. (2)The higher incidence rates are in countries with high development index (HDI) while average case fatalities occur in lower HDI settings. Similar regional distribution and incidence rates have also been described for rectal cancer, although the highest rates among males are seen in the Republic of Korea and in Macedonia among females. Both colon and rectal cancer incidence tend to be low in most regions of Africa and in Southern Asia. (1) Because of the lack of population-based registry, data on mortality of CRC in Ethiopia are lacking. However, one population-based study in 2015 showed that CRC is third most common cancer case following Breast and Cervical cancer. According to this study men are more affected than women and Age standardized Ratio (ASRIR) was 8 per 100,000 populations. (3)

Patients might present with symptoms such as weight loss, rectal bleeding or constipation (4) Several factors have been shown to put individuals at risk for CRC, including age, the presence of polyps, inflammatory bowel disease, lifestyle, genetic background and family medical history. (5) Environmental factors such as obesity, physical inactivity, poor diet, and smoking and heavy alcohol consumption account for approximately 80% of all colorectal cancer cases. (6) Genetic susceptibility is associated with familial adenomatous polyposis (FAP) and Lynch Syndrome (hereditary non-polyposis colorectal cancer (HNPCC) which accounts for 10% of all colorectal cancer cases. Individuals who have these diseases have an increased lifetime risk of CRC of up to 80%. (6)

International treatment guidelines recommend to evaluate and treat colorectal cancer (CRC) in multidisciplinary team setting comprising specialists from colorectal surgery,

medical and radiation oncology, nursing, pharmacy and social workers. (7) The three major types of therapy in CRC are surgery, chemotherapy and radiation therapy, each of which is applied differently depending on whether the aim of treatment is curative or palliative (i.e. to control symptoms and extend survival). When used in the curative setting, the purpose of surgery is to completely excise the tumour with tumour free margin; chemotherapy is used to eradicate micro metastatic disease and radiation therapy is used to enhance sphincter sparing and local control of the tumour. In the palliative setting, the tumour may be partly excised to relieve obstruction, chemotherapy is used to achieve an objective response or to stabilize the disease and radiotherapy can help to provide pain relief and to delay symptomatic progression. (8)

The survival of colorectal cancer greatly rely on the stage of the disease at diagnosis and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage; 70% for regional; to 10% for people diagnosed for distant metastatic cancer. (9). survival is likely due to differences in access to diagnostic and treatment services (10) Approximately 80% of patients now survive the first year after diagnosis, and approximately 62% survive 5 years and more. Besides, more recently in advanced CRC other non-classical measures of treatment outcome has gained greater popularity and widely included in majority of studies published these days. They include, stabilization of disease, improvements in quality of life, patient satisfaction and convenience of treatments for patients, and the overall cost-effectiveness or cost benefits associated with therapy; which are increasingly being considered equally important measure of outcome to standard endpoints by clinicians and health care providers.

1.2 Problem Statement and rational

The fluoropyrimidine 5-fluorouracil (5-FU) and analogue compounds are an integral part of treatment for a wide range of solid tumours and remains to be the backbone for combination regimens used to treat metastatic colorectal cancer and as adjuvant therapy of early-stage colon cancer. In adjuvant setting three to six month of Oxaliplatin containing 5FU or its analogs based regimens (FOLFOX/XELOX) are indicated to eradicate micro metastatic disease that would otherwise progress to overt clinical disease in the subsequent years. (11)

Despite the improved outcome observed with cytotoxic treatment of CRC, disease control and long term survival are potentially affected by their adverse effects like myelosuppression and its sequel, representing the most common dose-limiting complications of FOLFOX chemotherapy. (12) With unnecessary or preventable delays leading to undesirable health system inefficiencies, additional costs and future clinical encounters for patients. (13)

Neutropenia is the commonest form of myelosuppression related with FOLFOX chemotherapy with risk of Febrile neutropenia(FN) in 10 to 20 % of the cases and causing chemotherapy dose reductions and delays, reducing relative dose intensity (RDI) and associated with considerable morbidity, mortality, and costs. (12) One of the main strategies used to maintain dose intensity during FOLFOX chemotherapy include prophylactic administration of Granulocyte Colony stimulating factor (G-CSF) in the presence of high risk patient related factors such as, older age >65 years, prior exposure to chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by the tumour, poor performance status, recent surgery and/or open wounds, renal or liver dysfunction, and HIV infection. In palliative setting, however, if the risk is due to the chemotherapy regimen, alternatives such as dose reduction or the use of less myelosuppressive chemotherapy is considered. (14)

Similarly revising dose cancellation policy and relaxing stringent hematologic criteria are suggested as dose intensity maintaining strategy. There is scant evidence that delaying chemotherapy using typical blood count thresholds is necessary to preserve patient safety and many cytopenia related delays may be unnecessary as the rate of FN reported during FOLFOX chemotherapy is low. (8,15) Evaluating RDI, assessing treatment delay, its cause is important to standardize clinical practice and compare outcomes. (16)

FOLFOX chemotherapy regimen is widely used regimen in CRC and data showing dose limiting neutropenia, frequency of chemotherapy infusion cancellations and resulting reduction in RDI, and use of Granulocyte Colony stimulating Factor (G-CSF) have been described in High Development Index Countries (HDICs). (13,15–20) (21) The purpose of this study is to calculate Relative dose intensity (RDI), describe the incidence of chemotherapy dose delay, dose limiting neutropenia during FOLFOX infusion at the largest tertiary hospital in Ethiopia, Tikur Anbessa Hospital (TASH).

1.3 Significance of the Study

This study provides demographic and clinical data of CRC patients admitted for FOLFOX chemotherapy during the year 2019 to 2020 at Oncology Department, TASH. The study evaluated chemotherapy infusion protocol, default rate, and reasons for delaying chemotherapy. The result of this study helps to formulate and devise recommendations on strategies that will help to decrease unplanned delays, including revision of dose cancellation policy, use of selective chemotherapy dose adjustment without concomitant delay in adjuvant setting, and use of supportive treatment for high risk patients for dose limiting neutropenia.

Chapter 2: Literature Review

In addition to direct chemotherapy associated complications such as neutropenia, anaemia, and thrombocytopenia, myelosuppression often results in chemotherapy dose reductions and delays, reducing delivered chemotherapy dose intensity and potentially compromising disease control and long-term survival particularly in patients with responsive and potentially curable malignancies. In this chapter literatures on use of FOLFOX chemotherapy, its clinical pharmacology, relative dose intensity, dose limiting neutropenia and its prevention are briefly discussed.

2.1 Indication of chemotherapy in CRC

Following curative surgery 50 to 60% of patients with CRC have residual micro metastatic disease, progressing to clinically evident disease in the following five years when left untreated. To eradicate this micro metastatic disease a three to six month of adjuvant chemotherapy with regimens containing flour pyrimidine in combination with Oxaliplatin (FOLFOX/CAPOX) is currently offered as the standard of care in CRC patients with stage III and high-risk stage II Patients. Similarly, in advanced stage disease, FOLFOX/CAPOX, or Irinotecan with flour pyrimidine (FOLFIRI) with or without targeted agents are used as first line treatment options after demonstrating clear survival benefit in multiple randomized clinical trials over no chemotherapy. However, with the lack of comparative head-to-head studies between many first-line and second-line regimens in advanced disease, the choice of one regimen versus another for first-line treatment depends on factors such as physician and patient preferences, comorbidities, and convenience rather than efficacy parameters (11,17)

2.2 Clinical Pharmacology

2.2.1 The fluoropyrimidine 5-fluorouracil (5-FU)

The fluoropyrimidine 5-fluorouracil (5-FU) and analogue compounds are an integral part of treatment for a wide range of solid tumours and remains to be the backbone for combination regimens used to treat metastatic cancer and early-stage colon cancer. 5-FU exerts its cytotoxic effects mainly through inhibition of Thymidylate Synthase, incorporation into RNA, and incorporation into DNA. The most common form of drug resistance is because

of alteration in the target enzyme TS with increased expression represents the most commonly described mechanism of resistance. (12)

The commonest route of 5FU administration is through Intravenous (IV) access, with rapid elimination resulting in short half-life of 8 to 15 minutes when given as bolus. The rate limiting hepatic enzyme, dihydropyridine dehydrogenase (DPD), is responsible for 60% to 80% of its inactivation, and its deficiency which is responsible for rare pharmacogenomics syndrome often presenting in the form of severe excessive toxicity involving mucositis and/or diarrhoea, myelosuppression, neurologic toxicity, and in rare cases, death; and if observed following the initial administrations should raise suspicions of possible DPD deficiency. However, routine phenotypic and genotypic screenings for DPD deficiency prior to 5-FU therapy are not yet readily available in the clinic.(22)

Body surface based (BSA) dosing of 5FU is commonly used in clinical practice, however, shown to be related with wide range of variation in 5-FU plasma drug levels, the FU dosing based on plasma 5-FU drug level is being investigated as feasible alternative with 5-FU therapeutic drug monitoring probably improving clinical outcomes and decreasing toxicity. (22)

The antitumor activity of 5-FU is enhanced when used in combination with its biochemical modulator and activator, the reduced folate-Leucovorin (LV), prolonging binding of the drug to its target enzyme. Another strategy which exploits s-phase specificity of drug is to alter schedule of administration to continuous infusion (CI) and prolonging exposure, associated with an improvement in overall safety profile and response rate that also translated into progression free survival benefit (PFS). The predominant myelotoxicity seen with bolus regimen is less severe with CI schedules, but with more dose limiting gastrointestinal toxicities. The dermatologic hand-foot syndrome and cardiac toxicity is more associated with in fusional 5-FU than bolus administration. (12) In CRC, a simple hybrid regimen of bolus and CI schedule of LV-modulated 5-FU is given every two-weekly based on principles originally described by De Graymont. These regimens in general employ a loading dose of 400 mg/ m2 of 5-FU given as an IVB, LV 400 mg/ m2, and then 5-FU by a CI for 22 hours (1,200 mg/ m2) or 2,400 mg/ m2 over 46 to 48 hours. (22)

2.2.2 Oxaliplatin

Oxaliplatin is the only approved active platinum agent in the treatment of colorectal cancer, probably because its better efficacy resulting from less dependence on MMR unlike its other two platinum analogues. (22) It was evaluated in the pivotal Multicentre International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer trial which clearly demonstrated that oxaliplatin plus infusional fluorouracil and LV (FOLFOX) is superior to fluorouracil with LV in terms of 3-year DFS, establishing FOLFOX as standard of care. (23) In advanced setting three European phase III trials of combination protocols of infusional fluorouracil/LV/oxaliplatin (biweekly FOLFOX or weekly FUFOX) were compared with 5-FU/LV as first-line therapy. In all three studies, a higher antitumor activity was noted for the combination regimens, with response rates of approximately 50% and PFS in the range of 8 to 9 months. (23–25)

In the FOLFOX regimen, 85mg/m2 of Oxaloplatin is administerd as Iv bolus over 2 hour every two with 5-FU. Oxaliplatin clinical toxicity is distinct from other platinum drugs: it has no renal toxicity and minimal hematotoxicity. (25) The key side effect and dose-limiting toxicity of oxaliplatin is neurotoxicity, which comes in two distinct forms: an acute, cold-triggered sensory neuropathy, which is temporary, rapidly reversible, and does not appear to cause structural nerve damage; and a chronic cumulative sensory neurotoxicity, which is related to the cumulative dose of oxaliplatin administered over time and constitutes the dose-limiting side effect of oxaliplatin. (22)

2.4 Relative Dose Intensity

Dose intensity (DI) is the total amount of drug delivered over the total time course of treatment. (12) The relative dose intensity (RDI) is the percentage of the planned treatment dose administered during a course of treatment per unit of time (28) APPENDIX II. Retrospective data show increased survival for patients who receive 85% RDI and conversely, mortality curves similar to untreated populations when this threshold RDI is not administered. (29,30)

However a retrospective review by Martin S. et al 2014 failed to show survival benefit for CRC patients receiving lower RDI of Adjuvant oxaloplatin and 5-FU as in mFOLFOX6. (31). Patient and treatment that may contribute to reduced RDI are listed below. (16)

Treatment-related factors

- Planned Dose intensity (DI) reductions (eg,comorbidities),
- Under dosing in overweight or obese patients (eg, using ideal or adjusted body weight for calculations),
- Prolonged and/or severe myelosuppression,
- Under- or non-use of granulocyte colony-stimulating factors (G-CSF), and
- Poor performance status.

Patient-related factors that may contribute to reduced RDI may include

- Appointment cancellations,
- Patient noncompliance,
- Patient knowledge deficits, and restricted access to care.

2.5 Risk factors for febrile neutropenia

Neutropenia could be considered as surrogate marker for RDI and associated with decreased survival in colorectal cancer patients. (19) The National Comprehensive Cancer Network (NCCN) recommends the risk FN assessment model developed by Lyman et al. The patient related risk factors are most important in intermediate chemotherapy category like FOLFOX and their presence upgrade patients to high risk category which in turn prompts the use of prophylactic G-CSF. (14) They include,

- Older age >65
- Prior exposure to chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement by the tumor
- Poor performance status
- Recent surgery and/or open wounds
- Renal or liver dysfunction, and HIV infection

2.9Treatment delay, RDI and dose limiting neutropenia during FOLFOX in literatures

In the land mark MOSAIC trial the addition of oxaliplatin to 5-FU/leucovorin (LV) resulted in a substantial increase in grade III/IV adverse events requiring dose reductions and delays, in particular neutropenia (41.1 vs 4.7 %) and paraesthesia (12.4 vs 0.2 %). Overall, dose-limiting toxicities (DLTs) resulted in the administration of 80.5 and 84.4 % of the planned oxaliplatin and 5-FU doses, respectively. Interestingly, neutropenia was complicated by fever or infection in only 1.8 % of patients. (23)

A 2019 retrospective analysis of 214 patients receiving FOLFOX as standard-of-care therapy was reported by Lawrence G**.** et al. Of 961 evaluable treatment cycles, 124 (13%) had unplanned delays, and 92 of 214 patients (43%) had one or more unplanned delays in cycles 2–6. Cytopenias (neutropenia and/ or thrombocytopenia) were the most common cause of unplanned delays, affecting 34% of patients and accounting for 74 of 124 unplanned delays (60%). (18)

Smoragiewicz *et al.* studied 114 patients receiving FOLFOX as adjuvant chemotherapy for colon cancer; they observed dose-limiting toxicities in 22% of treatment cycles, and most dose-limiting toxicities were associated with treatment delays. Neutropenia accounted for 51% of all dose-limiting toxicities in this series.(31)

Kim *et al.* reported on 246 patients receiving adjuvant chemotherapy for colon cancer, primarily with FOLFOX (2). After three months of treatment (approximately six treatment cycles) 30% of patients had experienced a treatment delay, with hematologic toxicities accounting for most delays. (21)

Chiarotto and Dranitsaris report very low rates of chemotherapy treatment delays during FOLFOX chemotherapy (2.2% of all chemotherapy cycles) (8). Typical thresholds for neutrophil or platelet counts were not applied in this observational series, and treatment was delivered without delay in patients with neutrophil counts as low as 100 neutrophils/mm3 (with dose-reductions in some cases). Despite this aggressive approach, febrile neutropenia was observed in only six patients (4.6%) in this cohort. (20)

A quality improvement review of 84 patients' chart with diagnosis of lymphoma, breast, lung, ovary, or colon cancer who received chemotherapy at an outpatient department. The overall RDI was 83% (n=65, reaching threshold RDI of 85% (n=51) in those receiving adjuvant treatment, whereas for those receiving chemotherapy for metastatic disease the RDI was 76% (n=14). RDI by colon cancer diagnosis was 80%. (16)The second report which assessed *G*-CSF use and appropriateness and chemotherapy cancellation rate and results showed that G-CSF was either prescribed inappropriately or not prescribed when it was indicated in a total of 34.4% of patients of 81 evaluated patients. The cancellation rate was 7.2% with the most common reasons for cancellations being haematological toxicity (21.1%), illness or hospitalization (36.8%), poor physical condition (10.5%), unknown (13.2%), and "other" (18.4%). (28)

In summary, the existing literature suggests that delays and "dose-limiting" toxicities are frequent in routine practice; however, there is scant evidence that delaying chemotherapy using typical blood count thresholds is necessary to preserve patient safety and many cytopenia related delays during FOLFOX chemotherapy may be unnecessary. Evaluating RDI, assessing treatment delay, its cause and use of G-CSF helps to standardize clinical practice in the institutions.

Chapter 3: Objectives

3.1 Primary Outcome

To calculate RDI of FOLFOX chemotherapy and asses its predictive factors

3.2 Secondary outcomes

- To assess incidence of unplanned FOLFOX dose delay
- To describe reasons for unplanned FOLFOX dose delay
- To assess rate of dose limiting neutropenia during FOLFOX

Chapter 4: Methodology

4.1 Study setting

The study was conducted at Tikur Anbessa Hospital, Oncology department, Addis Ababa University, College of Health Sciences. It is largest tertiary hospital and the only hospital with Radiotherapy facility and located in the capital. The Department has OPDs, admission and emergency wards, Day care units, and RT planning and treatment divisions. Currently, it has got also additional rooms at nearby health centre. The department staffs are: nurses, residents, senior oncologists, radiotherapy technicians, physicists, chart keepers and porters.

4.2 Study design

A cross sectional study design in CRC patients taking chemotherapy during the year 2019 to 2020.

4.3 Source population

Patients who were admitted to oncology ward for chemotherapy infusion between May 2019 and July 2020.

4.4 Study Population

Patients with CRC diagnosis who received FOLFOX chemotherapy infusion at Tikur Anbessa Hospital between May 2019 and July 2020 fulfilling the Inclusion criteria.

4.5 Inclusion Criterion

All cases of CRC with histopathology confirmed diagnoses and received FOLFOX chemotherapy as first line treatment during study period and, Age >18 and <80; with evaluable demographic, clinical and treatment related data including staging information, Pre-treatment CBC, RFT, LFT, weight and Height, CBC during each cycle evaluation

4.6 Exclusion Criterion

- Missing chart
- Took less than two cycles

- Age < 18 and > 80
- Multiple tumours
- Non adenocarcinoma histology
- Admitted for FOlFIRI, CAPOX, or 5-FU/LV

4.7 Sampling technique and Sample size

All patients diagnosed with CRC and admitted for FOLFOX chemotherapy as their first line and fulfilling inclusion criterion were analysed.

4.8 Variables

4.8.1 Dependent Variables

RDI, Dose Delay in weeks, Dose limiting neutropenia

4.8.2 Independent Variables

- Age
- Sex
- ECOG Performance status
- Primary tumour site
- BMI
- Comorbidity
- TNM Stage
- Cycle number for nadir neutropenia

4.9 Operational Definition of Variables

1. Age; Age at start of the treatment
2. ECOG performance status was rated from 0 to 5 according to (Oaken M et al, 1982)
3. Comorbidity- comorbidity data documentation in the chart before the diagnosis will be collected. The modified Charleston comorbidity index will be used as the instrument of comorbidity assessment to assess the comorbidity burden. (33)
4. BMI- From the height and weight data, BMI was calculated, and each participant was categorized as underweight (BMI < 18.5), normal weight (BMI: 18.5–24.9), overweight (BMI 25.0–29.9), or obese (BMI ≥30.0), according to WHO and NIH recommended Guidelines.

5. TNM- Tumours will be classified by the tumour-node-metastasis (TNM) system and staged according to the American Joint Committee on Cancer (AJCC) system as Stages I, II, III, or IV. (34)
6. Primary tumour site will be classified as colon or rectal based on WHO CDIC
7. Neutropenia ANC less than < 1500 at baseline or any cycle according to the CTAE.5
8. Dose intensity (DI) is the total amount of drug delivered over the total time course of treatment. (12)
9. Treatment delay in weeks; delay greater 7 days will be used to identify cycles with dose/treatment delay
10. The relative dose intensity (RDI) is the percentage of the planned treatment dose administered during a course of treatment per unit of time and is calculated (28)

4.10 Data entry and cleaning

A protocol for data identification and abstraction were developed and pretested. Data was collected from patient's medical record chart by a single data collector using pretested format. Before data collection, training was given to data the abstractor on the purpose of the study and how to fill the information on structured (formulated) Excel sheet including the exclusion and inclusion criteria. The data collection process was supervised by the principal investigator for completeness and accuracy. Data was cleaned with Microsoft Excel and Entered in to SPSS 26.0

4.11 Calculation of RDI

Excel 2019 was used for calculation of RDI. For each patient, the intervals between chemotherapy administrations and the body surface area were collected. The dose of chemotherapy in milligrams per metre squared (mg/m2) was independently recorded for Oxaliplatin and 5-FU. Dose intensity was calculated using the method reported by Hryniuk and Bush, 1984. (35) and Hryniuk and Levine (36) (see Appendix II)

4.12 Data Analysis

SPSS statistical software version 26.0 (SPSS Inc., Chicago, IL, USA) was used for descriptive and inferential analysis. These descriptive statistics include means, 95 % CIs, and ranges for continuous endpoints and frequencies, percentages, and 95 % CIs for categorical endpoints. Patient characteristics were compared with chi square and fishers exact test, for categorical variables, and Independent t-test and ANOVA for continuous variables. Missing

values were not imputed for these analyses. Sensitivity analyses was done based on percentiles. RDI, was classified as <35%, 35 to 59% and >60%. Covariates identified to be significantly at associated with (p=0.025) the benchmark cut off were entered in to Multivariable regression model.

4.13 Ethical Clearance

Letter of ethical clearance was received form Addis Ababa University College of Heath Science institute of research bureau, department of oncology and other responsible bodies. Confidentiality, accountability and neutrality on patients' data was kept throughout the study and afterwards.

Chapter 5: Results and Discussion

5.1 Characteristics of study population

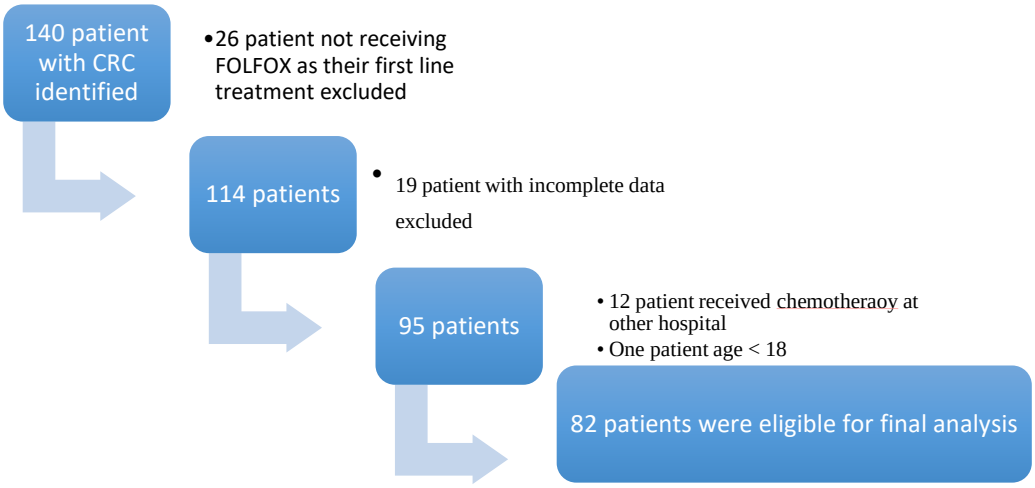

Figure 5. 1 Patient selection and number of patients excluded from the study

Demographic and clinical characteristics of our study population is shown in *Table 5.1* Mean patient age was 44.9 years (range: 73–20 years), and 42.7 % were females. Mean Charleston comorbidity index is 0.9(SD;1.41) and 0.5(SD;0.83) among patients receiving RDI less than 85% and greater than 85%, respectively. The patients mean BSA was 1.58 m2 (range: 2–1.1 m2). Calculates mean BMI is 20.96 kg/m2 (range: 38.5-10.3 kg/m2), and the proportion of underweight and overweight patients were 24% and 8.7 % respectively at chemotherapy initiation.

5.2 Relative dose Intensity

As shown in *Table 5.2* The overall mean RDI for FOLFOX was 48.6 % (SD: 21.71). RDI ranged from 97.7% to 12.7 % across study population. The proportion of patients receiving average RDI more than 85% is 7.3% (N=6). Table 1 also shows that, none of the patients older than 65 years, received average RDI more than 85%. However, there was a higher mean RDI (55%) among patients older than 65 years ranging from 70.3% to 40.3%, as

compared to mean RDI of 48.2% among patients younger than 65, but there was no statistically significant difference on independent to t-test(p=0.49).

The mean RDI is 46.0 % and 47.7% respectively among patients with Stage II and III subgroups, respectively. (*Figure 5.1*) Stage III patients receiving RDI greater than 85% were only 11.11% (N=3), although, at higher percentage (19%) when a lower threshold is used (<70%).

Table 5. 1 Baseline demographic and clinical characteristics of CRC patients receiving FOLFOX4 at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

Variables	**RDI < 85 (%, N)**	**RDI > 85(%, N)**	**Sig.(p)**
Total	**92.7(76)**	**7.3(6)**	
Age(years)			0.67
<65	93.41 (71)	6.61 (5)	
>65	100.00 (6)	0.00 (0)	
Mean (SD, R)	45(13, 73-20)	41(15, 60-20)	
Median (IQR)	45(36-55)	44(29-50)	
Sex			0.69
Male	91.30 (42)	8.70 (4)	
Female	94.44 (34)	5.56 (2)	
Charleston comorbidity Index			
Mean (SD)	0.9(1.41)	0.5(0.83)	0.43
Primary Tumour			0.21
Colon	97.56 (40)	2.44 (1)	
Rectum	87.80 (36)	12.20 (5)	
ECOG			0.93
1	92.00 (69)	8.00 (6)	
2	100.00 (5)	0.00 (0)	
AJCC Stage			0.28
II	100.00 (21)	0.00 (0)	
III	88.89 (24)	11.11 (3)	
IV	91.18 (31)	8.82 (3)	
BSA(m2)			
Mean (SD, R)	1.6 (0.2, 2.0-1.1)	1.6 (0.2,1.8-1.2)	0.81
Median (IQR)	1.6 (1.4-1.7)	1.6(1.5-1.8)	

RDI, Relative dose intensity. SD, Standard deviations. IQR, Interquartile range. R, range.

Table 5. 2 Treatment Characteristics and determinants of mean FOLFOX4 RDI among CRC patients receiving FOLFOX4 at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

Variables	Mean, 95 % CL for Mean	SD, Range
BSA	1.6(1.5, 1.6)	2(2.0, 1.1)
Total Cycles Received	8(7, 8)	3(12, 2)
Total Treatment duration (wks.)	26(24, 28)	9(74, 14)
Oxaliplatin CDI	20.5(18.5, 22.5)	9.1(41.5, 5.4)
5FU CDI	388.6(349.1, 428.2)	179(830.6, 70.0)
Mean FOLFOX4 RDI	48.6 (43.8%, 53.4%)	21.7(97.7%, 12.7%)

CDI, Cumulative dose intensity.

5.3 Dose delay and Myelosuppression

The median dose delay is 4.14 weeks (iqr: 0.54-10.0 weeks). As shown in *Table 5.3* dose delay because of neutropenia's increase from 46.2% (n=12), for delay lasting less than a week, to 87.5% (n=7) and 64.6%(n=31), for delays 7 to 18 days and more than 18 days respectively. Interestingly, the proportion of patients for whom GCSF was used were higher among those experiencing delays lasting longer than 18 days compared to those delays ranging between seven to 18 days.

Table 5. 3 Proportion of patients with dose delays less than seven days, seven to 18 days and more than 18 days among Cytopenia's, frequency of GSCF use and treatment intent among CRC patients receiving FOLFOX4 at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

		Dose Delays (%, N)				
		<= 7 days	7 to 18 days	> 18 days	P=value	Total
Reason for Dose Delays	Non cytopenia related	50.0 (13)	12.5(1	25.0(12)	0.75	31.7(26)
	Neutropenia	46.2(12)	87.5(7)	64.6(31)		61.0(50)
	Anaemia	3.8(1)	-	6.3(3)		4.9(4)
	Thrombocytopenia	-	-	4.2(2)		2.4(2)
GSCF use	No	57.7(15)	25.0(2)	35.4(17)	0.11	41.5(34)
	Yes	42.(11)	75.0(6)	64.6(31)		58.5(48)
Treatment intention	Curative	42.3(11)	75.0(6)	62.5(30)	0.40	57.3(47)
	Palliative	57.7 (15)	25.0(2)	37.5(18)		42.7(35)

.

Myelosuppression, in particular Grade II to IV neutropoenias were dose delaying reason in 61.3% of the cases, while non cytopenia related dose delays were seen in 31.7% (n=26), p=0.75. The dose delay because of isolated severe anaemia or thrombocytopenia accounts for 4.9% (n=4) and 2.9%(n=2) respectively. However, since dose delay because of

bi-cytopenia's were considered as neutropenia, the incidence of dose delaying thrombocytopenia and anaemias could be higher. Furthermore, Of the total 623 chemotherapy cycles delivered to the study population, the average number of completed cycles were 7.6 (SD=3.22, R=12-2) with only 19.5% of patients completing the full planned 12 cycle. As shown in *Figure 5.2* there was a delay of greater than 18 days in 38.3% (N=239) of cycles because of Grade II to grade III neutropenia.

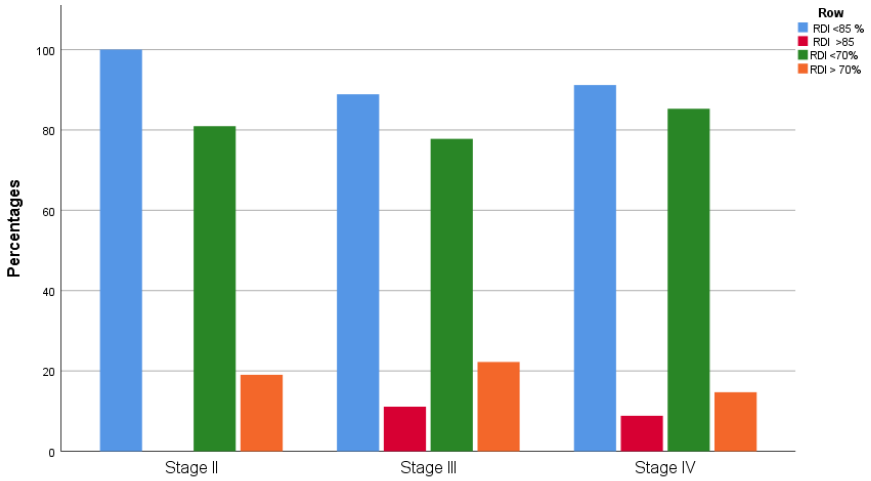

Figure 5. 2 Proportion of stage II, III and IV CRC receiving chemotherapy greater than 85% as compared to RDI >70% at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

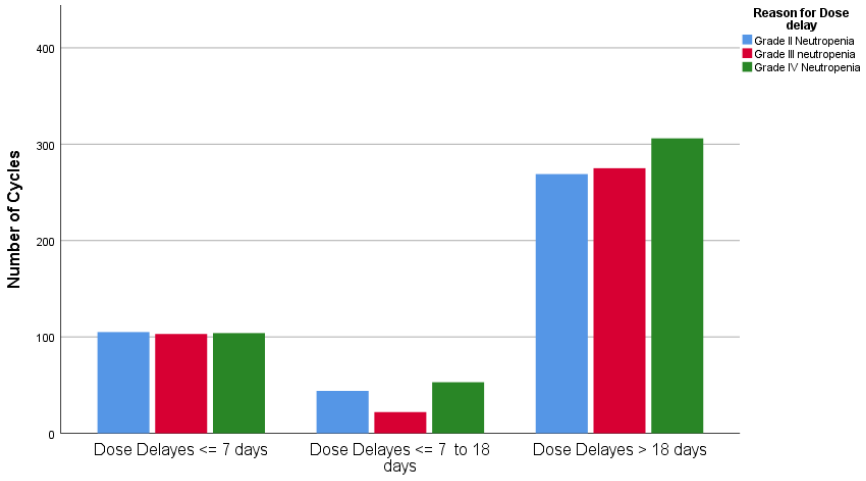

Figure 5. 3 Incidence of dose delays among chemotherapy cycles because of Myelotoxicity among CRC patients receiving FOLFOX4 at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

5.4 Sensitivity Analysis

Among five variables considered for this analysis, four were found to be at statistically significant correlation with the RDI on bivariate analysis. They include, Cycle number for nadir neutropenia, Charleston comorbidity Index, frequency of grade II neutropenia and GCSF use. Further multivariate analysis was calculated for controlling possible confounders, and in order to identify independent predictor; the only predictive factor that showed statistical significance association was cycle for nadir neutropenia.

The model was assessed using chi-square statistic. The chi-square was 26.1 and the P-value was 0.001, providing us that the final model would contain significant relationship between covariates and RDI threshold. The Pearson and variance proved model fitness at P>0.05 The model accounts for 41.8%, 48.0% and 26.5% variance and represents relatively modest sized effects. Two Covariates, Charleston comorbidity Index and Timing of nadir neutropenia were at significant interaction with RDI with the likelihood ratio test, ensuring greater contribution to the final model. Sensitivity of the test was 77.8%, 72.2% for RDI <35% and >60% respectively, with 58.8% specificity.

Our model showed for each one cycle increase of nadir neutropenia cycle number, the log-odds of a case falling in to the RDI < 35% category relative to RDI >60% is predicted to decrease by .817. Compared to RDI>60%, with increasing number of cycles for nadir neutropenia, the odds of falling in to RDI <35% decrease by about 66%. (AOR= 0.44, CI; 0.22, 0.88) with statistically significant p-value=0.022. Overall, these results suggest that patients experiencing nadir neutropenia at earlier cycles are at higher risk of receiving lower RDI as compared to patients experiencing nadir neutropenia at later cycles.

Table 5. 4 Bivariate and Multivariate logistic regression showing predictors of RDI among CRC patients receiving FOLFOX4 at TASH, between May 2019 and July, 2020, A. A, Ethiopia.

		COR, 95% CI, P-value		B	AOR, 95%, CI	P=value
FOLFOX RDI<35%	Ch. Comorbidity Ix.	0.54(0.31, 0.95)	0.024	-1.0	346 (0.092, 1.303)	.117
	Rate of grade II neutropenia	0.09(0.12, 0.68)	0.021	-2.703	.067 (0.004, 1.089)	.057

	Cycle number for Nadir neutropenia	0.36(0.55,0,87)	0.001	-.817	0.442 (0.22, 0.887)	.022
	GCSF use=No	0.27(0.08, 0.80)	0.011	2.983	19.7 (0/140, 2793.09)	.238
The Intercept				3.8		0.01

N.B the Reference group being compared is FOLFOX RDI > 60% and the third group RDI 35% to 60% is not shown. These variables are entered form crosstabulation after showing correlation with RDI at statistically significant p=value, 0.025. COR, Crudes Odds Ratio. AOR, Adjusted Odds Rati

5.5 Discussion

Relative dose intensity (RDI) is increasingly recognized as quality care indicator for systemic chemotherapy and correlates with survival in potentially curable malignancies. We determined an overall average FOLFOX4 regimen RDI to be 49%, with substantially low percentage of patients exceeding the prespecified threshold RDI of 85%. The most common reason for dose delays were neutropenia affecting about two third of cases and patients. On sensitivity analysis, percentile based RDI thresholds, earliest number for nadir neutropenia independently predicted higher risk of receiving lower RDI, OR=0.44, 95% CI (0.22, 0.89) at statistically significant p=0.02.

Our overall mean RDI finding is lower by third as compared to the reference standard used in clinical trials and qualitative reports. The FOLFOX4 RDI reported in the MOSAIC trial was 82.5% in the treatment arm of the study with oxaliplatin plus 5-FU/LV. (23) One of the reasons why higher RDI is seen in clinical trials could be because of adherence strategies including frequent assessment of adherence, and particular patients behaviour such higher expectation from the treatment. Neelam D. et al, Smoragiewicz et al and Aspinall et al. reported higher RDI of 80% to 82.3% among colorectal cancer patients receiving FOLFOX chemotherapy compared to our findings. (31,32,37). However, it must be noted that, most of these studies are conducted in western setting and the larger figures mostly indicates better health care quality, with highly aware practitioners of the importance of dose maintaining. (35,38) Nevertheless, the finding that 30% lesser in delivery of planned relative dose observed at our institution could be used as a benchmark for further quality improvement intervention in similar setting.

Our study also illustrates high rate of planned dose intensity delivery below commonly used threshold for clinical effectiveness, however comparable findings in stage III

subgroups are observed. We found that about 90% of the patients received RDI less than 85%. Similarly, low rate of RDI of 80% was reported by Denduluri. et al. among CRC patients receiving FOLFOX4 chemotherapy. (32). Similarly, low RDI ranged in studies from 26% to 56% when 85% cut off is used. (31) (39) (40) (41). Our observation that all patient above age 65 received less than the desired threshold is also consistent with the notion that this subgroup is mostly undertreated. (19). Furthermore, Stage II and III subgroups receiving more than 70% of the mean RDI, however, were in higher proportion 22% and 19.2% with this cut off. Whilst the findings are supported by literature to a moderate degree, (i.e Aspinall et al. of 19.8% and 40.7%. in Meijiao Z. et al .report. (42), more importantly the fact that these thresholds haven't affect outcomes in CRC patients, (37) it is likely that lower thresholds could be utilized for conducting comparative studies in resource restricted setting in the future.

We have also analysed the reason for treatment delay and observed that myelosuppression was the most common reason for dose schedule change. A delay more than 18 days cycles were cancelled because of Grade II to IV neutropenia in 65.5% of the cycles, affecting 61% of our study population. The incidence is similar to a report by Vanessa et al and kogan et al ranging from 50 to 64%..(43) (18). Incontrast Kim *et al*, reported lower rate of neutropenia's among CRC patients .(21) However, Chiarotto and Dranitsaris reported very low rate of neutropenia resulting in chemotherapy treatment delays during FOLFOX chemotherapy (2.2% of all chemotherapy cycles), moreover, a study using less stringent criteria for neutropenia related dose delays or modification reported interestingly low rate of neutropenia in order of 2%. (20).

Neutropenia's are considered to be a surrogate for higher RDI and previously described to be related to improved outcome. However, on sensitivity analysis, while incidence of grade 2 neutropoenias predicted higher RDI on univariate analysis, a percentile (25% and 75%) based RDI cuts were more likely to be predicted independently by cycle number for nadir neutropenia's, and with reverse relationship, increasing the risk of being in the lower percentile by 66% for every decrement in the cycle number for nadir neutropenia, OR=0.44(CI; 0.22 to 0.89), p=0.02. Our finding confirms previous notions on the impact of depth on the subsequent risk of febrile neutropenia complications and its prevention.(14,27,44,45)

The strength of our study is collection of detailed chemotherapy data, including chemotherapy regimens, dosage and duration of treatment that would offers insight into real world practice in low income setting. Limitations of this study include the retrospective nature and limited sample size since we excluded large number of patients due to inadequate or missing data. It should be noted also that our study was observational, and outcomes may have been influenced by unmeasured clinical characteristics or biases.

5.6 Conclusion

In general, the present study is in agreement with previous qualitative studies. The average RDI of FOLFOX4 chemotherapy was low. Most of dose delays were neutropenia related and associated with myelosuppression of which neutropoenias are found to be the main reason in about two third of patients and the total cycles delivered. The average RDI could be predicted by earliest cycle count for nadir neutropenia. The implication being additional clinical predictor enhancing identification of high-risk patients and prophylactic intervention with GCSFs. The high incidence of Myelotoxicity in our patient population implies low tolerability of FOLOFX chemotherapy and needs to be confirmed in well-designed prospective studies.

Recommendations

- To our institution is devising dose cancellation and modification policy with laboratory criteria.
- To the clinician is to increase their knowledge on dose maintaining strategy and utilization of prophylactic interventions rather than using dose postponing as main strategy.

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Appendix I: Data collection format

Date……
Name of Abstractor……..

Demographic Data
MRN…….Name……
Age…….Sex……
Weight…….Height……BSA……

1. Date of Diagnosis……..
2. Comorbidity…….
3. If HIV patient, recent CD4 count…….HAART started? Yes/No
4. Primary tumor Site……..Date of recent surgery……
6. Sites of Metastasis…….Bone marrow involvement? Yes/No
7. Baseline WBC……ANC……..Hg…….PLT…….
8. Baseline serum Creatinine (Cr)……..Liver Transaminases (ALT)…….
9. Treatment intention (palliative/curative)……..
10. Date Started treatment……
11. Dose of 5-FU (bolus + Infusion)……..Dose of Oxaloplatin……
12. Any Incident of unplanned Dose delay…..Yes/N
13. Any Incident of unplanned dose reduction? Yes/No

Cycles during dose delay corresponding lab values and use of GCSF

Dose and Lab during Each cycle	1st D15	2nd D1	2nd D15	3rd D1	4th D1	4th D15	5th D1	5th D15	6th D1	6th D15
5-FU dose(mg/m2)										
Oxaliplatin dose(mg/2)										
WBC/uL										
ANC/uL										
Hemoglobin										
PLT										
Dose Delay (weeks)										
G-CSF Use(yes/No)										
Antimicrobial use(yes/No)s										

14 Date of last chemotherapy cycle…….
15. Date of disease progression/death/last follow up date…….

Appendix II: Steps used in calculation of RDI for individual patient (i,ii)

Step 1: Calculate Cumulative Dose of Drug
C1 CDFU + C2 CDFU + C3 CDFU + C4 CDFU + C5 CDFU + C6 CDFU+ C7 CDFU+C8 CDFU+C9 CDFU+C10 CDFU C11 CDFU + C12 CDFU = total mg CDFUx

Step 2: Calculate Total Duration of Treatment
Total number of weeks of treatment is calculated by dividing the interval of time in days between cycle (C) 1, day (D) 1 and the last cycle, D16 by 7= No of weeks

Step 3. Calculate DI
Dose intensity (DI) = Cumulative dose received (mg/m2)/(Total duration of treatment in weeks + plus the theoretical number of weeks that would have been required to deliver the missing cycles)

Step 4 Calculate projected DI
Dose of 5-FU per square meter in each cycle divided by the no. of weeks in a cycle
Projected DI for 5FU = (2400mg/m2)/two week)=1200mg/m2/week and for Oxaloplatin projected DI= (85mg/m2)/2=42.5mg/m2/week

Step 5 Calculate Relative Dose intensity of the durg
The RDI for each drug in the combination is calculated as the ratio between the delivered DI and the projected DI

Step 6 Calculate mean Relative dose intensity for both Drugs
For each patient, the RDI for the FOLFOX4 regimen is calculated as the arithmetical mean of the RDI of the two drugs that compose this regimen.
For each patient mean RDI= (RDI of 5-FU + RDI of Oxaloplatin)/2

Step 7 Calculate Summary Statistics for the Group of Patients
To quantify the amount and intensity of the treatment administered to the group of patients, rather than an individual patient, next summary statistics for each variable was performed. After completing calculations for each individual patient, we calculated the mean for each column.

References to Appendix II

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ii. Hryniuk WM, Goodyear M. The calculation of received dose intensity. *J Clin Oncol*. 1990;8(12):1935-1937. doi:10.1200/JCO.1990.8.12.1935

Appendix III: Excel Data entry sheet

CDI Irinotecan	RDI oxalo	RDI 5FU	RDI capcitabine	RDI Irinotecan	meanRDIfolfox	mean RDI folfiri	mean EDI capox	listDateschemotherapycyclesarereceived+AF1:AF
0	31.53%	31.53%	0.00%	0.00%	31.53%	15.77%	15.77%	(13/6/12, 1/7/12), (26/7/12, 27/8/12\anc=700-
0	55.51%	61.06%	0.00%	0.00%	58.28%	30.53%	27.75%	(12/1/12, 26/1/12,) (10/2/12, 28/2/12),(12/3/1
0	49.49%	49.49%	0.00%	0.00%	49.49%	24.75%	24.75%	06/12/11, 20/12/11,(5/13/11,12/1/12) (26/1/12
0	38.28%	42.11%	0.00%	0.00%	40.20%	21.05%	19.14%	4/12/11, 24/12/2011(1100-5), 19/1/12, 20/2/12
0	5.70%	5.70%	0.00%	0.00%	5.70%	2.85%	2.85%	6/2/11, 24/12/11,9/1/12
0	41.85%	41.85%	0.00%	0.00%	41.85%	20.92%	20.92%	(29/11/11, 25/12/11). (5/1/12. 26/1/12(1300).
38	42.21%	42.21%	0.00%	42.29%	42.21%	42.25%	21.11%	(09/08/12, 28/8/12)(17/9/12, 03/10/12)(7/11/1
0	4.27%	4.27%	0.00%	0.00%	4.27%	2.14%	2.14%	5/9/11,19/9/11)(10/10/11,24/11/11)(29/11/11
0	45.65%	47.06%	0.00%	0.00%	46.36%	23.53%	22.83%	(28/8/11, 19/9/11,)(3/10/11,17/10/11)(1/11/1
0	49.04%	49.04%	0.00%	0.00%	49.04%	24.52%	24.52%	(2/1/12, 16/1/12), (14/2/12, 30/2/12)(17/3/12,
38	41.38%	47.06%	0.00%	42.22%	44.22%	44.64%	20.69%	(21/8/11),(12/9/11(capcitabine), 7/10/11), folfi
0	33.18%	34.00%	0.00%	0.00%	33.59%	17.00%	16.59%	26/11/2011, 8/12/11)(9/1/12, 5/2/12, 4/3/12
0	69.42%	71.14%	0.00%	0.00%	70.28%	35.57%	34.71%	10/11/11, 24/11/11, (8/12/11, 21/1/12)(5/2/12
0	71.19%	72.99%	166.84%	0.00%	72.09%	36.49%	119.01%	(14/12/11,15/1/12, 2/7/2, 19/02/12, 26/2/12, 4
0	30.25%	31.37%	0.00%	0.00%	30.81%	15.68%	15.12%	(18/8/11, 16/9/11, 7/10/11,28/10/11), (19/11/1
0	15.14%	19.51%	0.00%	0.00%	17.32%	9.76%	7.57%	20/8/11, 16/9/11=hg=7.3-2, 21/2/12, 26/3/12(c
0	68.71%	70.43%	0.00%	0.00%	69.57%	35.21%	34.36%	(8/12/11,24/11/11)(07/01/2012)(7/1/12,21/1/1
0	39.55%	39.55%	0.00%	0.00%	39.55%	19.77%	19.77%	(24/11/11,8/12/11),(29/12/11, 8/1/12) (28/1/1
0	34.62%	35.48%	73.17%	0.00%	35.05%	17.74%	53.89%	5/9/11, 26/9/11, 26/10/11,11/1/12, 25/2/12=ar
0	71.79%	71.82%	0.00%	0.00%	71.81%	35.91%	35.90%	6/12/11, 20/12/11, 1/13/11, 14/1/12, 30/1/12,
0	77.06%	77.06%	0.00%	0.00%	77.06%	38.53%	38.53%	(22/6/11,6/7/11) 20/7/11,11/8/11)(25/8/11,16
0	78.14%	80.09%	0.00%	0.00%	79.11%	40.04%	39.07%	(17/02/2012, 5/3/12,)(19/3/12, 6/4/12,)(22/4/
0	39.62%	40.61%	0.00%	0.00%	40.12%	20.30%	19.81%	(14/10/11,5/11/11),(1/12/11, 29/12/11), (16/1/
0	37.17%	36.46%	0.00%	0.00%	36.81%	18.23%	18.58%	(30/9/11, 21/10/11)=5Fu/lv, 29/11/11, 15/12/1
0	16.09%	16.49%	0.00%	0.00%	16.29%	8.25%	8.05%	20/5/12, 09/06/2012,
0	26.13%	0.00%	67.55%	0.00%	13.07%	0.00%	46.84%	18/7/11, 17/8/11, 16/9/11=plt=40, 2/3/12, 11/3