A Systematic Review on the Comparison of FOLFIRI and FOLFOX based Chemotherapies in the Treatment of Metastatic Colorectal Cancer

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A systematic review on the comparison of FOLFIRI and FOLFOX based chemotherapies in the treatment of metastatic colorectal cancer" submitted by Nurjahan Islam (16346004) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 30 March,2022.

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Ethics Statement

This is to certify that this project titled “Comparison of FOLFIRI and FOLFOX based Chemotherapies in the Treatment of Metastatic Colorectal Cancer” is submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the School of Pharmacy, Brac University constitutes my own work under the supervision of Mohd. Raeed Jamiruddin, Assistant Professor, School of Pharmacy, Brac University andI have given appropriate credit where I have used language, ideas or writings of another. This project does not involve any human or animal trials. No animals were used or harmed in this project.

Abstract

Metastatic colorectal cancer is a leading cause of cancer death. FOLFIRI and FOLFOX based chemotherapies are known as first line treatments of metastatic colorectal cancer and they are used widely. In this systematic review, a search of PubMed, Google Scholar and www.ClinicalTrials.gov were conducted in order to find the data. Association between efficacy, adverse effects, outcomes and targets of drugs used for the treatment of metastatic colorectal cancer were systematically identified. The study included 13 clinical trials that comprised 2021 patients who received the FOLFIRI and FOLFOX based chemotherapies. Among all the FOLFIRI based chemotherapies, AFLIBERCEPT plus FOLFIRI based combination had higher PFS, higher OS and lower adverse effects. On the other hand, patients receiving panitumumab Plus mFOLFOX6 combination had higher ORR and higher median PFS in comparison to other mFOLFOX6 based chemotherapies. However, AFLIBERCEPT plus FOLFIRI based combination was more efficient but less effective than Panitumumab Plus mFOLFOX6 combination.

Keywords: Metastatic colorectal cancer; FOLFIRI; mFOLFOX6; epidermal growth factor receptor; vascular endothelial growth factor receptor

Dedication

Dedicated to Almighty Allah who gave me the strength and patience to finish this work. My dedication also goes to my beloved parents.

Acknowledgements

All honors belong to Almighty for strengthening me with patience to complete my project work along with the courses necessary to complete Bachelor of Pharmacy (B.Pharm) program.

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List of Acronyms

mCRC	Metastatic colorectal cancer
CIN	Chromosomal instability
MSI	Microsatellite instability
HNPCC	Hereditary non-polyposis colorectal cancer
CIMP	CpG Island Methylator Phenotype
PlGF	placental growth factor
VEGFR1	vascular endothelial growth factor receptor 1
PDGFR	platelet-derived growth factor receptor
VEGFR2	vascular endothelial growth factor receptor 2
VEGF-A	vascular endothelial growth factor-A receptor
VEGFB	vascular endothelial growth factor-B receptor
VEGF	vascular endothelial growth factor
ORR	Objective response rate
PFS	Progression free survival
OS	Overall survival
EGFR	epidermal growth factor receptor
IgG2	Immunoglobulin G2

Chapter 1

Introduction

Colorectal cancer is the third leading cause of cancer that accounts for 10% of all new cancer cases and cancer deaths worldwide (Goldberg, 2005). There are various types of colorectal cancer and metastatic colorectal cancer is a subtype among them. There are three molecular pathways of colorectal cancer that have been identified which are- the chromosomal instability (CIN), the microsatellite instability (MSI), and the CpG Island Methylator Phenotype (CIMP) pathways (Al-Sohaily et al., 2012). In the CIN pathway, APC is an important tumor suppressor gene (Worthley & Leggett, 2010). Microsatellite instability (MSI) occurs in about 15 per cent of sporadic colorectal cancers (-a type of colorectal cancer) and causes hereditary non-polyposis colorectal cancer (HNPCC) (Söreide et al., 2006). CpG island methylator phenotype (CIMP) occurs through epigenetic instability pathway which results in the inactivation of various tumor suppressor genes or other tumor related genes (Wielandt et al., 2020). Although the treatment of metastatic colorectal cancer (mCRC) is complex, various drug combinations are available for the treatment of this disease. However, the efficacy, adverse effects and targets of these drug combination varies. Most of these drugs bind to epidermal growth factor receptor. First line of treatment for metastatic colorectal cancer include- cytotoxic combinations of fluorouracil, leucovorin, and irinotecan (FOLFIRI), infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX), and capecitabine plus oxaliplatin (XELOX), as well as the triplet combination fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) (Fakih, 2015). Of all the chemotherapeutic regimens that are used to treat colorectal cancer, FOLFOX is one of the widely used chemotherapeutic regimen (Hon et al., 2018). Bevacizumab is a drug (which is a monoclonal antibody) and it works against vascular endothelial growth factor that has superior progression-free survival (PFS) and overall survival (OS) outcomes when it is added to 5-FU–based chemotherapy in patients with previously treated and untreated mCRC (Shuch,

Brian; Linehan, B. W. M.L.; Srivasan, 2012). FOLFOX–bevacizumab and FOLFIRI–bevacizumab have similar safety profiles (Shuch, Brian; Linehan, B. W. M.L.; Srivasan, 2012). For this reason, FOLFOX and FOLFIRI are equally compatible chemotherapy partners for bevacizumab (Shuch, Brian; Linehan, B. W. M.L.; Srivasan, 2012). FOLFOX and FOLFIRI are also used with many other drugs (like regorafenib, placebo, cetuximab, bevacizumab, panitumumab etc.) as combination therapy in the treatment of metastatic colorectal cancer. However, metastatic colorectal cancer (mCRC) still remains incurable (Shuch, Brian; Linehan, B. W. M.L.; Srivasan, 2012). Patients who received oxaliplatin regimen suffered more sensory neuropathy and neutropenia while patients receiving FOLFOX had lower rates of severe nausea and vomiting, diarrhea and febrile neutropenia (Kurkjian & Kummar, 2010). Although there are many adverse effects of these drug combinations, advances are developed (in order to treat metastatic colorectal cancer) due to many benefits that these combination chemotherapies give (Kurkjian & Kummar, 2010).

Chapter 2

Drugs used in metastatic colorectal cancer

There are several drug combinations that are available for the treatment of metastatic colorectal cancer. Most of these drug combinations include FOLFIRI based chemotherapy or FOLFOX based chemotherapy. These drug combinations work against various receptors like- epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), placental growth factor (PlGF)/vascular endothelial growth factor receptor 1 (VEGFR1), platelet-derived growth factor receptor (PDGFR). So, the targets of these drug combinations are different and they give different outcomes.

2.1 Bevacizumab:

Bevacizumab is a humanized monoclonal antibody that is directed against vascular endothelial growth factor receptor/ VEGF receptor (Prenen et al., 2013). It is an IgG (immunoglobulin G) antibody that selectively attaches to VEGF-A (vascular endothelial growth factor-A receptor), demonstrating anti-tumor activity by blocking VEGFR2 (vascular endothelial growth factor 2 receptor) (Ohhara et al., 2016). As the side effects of bevacizumab are predictable, it is well suited for use in combination with first- or second-line chemotherapy in the treatment of metastatic colorectal cancer (mCRC) (Hurwitz & Saini, 2006).

2.2 AFLIBERCEPT:

AFILIBERCEPT (VEGF trap) is a totally refined recombinant fusion protein that inhibits angiogenesis (Wang & Lockhart, 2012). Angiogenesis is a process in which new blood vessels are formed. It is necessary for the multiplication and evolution of normal tissues and tumors (Wang & Lockhart, 2012). Aflibercept is a novel agent that targets the process of angiogenesis and has shown effectiveness (in the treatment of metastatic colorectal cancer) in a recent

randomized Phase III trial (Wang & Lockhart, 2012). Though the advantage is confined and the commercial expenses are high, Aflibercept is proved effective when it is used in combination with FOLFIRI for mCRC patients (who have proceeded on an oxaliplatin-based chemotherapy treatment) (Ciombor et al., 2013).

2.3 Panitumumab:

Panitumumab is a fully human monoclonal antibody and it is directed against the epidermal growth factor receptor (EGFR) (Dubois & Cohen, 2009). panitumumab bindings to EGFR reduces cell proliferation and mediator production while also inducing apoptosis (Weber & McCormack, 2008). It is an IgG2 antibody and under evaluation as a single agent in patients not responding to systemic chemotherapy (Weber & McCormack, 2008). Tolerability is high and it can be administered successfully alongside conventional chemotherapy (Weber & McCormack, 2008). Panitumumab + mFOLFOX6 can be considered an effective first-line treatment for patients with metastatic colorectal cancer (Rivera et al., 2017).

2.4 Regorafenib:

Regorafenib is an orally active, potent multi-kinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1,2 and 3 (Strumberg et al., 2012). Regorafenib is a little particle. It prevents angiogenesis, cell growth in the tumor microenvironment and shows activity against neoplasms. (C. J. Ma et al., 2019a). As it inhibits multiple pathways, various adverse effects like- thrombocytopenia, gastrointestinal bleeding, hypertension, diarrhea, proteinuria, hepatoxicity and mucositis are induced (C. J. Ma et al., 2019a). The administration of regorafenib with FOLFIRI is likely to result in satisfactory toxicities and beneficial oncological results in mCRC patients who are treated previously (Ma et al., 2019).

2.5 Cetuximab:

Cetuximab is a monoclonal antibody that works against epidermal growth factor receptor (Jonker et al., 2007). EGFR commonly appears on bowel cancer cells (Cunningham et al., 2004). Cetuximab Can be used alone or in combination with FOLFIRI or FOLFOX in the treatment of metastatic colorectal cancer (mCRC). However, treatment with cetuximab is comparatively costly (Peter C. Fong, 2009). Cetuximab in combination with FOLFIRI had shown to reduce the rate of disease progression (Peter C. Fong, 2009). In patients suffering from mCRC, cetuximab plus FOLFIRI combination was well tolerated and had anti-tumor activity as a second-line therapy (Iwamoto et al., 2014). When cetuximab binds to EGFR, it leads to receptor dimerization followed by endocytosis (Moosmann & Heinemann, 2007). Receptor dimerization is a process that is essential for signaling by the epidermal growth factor receptor (EGFR) tyrosine kinase (Arteaga et al., 1997). After ligand or bivalent antibodies bind to the receptor's extracellular domain, Receptor dimerization occurs (Arteaga et al., 1997).

2.6 Sunitinib:

Sunitinib is an oral, multitargeted inhibitor of VEGFR (vascular endothelial growth factor receptor) (Bello et al., n.d.). In patients with metastatic colorectal cancer, sunitinib monotherapy does not have clinical activity (Al Baghdadi et al., 2020). However, sunitinib can be combined with FOLFIRI or mFOLFOX6 based chemotherapies in the treatment of patients with metastatic colorectal cancer. However, the sunitinib-FOLFIRI combination was more toxic than FOLFIRI or FOLFIRI-bevacizumab combination (Mrossl et al., 2014).

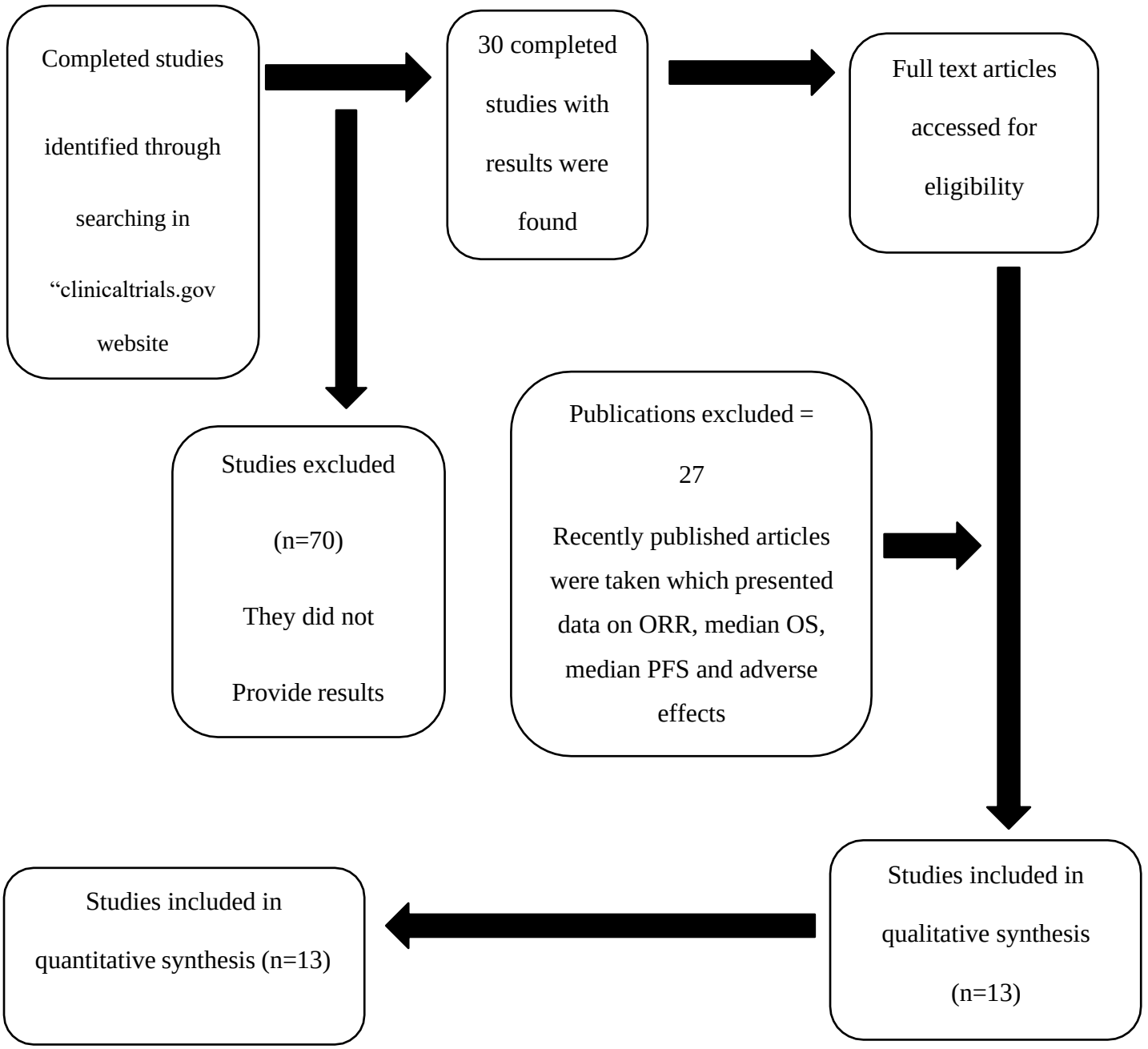
Chapter 3

Methodology:

A total of 13 clinical studies had been identified that included 2021 patients. Studies exploring the association between efficacy, adverse effects, outcomes and targets of drugs (that are used to treat metastatic colorectal cancer) were systematically identified. The primary clinical outcomes included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). A search of PubMed, Google Scholar and www.ClinicalTrials.gov were conducted in order to find the data. Keywords included in the search were 'efficacy', 'outcome in targeting receptors', 'adverse effects', 'Bevacizumab + FOLFIRI-3', 'regorafenib plus perindopril', 'pembrolizumab plus azacytidine', 'AFLIBERCEPT AVE0005 + FOLFIRI', 'Panitumumab + FOLFIRI', 'Regorafenib + FOLFIRI', 'Placebo + FOLFIRI', 'Cetuximab + FOLFOX4', 'Panitumumab Plus mFOLFOX6' and 'Bevacizumab Plus mFOLFOX6', 'Cetuximab Plus FOLFIRI', 'Sunitinib plus FOLFIRI', 'mFOLFOX6 plus sunitinib' and 'mFOLFOX6 plus regorafenib'. The search was limited to clinical trials that had results and articles published in English. If there were any duplicate publications, only the most complete, recent, and updated report of the study was included. The reference lists of included trials and of large systematic reviews were explored as well in order to find supplementary relevant trials. The trials were registered by ClinicalTrials.gov website. The ID numbers of the trials were NCT03288987, NCT02651415, NCT02260440, NCT01571284, NCT00508404, NCT01298570, NCT01228734, NCT00819780, NCT00778830, NCT00668863, NCT01289821 and NCT00609622 respectively. Inclusion criteria were- patients with metastatic CRC, clinical trials that were completed and had results, inclusion of patients who were exposed to a first-line FOLFIRI or mFOLFOX6 based regimen in combination with other drugs (that are used to treat metastatic colorectal cancer), trials reporting OS, PFS and ORR,

various targets and receptors of different drugs that were used in the treatment of metastatic colorectal cancer, adverse effects and efficacy of the drugs used in the treatment of metastatic colorectal cancer, DOI numbers and clinical trial ID numbers of the reported clinical trials, adverse effects that were common like diarrhea, constipation etc. Exclusion criteria were- trials that had no results and were not completed, drugs that were not used in the treatment of metastatic colorectal cancer, early tumor shrinkage of the drugs, trials that had no publications, adverse effects and efficacy that had no data for the similar group of drugs that were reported and some trials (that were not printed in English). In case of the series (which were published by the same institution in different years), simply the current publications were recorded in the analysis in order to exclude feasible overlapping patients. In case of adverse effect and efficacy, two separate tables were generated for FOLFIRI and FOLFOX6 based chemotherapy as well.

Flowchart:


Completed studies identified through searching in "clinicaltrials.gov website
30 completed studies with results were found
Full text articles accessed for eligibility
Studies excluded (n=70) They did not Provide results
Publications excluded = 27 Recently published articles were taken which presented data on ORR, median OS, median PFS and adverse effects
Studies included in qualitative synthesis (n=13)
Studies included in quantitative synthesis (n=13)

Chapter 4

Result:

The study included 13 trials comprising 2021 patients who received the combined treatments (Bevacizumab + FOLFIRI-3, regorafenib plus perindopril, pembrolizumab plus azacytidine, AFLIBERCEPT AVE0005 + FOLFIRI, Panitumumab + FOLFIRI, Regorafenib + FOLFIRI, Cetuximab + FOLFOX4, Panitumumab Plus mFOLFOX6, Bevacizumab Plus mFOLFOX6, Cetuximab Plus FOLFIRI, Sunitinib plus FOLFIRI, sunitinib plus mFOLFOX6 and regorafenib plus mFOLFOX6) that are used in treating metastatic colorectal cancer. Patients who received AFLIBERCEPT AVE0005 + FOLFIRI, had higher PFS (8.4) and higher OS (20.9) (Pentheroudakis et al., 2018) in comparison to other FOLFIRI based chemotherapies. On the other hand, patients who received Cetuximab Plus FOLFIRI, had higher ORR (78%) (Stintzing et al., 2019a) in comparison to other drug combinations used in the treatment of metastatic colorectal cancer. In terms of FOLFIRI based chemotherapy, patients receiving regorafenib plus FOLFIRI had higher death rates (93.33%) (Sanoff et al., 2018). However, Patients receiving Sunitinib plus FOLFIRI had higher abdominal pain (18.31%), diarrhea (77.46%), nausea (76.06%), constipation (40.85%), vomiting (54.93%), headache (16.90%), hypertension (33.80%), anemia (5.63%), abdominal distension (8.45%), fatigue (66.20%) and myocardial infarction (1.41%) (Tsuji et al., 2012) in comparison to other FOLFIRI based chemotherapies. Moreover, patients who received sunitinib plus mFOLFOX6, had higher abdominal pain (20.83%), diarrhea (68.75%), nausea (64.58%), vomiting (34.38%), anemia (28.13%), fatigue (67.71%), dehydration (11.46%) and neutropenia (69.79%) (Hecht, Mitchell, Yoshino, et al., 2015) in comparison to the patients receiving other mFOLFOX6 based chemotherapies. Regarding the efficacy, patients receiving panitumumab Plus mFOLFOX6 had higher ORR (65%) and higher median PFS (13.1 months) (Rivera et al., 2017) in

comparison to the patients receiving other mFOLFOX6 based chemotherapies. However, patients receiving bevacizumab Plus mFOLFOX6 combination had higher median OS (Yamazaki et al., 2016) in comparison to the patients receiving other mFOLFOX6 based chemotherapies.

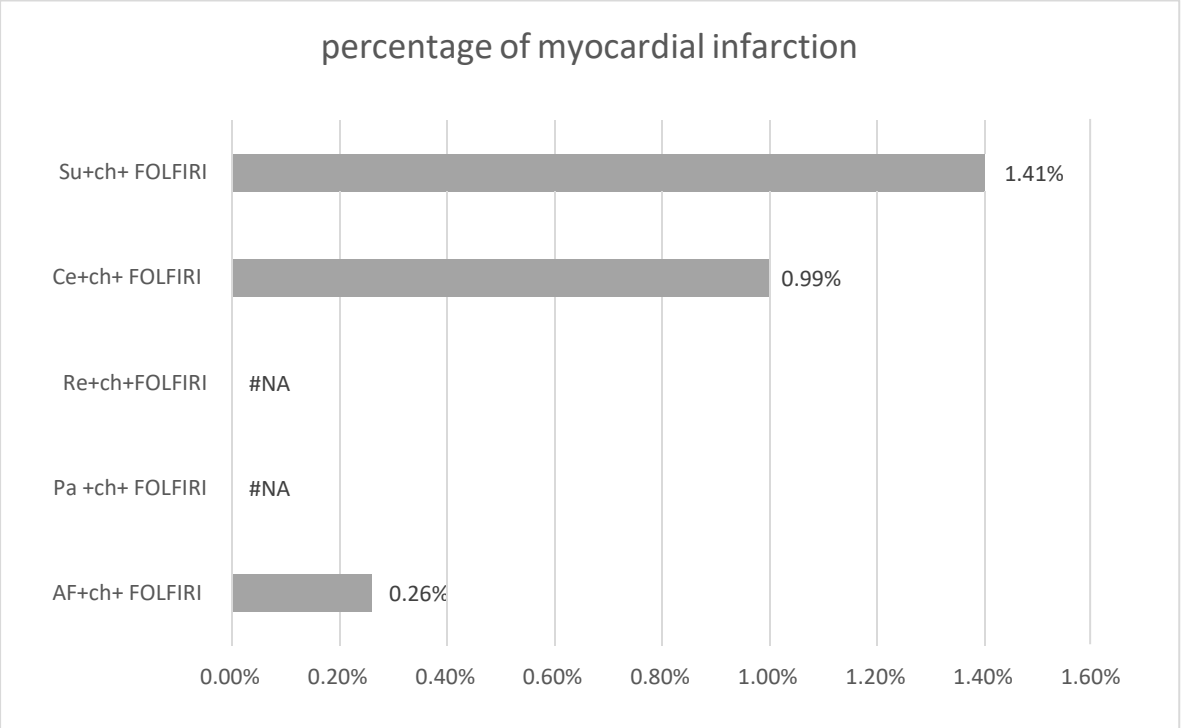
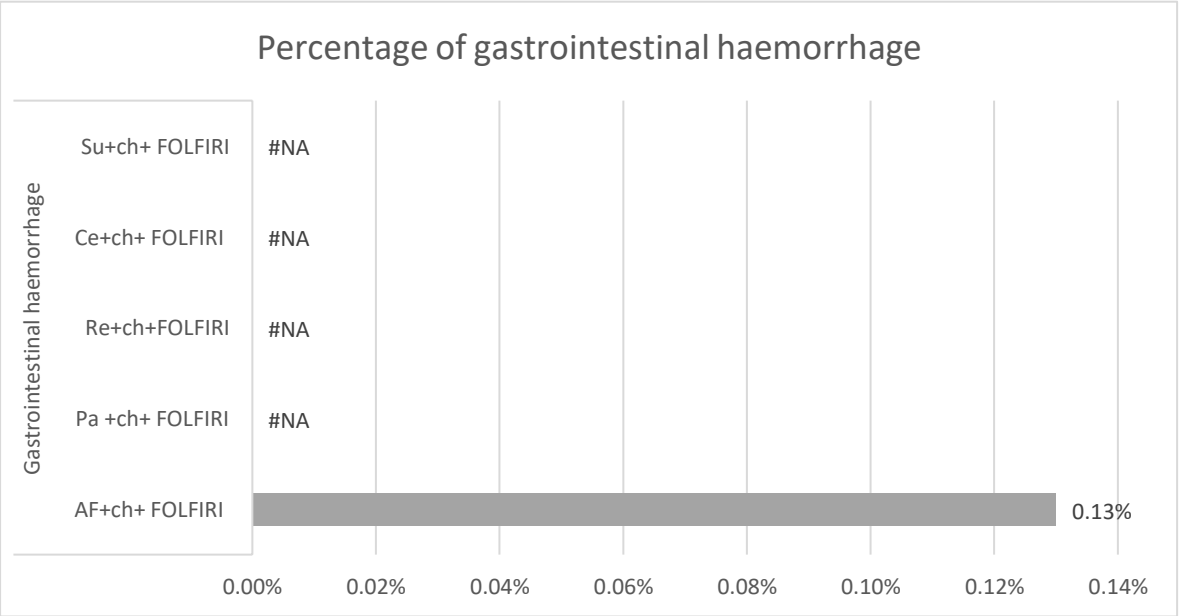


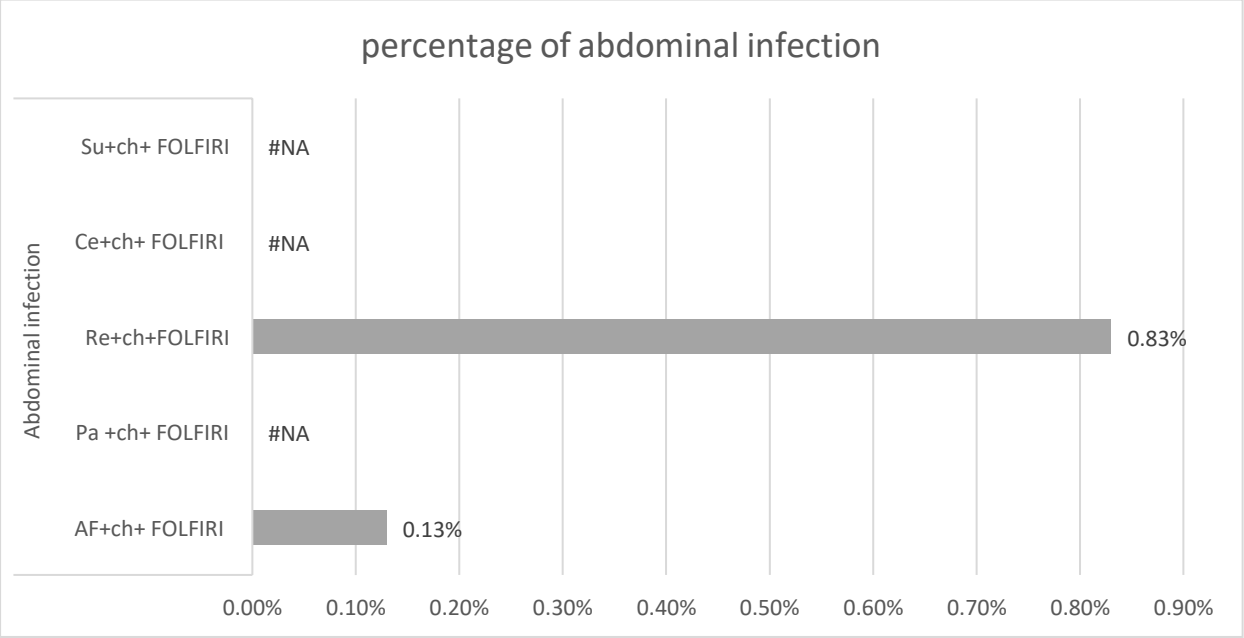
FIGURE 1: Percentage of cardiovascular disorder occurred in patients receiving FOLFIRI based drug chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Myocardial infarction is a common cardiovascular disorder observed in metastatic colorectal cancer patients receiving FOLFIRI based chemotherapies. Figure 1 represents percentage of myocardial infarction occurred in patients receiving FOLFIRI based chemotherapies. Patients receiving FOLFIRI based chemotherapy with sunitinib had the highest rate of myocardial infarction which is 1.41%. On the other hand, 0.99% myocardial infarction rate was observed in patients receiving FOLFIRI based chemotherapy with cetuximab.

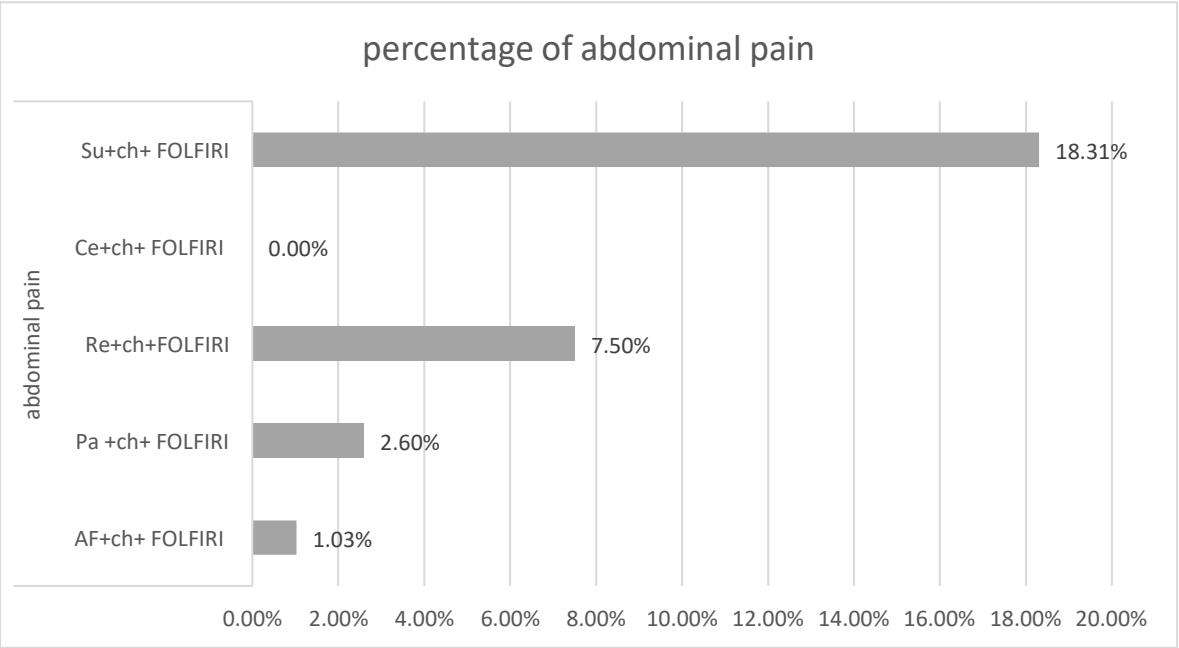
2(A):


Percentage of gastrointestinal haemorrhage
Gastrointestinal haemorrhage
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
#NA
#NA
#NA
#NA
0.13%
0.00%
0.02%
0.04%
0.06%
0.08%
0.10%
0.12%
0.14%

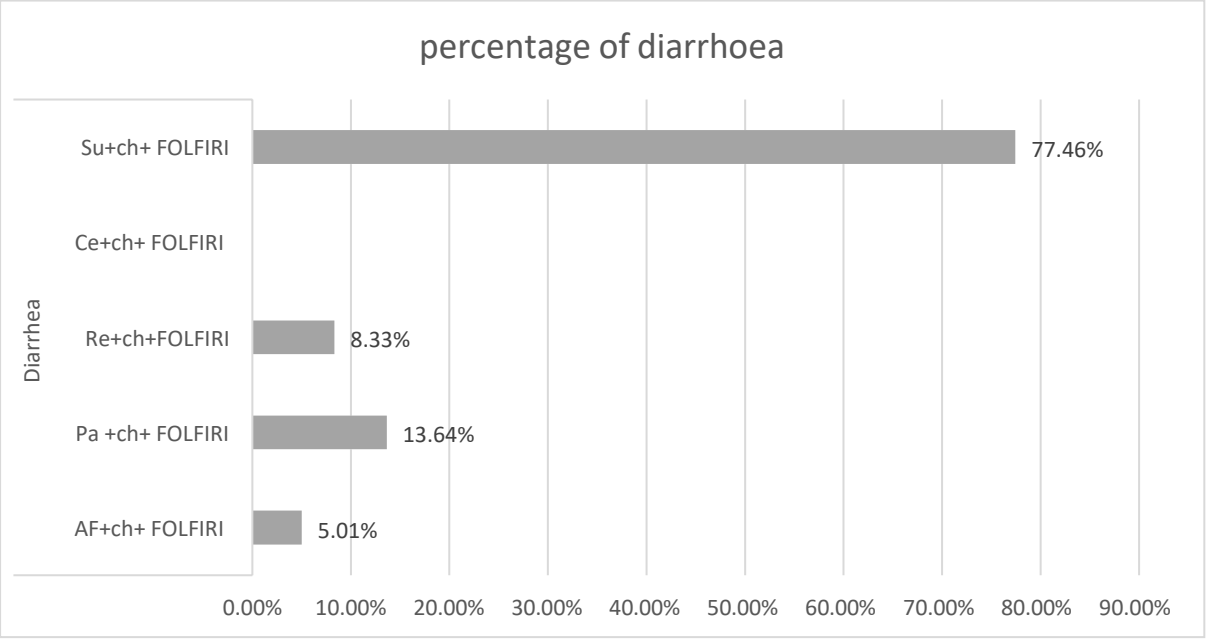
2(B):


percentage of abdominal infection
Abdominal infection
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
#NA
#NA
0.83%
#NA
0.13%
0.00%
0.10%
0.20%
0.30%
0.40%
0.50%
0.60%
0.70%
0.80%
0.90%

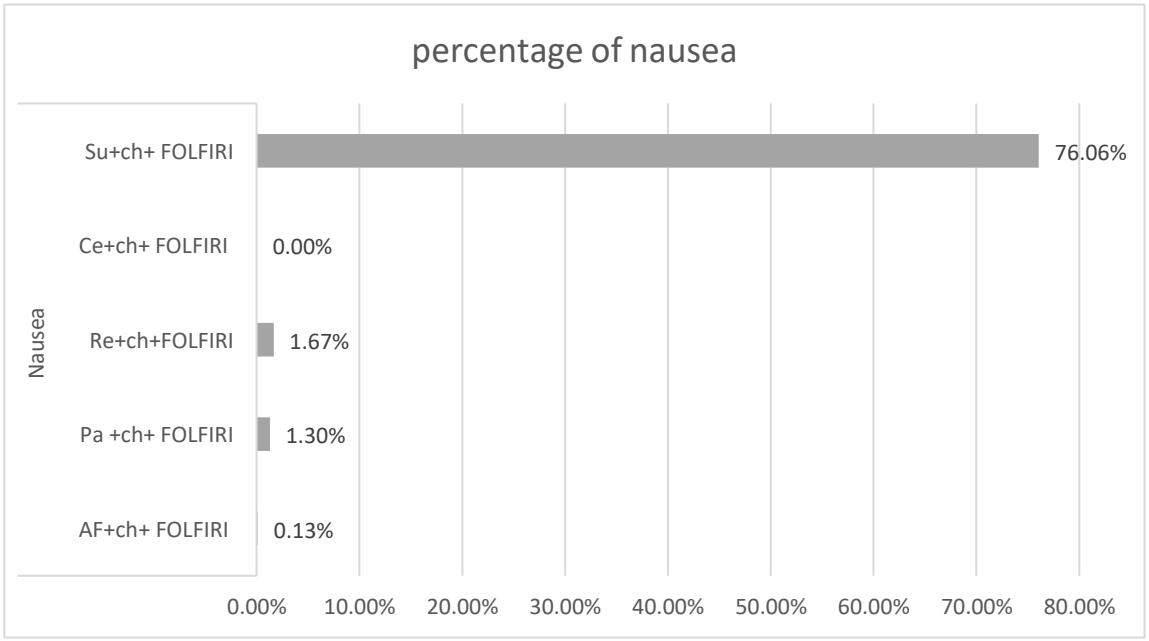
2(C):


percentage of abdominal pain
abdominal pain
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
18.31%
0.00%
7.50%
2.60%
1.03%
0.00% 2.00% 4.00% 6.00% 8.00% 10.00% 12.00% 14.00% 16.00% 18.00% 20.00%

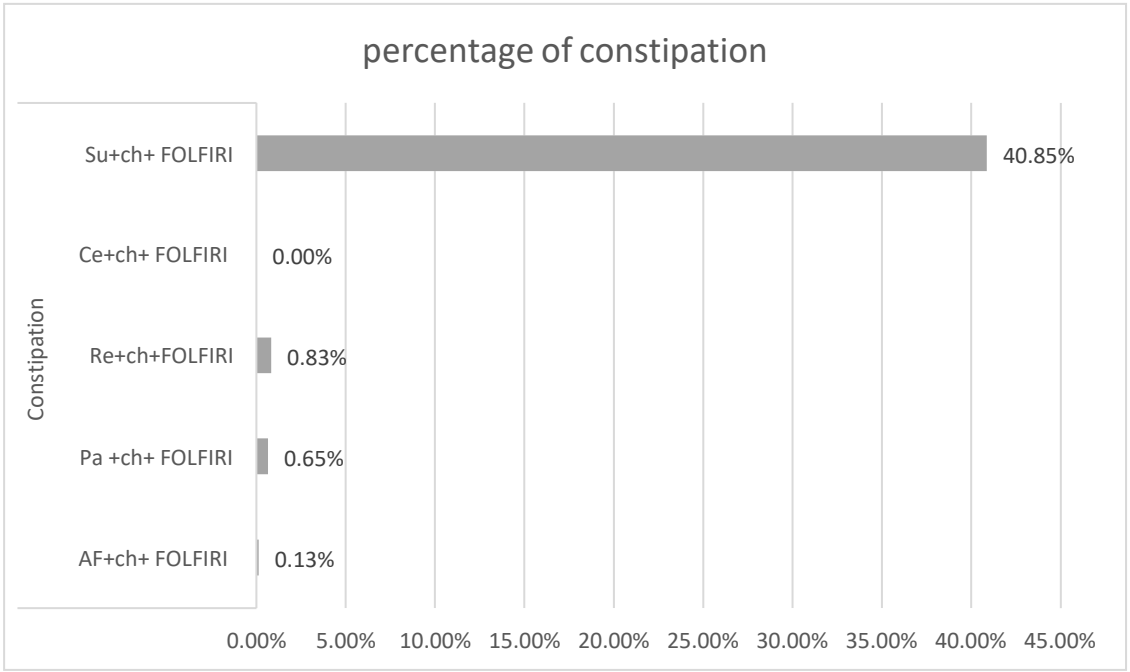
2(D):


percentage of diarrhoea
Diarrhea
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
77.46%
8.33%
13.64%
5.01%
0.00% 10.00% 20.00% 30.00% 40.00% 50.00% 60.00% 70.00% 80.00% 90.00%

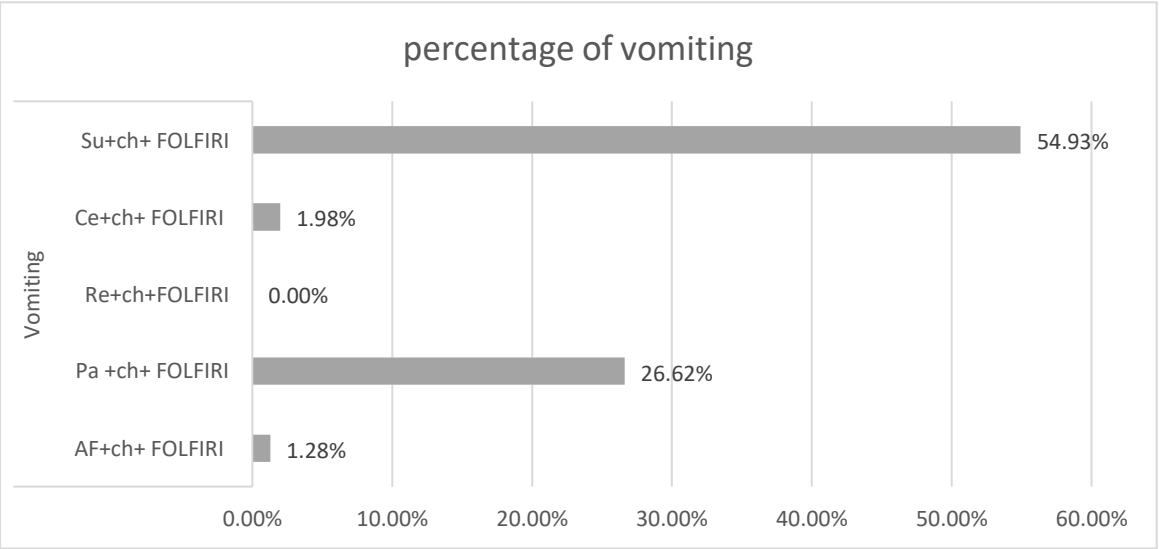
2(E):


percentage of nausea
Nausea
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
76.06%
0.00%
1.67%
1.30%
0.13%
0.00% 10.00% 20.00% 30.00% 40.00% 50.00% 60.00% 70.00% 80.00%

2(F):


percentage of constipation
Constipation
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
40.85%
0.00%
0.83%
0.65%
0.13%
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00% 45.00%

2(G):


percentage of vomiting
Vomiting
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
54.93%
1.98%
0.00%
26.62%
1.28%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%

2(H):

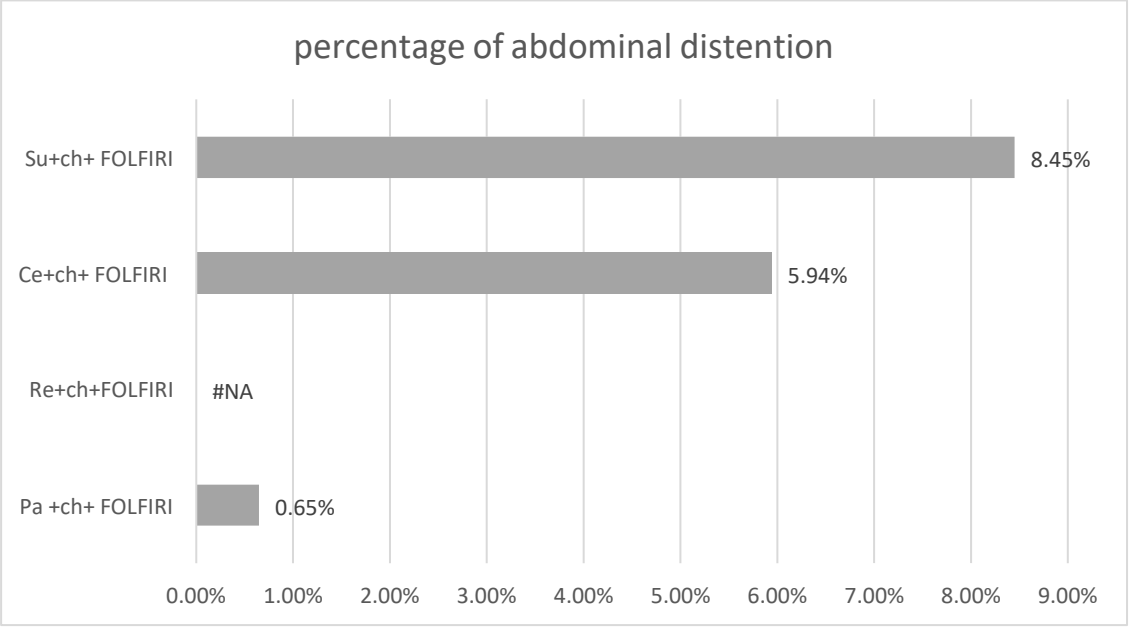
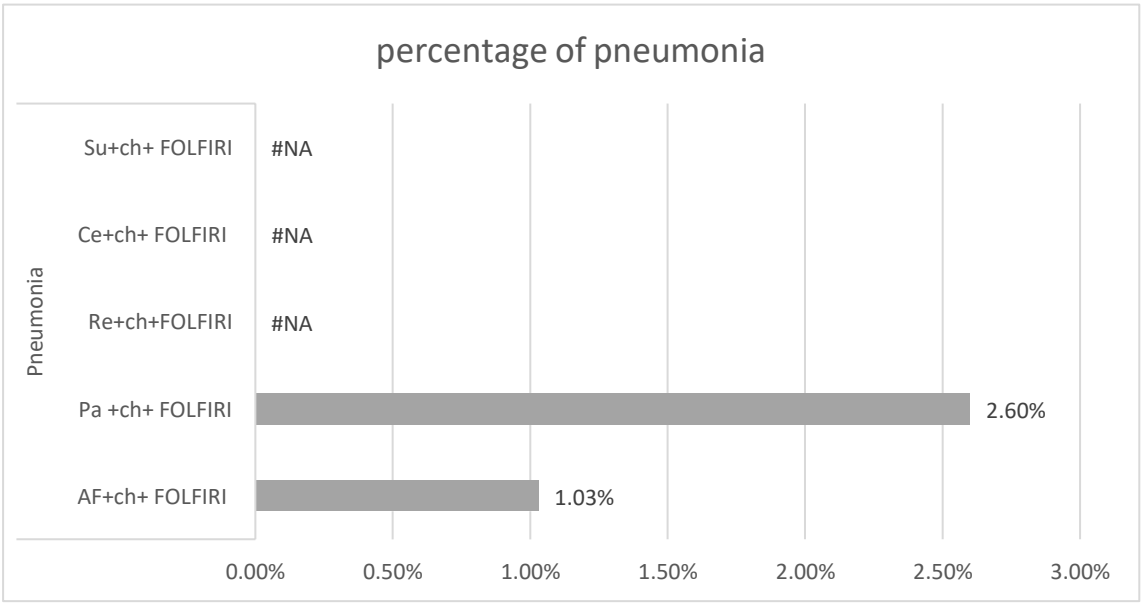

percentage of abdominal distention
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
8.45%
5.94%
#NA
0.65%
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
8.00%
9.00%

Figure 2: percentage of gastrointestinal disorder occurred in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer**.** The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Gastrointestinal disorder is a common adverse effect observed in patients receiving FOLFIRI based chemotherapies. (A) represents percentage of gastrointestinal hemorrhage observed in patients receiving FOLFIRI based chemotherapies. The highest rate of gastrointestinal hemorrhage was observed in patients receiving FOLFIRI based chemotherapy with AFILIBERCEPT. (B) represents percentage of abdominal infection observed in patients receiving FOLFIRI based chemotherapies. The highest rate of abdominal infection was observed in patients receiving FOLFIRI based chemotherapy with regorafenib (0.83%). 0.13% abdominal infection rate was seen in patients who received FOLFIRI based chemotherapy with AFILIBERCEPT. (C) represents percentage of abdominal pain occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of abdominal pain was noticed in patients who received FOLFIRI based chemotherapy with sunitinib (18.31%). 7.50% abdominal pain rate was noticed in patients who received FOLFIRI based chemotherapy with regorafenib. (D) represents percentage of diarrhea occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of diarrhea (77.46%) was observed in patients receiving FOLFIRI based chemotherapy with sunitinib. (E) represents percentage of abdominal nausea occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of nausea (76.06%) was observed in patients receiving FOLFIRI based chemotherapy with sunitinib. (F) represents percentage of constipation occurred in patients receiving FOLFIRI based

chemotherapies. The highest rate of constipation (40.85%) was observed in patients receiving FOLFIRI based chemotherapy with sunitinib. (G) represents percentage of vomiting occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of vomiting (54.93%) was seen in patients who received FOLFIRI based chemotherapy with sunitinib. 26.62% vomiting rate was noticed in patients who received FOLFIRI based chemotherapy with panitumumab. (H) represents percentage of abdominal distension observed in patients receiving FOLFIRI based chemotherapies. The highest rate of abdominal distension (8.45%) was seen in patients who received FOLFIRI based chemotherapy with sunitinib. 5.94% abdominal distension rate was noticed in patients who received FOLFIRI based chemotherapy with cetuximab.

3(A):



3(B):

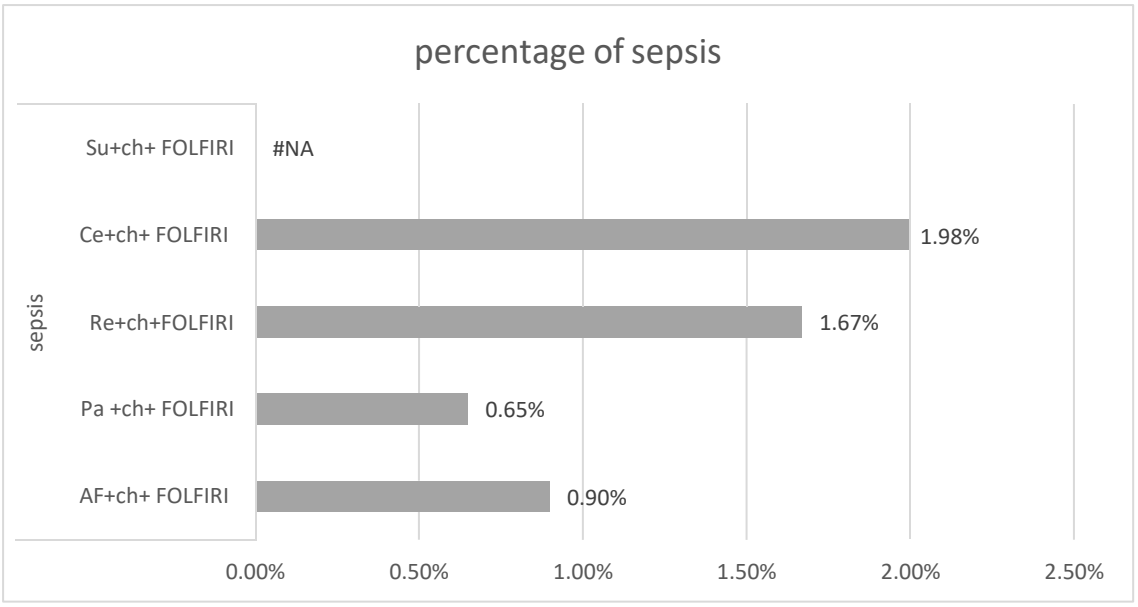
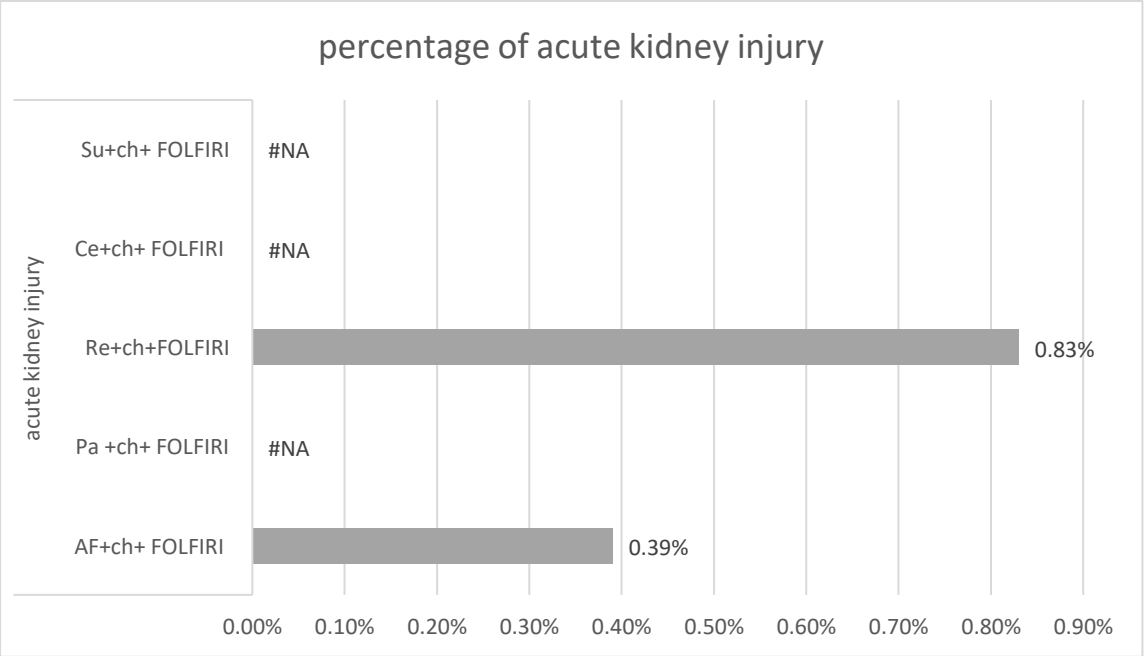


Figure 3: percentage of infections occurred in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch

+FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Infection is a common adverse effect seen in patients receiving FOLFIRI based chemotherapies for the treatment of metastatic colorectal cancer. (A) represents percentage of pneumonia occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of pneumonia (2.60%) was seen in patients who received FOLFIRI based chemotherapy with panitumumab. 1.03% pneumonia rate was observed in patients receiving FOLFIRI based chemotherapy with AFILIBERCEPT. (B) represents percentage of sepsis occurred in patients receiving FOLFIRI based chemotherapies. 1.98% (which is the highest rate of sepsis observed) sepsis rate was noticed in patients who received FOLFIRI based chemotherapy with cetuximab. 1.67% sepsis rate was noticed in patients who received FOLFIRI based chemotherapy with regorafenib.

4(A):



4(B):

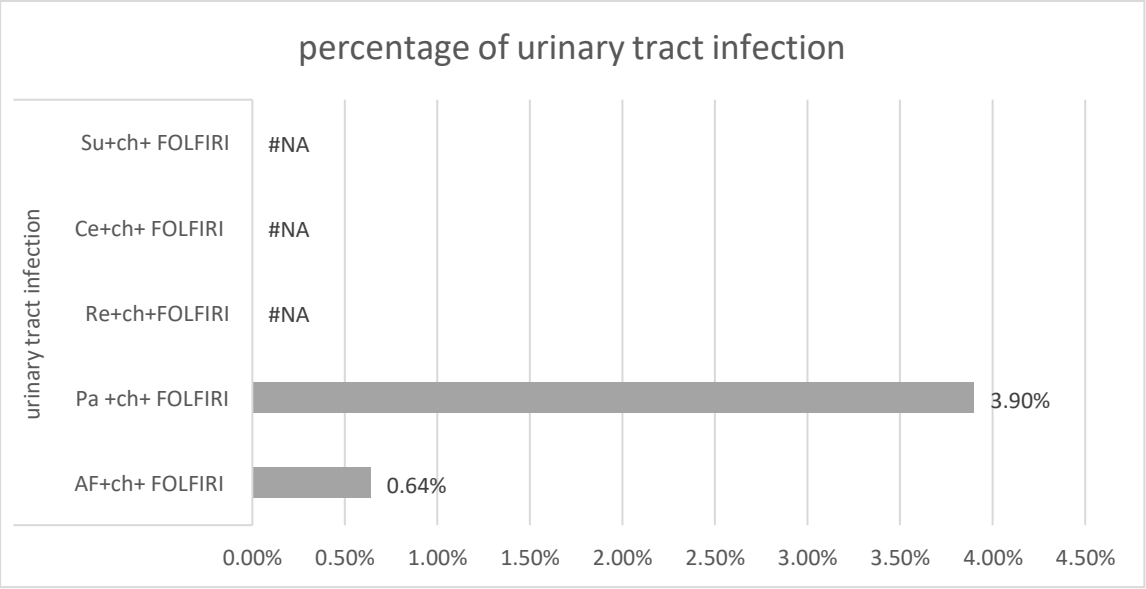
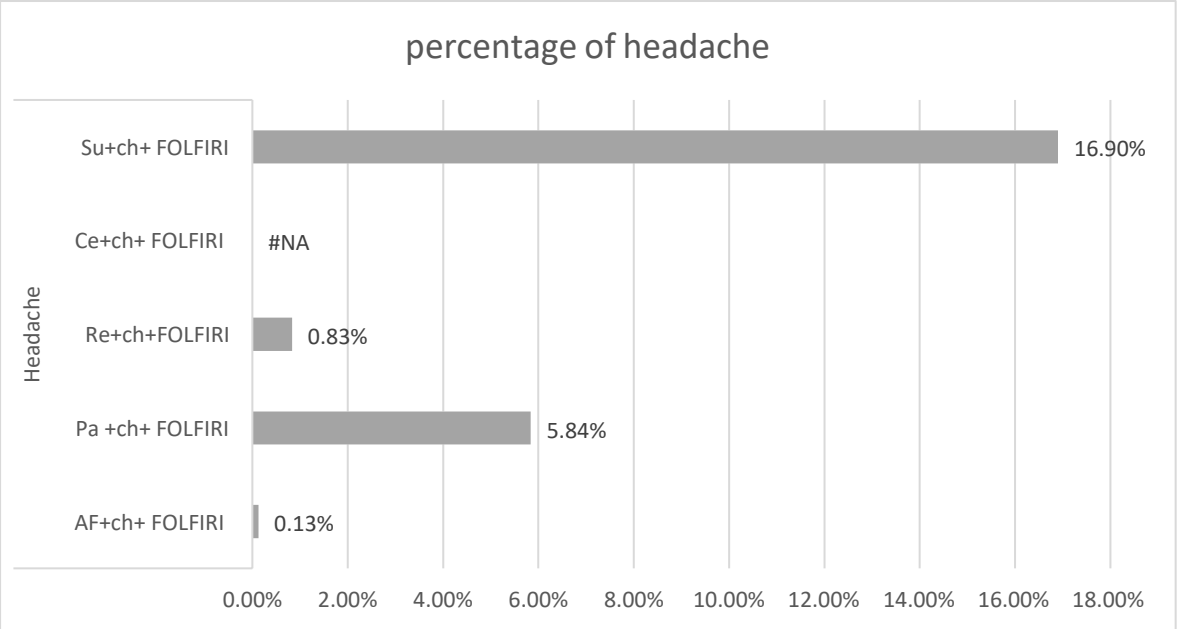


Figure 4: percentage of renal and urinary disorder occurred in patients who received FOLFIRI based chemotherapies for the treatment of metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch

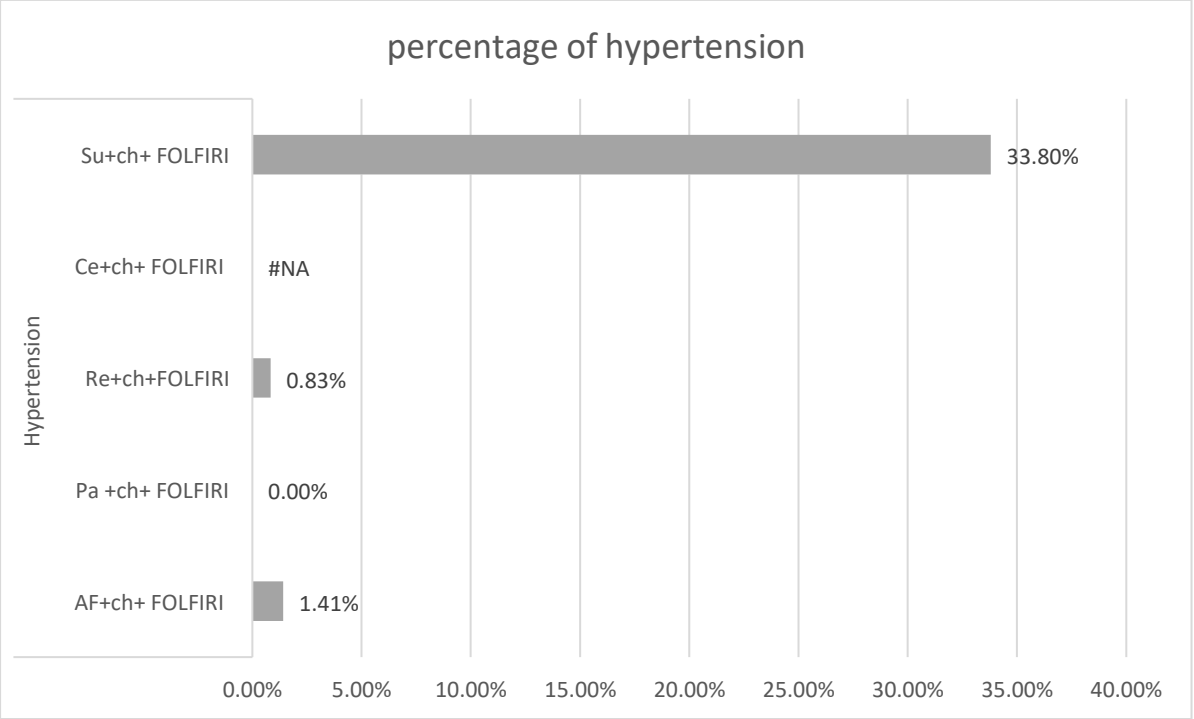
+ FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Renal and urinary disorder is a common adverse effect observed in patients receiving FOLFIRI based chemotherapies. (A) represents percentage of acute kidney injury observed in patients receiving FOLFIRI based chemotherapies. The highest rate of acute kidney injury (0.83%) was seen in patients who received FOLFIRI based chemotherapy with regorafenib. 0.39% acute kidney injury rate was seen in patients who received FOLFIRI based chemotherapy with AFILIBERCEPT. (B) represents percentage of urinary tract infection occurred in patients receiving FOLFIRI based chemotherapies. The highest rate of urinary tract infection (3.90%) was noticed in patients who received FOLFIRI based chemotherapy with panitumumab. 0.64% urinary tract infection rate was noticed in patients who received FOLFIRI based chemotherapy with AFILIBERCEPT.

5(A):


percentage of headache
Headache
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
16.90%
#NA
0.83%
5.84%
0.13%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%
16.00%
18.00%

5(B):


percentage of hypertension
Hypertension
Su+ch+ FOLFIRI
Ce+ch+ FOLFIRI
Re+ch+FOLFIRI
Pa +ch+ FOLFIRI
AF+ch+ FOLFIRI
33.80%
#NA
0.83%
0.00%
1.41%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
40.00%

5(C):

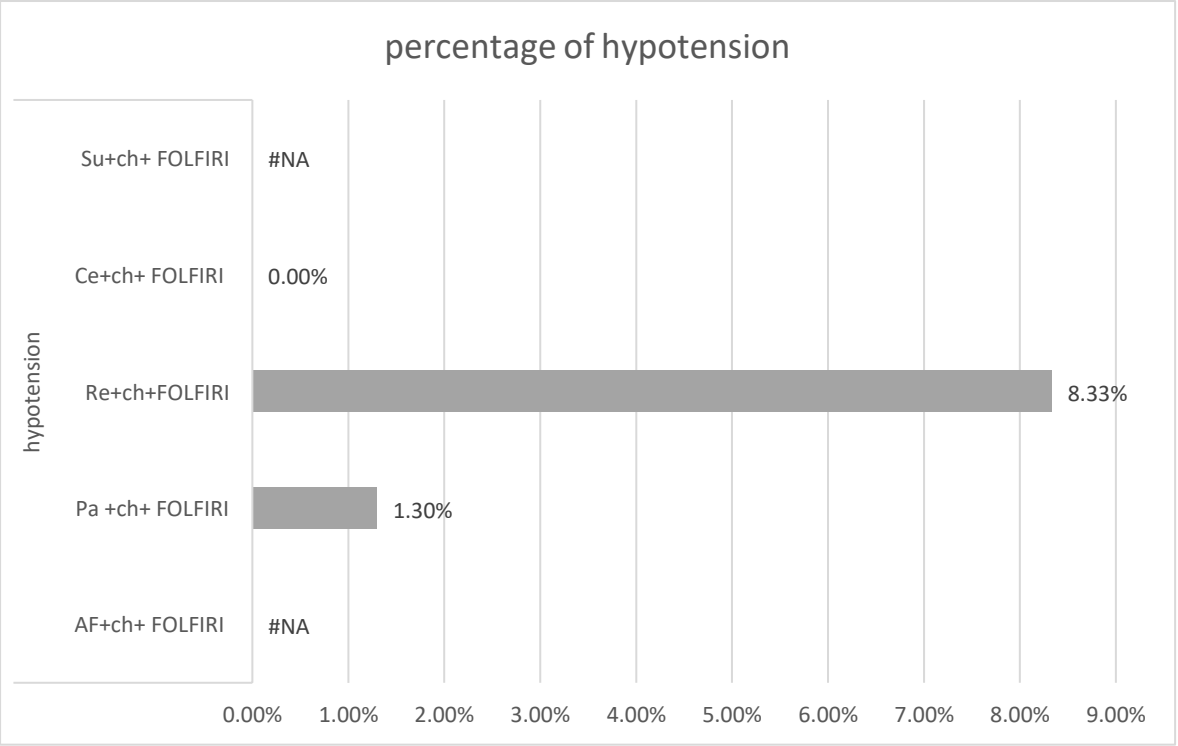
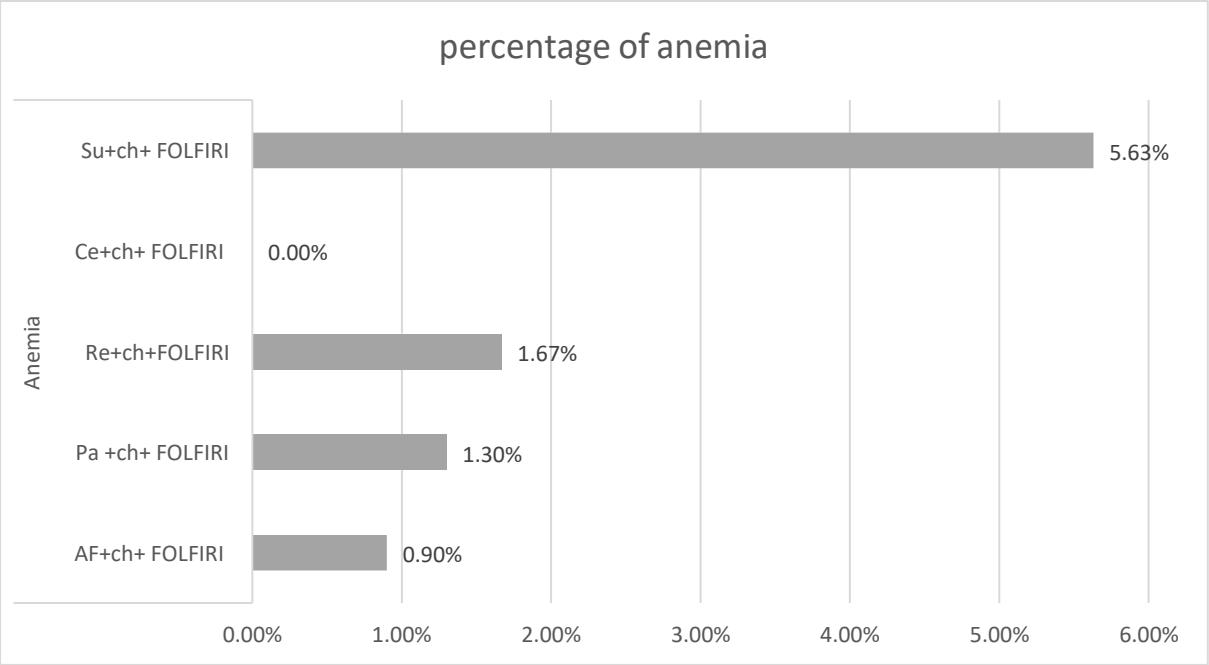


Figure 5: percentage of vascular disorder occurred in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Vascular disorder is a common adverse effect occurred in patients receiving FOLFIRI based chemotherapies in the treatment of metastatic colorectal cancer. (A) represents percentage of headache observed in patients receiving FOLFIRI based chemotherapies. The highest rate of headache (16.90%) was observed in patients receiving FOLFIRI based chemotherapy with sunitinib. (B) represents percentage of hypertension observed in patients receiving FOLFIRI based chemotherapies. The highest rate of hypertension (33.80%) was observed in patients

receiving FOLFIRI based chemotherapy with sunitinib. (C) represents percentage of hypotension observed in patients receiving FOLFIRI based chemotherapies. The highest rate of hypotension (8.33%) was noticed in patients who received FOLFIRI based chemotherapy with regorafenib. 1.30% hypotension rate was seen in patients who received FOLFIRI based chemotherapy with panitumumab.

6(A):



6(B):

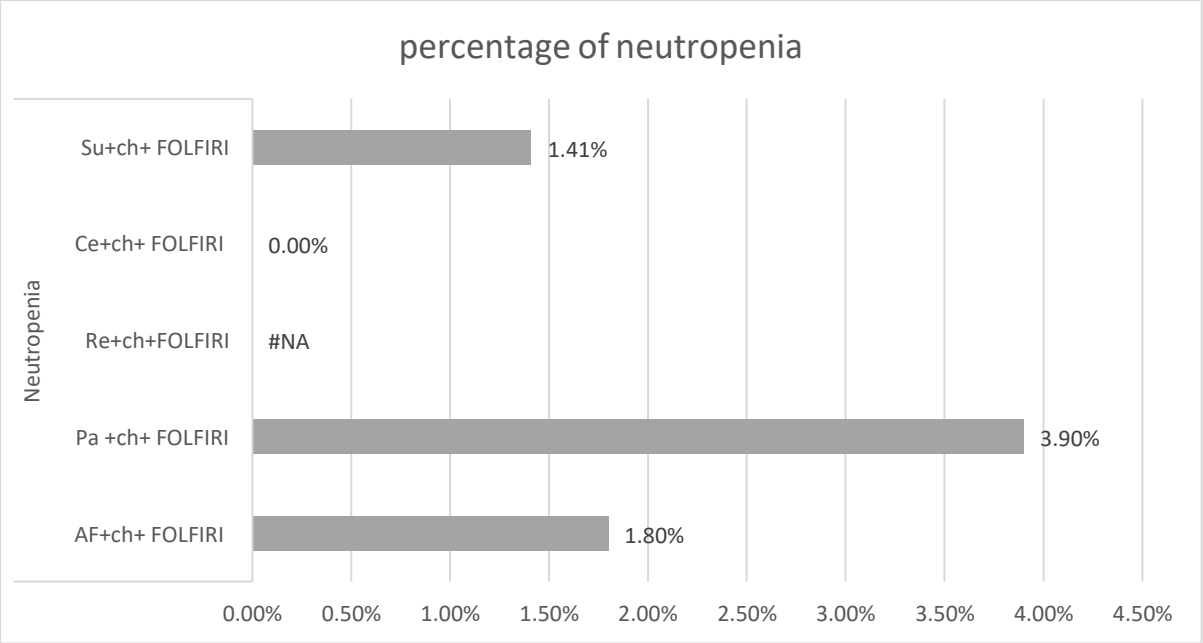


Figure 6: percentage of blood and lymphatic system disorder observed in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF

+ ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Blood and lymphatic system disorder is a common adverse effect observed in patients receiving FOLFIRI based chemotherapies in the treatment of metastatic colorectal cancer. (A) represents percentage of anemia observed in patients receiving FOLFIRI based chemotherapies. The highest rate of anemia (5.63%) was observed in patients receiving FOLFIRI based chemotherapy with sunitinib. (B) represents percentage of neutropenia observed in patients receiving FOLFIRI based chemotherapies. The highest rate of neutropenia (3.90%) was observed in patients receiving FOLFIRI based chemotherapy with panitumumab.

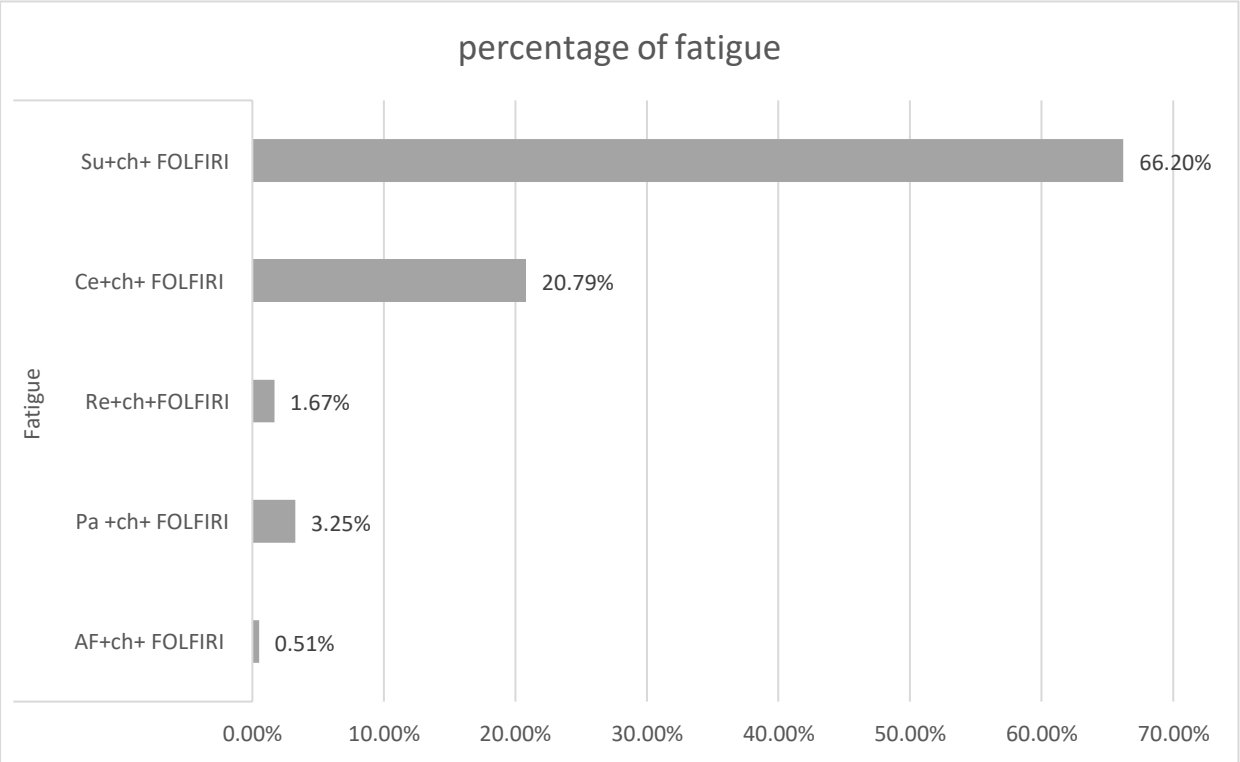


Figure 7: percentage of general disorder observed in patients receiving FOLFIRI base**d** chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Fatigue is a common adverse effect seen in patients receiving FOLFIRI base**d** chemotherapies in the treatment of metastatic colorectal cancer. Figure 7 represents percentage of fatigue observed in patients receiving FOLFIRI base**d** chemotherapies. The highest rate of fatigue (66.20%) was seen in patients who received FOLFIRI based chemotherapy with sunitinib. 20.79% fatigue rate was noticed in patients who received FOLFIRI based chemotherapy with cetuximab.

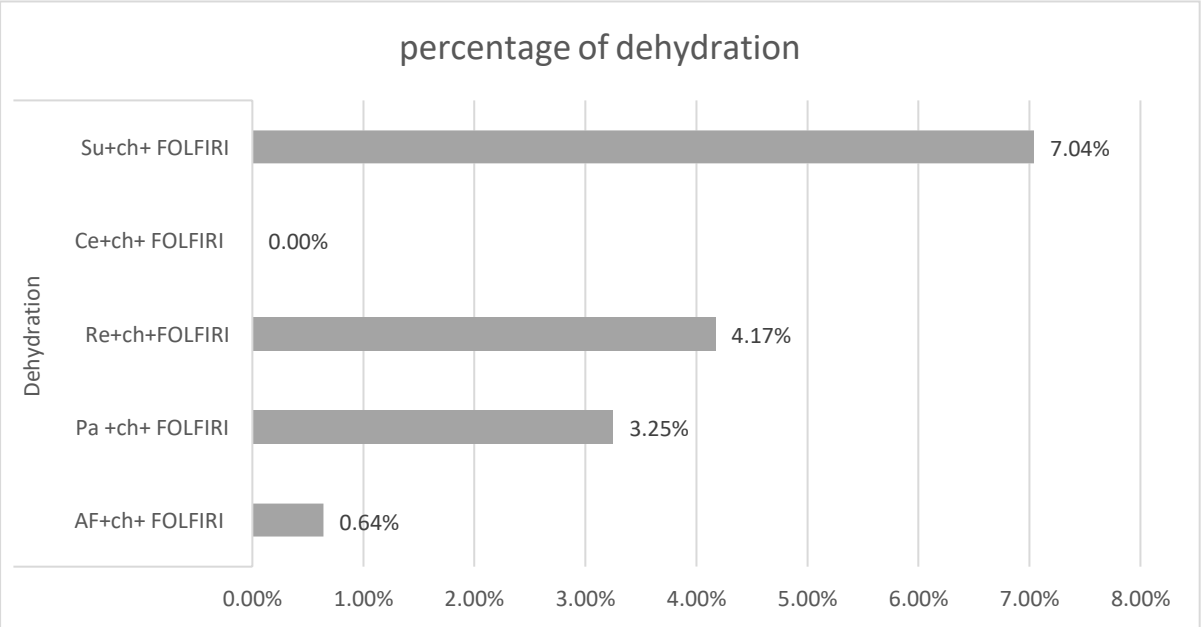
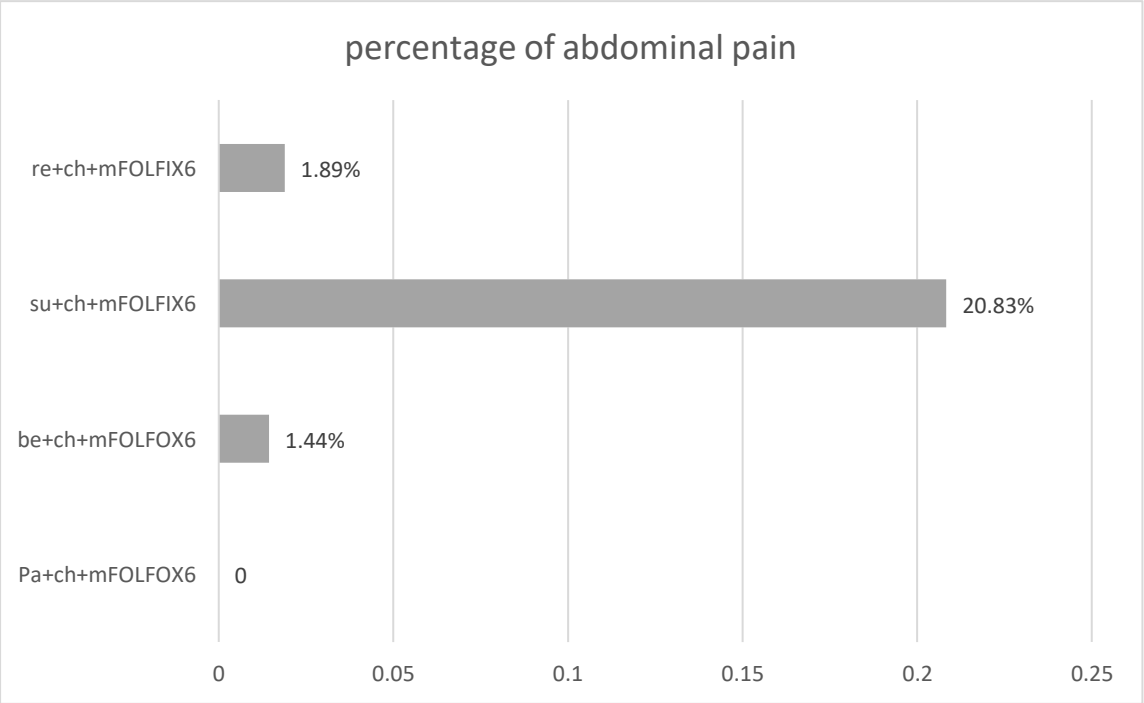


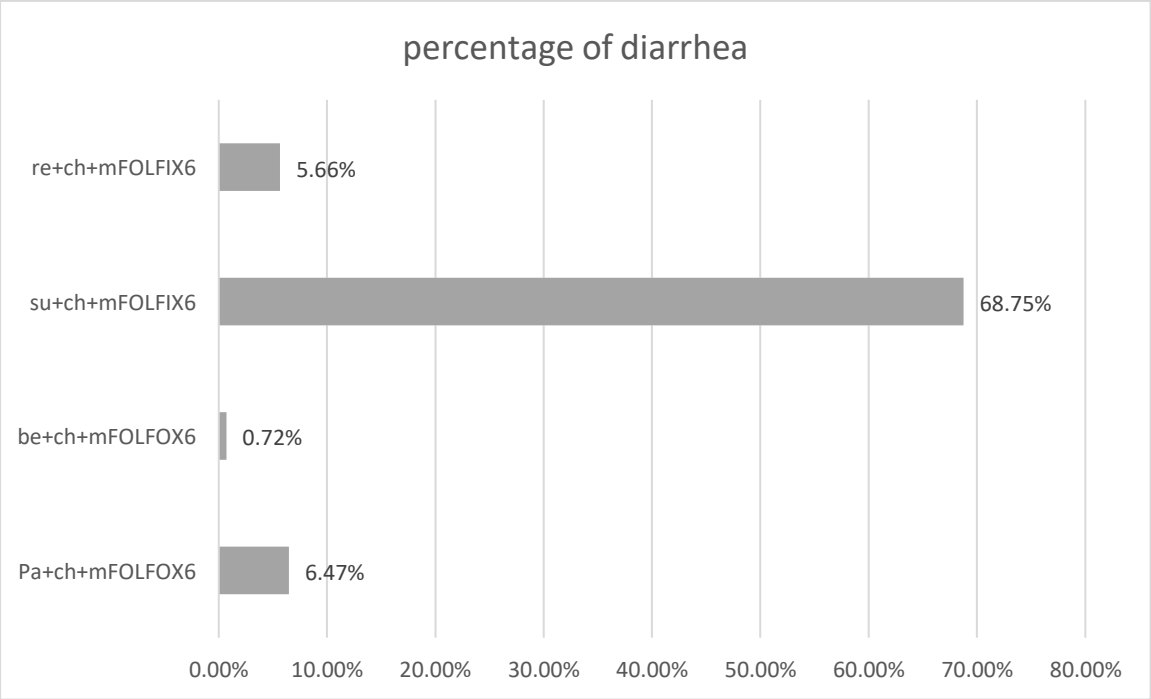
Figure 8: percentage of metabolism disorder observed in patients receiving FOLFIRI base**d** chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

Dehydration is a common adverse effect observed in patients receiving FOLFIRI base**d** chemotherapies. Figure 8 represents percentage of dehydration seen in patients receiving FOLFIRI base**d** chemotherapies. The highest rate of dehydration (7.04%) was seen in patients who received FOLFIRI based chemotherapy with sunitinib. 4.17% dehydration rate was noticed in patients who received FOLFIRI based chemotherapy with regorafenib.

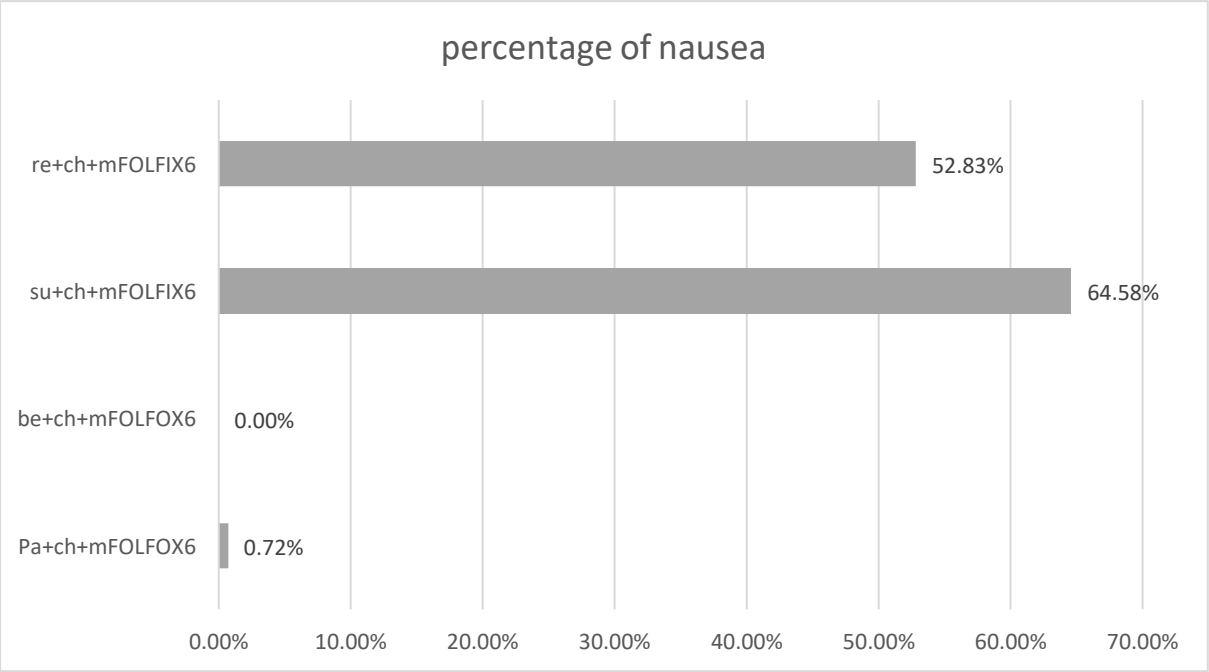
9(A):


percentage of abdominal pain
re+ch+mFOLFIX6
1.89%
su+ch+mFOLFIX6
20.83%
be+ch+mFOLFOX6
1.44%
Pa+ch+mFOLFOX6
0
0
0.05
0.1
0.15
0.2
0.25

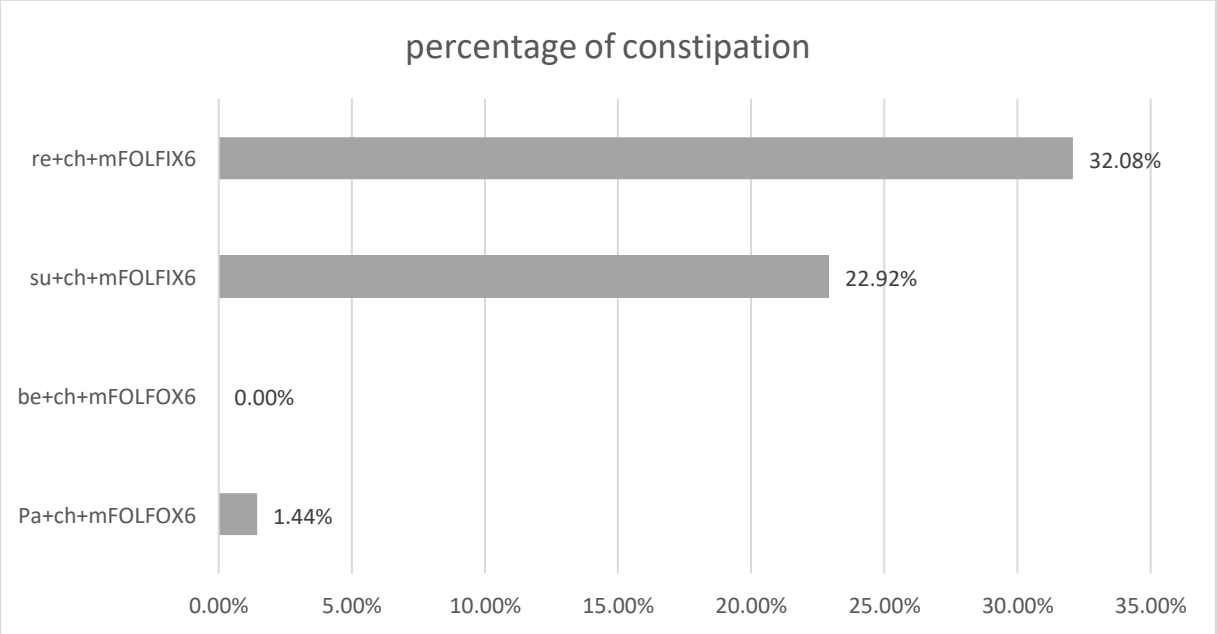
9(B);


percentage of diarrhea
re+ch+mFOLFIX6
5.66%
su+ch+mFOLFIX6
68.75%
be+ch+mFOLFOX6
0.72%
Pa+ch+mFOLFOX6
6.47%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%

9(C):


percentage of nausea
re+ch+mFOLFIX6
52.83%
su+ch+mFOLFIX6
64.58%
be+ch+mFOLFOX6
0.00%
Pa+ch+mFOLFOX6
0.72%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%

9(D):


percentage of constipation
re+ch+mFOLFIX6
32.08%
su+ch+mFOLFIX6
22.92%
be+ch+mFOLFOX6
0.00%
Pa+ch+mFOLFOX6
1.44%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%

9(E):

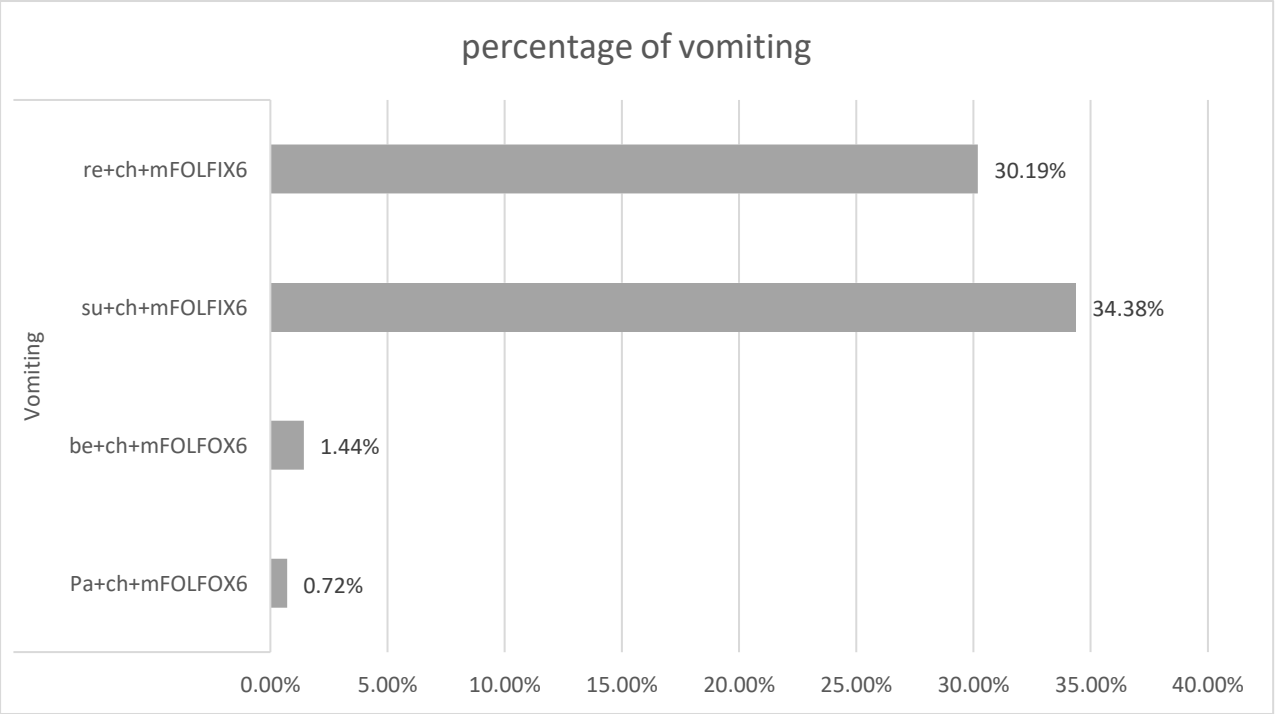
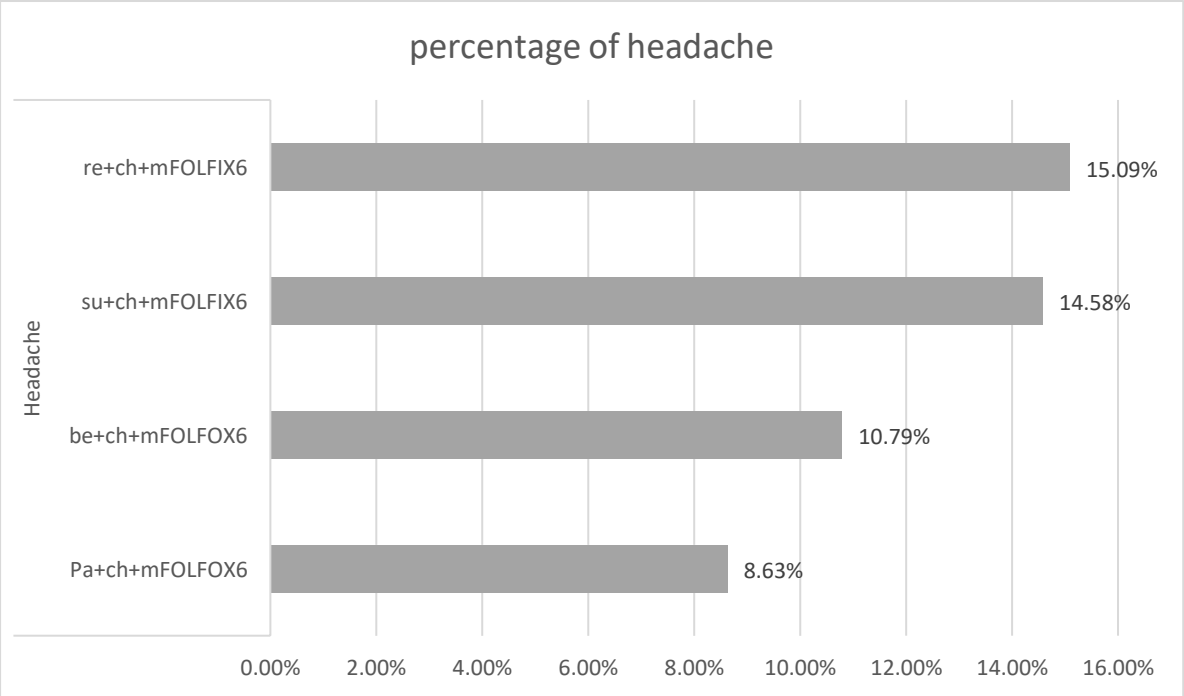


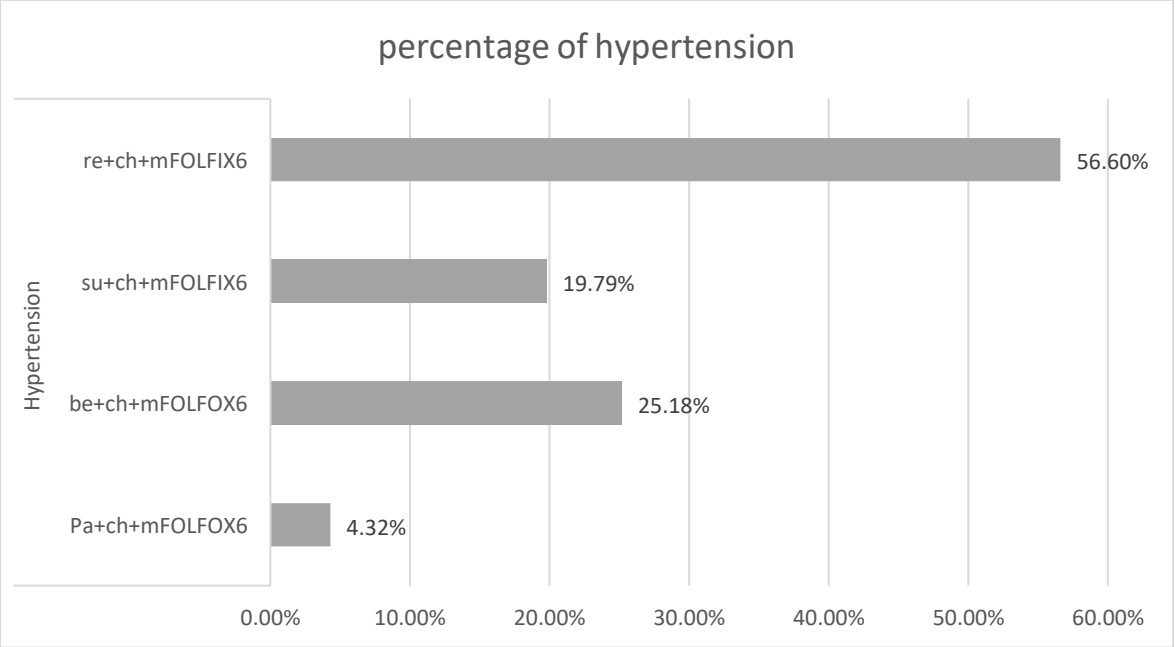
Figure 9: percentage of gastrointestinal disorders occurred in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Gastrointestinal disorder is a common adverse effect in patients receiving mFOLFOX6 based chemotherapies. (A) represents percentage of abdominal pain occurred in patients receiving mFOLFOX6 based chemotherapies. The highest rate of abdominal pain (20.83%) was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib. (B) represents percentage of diarrhea occurred in patients receiving mFOLFOX6 based chemotherapies. The highest rate of diarrhea (68.75%) was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib. (C) represents percentage of nausea observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of nausea (64.58%) was seen in patients receiving mFOLFOX6 based chemotherapy with sunitinib. 52.83% nausea rate was observed in patients receiving mFOLFOX6 based chemotherapy with regorafenib. (D) represents percentage of constipation occurred in patients receiving mFOLFOX6 based chemotherapies. 32.08% (which is the highest rate of constipation observed) constipation rate was seen in patients receiving mFOLFOX6 based chemotherapy with regorafenib. 22.92% constipation rate was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib. (E) represents percentage of vomiting observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of vomiting (34.38%) was seen in patients who received mFOLFOX6 based chemotherapy with sunitinib. 30.19% vomiting rate was noticed in patients who received mFOLFOX6 based chemotherapy with regorafenib.

10(A):


percentage of headache
Headache
re+ch+mFOLFIX6
su+ch+mFOLFIX6
be+ch+mFOLFOX6
Pa+ch+mFOLFOX6
15.09%
14.58%
10.79%
8.63%
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%
16.00%

10(B):


percentage of hypertension
Hypertension
re+ch+mFOLFIX6
su+ch+mFOLFIX6
be+ch+mFOLFOX6
Pa+ch+mFOLFOX6
56.60%
19.79%
25.18%
4.32%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%

10(C):

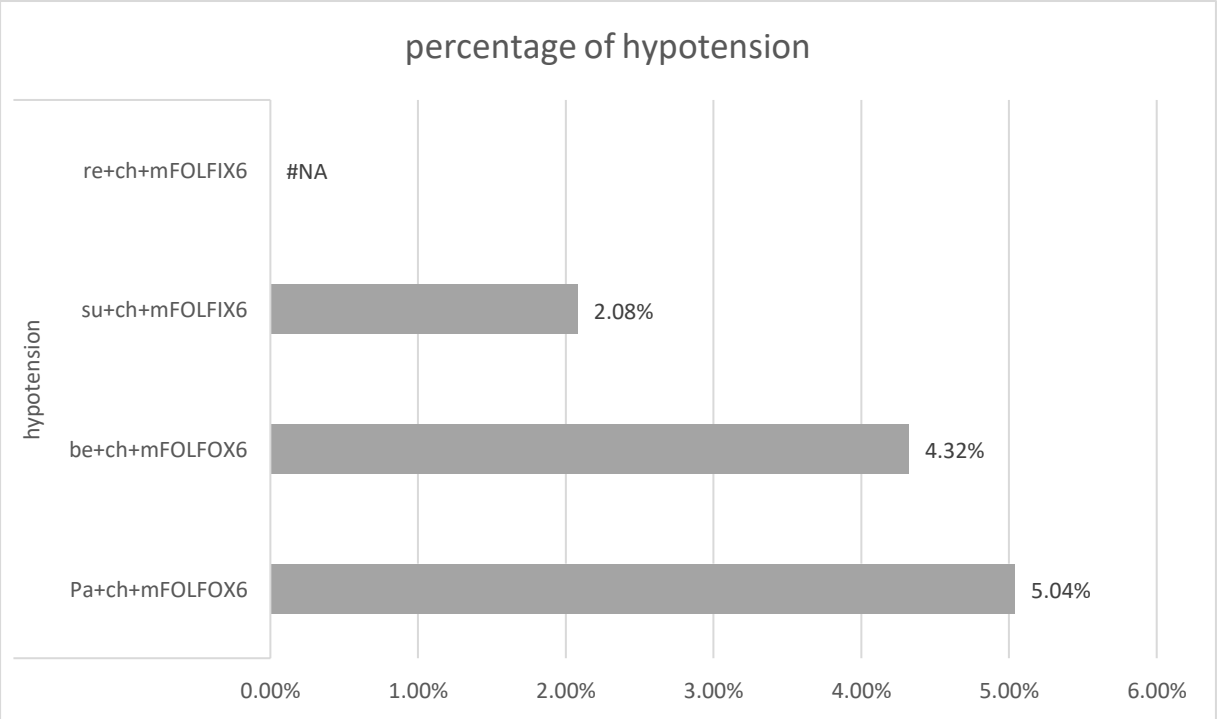
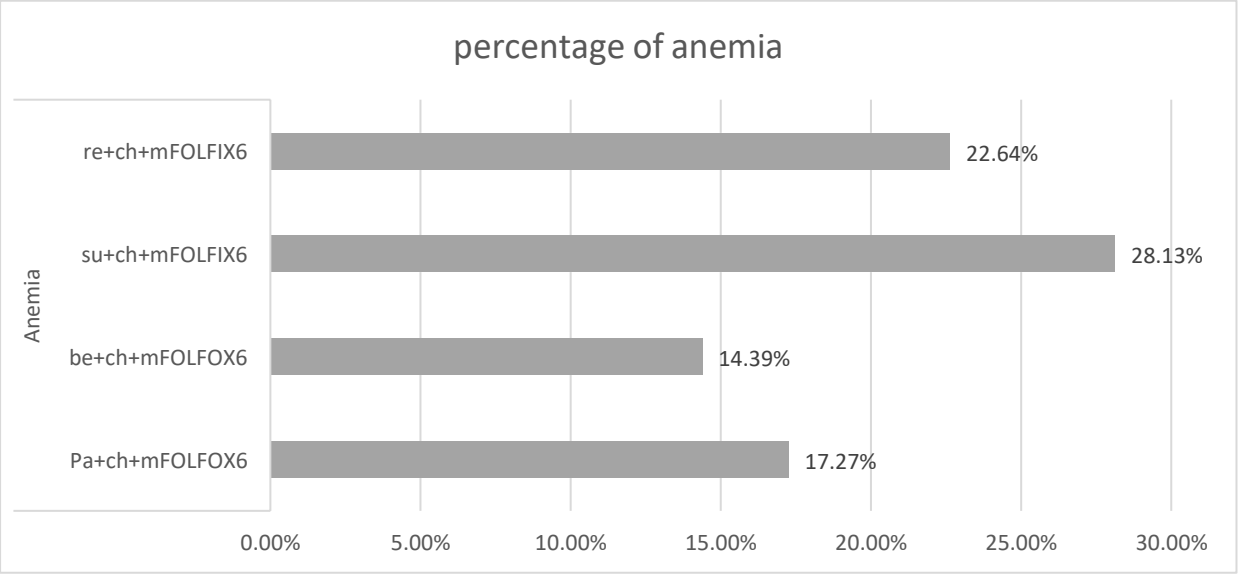


Figure 10: percentage of vascular disorder observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Vascular disorder is a common adverse effect seen in patients receiving mFOLFOX6 based chemotherapies. (A) represents percentage of headache observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of headache (15.09%) was seen in patients receiving mFOLFOX6 based chemotherapy with regorafenib. 14.58% headache rate was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib. (B) represents percentage of hypertension observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of hypertension (56.60%) was observed in patients receiving mFOLFOX6 based chemotherapy with regorafenib. (C) represents percentage of hypotension seen in patients receiving mFOLFOX6 based chemotherapies. The highest rate of hypotension (5.04%) was noticed in patients who received mFOLFOX6 based chemotherapy with panitumumab. 4.32% hypotension rate was noticed in patients who received mFOLFOX6 based chemotherapy with bevacizumab.

11(A):



11(B):

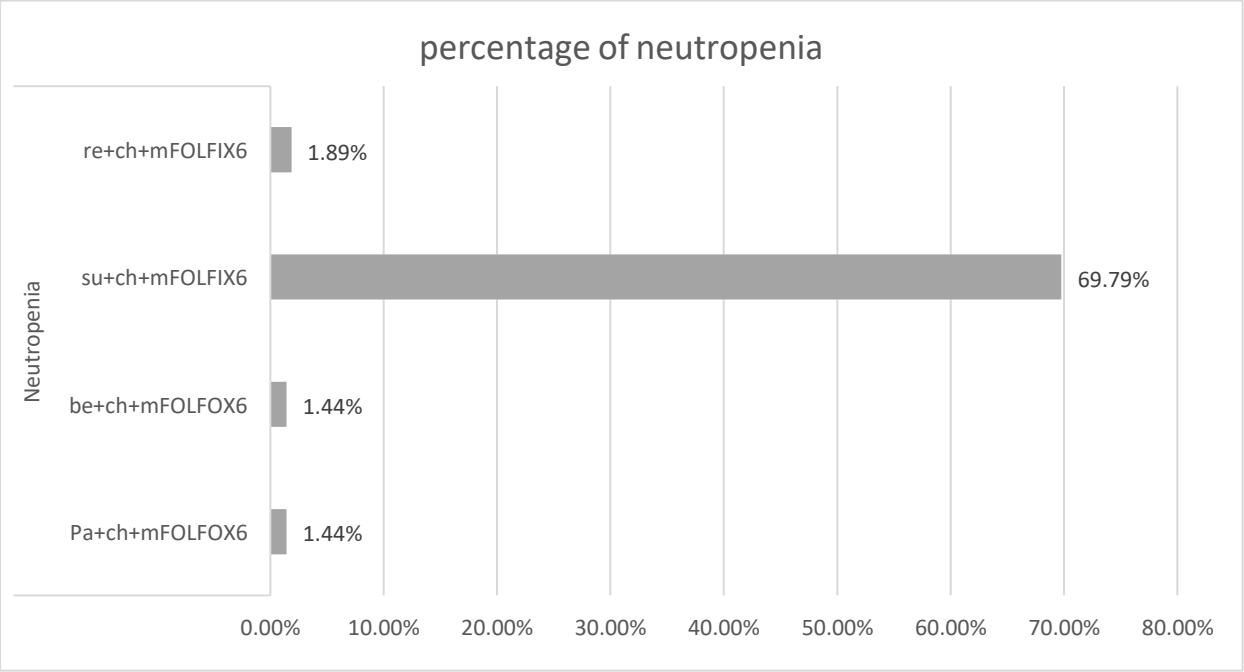


Figure 11: percentage of blood and lymphatic system disorder observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. Various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+

ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Blood and lymphatic system disorder is a common adverse effect in patients receiving mFOLFOX6 based chemotherapies. (A) represents percentage of anemia observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of anemia (28.13%) was seen in patients who received mFOLFOX6 based chemotherapy with sunitinib. 22.64% anemia rate was noticed in patients who received mFOLFOX6 based chemotherapy with regorafenib. (B) represents percentage of neutropenia seen in patients receiving mFOLFOX6 based chemotherapies. The highest rate of neutropenia (69.79%) was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib.

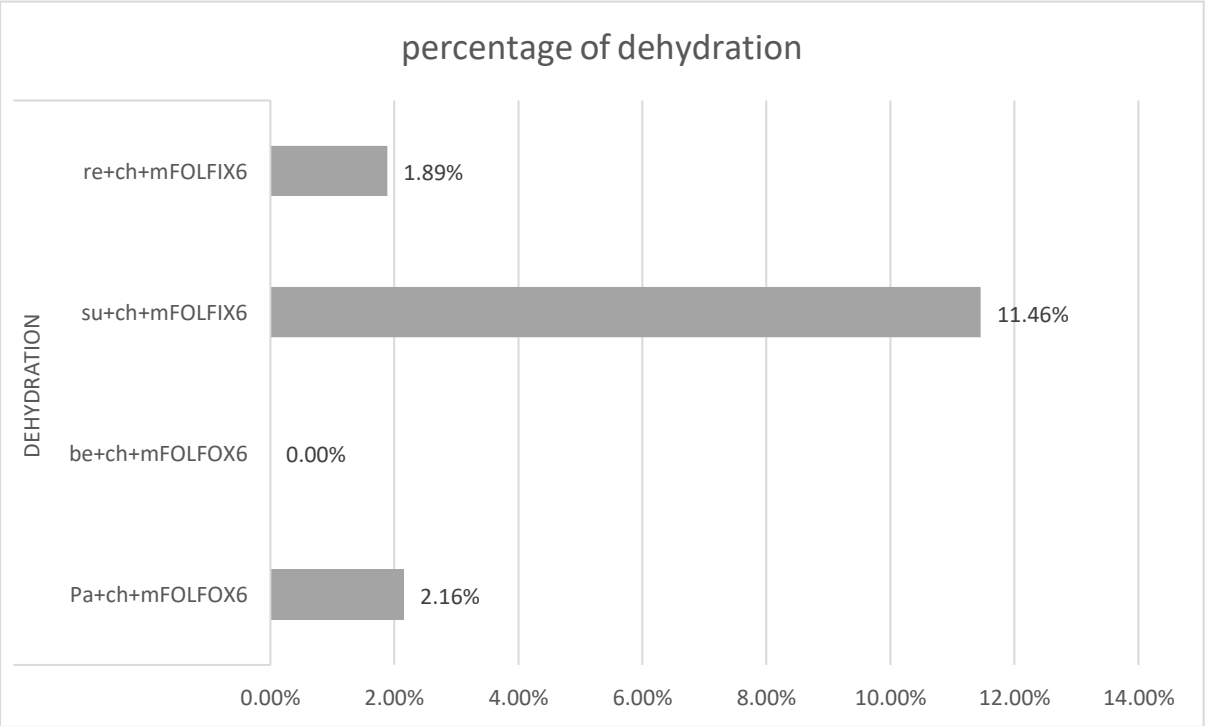
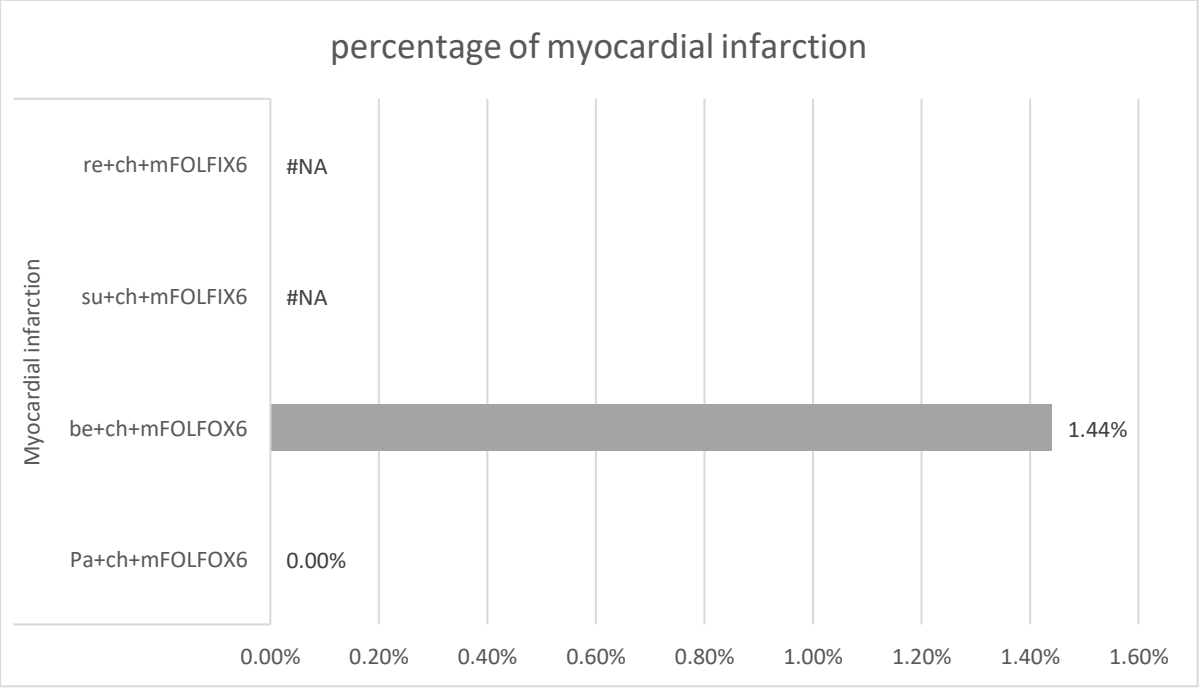


Figure 12: percentage of metabolism disorder observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Metabolism disorder is a common adverse effect observed in patients receiving mFOLFOX6 based chemotherapies. Figure 12 represents percentage of dehydration occurred in patients receiving mFOLFOX6 based chemotherapies. The highest rate of dehydration (11.46%) was observed in patients receiving mFOLFOX6 based chemotherapy with sunitinib.

13(A):


percentage of myocardial infarction
Myocardial infarction
re+ch+mFOLFIX6
#NA
su+ch+mFOLFIX6
#NA
be+ch+mFOLFOX6
1.44%
Pa+ch+mFOLFOX6
0.00%
0.00%
0.20%
0.40%
0.60%
0.80%
1.00%
1.20%
1.40%
1.60%

13(B):

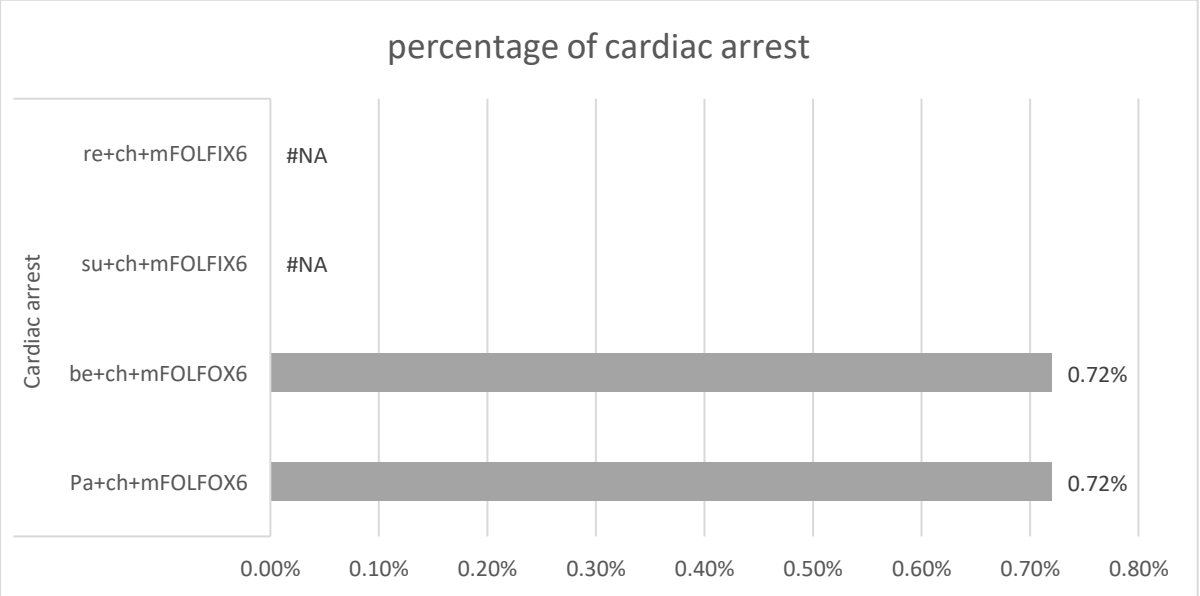

percentage of cardiac arrest
Cardiac arrest
re+ch+mFOLFIX6
#NA
su+ch+mFOLFIX6
#NA
be+ch+mFOLFOX6
0.72%
Pa+ch+mFOLFOX6
0.72%
0.00%
0.10%
0.20%
0.30%
0.40%
0.50%
0.60%
0.70%
0.80%

Figure 13: percentage of cardiovascular disorder occurred in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Cardiovascular disorder is a common adverse effect in patients receiving mFOLFOX6 based chemotherapies. (A) represents percentage of myocardial infarction observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of myocardial infarction (1.44%) was observed in patients receiving mFOLFOX6 based chemotherapy with bevacizumab. (B) represents percentage of cardiac arrest observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of cardiac arrest (0.72%) was observed in case of patients receiving mFOLFOX6 based chemotherapy with bevacizumab and mFOLFOX6 based chemotherapy with panitumumab.

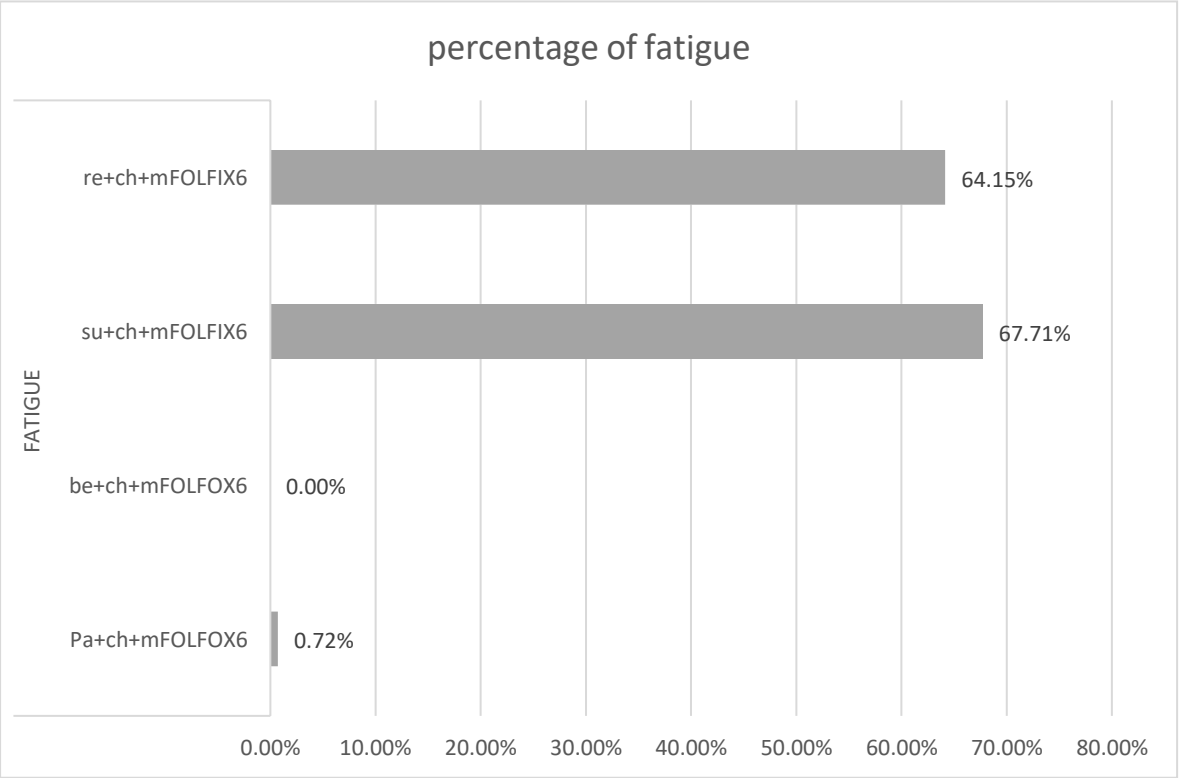


Figure 14: percentage of general disorder observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

General disorder is a common adverse effect in patients receiving mFOLFOX6 based chemotherapies. Figure 14 represents percentage of fatigue observed in patients receiving mFOLFOX6 based chemotherapies. The highest rate of fatigue (67.71%) was seen in patients who received mFOLFOX6 based chemotherapy with sunitinib. 64.15% fatigue rate wasnoticed in patients who received mFOLFOX6 based chemotherapy with regorafenib.

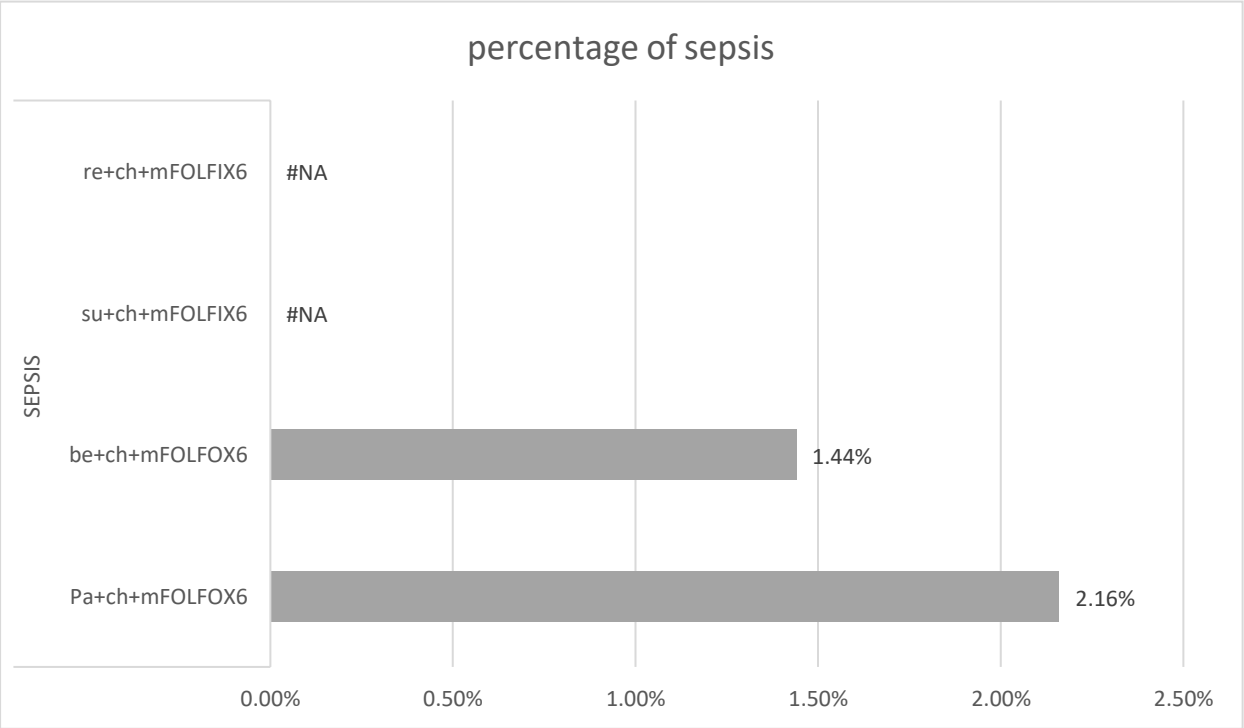


Figure 15: percentage of infection observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

Infection is a common adverse effect in patients receiving mFOLFOX6 based chemotherapies. Figure 15 represents percentage of sepsis occurred in patients receiving mFOLFOX6 based chemotherapies. The highest rate of sepsis (2.16%) was noticed in patients who received mFOLFOX6 based chemotherapy with panitumumab. 1.44% sepsis rate was seen in patients who received mFOLFOX6 based chemotherapy with bevacizumab.

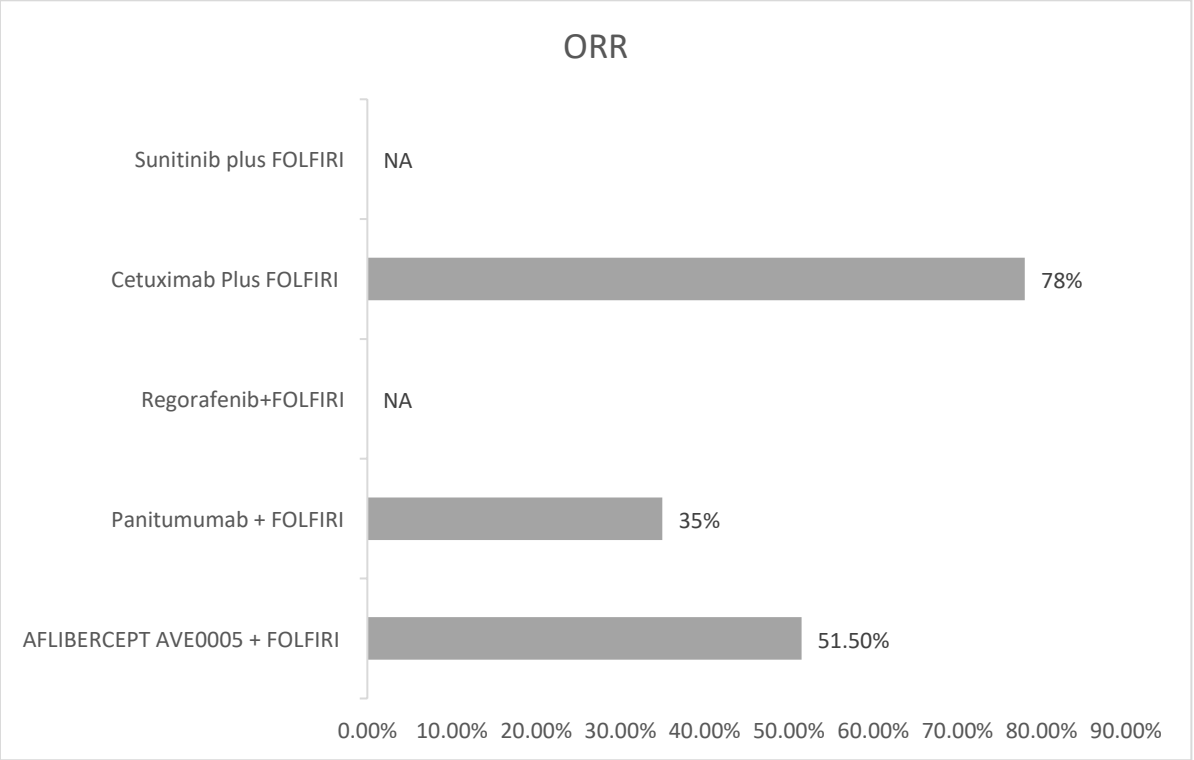


Figure 16: percentage of ORR observed in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

The highest rate of ORR (objective response rate) was observed in patients receiving FOLFIRI based chemotherapy with cetuximab which is 78%. In case of FOLFIRI based chemotherapy with AFILIBERCEPT, the objective response rate was 51.50%.

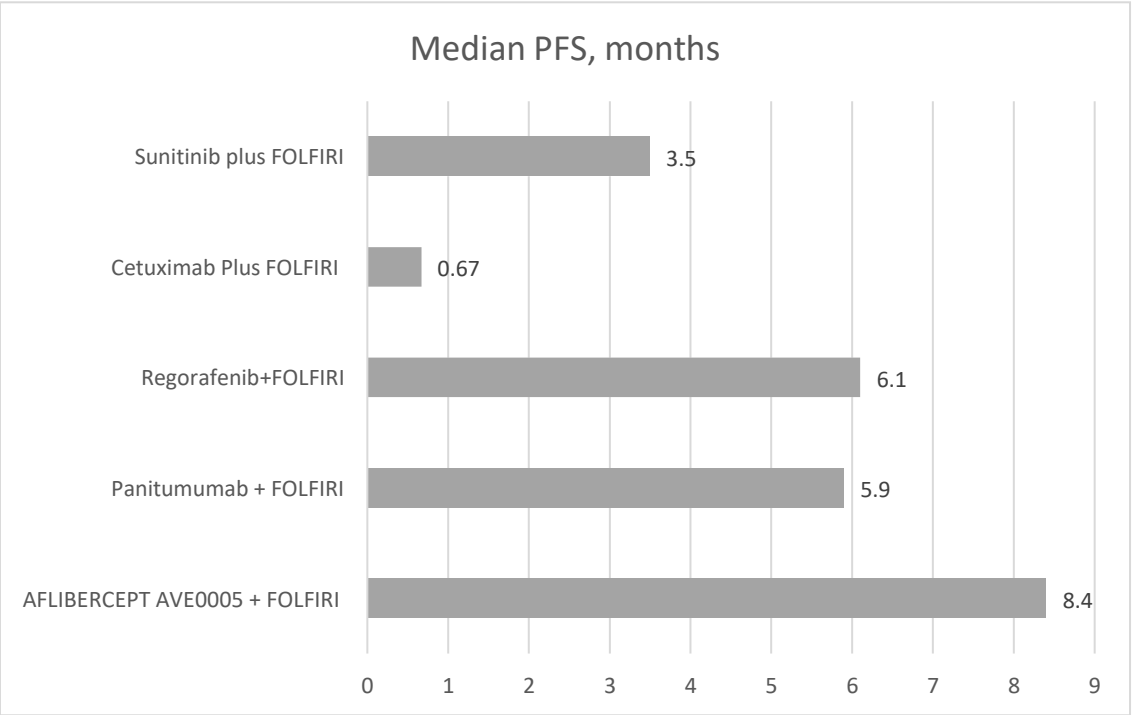


Figure 17: value of median progression free survival (in months) noticed in in patients who received FOLFIRI based chemotherapies for the treatment of metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

PFS stands for progression free survival. The highest rate of median PFS (8.4 moths) was noticed in patients who received FOLFIRI based chemotherapy with AFILIBERCEPT. On the other hand, progression free survival of 6.1 months was seen in patients who received FOLFIRI based chemotherapy with regorafenib.

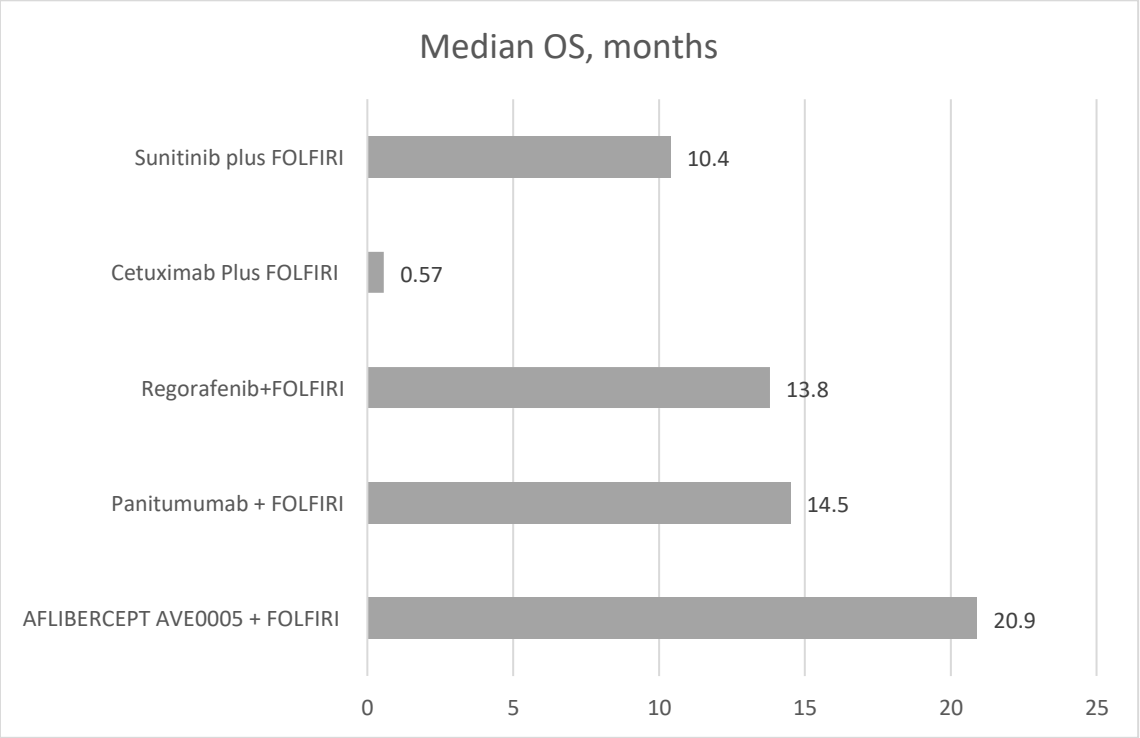


Figure 18: value of median OS (in months) observed in in patients receiving FOLFIRI based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- AFILIBERCEPT+ chemotherapy+ FOLFIRI (AF + ch + FOLFIRI), panitumumab+ chemotherapy+ FOLFIRI (pa+ ch + FOLFIRI), regorafenib+ chemotherapy+ FOLFIRI (re+ ch +FOLFIRI), cetuximab+ chemotherapy+ FOLFIRI (ce+ ch +FOLFIRI), sunitinib+ chemotherapy + FOLFIRI (su+ ch+ FOLFIRI). The values are presented as percentages in graphs.

The highest rate of OS (overall survival) was observed in patients receiving FOLFIRI based chemotherapy with AFILIBERCEPT (which is 20.9 months). In case of FOLFIRI based chemotherapy with panitumumab, the overall survival rate was 14.5 months.

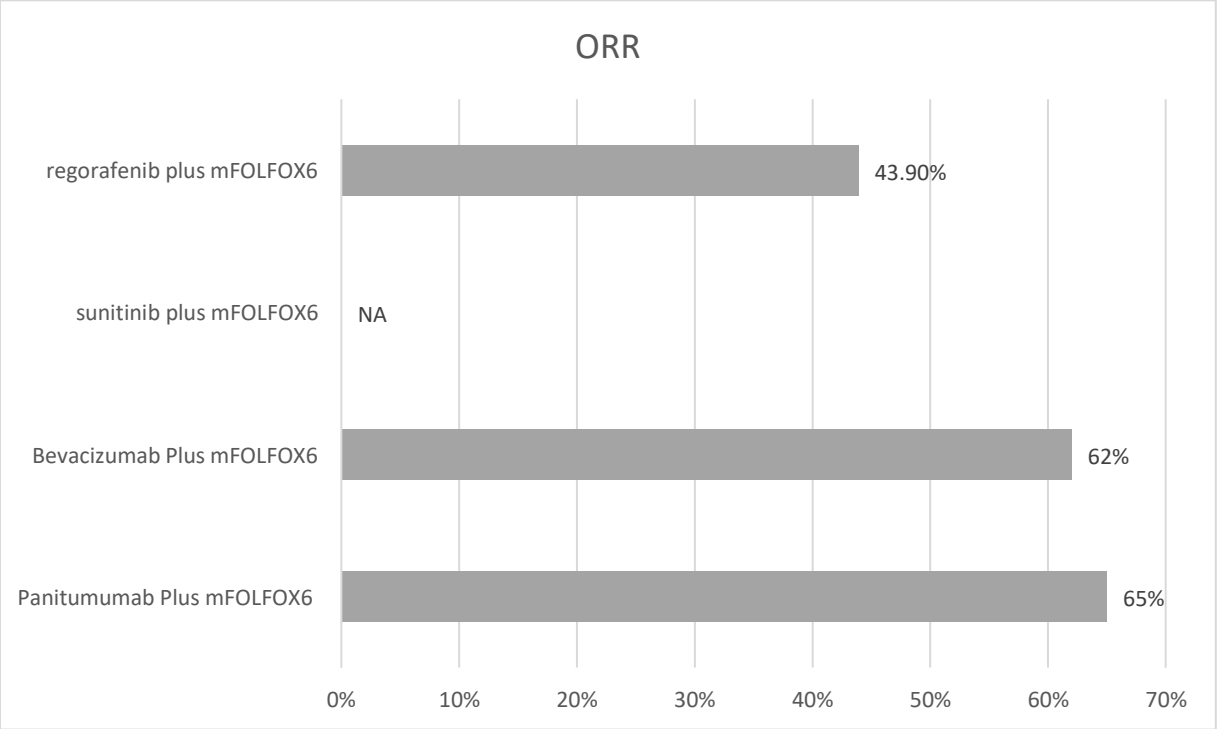


Figure 19: percentage of ORR observed in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. Various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

The highest rate of ORR (objective response rate) was observed in patients receiving mFOLFOX6 based chemotherapy with panitumumab which is 65%. In case of mFOLFOX6 based chemotherapy with bevacizumab, the objective response rate was 62%.

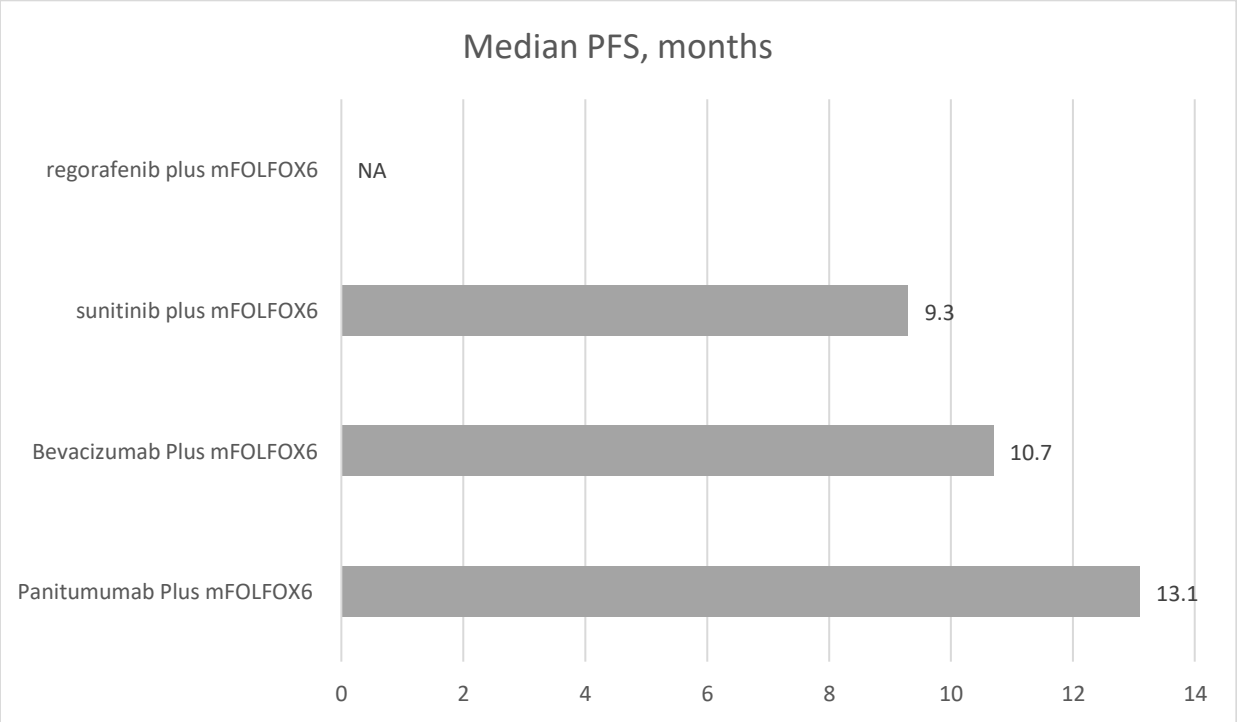


Figure 20: value of median PFS (in months) observed in in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. The various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

PFS stands for progression free survival. The highest rate of median PFS (13.1 moths) was seen in patients who received FOLFIRI based chemotherapy with panitumumab. On the otherhand, progression free survival of 10.7 months was noticed in patients who received FOLFIRIbased chemotherapy with bevacizumab.

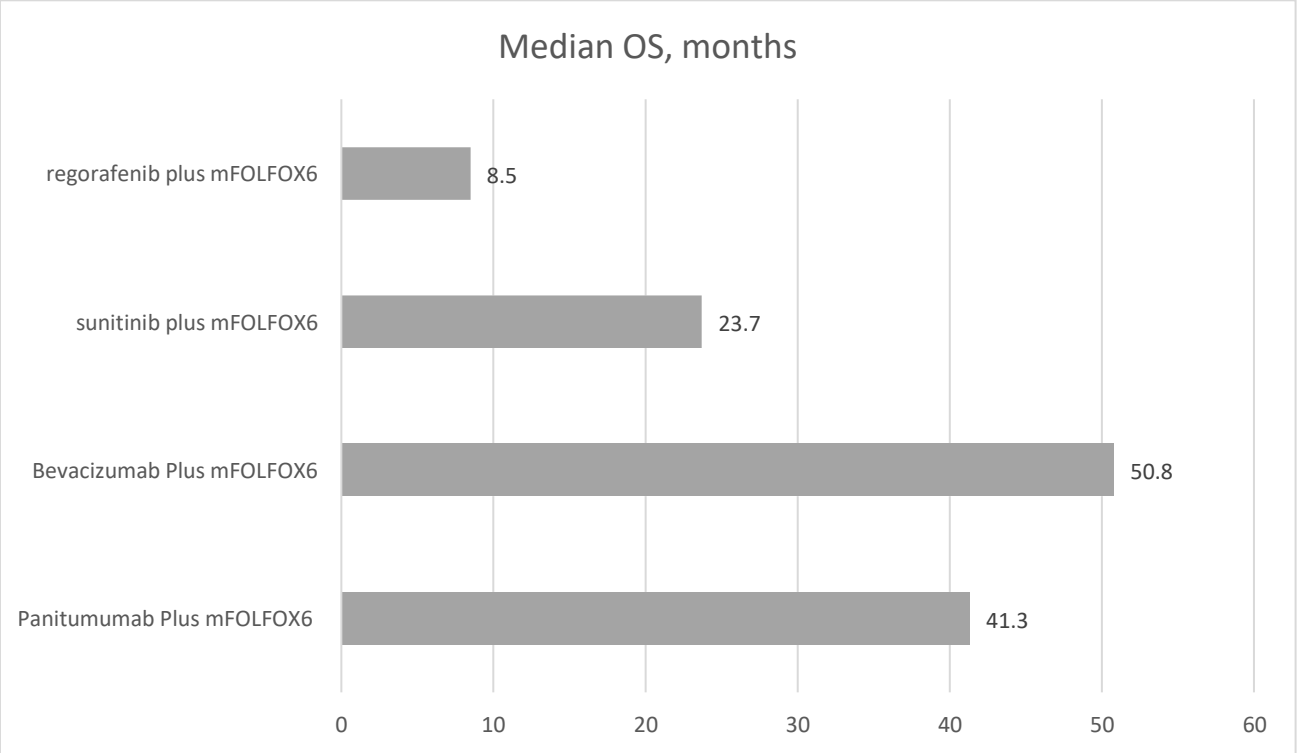


Figure 21: value of median OS (in months) observed in in patients receiving mFOLFOX6 based chemotherapies that are used to treat metastatic colorectal cancer. Various drug combinations that were observed are- panitumumab+ chemotherapy+ mFOLFOX6 (pa+ ch + mFOLFOX6), regorafenib+ chemotherapy+ mFOLFOX6 (re+ ch + mFOLFOX6), sunitinib+ chemotherapy + mFOLFOX6 (su+ ch+ mFOLFOX6), bevacizumab+ chemotherapy+ mFOLFOX6 (be+ ch+ mFOLFOX6). The values are presented as percentages in graphs.

The highest rate of OS (overall survival) was observed in patients receiving mFOLFOX6 based chemotherapy with bevacizumab (which is 50.8 months). In case of mFOLFOX6 based chemotherapy with panitumumab, the overall survival rate was 41.3 months.

Chapter 5:

Discussion:

Different drug combinations show different efficacies and adverse effects in patients with metastatic colorectal cancer (mCRC). However, these efficacies and adverse effects vary when those drugs are used alone rather than used as combinations. For example, when bevacizumab (-a humanized monoclonal antibody) is used alone, PFS and OS remain similar as combination chemotherapy but it shows less adverse effects (Wu et al., n.d.). However, when it is combined with FOLFOX, it improved response rates, overall survival (OS) and progression-free survival (PFS) (Van Cutsem et al., 2009). On the other hand, FOLFIRI-Bevacizumab combination improved objective response, progression-free survival (PFS) and overall survival (OS) as compared to FOLFIRI alone (Cao et al., 2015). However, FOLFIRI + Bev combination was superior to mFOLFOX6 + Bev combination in terms of PFS (Yamazaki et al., 2016). Moreover, FOLFIRI + Bev had higher incidences of leukopenia and neutropenia than FOLFOX-bevacizumab combination (Yamazaki et al., 2016). Aflibercept is an anti-VEGF agent that is administered intravenously (Ciombor et al., 2013). When afilibercept is combined with FOLFIRI, it improved survival significantly compared with FOLFIRI alone (Ciombor et al., 2013). Moreover, afilibercept- FOLFIRI combination prolonged median overall survival, progression free survival and increased the objective response rate compared with FOLFIRI alone (Syed & McKeage, 2015). Furthermore, there was no treatment related death but some adverse effects like- mucositis, diarrhea, abdominal pain etc. were reported (Lapeyre-Prost et al., 2020). On the contrary, panitumumab (anti-EGFR Monoclonal antibody) has antitumor activity in patients with mCRC both as monotherapy and in combination with chemotherapy (Schwartzberg et al., 2014). When panitumumab was combined with mFOLFOX6; ORR, median PFS and median OS was improved (Rivera et al., 2017). However, panitumumab

showed some adverse effects like- rash, hypomagnesaemia, stomatitis, decreased appetite, dehydration, acne, dermatitis acneiform, deep vein thrombosis, and hypertension when combined with mFOLFOX6 (Rivera et al., 2017). Although toxicities were manageable in panitumumab monotherapy, overall response, median PFS, median OS were low (Hecht et al., 2007) compared with panitumumab combination therapy. However, panitumumab monotherapy showed less adverse effects like- nausea, vomiting, fatigue, pain etc (Liao et al., 2021). Considering all these, it can be said that combination chemotherapy (FOLFIRI and FOLFOX based) has more significance over monotherapy in the treatment of patients suffering from metastatic colorectal cancer. Different drug combinations have different working mechanisms- some drugs work in epidermal growth factor receptor, while others work in vascular endothelial growth factor receptor/ VEGF receptor. Bevacizumab is a human monoclonal antibody that targets vascular endothelial growth factor receptor (Liu et al., 2015). When bevacizumab is combined with FOLFIRI as a combination chemotherapy, it was effective in treating patients with mCRC in second-line setting and had tolerable toxicity profiles (Liu et al., 2015). Afilibercept (a recombinant fusion protein) blocks the activity of placental growth factor (PlGF) receptor, VEGFA and VEGFB receptor (Van Cutsem et al., 2012). When afilibercept was added to FOLFIRI and it was given intravenously, the tolerability of it was acceptable in patients with mCRC (Syed & McKeage, 2015). Panitumumab is a fully humanized monoclonal antibody that targets EGF receptor, leading to inhibition of tumor growth, induction of apoptosis and inhibition of angiogenesis (Hocking et al., 2013). The first-line FOLFIRI plus panitumumab was well tolerated and lead to favorable efficacy in mCRC patients (McGregor & Price, 2018). Regorafenib is a multi-targeting inhibitor of kinase that is accepted for the purpose of treating metastatic colorectal cancer patients (Arai et al., 2019). The administration of regorafenib-FOLFIRI combination resulted in manageable toxicities and satisfactory oncological outcomes in mCRC patients who were previously treated (C. J. Ma et

al., 2019b). Cetuximab is an antibody that is directed against EGFR (Brand et al., 2011). However, The FOLFIRI-cetuximab combination was generally better tolerated than FOLFOX6-cetuximab combination with regard to grade 3/4 related adverse effects (Ocvirk et al., 2010). Sunitinib is a multitargeted tyrosine-kinase inhibitor that has activity againstvascular endothelial growth-factor receptor (VEGFR) (Sungkyoung Kim et al., 2014). The toxicity of sunitinib-FOLFIRI combination was remarkable and treatment delays, interruptions, or reductions were necessary to manage the toxicity (Mrossl et al., 2014). Panitumumab plus mFOLFOX6 demonstrated better efficacy outcomes for patients with mCRC (Graham et al., 2014). On the other hand, when bevacizumab was combined with mFOLFOX6, PFS was similar and OS was improved in comparison to bevacizumab in patients with metastatic colorectal cancer (Schwartzberg et al., 2014). Sunitinib plus mFOLFOX6 combination was related to more toxicity than that observed with mFOLFOX6 based combination with bevacizumab. Hence, Sunitinib plus mFOLFOX6 was not approved for patients suffering from metastatic colorectal cancer (Hecht, Mitchell, Welslau, et al., 2015). However, regorafenib plus mFOLFOX6 was not related to markedly worse tolerability profile in comparison to mFOLFOX6 alone (Argilés et al., 2015). If we compare the drug combinations that are used in the treatment of metastatic colorectal cancer in terms of adverseeffect (Bordonaro et al., 2014), median PFS and median OS (Pentheroudakis et al., 2018), FOLFIRI based chemotherapy with AFLIBERCEPT has much more advantages than other FOLFIRI based chemotherapies. On the other hand, mFOLFOX6 based chemotherapy with panitumumab has more advantages than other mFOLFOX6 based chemotherapies in terms ofORR, median PFS and adverse effects (Rivera et al., 2017). However, Panitumumab Plus mFOLFOX6 combination had higher ORR, median PFS and median OS (Rivera et al., 2017) than AFLIBERCEPT AVE0005 + FOLFIRI combination (Pentheroudakis et al., 2018). In case of adverse effects, AFLIBERCEPT AVE0005 + FOLFIRI combination has lower adverse

effects (Bordonaro et al., 2014) than Panitumumab Plus mFOLFOX6 combination (Rivera et al., 2017). Regarding the outcome, Aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin (Van Cutsem et al., 2012). On the other hand, PFS was similar and OS was improved with panitumumab relative to bevacizumab when combined with mFOLFOX6 in patients with WT KRAS exon 2 tumors (Schwartzberg et al., 2014). Considering all these, we can say that AFLIBERCEPT AVE0005 + FOLFIRI combination is more efficient than Panitumumab Plus mFOLFOX6 combination. However, FOLFOX based chemotherapy with panitumumab is more effective than FOLFIRI based chemotherapy with AFLIBERCEPT.

Chapter 6:

Conclusion:

Various drug combinations are available for the treatment of metastatic colorectal cancer and they are different from each other due to their different mechanism of actions, efficacies and adverse effects. Patients receiving AFLIBERCEPT AVE0005 + FOLFIRI combination had lower adverse effects than those receiving Panitumumab Plus mFOLFOX6 combination. Hence, AFLIBERCEPT AVE0005 + FOLFIRI combination is more efficient than Panitumumab Plus mFOLFOX6 combination. However, Panitumumab Plus mFOLFOX6 combination is more effective than AFLIBERCEPT AVE0005 + FOLFIRI combination. FOLFIRI and FOLFOX based combinations are known as first line treatments of metastatic colorectal cancer and they are used widely. Most of these drug combinations work on vascular endothelial growth factor receptor/ VEGF receptor. Various molecular pathways of colorectal cancer have been identified such as- the chromosomal instability (CIN), the microsatellite instability (MSI), and the CpG Island Methylator Phenotype (CIMP) pathways. Some of the drugs used in FOLFIRI or FOLFOX based chemotherapies are monoclonal antibodies. However, XELOX and FOLFOXIRI are other drug combinations that are also used to treat metastatic colorectal cancer.

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Appendix:

parameters	AFLIBERCEPT AVE0005 + FOLFIRI	percentage	Panitumumab + FOLFIRI	percentage	Regorafenib+FOLFIRI	percentage	Cetuximab Plus FOLFIRI	percentage	Sunitinib plus FOLFIRI	percentage
Death rate	48/779	6.16 %	--/--	--/--	112/120	93.33%	--/--	--/--	--/--	--/--
Myocardial infarction	2/779	0.26 %					1/101	0.99 %	1/71	1.41 %
Gastrointestinal haemorrhage	1/779	0.13 %								
Abdominal infection	1/779	0.13 %			1/120	0.83 %				

Pneumonia	8/779	1.03%	4/154	2.60%						
Sepsis	7/779	0.90%	1/154	0.65%	2/120	1.67%	2/101	1.98%		
Acute kidney injury	3/779	0.39%			1/120	0.83%				
Disease progression	23/779	2.95%					1/101	0.99%		
Abdominal pain	8/779	1.03%	4/154	2.60%	9/120	7.50%	0/101	0.00%	13/71	18.31%
Diarrhea	39/779	5.01%	21/154	13.64%	10/120	8.33%	4/101	3.96%	55/71	77.46%
Nausea	1/779	0.13%	2/154	1.30%	2/120	1.67%	0/101	0.00%	54/71	76.06%
Constipation	1/779	0.13%	1/154	0.65%	1/120	0.83%	0/101	0.00%	29/71	40.85%
Vomiting	10/779	1.28%	41/154	26.62%	0/120	0.00%	2/101	1.98%	39/71	54.93%
Urinary tract	5/779	0.64%	6/154	3.90%						

infection										
Headache	1/779	0.13%	9/154	5.84%	1/120	0.83%			12.0/71	16.90%
Hypertension	11/779	1.41%			1/120	0.83%			24.0/71	33.80%
Anemia	7/779	0.90%	2/154	1.30%	2/120	1.67%	0/101	0.00%	4.0/71	5.63%
Confusion							0/101	0.00%		
Abdominal distension			1/154	0.65%			6/101	5.94%	6.0/71	8.45%
Fatigue	4/779	0.51%	5/154	3.25%	2/120	1.67%	21/101	20.79%	47/71	66.20%
Dehydration	5/779	0.64%	5/154	3.25%	5/120	4.17%	0/101	0.00%	5.0/71	7.04%
Neutropenia	14/779	1.80%	6/154	3.90%			4/101	3.96%	1.0/71	1.41%
hypotension			2/154	1.30%	10/120	8.33%	0/101	0.00%		

clinical trial ID	NCT01571284		NCT0050840 4		NCT01298570		NCT0077883 0		NCT0066886 3	
citation	(Bordonaro et al., 2014)		(Karthaus et al., 2018)	-	(Sanoff et al., 2018)	-	(Price et al., 2018)	-	(Tsuji et al., 2012)	-

Supplementary table 1: adverse effects observed in patients receiving FOLFIRI based chemotherapies used for the treatment of metastatic colorectal cancer

parameters	**Panitumumab Plus mFOLFOX6**	**percentage**	**Bevacizumab Plus mFOLFOX6**	**percentage**	**sunitinib plus mFOLFOX6**	**percentage**	**regorafenib plus mFOLFOX6**	**percentage**
Death rate	--/--	--/--	--/--	--/--	--/--	--/--	--/--	--/--
Myocardial infarction	0/139	0.00%	2/139	1.44%				
Peritonitis	0/139	0.00%	1/139	0.72%				
Sepsis	3/139	2.16%	2/139	1.44%				
Abdominal pain	0/139	0.00%	2/139	1.44%	20/96	20.83%	1.00/53	1.89%
Diarrhea	9/139	6.47%	1/139	0.72%	66/96	68.75%	3/53	5.66%
Nausea	1/139	0.72%	0/139	0.00%	62/96	64.58%	28/53	52.83%
Constipation	2/139	1.44%	0/139	0.00%	22/96	22.92%	17/53	32.08%
Vomiting	1/139	0.72%	2/139	1.44%	33/96	34.38%	16/53	30.19%
Headache	12/139	8.63%	15/139	10.79%	14/96	14.58%	8/53	15.09%

Hypertension	6/139	4.32%	35/139	25.18%	19/96	19.79%	30/53	56.60%
Anemia	24/139	17.27%	20/139	14.39%	27/96	28.13%	12/53	22.64%
Fatigue	1/139	0.72%	0/139	0.00%	65/96	67.71%	34/53	64.15%
Dehydration	3/139	2.16%	0/139	0.00%	11/96	11.46%	1/53	1.89%
Neutropenia	2/139	1.44%	2/139	1.44%	67/96	69.79%	1/53	1.89%
Cardiac arrest	1/139	0.72%	1/139	0.72%				
hypotension	7/139	5.04%	6/139	4.32%	2/96	2.08%		
clinical trial ID	NCT00819780		NCT00819780		NCT00609622		NCT01289821	
Citation	(Rivera et al., 2017)		(Rivera et al., 2017)		(Hecht, Mitchell, Yoshino, et al., 2015)		(Argilés et al., 2015)	

Supplementary table 2: adverse effects observed in patients receiving mFOLFOX6 based drug combinations used for the treatment of metastatic colorectal cancer

	ORR	Median PFS, months	Median OS, months	**citation**
Bevacizumab + FOLFIRI-3	67%	12.72	24.5	(Stefano Kim et al., 2013)
regorafenib plus perindopril		2.60 (1.74–3.61)	7.33 (2.33–11.76)	(Melosky et al., 2019)
pembrolizumab plus azacitidine	10 (19.6)	8%	11.9	(Levy et al., 2019)
AFLIBERCEPT AVE0005 + FOLFIRI	51.50%	8.4	20.9	(Pentheroudakis et al., 2018)
Panitumumab + FOLFIRI	35%	5.9	14.5	(Marc Peeters et al., 2010)
Regorafenib+FOLFIRI		6.1	13.8	(Sanoff et al., 2018)
Cetuximab + FOLFOX4	46 (38—54)	7.3 (5.6—7.8)	18.3 (14.8—20.4)	(Bokemeyer et al., 2011)
Panitumumab Plus mFOLFOX6	65%	13.1 month	41.3	(Rivera et al., 2017)
Bevacizumab Plus mFOLFOX6	62%	10.7	50.8	(Yamazaki et al., 2016)

Cetuximab Plus FOLFIRI	78%	0.67	0.57	(Stintzing et al., 2019b)
Sunitinib plus FOLFIRI		3.5	10.4	(Moehler et al., 2016)
sunitinib plus mFOLFOX6	42.90%	9.3	23.7	(Hecht, Mitchell, Yoshino, et al., 2015)
regorafenib plus mFOLFOX6	43.90%	not reached	8.5	(Argilés et al., 2015)

Supplementary table 3: efficacy of FOLFIRI and mFOLFOX6 based drug combinations used for the treatment of metastatic colorectal cancer

drugs	receptor that the drug binds	Citation	outcome in targeting receptor	Citation
Bevacizumab + FOLFIRI-3	epidermal growth factor receptor	(W. W. Ma et al., 2009)	well tolerated, no gi perforations or grades 3 and 4 proteinuria	(Dranitsaris et al., 2010)
regorafenib plus perindopril	vascular endothelial growth factor receptor	(Melosky et al., 2019)	the addition of perindopril did not lead to a reduced level of hand-foot skin reaction (HFSR) compared with regorafenib alone.	(Melosky et al., 2019)
pembrolizumab plus azacitidine	epidermal growth factor receotor	(Nsclc, 2021)	has tolerable safety profile but appears to have minimal anti-tumor effect for MSS mCRC	(Lee et al., 2017)
AFLIBERCEPT AVE0005 + FOLFIRI	vascular endothelial growth	(Gaya & Tse, 2012)	Aflibercept in combination with FOLFIRI conferred	(Van Cutsem et al., 2012)

	factor receptor		a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin.	
Panitumumab + FOLFIRI	epidermal growth factor receptor	(M Peeters et al., 2010)	The first-line FOLFIRI plus panitumumab was associated with favourable efficacy in the patients with wild-type KRAS and wild-type NRAS mCRC, and it was well tolerated.	(McGregor & Price, 2018)
Regorafenib+FOLFIRI	placental growth factor (PlGF)/vascular	(Giordano et al., 2014)	The administration of regorafenib and concomitant reintroduction of FOLFIRI with	(C. J. Ma et al., 2019b)

	endothelial growth factor receptor 1 (VEGFR1)		dose-escalated irinotecan according to *UGT1A1* genotyping are clinically feasible and result in tolerable toxicities and favorable oncological outcomes in previously heavily treated mCRC.	
Cetuximab + FOLFOX4	epidermal growth factor receptor (EGFR)	(Díaz Rubio et al., 2005)	Cetuximab in combination with FOLFOX-4 is a highly active first-line treatment for mCRC, showing encouraging RR, mPFS, and mOS values.	(Tabernero et al., 2022)
Panitumumab Plus mFOLFOX6	epidermal growth factor	(Khattak et al., 2015)	PFS was similar and OS was improved with	(Schwartzberg et al., 2014)

	receptor (EGFR)		panitumumab relative to bevacizumab when combined with mFOLFOX6 in patients with WT KRAS exon 2 tumors	
Bevacizumab Plus mFOLFOX6	vascular endothelial growth factor (VEGF) receptor	(Khattak et al., 2015)	PFS was similar and OS was improved with panitumumab relative to bevacizumab when combined with mFOLFOX6 in patients with WT *KRAS* exon 2 tumors	(Schwartzberg et al., 2014)
Cetuximab Plus FOLFIRI	epidermal growth factor receptor (EGFR)	(Yen et al., 2010)	improved progression-free survival, overall survival, and objective response rates relative to	(Lyseng-Williamson, 2012)

			treatment with FOLFIRI alone in patients with EGFR-expressing mCRC with KRAS wild-type tumors	
Sunitinib plus FOLFIRI	vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR)	(Imbulgoda et al., 2015)	The combination FOLFIRI plus suni-tinib is more toxic than what is known from FOLFIRI or FOLFIRI plus bevacizumab. The cancer control rate is high, but the objective response rate of the combination does not exceed those rates for FOLFIRI alone.	(Mrossl et al., 2014)
sunitinib plus mFOLFOX6	vascular endothelial growth factor	(Starling et al., 2008)	sunitinib-based combination was associated with more toxicity than	(Hecht, Mitchell, Yoshino, et al., 2015)

	receptor (VEGFR)		that observed with bevacizumab and mFOLFOX6.	
regorafenib plus mFOLFOX6	vascular endothelial growth factor receptor 1,2,3 (VEGFR-1/2/3)	(Papadimitriou & Papadimitriou, 2021)	Regorafenib+mFOLFOX6 as first-line treatment in patients with metastatic CRC did not improve ORR over historical controls. Regorafenib plus mFOLFOX6 did not appear to be associated with a markedly worse tolerability profile versus mFOLFOX6 alone.	(Argilés et al., 2015)

Supplementary table 4: targets and outcomes of FOLFIRI and mFOLFOX6 based drug combinations used for the treatment of metastatic colorectal cancer