Application of pharmacoepidemiological approaches to generate real-world evidence on the use and impact of metastatic colorectal cancer medicines

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Declaration

This thesis is the result of the author's original research. It composed by the author and has not been previously submitted for examination which has led to award of the degree.

Signed: Haya Yasin

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“In the name of Allah, the most Gracious, the most Merciful”

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Publications and Poster Presentations

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Abstract

Introduction: Metastatic colorectal cancer (mCRC) is characterised by multiple treatment strategies. Randomised clinical trials are not always aligned with clinical practice, and greater use of real-world (RW) studies has been suggested to inform health care decisions by providing results that reflect RW practice.

Methods: This thesis utilised multiple methods. First, a systematic review and meta-analyses (SRMA) of RW studies including mCRC patients treated with first-line (1L) systemic anti-cancer therapy (SACT) was conducted to explore the comparative safety and effectiveness, including overall survival (OS), progression free survival (PFS) and objective response of 1L mCRC SACTs. Second, a retrospective observational cohort study using linkage of routinely collected data of mCRC patients treated with 1L SACT in NHS GGC from 01/01/2015 to 31/12/2016 was performed to investigate the factors influencing selection of 1L mCRC SACTs, treatment pathways, and treatment outcomes including median OS (mOS) and time-to-next-treatment (TTNT) of mCRC patients.

Results: Between 2015 and 2016, A total of 220 new mCRC SACT users were identified in NHS GGC, with 52.3% (N=115) of the patients treated with a doublet of FOLFOX or FOLFIRI, 22.3% (N=49) with 5FU, 19.5% (N=43) with cetuximab+FOLFIRI, and 5% (N=11) of patients treated initially with aflibercept+FOLFIRI. Treatment choices for 1L mCRC were made based on patients' age and gender, tumour RAS status, and previous treatment response.
The median overall survival (mOS) for these patients was statistically influenced by the initial mCRC SACT and the performance status. The combination of cetuximab+FOLFIRI demonstrated a statistically significant prolonged mOS compared to 5FU (HR 0.4 (95% CI 0.24-0.85) and the longest time to next treatment (TTNT (12.93 months (95%CI 5.85-15.25)). The SRMA also indicated an OS, PFS, and overall response rate benefit for bevacizumab+chemotherapy over chemotherapy alone with a statistically increased risk of non-haematological toxicities and a non-statistically significant increased risk for haematological toxicity.

Conclusions: Real-world evidence can help understand the impact of mCRC SACT on evidence-based practice.

Thesis summary

Introduction: Colorectal cancer (CRC) is one of the most common cancers worldwide and the second leading cause of cancer-related death. Approximately 40-50% of all CRC patients will develop metastatic CRC (mCRC). mCRC is characterised by multiple treatment strategies, and the last two decades have witnessed major advances in the management of mCRC, accompanied by a global change in clinical management guidelines (CMGs), which present challenges for clinicians in deciding the optimal treatment plan for their patients.

Despite the fact that randomised controlled trials (RCTs) are considered to be the gold standard for evidence-based practice, it is now widely accepted by health bodies that evidence-based practice should embrace other sources such as electronic health records and other sources of real-world evidence (RWE). Consequently, RWE is currently used to provide complementary evidence to RCTs to inform regulatory decisions and develop CMGs. Generating evidence about how patients may respond to treatments in routine clinical practice enables patients and clinicians to make better-informed treatment decisions.

Aims and objectives: The aim of this thesis was to increase evidence generation from clinical practice regarding the use of first-line mCRC medicines in real-world settings to better inform clinical decisions and optimise clinical outcomes among mCRC patients treated in a real-world setting. The objectives were: to compare the effectiveness and safety of first-line mCRC medicines in observational studies; to describe the characteristics of mCRC patients initiating first-line mCRC SACT in NHS Greater Glasgow and Clyde health board (NHS GGC) in Scotland; to examine the factors associated with the prescribing of first-line mCRC SACTs in patients treated in NHS GGC, and; to determine the clinical outcomes and treatment pathways of first-line SACT regimens for mCRC patients in NHS GGC.

Methods: First, a systematic review and meta-analysis (SRMA) was conducted. Relevant databases were searched from inception until July 2021. Inclusion criteria were observational studies; published in English; patients ≥ 18 years; mCRC; first-line SACT for treatment of mCRC. No restrictions were placed on the country of publication. The effectiveness outcomes included overall survival (OS), the primary outcome, progression-free survival (PFS), and objective response, which was assessed by the overall response rate (ORR) and disease control rate (DCR). Safety was assessed by the occurrence of grade 3 or 4 adverse effects based on the national cancer institute common terminology criteria for adverse events (NCI

CTCAE). The results were synthesised using a random-effect meta-analysis model based on hazard ratio and 95% confidence interval (95% CI) for survival outcomes, while risk ratio and 95% CI was used for safety outcome and objective response. Subgroup analysis was performed to explore differences between different treatment strategies. Heterogeneity was assessed using I^2.

Second, a retrospective observational cohort study using linkage of routinely collected data from 10 national and local Scottish datasets of patients diagnosed with mCRC and receiving SACT in NHS GGC from 01/01/2015 to 31/12/2016 was conducted. Patients were identified through the chemotherapy electronic prescribing and administration system (CEPAS), and datasets were linked retrospectively using the Scottish community health index (CHI) number as a common identifier. Summary statistics were used to describe the baseline characteristics of the patients. To examine the association of relevant covariates with the selection of each first-line (1L) mCRC systemic anti-cancer therapy (SACT) regimen, a multinomial logistic regression model was employed using odds ratio (OR) and 95% CI between the outcome (SACT prescribing) and the exposure covariate. Median overall survival (mOS) was estimated using the Kaplan-Meier method and chi-squared test used to compare differences between the treatment groups. Patients were followed up until death, loss to follow up or end of the study on February 28, 2018, whichever occurred first. To assess the impact of mCRC SACT on the overall survival under the adjustment of different covariates, hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazard models. Finally, patients' pathways across SACT lines were described and visualised using a Sankey diagram.

Results: For the SRMA, the search strategy identified 5662 studies, of which 29 met the inclusion criteria and were included in the overall survival meta-analysis. The pooled HR (95% CI) for overall survival, including all SACTs, was 1.19 (1.1-1.29). The overall heterogeneity of included studies was 76.6%. Subgroup analysis identified a significant difference between different treatment comparisons (p=0.01). The pooled overall survival was significant for chemotherapy only versus Bevacizumab+ chemotherapy (HR: 1.15 (95% CI 1.05-1.26), favouring the latter combination.

For PFS, 20 studies were included in the meta-analysis. The pooled HR (95% CI), including all SACTs, was 1.19 (1.08-1.3), with an overall heterogeneity of 64.4% for the included studies. Subgroup analysis showed a significant difference between different comparisons (p=0.001).

The pooled PFS was significant for (1) chemotherapy only versus bevacizumab+ chemotherapy (pooled estimate: HR 1.36 (95% CI 1.05-1.26) and (2) bevacizumab+ irinotecan-based chemotherapy versus bevacizumab+ oxaliplatin-based chemotherapy (pooled estimate: HR 1.22 (95%1.07-1.38).

For the safety outcomes, 13 studies were included in the meta-analysis. The pooled relative risk (RR, 95% CI) of haematological and non-haematological toxicities was 1.25 (0.89-1.76) and 1.03 (0.73-1.46), respectively, with no statistically significant difference between different treatment strategies for the haematological toxicities ($p > 0.05$). However, the pooled estimate for non-haematological toxicities was significant for two subgroups (1) bevacizumab+ XELIRI versus bevacizumab+ FOLFIRI (pooled RR: 1.66 (1.03-2.7), and bevacizumab+ FOLFOXIRI versus bevacizumab+ XELOXIRI (pooled RR: 3.5 (1.9-6.4).

In NHS GGC, a total of 220 new mCRC SACT patients were identified between the years 2015 and 2016. Most patients received a doublet of either FOLFOX (N=68, 30.9%) or FOLFIRI (n=47, 21.4%) as an initial SACT, whilst 49 (22.3%) patients received 5FU monotherapy, and 56 (26.1%) patients received triplet therapy of cetuximab + FOLFIRI (n=43, 19.5%) or aflibercept + FOLFIRI (N=11, 5%).

The included cohort comprised slightly more male patients (N=115, 52.3%) than female patients (N=105, 47.7%), with a median age of 66 years for the entire cohort. Around one-third of all patients in our study resided in the most deprived areas (30.9%, N=68), and 20% (N=44) of the patients resided in the least deprived areas. A total of 14 patients (6.4%) had a poor performance status before initiating index SACT, while 22.7% (N=50) of the patients had a good performance status (PS=0). Around one-third (30.5%, N= 67) of the patients had the primary tumour located in the right side of the colon, and only 26.8% (N=59) of the entire cohort underwent primary tumour resection. Mutation in the BRAF gene was detected in 7.7% (N=17) of the patients, while wild-type RAS tumour was found in 35% (N=77) of the tested patients.

Overall, 46 unique SACT pathways were identified. A total of 166 (75.5%) patients received only one SACT line, and 54 (24.5%) patients received at least two different lines of SACT during the study. Of these, 6 (11.1%) and 11 (20.4%) patients had their treatment intensified from monotherapy to a doublet or triplet SACT or from a doublet SACT to a triplet SACT, while 8 (14.8%) patients had their initial SACT stepped down in the second line (2L) from a

triplet to a doublet or from a doublet to a monotherapy. Only six patients received three treatment lines during the study. The most prescribed 2L SACT was FOLFIRI (N=19, 35.2%), followed by FOLFOX (N=16, 29.6%). By the end of the study, 183 patients were deceased.

This study identified patient, tumour, and treatment response-related factors associated with selecting 1L mCRC SACTs. Among the patient-related factors, older patients were 10% more likely to be prescribed 5FU than younger patients (OR 1.1 (95% CI 1.05-1.16)). Female patients were less likely to be prescribed an intensive therapy such as the triplet regimen cetuximab+FOLFIRI than male patients (OR 0.19, (95% CI 0.06-0.59)). Of the explored tumour-related factors, harbouring RAS wild-type tumour demonstrated more likelihood of being prescribed cetuximab+FOLFIRI (OR 65.2 (95% CI 16.1-122.8)). And among the treatment response-related factors, patients who had undergone resection of the primary tumour were significantly more likely to be prescribed a 1L SACT of either FOLFIRI (OR 3.64, 95% CI 1.64-8.1) or cetuximab+FOLFIRI (OR 4.4, 95% CI 1.4-13.8).

The median OS for the total cohort was 13.3 months (95% CI 10.8-15.4), with the longest observed median OS being 23.72 months (95% CI 13.75-NA) for patients treated with cetuximab+FOLFIRI as 1L regimen while patients treated with a 5FU monotherapy as 1L regimen had the shortest median OS of 9.57 months (95%CI 7.81-15.41). The multivariate Cox regression model adjusting for the baseline characteristics of the patients showed that the combination of cetuximab+FOLFIRI (HR 0.4, 95% CI 0.24-0.85) was significantly associated with less hazards of death compared to 5FU monotherapy. Furthermore, initial treatment with doublet therapy of FOLFOX (HR 0.7, 95% CI 0.52-1.18) or FOLFIRI (HR 0.93, 95% CI 0.49-1.22) was associated with a non-statistically significant improvement in OS compared to monotherapy of 5FU. The model also indicated that poor PS (PS ≥ 2) had a negative impact on the median OS and was associated with more inferior survival outcomes (HR 4.3, 95% CI 1.52-10.30) compared to patients with PS= 0.

Conclusion: Real-world evidence can help to better understand the impact of SACTs on mCRC, including the effectiveness and safety of different treatments in routine clinical practice, the factors that influence treatment choice, and the interplay between these factors and treatment outcomes.

List of abbreviations

1L	First-Line
2L	Second Line
3L	Third Line
5FU	5-fluorouracil+leucovorin
A&E	Accident And Emergency
AE	Adverse Events
AJCC	American Joint Committee on Cancer
APC	Adenomatous Polyposis Coli
ARIA	Radiotherapy Treatment Records
ASR	Age-Standardised Rate
ASR	Age-Standardised Rate
BRAF	B-Raf Proto-Oncogene Serine/Threonine Kinase
CCI	Charlson Comorbidity Index
CEA	Carcino-Embryonic Antigen
CEL	Chief Executive Letter
CEPAS	Chemotherapy Electronic Prescribing and Administration System
CHI	Community Health Index
CHIAG	Community Health Index Advisory Group
CI	Confidence Interval
CIMP	Cpg Island Methylator Phenotype
CMG	Clinical Management Guideline
CMO	Chief Medical Officer
CMOP	Cancer Medicines Outcomes Programme
CORECT-R	Colorectal Repository
CR	Complete Response
CRC	Colorectal Cancer
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic-T-Lymphocyte Associated Antigen
DCR	Disease Control Rate
dMMR	Deficient Mismatch Repair
DPYD	Dihydropyridine Dehydrogenase
DQA	Data Quality Assurance
ECOG	Eastern Cooperative Group
eDRIS	Electronic Data Research and Innovation Services
EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Records

ENCEPP	European Network for Centres of Pharmacoepidemiology and Pharmacovigilance
EOCRC	Early-Onset CRC
EORTC	European Organisation for Research and Treatment of Cancer
ES	Effect Size
ESMO	European Society for Medical Oncology
EU	European
FAP	Familial Adenomatous Polyposis
FDA	Food And Drug Administration
FDG-PET	Fludeoxyglucose Positron Emission Tomography
FOFLOX	5-Fluorouracil, Leucovorin, Oxaliplatin
FOLFIRI	5-Fluorouracil, Leucovorin, Irinotecan
GGC	Greater Glasgow and Clyde
GIT	Gastrointestinal Tract
GP	General Practitioner
GROS	General Register Office for Scotland
HFSR	Hand-Foot Skin Reaction
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICI	Immune Checkpoint Inhibitors
IIA	Independence Of Irrelevant Alternatives
IQR	Interquartile Range
ISD	Information And Statistics Division
KM	Kaplan-Meier
KRAS	Kirsten Rat Sarcoma
LIMS	Laboratory Information Management System
LOCF	Last Observation Carried forward
log	Logarithmic Transformation
MA	Meta-Analysis
MAPK	Mitogen-Associated Protein Kinase
MAR	Missing At Random
MCAR	Missing Completely at Random
mCRC	Metastatic Colorectal Cancer
MeSH	Medical Subject Headings
MI	Multiple Imputations
MLR	Multinomial Logistic Regression
MMR	Mismatch Repair
MNAR	Missing Not at Random
MoAB	Monoclonal Antibodies

mOS	Median Overall Survival
MRI	Magnetic Resonance Image
MSI	Microsatellite Instability
MSI-H	High Microsatellite Instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCICTG	National Cancer Institute of Clinical Trials Group
NHS	National Health Service
NHS GGC	National Health Service Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
NLR	Neutrophiles To Lymphocytes Ratio
NoSCAN	North Of Scotland Cancer Network
NRS	National Records of Scotland
NRS	Non-Randomised Studies
NSS	National Services Scotland
OPCS-4	Office Of Population Censuses and Surveys Procedural Codes, 4th Revision
OPERA	Elective & Emergency Operations
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
P&CFS	Practitioner And Counter Fraud Services
PAC	Privacy Advice Committee
PBPP	Public Benefit and Privacy Panel
PD	Progressive Disease
PD-1	Programmed Cell-Death-1 Protein
PFS	Progression-Free Survival
PH	Proportional Hazard
PHS	Public Health Scotland
PI	Prediction Interval
PICO	Participants, Intervention, Comparison, And Outcome
PIS	Prescribing Information System
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSD	Practitioner Services Division
RAS	Rat Sarcoma Viral Oncogene Homolog
RCT	Randomised Control Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RoB	Risk Of Bias
ROBINS-I	Risk Of Bias in Non-Randomised Studies-Of Interventions
RR	Risk Ratio

RWD	Real-World Data
RWE	Real-World Evidence
SACT	Systemic Anti-Cancer Therapy
SBoSP	Scottish Bowel Screening Programme
SCAN	South-East Scotland Cancer Network
SCI	Scottish Care Information
SCR	Scottish Cancer Registry
SD	Stable Disease
SE	Standard Error
SG	Scottish Government
SGHSC	The Scottish Government Health and Social Care Directorates
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicine Consortium
SMR	Scottish Morbidity Records
SMR00	Scottish Morbidity Records - Outpatient Appointments and Attendances
SMR01	Scottish Morbidity Records - General Acute Inpatient and Day Case
SMR06	Scottish Morbidity Records - The Scottish Cancer Registry
SQ	Signalling Questions
SR	Systematic Review
SR-MA	Systematic Review and Meta-Analysis
TB	Tumour Burden
TP53	Tumour Protein 53
TTE	Time-To-Event
TTNT	Time To Next Treatment
UFT	Tegafur Plus Uracil
UK	United Kingdome
USA	United States of America
USC	Urgent Suspicion of Cancer
VEGF	Vascular Endothelial Growth Factor
VIF	Variance Inflation Factor
VPN	Virtual Private Network
WoSCAN	West of Scotland Cancer Network

1 Chapter 1: Background

1.1 Thesis outline

This thesis describes the study of systemic anti-cancer treatments (SACTs) used by patients with metastatic colorectal cancer (mCRC) in NHS Greater Glasgow and Clyde (NHS GGC) using routinely collected healthcare data. In addition, the published real-world evidence on the comparative effectiveness and safety of metastatic colorectal medicines is presented using a meta-analysis. This thesis comprises seven chapters, starting with a background chapter introducing metastatic colorectal cancer and the concepts of real-world evidence in pharmacoepidemiology. The second chapter is a systematic review and a meta-analysis that summarises the published real-world evidence comparing effectiveness measures, including overall survival (OS), progression-free survival (PFS), objective response, and safety measured by the occurrence of severe toxicities for first-line mCRC SACTs. Chapter 3 introduces the data sources and data variables, in addition to describing the data management processes in data governance, access, preparation, and data manipulation. Following in chapter 4 is a description of the baseline characteristics of the included cohort, which also prepares for the subsequent chapters 5 and 6. Chapter 5 describes the patient, treatment, and tumour-related factors that influenced the selection of first-line SACTs for mCRC patients in NHS GGC. Chapter 6 details the clinical outcomes, including overall survival and time to next treatment, plus the treatment pathways for mCRC initiating first-line mCRC SACT in NHS GGC.

1.2 Colorectal cancer

1.2.1 Colorectal cancer epidemiology

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related death, with almost 1.93 million new cases and 940,000 CRC-caused deaths in 2020 (Xi and Xu, 2021). The global burden of CRC is expected to increase by 60% by the year 2030, with more than 2.2 million new cases and 1.1 million deaths (Arnold et al., 2017a). The incidence of CRC across the two genders remains stable over the years, with the incidence approximately 25% higher in males compared to females (Bray et al., 2018, Arnold et al., 2017a). The global pattern and mortality rates of CRC vary widely. In general, it has been observed that CRC incidence and mortality are increasing in

low and middle-income countries as they become westernised, which reflects an increased prevalence of risk factors for CRC that are associated with westernisation, such as physical inactivity, unhealthy diet, obesity, and smoking prevalence in low-middle income countries, while the risk is stabilising or decreasing in high-income countries, particularly those countries that have enforced screening for CRC (Favoriti et al., 2016, Siegel et al., 2019, Xi and Xu, 2021). Classically, the incidence rates of CRC rise with increasing age. However, in recent years, a rising global incidence of early-onset CRC (EOCRC) has been observed in younger age groups before the age of 50 years, which was found to be related to westernised diets, stress, synthetic food diets, and sedentary lifestyle (Hofseth et al., 2020).

1.2.2 Anatomy of the colon and rectum

The lower digestive system comprises the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The large intestine (colorectum) starts at the cecum, a 2 to 3-centimetre-long pouch (Figure 1.1). The ascending colon ascends from the cecum along the right abdominal posterior wall to the right upper quadrant and the undersurface of the liver, where the hepatic flexure moves toward the midline to become the transverse colon. The transverse section crosses the abdominal cavity in the upper left quadrant toward the spleen. At this point, the transverse colon turns downward to the splenic flexure. The descending colon continues along the left side of the abdomen before turning medially and inferiorly to form the S-shaped sigmoid colon. From the end of the sigmoid colon to the anal canal, the rectum comprises the final 12 to 25 cm of the large intestine (Irving and Catchpole, 1992).

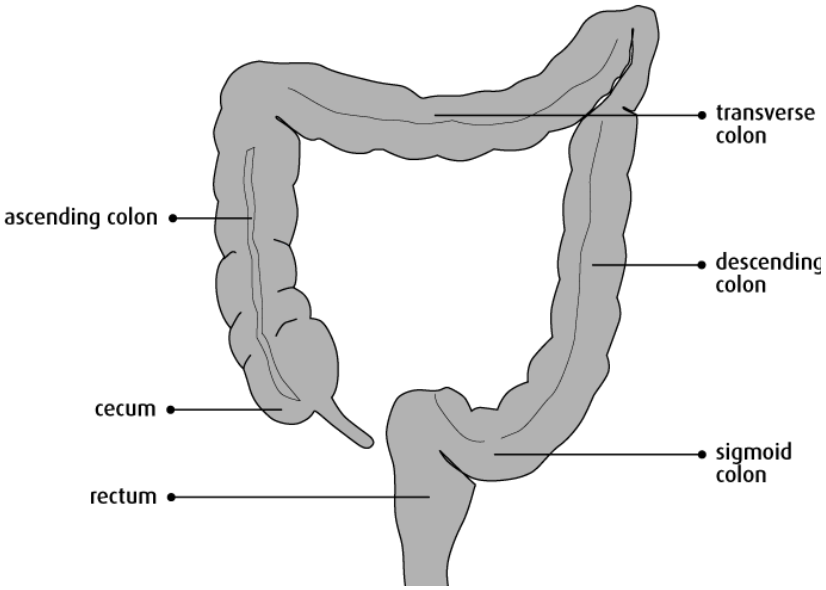

Figure 1.1 The anatomy of the colon and rectum.

1.2.3 Risk factors and pathogenesis.

Both environmental and genetic factors contribute towards the risk of CRC, with the mode of presentation of CRC following one of the following three patterns reflecting these risk factors:

1- Sporadic (non-hereditary) CRC, in which no family history is involved. This pattern of CRC occurs in around 70% of the patients, with patients above the age of 50 years being the most affected age group (Carethers and Jung, 2015). Sporadic CRCs develop from normal colonic mucosa by one of three suggested genetic and morphologic pathways; first, by the progressive accumulation of genetic alterations, such as mutations in adenomatous polyposis coli (APC) in earlier stages and mutations in rat sarcoma viral oncogene homolog (RAS) and tumour protein 53 (TP53) in later stages (Fearon and Vogelstein, 1990). Second is the Microsatellite instability (MSI), accounting for around 15% of sporadic CRCs. This pathway is activated when DNA mismatch repair genes are disrupted (MMR deficiency), which is responsible for proofing newly synthesised DNA and correcting replication mistakes. When this system is deactivated, DNA mutations rapidly rise, allowing cancerous cell lines to proliferate. B-Raf proto-oncogene serine/threonine kinase

(BRAF) is an oncogene that can stimulate cell proliferation, and it is frequently mutated in MSI cancers, increasing the proliferation of malignant cells. These tumours frequently form in the colon's proximal region (right side of the colon) and are characterised by elevated mucin production and low-grade differentiation (Boland and Goel, 2010). The third pathway, known as CpG island methylator phenotype (CIMP), involves inactivating tumour suppression genes, which leads to abnormal growth of malignant cells (Toyota et al., 1999).

2- Hereditary CRC, which can be subclassified into two groups depending on the presence of colon polyps:
    a. Familial adenomatous polyposis (FAP), which includes the presence of polyps. This syndrome is caused by a mutation in the APC gene. Most patients with FAP develop hundreds of polyps in the colon, and almost all patients with this genetic mutation will develop CRC by the age of 40 years (Half et al., 2009)
    b. Lynch syndrome (hereditary nonpolyposis CRC), which does not involve the presence of polyps. This syndrome represents 3% of all CRCs, and it is associated with an increased risk of CRC and other types of cancer, such as endometrial ovarian, gastric, small bowel, pancreatic, and urothelial cancer (Lynch et al., 2015)
3- Inflammatory bowel disease (IBD): Chronic colitis due to IBD is associated with an increased risk of CRC. The extent, duration, and activity of the disease are deemed to be the primary determinants for CRC. IBD explains 1% of all CRCs (Stidham and Higgins, 2018).

Approximately 40% of CRC patients harbour a Kirsten rat sarcoma viral oncogene homolog (KRAS) or neuroblastoma N-Ras (NRAS) tumour gene mutation. In comparison, 10% of CRC patients carry a mutation of the BRAF gene. Mutations in these genes result in dysregulation of the mitogen-associated protein kinase (MAPK) pathway. The activation of this pathway is responsible for cell proliferation, differentiation, angiogenesis, and metastasis. One of the most important receptors for the MAPK pathway is the transmembrane protein endothelial growth factor receptor (EGFR). As shown in Figure 1.2, the ligand binding to EGFR results in the activation of the EGFR receptor, which causes a cascade activation of RAS, RAF, MEK, and

ERK1. Ultimately, this pathway induces cell proliferation, differentiation, angiogenesis, and metastasis (Yarden, 2001, Bos, 1989). In the context of CRC, the most common cause of the MAPK pathway dysregulation is the presence of activating mutations of genes encoding for the RAS and RAF proteins (Bos, 1989).

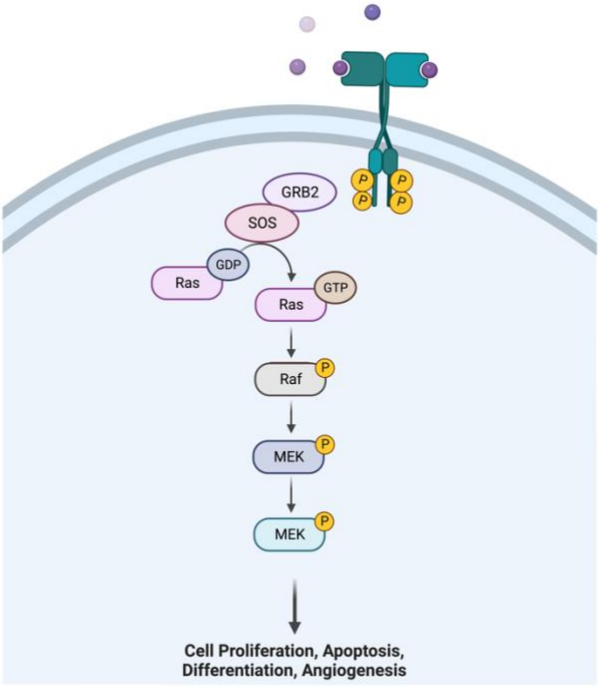

Figure 1.2. MAPK signalling pathway in colorectal cancer (Adapted from (Bos, 1989)).

1.2.4 CRC staging.

Staging cancer provides a standardised framework for describing the extent of a disease. The stage of a CRC consists of three components, primary tumour (T), the status of the regional nodes (N), and distant metastasis (M), which together are combined to form stage groupings from I to IV. Stage groupings allow the classification of prognosis, which is useful for treatment choice. Table 1 illustrates the American Joint Committee on Cancer (AJCC) 8th Edition TNM staging for CRC (Weiser, 2018). Noteworthy, this edition of TNM staging has introduced a modification to the M category by adding a new M stage incorporating peritoneal metastasis based on growing evidence supporting it as a sign of a poor prognosis.

However, the current M category still covers a heterogenous group of metastatic CRCs in terms of survival outcomes and potential treatment strategies (Primrose et al., 2013).

Approximately 25% of patients with CRC present with overt metastatic disease at the time of primary diagnosis, and 40-50% of all CRC patients will develop metastatic colorectal cancer (mCRC). (Van Cutsem et al., 2014b, van der Geest et al., 2015). Metastases are considered the leading cause of CRC-related mortality, and patients with mCRC have a poor prognosis, with a 5-year survival rate of 14% compared to 90% and 71% for patients with localised CRC (stages I, IIA, and IIB), and regional cancer (stages IIC and III), respectively (Mattiuzzi et al., 2019). Nevertheless, recent advances in the treatment of mCRC as shown to increase survival for 2-3 years (Biller and Schrag, 2021).

Table 1.1 Colorectal cancer staging according to the American Joint Committee on Cancer (AJCC) (adapted from the American Cancer) (Weiser, 2018).

AJCC Stage	Stage grouping	Stage description
0	Tis N0 M0	The cancer is in its earliest stage, known as carcinoma in situ (Tis). It has not grown beyond the inner layer of the colon or rectum
I	T1 or T2 N0 M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IIA	T3 N0 M0	The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
IIB	T4a N0 M0	The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIC	T4b N0 M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIIA	T1 or T2 N1/N1c M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0).
	T1 N2a M0	The cancer has grown through the mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
IIIB	T3 or T4a N1/N1c M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a or N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0)
	T2 or T3 N2a M0	The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0).

AJCC Stage	Stage grouping	Stage description
	T1 or T2 N2b M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
IIIC	T4a N2a M0	The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
	T3 or T4a N2b M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
	T4b N1 or N2 M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites (M0)
IVA	Any T Any N M1a	The cancer may or may not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to **1 distant organ** (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1a)
IVB	Any T Any N M1b	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to **more than 1 distant organ** (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b)
IVC	Any T Any N M1c	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to **distant parts of the peritoneum** (the lining of the abdominal cavity), and may or may not have spread to distant organs or lymph nodes (M1c)
KEY: AJCC=American Joint Committee on Cancer		

1.2.5 Clinical presentation and diagnosis of CRC.

Patients with CRC can present with one of three modes: 1- suspicious signs and symptoms, 2- asymptomatic but diagnosed through routine screening, or 3- patients who present with emergency symptoms such as intestinal obstruction, haemorrhage, or peritonitis (Hamilton et al., 2005). The majority of the patients with early stages of CRC present with no symptoms, and these are usually diagnosed through routine screening (Hamilton et al., 2005). However, a strong body of evidence suggests that screening for CRC increases the detection of early-stage cancer diagnosis (Stage I and stage II), resulting in reduced cancer-specific mortality (Hardcastle et al., 1996, Mandel et al., 1993) in addition to reducing the incidence of CRC through the removal of cancerous polyps (Mandel et al., 2000). Regrettably, most CRCs are diagnosed after the onset of symptoms (Force et al., 2021). These symptoms typically occur as a result of the tumour growth in the lumen or in the adjacent structures. For patients presenting with a localised tumour, the most common symptoms include melena (black tarry stool), haematochezia (presence of red fresh blood in the stool), microcytic anaemia, abdominal pain, and change in bowel habits (Moiel and Thompson, 2011, Hamilton et al., 2005).

For patients presenting at the metastatic stage, the signs and symptoms usually depend on the site of metastasis. The regional lymph nodes are the most common metastatic site, followed by the liver, the lung, and the peritoneum (Riihimaki et al., 2016). The presence of pain in the right upper quadrant of the abdomen, abdominal distention, early satiety or periumbilical nodules usually suggest metastatic disease (Holch et al., 2017).

The liver is the most common organ involved in CRC metastasis occurring in 20-25% of patients presenting with metastatic disease at the time of initial diagnosis (Riihimaki et al., 2016). Peritoneal metastasis occurs in 7-10% of the patients at initial diagnosis (Koppe et al., 2006), while lung metastasis is reported to occur in 6-8% of colon cancer and 10-18% of rectal cancer metastases (Jördens et al., 2021). Finally, bone metastasis occurs in 2-12% of mCRC patients (Mege D, 2013). The prognosis of the disease varies by the site of metastasis, with lung-only metastasis resulting in the best prognosis, whereas bone-only metastasis and brain-only metastasis have the worst prognosis (Wang et al., 2020).

CRC may be suspected based on one or more of the aforementioned signs and symptoms, or it may be asymptomatic and detected by routine screening of average- and high-risk

individuals. Once a CRC is suspected, a colonoscopy may be performed as the next step (Świderska et al., 2014). A colonoscopy-guided biopsy is used to confirm primary cancer, while a biopsy of the liver, lung, or lymph nodes confirms the metastases (Świderska et al., 2014). Colonoscopy can detect synchronous neoplasms, which is defined as two or more distinct primary tumours in one patient diagnosed within six months of the primary CRC (Lam, 2014), whereas a CRC metastasis diagnosed after six months of the primary diagnosis denotes a metachronous metastasis (Rao and Jayaraman, 2011).

1.2.6 Management of CRC

Treatment options for CRC rely mainly on the stage of the disease, patient's performance status, and the tumour molecular profile. Primary CRC without metastasis is treated by surgical resection with curative intent (Hohenberger et al., 2009, Sehgal and Coffey, 2014). Surgery is considered the only curative method for the localised primary tumour, which aims to completely remove the tumour, the vascular pedicles, and the lymph vascular drainage of the site of the tumour (Vogel et al., 2017). Additionally, in emergency settings, presenting with symptoms of colonic obstruction, bleeding, or perforation warrant resection of the tumour with palliative intent (De Rosa et al., 2015). For locally advanced rectal cancer, neoadjuvant (perioperative) radiotherapy with or without chemotherapy is usually administered (Body et al., 2021). On the other hand, postoperative (adjuvant) chemotherapy is administered to patients who have undergone curative resection of the primary tumour, aiming to eradicate micrometastases, hence reducing the likelihood of tumour recurrence and improving the cure rate, with oxaliplatin-containing chemotherapy usually recommended (Dubé et al., 1997).

For stage IV CRC (metastatic colorectal cancer), the management strategy involves a multifactorial approach based on treatment aim (survival prolongation, controlling progression, tumour shrinkage, etc.), tumour-related characteristics (e.g., number and localization of metastases) and patient-related factors (e.g., co-morbidity, performance status) (Schmoll et al., 2012). Patients' prognosis declines as the number of metastatic sites increase (Köhne et al., 2002). Moreover, the resectability of the primary tumour and the metastasis is a crucial component in making the decision regarding the treatment modality for patients presenting with metastatic disease. In general, potentially curative resection of the metastases is the goal for patients presenting with one site of surgically resectable metastasis, especially in metachronous settings. However, for patients presenting with more

than one site of metastasis, controlling the disease progression is usually the aim of the treatment (Chakedis and Schmidt, 2018).

Several therapeutic options are available for patients presenting with synchronous metastasis, especially if the metastatic sites are amenable to surgical resection (Chakedis and Schmidt, 2018). Nevertheless, the prognosis in the synchronous settings is generally worse than the metachronous settings, with only 6% of the patients presenting with synchronous metastasis eligible for curative resection in contrast to 17% of the patients presenting with metachronous metastasis (Chakedis and Schmidt, 2018, Manfredi et al., 2006). Traditionally, for patients presenting with potentially resectable metastasis, the primary tumour in the colon or rectum is resected surgically, followed by systemic anticancer therapy (SACT), and then excision of the metastasis is considered (Manfredi et al., 2006). However, for patients presenting with potentially unresectable metastasis, downstaging SACT conversion therapy is administered in an attempt to convert the metastasis from unresectable into a resectable metastasis (Chakedis and Schmidt, 2018). Unfortunately, most patients present with initially unresectable metastasis, where SACT is administered and resumed to control the progression of the disease. For these patients, the treatment intent is palliative rather than curative, with the treatment goal of prolonging overall survival and maintaining the quality of life (Chibaudel et al., 2011).

Systemic anticancer therapies used in unresectable mCRC are presented in table 1.2, outlining the medicines used, their indication, and selected severe toxicities occurring in more than 10% of the patients. However, these medicines fall broadly into the following categories:

1- Chemotherapeutic agents, which encompass three cytotoxic drugs; Fluoropyrimidine chemotherapy (5-fluorouracil [5-FU], Capecitabine, Tegafur), which is recognised as the backbone of first-line palliative chemotherapy for mCRC (Rougier and Mitry, 2009), Irinotecan, and oxaliplatin. The later chemotherapeutic drugs are widely used in combination with 5-FU and leucovorin (folinic acid) as first- or second-line treatment for mCRC (de Gramont et al., 2000, Yamaguchi et al., 2016). Moreover, the use of monoclonal antibodies in combination with 5-FU/oxaliplatin or irinotecan has become common to improve survival rates in patients with mCRC (Yamaguchi et al., 2016, Meyerhardt et al., 2012a).

2- Molecular targeted treatments, this treatment group encompass two subgroups:
    a. Antiangiogenic agents, which act by inhibiting the formation of new blood vessels, hence preventing tumour cell proliferation. Vascular endothelial growth factor inhibitors (VEGF) such as bevacizumab, aflibercept, and regorafenib bind to VEGF receptors and block receptor activation, hence, preventing tumour cell proliferation.
    b. Anti-epidermal growth factor agents (anti-EGFR), including cetuximab and panitumumab act by inhibiting the EGFR, which modulates tumour cell growth, signalling, differentiation, and proliferation. (Grandis and Sok, 2004). It was found that only patients with wild-type KRAS tumours respond to anti-EGFR treatment (Lievre et al., 2008). Thereby, the KRAS tumour gene has been validated as a negative predictive marker for anti-EGFR treatment activity (Chibaudel et al., 2011).

3- Immunotherapy with immune checkpoint inhibitors (ICIs) that target programmed cell-death-1 protein (PD-1), such as nivolumab and pembrolizumab (Sahin et al., 2019) were shown to have a beneficial effect on patients with high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) mCRC that has progressed beyond using chemotherapy.

4- Other treatment groups include BRAF kinase inhibitors such as encorafenib, which in combination with cetuximab is used for patients with confirmed BRAF V600 mutation after prior chemotherapy.

Advances in mCRC therapies have directly resulted in an improvement of median overall survival (mOS) from approximately 11–12 months in the 5-FU single-agent era to more than 24 months with multiple regimens in the modern era (Kopetz et al., 2009, Ikoma et al., 2017). The addition of irinotecan (5-fluorouracil, leucovorin, irinotecan [FOLFIRI]) and oxaliplatin (5-fluorouracil, leucovorin, oxaliplatin [FOLFOX]) has led to increased efficacy and raised overall survival (OS) to a median of about 20 months (Tournigand et al., 2004b). Moreover, the addition of biologicals, such as bevacizumab or cetuximab and panitumumab, to those standard regimens has led to OS times of about 24 months (Saltz et al., 2008, Van Cutsem et al., 2011, Douillard et al., 2014a). Although the introduction

of these therapies has led to an improved OS, it has been recognized that the presence of mutations in RAS biomarkers infers that the patient will not respond to EGFR inhibitors such as cetuximab, whilst mutation in BRAF biomarkers has a negative prognostic value.

Table 1.2 Medicines used for the management of mCRC, their mechanism of action and most common severe adverse effects.

Pharmacological group	Medicine	Mechanism of action	Activity	Most common severe adverse effects
Fluorouracil (5FU)	5FU/leucovorin Capecitabine S-1 Tegafur plus uracil (UFT)	Antimetabolite Inhibits thymidylate synthase (Longley et al., 2003)	In mCRC, Neoadjuvant chemoradiation in stage II and stage III rectal cancer (de Gramont et al., 1997b)	Neurotoxicity, cardiovascular complications Diarrhoea, nausea, poor appetite, photophobia, leukopenia, thrombocytopenia (Pinedo and Peters, 1988)
Oxaliplatin	Oxaliplatin	Alkylating agent Binds to DNA and prevent DNA replication and transcription (Raymond et al., 1998)	mCRC in combination with 5FU/leucovorin (FOLFOX) or In combination with capecitabine (XELOX), Stage III adjuvant chemotherapy in combination with fluorouracil after complete resection of primary tumour (Stein and Arnold, 2012)	Peripheral neuropathy, abdominal pain, nausea, diarrhoea, vomiting, fever, elevated liver enzymes, anaemia, and thrombocytopenia (Raymond et al., 1998, Cassidy and Misset, 2002)
Irinotecan	Irinotecan	Topoisomerase I Inhibitor: binds to topoisomerase-I DNA and prevents relegation of the cleaved DNA strands leading to termination of cellular replication (Xu and Villalona-Calero, 2002).	mCRC either as first or second line in combination with 5FU/leucovorin (FOLFIRI) In combination with capecitabine (XLEIRI) In combination with 5FU/leucovorin and oxaliplatin (FOLFOXIRI) In combination with capecitabine and oxaliplatin (XELOXIRI), For progressive disease following initial 5-FU based therapy (Vanhoefer et al., 2001).	Diarrhoea, nausea, abdominal pain, vomiting, cholinergic syndrome, alopecia, anaemia, leukocytopenia, neutropenia, elevated liver enzymes. (Vanhoefer et al., 2001, Bailly, 2019).
Anti-EGFR	Cetuximab	Epidermal Growth Factor Receptor (EGFR) Inhibitor: binds to the EGFR and competitively inhibits the binding of EGF, resulting in the blockade of	Cetuximab: KRAS- wild type mCRC as single agent or in combination with irinotecan or FOLFIRI (Blick and Scott, 2007)	Dermatological toxicity, weight loss, hypomagnesemia, constipation, nausea, elevated liver

Pharmacological group	Medicine	Mechanism of action	Activity	Most common severe adverse effects
		phosphorylation and activation of the receptor-associated kinases, thereby inhibiting cell growth, inducing apoptosis and decreased vascular endothelial growth factor production (Vincenzi et al., 2008).	Panitumumab: KRAS-wild type mCRC as first-line in combination with FOLFOX or as single agent following disease progression despite the use of oxaliplatin or irinotecan-based chemotherapy (Amado et al., 2008).	enzymes, peripheral neuropathy (Blick and Scott, 2007)
VEGF-receptor 2 blockers	Bevacizumab Ramucirumab	Bind to vascular endothelial growth factor (VEGF) and prevent its binding to the receptor, hence, inhibits metastatic tissue growth (Ellis, 2006).	Bevacizumab: for mCRC in combination with fluorouracil-based chemotherapy (Hurwitz et al., 2004). Ramucirumab: for resistant mCRC or mCRC that progressed after bevacizumab and oxaliplatin based chemotherapy: in combination FOLFIRI until disease progression or death (Tabernero et al., 2015).	Hypertension, venous thromboembolism, leukopenia, nausea, abdominal pain, diarrhoea, headache thrombocytopenia (Kazazi-Hyseni et al., 2010, Hurwitz et al., 2004)
VEGF-receptor 1 blocker	Aflibercept	Prevent VEGF-A and VEGF-B from binding to their receptors, hence leading to antiangiogenics and tumour regression (Ciombor and Berlin, 2014).	In resistant mCRC or mCRC that progressed after using an oxaliplatin based therapy: in combination with FOLFIRI until disease progression or death (Van Cutsem et al., 2012).	Hypertension, weight loss, diarrhoea, stomatitis, proteinuria, haemorrhage, leukopenia, neutropenia, thrombocytopenia, elevation in the liver enzymes, elevated serum creatinine (Wang and Lockhart, 2012)
VEGF inhibitor	Regorafenib	Multikinase inhibitor targeting kinases involved in tumour angiogenesis and oncogenesis, hence, inhibiting tumour growth.	Treatment of mCRC patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based therapy, an anti VEGF, or ant-EGFR therapy.	Hypertension, alopecia, dermatological toxicities, reduced appetite, diarrhoea, anaemia, thrombocytopenia, hyperbilirubinemia, elevated liver enzymes, fatigue
Thymidine Phosphorylase Inhibitor	Trifluridine and tipiracil	Trifluridine is a thymidine-based nucleic acid analogue that is incorporated into	In mCRC patients previously treated, oxaliplatin, and irinotecan-	Fatigue, nausea, reduced appetite, anaemia, neutropenia,

Pharmacological group	Medicine	Mechanism of action	Activity	Most common severe adverse effects
		DNA and interferes with DNA synthesis and inhibits cell proliferation. Tipiracil is a potent thymidine phosphorylase inhibitor preventing the rapid degradation of trifluridine (Lenz et al., 2015).	based chemotherapy, an anti-VEGF therapy.	thrombocytopenia, Infection, asthenia (Mayer et al., 2015)
Immune check point inhibitors	Nivolumab and ipilimumab Pembrolizumab	Nivolumab and pembrolizumab: Immune check point inhibitor that inhibits the programmed death-1 receptor (PD-1) resulting in antitumour immune response. ipilimumab: a recombinant immunoglobulin monoclonal antibody that binds to cytotoxic-t-lymphocyte associated antigen (CTLA-4). When combined with Nivolumab, an enhanced T-cell function occurs resulting in improved anti-tumour response (Overman et al., 2018).	Microsatellite instability mCRC or mismatch repair deficient: nivolumab alone or in combination with ipilimumab in patients who have progressed following treatment with fluoropyrimidine, oxaliplatin or irinotecan-based therapy Overman et al., 2018).	Oedema, hypertension, pruritis, hyperglycaemia, hyperkalaemia, nausea, vomiting, diarrhoea, elevated liver enzymes, asthenia Overman et al., 2018)
BRAF kinase inhibitor	Encorafinib	ATP competitive inhibitor of protein kinase B-raf (BRAF) which suppresses the MAPK pathways (Dummer et al., 2018). The combination of encorafinib and ant-EGFR has a great anti-tumour activity (Tabernero et al., 2021).	BRAF V600E mCRC in combination with cetuximab until disease progression or death (Kopetz et al., 2019, Tabernero et al., 2021).	Alopecia, hyperkeratosis, hyperglycaemia, constipation, decreased appetite, diarrhoea, vomiting, anaemia, elevated liver enzymes, arthralgia, increased serum creatinine (Tabernero et al., 2021)

KEY: 5FU= Fluorouracil; S-1 mCRC= metastatic colorectal cancer; DNA= Deoxyribonucleic acid; EGFR= epidermal Growth Factor Receptor; KRAS = Kirsten rat sarcoma viral oncogene; VEGF= vascular endothelial growth factor; BRAF= protein kinase B-raf.

1.2.7 Management of metastatic colorectal cancer in Scotland.

In Scotland, medicines are only routinely available on NHS prescription if approved for use by the Scottish Medicine Consortium (SMC) (Scottish Medicine Consortium, 2022). The process starts with pharmaceutical companies presenting evidence from published clinical trials, preclinical data, and pricing details which may adjust the cost-effectiveness analysis of the medicine. The SMC committee examines the evidence then, a decision is made as to whether or not the medicine will be used within NHS Scotland (Scottish Medicine Consortium, 2022). Figure 1.3 shows the timeline in which mCRC medicines were licenced for use in NHS Scotland.

In Scotland, clinical management guidelines are developed by the Scottish Intercollegiate Guidelines Network (SIGN) for NHS Scotland (Miller, 2002). According to the SIGN 126 guideline for the management of colorectal cancer, all mCRC patients should be offered SACT. The choice of first-line SACT depends on the patient's fitness, comorbidity, and the aim of treatment. Patients with good performance status and adequate organ function should be initially treated with FOLFOX, XELOX, or FOLFIRI. However, patients who cannot tolerate combination chemotherapy, 5FU or raltitrexed should be considered. Cetuximab, combined with FOLFOX or FOLFIRI, should be considered a first-line treatment for patients with RAS wild-type tumours. For second-line SACT, irinotecan (FOLFIRI or XELIRI) should be used following first-line oxaliplatin (FOLFOX) and vice versa (Scottish Intercollegiate Guidelines Network, 2011a). The SMC has also approved aflibercept in combination with FOLFIRI to be used in resistant mCRC or mCRC that has progressed despite the use of an oxaliplatin-containing regimen in the first-line (Scottish Medicine Consortium, 2014). Noteworthy, the SIGN 126 guidance for the management of mCRC provides limited detailed recommendations on the choice of appropriate SACT based on the individual characteristics of the patients.

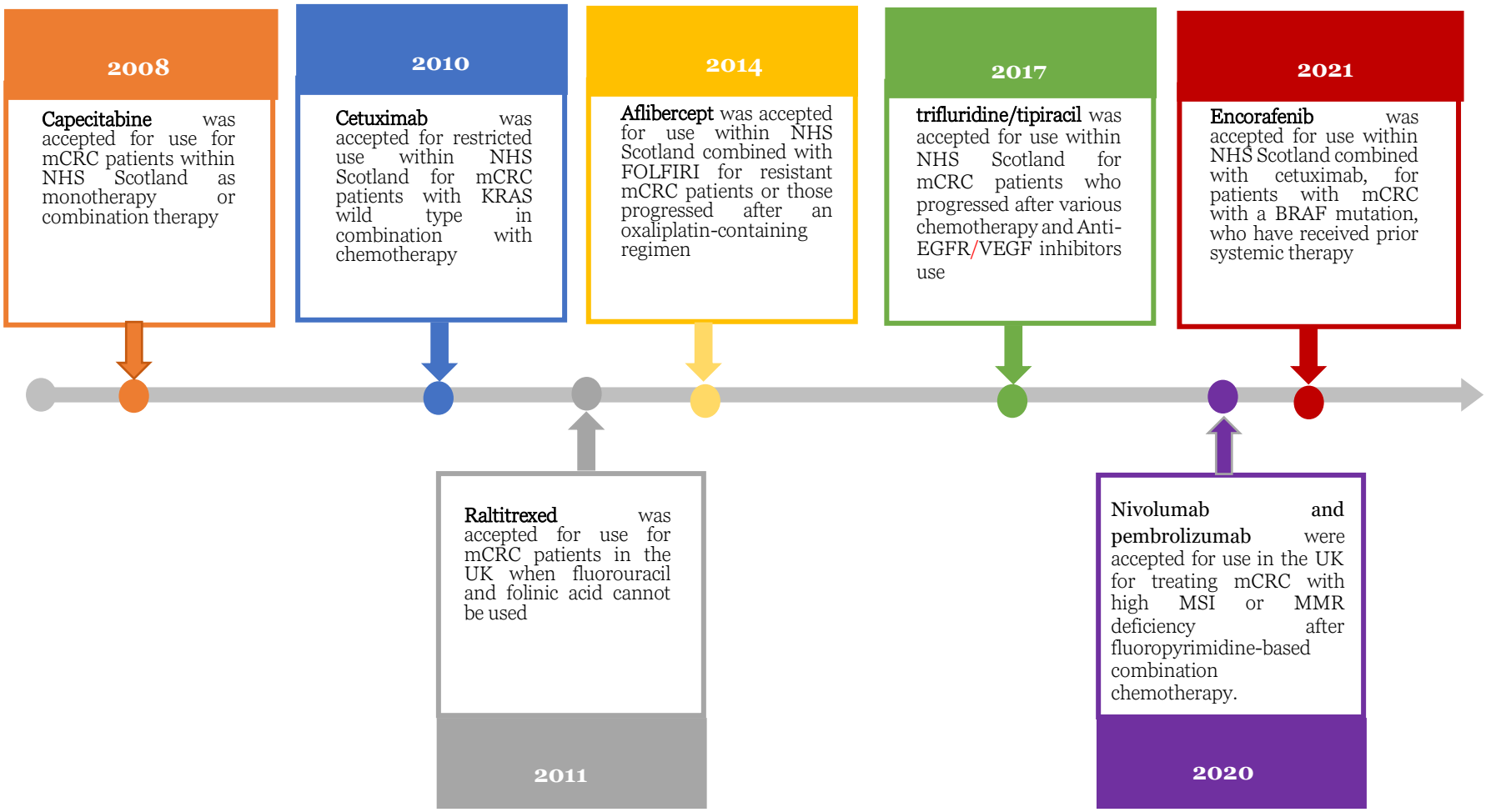

Figure 1.3 Treatments approved in Scotland for unresectable metastatic colorectal cancer since 2008.

KEY; EGFR=epidermal growth factor receptor; FOLFIRI= Folinic acid-Fluorouracil-Irinotecan regimen; KRAS =Kirsten rat sarcoma; MMR= mismatch repair; MSI= Microsatellite instability; NHS= National Health Services; mCRC: metastatic colorectal cancer; VEGF= Vascular endothelial growth factor

1.3 Real-world data and real-world evidence.

Randomised control trials (RCTs) are viewed as the current gold-standard primary study design for the determination of the efficacy and safety of medical interventions (Schulz et al., 2010). In RCTs, the investigators are able to reduce bias and confounding by utilizing randomization and strict patient inclusion and exclusion criteria. However, since they are conducted under idealized and rigorously controlled conditions and often exclude large portions of patients, including children, the elderly and patients with multiple co-morbidities, the external validity of RCTs might be compromised since the populations enrolled in RCTs may differ significantly from those found in everyday practice. Also, RCTs do not always reflect the heterogeneous patient population encountered in clinical practice (Fortin et al., 2006). Moreover, RCTs often have short follow-up durations, preventing the detection of rare or long-term adverse events of interventions. In these circumstances, studies of observational design are used to assess the effectiveness of an intervention in non-experimental, 'real world' settings at the population level as well as providing a line of complementary evidence to that provided by RCTs (Blonde et al., 2018).

Data from real-world studies can provide evidence that informs payers, clinicians, and patients on how an intervention works outside the research setting, which provides essential information on the long-term safety and effectiveness of a drug in large populations, and for assessment of comparative effectiveness with other treatments (Blonde et al., 2018). The study of the utilisation and effects of medicines in large populations is termed pharmacoepidemiology (Montastruc et al., 2019). In pharmacoepidemiology, Real-world evidence (RWE) refers to the clinical findings on the use, risk, and benefit of using medicines generated from the analysis of real-world data (RWD) (Bérard, 2021).

The value of RWD has been recognized by regulatory bodies such as the US Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) in the UK, which use RWD as a key component of healthcare technology assessments to guide clinical decision-making (NICE, 2022, FDA, 2022). The overarching objective of utilising RWD is to develop decision-support tools and practise guidelines, monitor post-marketing safety and adverse events of approved medicines, and support the efficacy of therapeutic products while allowing assessment of the effects of off-label use. (Ramamoorthy and Huang, 2019). For that purpose, many resources can be utilised, including large national administrative

databases and health registries, electronic health records (EHR), insurance claims, pharmacy data, and data obtained from wearable and mobile (Curtis et al., 2019).

Since pharmacoepidemiology relates to both the pharmacological evaluation of medicines and different methods used in epidemiology, its methodology is observational (Sommet and Pariente, 2019). Two main approaches are used in pharmacoepidemiology: 1- the descriptive (non-comparative) approach and 2- the etiologic (comparative) approach. The descriptive method examines phenomena in a retrospective or prospective manner. Descriptive studies are conducted to examine the modalities of exposure and the characteristics of exposed and unexposed subjects. In the context of pharmacoepidemiology, descriptive studies allow for quantifying the use of medicines in a large population (Wettermark, 2013). In contrast, the etiologic approach examines the association between exposure to medicine and occurrences of a beneficial or adverse effect (Montastruc et al., 2019). The major problem with etiological studies involves the effect of modifiers or factors on the exposure or the outcome, in what is termed confounding. In clinical trials, confounding is avoided through randomisation. However, in observational etiological studies, pharmacoepidemiologists have proposed several methods to avoid confounding bias, including propensity score matching and adjustment in the statistical analysis (Suissa, 2009). Additionally, selection bias, which refers to the instances in which some eligible participants or outcome events are excluded, is one of the major flaws in real-world studies, which can also be adjusted statistically (Hammer et al., 2009).

To date, RWD has lower acceptability in regulatory decision-making, especially when the outcome of interest is treatment effectiveness (Skovlund et al., 2018). The European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) has identified four criteria that determine the acceptability of RWE in supporting regulatory decision-making: 1- RWE should be derived from a good quality data source, 2- RWE should have both internal and external validity, 3- RWE should be consistent (or heterogeneity should be explained), and 4- RWE should be adequate in terms of the amount of provided information (Cave et al., 2019). Furthermore, the study design from which the evidence is derived must use valid methods to minimise the bias, with the recommendation to use the target trial framework to design the RWE study (Groenwold, 2021). Emulating target trials has emerged with the target trial emulation known as the application design concepts from RCTs to the analysis of

the observational study, hence, linking the analysis to the RCT it is emulating (Labrecque and Swanson, 2017).

1.4 Thesis rationale

In the process of developing treatment decisions and clinical management guidelines, obtaining evidence from clinical trials is crucial, with RCTs considered the gold standard for evaluating therapeutic interventions (Frieden, 2017). However, with the increased cost of cancer medicines and the challenges with conducting RCTs, it is now increasingly recognised that RCTs do not fully reflect real-world settings due to the strict inclusion and exclusion criteria applied in RCTs and the short follow-up period (Kim et al., 2018). Moreover, research has demonstrated that cancer RCTs represent only 10% of cancer patients treated in routine clinical practice (Karim et al., 2019). Hence, it remains unclear whether the findings of these RCTs can be generalisable to the remaining 90% of the patients and whether patients in real-world settings respond to treatments in a similar manner as clinical trial participants (Karim et al., 2019). Usually, patients who are ineligible to be enrolled in cancer RCTs include patients who are older, frailer, or patients with comorbidities and organ dysfunction (Duma et al., 2019, Dunn et al., 2017). This, however, poses problems regarding the generalisability of the findings and evidence derived from the RCTs (Fortin et al., 2006).

A similar case holds true for RCTs in CRC. For example, in the X-ACT trial, in which the approval of capecitabine as adjuvant therapy for stage III CRC was granted, a total of 1987 patients were included, with only patients 18-75 years of age permitted to participate (Twelves et al., 2005). Although capecitabine is frequently used in older patients with CRC, imposing these age criteria has resulted in a lack of data regarding the effect of capecitabine in the advanced-age population. Moreover, the time to initiate treatment is also a concern that is often examined in real-world studies. In the X-ACT trial, the adjuvant therapy was mandated to be initiated within eight weeks of surgery (Twelves et al., 2005). However, whether this timeframe is consistently followed in practice is unclear. Multiple real-world studies have explored this issue and shown that the time to initiate adjuvant therapy after surgery is variable, with some patients waiting between 12 to 16 weeks after surgical resection of the primary tumour (Cheung et al., 2009, Gresham et al., 2015, Peixoto et al., 2015b).

Furthermore, the effect of delayed administration of adjuvant therapy for CRC patients has shown poor survival outcomes for delayed receipt (i.e., more than eight weeks) of adjuvant

therapy after surgical resection of the primary tumour (Peixoto et al., 2015b). Additionally, RWD has provided an effective tool in assisting health technology assessment and funding decisions. For example, Ho et al. indicated that treatment attrition among patients with mCRC is high and that only 42% of patients in the real world reached the third-line situation and were eligible for cetuximab or panitumumab monotherapy, thus considerably modifying the projected budget impact (Ho et al., 2016).

Despite the information produced by RWD in CRC and the underrepresentation of cancer patients in clinical trials, it is still recognised that cancer clinicians continue to place RCTs in high regard as a source of evidence (Saesen et al., 2022). Nevertheless, generating information and evidence about how patients may respond to treatments in routine clinical practice enables patients and clinicians to make better-informed treatment decisions. Moreover, given the vital role of systemic anti-cancer medicines in the management of mCRC in terms of prolonging overall survival, additional information is thereby needed to provide a sufficient evidence base to inform treatment decisions for mCRC patients initiating first-line treatment. This is important in determining the further course of the disease for several reasons:

- First, the characteristics of mCRC patients treated in clinical practice may differ from that of patients participating in clinical trials and understanding the variability in the characteristics is vital to allow for a better understanding of the treatment decisions and outcomes in real-world settings.
- Second, guideline recommendations for the choice of first-line mCRC medicine are not detailed despite the fact that not every mCRC medicine is appropriate for every patient. Therefore, identifying the factors that influence prescribing decisions is important to help to optimise individual patient care and achieve the best treatment outcomes.
- Third, no direct comparison between all first-line mCRC SACTs in real-world settings has been performed and understanding the comparative effectiveness and safety of first-line mCRC medicines is crucial for clinicians and patients in addition to decision-makers and payers.

For this thesis, it was hypothesised that differences exist between the use of first-line mCRC medicines in real-world practice and clinical trial settings. It was proposed that the effectiveness and safety of these medicines may vary when applied to a broader population of mCRC patients. Furthermore, it is assumed that patient characteristics, prescribing factors, and clinical outcomes associated with the use of first-line mCRC medicines will differ in real-world clinical practice compared to clinical trials.

This thesis aims to increase evidence generation from clinical practice regarding the use of first-line metastatic colorectal cancer medicines in real-world settings to better inform clinical decisions and optimise clinical outcomes among mCRC patients treated in a real-world setting. The objectives are to:

1- Conduct a systematic review and a meta-analysis to compare the effectiveness and safety of first-line mCRC medicines,
2- Understand the characteristics of mCRC patients initiating first-line mCRC SACT in NHS Greater Glasgow and Clyde health board (NHS GGC) in Scotland,
3- Examine the factors associated with the prescribing of first-line mCRC SACTs in patients treated in NHS GGC,
4- Determine the clinical outcomes and treatment pathways of first-line SACT regimens for mCRC patients in NHS GGC.

1.5 Thesis methodology overview

The first objective, covered in chapter 2, was met through performing 6 random effect meta-analyses of all observational studies exploring the comparative effectiveness and safety of first-line mCRC SACTs, including overall survival, progression-free survival, and objective response (which encompass both overall response rate and disease control rate), in addition to the comparative safety (including both haematological and non-haematological toxicities).

The second, third, and fourth objectives (chapter 4, 5, and 6) used routinely collected administrative health data from the largest health board in Scotland, NHS Greater Glasgow and Clyde (NHS GGC), with objective two utilising descriptive statistics to describe the sociodemographic, clinical, and disease characteristics of mCRC patients initiating SACT therapy in NHS GGC, the following objective was met through using multinomial logistic

regression to explore the factors that influence the clinician's selection of mCRC for the patients. For treatment outcomes, median overall survival was estimated using the Kaplan-Meier method, with Cox models used to assess the impact of mCRC SACT on the overall survival under the adjustment of different covariates. Finally, Patients' pathways across SACT lines until death, loss at follow-up, or end of the study were described and visualised using a Sankey diagram. The methodological details used for each objective will be provided in greater details in each respective chapter.

2 Chapter 2: Comparative effectiveness and safety of first-line metastatic colorectal cancer medicines: a systematic review and meta-analysis of real-world studies.

2.1 Introduction

Clinical outcomes of metastatic colorectal cancer (mCRC) patients have improved significantly over the last couple of decades, which can be attributed mainly to the increased efficacy of systemic anti-cancer treatments (SACTs) (Van Cutsem et al., 2014b, Arnold et al., 2017a). For unresectable, untreated mCRC, median overall survival of 6-9 months has been reported with a clear consensus that SACTs prolong median overall survival (OS) in patients with mCRC up to 30 months (Petrelli et al., 1989, Douillard et al., 2000, Giacchetti et al., 2000, de Gramont et al., 2000, Saltz et al., 2000, Cunningham et al., 2004, Tournigand et al., 2004a, Hurwitz et al., 2004, Kohne et al., 2005, Kabbinavar et al., 2005).

SACTs remain the mainstay of the management of mCRC treatment across all the treatment lines (Kopetz et al., 2009), with the therapeutic options for first-line treatment expanded, especially with the emergence of targeted treatments to include combinations of chemotherapeutic agents alone (5FU, oxaliplatin, irinotecan) or in combination with monoclonal antibodies (MoAbs) targeting epidermal growth factor receptor (EGFR; cetuximab and panitumumab) or vascular endothelial growth factor receptor (VEGFR; bevacizumab), thereby providing effective first-line therapeutic regimens for mCRC (Saltz et al., 2004). Nevertheless, the increased number of available treatments and combinations for first-line along with the high inter-patient variability of CRC has resulted in more challenges concerning the choices of treatment that should be used as the first line of treatment (Vera et al., 2015).

Many clinical trials were performed to compare the clinical outcomes following a first-line treatment in mCRC. Although clinical trials remain the current gold-standard primary study design for the determination of the efficacy and safety of medical interventions (Schulz et al., 2010), they cannot be used to assess all relevant combinations for treatment given the required time and cost and the rate at which new therapies and combinations are being made available; thus, evidence from RCTs might not fully inform treatment choices.

Observational studies based on RWD are often considered a substitute when RCTs are unavailable or not feasible. Data from real-world studies can provide a complement to clinical trials evidence on comparative effectiveness and safety research by providing results on how an intervention works outside the settings of research, which provide essential information on the long-term safety and effectiveness of a drug in large populations and patients who are frequently excluded from clinical trials (Blonde et al., 2018).

Several observational studies have been conducted to compare the clinical outcomes of various mCRC SACTs to address the need for comparative evidence. The results of these studies have been variable, which could be attributed to the heterogeneity in the study designs, applied analytical methods, different characteristics of the patients included in these studies, and the variable levels of confounding and selection bias introduced to observational studies as a result of lack of randomisation. However, a meta-analysis that quantifies and summarises the findings of these studies is lacking.

Aims and objectives.

This review aims to systematically synthesise and summarises the published real-world evidence comparing effectiveness measures, including overall survival (OS), progression-free survival (PFS), objective response, and safety measured by the occureness of severe toxicities for first-line mCRC SACTs. Furthermore, this review aims to determine whether the comparative effectiveness and safety estimates show significant heterogeneity across studies.

2.2 Methods.

This systematic review and meta-analysis (SR-MA) was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of studies evaluating healthcare intervention (Moher et al., 2009). The protocol for the current SR-MA was registered in the international prospective register of systematic reviews (PROSPERO) (Registration number: CRD42020164593). Due to the nature of the review (a meta-analysis), ethical approval was not necessary for the legislation (Wormald and Evans, 2018).

2.2.1 Inclusion and exclusion criteria

Only comparative, observational retrospective or prospective cohort studies published in English from inception until 31st July 2021 were included in this SR-MA. Studies with no comparison were not included in this review. Moreover, single case series, case studies, conference abstracts, and qualitative studies were excluded. Although no previous SRs have been conducted to compare the effectiveness and safety of all first-line mCRC SACTs, SRs, MAs, or studies reporting previously published data for first-line mCRC SACTs were similarly excluded to avoid duplicates in the data (Senn, 2009). Studies that did not provide relevant information to compute effect sizes (ESs) were also excluded unless data could be obtained from the authors.

Guided by the PICO framework (Participants, Intervention, comparison, and outcome), the following eligibility criteria were considered for the SR-MA (Richardson, 1995).

2.2.1.1 Participants

Studies were included if the participants were 18 years or over. Studies with participants younger than the age of 18 years were excluded. Included participants must have been diagnosed with unresectable mCRC. Studies that included patients who were diagnosed with stage I-III CRC were not included in this review. No gender or ethnicity restrictions were placed on the population of this review.

2.2.1.2 Intervention/ Comparator

Given the nature of this comparative effectiveness MA, different interventions were compared against each other. Hence, both the intervention and comparison elements of the PICO framework were combined into the same section.

Studies were included if they investigated the comparative effectiveness of first-line mCRC SACTs. Those SACTs included single agents (e.g., capecitabine) any combination of chemotherapeutic agents (e.g., FOLFOX) or a combination of chemotherapy with targeted therapy (e.g., bevacizumab+ FOLFIRI). Studies that investigated the effect of first-line mCRC SACTs in settings other than metastatic CRC (e.g., adjuvant therapy) were excluded from the review. Additionally, studies that compared treatment strategies (e.g., combination chemotherapy versus sequential chemotherapy), frequency of administration (e.g., once

weekly versus twice weekly), dose intensity (e.g., single dose versus double dose) were not included in the present review.

2.2.1.3 Outcomes

This MA measured the effectiveness and safety of first-line SACTs administered for unresectable mCRC. The effectiveness measures investigated included overall survival, progression-free survival, and objective response, while the safety measures included the occurrences of severe adverse events. The outcomes were divided into primary and secondary outcomes.

Primary outcome: overall survival

The primary outcome measure for the present MA was overall survival (OS), measured by the time interval between initiating treatment of interest and death from any cause (Fiteni et al., 2014). OS is the most widely acknowledged method used for evaluating the outcomes of cancer therapy (Driscoll and Rixe, 2009). It was also agreed by the American and European oncology groups that OS should be the primary outcome measure in clinical studies (Ellis et al., 2014, Wild et al., 2016). Studies in this MA were included if they reported OS as an outcome.

Secondary outcomes

In addition to the primary outcome of this MA, OS, two other effectiveness measures were included: progression-free survival (PFS) and objective response. The safety was also measured by the occurrences of severe toxicities. For the current review, studies that reported any of the secondary outcomes without reporting OS were excluded as OS is the primary outcome in which the quality of the studies was assessed based on.

Progression-free survival (PFS)

PFS is defined as the time from initiating treatment of interest to disease progression or death from any cause in the metastatic stage (Fiteni et al., 2014). PFS has been validated and accepted as a clinically meaningful endpoint, and it was shown to be superior to OS in instances where collecting data on OS may require a prolonged observation period to attain sufficient data to achieve a statistical power (Brody, 2012, Ellis et al., 2014). However, when used alone, PFS is not considered to provide sufficient evidence of benefit to patients (Ellis et al., 2014). Hence, OS is considered a measure of effectiveness in new cancer therapies,

with a significant effect on OS, implying a significant impact on PFS (Ferguson et al., 2000, Gyawali et al., 2018). As a result of that, PFS was considered a secondary outcome in this MA.

Objective response

The objective response is defined as the assessment of tumour burden (TB) after a specific treatment (Zubrod CG, 1960, Gehan and Schneiderman, 1990). One of the methods that have been widely embraced for evaluating the objective response of solid tumours to treatment is The Response Evaluation Criteria in Solid Tumours (RECIST). This method was developed and published by an international collaboration comprising the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Clinical Trials Group (NCIC CTG) to assess the objective response of solid tumours treated by cytotoxic chemotherapies according to anatomic imaging (e.g., Computed topography scans (CT scan), Magnetic resonance imaging (MRI)) (Miller et al., 1981, Therasse et al., 2000). Since the efficacy of a chemotherapy is typically associated with tumour shrinkage over time, RECIST has been utilised as a surrogate endpoint for OS in clinical trials (Burzykowski et al., 2008, Borcoman et al., 2018) and hence was explored as a secondary outcome in this review.

According to RECIST, objective status at the patient level is evaluated using unidimensional tumour measures of target lesions, nontarget lesions, and new lesions. RECIST rules were initially introduced in 2000 (RECIST V1.0) and revised in 2009 (RECIST V1.1). These rules classify the objective response of the tumour to treatment into four categories: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) (Therasse et al., 2000, Eisenhauer et al., 2009). Table 2.1 shows RECIST rules for both version 1.0 and 1.1. Alternative categorical endpoints were suggested and explored to report the results of the objective response within RECIST to facilitate clinical decision making in routine practice and to serve as a significant endpoint for reporting the results in clinical trials as follows: Overall response rate (ORR), which is defined as the percentage of patients with tumour who respond completely or partially to a specific treatment within a definite period of time and Disease Control Rate (DCR) which is a composite of ORR and stable disease (Aykan and Ozatli, 2020). ORR and DCR were used to assess the objective response in the current review.

Table 2.1: RECIST version 1.0 and RECIST version 1.1 criteria.

	RECIST guideline (Version 1.0) (Therasse et al., 2000)	**RECIST guideline (Version 1.1) (Eisenhauer et al., 2009)**
Method	Sum of longest diameters of target lesions (unidimensional)	Sum of longest diameters of non-nodal target lesions and short axis of nodal target lesions (unidimensional)
Number of measured lesions	Target lesions: maximum 5 per organ, 10 in total	Target lesions: Maximum 2 per organ, 5 in total
Response assessment		
Complete response (CR)	Disappearance of all target lesions at 4 weeks	Disappearance of all known disease, confirmed at 4 weeks, lymph nodes must be < 10 mm short axis
Partial response (PR)	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline
Progressive disease (PD)	≥20% increase in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded since treatment started. **OR** The appearance of 1 or more new lesions	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded. **OR** The appearance of new lesions, including those detected by FDG-PET
Stable disease (SD)	Neither PR nor PD	Neither PR nor PD

KEY: RECIST= Response Evaluation Criteria in Solid Tumours, CR: complete response; PR: partial response; PD: progressive disease; FDG-PET: fludeoxyglucose positron emission tomography; SD: stable disease.

Severe toxicities

In Phase IV trials, safety is evaluated through various methods, including adverse event reporting, where data on adverse events arising during the treatment course is documented. However, this approach encounters several limitations, such as underreporting of adverse events, reporting bias, incomplete data, and disparities in reporting quality. Moreover, the absence of a control group in Phase IV trials presents challenges in establishing causality between treatment and outcomes (Suvarna, 2010). Other safety assessment methods in Phase IV trials encompass post-marketing surveillance, entailing continuous monitoring of safety signals and reports from healthcare providers and patients once the treatment enters

the market post-clinical trials (Vlahovic-Palcevski and Mentzer, 2011). Post-marketing surveillance methods encompass diverse strategies, including spontaneous reporting systems, pharmacovigilance databases, signal detection, electronic health records integration, patient registries, comparative effectiveness research, and collaborative efforts with healthcare professionals, all aimed at continuously monitoring the safety and effectiveness of medical treatments in real-world settings (Vlahovic-Palcevski and Mentzer, 2011).

Post-marketing surveillance methods facilitate the identification and evaluation of potential safety issues, offer insights into real-world treatment effects, and guide regulatory decisions. For example, spontaneous reporting systems, a component of post-marketing surveillance, involve soliciting voluntary reports from healthcare professionals, patients, and consumers regarding adverse events encountered during treatment. These reports are directed to regulatory agencies or manufacturers, and the ensuing data is subject to analysis for potential safety indicators (Edwards, 1999). Additional techniques within post-marketing surveillance encompass signal detection, which employs advanced statistical and data mining methodologies to identify potential safety signals from significant volumes of adverse event reports (Meyboom et al., 1997). These methodologies aid in prioritising events warranting further scrutiny. Despite their great benefits, these methods are limited by underreporting and reporting bias of adverse events, challenges in confirming causality, incomplete or variable data quality, and difficulties in comparing data due to variability in reporting standards and sampling biases (McNeil et al., 1999).

The occurrence of severe adverse events (AE) was measured based on the Common Terminology Criteria for Adverse Events (CTCAE) grading system which was developed by the NCI to describe the severity of organ toxicity for patients receiving SACT. This scaling system uses a range of grades from 1 to 5 to denote the severity of each AE in an ascending order with 1 standing for mild toxicity, 2 for moderate toxicity, 3 for severe toxicity, 4 for life threatening toxicity, and 5 indicating death (National Cancer Insitute, 2017). Studies that reported adverse events using methods other than the NCI-CTCAE were not included for the safety outcome due to the variability in reporting.

The CTCAE grading system is widely utilised in safety assessment in regulatory pharmacovigilance studies in the field of cancer to systematically assess and grade adverse events. Data collection is conducted prospectively from various sources, and the severity of AEs is categorized according to CTCAE criteria. The collected safety data, including CTCAE-

based AE information, is submitted to regulatory authorities to inform decision-making and regulatory actions (Crestan et al., 2020). The US National Cancer Institute has recently introduced a new tool called PRO-CTCAE (Patient-reported outcomes CTCAE) to aid patients in reporting symptomatic toxicity during cancer clinical trials. PRO-CTCAE serves as a companion to the CTCAE and is designed to enhance patient involvement in reporting their own experiences of treatment-related symptoms (Kluetz et al., 2016).

For the current review, severe toxicities with grade ≥ 3 were investigated and categorised into haematological and non-haematological toxicities. Severe toxicities were specifically chosen because reporting of toxicities in RCT and observational publications is often restricted to severe toxicities (Zhang et al., 2016, Phillips et al., 2019). Haematological toxicities included hypertension, anaemia, bleeding, neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, venous and arterial thromboembolic events, whereas non-haematological toxicities included acne, allergic reactions, anorexia, asthenia, diarrhoea, gastrointestinal (GI) perforation, hand-foot skin reaction (HFSR), liver dysfunction, mucositis, nausea, neuropathy, proteinuria, and stomatitis.

2.2.2 Systematic search strategy

2.2.2.1 Databases searched.

The following medical and allied health professionals' electronic databases were searched from their respective inception dates until the 31st of Dec 2019 and was later supplemented until the 31st of July 2021 (the date of starting data analysis): MEDLINE (OVID), EMBASE (OVID), and CINAHL. The citation databases Scopus and Web of Science were also searched. A number of additional search strategies were also applied to ensure that the literature search was as comprehensive as possible. The ancestry approach to find relevant papers from the reference lists of included studies was utilised. additionally, the following clinical trial registers were searched for unpublished prospective comparative cohort studies: 1- EU clinical trials register (https://www.clinicaltrialsregister.eu/), and 2- the US national library of medicine registry of clinical trials (https://clinicaltrials.gov/). Moreover, ProQuest and Ethos dissertation databases were searched for additional unpublished work. Finally, key journals such as Annals of Oncology, BMC cancer, and Clinical Colorectal Cancer were hand-searched as they were likely to contain information relevant to the population, the interventions, or the outcomes of interest.

2.2.2.2 Search terms.

Articles were identified by the use of key terms guided by the PICO framework. The search keywords contained terminology from the United Kingdom and the United States of America, as well as truncation. Additionally, synonyms of each search domain containing both free text and Medical Subject Headings (MeSH) were utilised. Finally, an age filter was used to guarantee that research with people aged 18 years and over was included.

The search strategy was independently assessed by an academic librarian at the University of Strathclyde as well as a postdoctoral researcher with expertise in conducting systematic reviews. For the full Medline search strategy see appendix I.

2.2.2.3 Study selection

Following a search in each of the aforementioned resources, sourced studies were imported into the Endnote software, where an initial removal of duplicated articles was performed. Sourced studies were then imported into Covidence online software, a software program specifically developed to facilitate the production of systematic reviews (https://www.covidence.org/), where the remaining duplicates were removed, and a two-stage screening was performed: first, an initial study screening was executed in which the titles and abstracts of the studies were evaluated to determine whether they matched the study inclusion criteria. This was followed by full text screening where the full text was read and assessed for inclusion in the review. PRISMA flow diagram which illustrate the process of identifying, screening, including, and excluding all items with explicit justification was generated (Moher et al., 2009) (See section 2.3.1 - results).

The study selection process was entirely performed by the principal reviewer (HY). In addition to that, each of the screening steps was independently and separately reviewed by two independent researchers in which a 10% random subset was generated for each researcher at each screening step. The level of agreement between the reviewers for each step was calculated as a percentage and was classified as poor (less than 70%), fair (70-79%), good (80-89%) and excellent (>90%) (Watkins and Pacheco, 2000). Disagreements between the reviewers where they occurred were resolved following discussions.

2.2.3 Data extraction

A data extraction form was piloted based on the PICO framework in Microsoft® Excel using a 10% random subset of the included articles. This step was performed to ensure that the information to be extracted was both standardised and relevant. The primary reviewer (HY) extracted pertinent data from each included publication, and it was then independently reviewed by two independent researchers using a 10% random subset selected for each researcher. The extraction items are listed in Table 2.2.

Table 2.2: Extraction form items.

Domain	Extracted data
Identifications	Study number, lead author, publication year, country, funding source.
Methods	Design, study duration, setting, data source, duration of follow-up, RECIST version, survival method measurement.
Population	Age, gender, performance status (ECOG), comorbidities, RAS/BRAF mutation, mucinous histology, primary tumour location, number of organs involved, localisation of metastasis, disease stage at diagnosis, tumour sidedness, primary tumour resection.
Intervention	SACT name, SACT dose, number of cycles, duration of treatment, frequency of administration, previous neo/adjuvant therapy.
Outcome	Outcome definition, sample size. For each outcome: OS: survival probability, median OS, HR (95% CI) PFS: survival probability, median PFS, HR (95% CI) RECIST: number of evaluable patients, CR, PR, SD, PD Grade ≥ 3 toxicities: haematological and non-haematological toxicities.

KEY: RECIST=Response evaluation criteria in solid tumour, ECOG=Eastern cooperative oncology group, SACT=Systemic anti-cancer treatment, OS=Overall survival, PFS= progression-free survival, HR= Hazard ratio, CI= confidence interval, CR= complete response, PR= partial response, SD= stable disease, PD = progressive disease

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2.2.4 Assessment of risk of bias

To conduct a SR-MA, it is critical to assess the methodological quality of the primary included studies; this assessment would be necessary before including the primary studies in the SR-MA. While quality encompasses internal and external validity (Campbell, 1957, Higgins and Green, 2011), methodological quality is frequently used to refer to internal validity. Internal validity is also recommended by the Cochrane Collaboration as a measure of "risk of bias (RoB)" (Higgins and Green, 2011).

The internal validity and methodological rigour of each study within this review was assessed using the “Risk of Bias in Non-randomised studies-of Interventions” (ROBINS-I) (Sterne et al., 2016b). This tool was developed by the Cochrane Bias Methods Group, with input from a wide international group of leading epidemiologists and methodologists. ROBINS-I focuses on internal validity by evaluating seven distinct bias domains; the first three domains of bias feature the pre or at-intervention bias arising in non-randomised studies (NRS), which are distinct from the biases that arise in RCTs, whereas the four remaining domains represent the bias arising post intervention in both observational studies and RCTs (Sterne et al., 2016b).

After determining the outcome in which the risk of bias will be assessed, it is essential to consider any confounder or cointerventions deemed to have the potential to lead to biased outcomes. These confounders/cointerventions were identified from the literature and clinical management guidelines to be the factors that moderate survival for patients with mCRC. For this review, the main outcome, which is overall survival, was assessed for the risk of bias with the most significant prognostic factors including the performance status (Sargent et al., 2009) and SACT (Aparicio et al., 2003, Stillwell et al., 2011, Eker et al., 2015).

Table 2.3: Types of domains and biases within ROBINS-I.

Domain stages	Type of bias
Pre-intervention domain	1- Confounding bias 2- Selection of participants at study
At- intervention domain	3- Classification of interventions
Post intervention domain	4- Deviation from intended intervention. 5- Missing data 6- Measurement of outcomes 7- Selection of reported results

In addition, signalling questions (SQs) are provided by the tool developers to help the review assessor determine the appropriate assessment for each domain. ROBINS-I defines bias as a systematic difference between the outcomes of the NRS and the outcomes anticipated from an unrestricted hypothetical target trial. This is because the NRS is intended to replicate an RCT and comparing it to a hypothetical target trial enables assessment of the bias in the NRS data in comparison to a hypothetical RCT addressing the same question (Sterne et al., 2016b). Table 2.3 provides more information on the bias domains within ROBINS-I, and Figure 2.1 depicts the assessment process of using ROBINS-I.

The principal reviewer (HY) assessed the quality of included studies, and two independent reviewers validated a random 10% of included studies. Any disagreements were settled through conversation and resolved through consensus.

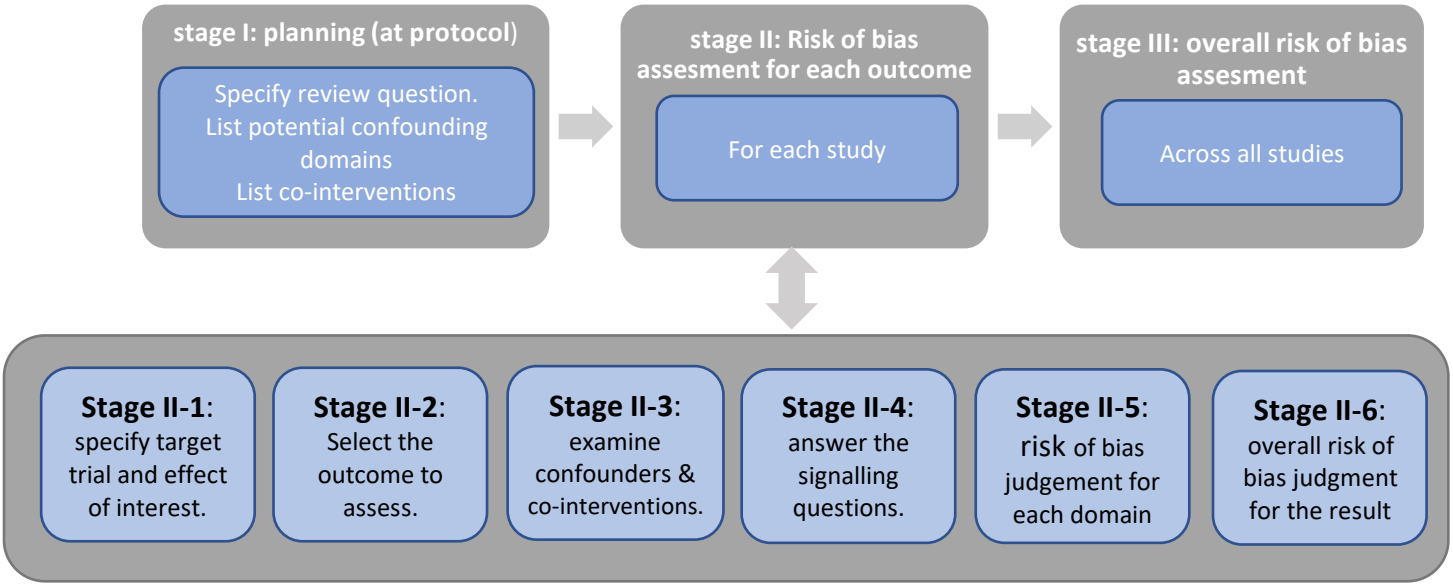


Figure 2.1 The process of using ROBINS-I tool (adopted from (Schunemann et al., 2019).

Risk of bias was classified as low, moderate, serious, critical, or no information. Studies with no flaw in any of the 7 categories were deemed to have low risk of bias. Studies with one or more flaws received a rating equivalent to the highest risk of bias in any one category. For example, if a study scored low risk of bias in 6 domains but serious risk of bias in one domain, the overall risk of bias for this study would be serious risk of bias. Robvis visualising tool, a web app designed to visualise the assessment of risk of bias was used to tabulate and visualised risk of bias for all studies (https://www.riskofbias.info/welcome/robvis-visualization-tool) (McGuinness and Higgins, 2021).

Throughout the assessment of risk of bias process, the ROBINS-I guidance published by Cochrane methods bias group was followed to ensure an accurate assessment for each of the seven domains in each study (Sterne et al., 2016b). Furthermore, a random 10% of the included studies were validated for the risk of bias by one independent researcher. An agreement for each domain accounted for one point. At the end of the validation process, the points were summed and divided by the total number of assessed domains to calculate the percentage of agreement.

2.2.5 Data synthesis

Traditional, pairwise MA is a statistical tool for pooling the results of several comparable studies that perform a direct comparison of the same two interventions (Borenstein et al., 2009). A MA provides a more precise estimate of a treatment effect by increasing the overall

sample size of the study, which is critical to make inferences from a large body of evidence (Sutton et al., 2000, Nordmann et al., 2012). In general, a MA is a two-stage process: the first stage involves calculating the appropriate summary statistics of effect measure for each of the outcomes of the included studies, while the second stage involves combining these statistics into a weighted average of effects for each of the outcome of the included studies (Cooper and Hedges, 1994, Normand, 1999, Deeks and Higgins, 2010).

2.2.6 Meta-analysis method

The most common approach for implementing a MA is the inverse-variance method. This method assigns weights for each effect size based on the inverse of the effect size variance, given that the variance is calculated as the square of the effect size' standard error (SE). This means that a study's effect size with small SE (hence, variance) is given a larger weight in a MA than a study with higher SE for the effect size (Hedges, 1983). This can be illustrated in formula 1.

$$w = \frac{1}{\mathrm{SE}^2} \quad \textbf{...Formula 1}$$

Where w is the weight calculated and given to each study, SE is the standard error of the effect size, and SE^2 is the variance.

Although rigorously conducted MAs can be useful tools in evidence-based medicine, MAs can produce misleading effect sizes if critical issues are not handled appropriately; this can include the choice of the proper model (random effect model or fixed effect model), selecting the correct type of ES, investigating heterogeneity, and assessing publication bias (Egger et al., 2001, Haidich, 2010).

2.2.6.1 Meta-analysis models

When pooling data from multiple comparable studies in an MA, it is important to make a reasonable assumption about the distribution of effect sizes (ESs) among the included studies and how to model them. An MA can be modelled in two ways: the fixed effect or random effect models (Borenstein et al., 2009). The fixed effect model assumes that all studies included in the MA have been sampled from the same population (i.e., homogenous population), resulting in one common (true) effect size. As a result, sample ESs are assumed

to be derived from a homogenous population and that any differences in the distribution of ESs are attributed only to sampling error (i.e., within-study variance) (Cohn and Becker, 2003, Borenstein et al., 2009). However, in practice, the assumption of homogeneity required for a fixed-effect model is frequently implausible (Field, 2003). In contrast, the random effect model allows for heterogeneity between studies by assuming that the population ESs could vary randomly between studies due to factors such as the methods utilised and the research context (Cohn and Becker, 2003, Field, 2003, Hunter and Schmidt, 2008). The random effect model estimates the average effect size across a range of similar populations; hence results can be generalised to other populations (Borenstein et al., 2009). The main difference between the two models is regarding the source of error that is accounted for. For both models, there is a within-study error that arises from the sampling error. However, the random effect model assumes an additional source of error, which is the between-study error as a result of sampling populations from individual super-population (Michael Borenstein, 2009, Mikolajewicz and Komarova, 2019).

Rational for the use of the random effect model

The choice of using a fixed or random effect methods depends on two factors: 1- the assumptions that can be made regarding the population from which studies are sampled, and 2- the types of inferences to be made from the MA (Field, 2003).

Firstly, Real-world data have wide variable population parameters. It has been observed that substantive moderator variables exist in all study domains resulting in variability in population parameters such as the methodological approaches implemented in each study (Hunter and Schmidt, 1990, Osburn, 1992, National research council, 1992). Besides, real-world data tends to have heterogenous population effect sizes even in the absence of known moderator variables, and as a result of that, it was suggested that real-world data does not fit the assumptions of fixed population parameters. (Schmidt and Hunter, 1998). Secondly, while the fixed effect model can be used to make inferences applied only to the studies included in the MA, the inferences drawn from a random effect model can be extended to a population of studies larger than the sample (i.e., use MA to make generalisations beyond the studies included in the MA. (Hedges and Vevea, 1998, Cohn and Becker, 2003). For these two reasons, this MA was modelled using the random effect model.

Although the random effect model accounts for heterogeneity by assuming that a range of effect sizes in individual studies is around the average effect size to estimate, the model itself does not explain the heterogeneity. Traditionally, the between-study variance is denoted as τ^2 in the meta-analytic literature.

2.2.6.2 Heterogeneity assessment

Heterogeneity is an important element that should be considered when conducting an MA. it arises from the variability among the included studies. As stated in section 2.2.6.1, there are mainly two sources of variability: the within-study variability due to sampling error and the between-study variability (Huedo-Medina et al., 2006). Within-study variability is inevitable in any MA because every study uses a different sample. Nevertheless, between-study variability is attributed to the effect of many characteristics that vary across studies, such as the variation in participants, interventions, study design, risk of bias... etc (Brockwell and Gordon, 2001, Field, 2003, Hunter and Schmidt, 2008). Hence, assessing the heterogeneity in an MA is a key issue since the presence or absence of between-study variability can influence the model of the MA.

The conventional method used to assess the presence of true heterogeneity (between-study variability) in a MA has been to utilise the Q test (Cochran's Q). This statistical test examines the null hypothesis that all studies included in an MA evaluate the same effect. Failing to reject the homogeneity hypothesis leads the MA to adopt the fixed-effect model because it assumes that the ESs differ only due to sampling error. By contrast, rejecting the homogeneity hypothesis can result in implementing the random effect model that includes both within-study variability and between-study variability (Cochran, 1954). However, the Q test has poor power to detect the true heterogeneity among studies when an MA includes a small number of studies. It has an excessive power to detect negligible heterogeneity with a high number of studies included in an MA, especially when these studies are large (Osburn et al., 1983, Sackett et al., 1986, Paul and Donner, 1992, Hardy and Thompson, 1998, Sterne and Egger, 2001, Higgins et al., 2002). As a result, the Q test has been used only to inform about the presence or absence of heterogeneity in an MA but not the extent of the heterogeneity.

An alternative method that has been suggested to assess the extent of heterogeneity is the I^2 test statistic. The I^2 was proposed by Higgins and Thomson (Higgins et al., 2003) to quantify the degree of heterogeneity between the studies of the MA. It can be interpreted as the

percentage of the overall variability in a group of ESs due to true heterogeneity (between-study variability) (Higgins et al., 2003). For instance, I^2 value of zero percent would be interpreted that all variability in ESs is due to sampling error. In contrast, an I^2 value of 50% indicates that half of the total variability across ESs is due to true heterogeneity and not only due to sampling error. A value of 100% means that all the variation in the meta-analysis is attributed to true heterogeneity rather than to sampling error. Higgins et al. suggested the following classification to help interpret the magnitude of heterogeneity where I^2=25, I^2=50, and I^2=75, indicates low, medium, and high heterogeneity, respectively.

Nevertheless, despite its widespread use in the literature, I^2 is not an absolute indicator of heterogeneity, and its significance remains highly dependent on the precision of the research included (Borenstein et al., 2009). I^2 is simply the percentage of the overall variability that is not attributed to sampling error. Hence, when the sample size of the included studies increases, the sampling error decreases, while I^2 might approach 100% merely because the included studies have a larger sample size. Although the use of the variance (τ^2) confers a solution for this problem since τ^2 is insensitive to the number of studies, it is difficult to draw conclusions about the clinical implications of the observed heterogeneity (Borenstein et al., 2009).

Another estimator was proposed to circumvent this limitation which is the prediction interval (PI). This approach predicts where the true effects are to be expected for similar studies that might be conducted in future based on current evidence (IntHout et al., 2016).

2.2.6.3 Effect size calculation and estimation

An effect size (ES) is a numerical value that indicates the magnitude of a treatment effect (Borenstein et al., 2009). For the current MA, four distinctive outcomes were measured. Selection of the appropriate ES is dictated by several considerations, including 1- the comparability of ESs across the included studies and the independency of the ES from study design aspects (e.g., sample size, covariates), 2- the ability to calculate the ES from the information provided by the primary studies, 3- the availability of other details that describe the ES such as the sampling distribution which allows for calculating the variance and confidence interval of the ES. In addition to that, the type of data is an important determinant for the type of ES used. (Borenstein et al., 2009). For the current MA, 2 types of ESs were used based on the type of outcome data.

OS and PFS - Hazard ratio (HR) was used to summarise time-to-event (TTE) data which are OS and PFS. Since both outcomes measure survival, time to death is the outcome of interest, and the term event within time to event will be substituted by death over the rest of the chapter when a reference is made for survival outcomes. Within the same context, TTE analysis is also known as survival analysis.

HR is known to be the most appropriate and acceptable method to express the intervention effect of TTE data as it measures the instantaneous risk of developing death, taking into consideration the concept of censoring, which arises from the unavailability of information pertaining to death due to loss at follow up or non-occurrence of death before the end of the study (Parmar et al., 1998, Higgins and Green, 2011).

An MA of HRs involves obtaining the HR for each single study (or treatment comparison where a study contains multiple independent treatment comparisons), performing a natural logarithmic transformation of the HR ((log)HR) then pooling the log HRs into an inverse variance weighted MA. Two methods were used to extract the log (HR) and its variance for each comparison:

- **Direct method**: this method involves extracting HR and 95% CI from a Cox proportional hazard model whenever reported in the primary study and incorporating mCRC SACT. Cox models produce direct estimates of the HR and its corresponding 95% CI. A logarithmic transformation of HR is done through simple calculation, whereas the variance is calculated from the CI via the following equation.

$$\text{var}(\ln(\text{HR}_i)) = \left[\frac{\text{UPPCI}_i - \text{LOWCI}_i}{2\Phi^{-1}(1-\alpha_i/2)}\right]^2 \text{... formula 2}$$

Where UPPCIi and LOWCIi are the upper and lower confidence limits for $\boldsymbol{l}\text{og}(\boldsymbol{HRi})$ respectively.

Φ is the cumulative distribution function of the normal distribution and $\Phi^{-1}\left(1-\frac{\boldsymbol{\alpha i}}{2}\right)$ = 1.96 for 95% CI.

- **Indirect method (curve approach):** previous work in oncology has shown that TTE statistics are poorly and inconsistently reported in published literature (Altman et al., 1995). The curve approach method was used where survival estimates were presented only graphically without reporting the Cox proportional hazard model. This method was first described by Parmar et al., and it relies on the concept that the HR is a summary of the difference between two Kaplan-Meier (KM) curves. It estimates the total reduction in the risk of death during treatment compared to control over the course of the patient's follow-up (Parmar et al., 1998). The curve approach method was further extended beyond the estimation of HR to the reconstruction of TTE data on the individual level (Guyot et al., 2012). Furthermore, Guyot et al. proposed an R-code for an algorithm to produce the statistics details required to estimate HR from the reconstructed KM curves (Guyot et al., 2012). The following steps were performed to obtain the log (HR) and its variance from graphical KM curves.

  First, a KM graph was imported into WebPlotDigitizer, A web-based tool used to extract data from graphical KM curves (https://automeris.io/WebPlotDigitizer/). Both the X and Y axis of the KM curve, representing time from treatment initiation and probability of survival, respectively, were defined by the input of the minimum and maximum values for each axis. Afterwards, manual mouse clicks were applied to select points to read off from the KM curve. The resulting data pair was then exported into an excel sheet. Table 2.4 represents an illustrative example of the outcome data pairs generated following the data extraction from a KM curve. Following that, the data pair sheet was exported to R, where each KM curve data points were processed along with the data pertaining to the total number of enrolled patients and the total number of deaths to generate pooled survival curves using IPDfromKM R package (Liu et al., 2021). Finally, the estimates for the two compared curves were processed to generate the required Cox statistics, including the log (HR) and SE. SE was squared to obtain the variance of the log (HR). This method requires a sufficiently clear copy of the KM curve to be extracted and segmented into a number of time intervals showing the death rate over time. For studies where the two KM curves were tangled, adobe illustrator was used to separate the curves. In instances where the curves were overlapping and very tangled where it was rendered impossible to separate them, studies were excluded from further analysis. The data extraction step

from graphical KM curves was validated by an independent researcher, in which 20% of the graphs were validated.

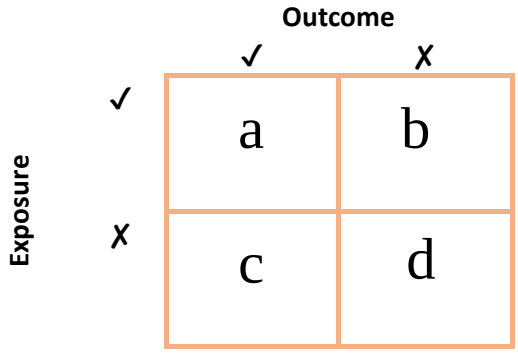
Table 2.4: Example of the outcome data pairs generated from WebPlotDigitizer.

Time in months	Survival probability
0	100
1.904762	89.0411
2.02381	87.21461
3.690476	79.45205
4.404762	79.45205
5.714286	63.92694
6.190476	63.92694
7.738095	54.3379
8.928571	51.14155
11.78571	40.18265
12.61905	34.24658
16.66667	34.24658
18.45238	24.20091
20.59524	12.32877
24.88095	5.936073
25	0.456621

Objective response and severe toxicities - Both odds ratio (OR) and risk ratio (RR) are used to determine the association between an exposure (intervention) and an outcome in binary data. RR represents the probability of the occurrence of an outcome in the presence of certain exposure compared to the probability of the occurrence of an outcome in the absence of exposure (Szumilas, 2010). In contrast OR measures the odds of the occurrence of an outcome in the exposed group over the odds of the outcome in the comparison group (Borenstein et al., 2009). A RR (or OR) of 1 indicates no difference in risk (or odds) exists between the groups being compared. A RR (or OR) greater than 1 implies an increase in risk (or odds) for the exposed group when compared to a comparison (or non-exposed) group, whereas a RR (or OR) less than 1.0 suggests a decrease in risk (or odds) for the exposed group.

It has been suggested that the OR is almost identical to RR and can be interpreted as RR when the outcome is rare (less than 10%) (Zhang and Yu, 1998). However, when the incidence of the outcome is relatively high (more than 10%) OR might overestimate the effect of the treatment on the outcome. The OR will be greater than the RR if the RR is greater than one and less than the RR otherwise (Zhang and Yu, 1998). In addition to that, ORs are less intuitive

than RR and hence more subjected to misinterpretation. As a result of that, for this MA, the outcome data on the effect of treatment on the objective response (both ORR and DCR) and severe toxicities (both haematological and non-haematological) were presented in the form of RRs and their corresponding variance. Crude data from 2x2 table were used to compute unadjusted RR and their corresponding variance, as illustrated in Figure 2.2. Where no event was contained in one of the cells of the 2x2 table (i.e., the value of the cell = zero), Haldane-Anscombe correction (zero-cell correction) was applied in which all cells in that table were inflated by adding 0.5 (Haldane, 1956, Weber et al., 2020). All effect size computations were carried out manually and verified using Practical Meta-Analysis Effect Size Calculator which was developed by Campbell collaboration (Wilson, 2017).



$$RR = \frac{a/(a+b}{c/(c+d)} \quad \text{.... formula 3}$$

$$V_{\ln(RR)} = \frac{b/a}{a+b} + \frac{d/c}{c+d} \quad \text{... formula 4}$$

Figure 2.2 Computation of relative risk and the natural logarithm of Variance
KEY: RR= relative risk, $V_{\ln(RR)}$= Variance of ln Risk ratio

2.2.6.4 Publication bias

The term publication bias, or the "file drawer problem" as described by (Rosenthal, 1979), refers to the tendency for a publication to be disseminated based on its findings (Vevea and Woods, 2005). It has been suggested that approximately 50% of completed studies remain unpublished (Dwan et al., 2010, Song et al., 2010). Thereby, bias can be manifested if only publications with statistically significant findings are published, leaving all other studies unpublished. This condition emerges either because the researchers are less likely to submit these studies or as a result of journal reviewers or editors rejecting the studies (Vevea and Woods, 2005, Song et al., 2010). This will result in an MA overestimating the population effect size, which could lead to incorrect inferences from the MA (van Assen et al., 2015).

Methods used to explore publication bias can be classified into two groups: 1- methods that examine the presence of publication bias, and 2- methods that estimate ESs corrected for

publication bias which usually provides a confidence interval and test the null hypothesis that there is no effect corrected for publication bias.

One of the most common methods used to examine publication bias is by using funnel plots. The funnel plot is a simple scatter plot of the individual studies in an MA, with the treatment effect on the horizontal axis and a measure of study size (such as the inverse variance or SE) on the vertical axis (Light and Pillemer, 1986). A funnel plot shows whether small-study effects are present. The name funnel plot is derived from the notion that as individual study sample size increases, the precision in the estimation of the underlying treatment effect will also increase. Thus, when a measure of study size is plotted on the vertical axis, results from small studies will be widely scattering at the bottom of the graph, whereas the spread between larger studies will be narrower (Egger et al., 1997). In the absence of publication bias (and when all studies estimate the same underlying effect), the plot will resemble an inverted symmetrical funnel (Light and Pillemer, 1986). Publication bias is frequently taken as a reason for the small-study effect and is thus interpreted as evidence for publication bias (Lin et al., 2020). Generally, the presence of symmetry or asymmetry has been determined informally, via visual assessment. As a result of that, the evaluation of funnel plots is rather subjective (Terrin et al., 2005). Hence, Egger's regression test was developed to examine the presence of a small-study effect in an MA (Egger et al., 1997). It utilises linear regression with observed ESs as the dependent variable and a measure of the precision of primary studies as the predictor variable. Evidence of small-study effects is assumed if the slope of this regression line is significantly different from zero. The limitation of this test is that its statistical power for detecting publication bias is poor, especially when a meta-analysis has a small number of ESs (Begg and Mazumdar, 1994, Sterne et al., 2000). Therefore, this method should be reserved for MA with ten or more effect sizes (Sterne et al., 2011).

Several statistical methods were proposed to correct publication bias or small study effect. One of the most common methods is called trim and-fill (Duval and Tweedie, 2000). This method was derived from the funnel plot. The basis of this method is that it removes (trims) the small effect sizes that caused funnel asymmetry and uses the trimmed plot to estimate an adjusted pooled estimate. This is followed by imputing (filling) the excluded studies with their missing counterparts around the adjusted pooled estimate. However, since it assumes that funnel asymmetry arises seldomly from publication bias, it was criticised despite its wide use in literature. In addition to that, it was demonstrated by simulation studies that this

method performs poorly with increasing between-study heterogeneity. When the between-study heterogeneity increases, there is a possibility that even large effect sizes diverge from the average overall effect, which might allow these studies to be trimmed and filled, resulting in misleading results (Terrin et al., 2003, Peters et al., 2007). However, this method is still argued to be useful as a sensitivity analysis, which was used in this MA.

2.2.6.5 Moderator analysis

An MA aims to assess the effect of a given treatment on a certain sample from a certain population (Borenstein et al., 2009). Synthesising findings entails analysing studies that use a wide range of different characteristics (Ost, 2014). Thereby, this introduces many variables into the MA that may impact the ESs. These variables are referred to as moderator variables since they can influence the strength and direction of the overall pooled ESs. The selection of various moderators was made based on several approaches. Most of the variables were selected based on a comprehensive literature review conducted to assess the association between different variables on treatment outcomes of mCRC. For instance, Numerous factors have been identified in the literature as impacting survival outcomes for metastatic colorectal cancer (mCRC) patients. Key factors consistently reported include performance status and type of systemic anticancer therapy (Stillwell et al., 2011). Additionally, various other factors have been found to influence mCRC prognosis, such as age, gender, primary tumour characteristics, number and location of metastatic sites, tumour molecular profile, and several clinical and inflammatory biomarkers (Aparicio et al., 2003; Eker et al., 2015; Arnold et al., 2017b; Garcia Alfonso et al., 2018; Loupakis et al., 2014; Stintzing et al., 2016; Zacharakis et al., 2010). These biomarkers include C-reactive protein, carcinoembryonic antigen, albumin, haemoglobin, neutrophil-to-lymphocyte ratio, and alkaline phosphatase (Garcia Alfonso et al., 2018; Zacharakis et al., 2010; Eker et al., 2015; Stillwell et al., 2011). The availability of these variables was determined their inclusion in the moderator analysis. For example, very few studies reported the influence of clinical inflammatory biomarkers on treatment outcomes. Hence, they were not included in the moderator analysis. Additionally, a number of characteristics of the primary studies were deemed in the literature to potentially bias the findings. For instance, pharmaceutical funding in meta-analysis studies has been identified as a potential source of bias. When pharmaceutical companies fund or sponsor research studies, there is a concern that their financial interests may influence the design, conduct, analysis, and reporting of the research, leading to biased results (Fabbri et

al., 2018). In this study, the effect of different first-line mCRC SACTs within a sample of mCRC patients was explored. Moderator variables included two domains: (1) study characteristics such as study design, study settings, and the items included to assess the risk of bias, and (2) the clinical characteristics of the patients, such as the age group (elderly versus non-elderly), gender, performance status, RAS status, primary tumour location, primary tumour resection, number of metastatic sites, and localisation of metastasis. The moderator analysis was performed for the survival outcomes of this review (OS and PFS). However, for the objective response and the toxicities, the small number of studies did not allow for a proper moderator analysis to be carried out.

2.2.6.6 Sensitivity analysis

Undertaking an MA dictates making several decisions regarding the selection of studies under review and the methods of analysis. Thereby, it is essential to make sure that the inferences made from the MA are robust and have not resulted from decisions made when they were obtained (Deeks et al., 2021). Thus, the MA should be repeated under several assumptions and after many decisions to determine the degree to which the obtained findings are consistent. Where outliers were identified, the MA was repeated to verify the effect of trimming the outliers on the overall pooled estimate.

2.2.6.7 Statistical software

All of the analysis tests were carried out using the R 3.0.1. software. Packages used included dplyr, ggplot2, gridExtra, readbitmap, IPDfromKM, metafor, forestplot, and dmetar. Appendix VI contains information on the R syntax used for all of the tests that were performed.

2.3 Results

2.3.1 Literature search outcome

The systematic literature search yielded a database of 8598 articles from electronic databases outlined in section 2.2.1. The initial pool of studies underwent titles and abstracts screening to determine their eligibility. A total of 2551 studies were eliminated, leaving 611 studies subjected for full text examination. Five hundred and seventy-nine studies were excluded for various reasons as depicted in Figure 2.3. A total of 32 studies proceeded to extraction, and three further studies were excluded due to the unavailability of data needed to calculate or estimate the effect size (see section 2.7.3). The authors of these studies were contacted, but no extra data were provided by them. A total of 29 studies met the inclusion and exclusion criteria and were used to synthesise the data of the four outcomes: the overall survival, progression-free survival, objective response, and severe toxicities. one main meta-analysis was generated for both OS and PFS outcomes, while two MAs were generated for the objective response (including the ORR and DCR MAs), and the severe toxicities (including haematological and non-haematological toxicities). As a result, a total six MAs were generated in this review. Additionally, further analysis for SACT groups was carried out and resulted in one additional MA for each the OS and PFS outcomes.

The percentage of agreement between reviewers at the stages of abstract screening and full text screening were 957% and 93.1%, respectively, while for the risk of bias, the percentage of agreement was 85.7%. Figure 2.3 shows the PRISMA flowchart for the screening process of the identified and included studies.

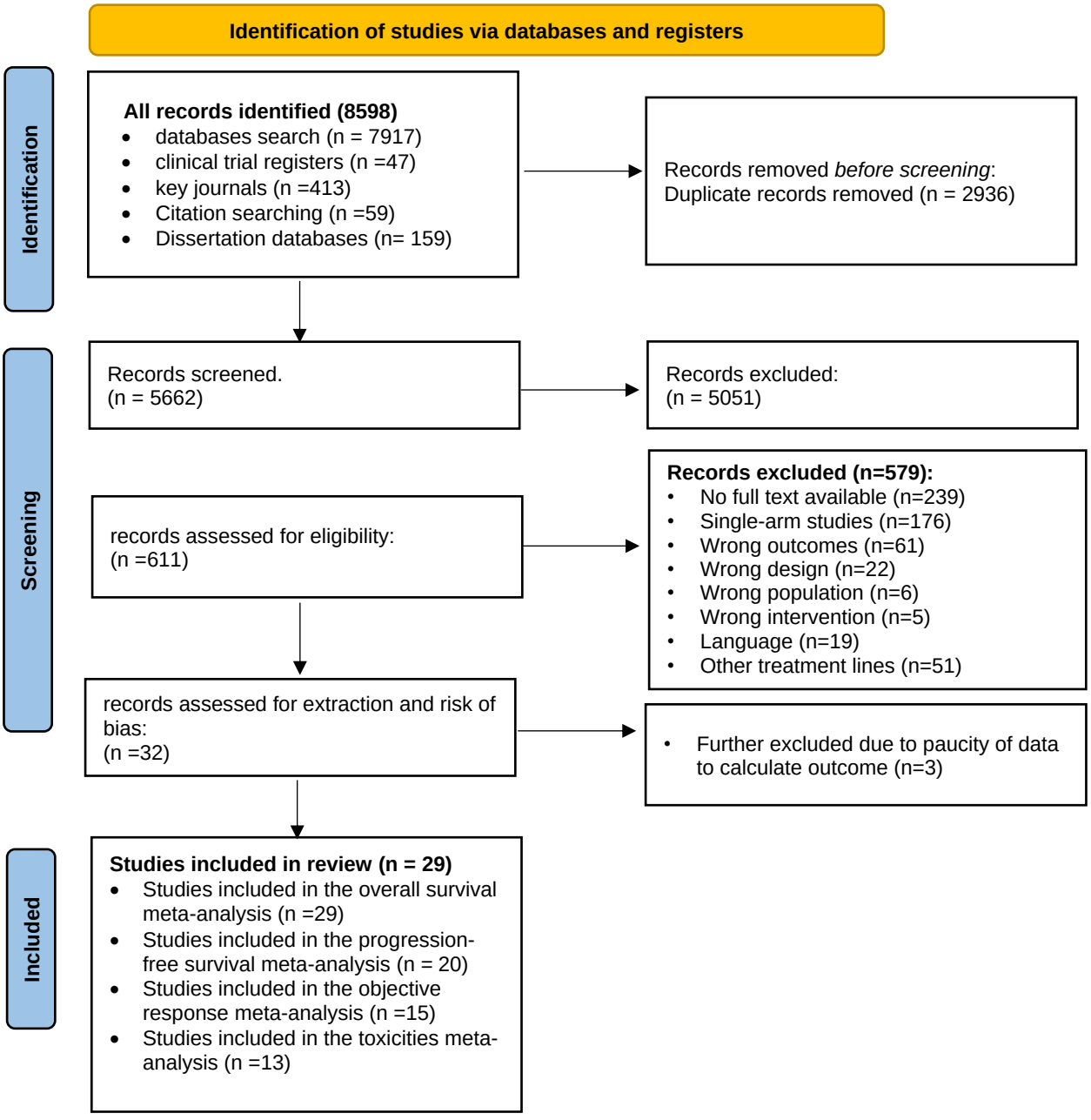


Figure 2.3: Flow chart of screening process to identify relevant studies.

2.3.2 Study characteristics

The characteristics of the included studies are summarised in appendix II.All studies were published after the year 2010, with around two-thirds of them published in and after the year 2015 (n=19, 65%) (Bai et al., 2015, Cheng and Song, 2015, Hammerman et al., 2015, Kocakova et al., 2015, Marschner et al., 2015, Stein et al., 2015b, Artac et al., 2016, Bai et al., 2016, Razenberg et al., 2016, Lee et al., 2017, Degirmencioglu S, 2019, Franchi et al., 2019, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Neugut et al., 2019, Guo et al., 2020, Cainap et al., 2021, Zhou et al., 2021). Similarly, more than two-thirds of the studies were of retrospective cohort design (n=20, 69%) (Stec et al., 2010, Ocvirk et al., 2011, Satram-Hoang et al., 2013, Buchler et al., 2014, Duran et al., 2014, Suenaga et al., 2014, Yang et al., 2014, Bai et al., 2015, Cheng and Song, 2015, Kocakova et al., 2015, Artac et al., 2016, Bai et al., 2016, Razenberg et al., 2016, Degirmencioglu S, 2019, Houts et al., 2019a, Houts et al., 2019b, Neugut et al., 2019, Guo et al., 2020, Cainap et al., 2021, Zhou et al., 2021).

Around 20% of the studies (n=6) originated from the United States (Bendell et al., 2012, Houts et al., 2019a, Houts et al., 2019b, Meyerhardt et al., 2012b, Neugut et al., 2019, Satram-Hoang et al., 2013) while almost a similar proportion (n=5, 17.2%) were carried out in China (Bai et al., 2016, Bai et al., 2015, Cheng and Song, 2015, Guo et al., 2020, Zhou et al., 2021).The duration in which the studies were carried out varied considerably and ranged from 17 months to 132 months. Eighteen studies (62%) declared a conflict of interest (Bendell et al., 2012, Buchler et al., 2014, Cainap et al., 2021, Franchi et al., 2019, Guo et al., 2020, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Kocakova et al., 2015, Lee et al., 2017, Marschner et al., 2015, Meyerhardt et al., 2012b, Neugut et al., 2019, Razenberg et al., 2016, Satram-Hoang et al., 2013, Stec et al., 2010, Stein et al., 2015b, Zhou et al., 2021) with ten (34.5%) of these studies having been funded by pharmaceutical companies (Bendell et al., 2012, Buchler et al., 2014, Franchi et al., 2019, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Lee et al., 2017, Meyerhardt et al., 2012b, Satram-Hoang et al., 2013, Stein et al., 2015b) while the rest were funded by other institutes. Also, nine (31%) of the included studies declared no conflict of interest (Artac et al., 2016, Bai et al., 2016, Bai et al., 2015, Cheng and Song, 2015, Degirmencioglu S, 2019, Hammerman et al., 2015, Ocvirk et al., 2011, Uygun et al., 2013, Yang et al., 2014) and two studies (6.9%) did not report this information (Duran et al., 2014, Suenaga et al., 2014).

2.3.3 Clinical characteristics of the studies' participants

The sociodemographic and clinical characteristics of the participants enrolled in the studies are summarised in appendix III. A total of 26574 participants were included in all studies of this review. Bevacizumab was the most extensively studied SACT as it was investigated in the majority of the studies (n= 25, 86.2%) (Artac et al., 2016, Bai et al., 2016, Bai et al., 2015, Bencsikova et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Degirmencioglu S, 2019, Duran et al., 2014, Franchi et al., 2019, Hammerman et al., 2015, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Kocakova et al., 2015, Lee et al., 2017, McNab et al., 2020, Meyerhardt et al., 2012b, Ocvirk et al., 2011, Razenberg et al., 2016, Sogabe et al., 2011, Stein et al., 2015b, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021). The sample size of the studies ranged between 123 and 4250 participants, and 43.9% were female (N=11,666). Age was reported either as mean (± standard deviation), median (interquartile range) or in the form of age groups.

A total of 18 studies (62.1%) have reported the ECOG PS of the participants at baseline, with 11200 participants were assessed for PS (Artac et al., 2016, Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cheng and Song, 2015, Duran et al., 2014, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Kocakova et al., 2015, Lee et al., 2017, Marschner et al., 2015, Ocvirk et al., 2011, Stec et al., 2010, Stein et al., 2015b, Suenaga et al., 2014, Uygun et al., 2013). More than three-quarters of the participants (n=9243, 78.3%) had a PS of less than or equal to one, whereas 7.7% (N=862) had a PS of 2 or more, indicating a worse performance status. For the remaining participants, the PS was unknown within the studies that reported.

2.3.4 Risk of bias results

Detailed results of stage II of the risk of bias assessment using Cochrane ROBINS-I tool are summarised in appendix III which displays the brief answers to the signalling questions as explained in section 2.2.4, and the detailed answers to the signalling questions for each domain and the reason behind the judgment for each domain per study.

The weight bar plot in Figure 2.4 shows the distribution of risk-of-bias judgment within each bias domain, while the risk of bias traffic light plot presented in Figure 2.5 shows the domain-

level judgment for each individual study. As shown, all of the studies had an overall serious risk of bias, which is interpreted that the studies have some important problems. A study is judged to be at serious risk of bias if at least one domain was judged at serious risk of bias. Only 4 studies (13.8%) had serious risk of bias in only one domain (Artac et al., 2016, Lee et al., 2017, Marschner et al., 2015, Yang et al., 2014).

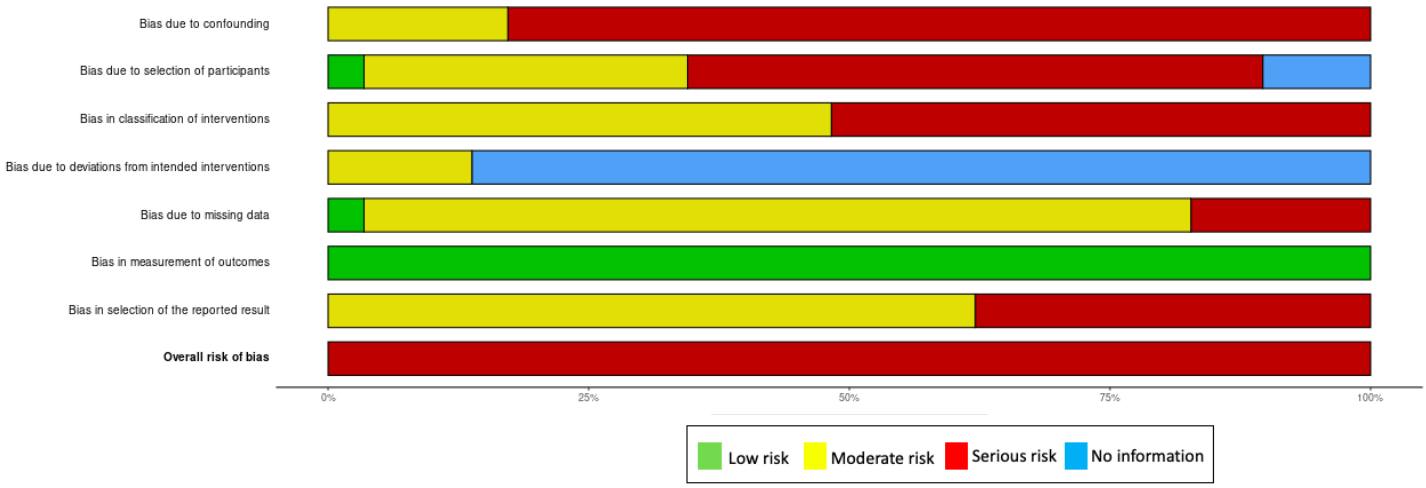


Figure 2.4 Weight bar risk of bias plot of the 29 eligible studies using the Cochrane ROBINS-I tool.

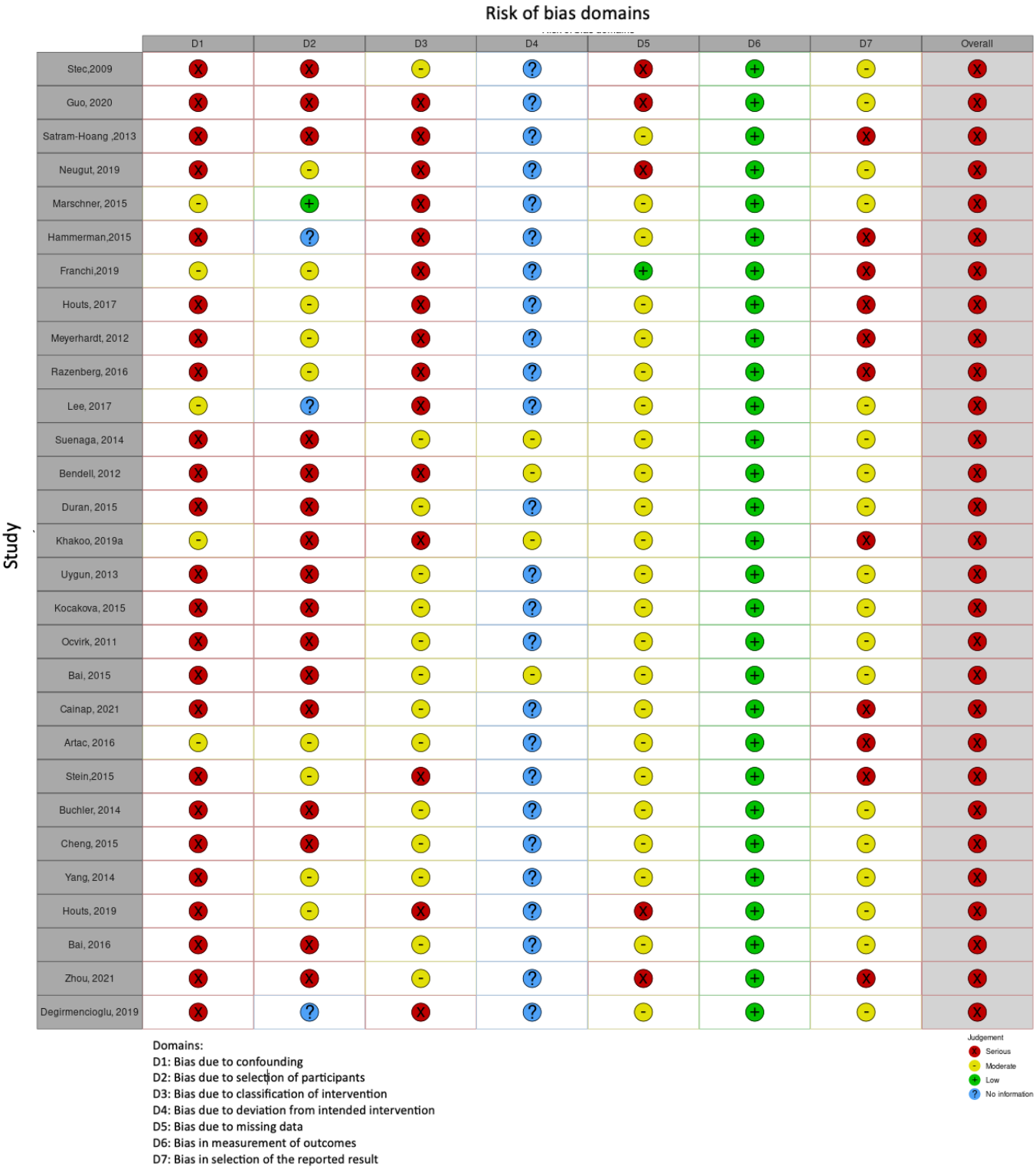


Figure 2.5 Risk of bias traffic light plot for the 29 eligible studies using the Cochrane ROBINS-I tool.

*The left column represents the studies assessed for risk of bias. Next columns from 1 to 7 represent the domains of risk of bias and the last column represent the overall risk of bias. If a study was judged to be at serious risk of bias at any domain (red), the overall risk of bias would be serious risk of bias.

2.3.4.1 Bias due to confounding

Confounding is inherent in the observational studies design. For the studies included in the current review, baseline confounding was assessed for all studies. Only five studies (17.2%) successfully adjusted for potential confounders that are pre-specified in the protocol stage which are the metastatic SACT, and ECOG PS (Artac et al., 2016, Franchi et al., 2019, Khakoo et al., 2019, Lee et al., 2017, Marschner et al., 2015). Seventeen studies (58.6%) did not take into account important confounding factors in the multivariate Cox proportional model (ECOG PS or SACT) or did not report the value of the adjusted effect size, but rather the unadjusted effect size (performed univariate Cox models) (Bai et al., 2016, Bendell et al., 2012, Buchler et al., 2014, Guo et al., 2020, Hammerman et al., 2015, Houts et al., 2019b, Kocakova et al., 2015, Meyerhardt et al., 2012b, Razenberg et al., 2016, Satram-Hoang et al., 2013, Stec et al., 2010, Suenaga et al., 2014, Zhou et al., 2021, Bai et al., 2015, Cheng and Song, 2015, Houts et al., 2019a, Yang et al., 2014). The remaining seven studies provided only crude survival and a Kaplan-Meier curve, hence, the effect size generated after reconstructing the Kaplan-Meier curve was considered unadjusted for the important confounders (Cainap et al., 2021, Degirmencioglu S, 2019, Duran et al., 2014, Neugut et al., 2019, Ocvirk et al., 2011, Stein et al., 2015b, Uygun et al., 2013). Time-varying confounding, an element of the ROBINS-I tool was not applicable for the studies included in the current review because analysis was not based on splitting participants' follow-up time.

2.3.4.2 Bias in selecting participants into the study.

Selection bias stems from selecting participants based on certain characteristics observed after the initiation of intervention (Sterne et al., 2016b). In the present review, more than half of the studies had serious risk of bias in selecting participants into the study domain (N=16, 55.2%) (Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Duran et al., 2014, Guo et al., 2020, Khakoo et al., 2019, Kocakova et al., 2015, Ocvirk et al., 2011, Satram-Hoang et al., 2013, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Zhou et al., 2021). Of these, fourteen studies (48.3%) excluded patients with comorbidities or poor performance status (Bai et al., 2016, Bai et al., 2015, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Duran et al., 2014, Kocakova et al., 2015, Ocvirk et al., 2011, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Zhou et al., 2021, Guo et al., 2020, Satram-Hoang et al., 2013) while 2 studies (6.9%)

reported that the follow-up was not initiated at the start of the intervention leading to loss in follow-up and hence inception bias (Khakoo et al., 2019, Bendell et al., 2012). Moreover, 9 studies (31%) used minimal patient selection criteria and therefore had moderate selection bias according to ROBINS-I guidance (Artac et al., 2016, Franchi et al., 2019, Houts et al., 2019a, Houts et al., 2019b, Meyerhardt et al., 2012b, Neugut et al., 2019, Razenberg et al., 2016, Stein et al., 2015b, Yang et al., 2014), 1 study (3.4%) adjusted for immortal time bias, therefore was classified as low selection bias (Marschner et al., 2015), and 3 studies (10.3%) did not provide information on the selection of patients into the studies, hence, were classified as unknown risk of selection bias (Degirmencioglu S, 2019, Hammerman et al., 2015, Lee et al., 2017).

2.3.4.3 Bias in classification of intervention.

Appropriate definition of the intervention is essential to avoid bias in the classification of participants. In the current review, around half of the studies (n= 15, 51.7%) did not provide a clear definition of the intervention in terms of the dose, frequency of administration, intensity and/or timing of intervention; therefore, they were classified at serious risk of bias in this domain (Bendell et al., 2012, Degirmencioglu S, 2019, Franchi et al., 2019, Guo et al., 2020, Hammerman et al., 2015, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Lee et al., 2017, Marschner et al., 2015, Meyerhardt et al., 2012b, Neugut et al., 2019, Razenberg et al., 2016, Satram-Hoang et al., 2013, Stein et al., 2015b). The remaining 14 studies have defined the intervention properly, yet the assignment of intervention status was determined retrospectively. (Artac et al., 2016, Bai et al., 2016, Bai et al., 2015, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Kocakova et al., 2015, Ocvirk et al., 2011, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021). Hence, they were considered at moderate risk of bias in this domain based on ROBINS-I guidance published by Cochrane Bias methods group (Sterne et al., 2016b).

2.3.4.4 Bias due to deviation from intended intervention.

The majority of the studies included in this review did not provide information on the treatment pattern and adherence to treatment (n= 25, 86.2%) (Artac et al., 2016, Bai et al., 2016, Bencsikova et al., 2015, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Degirmencioglu S, 2019, Duran et al., 2014, Franchi et al., 2019, Guo et al., 2020, Hammerman et al., 2015, Houts et al., 2019a, Houts et al., 2019b, Kocakova et al., 2015, Lee

et al., 2017, Marschner et al., 2015, Meyerhardt et al., 2012b, Neugut et al., 2019, Ocvirk et al., 2011, Razenberg et al., 2016, Satram-Hoang et al., 2013, Stec et al., 2010, Stein et al., 2015b, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021). Therefore, these studies were classified as unknown risk of bias due to deviation from intended intervention. Only 4 studies (13.8%) discussed treatment initiation and discontinuation and the reasons for discontinuation and non-adherence to treatment (Bai et al., 2015, Bendell et al., 2012, Khakoo et al., 2019, Suenaga et al., 2014) and they were at moderate risk of bias in this domain as the impact of deviation from intervention (i.e., usual care) was expected to be slight.

2.3.4.5 Bias in measurement of outcomes

The primary measured outcome in this study is overall survival which involves negligible assessor judgment. In addition to that, the data collection method used in each study was comparable between interventions within this domain. For those reasons, all included studies were classified at low risk of bias within the domain of measurement of outcomes.

2.3.4.6 Bias in selection of reported results

Within this domain, 11 studies (37.9%) were at serious risk of bias, either due to generating multiple effect sizes for different subgroups (Artac et al., 2016, Cainap et al., 2021, Khakoo et al., 2019, Razenberg et al., 2016, Stein et al., 2015b, Zhou et al., 2021), or due to reporting multiple analyses of the effect size (e.g., crude and adjusted HR) (Satram-Hoang et al., 2013), or for both reasons combined (Franchi et al., 2019, Hammerman et al., 2015, Meyerhardt et al., 2012b). The remaining 18 studies (62.1%) were at moderate risk of bias as there was no indication of selection of the reported analyses from multiple analysis and also no indication existed of selection of the subgroups for analysis (Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cheng and Song, 2015, Degirmencioglu S, 2019, Duran et al., 2014, Guo et al., 2020, Houts et al., 2019a, Kocakova et al., 2015, Lee et al., 2017, Marschner et al., 2015, Neugut et al., 2019, Ocvirk et al., 2011, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021).

2.3.5 Synthesis of effectiveness and safety outcomes of first-line mCRC medicines

Studies comparing first-line mCRC SACTs were classified into 4 groups depending on the compared interventions:

1- Group 1: different chemotherapies compared to each other (CT-1 versus CT-2): this group included chemotherapeutic agents compared to each other (e.g., FOLFOX vs FOLFIRI) regardless of the intensity (mono or combination): 5 studies were included in this group. (Guo et al., 2020, Neugut et al., 2019, Satram-Hoang et al., 2013, Stec et al., 2010, Marschner et al., 2015),

2- Group 2: Chemotherapy alone compared to a combination of chemotherapy and bevacizumab (CT versus bevacizumab+ CT): this group comprised 7 studies (Franchi et al., 2019, Hammerman et al., 2015, Houts et al., 2019b, Cho et al., 2017, Meyerhardt et al., 2012b, Razenberg et al., 2016, Suenaga et al., 2014)

3- Group 3: Various combinations of chemotherapies combined with bevacizumab compared to each other (bevacizumab+ CT-1 versus bevacizumab+ CT-2): 12 studies with 13 effect sizes compared different combination of chemotherapies with bevacizumab to each other where the combination of bevacizumab and oxaliplatin-based chemotherapy was compared to the combination of bevacizumab and irinotecan-based chemotherapy in 7 studies (Artac et al., 2016, Bai et al., 2015, Bendell et al., 2012, Cainap et al., 2021, Duran et al., 2014, Khakoo et al., 2019, Stein et al., 2015b), the combination of bevacizumab and FOLFIRI was compared to the combination of bevacizumab and XELIRI in 3 studies (Kocakova et al., 2015, Ocvirk et al., 2011, Uygun et al., 2013), the combination of bevacizumab and FOLFOX was compared to the combination of bevacizumab and XELOX in 1 study (Buchler et al., 2014), and the combination of bevacizumab with FOLFOXIRI was compared to the combination of bevacizumab and XELOXIRI in one study (Cheng and Song, 2015).

4- Group 4: Combination of chemotherapy and bevacizumab compared to the combination of chemotherapy and cetuximab (bevacizumab+ CT versus cetuximab+ CT): 5 studies (Bai et al., 2016, Degirmencioglu S, 2019, Houts et al., 2019a, Yang et al., 2014, Zhou et al., 2021).

The outcomes of these studies, including OS, PFS, objective response (including ORR and DCR) and severe haematological and non-haematological toxicities are summarised in Table 2.5.

Table 2.5: Description of the outcomes of the 29 studies included in synthesising the pooled estimates using meta-analyses approach.

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
CT1 Vs. CT2							
Stec,2010 (Stec et al., 2010)	**123**	**Median (months)**		**N (%)**	**N (%)**	**N (%)**	**N (%)**
Capecitabine	56 (45.5)	15.4	NR	8 (16.4)	36 (73.5)	7 (12.5)	23 (41.1)
FOLFIRI	67 (54.5)	19	NR	18 (28.1)	53 (81.5)	14 (20.9)	22 (32.8)
P value		0.93	NR	0.139		NR	NR
Guo, 2020 (Guo et al., 2020)	**1066**	**2- year survival (days)**				**N (%)**	**N (%)**
Capecitabine	533 (50)	335	NR	NR	NR	95 (19.1*)	64 (18*)
S-1	533 (50)	330	NR	NR	NR	113 (22.6*)	26 (6.8)
P value		0.495	NR	NR	NR	NR	NR
Satram-Hoang ,2013a (Satram-Hoang et al., 2013)	**2830**	**Median (months)**					
Capecitabine	617 (21.8)	32.6	NR	NR	NR	NR	NR
5FU	2213 (78.2)	31.9	NR	NR	NR	NR	NR
P value		0.69	NR	NR	NR	NR	NR
Satram-Hoang ,2013a (Satram-Hoang et al., 2013)	**1420**	**3-year survival rate**					
XELOX	122 (8.6)	71.6%	NR	NR	NR	NR	NR
FOLFOX	1298 (91.4)	68.5%	NR	NR	NR	NR	NR
P value		0.67	NR	NR	NR	NR	NR
Neugut, 2019 (Neugut et al., 2019)	**3785**	**Median (months)**	NR	NR	NR	NR	NR
FOLFIRI (± Bevacizumab)	785 (20.7)	20.5	NR	NR	NR	NR	NR
FOLFOX (± Bevacizumab)	3000 (79.3)	19.1	NR	NR	NR	NR	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Marschner, 2015 (Marschner et al., 2015)	605	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**		
Oxaliplatin based CT	430 (71)	26.8 (22.4-31.9)	9 (8.1-10.2)	178 (45.2 *)	258(65.5*)	NR	NR
irinotecan based CT	175 (29)	18.3 (15.1-23.2)	7.9 (7.2-10.2)	55 (34.6*)	93 (58.5*)	NR	NR
P value		NR	NR	NR	NR	NR	NR
Bevacizumab+ CT vs. CT							
Hammerman,2015 (Hammerman et al., 2015)	**1739**	**Median (months) (95% CI)**	**Median (months) (95% CI)**				
Bevacizumab + CT	1052 (60.5)	23 (21.7–24.3)	14.0 (13.0–15.0)	NR	NR	NR	NR
CT	687 (39.5)	15.0 (13.4–16.6)	9.8 (9.0–10.5)	NR	NR	NR	NR
P value		< 0.0001	< 0.0001	NR	NR	NR	NR
Franchi,2019 (Franchi et al., 2019)	**480**	**Median (months) (95% CI)**					
Bevacizumab + CT	101 (21)	22.5	NR	NR	NR	NR	NR
CT	379 (79)	14.6	NR	NR	NR	NR	NR
P value		0.011	NR	NR	NR	NR	NR
Houts,2019 (Houts et al., 2019b)	**373**	**Median (months) (95% CI)**	**Median (months) (95% CI)**				
Bevacizumab + CT	264 (70.8)	26.9 (24.3- 29.3)	10.4 (9- 11.3)	NR	NR	NR	NR
CT	109 (29.2)	23.3 (19.7- 29.2)	7.7 (6.5- 9.1)	NR	NR	NR	NR
P value		0.57	0.17	NR	NR	NR	NR
Meyerhardt, 2012 (Meyerhardt et al., 2012b)	**2526**	**Median (months) (95% CI)**				**Adverse events were not measured through NCI-CTCAE**	
Bevacizumab + CT	903 (35.7)	19 (17.9- 20.5)	NR	NR	NR	NR	NR
CT	1623 (64.3)	15.9 (14.8- 18.2)	NR	NR	NR	NR	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
P value		0.003	NR	NR	NR	NR	NR
Razenberg, 2016 (Razenberg et al., 2016)	**361**	**Median (months) (95% CI)**					
Bevacizumab + CT	185 (51.4)	22 (19-24)	NR	NR	NR	NR	NR
CT	176 (48.6)	14 (11-16)	NR	NR	NR	NR	NR
P value		< 0.0001	NR	NR	NR	NR	NR
Lee, 2017a (Lee et al., 2017)	**313**	**Median (months) (95% CI)**	**Median (months) (95% CI)**			**Adverse events were not measured through NCI-CTCAE**	
Bevacizumab + CT	200 (63.9)	20	8.5	NR	NR	NR	NR
CT	113 (36.1)	14.8	4.7	NR	NR	NR	NR
P value		0.005	0.017	NR	NR	NR	NR
Lee, 2017b (Lee et al., 2017)	**513**	**Median (months) (95% CI)**	**Median (months) (95% CI)**			**Adverse events were not measured through NCI-CTCAE**	
Bevacizumab + CT	357 (69.6)	24.4	10.8	NR	NR		
CT	156 (30.4)	17.3	5.8	NR	NR		
P value		0.004	<0.001	NR	NR		
Suenaga, 2014 (Suenaga et al., 2014)	**213**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFOX	85 (39.9)	38.8 (32.9-44.8)	17 (11.8-22.3)	52 (62)	81 (96)	39	16
FOLFOX	128 (60.1)	20.5 (16.9-24)	9.9 (8.4-11.4)	56 (46)	106 (88)	52	15
P value		< 0.001	0.002	0.02	0.01	NR	NR
Bevacizumab+ CT-1 versus bevacizumab+ CT-2							
Bendell, 2012 (Bendell et al., 2012)	**1550**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIRI	243 (15.7)	25.5 (20.9–28.4)	10.2 (9.0–11.4)	127 (52.3)	209 (86)	3 (1.2)	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Bevacizumab+ FOLFOX	968 (84.3)	23.7 (22.1- 25.6)	10.3 (9.9–11.0)	546 (56.4)	838 (86.6)	34 (3.5)	NR
P value		NR	NR	NR	NR	NR	NR
Duran,2014 (Duran et al., 2014)	**409**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIRI	111 (27.1)	20 (16.8- 23.1)	9 (7.4- 10.5)	29 (26.1)	78 (70.3)	43 (38.7)	28 (25.2)
Bevacizumab + XELOX	298 (72.9)	25 (22.2- 27.7)	9.6 (8.8- 10.4)	168 (56.4)	256 (85.9)	55 (18.5)	26 (8.7)
P value		0.036	0.019	<0.001	NR	NR	NR
Khakoo, 2019 (Khakoo et al., 2019)	**677**	**Median (months) (95% CI)**	**Median (months) (95% CI)**			**Adverse events were reported combined for both haematological and non-haematological toxicities (N%)**	
Bevacizumab + XELOX	265 (39.1)	19.6 (17.4- 22.1)	9.2 (8.4- 9.7)	NR	NR	151 (57)	
Bevacizumab + Capecitabine	107 (15.8)	15.1 (12.8- 16.9)	7.9 (5.7- 9.0)	NR	NR	46 (43)	
Bevacizumab + FOLFIRI	101 (14.9)	18.7 (14.7- 23.3)	8.7 (7.2- 9.8)	NR	NR	65 (64.3)	
Bevacizumab+ FOLFOX	204 (30.2)	16.5 (13.6- 21.2)	8.5 (7.1- 9.3)	NR	NR	131 (64.2)	
P value							
Uygun, 2013 (Uygun et al., 2013)	**132**	**Median (months)**	**Median (months)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIRI	64 (48.5)	37.8	14.2	33 (51.6)	52 (81.3)	18 (28.1)	17 (26.5)
Bevacizumab + XELIRI	68 (51.5)	28.7	Not reached	28 (41.2)	54 (79.4)	33 (48.5)	37 (54.4)
P value		0.58	0.3	0.38	NR	NR	NR
Kocakova,2015 (Kocakova et al., 2015)	**558**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIRI	357 (64)	25.4 (22.0-28.8)	11.5 (10.3-12.8)	152 (43)	265 (74)	43	28
Bevacizumab + XELIRI	201 (36)	27.2 (23.6-30.8)	13.3 (10.9-15.7)	97 (48)	175 (87)	55	26
P value		0.87	0.89	0.215	0.001	NR	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Ocvirk, 2011 (Ocvirk et al., 2011)	**139**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIRI	45 (32.4)	24.8 (22.3-32.5)	11.6 (9.1-14.2)	18 (40)	34 (76)	30 (66.7)	7 (15.6)
Bevacizumab + XELIRI	94 (67.6)	27.8 (24.0–not reached)	11.7 (10.5-13.1)	46 (49)	81 (86)	17 (18.1)	20 (21.3)
P value		0.072	0.41	0.26	0.03	NR	NR
Bai, 2015 (Bai et al., 2015)	**175**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + Irinotecan-based	83 (47.4)	27.5 (21.8–33.2)	10.8 (9.9- 11.7)	33 (93.7)	73 (87.9)	25 (30.1)	29 (34.9)
Bevacizumab + Oxaliplatin-based	92 (52.6)	23.7 (19.9–27.6)	10.1 (8.8-11.3)	34 (37)	78 (84.8)	27 (29.3)	34 (37)
P value		0.21	0.68	0.75	0.93	NR	NR
Cainap, 2021 (Cainap et al., 2021)	**151**	**Median (months) (95% CI)**	**Median (months) (95% CI)**				
Bevacizumab + Irinotecan-based	60 (39.7)	25 (22- 36)	13 (12- 18)	NR	NR	NR	NR
Bevacizumab + Oxaliplatin-based	91 (60.3)	25 (23- 30)	12 (9-13)	NR	NR	NR	NR
P value		0.21	0.3	NR	NR	NR	NR
Artac, 2016 (Artac et al., 2016)	**625**	**Median (months) (95% CI)**	**Median (months) (95% CI)**				
Bevacizumab + Irinotecan-based	414 (66.2)	26.3 (21.7–30.9)	10.9 (10–11.8)	NR	NR	NR	NR
Bevacizumab + Oxaliplatin-based	211 (33.8)	27 (24.3–29.7)	9.4 (8.3–10.4)	NR	NR	NR	NR
P value		NR	NR	NR	NR	NR	NR
Stein,2015 (Stein et al., 2015a)	**1777**	**Median (months)**	**Median (months)**	**N (%)**	**N (%)**		

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Bevacizumab + Irinotecan-based	1200 (67.5)	24.8	10.4	697 (61)	1004 (88)	**Adverse drug reactions potentially related to antibody treatment were recorded by use of open questions**	
Bevacizumab + Oxaliplatin-based	332 (18.7)	27.3	10.6	203 (62)	298 (91)		
Bevacizumab + 5FU or capecitabin	209 (11.8)	25.5	9.2	113 (54)	182 (87)		
Bevacizumab + other	36 (2)	27.7	11.9	51 (52)	84 (85)		
P value		NR	NR	NR	NR		
Buchler, 2014 (Buchler et al., 2014)	**2191**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFIOX	1218 (55.6)	27 (24.6-29.5)	11.4 (10.7-12.1)	573 (47)	956 (78.5)	19 (1.6)	19 (1.6)
Bevacizumab + XELOX	973 (44.4)	30.6 (27.8-33.4)	11.5 (10.8-12.3)	432 (44.4)	626 (84.9)	16 (1.6)	17 (1.7)
P value		0.28	0.38	NR	NR	NR	NR
Cheng, 2015 (Cheng and Song, 2015)	**138**	**Months**	**Months**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Bevacizumab + FOLFOXIRI	69 (50)	31.3	13.5	49 (71)	62 (89.9)	45 (65.2)	54 (78.3)
Bevacizumab + XELOXIRI	69 (50)	24.6	10.4	36 (52.2)	58 (84)	24 (34.8)	20 (30)
P value		0.115	0.032	NR	NR	NR	NR
Bevacizumab+ CT versus cetuximab+ CT							
Yang, 2014 (Yang et al., 2014)	**158**	**Median (months)**	**Median (months)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Cetuximab+ chemotherapy	63 (39.9)	37.8	12.4	35 (66)	47 (88.7)	12 (19)	20 (31.7)
Bevacizumab+ chemotherapy	95 (60.1)	30.5	8.7	34 (47.2)	65 (90.3)	27 (28)	15 (15.8)
P value		0.45	0.05	0.037	0.77	0.18	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Houts, 2019 (Houts et al., 2019a)	**400**	**Median (months) (95% CI)**	**Median (months) (95% CI)**				
Cetuximab+ chemotherapy	146 (36.5)	30.6 (23.8- 38)	10.2 (8.3- 12.2)	NR	NR	NR	NR
Bevacizumab+ chemotherapy	254 (63.5)	31 (26.33- 36.1)	10.8 (10.1- 11.8)	NR	NR	NR	NR
P value		0.55	0.78	NR	NR	NR	NR
Bai, 2016 (Bai et al., 2016)	**289**	**Median (months) (95% CI)**	**Median (months) (95% CI)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Cetuximab+ chemotherapy	101 (34.9)	28.3 (22.7–33.9)	8.7 (7.5- 9.9)	54 (53.5)	89 (88.1)	53 (52.5)	63 (62.4)
Bevacizumab+ chemotherapy	188 (65.1)	27.7 (22.7–32.7)	10.6 (9.3–11.9)	81 (43.1)	163 (87.2)	32 (17)	41 (21.8)
P value		0.51	0.32	0.11	0.85	NR	NR
Zhou, 2021a (non-mucinous histology) (Zhou et al., 2021)	**479**	**Median (months)**	**Median (months)**	**N (%)**	**N (%)**		
Cetuximab+ chemotherapy	203 (42.2)	29.8	10.8	136 (67)	180 (88.7)	NR	NR
Bevacizumab+ chemotherapy	276 (57.6)	27	10.5	146 (52.9)	220 (79.7)	NR	NR
P value		0.005	0.41	0.002	0.009	NR	NR
Zhou, 2021a (mucinous histology) (Zhou et al., 2021)	**141**	**Median (months)**	**Median (months)**	**N (%)**	**N (%)**		
Cetuximab+ chemotherapy	55 (39)	26.3	9.5	29 (52.7)	44 (80)	NR	NR
Bevacizumab+ chemotherapy	86 (61)	30	11.5	46 (53.5)	71 (82.6)	NR	NR
P value		0.002	0.032	0.93	0.81	NR	NR
Degirmencioglu, 2019 (Degirmencioglu S, 2019)	**238**	**1, 3, and 5-year survival rate (%)**	Only reported through Kaplan Meier curves				
Cetuximab+ chemotherapy	92	93.9, 56.6, 45.7	NR	NR	NR	NR	NR
Bevacizumab+ chemotherapy	114	93.4, 58.2, 36.7	NR	NR	NR	NR	NR

Author, year, intervention	Sample size N (%)	Overall survival	Progression-free survival	Overall response rate	Disease control rate	Haematological toxicities	Non- haematological toxicities
Panitumumab+ chemotherapy	32	79.8, 57, not reached	NR	NR	NR	NR	NR
P value		0.033	NR	NR	NR	NR	NR

KEY: Ct1 = chemotherapy 1, CT2 = chemotherapy 2, NR= not recorded, 95% CI= 95% confidence interval.

* Calculated taking into considerations the missing data.

** original number of patients in the study is 1777 divided over 4 subgroups; oxaliplatin based+ bevacizumab, irinotecan based+ bevacizumab, 5FU and bevacizumab, and other chemotherapy.

Two of the included studies performed multiple comparisons resulting in more than one effect size; Satram-Hoang, 2013 compared capecitabine to 5FU and FOLFOX to XELOX (Satram-Hoang et al., 2013) and Khakoo, 2019 compared the combination of bevacizumab+ FOLFIRI to bevacizumab+ FOLFOX and bevacizumab+ capecitabine to bevacizumab+ XELOX.

Zhou, 2021 compared the combination of bevacizumab+ CT to the combination of cetuximab+ CT for mCRC patients with mucinous histology tumour and for mCRC patients with non-mucinous histology tumour resulting in 2 effect sizes for this study (Zhou et al., 2021). Moreover, 3 studies generated multiple effect size for different groups of the same population as shown in Table 2.6 (Meyerhardt et al., 2012b, Hammerman et al., 2015, Artac et al., 2016). The effect sizes generated by these studies were not included in the main MA to avoid violating the assumption of the independency of effect sizes from included studies (Cheung, 2019). This issue was handled by conducting a separate MA from the main effect MA including the subgroups generated by the studies in Table 2.6.

Table 2.6 Additional effect sizes generated by the studies and included in separate MA.

Author, year	Comparison	Subgroup comparison
Hammerman, 2014 (Hammerman et al., 2015)	Bevacizumab+ CT Vs. CT	Bevacizumab+ irinotecan-based CT Vs. irinotecan-based CT
Hammerman, 2014 (Hammerman et al., 2015)	Bevacizumab+ CT Vs. CT	Bevacizumab+ irinotecan-based CT Vs. Bevacizumab+ oxaliplatin-based CT
Meyerhardt, 2012 (Meyerhardt et al., 2012b)	Bevacizumab+ CT Vs. CT	Bevacizumab+ irinotecan-based CT Vs. irinotecan-based CT
Meyerhardt, 2012 (Meyerhardt et al., 2012b)	Bevacizumab+ CT Vs. CT	Bevacizumab+ oxaliplatin-based CT Vs. oxaliplatin-based CT
Artac, 2016 (Artac et al., 2016)	Bevacizumab+ FOLFOX Vs. Bevacizumab+ XELOX Bevacizumab+ FOLFIRI Vs. Bevacizumab+ XELIRI	Bevacizumab+ oxaliplatin-based CT Vs. bevacizumab+ irinotecan-based CT
KEY: CT= chemotherapy		

2.3.6 Meta-analysis results

This section covers the results of the six MAs, which were carried out to quantify the effectiveness and safety of first-line mCRC SACTs. All 29 included studies were used to synthesise the data for OS. Furthermore, of the 29 included studies, 23 studies reported PFS *(Marschner et al., 2015, Hammerman et al., 2015, Franchi et al., 2019, Houts et al., 2019b, Meyerhardt et al., 2012b, Razenberg et al., 2016, Lee et al., 2017, Suenaga et al., 2014, Bendell et al., 2012, Duran et al., 2014, Khakoo et al., 2019, Uygun et al., 2013, Kocakova et al., 2015, Ocvirk et al., 2011, Bai et al., 2016, Cainap et al., 2021, Artac et al., 2016, Stein et al., 2015b, Buchler et al., 2014, Cheng and Song, 2015, Yang et al., 2014, Houts et al., 2019a, Zhou et al., 2021, Degirmencioglu S, 2019),* 15 studies reported both ORR and DCR (Stec et al., 2010, Marschner et al., 2015, Suenaga et al., 2014, Bendell et al., 2012, Duran et al., 2014, Kocakova et al., 2015, Bai et al., 2016, Bai et al., 2015, Buchler et al., 2014, Cheng and Song, 2015, Ocvirk et al., 2011, Stein et al., 2015b, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021), and 13 studies were used to synthesise the results for both haematological and non-haematological toxicities (Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cheng and Song, 2015, Duran et al., 2014, Guo et al., 2020, Kocakova et al., 2015, Ocvirk et al., 2011, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014).

2.3.6.1 Overall survival meta-analysis

Overall estimate and heterogeneity

All of the included studies (n=29) reported overall survival of first-line SACTs for mCRC and were included in the overall survival MA. The included studies contributed toward 33 effect sizes with 26574 participants.

A total of 19 effect sizes were extracted directly from the primary studies (Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cainap et al., 2021, Franchi et al., 2019, Guo et al., 2020, Hammerman et al., 2015, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Kocakova et al., 2015, Marschner et al., 2015, Meyerhardt et al., 2012b, Razenberg et al., 2016, Satram-Hoang et al., 2013, Suenaga et al., 2014, Zhou et al., 2021), while the remaining 14 effect sizes were obtained indirectly through reconstruction of Kaplan-Meier curve (Houts et al., 2019b, Khakoo et al., 2019, Neugut et al., 2019, Ocvirk et al., 2011, Stein et al., 2015a, Uygun et al., 2013, Yang et al., 2014, Artac et al., 2016, Cheng and Song, 2015, Degirmencioglu S, 2019, Duran et al., 2014).

The overall pooled estimate for the overall survival MA was 1.14 (1.05- 1.24). Subgroup analysis shows that treatments comparisons included in group 1 (CT-1 Vs CT-2), group 3 (bevacizumab+ CT-1 vs bevacizumab+ CT-2), and group 4 (cetuximab+ CT VS bevacizumab+ CT) did not show statistically significant difference with a pooled estimate of 1.05 (0.99- 1.12) for group 1, a pooled estimate of 1.09 (0.97-1.22) for group 3 and a pooled estimate of 1.02 (0.73- 1.42) for the latter group. In contrast, treatment comparisons included in group 2 (bevacizumab+ CT vs CT) show that chemotherapy alone was significantly associated with 36% increased hazards of death compared to a combination of bevacizumab+ chemotherapy (HR 1.36 (95% CI 1.18- 1.56)). Figure 2.6 presents the forest plot of all included studies in the overall survival MA grouped based on the compared intervention.

The between-study heterogeneity variance was estimated at T^2= 0.0387 (95% CI: 0.0199- 0.1018), indicating that some between-study heterogeneity exists in the data, with an I^2 value of 76.2% (95% CI: 58.2- 79.3%) indicating high heterogeneity. The prediction interval ranged from -0.268 to 0.55 suggesting that negative intervention effects cannot be ruled out for future studies.

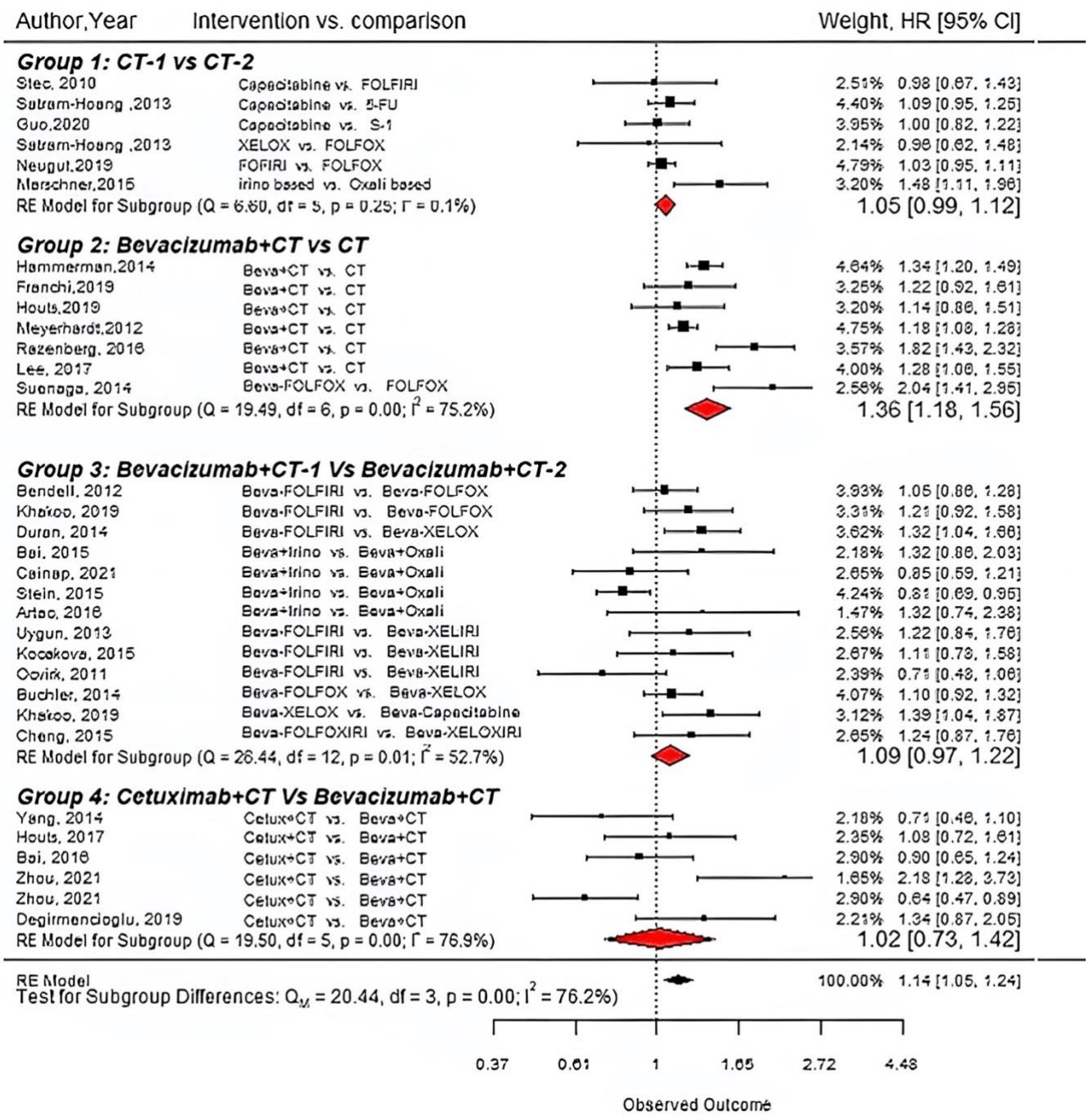


Figure 2.6: Forest plot of overall survival of first-line SACTs for mCRC, stratified by the four first line SACT groups.

A further analysis was carried out for group 3 separately to compare overall survival associated with the use of different chemotherapies in a combination with bevacizumab where additional comparisons were added (table 2.6). Similar treatment comparisons were categorised and compared against each other. The overall pooled estimate for all treatments included in group 3 was 1.12 (0.99-1.27) with no statistically significant difference found between: (1) bevacizumab+ irinotecan-based chemotherapy vs bevacizumab+ oxaliplatin-based chemotherapy (pooled estimate 1.05 (0.88- 1.25), (2) bevacizumab+ FOLFIRI vs bevacizumab+ XELIRI (pooled estimate 1.09 (0.083- 1.43)), and (3) bevacizumab+ FOLFOX vs bevacizumab+ XELOX (pooled estimate: 1.31 (0.88- 1.5). Only one effect size was reported for both treatment comparisons encompassing bevacizumab+ XELOX vs bevacizumab+ capecitabine and bevacizumab+ FOLFOXIRI vs bevacizumab+ XELOXIRI. The former comparison shows a statistically prolonged median OS for bevacizumab+ XELOX compared to bevacizumab+ capecitabine (HR 1.39, 95% CI 1.04-1.87), whereas the latter combination shows no statistically significant difference in OS between bevacizumab+ FOLFOXIRI vs bevacizumab+ XELOXIRI. Figure 2.7 shows the forest plot for bevacizumab combined with different chemotherapies.

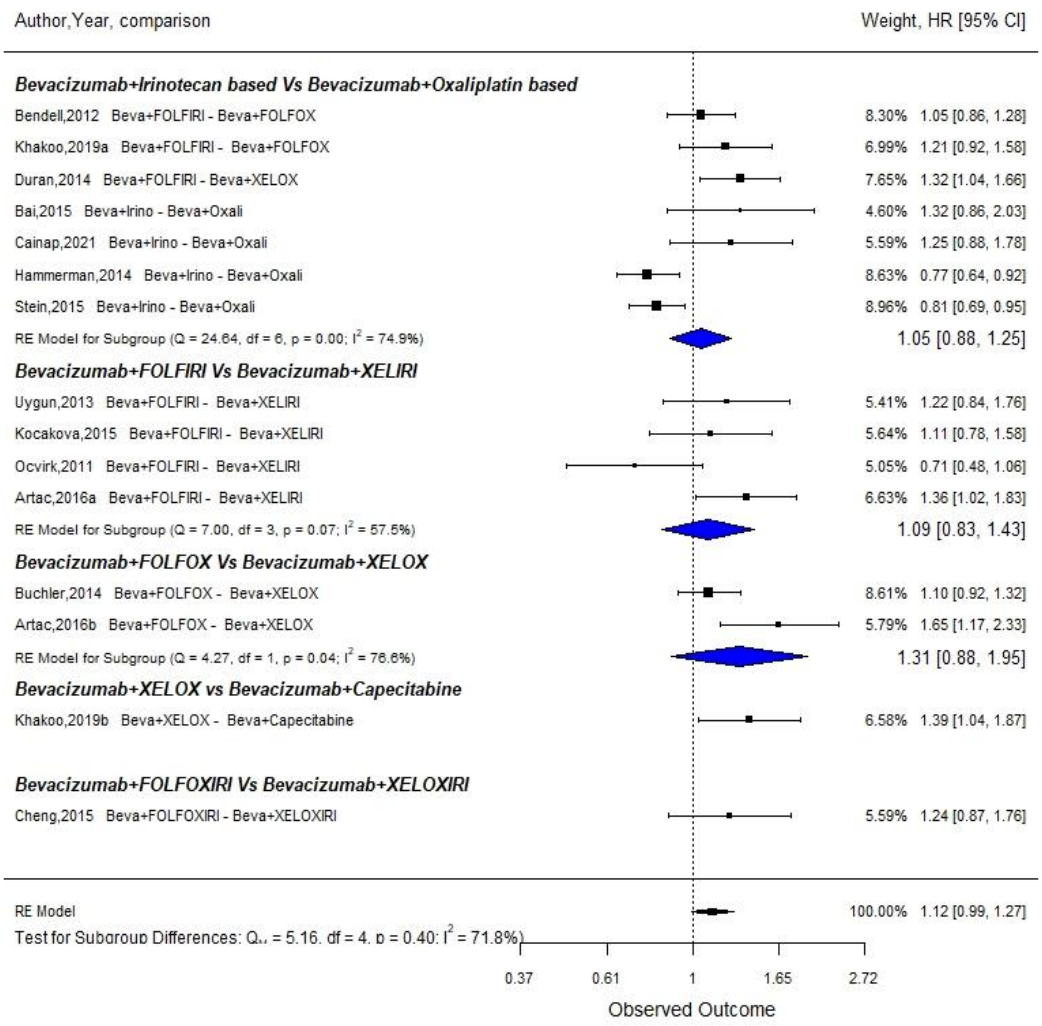


Figure 2.7: Forest plot for overall survival of first-line bevacizumab combinations with chemotherapy.

Moderator/sub-group analysis for overall survival meta-analysis

Variables that were expected to have an influence on the overall pooled estimate and the heterogeneity included study variables and clinical variables. Table 2.7 displays the moderator analysis of study characteristics variables for the overall survival meta-analysis. A range of the examined study characteristics revealed a significant impact on the heterogeneity including the effect size measurement method (direct vs. curve approach), the type of study setting (single centre vs. multiple centres), and the study duration. Additionally, the variability in the risk of bias across ROBINS-I domains, including confounding bias,

classification of intervention, deviation from intended intervention, missing data, and reporting of the outcomes has a statistically significant influence on the heterogeneity.

Most of the clinical characteristics of the studies' participants did not have an impact on the overall pooled estimate. Nevertheless, studies that included non-elderly participants were shown to have an influence on the overall result and the heterogeneity. Table 2.8 shows the moderator analysis of the clinical characteristics of the participants for the overall survival meta-analysis.

A further subgroup analysis was conducted for studies that exclusively included patients with RAS wild type in group 4 (cetuximab+ chemotherapy vs bevacizumab + chemotherapy) (Degirmencioglu S, 2019, Houts et al., 2019a). the overall pooled estimate was 1.19 (0.89-1.6), with patients treated with bevacizumab+ chemotherapy at higher risk of death. However, the overall pooled estimate was not significant (P value 0.47).

Table 2.7: Moderator analysis of study characteristics variables for the overall survival meta-analysis.

Tested variables	Number of effect sizes	Estimated pooled estimate (95% CI)	P value	I^2(%)	P subgroup (moderator analysis)
Measurement of effect size	**33**			**74.8%**	**0.005**
Reported	19	1.18 (1.06-1.27)	0.002		
Estimated (curve approach)	14	1.05 (0.93-1.21)	0.4		
Study design	**30**			**79.4%**	**0.11**
Retrospective cohort	25	1.17 (1.05-1.23)	0.02		
Prospective cohort	6	1.02 (0.83-1.26)	0.82		
Funding source	**31**			**73.6%**	**0.4**
Pharmaceutical company	12	1.17 (1.02-1.32)	0.02		
Non-pharmaceutical company	9	1.08 (0.92-1.25)	0.35		
Non declared	10	1.07 (0.91-1.25)	0.41		
Type of setting	**33**			**77.1%**	**0.001**
Single centre	10	1.05 (0.89-1.25)	0.5		
Multicentric	23	1.15 (1.05-1.26)	0.003		
Data source	**30**			**78.3%**	**0.19**
Medical chart	7	0.97 (0.78-1.19)	0.61		
Electronic medical records	7	1.24 (1.03 - 1.51)	0.02		
Registry	16	1.15 (1.03-1.28)	0.01		
Study duration	**30**	**0.97 (0.93-1.01)**	**0.03**	**75.3%**	**0.02**
Study sample	**33**	**1 (0.99-1.01)**	**0.81**	**76.9%**	**0.81**
Risk of bias					
Confounding bias	**32**			**77%**	**0.04**

Tested variables	Number of effect sizes	Estimated pooled estimate (95% CI)	P value	I^2(%)	P subgroup (moderator analysis)
Moderate	5	1.23(1.01-1.52)	0.04		
Serious	27	1.1 (1.01-1.21)	0.02		
Selection	**32**			**74.1%**	**0.36**
Low	1	1.48 (0.93-2.34)	0.10		
Moderate	9	1.12 (0.97-1.31)	0.11		
Serious	19	1.08 (0.97-1.2)	0.16		
NI	3	1.31 (1.02-1.69)	0.03		
Classification of intervention	**32**			**77%**	**0.02**
Moderate	15	1 .14 (0.87-1.55)	0.3		
Serious	17	1.19 (1.08-1.33)	0.005		
Deviation from intended intervention	**32**			**76.7%**	**0.003**
Moderate	5	1.29 (1.04-1.61)	0.02		
NI	27	1.1 (1-1.2)	0.03		
Missing data	**32**			**75.7%**	**0.002**
Moderate	25	1.16 (1.06-1.27)	0.002		
Serious	7	1.02 (0.85-1.23)	0.85		
Reporting outcome	**32**			**76.6%**	**0.02**
Moderate	18	1.11 (0.99-1.25)	0.05		
Serious	14	1.14 (1.01-1.3)	0.03		

KEY= 95% CI: 95% confidence interval; NI: no information; I^2 = heterogeneity

Table 2.8: Moderator analysis of the clinical characteristics of the participants for the overall survival meta-analysis

Tested variable	Number of effect sizes	Estimated poled estimate (95% CI)	P	I^2(%)
Age group	**32**			**75.7%**
Elderly	5	1.04 (0.85-1.27)	0.68	
Non-elderly	27	1.15 (1.04-1.26)	0.003	
Gender	**32**			**75.7%**
Male gender		0.48 (0.15-1.51)	0.21	
Female gender		2 (0.66- 6.5)	0.21	
Performance status				
PS 0-1	19	1.04 (0.55-1.98)	0.9	59.5%
PS ≥2	19	4.26 (0.05-9.07)	0.79	59.5%
RAS status				
RAS-wild	9	1.21 (0.44-2.7)	0.85	87.1%
RAS-mutant	9	0.7 (0.29-1.66)	0.42	85.4%
Primary tumour location				
Primary colon	17	1.13 (0.35-3.7)	0.83	75.8%
Primary rectum	17	0.87 (0.17-4.3)	0.86	75.9%
Number of metastatic sites				
0-1	8	0.1 (0.03-0.38)	0.006	55.5%
≥2	8	3.4 (0.99-11.4)	0.05	68.6%
Primary tumour resection	13	0.9 (0.45-1.82)	0.41	72.7%
Localisation of metastases				
Liver metastases	18	0.67 (0.23-1.97)	0.47	69%
Lung metastases	17	1.73 (0.49-5.8)	0.4	70.5%
Peritoneum metastases	14	4 (0.66-24.7)	0.12	74.7%

KEY= 95% CI: 95% confidence interval; NI: no information; I^2 = heterogeneity; PS: performance status.

Publication bias, outliers, and influential cases of overall survival meta-analysis

The funnel plot in Figure 2.8 shows that most of the studies are dispersed at the middle and top part of the plot (top part where a smaller standard error and larger sample size). Very few studies were located at the lower part of the plot. The visual inspection shows that the effect sizes are not evenly distributed around the overall estimate. As a result, the distribution of the studies does not resemble a funnel shape indicating a possible presence of publication bias or small study bias. Nevertheless, the asymmetry in the funnel plot was tested by performing egger's test which shows no significant possibility for the presence of asymmetry in the funnel plot (P =0.785).

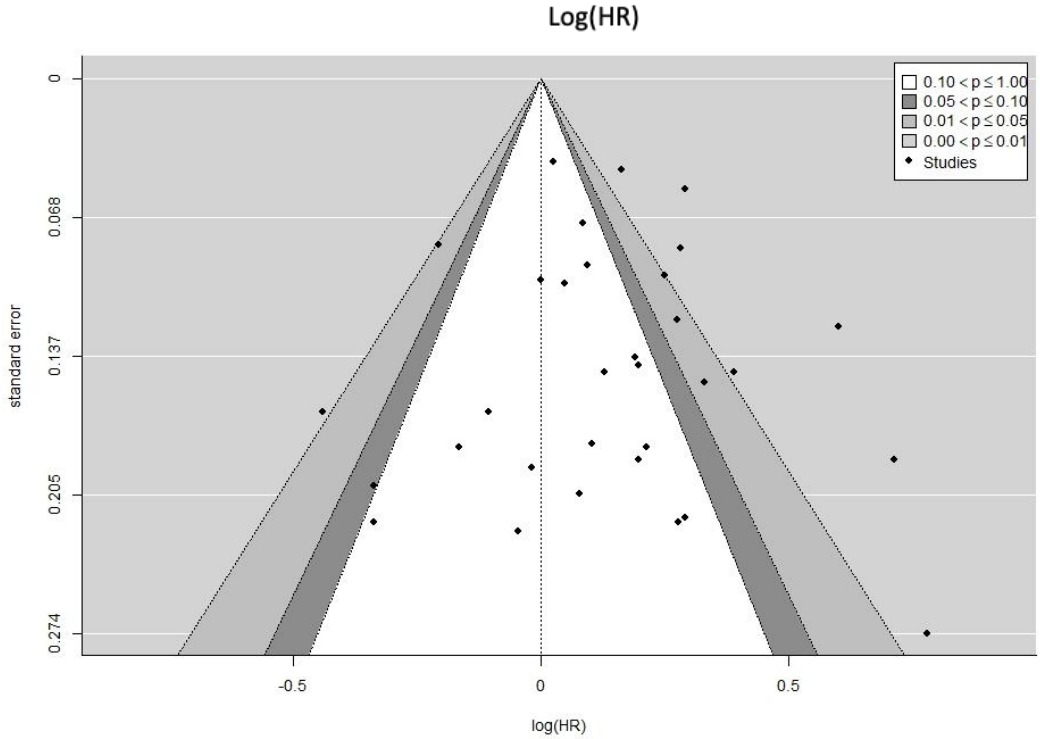


Figure 2.8: Funnel plot of the overall survival associated with the use of first-line mCRC SACTs.

Moreover, the model was tested for the presence of outliers and influential cases. A total of 5 out of 31 effect sizes were deemed to be outliers (Razenberg et al., 2016, Stein et al., 2015b, Suenaga et al., 2014, Zhou et al., 2021). A histogram was plotted to inspect the distribution of the outliers around the overall estimate as shown in Figure 2.9. Furthermore, to assess if any of the effect sizes would be considered as an influential case in the model, a cook's distance value was measured, and it was plotted as depicted in Figure 2.10. It shows that 3

of the effect sizes had a distance value exceeding 0.13. The three influential cases correspond to Razenberg et al., Zhou et al. and, Stein et al studies, (Razenberg et al., 2016, Stein et al., 2015b, Zhou et al., 2021).

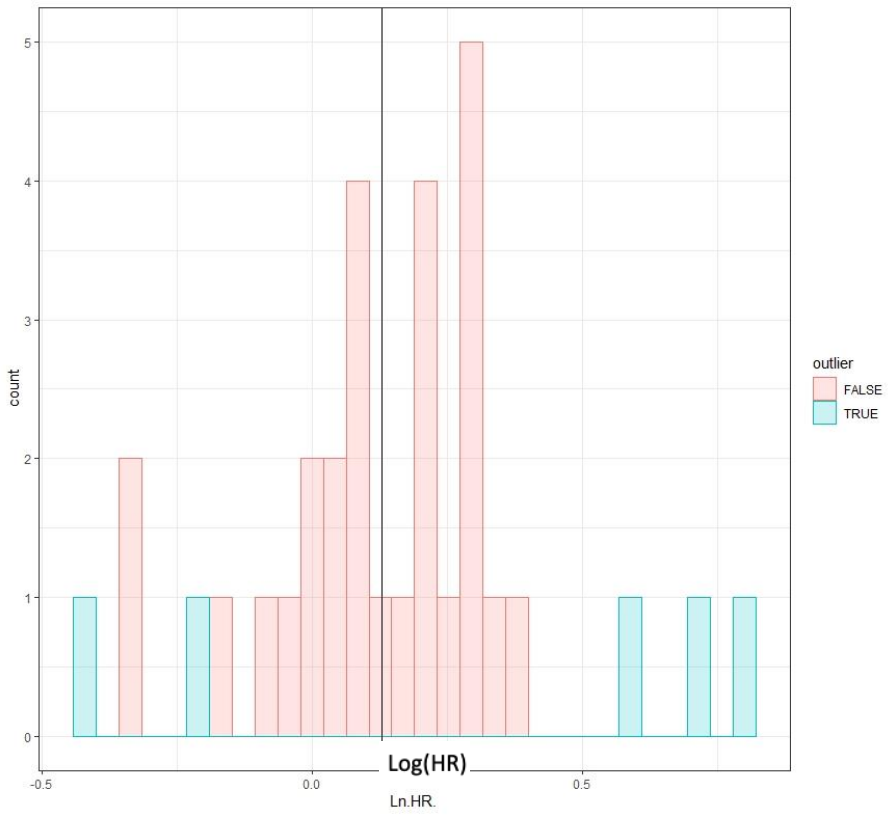


Figure 2.9: Histogram of overall survival data for outliers' distribution.

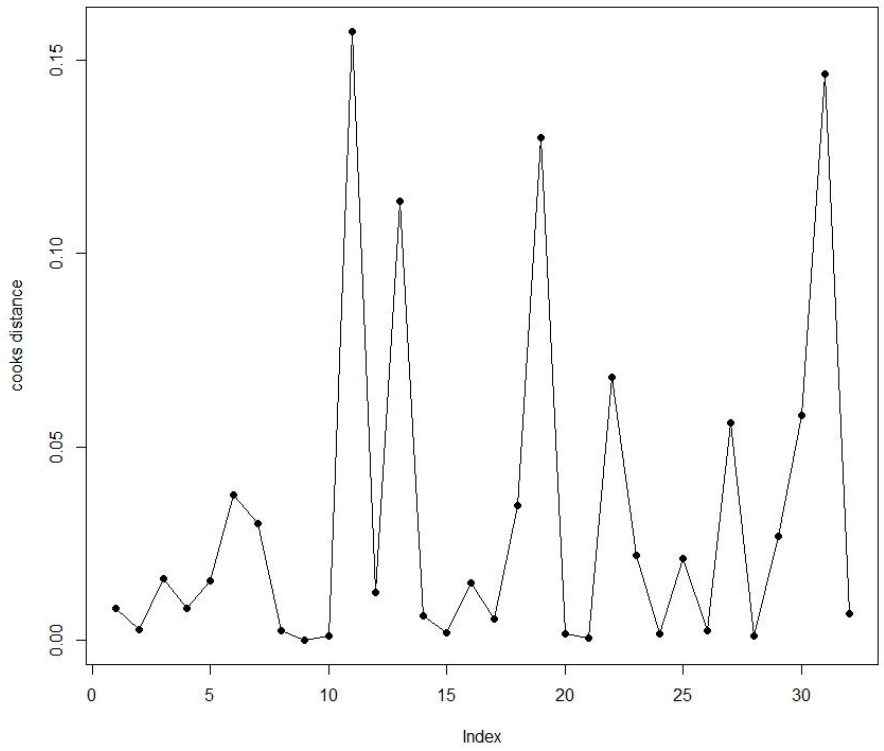


Figure 2.10: Influential observations of overall survival data by Cook's distance.

To correct for potential publication bias, the trim and-fill method was performed. In light of the substantial heterogeneity in this MA (I^2 = 76.2%), two trim and-fill analyses were conducted: one with all studies and the second with sensitivity analysis in which the identified outliers were excluded. For the first analysis, one smaller effect size with a relatively high effect was filled (HR 0.59, 95% CI (0.34-1)). The overall pooled estimate for the corrected HR was 1.13, which is very close to the originally obtained overall pooled HR of 1.14. Also, the 95% CI of the filled funnel plot (1.03-1.24) was overlapping with the one corresponding to the original MA (1.05-1.24). For the second analysis, which included eliminating the identified outliers, one small effect size with a relatively high effect was also filled (HR 1.84, 95% CI (1.2-2.8)). Similar to the first analysis, the overall pooled estimate for the corrected HR was 1.15, which is very close to the HR obtained initially overall pooled HR of 1.14. also, the 95% CI of the trimmed funnel plot with the outliers removed (1.08-1.23) was overlapping with the one corresponding to the original MA (1.05-1.24). Figure 2.11 and Figure 2.12 represent the funnel plots after applying the fill-and-trim methods for both

analyses. In these funnel plots, the imputed studies are represented by non-filled colour circles.

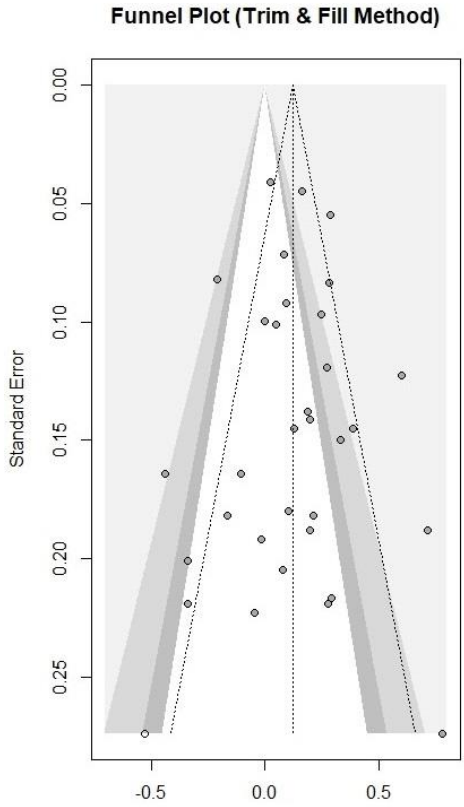


Figure 2.11 Trim and-fill funnel plot for all included studies in the overall survival meta-analysis.

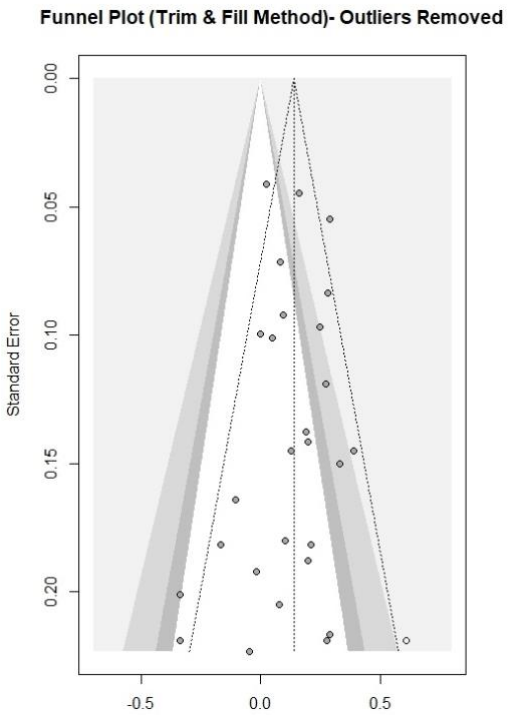


Figure 2.12 Trim and-fill funnel plot for studies included in overall survival meta-analysis after eliminating outliers.

2.3.6.2 Progression-free survival meta-analysis

A total of 20 studies reported PFS of first-line mCRC SACTs and were included in the PFS MA. (Artac et al., 2016, Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cainap et al., 2021, Cheng and Song, 2015, Degirmencioglu S, 2019, Duran et al., 2014, Hammerman et al., 2015, Houts et al., 2019a, Houts et al., 2019b, Khakoo et al., 2019, Kocakova et al., 2015, Lee et al., 2017, Ocvirk et al., 2011, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014, Zhou et al., 2021). The included studies contributed toward 21 effect sizes with a total of 12628 participants. Both Khakoo et al., 2019 and Marschner et al., 2015 have reported the PFS for the included SACTs but were not included in this MA because the KM curves for the comparison between bevacizumb+ FOLFIRI versus bevacizumab+ FOLFOX for the former study were too tangled hence the reconstruction of the KM curve to obtain the effect size was not possible (Khakoo et al., 2019), while, Marschner et al., 2015 reported only the median PFS for the corresponding SACTs without reporting the effect size or KM curve for the comparison (Marschner et al., 2015). Hence, these two studies were excluded from the PFS MA.

Overall estimate and heterogeneity of the progression-free survival meta-analysis

The overall pooled estimate for the PFS MA was 1.19 (1.08- 1.3). Subgroup analysis shows that treatment comparisons included in group 2 (bevacizumab+ CT vs. CT) and group 3 (bevacizumab+ CT1 versus bevacizumab+ CT2) show a statistical significant difference with a pooled estimate of 1.36 (1.25-1.48) for the former group indicating that patients who receive chemotherapy only are 36% at more risk of developing progression or death than patients who receive a combination of bevacizumab+ CT, and 1.17 (1.06- 1.29) for the latter group comparing different combinations of chemotherapy with bevacizumab. On the other hand, treatment comparisons included in group 4 (cetuximab+ CT vs. bevacizumab+ CT) did not show any statistically significant difference with a pooled estimate 1.06 (0.78- 1.43). Figure 2.13 presents the forest plot of all studies included in the PFS MA grouped based on the compared intervention.

The between-study heterogeneity variance was estimated at T^2= 0.0237 (95% CI: 0.007- 0.094) indicating that some between-study heterogeneity exists in the data, with an I^2 value of 64.4% (95% CI: 40.5- 77.2) indicating high heterogeneity.

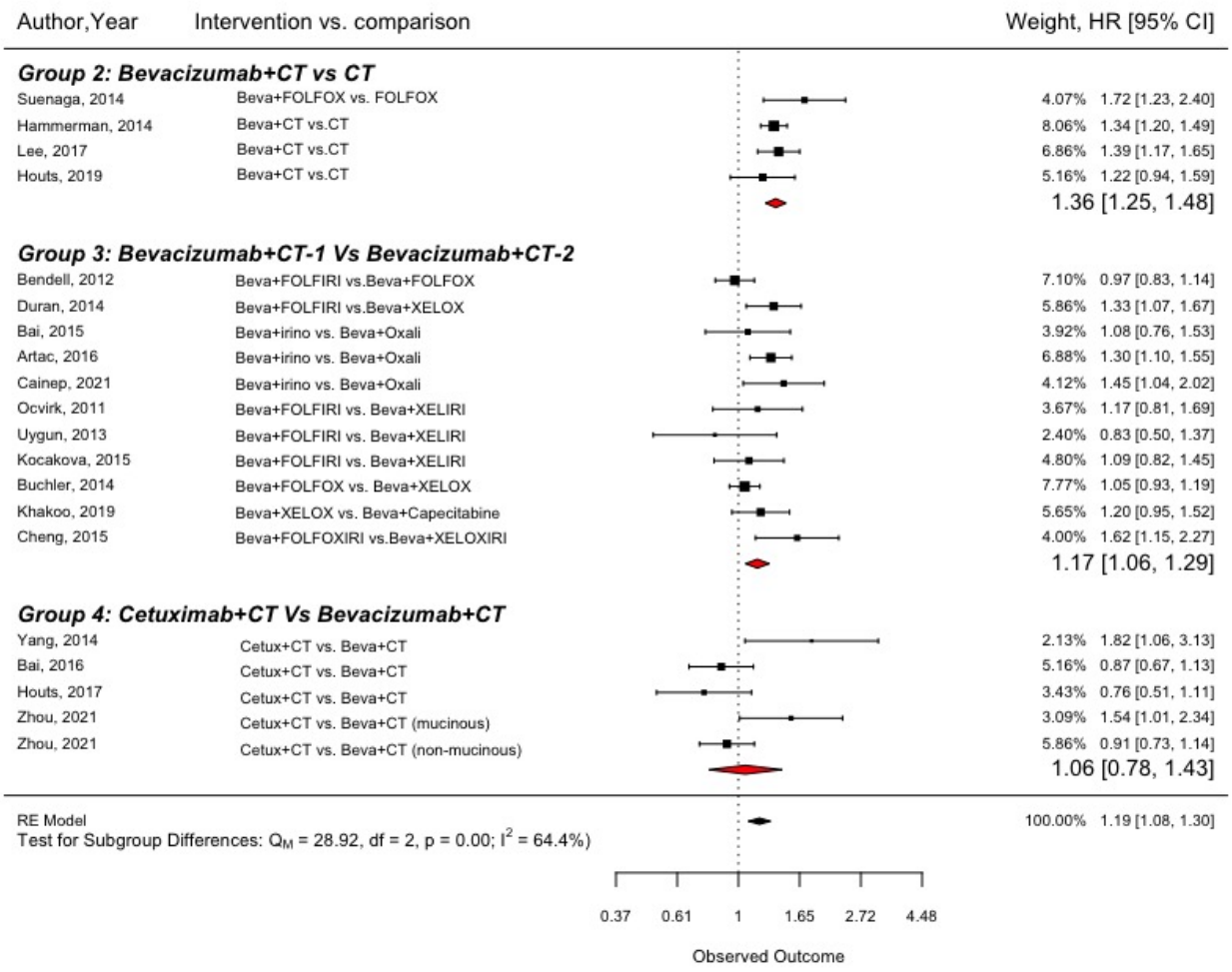


Figure 2.13 Forest plot of progression-free survival of first-line SACTs for mCRC.

Figure 2.14 shows a further analysis that was conducted for group 3 separately to compare the PFS associated with the use of different combinations of chemotherapy with bevacizumab. Only one additional comparison was added from Hammerman et al., 2015 which primarily compared the outcomes of treatment with chemotherapy only to these with a combination of bevacizumab and chemotherapy and performed a subgroup analysis comparing the outcomes of treatment with irinotecan-based chemotherapy + bevacizumab to these with oxaliplatin-based chemotherapy+ bevacizumab (Hammerman et al., 2015) . This subgroup analysis comparison was not added to the main PFS MA to avoid violating the independency of effect size assumption of the MA and hence was added in this separate

analysis. The overall pooled estimate for all treatments was 1.18 (1.08- 1.29) with no statistically significant difference between bevacizumab+ FOLFIRI vs bevacizumab+ XELIRI (pooled estimate 1.06, 95% CI (0.87- 1.31)). However, a statistically significant difference exists between bevacizumab+ irinotecan-based chemotherapy and bevacizumab+ oxaliplatin-based chemotherapy (HR 1.22, 95% CI (1.07- 1.36) where the latter combination was found to be associated with an increased risk of developing disease progression or death.

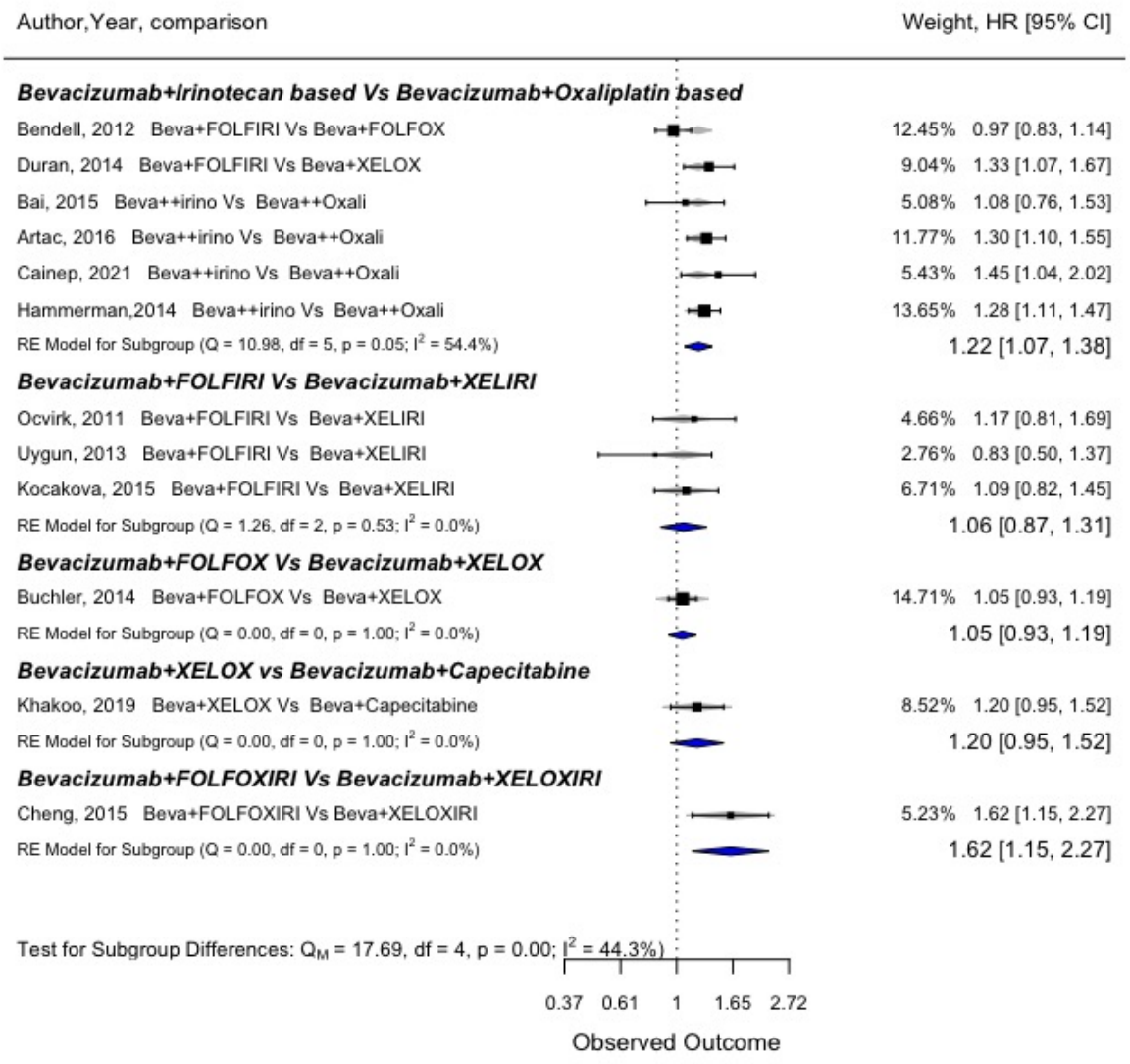


Figure 2.14: Forest plot for progression- free survival of first-line bevacizumab combinations with chemotherapy.

Moderator analysis for progression-free survival meta-analysis

For the PFS MA, moderator analysis included the studies' characteristics and the participants' clinical characteristics. However, the studies' characteristics did not include the risk of bias as it was measured based on the main outcome of this MA, which is the overall survival. Also, none of the studies that investigated PFS included an elderly cohort. Hence, the age group was removed from the patients' clinical characteristics table. Both Table 2.9 and Table 2.10 show the moderator analysis for study characteristics variables and the patients' clinical characteristics for the PFS MA, respectively. Of the study characteristics, the method of effect size calculation (direct extraction of the HR vs the curve approach), the study design, the funding source, and the type of treatment settings have all shown to have a statistically significant contribution toward the heterogeneity.

None of the examined study characteristics or the participants' clinical characteristics shows significant influence on the overall pooled estimate of PFS MA.

Table 2.9 Moderator analysis of study characteristics variables for the progression-free survival meta-analysis.

Tested variables	Number of effect sizes	Estimated effect (95% CI)	P value	I^2(%)	P subgroup (moderator analysis)
Measurement of effect size	**20**			**63.4%**	**0.007**
Reported (direct)	15	1.16 (1.05- 1.29)	0.004		
Estimated (curve approach)	5	1.28 (1.05- 1.54)	0.01		
Study design	**20**			**64.6%**	**0.002**
Retrospective cohort	15	1.19 (1.05-1.45)	0.005		
Prospective cohort	5	1.22 (1.03- 1.45)	0.024		
Funding source	**19**			**61.3%**	**0.005**
Pharmaceutical company	8	1.13 (0.99- 1.29)	0.07		
Non-pharmaceutical company	3	1.11 (0.86-1.42)	0.41		
Non declared	8	1.24 (1.07-1.43)	0.003		
Type of setting	**20**			66.8%	**0.001**
Single centre	9	1.19 (1.01-1.39)	0.03		
Multicentric	11	1.19 (1.05-1.34)	0.004		
Data source	**18**			**68.8%**	**0.09**
Medical chart	5	1.21 (0.97- 1.53)	0.09		
Electronic medical records	5	1.25 (1.02- 1.52)	0.03		
registry	8	1.1 (0.96-1.27)	0.15		
Study duration	**18**	**1 (0.98-1.03)**		**67.4%**	**0.61**
Study sample	**20**	**1 (0.99-1.01)**		**65.6%**	**0.56**

KEY= 95% CI: 95% confidence interval; NI: no information

Table 2.10. Moderator analysis of the clinical characteristics of the participants for the progression-free survival meta-analysis.

Tested variable	Number of effect sizes	Estimated effect (95% CI)	P	I^2(%)
Gender			**0.052**	**55.9%**
Male gender	20	0.15 (0.68- 1.02)		
Female gender	20	6.8 (0.98- 47)		
Performance status				
PS 0-1	15	0.93 (0.4- 2.1)	0.85	66.8%
PS ≥2	15	1.2 (0.11- 12.5)	0.88	66.3%
RAS status				
RAS-wild	6	0.53 (0.23- 1.22)	0.14	69.7%
RAS-mutant	6	1.3 (0.56- 3)	0.54	78%
Primary tumour location				
Primary colon	10	0.37 (0.03-3.7)	0.5	70.7%
Primary rectum		2.17 (0.22- 21.1)	0.39	68.7%
Number of metastatic sites				
0-1	6	0.27 (0.06- 1.19)	0.08	57%
≥2	6	2.2 (0.73- 6.67)	0.15	61.4%
Primary tumour resection	9	1.2 (0.49- 2.87)	0.68	69.1%
Localisation of metastases				
Liver metastases	14	0.76 (3.5- 2)	0.58	69.3%
Lung metastases	13	1.25 (0.39- 4)	0.71	69.2%
Peritoneum metastases	11	1.23 (0.16- 3.7)	0.75	68.9%

KEY= 95% CI: 95% confidence interval; NI: no information; PS= performance status

Publication bias, outliers, and influential cases of progression-free survival meta-analysis

The funnel plot in Figure 2.15 shows that the effect sizes are distributed evenly at the top and the bottom of the plot and on both sides of the plot. The effect sizes are also distributed within and outside the area of statistical significance, as shown in the contour-enhanced funnel plot, suggesting there is no possibility for a small study effect or publication bias. Furthermore, egger's test shows no significant possibility for the presence of asymmetry in the funnel plot (P =0.69). Additionally, the model was assessed for the presence of outliers, as presented in Figure 2.16, and none of the effect sizes was identified as an outlier. Furthermore, the influential cases were assessed using the cook's distance value which was computed based on the 4/n criterion where n represents the number of effect sizes and found to be 0.2. None of the effect sizes had a distance value exceeding 0.12, as demonstrated in Figure 2.17. Therefore, it can be concluded that none of the effect sizes can be considered an influential case. As a result of that, there was no need to conduct the trim and-fill analysis to correct for publication bias.

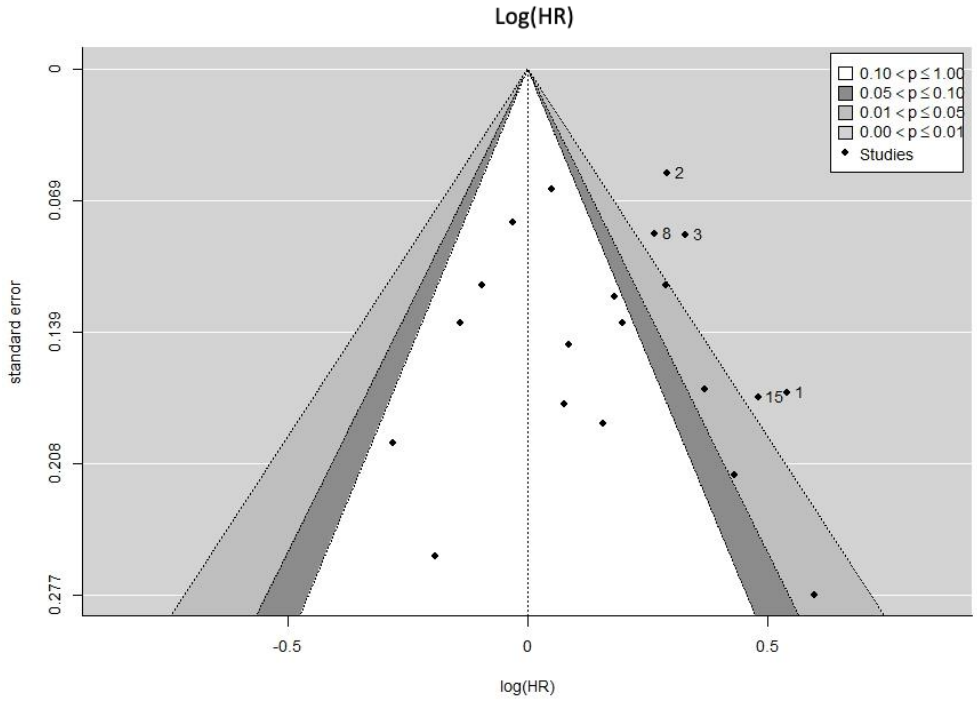


Figure 2.15: Funnel plot of the progression free survival associated with the use of first-line mCRC SACTs.

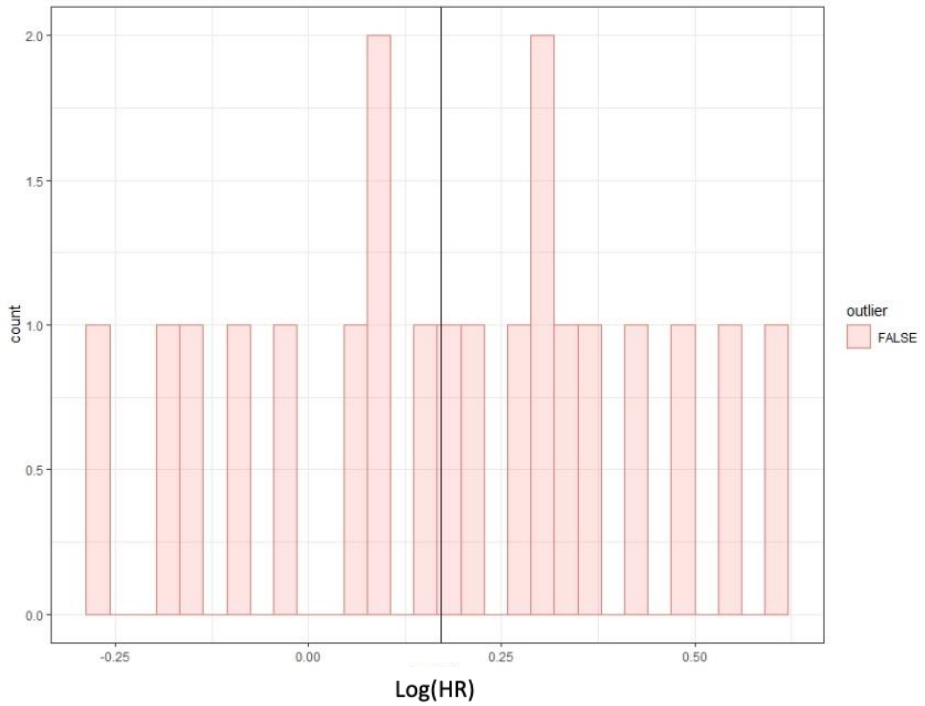


Figure 2.16: Histogram of progression-free survival data for outliers' distribution.

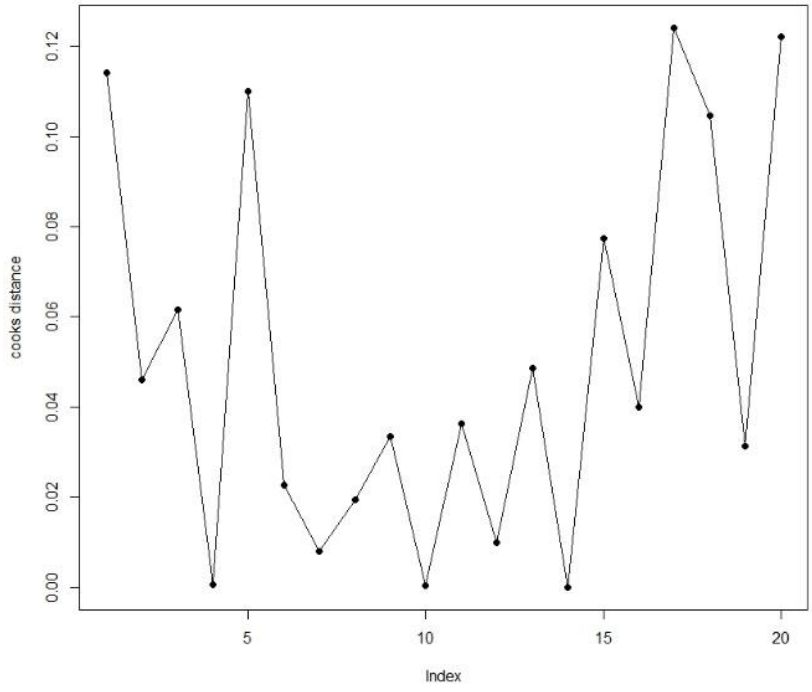


Figure 2.17: Influential observations of progression-free survival data by Cook's distance.

2.3.6.3 Objective response meta-analyses

A total of 15 studies reported objective response of first-line mCRC SACTs and were included in the overall response rate meta-analysis (ORR MA) and the disease control rate meta-analysis (DCR MA). Bai et al., 2016; Bai et al., 2015; Bendell et al., 2012; Buchler et al., 2014; Cheng & Song, 2015; Duran et al., 2014; Kocakova et al., 2015; Marschner et al., 2015; Ocvirk et al., 2011; Stec et al., 2010; Stein et al., 2015; Suenaga et al., 2014; Uygun et al., 2013; Yang et al., 2014; Zhou et al., 2021). The included studies contributed toward 16 effect sizes with a total of 9077 participants for each MA. Each of the two meta-analyses included four groups, namely: 1- different chemotherapies compared to each other (CT-1 vs CT-2) which included two effect sizes; 2- chemotherapy alone compared to combination of chemotherapy and bevacizumab (CT versus bevacizumab+ CT) with only one effect size in this group; 3- various combinations of chemotherapies combined with bevacizumab compared to each other (bevacizumab+ CT-1 versus bevacizumab+ CT-2) including nine effect sizes, and 4- combination of chemotherapy and bevacizumab compared to chemotherapy and cetuximab (bevacizumab+ CT versus cetuximab+ CT) which included four effect sizes. Section 3.6.4. reports the details about the ORR MA, while section 3.6.5 covers the DCR MA.

2.3.6.3.1 Overall response rate (ORR) meta-analysis

Overall estimate and heterogeneity of the overall response rate meta-analyses

The overall pooled estimate for the ORR MA was 1.04 (0.91-1.18). Subgroup analysis shows that treatment comparisons included in group 1 (CT-1 Vs CT-2) and group 3 (Bevacizumab+ CT-1 vs Bevacizumab+ CT-2) did not show a statistically significant difference with a pooled estimate of 0.94 (0.46-1.90) for the former group and 0.82 (0.52- 1.15) for the latter one. Nevertheless, treatment with cetuximab+ CT was associated with a 23% more likelihood of complete or partial response to SACTs compared to bevacizumab + CT (RR 1.23, 95% CI (1.1-1.37)). Also, group 2, which included only one effect size, shows that treatment bevacizumab+ FOLFOX was associated with 35% more likelihood of achieving complete or partial response compared to treatment with FOLFOX alone (RR: 1.35, 95% CI (1.05- 1.75)). The forest plot for the ORR MA is shown in Figure 2.18. The between-study heterogeneity variance was estimated at T^2= 0.048 (95% CI: 0.019- 0.184), indicating that some between-study heterogeneity exists in the data, with an I^2 value of 84% indicating high heterogeneity.

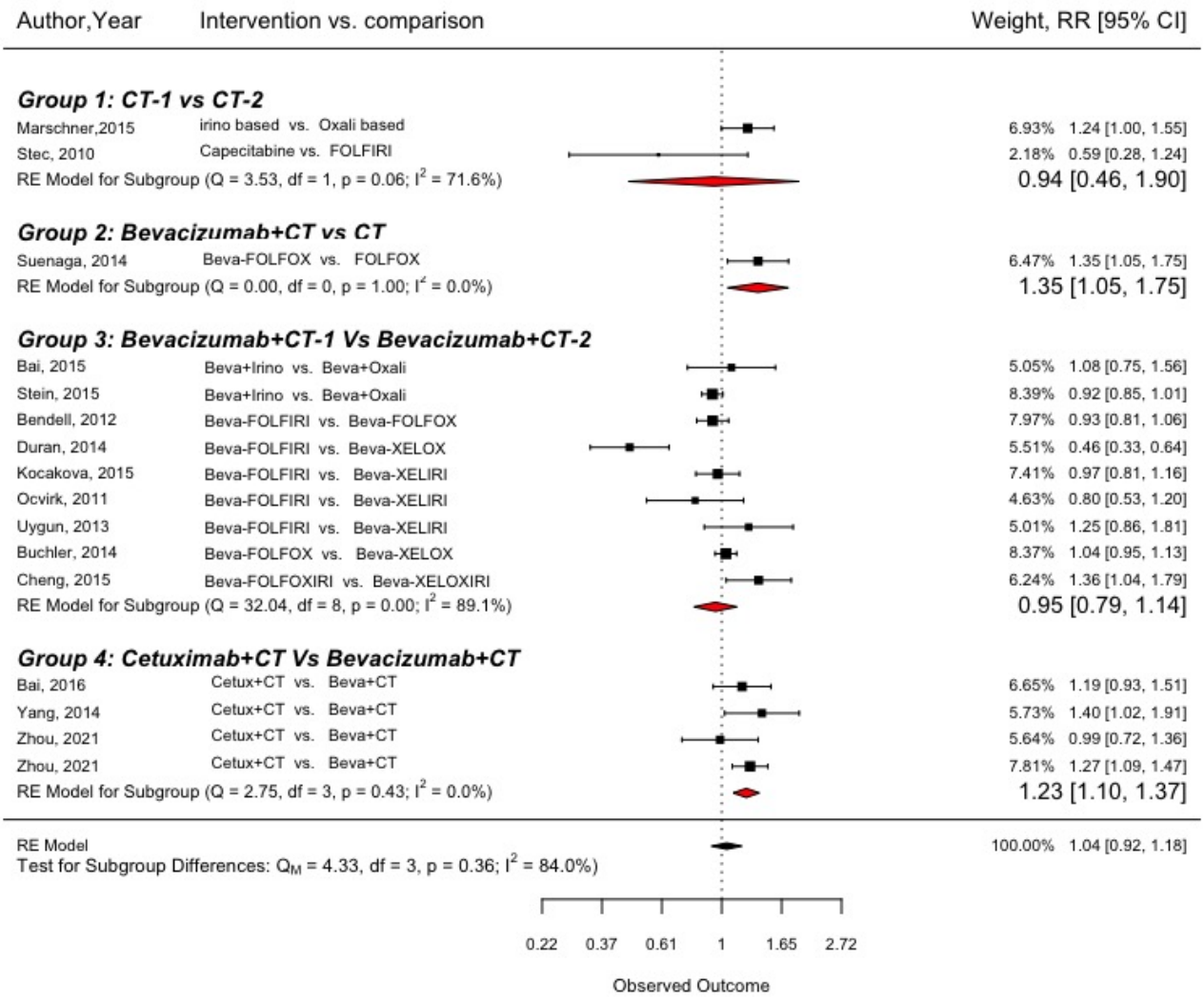


Figure 2.18: Forest plot of the overall response of first-line SACTs for mCRC.

Subsequent analysis for group 3, which compares various combinations of chemotherapy with bevacizumab (bevacizumab+ CT-1 vs. bevacizumab+ CT-2), shows that bevacizumab+ irinotecan-based chemotherapy was associated with less likelihood of achieving partial or complete response compared to bevacizumab+ oxaliplatin-based chemotherapy, yet the difference was not statistically significant (RR 0.82, 95% CI (0.58- 1.15)), as shown in Figure 2.19. Moreover, the analysis shows that no statistically significant difference in ORR exists between bevacizumab+ FOLFIRI vs bevacizumab+ XELIRI (RR 0.98, 95% CI (0.84- 1.14)). Within this separate subgroup analysis, only treatment with bevacizumab+ FOLFOIXRI was associated with 36% more likelihood of attaining complete or partial response compared to bevacizumab+ XELOXIRI, and the difference was statistically significant. However, only one study compared these two treatments against each other.

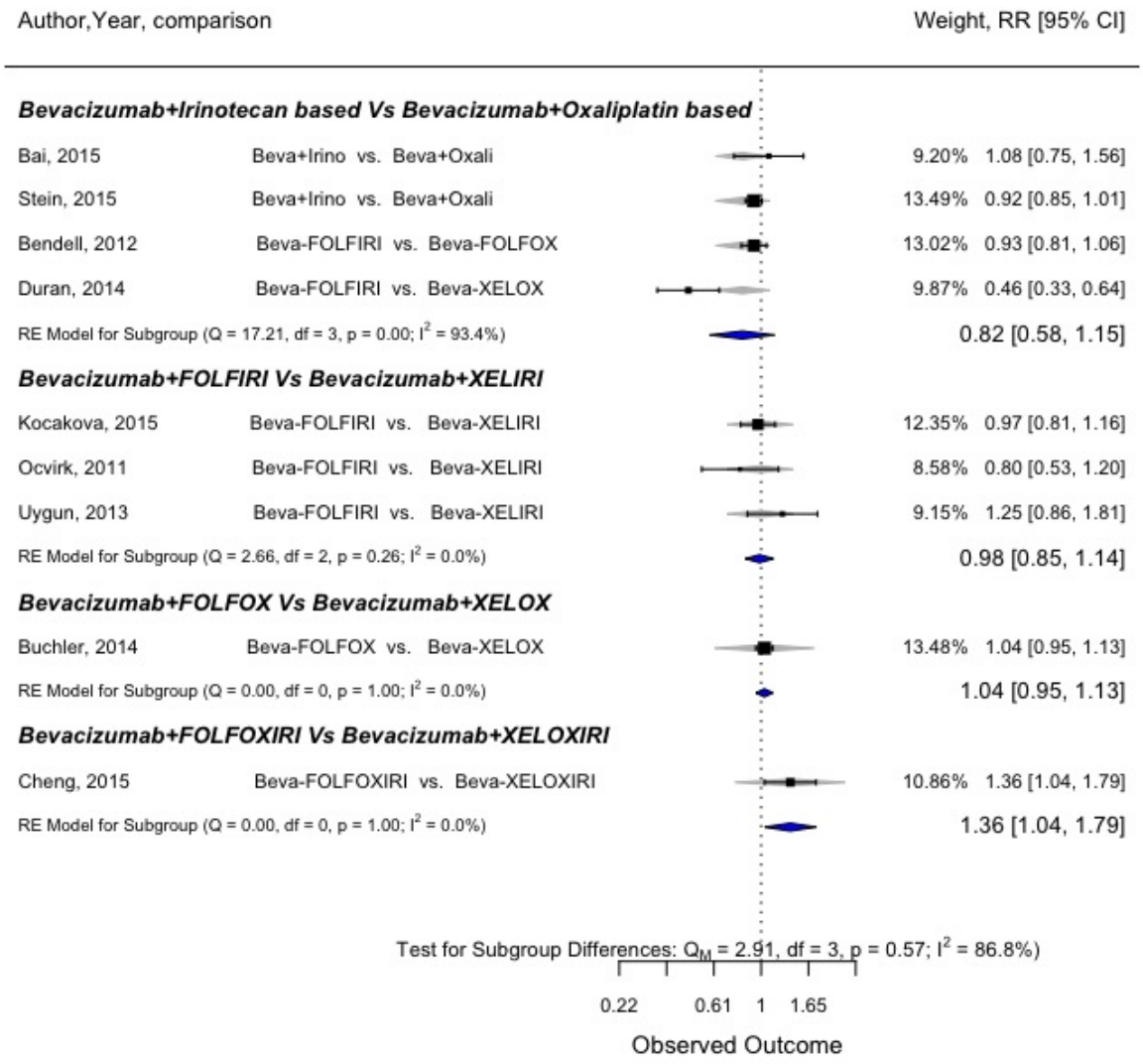


Figure 2.19. Forest plot for the overall response rate of first-line bevacizumab combinations with chemotherapy.

Publication bias, outliers, and influential cases of overall response rate meta-analysis

Figure 2.20 depicts the funnel plot for the ORR MA. It shows that most of the studies are distributed in the middle and top parts of the plot (less standard error, more sample size), with only one study located at the bottom of the plot. Moreover, most of the effect sizes are located in the non-significance area (P > 0.05). This funnel plot does not resemble a funnel shape suggesting a possible presence of publication bias or small study effect. However, the asymmetry of the plot was further tested through egger's test which shows no significant

possibility for the presence of funnel asymmetry in the funnel plot (p= 0.33). Additionally, the model was tested for the presence of outliers and influential cases. One effect size was identified as an outlier (Duran et al., 2014). A histogram was plotted to inspect the distribution of the outliers around the overall estimate as shown in Figure 2.21. Furthermore, to assess if any of the effect sizes would be considered as an influential case in the model, a cook's distance value was measured, and it was plotted as depicted in Figure 2.22. It shows that one effect size had a distance value exceeding 0.25 based on the 4/n criterion where n is considered as the number of effect sizes (4/16). Similar to the identified outlier, the effect size that was deemed to be influential corresponded to (Duran et al., 2014).

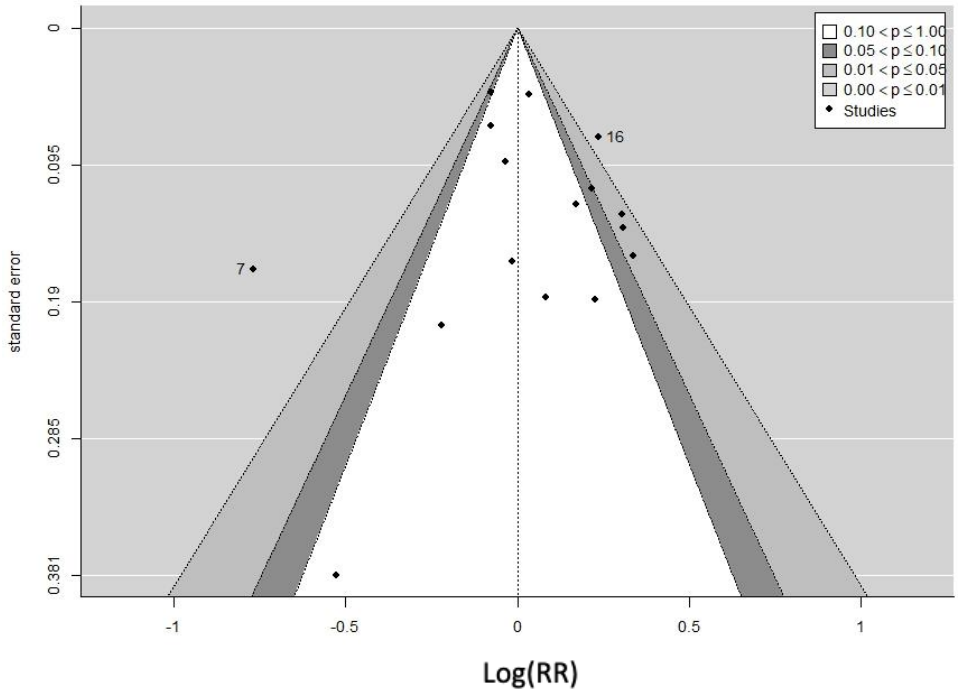


Figure 2.20: Funnel plot of the overall response rate associated with the use of first-line mCRC SACTs.

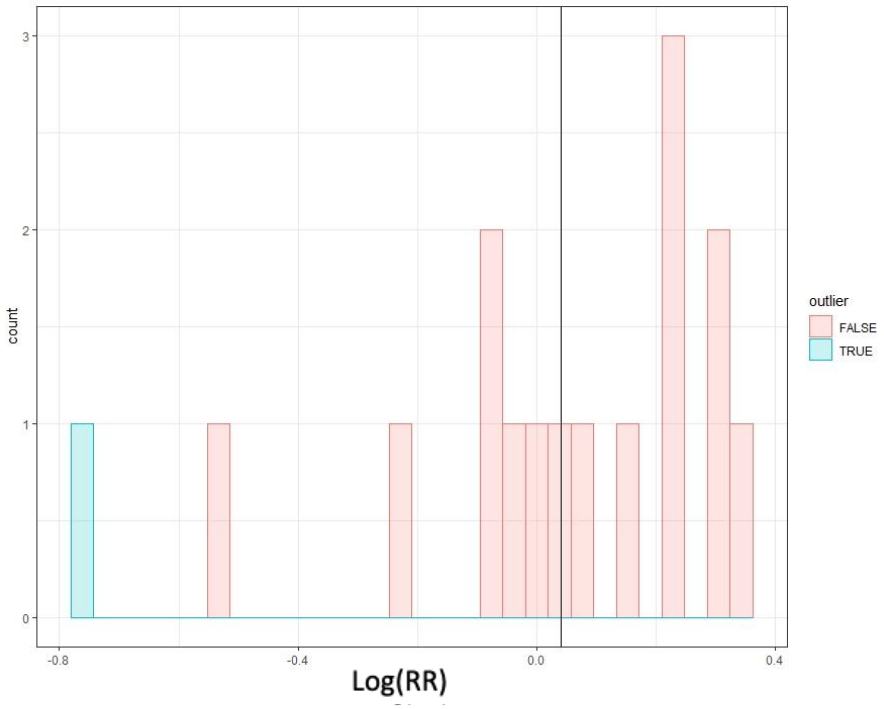


Figure 2.21: Histogram of overall response rate data for outliers' distribution.

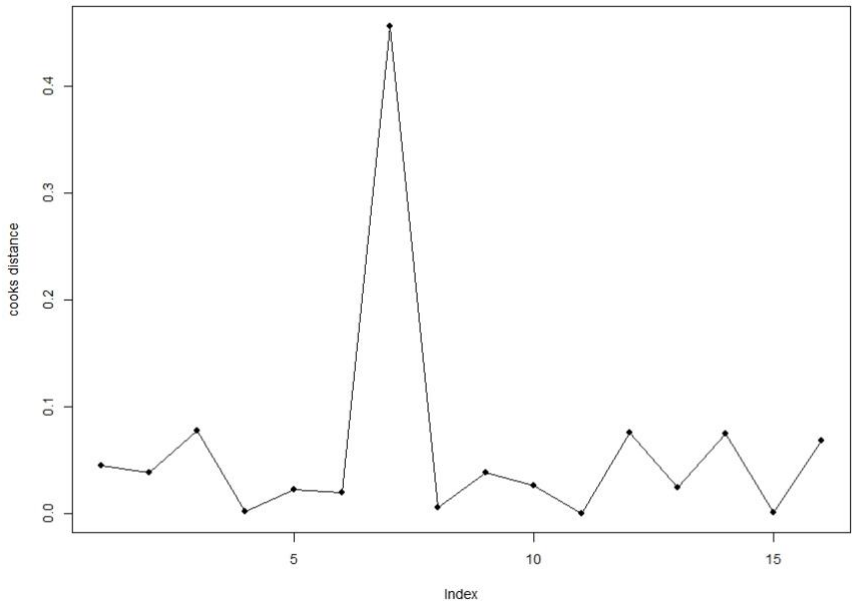


Figure 2.22: Influential observations of overall response rate data by Cook's distance.

Trim-and-fill method was used to correct for the potentiality of publication bias. One effect size was filled (RR 0.74, 95% CI (0.54-1.01)) resulting in an overall pooled estimate for the corrected overall pooled RR of 1.03 that is very close to the overall pooled RR before filling the effect size of 1.04. Furthermore, the 95% CI of the filled funnel plot (0.88- 1.18) was overlapping with the one before adding the effect size (0.92- 1.18). A second trim-and-fill analysis was carried out after eliminating the effect size that was considered an influential case and an outlier, and two effect sizes were filled (RR 0.77, 95% CI (0.59-1.01). Figure 2.23 and Figure 2.24 represent the funnel plots after applying the fill-and-trim methods for both analyses. In these funnel plots, the imputed studies are represented by non-filled colour circles.

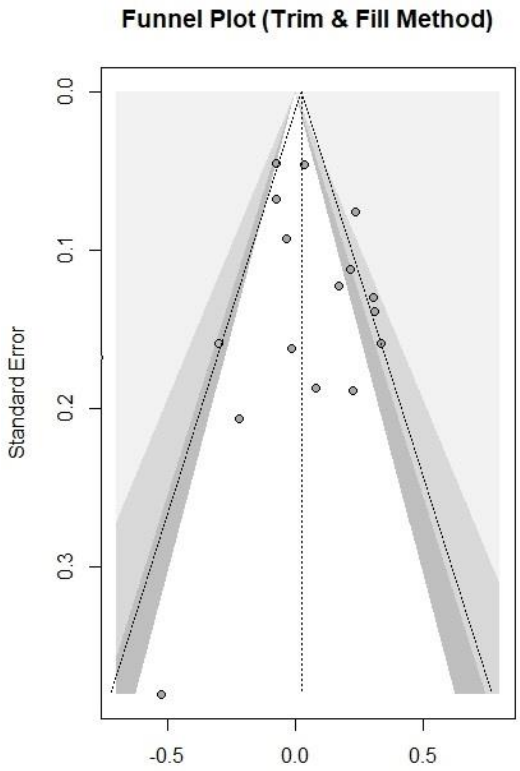


Figure 2.23 Trim and-fill funnel plot for all included studies in the overall response rate meta- analysis.

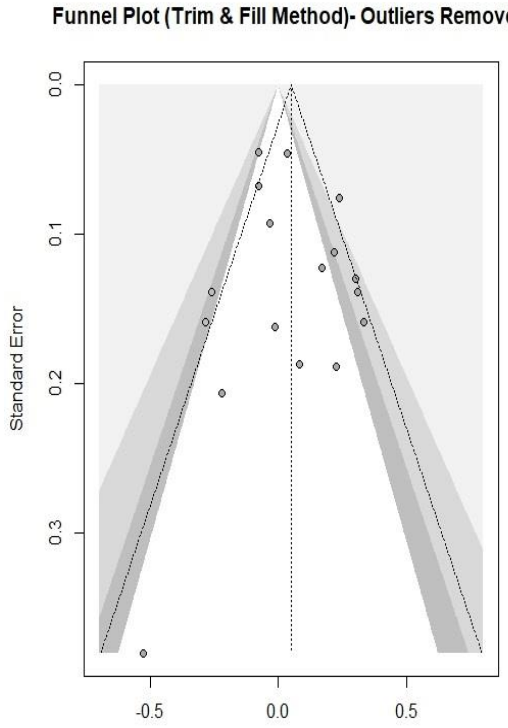


Figure 2.24 Trim and-fill funnel plot for studies included in overall response rate after eliminating outliers.

2.3.6.3.2 Disease control rate (DCR) meta-analysis

Overall estimate and heterogeneity of the disease control rate meta-analysis

The overall pooled estimate for the DCR MA was 0.98 (0.95-1.02). Subgroup analysis shows that treatment comparisons included in group 1 (CT-1 Vs. CT-2) and group 4 (cetuximab+ CT vs bevacizumab+ CT) did not show a statistically significant difference with a pooled estimate of 1 (0.86-1.17) for the former group and 1.02 (0.94-1.1) for the latter one. Nevertheless, group 2 which included only one effect size shows that treatment with bevacizumab+ FOLFOX was associated with 11% more likelihood of achieving complete response, partial response, or stable disease compared to treatment with FOLFOX alone (RR: 1.11, 95% CI (1.03- 1.20)). Also, various combinations of chemotherapy with bevacizumab resulted in a statistically significant pooled estimate as explained in the separate analysis for group 3 (RR 0.95, 95% CI (0.9- 0.99). The forest plot for the ORR MA is shown in Figure 2.25.

The between-study heterogeneity variance was estimated at T^2= 0.0058 (95% CI:0.002-0.017) indicating that some between-study heterogeneity exists in the data, with an I^2 value of 82.05% indicating high heterogeneity.

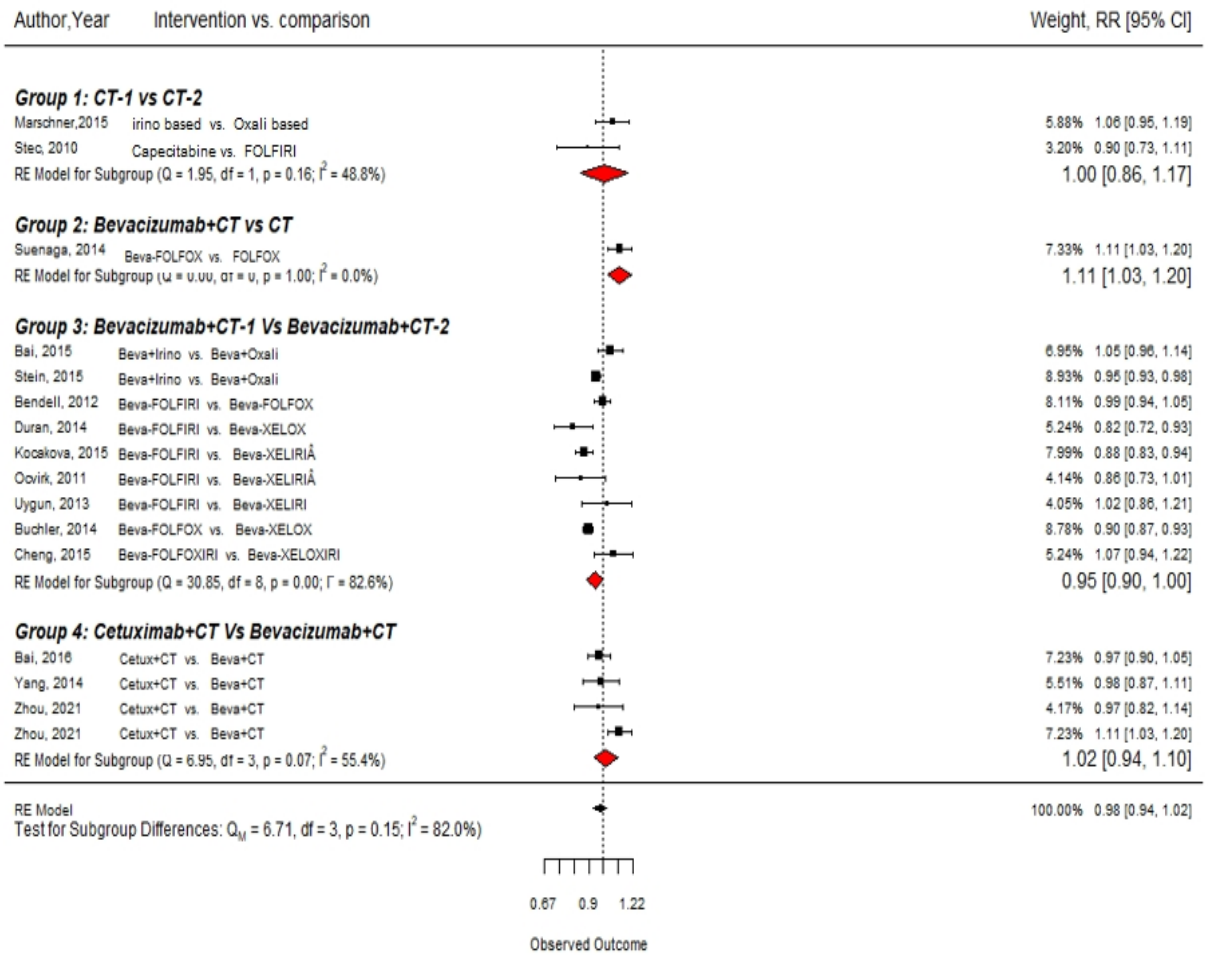


Figure 2.25: Forest plot of disease control rate of first-line SACTs for mCRC.

Further analysis for group 3 comparing various combinations of chemotherapy with bevacizumab (bevacizumab+ CT-1 vs. bevacizumab+ CT-2) shows that no statistically significant difference in DCR exists between bevacizumab+ irinotecan-based chemotherapy vs. bevacizumab+ oxaliplatin-based chemotherapy (RR 0.99, 95% CI (0.89- 1.09)) and between bevacizumab+ FOLFOXIRI vs. bevacizumab+ XELOXIRI (RR 1.07, 95% CI (0.94- 1.22)) (Figure 2.26). However, the analysis shows that treatment with bevacizumab+ FOLFIRI was associated with a statistically significant less likelihood of achieving complete response, partial response, or stable disease compared to bevacizumab+ XELIRI (RR 0.90, 95% CI (0.87-0.93)). Furthermore, despite that only one effect size existed to compare the DCR of

bevacizumab+ FOLFOX vs. bevacizumab+ XELOX, it was shown that treatment with bevacizumab+ FOLFOX was associated with a statistically significant less likelihood of attaining complete response, partial response, or stable disease compared to bevacizumab+ XELOX (RR 0.9, 95% CI (0.87- 0.93)).

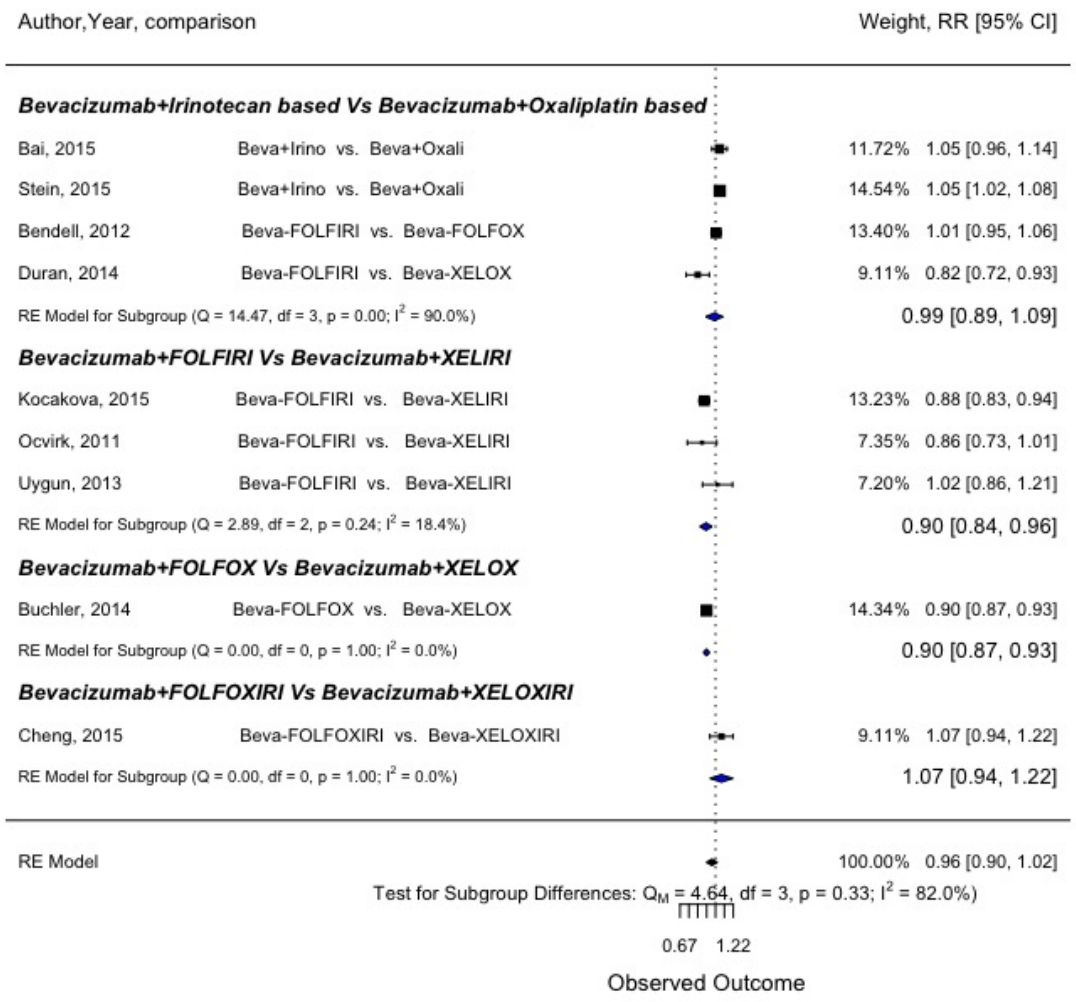


Figure 2.26 Forest plot for the disease control rate of first-line bevacizumab combinations with chemotherapy.

Publication bias, outliers, and influential cases of disease control rate meta-analysis

The funnel plot in Figure 2.27 shows that the effect sizes corresponding to the DCR MA are distributed evenly at the top and the bottom of the plot and on both sides of the plot. The effect sizes are also distributed within, and outside area of statistical significance as shown in the contour enhanced funnel plot suggesting no possibility for small study effect or publication bias. Furthermore, egger's test was performed and shows no significant possibility for the presence of asymmetry in the funnel plot (P =0.85). Additionally, the model was tested for the presence of outliers and influential cases. Five effect sizes were identified as outliers (Buchler et al., 2014, Duran et al., 2014, Kocakova et al., 2015, Suenaga et al., 2014, Zhou et al., 2021). A histogram was plotted to inspect the distribution of the outliers around the overall estimate as shown in Figure 2.28. Furthermore, to assess if any of the effect sizes would be considered as an influential case in the model, a cook's distance value was measured, and it was plotted as depicted in Figure 2.29. It shows that 4 effect sizes ((Duran et al., 2014, Kocakova et al., 2015, Suenaga et al., 2014, Zhou et al., 2021) had a distance value exceeding 0.25 based on the 4/n criterion where n is considered as the number of effect sizes (4/16).

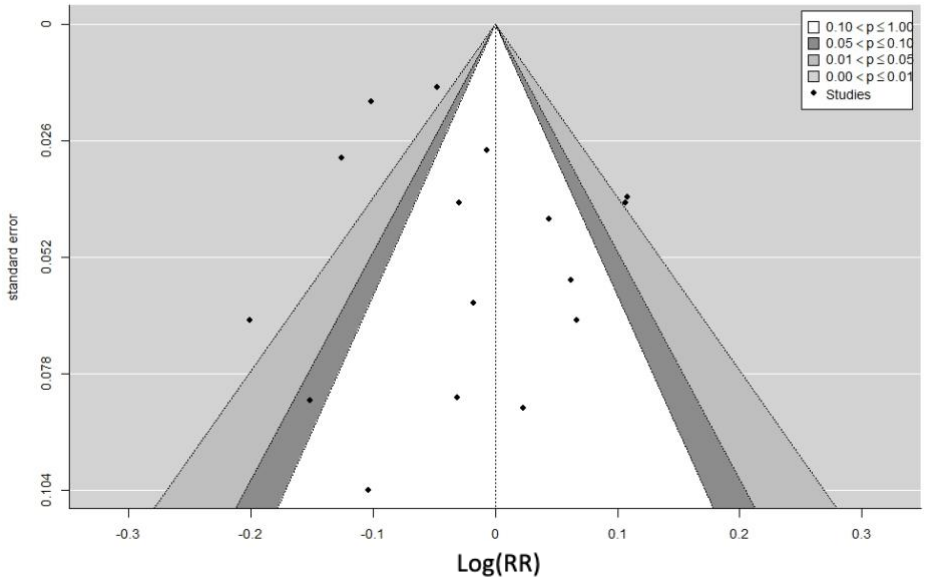


Figure 2.27: Funnel plot of the disease control rate associated with the use of first-line mCRC SACTs.

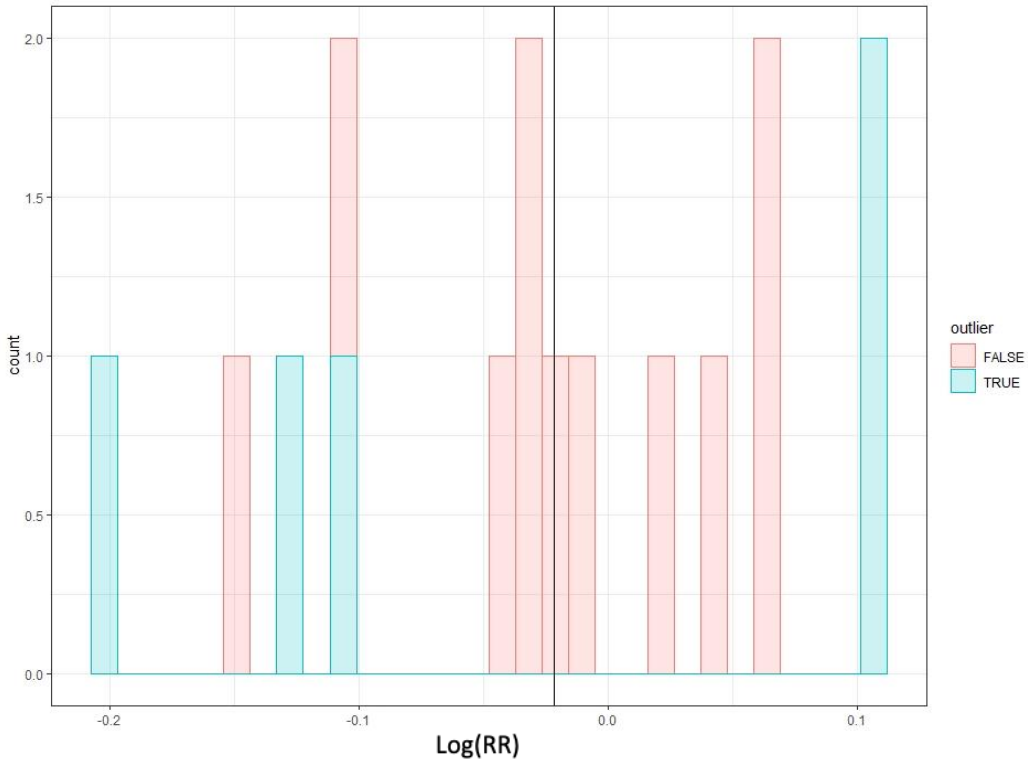


Figure 2.28: Histogram of disease control rate data for outliers' distribution.

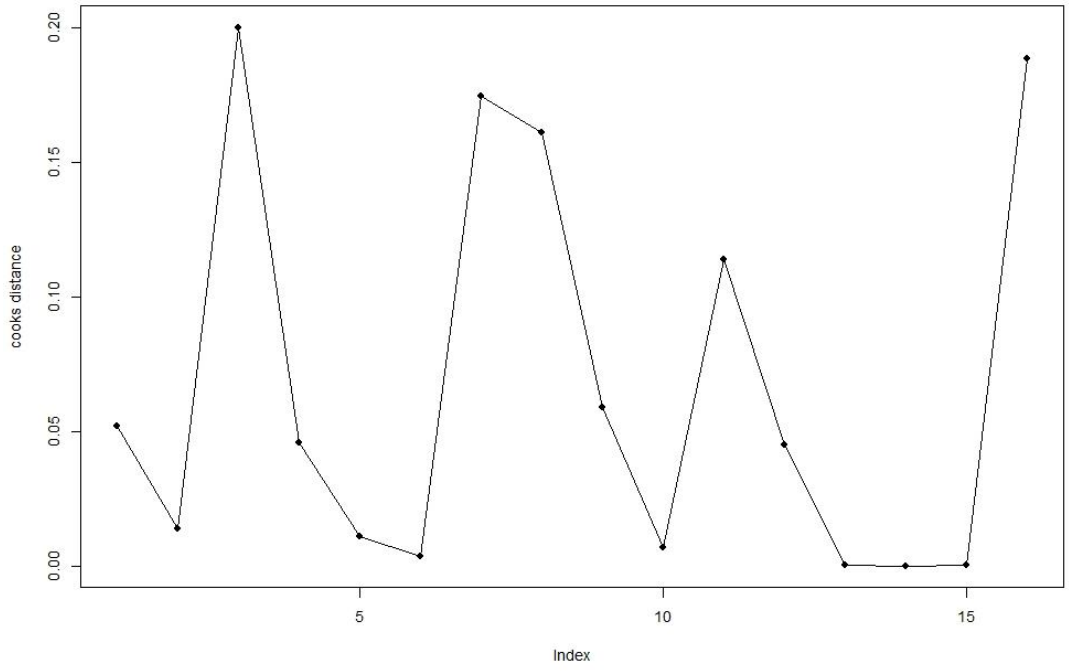


Figure 2.29: Influential observations of disease control rate data by Cook's distance.

2.3.6.4 Toxicities meta-analyses

A total of 13 studies reported the toxicities resulting from the use of first-line mCRC SACTs using NCI-CTCAE and were included in the haematological toxicities meta-analysis and the non-haematological toxicities meta-analysis (Bai et al., 2016, Bai et al., 2015, Bendell et al., 2012, Buchler et al., 2014, Cheng and Song, 2015, Duran et al., 2014, Guo et al., 2020, Kocakova et al., 2015, Ocvirk et al., 2011, Stec et al., 2010, Suenaga et al., 2014, Uygun et al., 2013, Yang et al., 2014).

The included studies contributed toward 13 effect sizes with a total of 8220 participants. Each of the two meta-analyses included four groups, namely: 1- different chemotherapies compared to each other (CT-1 vs. CT-2), which included 2 effect sizes; 2- chemotherapy alone compared to a combination of chemotherapy and bevacizumab (CT versus bevacizumab+ CT) with only one effect size in this group; 3- various combinations of chemotherapies combined with bevacizumab compared to each other (bevacizumab+ CT-1 versus bevacizumab+ CT-2) including eight effect sizes, and 4- a combination of chemotherapy and bevacizumab compared to chemotherapy and cetuximab (bevacizumab+ CT versus cetuximab+ CT) which included only two effect sizes.

2.3.6.4.1 Haematological toxicities meta-analysis

As displayed in Figure 2.30, which shows the forest plot for the MA of haematological toxicities of first-line mCRC SACTs, the overall pooled estimate for the haematological toxicities MA was 1.25 (0.88-1.78). Subgroup analysis shows that treatment comparisons included in group 1 (CT-1 Vs. CT-2) did not show a statistically significant differences with a pooled estimate of 0.8 (0.61- 1.05). A similar case holds for group 2, which includes only one effect size, shows that the combination of bevacizumab+ CT is associated with 8% more likelihood of haematological toxicities compared to CT alone, however the association was not statistically significant (RR 1.08, 95% CI (0.79- 1.47)). Furthermore, despite that cetuximab+ CT shows less likelihood for haematological toxicities compared to bevacizumab+ CT (group 4), the association was not statistically significant with an overall pooled estimate of 0.85 (0.62- 1.16). However, different combinations of chemotherapy with bevacizumab

(bevacizumab+CT-1 vs bevacizumab+ CT-2) shows a statistically significant difference with a pooled estimate of 1.69 (1.03- 2.8).

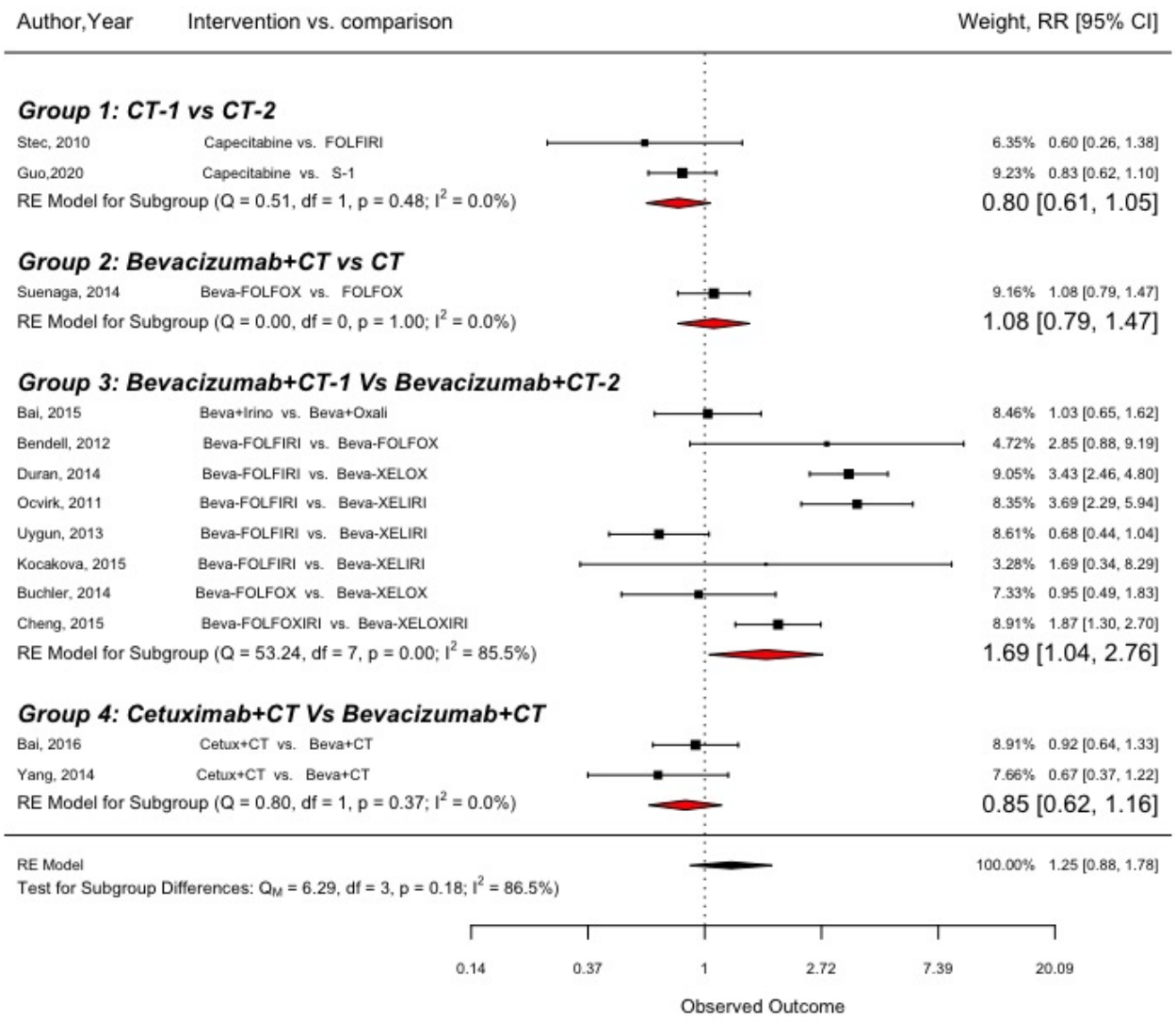


Figure 2.30. Forest plot of haematological toxicities of first-line SACTs for mCRC.

The subgroup analysis performed for group 3 (Figure 2.31) shows that the risk of occurrences of haematological toxicities is two times more in patients who were treated with bevacizumab+ irinotecan-based chemotherapy compared to patients treated with bevacizumab+ oxaliplatin-based chemotherapy. However, the difference was not statistically significant (RR: 2.09, 95% CI (0.92-4.77). Similarly, the analysis shows that treatment with bevacizumab+ FOLFIRI is associated with more likelihood of haematological toxicities, yet not significant (RR 1.60, 95% CI (052-4.93)). Although one effect size existed comparing between bevacizumab+ FOLFOXIRI and bevacizumab+ XELOXIRI, the former combination was associated with a statistically significant more likelihood for haematological toxicities compared to the latter combination (RR 1.87, 95% CI (1.3-2.7)).

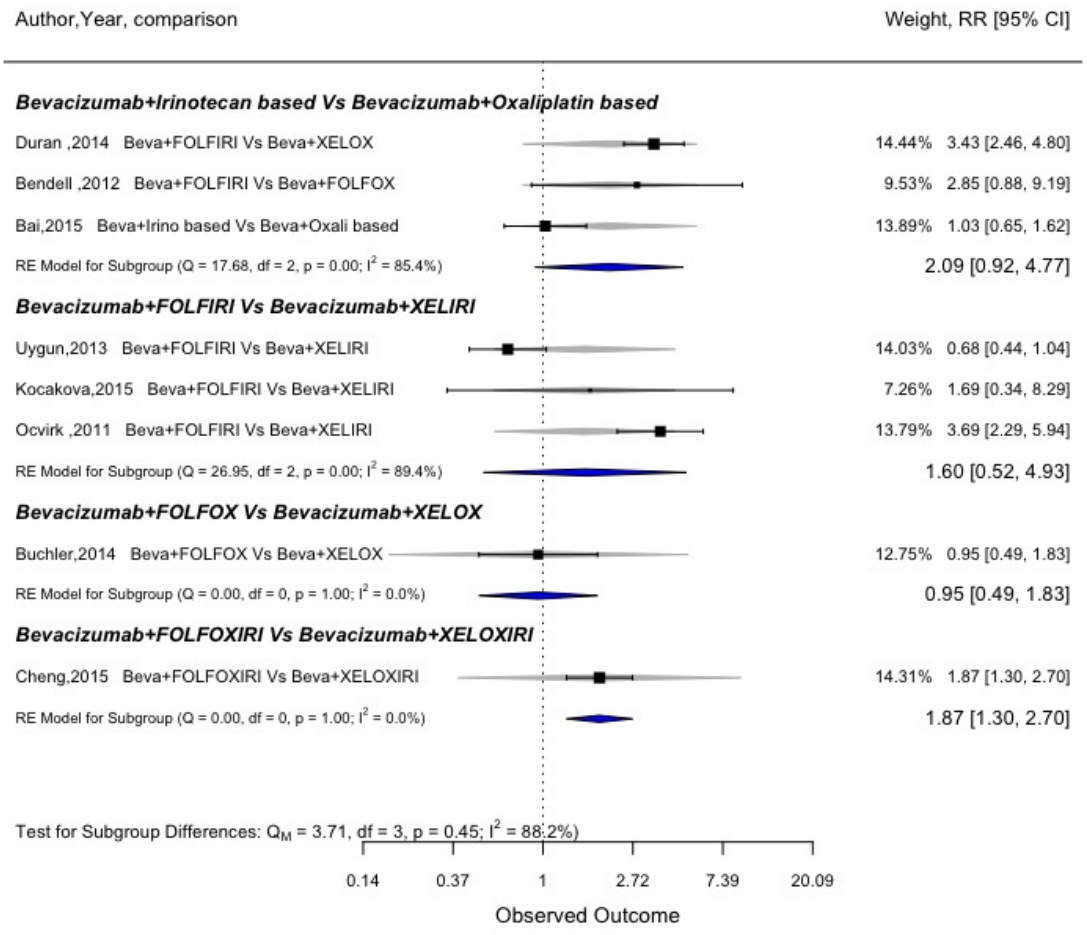


Figure 2.31. Forest plot for the haematological toxicities of first-line bevacizumab combinations with chemotherapy.

Figure 2.32 shows the funnel plot for the haematological toxicities MA. As displayed, most of the studies are distributed in the top part of the plot, with only one study located at the bottom of the plot. Also, most of the effect sizes are located in the non-significance area (P > 0.05), while three studies are located in the significance area. This funnel plot resembles a funnel shape suggesting no possible presence of publication bias or small study effect. This observation was further confirmed by performing egger's test, which shows no significant possibility for the presence of funnel asymmetry in the funnel plot (p= 0.84). Additionally, the model was tested for the presence of outliers (Figure 2.33) and influential cases (Figure 2.34), where two effect sizes were identified as outliers (Duran et al., 2014, Ocvirk et al., 2011). Also, cook's distance value was measured to assess if any of the effect sizes would be considered as an influential case in the model. It shows the two effect sizes corresponding to Duran et al., and 2014; Ocvirk et al., 2011, which have a distance value exceeding 0.35 based on the 4/n criterion where n is considered as the number of effect sizes (4/13). The overall pooled estimate after eliminating the outliers from the model was 0.99 (0.76- 1.29).

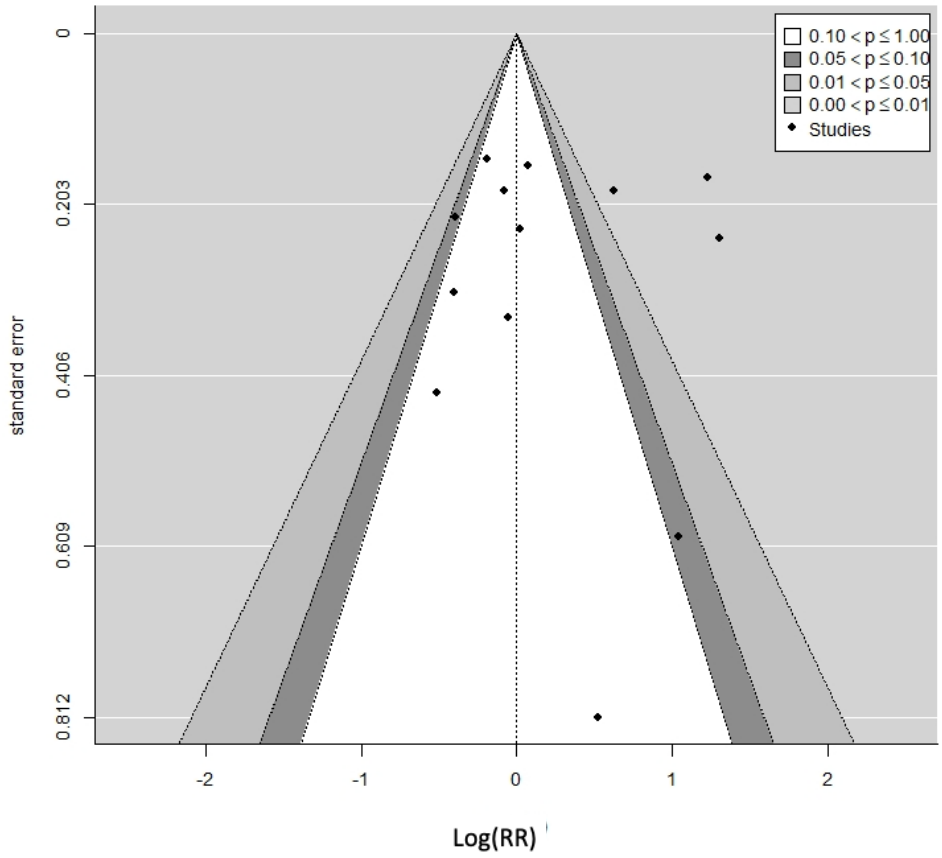


Figure 2.32: Funnel plot of the haematological toxicities associated with the use of first-line mCRC SACTs.

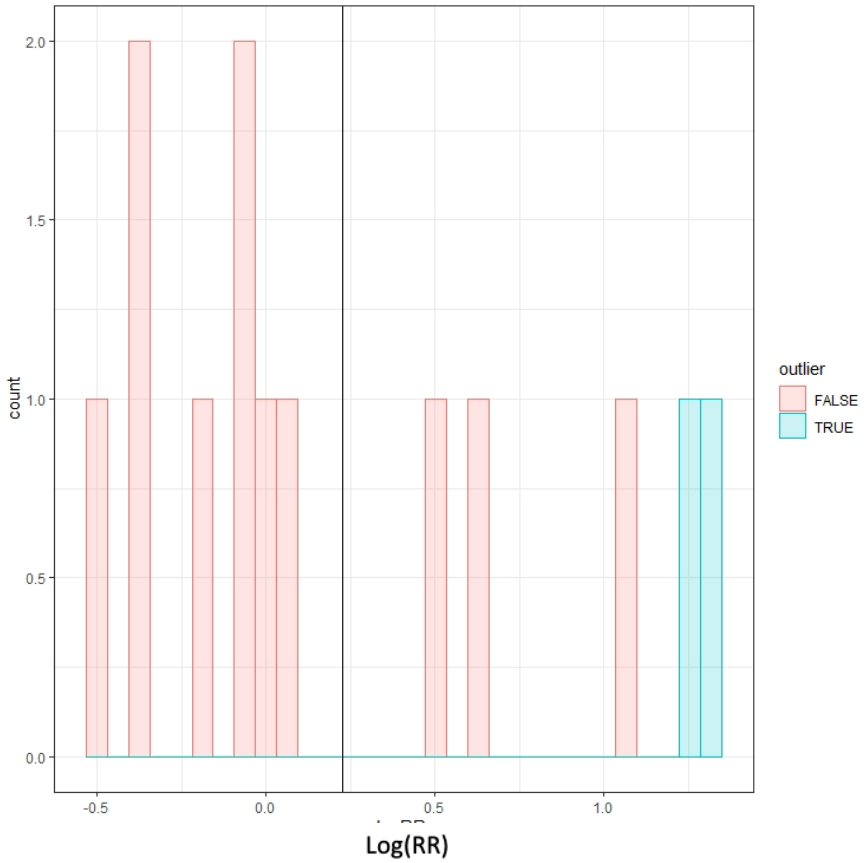


Figure 2.33: Histogram of haematological toxicity data for outliers' distribution.

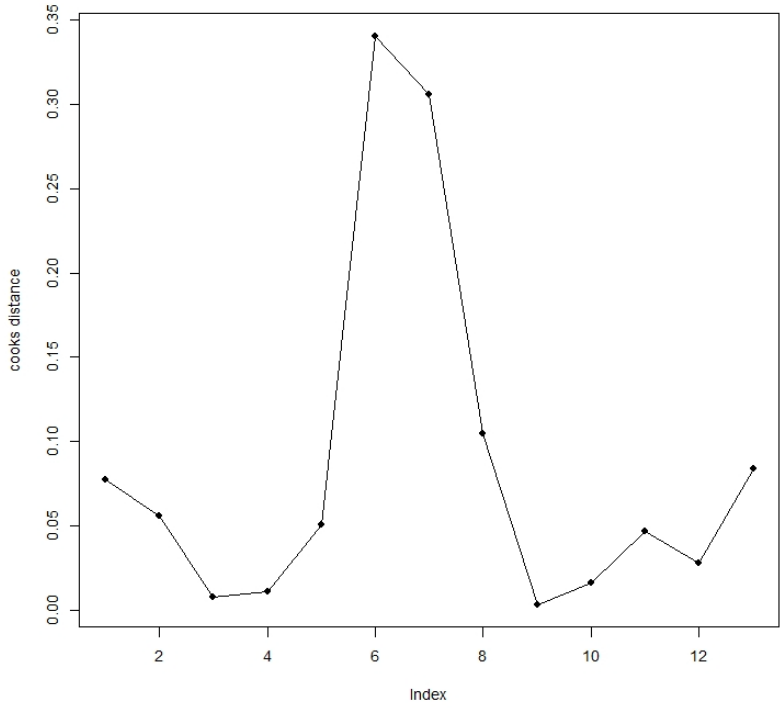


Figure 2.34: Influential observations of the haematological toxicity data by Cook's distance.

2.3.6.4.2 Non-haematological toxicities meta-analysis

The overall pooled estimate for the non-haematological toxicities MA was 1.18 (0.83- 1.69), as shown in Figure 2.35. Although group 2 (bevacizumab+ CT vs CT) contained only one effect size, it shows a significant trend for non-haematological toxicities for bevacizumab+ chemotherapy compared to chemotherapy alone. An individual non-haematological toxicities analysis was carried out for this group showing that bevacizumab+ chemotherapy is associated with an increased risk of nausea/vomiting compared to chemotherapy alone [RR 5.91 (95% CI 1.13-22.1)]. For the remaining groups, none show a statistically significant difference with a pooled relative risk of 1.75 (0.89- 3.43) for group 1 comparing different chemotherapies to each other (CT-1 vs CT-2), 1.2 (0.75-1.93) for group 3 comparing different combinations of chemotherapy with bevacizumab, and 0.62 (0.27-1.43) indicating that treatment with cetuximab+ chemotherapy results in less risk of non-haematological toxicities compared to treatment with bevacizumab+ chemotherapy. Nevertheless, subsequent analysis for group 3 (bevacizumab+ CT-1 vs bevacizumab+ CT-2) was carried out as shown in Figure 2.36 and shows that bevacizumab+ XELIRI was associated with significantly more risk of non-haematological toxicities compared to bevacizumab+ FOLFIRI with RR of 2.12 (95% CI

1.44-3.12). Further exploration of this finding shows that the risk of diarrhoea is significantly higher in patients treated with XELIRI compared to FOLFIRI [RR 2.5 (1.14-5.62)].

It also shows that bevacizumab+ oxaliplatin-based chemotherapy is associated with a higher risk of non-haematological toxicity compared to bevacizumab+ irinotecan-based chemotherapy [RR 0.57 (95% CI 0.36-0.92)]. Finally, Further analysis of the individual non-haematological toxicities for bevacizumab+ irinotecan-based chemotherapy vs bevacizumab+ oxaliplatin-based chemotherapy shows that bevacizumab+ oxaliplatin-based chemotherapy is significantly more likely to cause neuropathy compared to bevacizumab+ irinotecan-based chemotherapy [RR 4.93 (95% CI 1.11-21.8), P value 0.03].

Further exploration of the individual haematological toxicities for bevacizumab+ irinotecan-based chemotherapy vs bevacizumab+ oxaliplatin-based chemotherapy shows that bevacizumab+ oxaliplatin-based chemotherapy is significantly more likely to cause neuropathy compared to bevacizumab+ irinotecan-based chemotherapy [RR 4.93 (95% CI 1.11-21.8), P value 0.03].

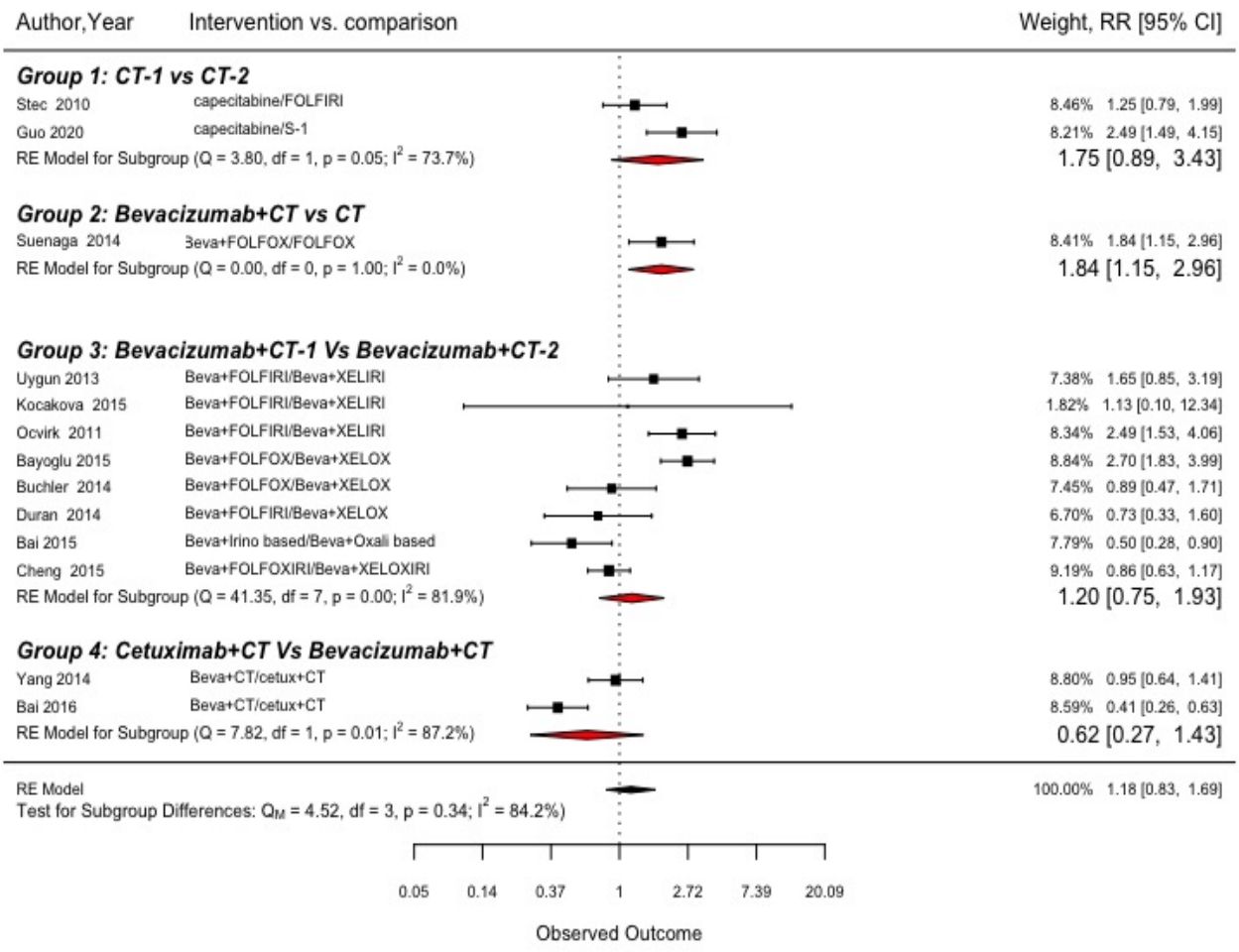


Figure 2.35: Forest plot of non-haematological toxicities of first-line SACTs for mCRC.

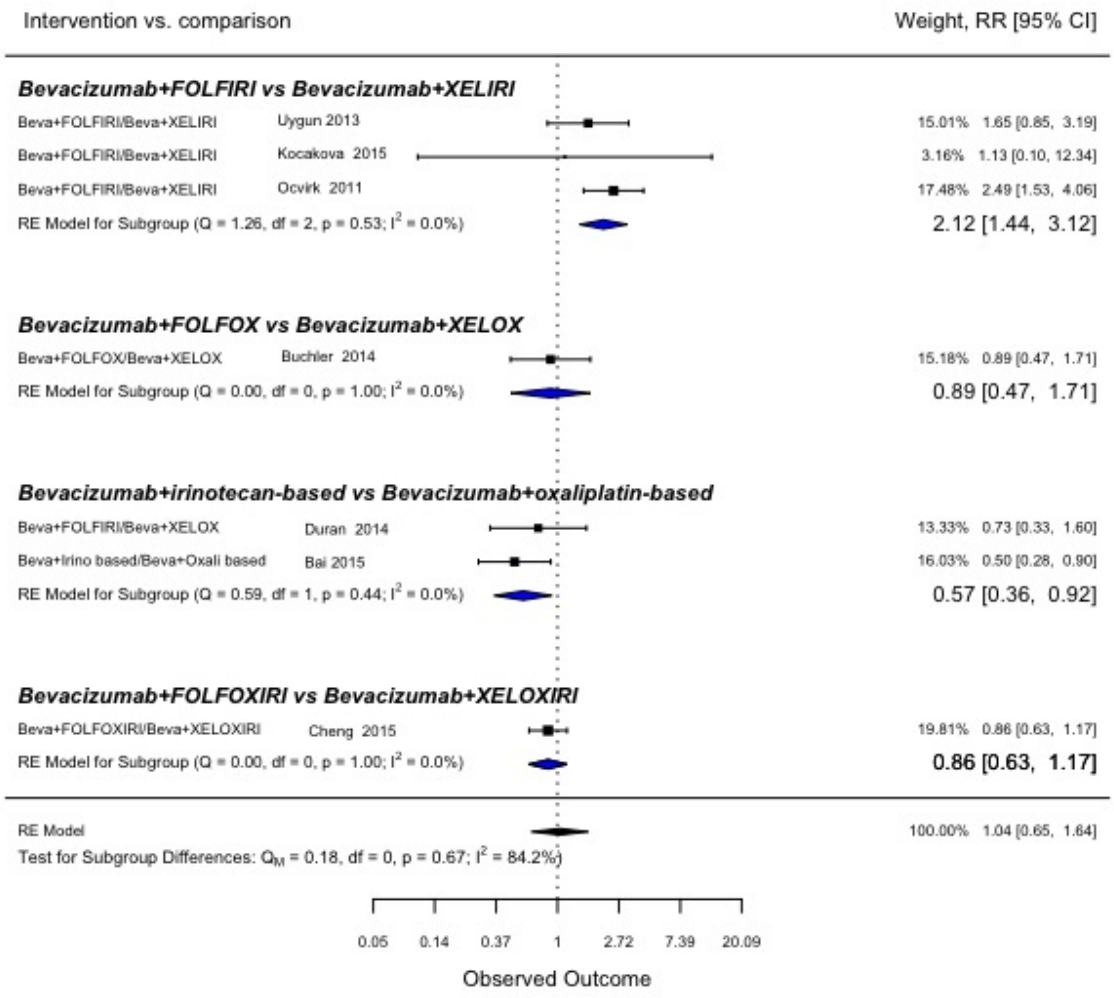


Figure 2.36: Forest plot for non-haematological toxicities of first-line bevacizumab combinations with chemotherapy.

The funnel plot for non-haematological toxicities is displayed in Figure 2.37. As seen, the majority of the studies are located at the top part of the plot with only one study located at the bottom of the plot. In addition, most of the effect sizes are located in the non-significant region (P > 0.05), whereas only three studies are located in the significance area. The funnel plot resembles a funnel shape indicating no possible presence of publication bias or small study effect. Furthermore, egger's test shows that there is no possible presence of funnel publication bias (P value 0.85).

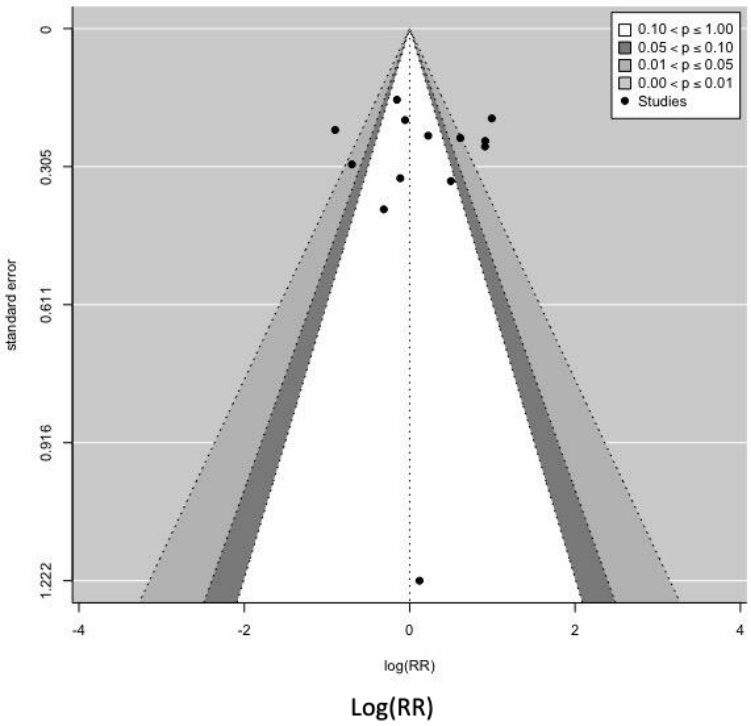


Figure 2.37: Funnel plot of the non-haematological toxicities associated with the use of first-line mCRC SACTs.

Additionally, the model was tested for the presence of outliers and influential cases were identified as outlier (Yang et al., 2014, Vedat Bayoglu et al., 2015). Figure 2.38 shows the distribution of the outliers around the overall estimate. Also, cook's distance value was measured to assess if any of the effect sizes would be considered as an influential case in the model, and it was plotted as depicted in Figure 2.39. It shows the 2 effect sizes had a distance value exceeding 0.35 based on the 4/n criterion where n is considered as the number of effect sizes (4/13).

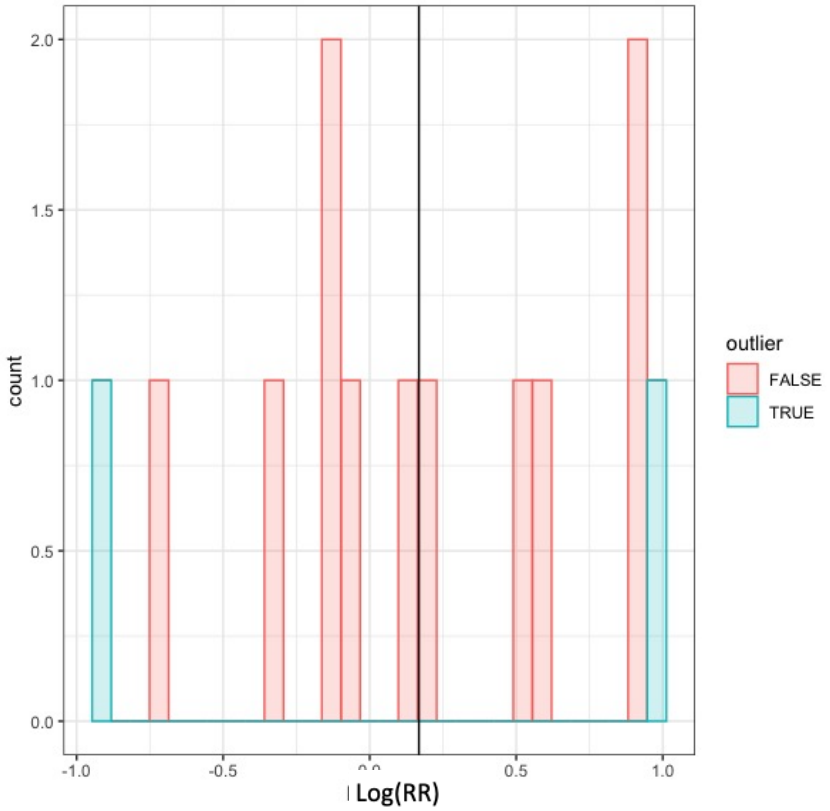


Figure 2.38: Histogram of the non-haematological toxicity data for outliers' distribution.

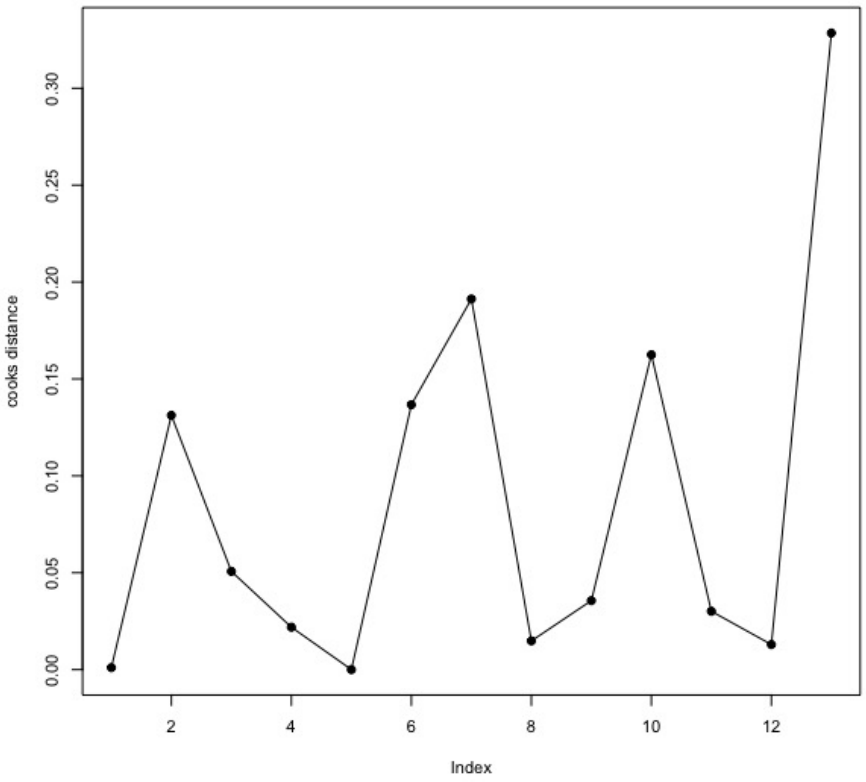


Figure 2.39: Influential observations of the non- haematological toxicity data by Cook's distance.

2.4 Discussion

2.4.1 Summary of the key findings

This SR-MA synthesised the findings of 29 studies that investigated the comparative effectiveness and safety of first-line mCRC SACTs in real-world practice settings. Six meta-analyses were quantitatively synthesised on six clinical outcomes, including the overall survival (OS), the progression-free survival (PFS), the overall response rate (ORR), the disease control rate (DCR), the severe haematological and non-haematological toxicities meta-analyses.

The Included studies in each of the six meta-analyses were classified into four groups according to the type of compared exposure: 1- studies comparing different chemotherapeutic regimens to each other, 2- chemotherapy alone compared to a combination of chemotherapy and bevacizumab, 3- various combinations of chemotherapies combined with bevacizumab compared to each other, and 4- a combination of chemotherapy and bevacizumab compared to a combination of chemotherapy and cetuximab. Among these categories, the most studied SACT in the first line (1L) settings was bevacizumab, which was investigated in 24 out of 29 studies.

Overall, the findings of this review showed that the combination of bevacizumab+ chemotherapy (group 2) demonstrated statistically significant improved effectiveness, including OS, PFS, and ORR over chemotherapy alone (Figure 2.7, Figure 2.13, and

Figure 2.18). However, the combination was associated with a statistically increased risk of non-haematological toxicities and a non-statistically significant increased risk for haematological toxicities (Figure 2.30 and Figure 2.35, respectively).
Moreover, our findings showed that various chemotherapy combinations with bevacizumab (group 3), regardless of the intensity and the type of the chemotherapy, did not show any statistically significant difference in overall survival (Figure 2.7). However, the combination of bevacizumab+ oxaliplatin-based chemotherapy was associated with an increased hazard of disease progression and neuropathy compared to bevacizumab+ irinotecan-based chemotherapy (Figure 2.14). Nevertheless, it demonstrated a higher non-significant trend

for complete or partial response (improved ORR) compared to bevacizumab+ irinotecan-based chemotherapy (Figure 2.14). The combination of bevacizumab+ irinotecan-based chemotherapy was, however, associated with significantly higher risk for severe diarrhoea compared to bevacizumab+ oxaliplatin.

The comparison between cetuximab+chemotherapy versus bevacizumab+ chemotherapy (group 4) did not show any statistically significant difference in OS, PFS, or toxicities (Figure 2.7, Figure 2.13, Figure 2.30, Figure 2.35). However, the combination of cetuximab+chemotherapy was associated with improved complete or partial response (i.e., overall response rate) compared to bevacizumab+ chemotherapy (Figure 2.18).

Finally, when compared against each other, first-line chemotherapeutic agents without additional targeted treatments (group 1) and regardless of the intensity of chemotherapy did not differ significantly in terms of OS, PFS, objective response, or toxicities (Figure 2.6, Figure 2.13, Figure 2.18, Figure 2.25, Figure 2.30, and Figure 2.35).

The included studies in the review showed variability in the general characteristics and design (Appendix II. Additionally, considerable clinical variability among the patients included in the studies existed. For instance, the representation of female patients ranged between 22.7% and 59.3% (Appendix II), while poor performance status (≥2) ranged between 0% (Ocvirk et al., 2011, Cheng and Song, 2015) and 15.7% (Artac et al., 2016). Similarly, within studies that reported the RAS status, two studies included only patients with RAS wild-type tumour (Houts et al., 2019a, Degirmencioglu S, 2019), while one study included only patients with RAS mutant-type tumour (Houts et al., 2019b), while for the remaining studies that reported the RAS status, RAS wild-type tumour ranged between 22.6% (Marschner et al., 2015) and 48% (Zhou et al., 2021).

All these differences across the studies contributed to the between-study variability (I^2), which varied across the six MAs based on the included effect sizes. However, for the OS MA, which included all studies, I^2 was 76.2%, indicating a high variability (heterogeneity) between the studies, which upon further exploration was found to be attributed to a range of the studies' design characteristics, such as the effect size calculation method and the type of primary study settings (Table 2.7). Additionally, the heterogeneity was partially explained by the variability of the characteristics of the included patients in the primary studies, such as the age group of the included patients (

Table 2.8). Finally, the variability in the applied SACT regimens, ranging between chemotherapeutic agent only (group 1), various combinations of chemotherapeutic agents with bevacizumab (group 2 and group 3), and various combinations of chemotherapeutic agents with cetuximab (group 4) was another leading cause for the heterogeneity in all MAs in this review. However, within the SACT groups, the heterogeneity was less profound. For example, the between-study variability in the PFS MA was 64.4% (P value <0.001), indicating high heterogeneity between individual studies (Figure 2.13). Nevertheless, within the compared SACT groups, the heterogeneity ranged between 0% (no heterogeneity) for group 2 (bevacizumab+ CT vs CT), 43.5% (moderate heterogeneity) for group 3 (bevacizumab+CT1 vs bevacizumab+CT2), and 74.3% (high heterogeneity) for group 3 (cetuximab+ CT vs bevacizumab+ CT) (Figure 2.13).

Interestingly, the moderator analysis demonstrated a significant statistical difference between studies funded by pharmaceutical companies and those without such sponsorship. However, it was not possible to conduct further analysis based on treatment groups due to the presence of four distinct subgroups. As a result, each group of the moderator analysis for the source of sponsorship of each study would have a small number of studies, leading to reduced statistical power and limiting the ability to draw meaningful conclusions.

Despite the advantages that observational studies introduce to provide evidence of the comparative effectiveness and safety of treatments, they are limited by their susceptibility to bias (Gershman et al., 2018, D'Agostino and D'Agostino, 2007, Levesque et al., 2010). In this review, the risk of bias was assessed for the primary outcome, which was overall survival, using the Cochrane ROBINS-I tool, which defines 7 bias domains, with the confounding bias and selection bias being the major methodological challenges in any observational study. Confounding bias is one of the most common types of bias in observational studies assessing the effectiveness and safety of interventions (Sterne et al., 2016b), which is addressed through several strategies, including multivariate adjustment, propensity score matching, and propensity score weighting (Sterne et al., 2016a). In this OS MA, 24 of the 29 studies were judged to be at serious risk of bias for the confounding domain either because the generated effect size was not adjusted for the predefined confounders (age and performance status) or because the crude survival was reported without any adjustment for confounders,

requiring the need to obtain the effect size indirectly by reconstructing the Kaplan-Meier curve.

For selection bias, 16 of the 29 studies were judged at serious risk of bias. The variability within the clinical characteristics of the patients revealed the presence of selection bias. For example, the effect sizes for the studies that excluded patients with poor performance status (Ocvirk et al., 2011, Cheng and Song, 2015) may be biased because poor performance status is a known poor prognostic factor for overall survival in mCRC patients (Sargent et al., 2009, Travers et al., 2021), resulting in biased estimates for these studies.

Overall, all studies included in the OS MA had an overall serious risk of bias, which means that each study was judged to be at serious risk of bias in at least one domain; therefore, caution is needed when the outcomes of this review are interpreted.

2.4.2 Overall survival meta-analysis

Overall survival was the primary outcome of this review. The 29 included studies in the OS MA contributed towards 33 effect sizes. Overall, the subgroup analysis for the OS MA showed that chemotherapy alone (fluoropyrimidine-based chemotherapy) was associated with an increased hazards of death compared to the combination of bevacizumab+ chemotherapy (HR 1.36 (95% CI 1.18-1.56)) (group 2, Figure 2.6), with all effect sizes included with this group on the same direction favouring the combination of bevacizumab+ chemotherapy over chemotherapy alone.

The superiority of the combination of bevacizumab+ chemotherapy over chemotherapy alone (group 2), regardless of the chemotherapy backbone, has also been proven in many clinical trials and MA of clinical trials. Multiple MAs of clinical trials have evaluated the comparative efficacy of chemotherapy vs chemotherapy+ bevacizumab, with the majority of these MAs favouring the combination of chemotherapy+ bevacizumab over chemotherapy only (Welch et al., 2010, Galfrascoli et al., 2011, Macedo et al., 2012, Lv et al., 2013, Zhang et al., 2015, Hurwitz et al., 2013, Baraniskin et al., 2019) . For example, in Welch et al.,2015 MA, which included five clinical trials, the overall pooled OS was 0.79 (95% CI 0.69- 0.9), P value <0.001, favouring bevacizumab+ chemotherapy over chemotherapy alone, with no significant heterogeneity between studies (Welch et al., 2010). Similarly, a MA of clinical

trials by Galfrascoli et al.,2011 reported a significantly improved OS associated with bevacizumab+ chemotherapy over chemotherapy alone (HR 0.8 (95% CI 0.71-0.91), P value <0.001) with non-significant heterogeneity between studies (I^2 =39%, P value 0.13) (Galfrascoli et al., 2011). Our subgroup MA, which compared CT to bevacizumab+ CT (group 2), resulted in an overall pooled HR of 1.36 (95% CI 1.18-1.56), with the hazard direction toward chemotherapy (chemotherapy was associated with 36% increased hazard of mortality).However, when this value is inverted to inverse the comparison to favour bevacizumab+ chemotherapy, the values becomes HR 0.74 (95% CI 0.64- 0.85), which is comparable to the findings of MAs of clinical trials comparing chemotherapy to bevacizumab+ chemotherapy.

Similar findings with different magnitudes and between-studies heterogeneity, yet a similar trend towards a superior OS with bevacizumab+ chemotherapy over chemotherapy alone, were reported in other meta-analyses of clinical trials by Macedo et al.,2012 [HR 0.84 (95% CI: 0.77-0.91), I^2 = 60%; P = 0.04] (Macedo et al., 2012), Lv et al., [HR, 0.76; 95% CI, 0.69 to 0.82] (Lv et al., 2013), Zhang et al., [HR 0.83 (95% CI 0.78-0.91), I^2 = 29%; P value <0.001] (Zhang et al., 2015), Hurwitz et al.,2013 [HR 0.8 (95% CI 0.71-0.9)] (Hurwitz et al., 2013), Botrel et al.,2016 [HR 0.87 (95% CI 0.8-0.95), I^2 = 40.5%; P value 0.15] (Botrel et al., 2016) and Baraniskin et al.2019 [HR 0.85 (95% CI 0.78-0.94), I^2 = 54%; P value 0.05] (Baraniskin et al., 2019) favouring bevacezumab+ chemotherapy over chemotherapy alone.

Similarly, an MA of observational studies evaluating the impact of the addition of monoclonal antibodies to chemotherapy alone for mCRC patients pointed to the overall survival advantage of adding bevacizumab to chemotherapy over chemotherapy alone for patients with mCRC (da Silva et al., 2018). However, unlike our findings which demonstrated a statistically significant overall survival advantage of adding bevacizumab to chemotherapy alone (HR 0.74 (95% CI 0.64- 0.85)), the finding by da Silva et al.,2018 was not statistically significant (mean difference 2.83, 95% CI (-1.76- 7.41)) (da Silva et al., 2018).

One reason that could have contributed toward the discrepancy in the statistical significance of the overall survival benefit of adding bevacizumab to chemotherapy between the findings by da Silva et al.,2018 OS MA and our review's OS MA findings could be related to the type of effect size used to pool the findings. While in our review the hazard ratio was used to pool survival outcomes as recommended by Cochrane collaboration (Higgins JPT, 2016), the OS

MA by da Silva et al. used the mean difference (MD) to pool survival findings, which is considered inappropriate as this might exclude censored patients who did not experience the event, hence introducing bias into the findings (Higgins JPT, 2016).

Another reason to explain the discrepancy in the statistical significance could be attributed to the high variability across the included studies in de Silva et al.,2018 review, which evaluated the impact of the addition of monoclonal antibodies to chemotherapy regardless of treatment line (first, second or beyond), and treatment type (metastatic or adjuvant therapy). In contrast, our review focused on the impact of first-line metastatic SACT for mCRC patients, resulting in less heterogeneity in the subgroup analysis comparing bevacizumab+ chemotherapy to chemotherapy alone in our OS MA (I^2 75.2%) (group 2, Figure 2.6) compared to the same subgroup analysis in de Silva et al review (I^2 87%).

A total of 12 studies (contributing to 13 effect sizes) investigated the addition of various chemotherapeutic agent combinations to bevacizumab (group 3 in the OS MA; bevacizumab+ CT1 vs bevacizumab+ CT2, Figure 2.6) did not show a statistically significant difference between the different combinations in terms of overall survival. A further subgroup analysis was performed for group 3, bringing together similar bevacizumab+ CT1 vs bevacizumab+ CT2 comparisons (Figure 2.7) and showed no statistically significant difference between the majority of the compared subgroups. The combination of bevacizumab+ irinotecan-based chemotherapy was associated with a non-statistically significant increased hazard of mortality compared to the combination of bevacizumab+ oxaliplatin-based chemotherapy (pooled estimate 1.05 (0.88- 1.25)). This was supported by the findings of a meta-analysis of clinical trials that compared bevacizumab+ irinotecan-based chemotherapy to bevacizumab+ oxaliplatin-based chemotherapy and found a non-statistically significant increased hazards of mortality with bevacizumab+ irinotecan-based chemotherapy compared to bevacizumab+ oxaliplatin-based chemotherapy (Dai et al., 2019).

The subgroup analysis for group 3 which compared different chemotherapeutic combinations with bevacizumab showed that bevacizumab+ capecitabine was associated with a statistically significant poorer OS compared to bevacizumab+ XELOX (Figure 2.7, HR 1.39 (95% CI 1.04-1.87)). However, since this comparison existed in only one effect size in the OS MA an no previous clinical trials were performed to support this finding, this finding could be considered exploratory.

The comparison between bevacizumab+ chemotherapy vs cetuximab+ chemotherapy (group 4) did not show any statistically significant difference between the two regimens in the OS MA (HR 1.02 (95% CI 0.73-1.42), Figure 2.6). Similar findings were reported in a MA of observational studies where no statistically significant difference was found between bevacizumab+ chemotherapy and cetuximab+ chemotherapy in mCRC patients (da Silva et al., 2018).

Nevertheless, the findings by other MAs contradict those found by our review. for example, while in Cui MA, which included both RCTs and observational studies, bevacizumab demonstrated a statistically significant prolonged OS compared to cetuximab (HR 0.81, 95% CI 0.74-0.9) (Cui and Guo, 2022), the MA by Zheng found a statistically significant prolonged OS associated with cetuximab compared to bevacizumab in mCRC (HR 0.89, 95% CI 0.81-0.98) (Zheng et al., 2019). This discrepancy could be attributed to the high heterogeneity in the studies exploring cetuximab. In our OS MA, the studies that explored cetuximab in the first-line mCRC settings varied in the context of clinical characteristics of the enrolled patients. For example, Houts, 2019 and Degirmencioglu, 2019 included only patients with RAS wild-type (Houts et al., 2019a, Degirmencioglu S, 2019), whereas Zhou, 2021 included a subset of patients with mucinous histology tumour and another subset with a non-mucinous histology tumour (Zhou et al., 2021). This discrepancy in the clinical characteristics, especially the tumour molecular profile has resulted in a paradoxical treatment effect across the effect sizes, hence resulted in an overall non-statistically significant differences between bevacizumab and cetuximab in our findings.

2.4.3 Progression-free survival meta-analysis

The PFS MA included 20 studies with 21 effect sizes. No studies comparing different chemotherapeutic agents (CT1 vs CT2) evaluated PFS. Hence, the PFS MA contained three groups for SACTs (Figure 2.13).

Similar to the findings of the OS MA, the subgroup analysis of the PFS MA showed that the addition of bevacizumab to chemotherapy (group 2, Figure 2.13) contributed towards a statistically significant prolonged PFS compared to chemotherapy alone, which was associated with 36% more hazards for disease progression (HR 1.36 (95% CI 1.25- 1.48)) when this value is inverted to inverse the comparison to favour bevacizumab+ chemotherapy, the values become HR (0.74 (95% CI 0.68- 0.8), which means that the hazard of disease

progression is 26% less in bevacizumab+ chemotherapy compared to chemotherapy alone. This finding was consistent with previously published findings of MAs of RCTs evaluating the efficacy, including PFS, of adding bevacizumab to chemotherapy in the first-line settings for mCRC patients. The results of these MAs clearly favoured bevacizumab+ chemotherapy over chemotherapy alone. Baranniskin et al. reported an overall pooled PFS of 0.71 (95% CI 0.65-0.77) favouring bevacizumab+ chemotherapy over chemotherapy alone (Baraniskin et al., 2019), whereas in Hurwitz et al. meta-analysis, the overall PFS was 0.57 (95% CI 0.64-0.71) (Hurwitz et al., 2013) and an overall pooled PFS of 0.62 (95% CI 0.48-0.69) was reported by Loupakis et al. (Loupakis et al., 2010). Notably, similar to our PFS MA which had a significant heterogeneity (I^2 64.4%, P value <0.001), all these RCT MAs reported a statistically significant heterogeneity in the findings (P value < 0.05).

Additionally, the subgroup analysis for group 3 (Figure 2.14) in the PFS MA (bevacizumab+ CT1 vs bevacizumab + CT2) showed that bevacizumab+ irinotecan-based chemotherapy was associated with a statistically significant prolonged PFS compared to bevacizumab+ oxaliplatin-based chemotherapy (HR 1.22 (95% CI 1.07-1.36) [after inverting the value: HR 0.82 (95% CI 0.74-0.93), favouring bevacizumab+ irinotecan-based chemotherapy, Figure 2.14]. Similar findings were confirmed in previously published MAs of RCTs comparing first-line bevacizumab+ oxaliplatin-based SACTs to bevacizumab+ irinotecan-based SACTs. For example, Ren et al. reported a pooled PFS of 0.92 (0.87-0.98) favouring bevacizumab+ irinotecan-based chemotherapy (Ren et al., 2021), whereas Kawai et al. reported a pooled PFS of 0.9 (95% CI 0.82-0.98), also favouring bevacizumab+ irinotecan-based chemotherapy over bevacizumab+ oxaliplatin-based chemotherapy (Kawai et al., 2021).

2.4.4 Objective response meta-analysis

Two MAs were generated to measure the objective response: the ORR MA and DCR MA (Figure 2.19 and Figure 2.25, respectively), with each of them including 15 studies and 16 effect sizes. Both MAs included four SACTs groups, although for both MAs only one effect size was included in the group comparing bevacizumab+ chemotherapy to chemotherapy alone. The subgroup analysis for both MAs showed that the combination of bevacizumab+ chemotherapy (group 2) is associated with improved ORR and DCR (RR 1.35 (95% CI 1.05-1.75) and 1.11 (95% CI 1.03-1.2), respectively). The wide confidence interval in both estimates reflects the small sample size, which was driven from one study only (Suenaga et

al., 2014). This finding is consistent with the results of the OS MA and PFS MA, where the combination of bevacizumab and chemotherapy showed a statistically significant improved OS and PFS compared to chemotherapy alone. Moreover, this finding has also been supported by several RCT MAs, which showed a heterogenous higher trend for ORR for bevacizumab+ chemotherapy compared to chemotherapy alone. However, the significance varied across different MAs. For instance, Botrel et al. reported a significantly higher ORR for patients treated with a combination of bevacizumab+ chemotherapy compared to chemotherapy alone (RR 0.81 (95% CI (0.68 to 0.95) P value 0.01) with high heterogeneity in the results (I^2 = 66 %) (Botrel et al., 2016). Similarly, Loupakis et al. reported a non-significant trend favouring bevacizumab+ chemotherapy over chemotherapy alone (RR 1.16 (95% CI 0.97-1.38), P value 0.85) with significant heterogeneity in the results (P value 0.03) (Loupakis et al., 2010). Moreover, in Qu et al. MA, which included 9 RCTs comparing bevacizumab+ chemotherapy to chemotherapy alone, a significantly higher trend for ORR for patients treated with bevacizumab+ chemotherapy was demonstrated compared to chemotherapy alone (1.62 (95% CI (1.19-2.07, P value =0.002), I^2 = 73%).

The subgroup analysis of the ORR MA analysis (Figure 2.19) shows a significantly higher trend for ORR for cetuximab+ chemotherapy compared to bevacizumab + chemotherapy (RR 1.23 (95% CI 1.1-1.37). The finding contradicts our OS MA (Figure 2.6) and PFS MA (Figure 2.14), which did not show a prolonged OS or PFS for cetuximab+chemotherapy compared to bevacizumab+ chemotherapy. A possible explanation for this could be that ORR is highly correlated to liver metastasectomy rate (i.e., surgical removal of the liver metastasis) (Folprecht et al., 2005). It was evidenced that for patients with mCRC, targeted therapy such as cetuximab in combination with chemotherapy results in significant improvement in liver metastasectomy and hence ORR (Bokemeyer et al., 2009, Douillard et al., 2014b, Folprecht et al., 2010). The findings of our ORR MA are supported by another MA of RCTs showing that cetuximab-based treatment is associated with an improved ORR over the bevacizumab group (RR 1.11 (95% CI 1.03-1.19), *P value* 0.01) (Zheng et al., 2019).

2.4.4.1 Toxicities meta-analyses

Severe toxicities measured by the NCI-CTCAE grading system (≥ 3) were quantitively synthesised using two MAs: the haematological toxicities MA (Figure 2.30) and non-

haematological toxicities MA (Figure 2.35), with a total of 13 effects sizes contributed to each MA.

For both the haematological and non-haematological toxicities MA, only one effect size existed for the subgroup comparing bevacizumab+ chemotherapy vs chemotherapy alone, showing a significantly increased risk for non-haematological toxicities for bevacizumab+ chemotherapy compared to chemotherapy alone, and a non-significant increased risk for haematological toxicities [haematological toxicity: RR 1.08 (95% CI 0.79-1.47)], [non-haematological toxicity: RR 1.84 (95% CI 1.15-2.96). This finding is consistent with the previously published body of evidence on the significantly increased risk for toxicities associated with the use of bevacizumab, including hypertension, bleeding, and proteinuria (Goldberg et al., 2004). Galfrascoli et al. demonstrated a significantly increased risk for hypertension [RR 2.98 (95% CI 2.32–3.84)], gastrointestinal perforations [RR 5.04 95% CI 1.72–14.79), and bleeding (RR 2.07 95% CI 1.19–3.62] for bevacizumab+ chemotherapy compared to chemotherapy alone (Galfrascoli et al., 2011). In another MA of clinical trials, Macedo et al. reported a non-significant increased risk of haematological toxicities associated with bevacizumab+ chemotherapy [OR 1.23 (95% CI 0.96- 1.57(], yet the study by Galfrascoli et al. found a significant trend for grade 3-5 hypertension [OR 7.8 (95% CI 4.36-13.94)] and grade 3-5 proteinuria [OR 5.57 (95% CI 1.23-25.32)] associated with bevacizumab+ chemotherapy versus chemotherapy alone (Macedo et al., 2012).

The subgroup analysis for group 3 comparing different chemotherapeutic agent combinations with bevacizumab for both the haematological (Figure 2.32) and non-haematological toxicities MA (Figure 2.36) showed an increased, yet non-significant trend for haematological toxicities associated with bevacizumab+ oxaliplatin-based chemotherapy compared to patients treated with bevacizumab+ irinotecan-based chemotherapy [RR: 2.1, 95% CI (0.92-4.8]. Many clinical trials reported haematological toxicities in patients treated with oxaliplatin and irinotecan (Goldberg et al., 2004). An MA of clinical trials comparing the efficacy and safety of oxaliplatin-based bevacizumab to irinotecan-based bevacizumab therapy found that irinotecan-based bevacizumab therapy is four times more likely to result in anaemia compared to oxaliplatin-based bevacizumab (P value <0.001) (Dai et al., 2019). Additionally, in our review, bevacizumab oxaliplatin was shown to be associated with a statistically significant higher risk for neuropathy compared to bevaizuamb+ irinotecan. Neurotoxicity is known to be one of the most common toxicities associated with the use of oxaliplatin (Cavaletti et al., 2001), with many meta-analyses of clinical trials reporting the

significant association of neurotoxicity with oxaliplatin compared to irinotecan-based therapy (Liang, 2010, Dai et al., 2019, Zhuang et al., 2010), and our finding was consistent with these previous meta-analyses.

2.5 Strengths and limitations

To our knowledge, this is the first meta-analysis of observational studies to compare the effectiveness and safety of first-line mCRC SACTs in real-world settings. This study captured three effectiveness measures, including overall survival, progression-free survival, and objective response, in addition to the safety measure assessing severe toxicities associated with firs-line SACTs to provide a full picture on the treatment outcome in the clinical practice settings.

Our analysis was comprehensive and did not exclude patients with specific features. For example, the OS MA included five studies that evaluated elderly patients, two studies for patients with RAS-wild type tumour, one study for patients with mutant-RAS tumour, and one study assessing the effectiveness of SACT in patients with a mucinous component. Although our analysis was not based on these features, the moderator analysis provided useful information on the effect of these factors on the overall estimate.

Second, our analysis used an indirect method to obtain the effect sizes for survival outcomes (OS and PFS) from primary studies that did not report the HR and 95% CI. Instead of excluding these studies for the lack of reporting the required effect size needed to synthesise the meta-analysis, the published Kaplan-Meier curve for the respective studies was deconstructed and reconstructed to obtain the effect sizes. Despite the limitations of this process, including the possibility of inaccuracies due to possible errors in controlling the mouse clicks, this method allowed for more studies to be included, hence increasing the reliability and usefulness of our findings.

Nevertheless, this review has several limitations inherent to meta-analysis. One main limitation of our meta-analysis was the inherent constraint in comparing different chemotherapeutic agents individually, as the paucity of relevant studies prevented us from conducting separate analyses for each agent. Therefore, we were compelled to categorize all the agents within a single group (CT 1 Vs CT 2), which could have impacted the findings of this group. Second, despite the exhaustive systematic literature search conducted to obtain

all relevant and updated studies, the visual inspection of the OS MA funnel plot and the ORR MA funnel plot shows a possibility for the presence of publication bias. Although egger's test did not show any statistical significance for the possibility of the presence of publication bias in these two meta-analyses, further steps were taken to correct the potential bias through the trim and fill process. It could be possible for the secondary meta-analyses in our study to suffer from publication bias because primary studies that reported any of the secondary outcomes (PFS, objective response, and severe toxicities) without reporting OS were not included in our study. This step was performed to ensure that the same outcome across all studies would be assessed for internal validity and risk of bias. Second, the observational nature of the studies included in the OS MA conveys in an underlying confounding and selection bias, which can lead to biased estimates. Since the risk of bias is considered a potential source for variability, a sensitivity analysis could have been done to exclude the studies with low credibility. Unfortunately, in our MA, all studies had an overall serious risk of bias, so a sensitivity analysis could not be performed. Nevertheless, a subgroup analysis was conducted, considering the variability in judgment across different domains of bias. The subgroup analysis based on the bias domains was helpful in revealing whether the presence of bias in any domain could impact the summary effect.

2.6 Conclusion

Despite of the high heterogeneity and the risk of bias in our findings, the results of this meta-analysis were comparable and consistent with the previously published findings of meta-analyses of clinical trials. Our findings pointed to the significant benefit of bevacizumab in the first-line settings of mCRC treatment in terms of OS, PFS, and ORR. However, this was accompanied by an increased risk of adverse events. Although our haematological and non-haematological toxicities meta-analyses were not able to draw a robust conclusion regarding the toxicities associated with the combination of bevacizumab+ chemotherapy compared to chemotherapy alone because of the sparsity of studies, the available data in our study was consistent with the findings from the literature on the increased risk for toxicities. However, the sparsity of the studies describing the safety of bevacizumab in combination with chemotherapy warrants further real-world studies to investigate this outcome.

Our findings also pointed to the differences among various chemotherapeutic regimens combined with bevacizumab. Although none of these combinations demonstrated improved overall survival, the combination of bevacizumab+ irinotecan-based chemotherapy shows

improved PFS compared to bevacizumab+ oxaliplatin-based chemotherapy. The later combination could be associated with more risk of neurotoxicity. Hence, it should be used cautiously, especially for patients who received oxaliplatin-based therapy in an adjuvant setting. For bevacizumab+ irinotecan combinations, bevacizumab+ XELIRI was associated with a higher risk of severe diarrhoea compared to bevaciuzmab+ FOLFIRI. Although the findings of the meta-analyses in this study were comparable to meta-analyses of clinical trials, the results of this study should be interpreted carefully in light of the intrinsic limitations.

3 Chapter 3: Data sources and data management

This chapter deals with the technical details of the baseline characteristics of the mCRC patients (chapter 4), factors influencing the selection of first-line mCRC SACTs (chapter 5), and treatment pathways and treatment outcomes of mCRC patients (chapter 6) by describing the data used, the structure of the datasets, the purpose of using them, and the information covered. Firstly, a background around record linkage in Scotland is provided, then the data sources are presented to elaborate on the reason behind utilising each dataset in this thesis. Background for each dataset is provided, along with information about the data controller and any recognised strengths and limitations. This is followed by describing the data management processes in data governance, access, preparation, and data manipulation. More detailed descriptions of the methodology applied to individual parts of the analysis – i.e., the baseline characteristics, factors influencing first-line SACT selection, and treatment pathways and outcomes of first-line mCRC SACT – can be found in chapters 4, 5 and 6, respectively.

3.1 Introduction

3.1.1 Record linkage framework in Scotland

Howard Newcombe, one of the pioneers in probability matching techniques, attributed record linkage to bringing together two or more separated recorded information for individuals (Newcombe et al., 1959). In Scotland, the system of linked medical records by the Information and Statistics Division (ISD) of the Scottish Health Service and by the Registrar General for Scotland stated that all hospitalisation records, cancer registrations, and death records would be held centrally in a machine-readable form that contains patient identifying information such as name, date of birth, and area of residency (Kendrick, 1993). By the end of the 1980s, when computing powers and storage capacities were increased, the current Scottish system was developed as a joint program between ISD and the Computer Centre of the Scottish Health Service, agreeing that the hospitalisations records, cancer registrations, and death records would be centrally held at ISD (Kendrick, 1997).

With the rising number of electronically stored administrative datasets in Scotland, the Scottish Government (SG) released a series of publications to support record linkage in Scotland. Firstly, a consultation was conducted to develop a Scotland-wide data linkage framework for statistics and research (The Scottish Government, 2012c). Overall, the responses to the consultation were positive regarding the benefits that record linkage would bring to Scotland despite concerns about privacy and potential breaches in confidentiality. Following, the SG published a set of guiding principles for data linkage in Scotland for research purposes, which stated that any risk to jeopardise privacy should be minimised and confidentiality should be enhanced; the data linkage process should be for the benefit of the public; a balance should be maintained between maximising the use of data linkage while protecting personal data; and any personnel who will be accessing data should undergo data linkage training about the Data Protection Act and good practice in data linkage activity (The Scottish Government, 2012a). The document also outlined the requirements for data controllers, who are the persons who determine the "'purposes for which, and how, personal data are to be processed" (Scottish Health Informatics Program, 2012).

In 2018, the SG undertook a consultation on a new national public health body known as Public Health Scotland (PHS), which aimed to strengthen the existing public health assets in Scotland and ensure the effective delivery of improved health and well-being outcomes for the population of Scotland. PHS took over the relevant functions and services of the following bodies: Health Protection Scotland (a division of NHS National Services Scotland (NSS), ISD (also a division of NSS), and NHS Health Scotland (The Scottish Government; COSLA, 2019).

NHS Scotland ensures the delivery of healthcare and services to the population through 14 health boards, each covering a distinct geographical area of Scotland. As shown in Table 3.1, NHS Greater Glasgow and Clyde (NHS GGC) is the largest health board covering more than 1.2 million inhabitants.

Table 3.1. The Scottish regional health boards.

NHS Health Board	Area covered	Population
NHS Ayrshire and Arran	East Ayrshire, North Ayrshire, South Ayrshire	367,000
NHS Boarders	Scottish Borders	110,000
NHS Dumfries and Galloway	Dumfries and Galloway	148,000
NHS Fife	Fife	370,000
NHS Forth Valley	Clackmannanshire, Falkirk, Stirling	300,000
NHS Grampian	Aberdeenshire, City of Aberdeen, Moray	500,000
NHS Greater Glasgow and Clyde	**City of Glasgow, East Dunbartonshire, East Renfrewshire, Inverclyde, Renfrewshire, West Dunbartonshire**	**1,200,000**
NHS Highland	Highland, Argyll and Bute	310,000
NHS Lanarkshire	North Lanarkshire, South Lanarkshire	563,185
NHS Lothian	City of Edinburgh, East Lothian, Midlothian, West Lothian	800,000
NHS Orkney	Orkney Islands	22,190
NHS Shetland	Shetland Islands	23,000
NHS Tayside	Angus, City of Dundee, Perth and Kinross	400,000
NHS Western Isles	Outer Hebrides	27,000
KEY: NHS= National Health Service		

Health data in Scotland is available on various levels, including at Scotland level (i.e., national), NHS health board, and local authority. ISD Scotland, now PHS, currently holds national datasets for over 5 million people in Scotland (Public Health Scotland, 2020b). Healthcare data for individual patients are collected as a series of Scottish Morbidity Records (SMR), where the record type denotes the type of health care received. Individual episode records are completed and submitted by hospitals and NHS health boards to PHS Scotland, which links the data and holds them together (Information Service Division Scotland, 2016). Additionally, PHS holds data on population and vital statistics, including birth records, death records, immunisation records, and many others. (Public Health Scotland, 2020a).

At present, PHS holds for more than 30 years (1981-2023] the hospital records (SMR01) along with data from outpatient appointment clinic records (SMR00), held since 1997 and data from the Scottish cancer registry records (SMR06). It also holds the National Records of Scotland (NRS) Death Records. (Information Service Division Scotland, 2020d, Information Service Division Scotland, 2020c, National Records of Scotland, 2016).

3.1.2 Data governance in Scotland

The Privacy Advice Committee (PAC), which was founded in 1990, advised the NHS NSS and the General Register Office for Scotland (GROS) on patient privacy to ensure the appropriate use of health data in Scotland for research and statistical purposes (The Scottish Government, 2011). The committee's overreaching goal was to ensure the balance between protecting personal data and approving the release of individual data needed for research, audit, and other essential uses. In 2015 PAC, along with the Community Health Index Advisory Group (CHIAG), which was set up in 2005 to advise the chief medical officer (CMO) and NHS Scotland on the access and use of data held in the CHI, and the National Caldicott Guardians application (National Health Service Scotland, 2010) were combined into the Public Benefit and Privacy Panel (PBPP) for Health (Information Services Division, 2017). PBPP approval needs to be in place for large-scale complex research projects involving multiple linked datasets and more than one site in Scotland. Otherwise, a local Caldicott approval needs to be obtained for a study undertaken in a single site in Scotland (Academic and Clinical Central Office for Research and Develpment, 2021).

3.1.3 Safe havens in Scotland

Safe havens are secure virtual environments staffed by trained, specialist personnel where researchers and analysts can access data in electronic patient records. Within Scotland, along with the national safe haven operated by PHS (Public Health Scotland, 2020c), four local safe havens operate in regional hubs of Aberdeen (Grampian Data Safe Haven), Dundee (Tayside Safe Haven), Edinburgh (Lothian Safe Haven) and Glasgow (Glasgow Safe Haven) as a partnership between local NHS health boards and academic institutions (University of Aberdeen, 2015, University of Dundee, 2021, Academic and Clinical Central Office for Research and Develpment, 2020, National Health Service Greater Glasgow and Clyde, 2021).

To mitigate the risk of breaching patients' confidentiality, the SG published a charter for the processing, linking, and analysing health data within a safe haven environment. The principles for operating the safe havens and handling NHS health data from patient records stated that researchers only have access to 'pseudonymised' data with the minimum necessary identifiable data such as the month and year of birth and part of the postcode; when anonymised and linked data is analysed by the researcher, only aggregated data that have been thoroughly checked by Safe Haven support staff for potentially identifiable data (i.e. small numbers) are disclosed from the Safe Haven (The Scottish Government, 2015).

3.1.4 The Cancer Medicines Outcomes Programme (CMOP)

In Scotland, efforts have been made to improve the use of cancer-specific administrative datasets to better understand the impact of treatments. For example, in 2016, funding was granted by the SG for the Cancer Medicines Outcomes Programme (CMOP) in response to the SG cancer strategy "Beating Cancer: Ambition and Action" (The Scottish Government, 2016). The ultimate goal of this program is to explore how to maximise the use of local and national electronic records to better understand treatment outcomes of cancer medicines in the Scottish population, such as survival and duration of treatment (Cancer Medicines Outcomes Programme team, 2020).

One key objective for phase 1 of CMOP was to test the connectivity and linkage of relevant datasets to determine the clinical outcomes of cancer medicines. This has facilitated testing this methodology's scalability across Scotland in phase 2 of this program (Cancer Medicines Outcomes Programme team, 2020). Several cancer work streams progressed in CMOP phase I, including metastatic colorectal cancer (mCRC), which this thesis examines.

3.2 Data sources

The data collected for this thesis has been extracted from ten different data sources: Community Health Index (CHI) database; National Records of Scotland (NRS); Scottish Morbidity Records Outpatient Attendance dataset (SMR00); Scottish Morbidity Records General/Acute Inpatient and Day Case dataset (SMR01); Scottish Cancer Registry (SMR06); Chemotherapy Electronic Prescribing and Administration System (CEPAS); laboratory tests (SCI store); Radiotherapy treatment records (ARIA); Elective & emergency operations (OPERA) and; molecular pathology records.

3.2.1 Community Health Index (CHI)

The (CHI) database is a population register comprising data generated for all people registered with a general practitioner in Scotland (Information Service Division Scotland, 2020a). The early use of CHI began to operate in Tayside health board only in the 1970s, and after that, extended across Scotland. CHI is governed by the Chief Medical Officer (CMO), which holds the responsibility for the overall administration of the CHI system on behalf of Scottish ministers. However, the management and development of the CHI system are overseen by the Practitioner Services Division (PSD) of NHS NSS on behalf of NHS health boards, who act as the data controller for CHI. PSD also carries the duty of registering people on the CHI system as a by-product of the GP registration process (Scottish Government eHealth Division, 2013, Scottish Government eHealth Division 2013).

One of the essential components of the CHI system is the CHI number, considered the major identifier for individuals in NHS Scotland and the only consistent way to positively identify a person in the health service. The CHI number provides the capability to identify and link information pertaining to an individual from different systems within and across the health boards. The CHI system is considered the principal source of demographic information for every person registered with the Scottish GP practice.

The CHI number is a ten-digit code consisting of the 6-digit date of birth (DDMMYY), two digits, a ninth digit which is always even for females and odd for males and an arithmetical check digit. The use of date of birth and gender makes the CHI number more disclosive than the NHS number as a unique identifier that ensures matched records relating to the same individual. Thus, the CHI number is considered a key feature to facilitate the linkage of datasets. As a result, linkage processes have been made more efficient and less expensive (Walesby et al., 2017, Information Service Division Scotland, 2020a).

In contrast, the NHS number (from NHS central registry) is mainly used to project socio-economic research by the national records of Scotland (NRS) (Information Service Division Scotland, 2020b). The Scottish record linkage using the CHI number offers the opportunity to link major healthcare records for around 95% of the Scottish population.

Figure 3.1 shows the health-related activity using the CHI number across the principal health records (Scottish Government eHealth Division 2013, Information Service Division Scotland,

2020a). The use of the CHI number across different systems has a major impact in improving person safety in terms of reducing the risk of incorrect identification and enhancing the effectiveness of care as it reduces delay and duplicate work as well as saving time by linking clinical information and test results. Information held in the CHI system is beneficial to link health data for epidemiological analysis and supporting research. The CHI number can be used as a matching variable across health records. (Scottish Government eHealth Division 2013, Information Service Division Scotland, 2020a).

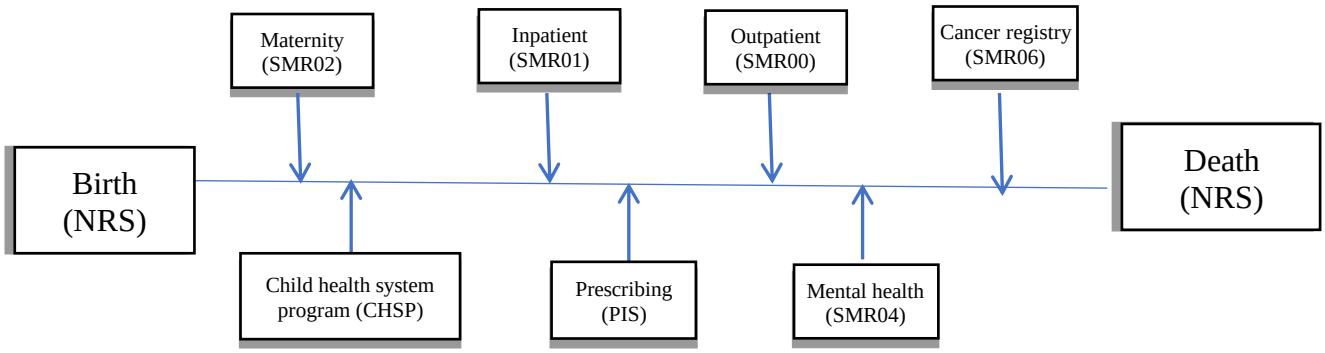


Figure 3.1. CHI linkable Scottish health records.

KEY: NRS= national records of Scotland SMR= Scottish medical records; PIS= prescribing information system

3.2.2 Chemotherapy Electronic Prescribing and Administration System (CEPAS)

In Scotland, cancer services within the NHS are structured on a regional basis. Cancer networks were established based on collaborations between the 14 NHS health boards across Scotland to maximise the clinical care for cancer patients. Three regional cancer networks are hosted within the NHS health boards, and they are (National Health Service National Services Scotland, 2022):

1- North of Scotland Cancer Network (NoSCAN), now known as Northern Cancer Alliance (NCA), with a population of 1,396,780, provides cancer care across 6 NHS health boards – Grampian, Highland, Orkney, Tayside, Shetland, and the Western Isles.

2- Southeast Scotland Cancer Network (SCAN) embraces the four NHS health boards in the east and south of Scotland; Borders, Dumfries and Galloway, Fife, and Lothian, with a population of 1,509,940.

3- West of Scotland Cancer Network (WoSCAN): embraces the four NHS health boards in the West of Scotland; Ayrshire and Arran, Forth Valley, Greater Glasgow and Clyde, and Lanarkshire, with a total population of 3,159,940.

Across Scotland, information on cancer diagnosis is collected through the Scottish cancer registry (section 3.2.4.3) from NHS health boards and hospital systems on new cancer diagnoses occurring in Scottish residents; however, detailed chemotherapy information is not nationally recorded. In 2010, a chemotherapy electronic prescribing and administration system (CEPAS) started to operate at the Beatson West of Scotland cancer hub, which then extended across the four NHS health boards in WoSCAN and subsequently across all three Scottish regional cancer networks. This system is used for prescribing and administration of Systemic Anti-Cancer Therapy (SACT) which includes cytotoxic chemotherapy and biological treatments (National Health Service Greater Glasgow and Clyde, 2015, CIS Oncology, 2018, NHS National Services Scotland, 2019). Guidance for the safe use and delivery of SACT was published in a Chief Executive Letter (CEL) in 2012 to provide NHS health boards with a structure for safe practice in prescribing, preparing, and administering of SACT (The Scottish Government, 2012b).

The implementation of CEPAS allowed for improving patient safety and enhancing the effective use of resources in addition to enabling monitoring prescribing practice (CIS Oncology, 2018). CEPAS provides a disease tree structure to guarantee that SACT regimens are allocated to specific tumour types. The disease tree structure can be modified to align with local requirements. Hence, disease tree structures differ in the systems used across Scotland. Unfortunately, to date, there is no data dictionary system to describe the information held in CEPAS. CEPAS captures all prescriptions of SACT in Scottish hospitals. Essential information related to SACT regimens assigned for specific diagnosis is recorded in CEPAS, including patients' age, weight, and eastern cooperative oncology group performance status (ECOG PS), which are recorded at every cycle. Additionally, the name of the SACT regimen, diagnosis for which the SACT was prescribed for, dose of SACT, number of cycles for each SACT, frequency of administration, date of treatment, and limited number of supportive medicines, such as dexamethasone, which is used as a premedication, are also recorded in CEPAS. Nevertheless, CEPAS is known to have certain limitations, one of which is the inability

to determine if certain treatment was actually given. It was presumed throughout the course of this thesis that patients received all prescription medications that had been prescribed.

Moreover, CEPAS does not include all hospital prescriptions pertaining to the patient during an inpatient stay. It would only provide information on SACT and supportive treatments that prevent the occurrents of adverse effects received by patients in inpatient and outpatient settings (Cancer Medicines Outcomes Programme et al., 2020). Other community prescriptions not related to SACT, or supportive medicines are recorded in the prescribing information system (PIS) dataset.

3.2.3 National Records of Scotland (NRS) – death data.

The National Records of Scotland (NRS) is a non-ministerial department of the Scottish Government that is accountable for collecting and producing information on births, deaths, marriages, civil partnerships, divorces, and stillbirths (National Records of Scotland, 2016). NRS death registration, which has been held by PHS and holds death records since 1974, classifies the underlying cause of death based on the information collected in the death certificate along with any added information supplied by official sources (e.g., the clinician who certified death, the pathologist). Death records hold one primary cause of death and up to three underlying causes that contributed to death. Other variables in this dataset include patient identifiers such as the CHI number, name, date of birth, date of death and place of death (Information Service Division Scotland, 2020a). The NRS undergoes regular quality assurance verification to ensure data accuracy (National Records of Scotland, 2020).

3.2.4 The Scottish Morbidity Records (SMR)

Healthcare data for individual patients are collected as a series of Scottish Morbidity Records (SMR), where the record type indicates the type of health care received during each episode (Information Services Division, 2020b). The SMRs used were:

3.2.4.1 Scottish Morbidity Record 00 (SMR00)

Outpatient Appointments and Attendances – Scottish Morbidity Record 00 (SMR00) denotes the dataset which collects all outpatient episode level data from patients attending Scottish hospitals with the exception of accident and emergency (A&E) and genito-urinary medicine appointments. This dataset has been available and held by ISD (now by PHS) since 1997, with

NHS health boards supplying PHS with data throughout the year. Around 4.4 million records are formed every year. This dataset contains patient identifiers such as CHI number, name, date of birth, postcode, and ethnicity. However, this data can be relatively incomplete, and there is a possibility of not capturing follow-up outpatient appointments. Additional variables collected in this dataset include operation information, a diagnosis field, and geographical measures, including the Scottish Index of Multiple Deprivation (SIMD) (Information Service Division Scotland, 2020c).

3.2.4.2 Scottish Morbidity Record 01 (SMR01)

General Acute Inpatient and Day Case – Scottish Morbidity Record 01 (SMR01) represents an episode-based record for all non-psychiatric, non-obstetric acute hospital admissions in Scotland. It has been available since 1997. For each patient hospitalisation episode, a new record is generated; therefore, patients may have multiple SMR01 records. Multiple episodes can make a single admission to the hospital as an episode is raised when any of the following occur: inpatient/ day case admission, change in a speciality, transfer to another hospital or department, change in a consultant, change in a significant facility or return to the hospital after being on pass for greater than five days. The dataset contains patient identifiers such as name, date of birth, CHI number, postcode, ethnicity, and episode management data. Other variables include patients' diagnosis, where a primary and up to five diagnoses are allocated, operations and discharge location. The tenth revision of the International Classification of Diseases (ICD-10) has been used since 1996 to assign codes to diagnoses for both SMR00 and SMR01.

In comparison, the Office of Population Censuses and Surveys procedural codes, 4th revision (OPCS-4), have been used in SMR returns to assign codes for operations, procedures and interventions (Public Health Scotland, 2021). Information contained in SMR01 can be useful for deriving indicators of co-morbidities, e.g., Charlson index (Information Services Division, 2020a). Data Quality Assurance (DQA) assessments for SMR01 are performed periodically and suggest that 89% - 94% of the main condition and main operation/procedure, respectively, have the correct codes, which has remained stable over time (National Health Service National Services Scotland, 2015).

3.2.4.3 Scottish Morbidity Record 06 (SMR06)

The Scottish Cancer Registry - Scottish Morbidity Record 06 (SMR06) or the Scottish cancer registry (SCR) began to collect personal, demographic, and diagnostic information (such as site, histology, behaviour, histological confirmation and hospital of diagnosis) on new cases of primary malignant neoplasms, carcinoma in situ, neoplasms of uncertain behaviour and benign tumours of the brain, spinal cord and teratoma of testis under the governance of PHS since 1958. The dataset continued to grow and upgrade, and in 1997 a new electronic cancer recording system was launched as part of a centralisation process at PHS. On a quarterly basis, the data in SMR06 are mapped and loaded into PHS, and the cases are verified when at least six months have passed since the date of diagnosis. (Information Service Division Scotland, 2020e).

SMR06 contains tumour diagnostic information such as the incidence date, the tumour site, laterality, histological confirmation of the disease, and other tumour contribution factors such as the tumour size, examination of nodes, and performance status. Other essential variables include the disease stage (for breast, cervical and colorectal cancer), tumour grade, and treatment information - such as surgical interventions, radiotherapy, chemotherapy, hormone therapy, biological or immunotherapy (yes/no). Noteworthy, these data are not necessarily complete and up to date since the primary purpose of SMR06 is to collect information relating to the diagnoses.

Cancer incidence is dated as the earliest point that the cancer is likely to have existed. This might predate pathological diagnosis if there were symptoms, signs, or radiological suggestions of the tumour before pathological diagnosis. Each cancer diagnosis constitutes an entry, and a patient can have more than one Cancer Registry entry if they have more than one cancer diagnosis. (Information Services Division, 2019, Public Health Scotland, 2020b).

The SMR06 uses two diagnostic classifications to record cancer: 1- International Classification of Diseases (ICD); and 2- International Classification of Diseases for Oncology (ICD-O).
One of the main limitations of SMR06 is that the records are not routinely updated, which implies that patients who develop metastases following an initial diagnosis might not be recorded. Hence, an assumption was made that all patients in this study presented initially

with stage IV (metastatic stage) at the time of diagnosis rather than progressing from previous stages of CRC (e.g., from stage III to stage IV CRC).

3.2.5 Scottish Care Information (SCI) store

The Scottish Care Information (SCI) store is a data repository which stores patient information at a health board level. Patients' demographics and clinical information, such as laboratory reports, are integrated into a single patient record. The SCI store accepts a wide range of clinical reports, including biochemistry, haematology, pathology, microbiology, and radiology. Originally, SCI store was considered a way of delivering online access to laboratory results. Hence, a database with a web browser was developed, allowing general practitioners (GPs) access to the whole range of patients' test results.

Furthermore, a web application was developed that is fully supported for retaining full clinical documentation pertaining to the patient. In SCI store, the integrity of a patient's demographics is retained through using a patient matching rule-based system. The CHI system is employed and linked to SCI store, which supports high-quality data. SCI store is deployed across each Scottish NHS health board; currently, there are 14 different SCI stores across Scotland. Each version of SCI store has its own data models according to the hospital system they support. Searching SCI stores for patient information in other NHS health boards is enabled through the use of a remote data source service with appropriate rule-based access controls (National Health Service National Services Scotland, 2016).

3.2.6 Elective & emergency operations (OPERA)

Electronic surgical records are increasingly becoming recognised for their role in automating the surgical practice process recording to improve efficiency, reduce costs and support the best care (Rockman, 2010). For this thesis, in addition to the surgical information provided by SMR00 and SMR01, the OPERA dataset was used as a supplementary resource to explore the details of operations. OPERA system uses the OPCS-4 coding system to record the operations. This dataset contains variables relevant to the operations, such as the date of surgery, name and OPCS-4 code for the surgery, and site of the surgery.

3.2.7 Radiotherapy treatment records (ARIA)

Radiotherapy information systems are becoming essential resources for managing core features of radiotherapy care. They serve as a repository for technical information, clinical notes, patient visits and radiotherapy treatment records (Lockhart et al., 2017). In Scotland, radiotherapy records should be kept on computer databases for no less than 30 years. However, records can be preserved permanently for research purposes(National Health Service National Services Scotland, 2012). The Beatson West of Scotland cancer centre has implemented the Radiotherapy information system (ARIA) to ensure safer patient treatment and records (the Beatson West of Scotland cancer centre, 2017). This dataset included the date of treatment as well as treatment intention. It was limited to details of planned radiotherapy only and did not provide specific details of the actual treatment given.

3.2.8 Laboratory information management system (LIMS)

The current Laboratory information management system (LIMS) in Scotland is implemented at the individual health board level providing clinical laboratory services, including haematology, clinical biochemistry, immunology, virology, cellular pathology, clinical microbiology, and genetic and blood transfusion disciplines. (Health Tech newspaper, 2020, Borland, 2018). LIMS supports CHI numbers which facilitates linkage enabling it to send electronic copies of the reports to other systems (e.g., SCI store, SMR06) (Borland, 2018). For this thesis, LIMS was used to collect information regarding the tumour molecular pathology. mCRC samples for BRAF codon 600 and RAS status mutations have been assayed by the West of Scotland laboratory Genetics Department since July 2015, with the results collected in a local database. Before July 2015, assaying mCRC samples for BRAF and RAS mutation was not mandatory.

3.3 Thesis data overview

In order to meet the aims and objectives of this thesis (objectives 2, 3, and 4- section 1.4), a wide range of variables were used for this thesis, including socio-demographic information, comorbidities, tumour-specific details, previous treatment details, and SACT detail. The main variables are described in the following sections.

However, many variables were duplicates, resulting in a substantial reduction in the total number of unique variables. Moreover, not all available variables have been used for analysis, either due to data quality issues (mostly the extent of missing values) or usefulness

(e.g., similar information expressed in slightly different ways; or information irrelevant to the purpose of this thesis).

3.3.1 Socio-demographic information

3.3.1.1 Age and gender

The socio-demographic data were obtained from multiple datasets, mainly via CHI (section 3.2.1) and NRS (section 3.2.3). These data encompassed patients' date of birth, gender, and deprivation. Additionally, the date of death was obtained if applicable from NRS. Patient age at the time of first SACT prescription was obtained by subtracting the date of the first prescription in the study timeframe, which was obtained from CEPAS (section 3.2.2), from the date of birth which was obtained from CHI. Furthermore, age was categorised into age groups ≥ 65 years and < 65 years at diagnosis. The age of 65 years was used as a cut-off point because the highest burden for colorectal cancer cases falls on the elderly (Safiri et al., 2019). Although there is no consensus regarding the definition of "elderly", conventionally, epidemiologists regard "elderly" as the chronological age of 65 years or older (Orimo et al., 2006, Ferrucci et al., 2008). All socio-demographic variables, except the age variable, were categorical variables, with gender being binary (male, female).

3.3.1.2 Deprivation

Deprivation is considered a multi-dimensional issue comprising a range of domains such as financial aspects, health, education, service, and crime (Townsend, 1987, Whitehead and Dahlgren, 1991). The Scottish Index of Multiple Deprivation (SIMD) measures seven aspects of deprivation; employment, income, health, education, access to services, crime, and housing across 6976 small areas (data zones). These domains are combined to produce a single index providing a relative rank for each data zone in Scotland from most deprived (ranked 1) to least deprived (ranked 5). Each data zone has an average of 800 people. The SIMD is continuously updated, taking into account changes within the social system and population. Commonly, SIMD is used to focus on the data zones below a certain rank, for example, 1% (percentile), 5% (vigintiles), 10% (decile), and 20% (quintile) of the most deprived data zones in Scotland. For this thesis, the quintile of SIMD 2012, splitting the data zones into five groups, with each comprising 20% of Scotland's data zones, was used.

3.3.1.3 Ethnicity and marital status

Ethnicity and marital status are recorded within SMR01 (section 3.2.4.1). However, reporting is not made mandatory (Information Service Division Scotland, 2020c, Information Service Division Scotland, 2020a). The result is a significant missing data for both variables (70% and 26.8% for marital status and ethnicity, respectively, for this thesis). Moreover, the reliability of data on ethnicity and marital status is doubtful as there is a lack of coding consistency, which, together with the level of missing in data, affects the data quality. Due to these issues, data on marital status and ethnicity were not included in the cohort description, the factors influencing prescribing, or in the adjustment for the outcome.

3.3.2 Metastatic colorectal cancer treatment

Data regarding the mCRC treatment were obtained from different data sources based on the type of treatment as described in the following sections:

3.3.2.1 Systemic anti-cancer therapy (SACT)

In this thesis, details regarding the type of SACT, treatment intention, and the date of SACT administration were obtained from CEPAS held in WoSCAN (Section 3.2.2).

Typically, mCRC patients receive different SACTs based on different conditions (e.g., line of therapy, patient response to treatment, the frailty of the patient, RAS gene status. etc.) with treatment being administered either as a single-drug treatment (e.g., 5FU), in a combination of chemotherapy as a doublet (e.g., FOLFIRI; 5FU and irinotecan), or in certain situations the patient might be treated with triplet combination of targeted therapy and combination chemotherapy as a triplet (e.g., cetuximab + FOLFIRI). The intensity/number of administered SACTS varies over the course of treatment for various reasons. For example, a patient might be prescribed FOLFIRI, and due to experiencing toxicities, the treatment can be stepped down into a monotherapy of 5FU, where irinotecan is removed from the originally prescribed regimen. Conversely, a treatment regimen could be stepped up by adding another drug to a previously prescribed regimen. Unfortunately, there is a lack of reporting on the reasons for changing or stopping the regimen in CEPAS. Additionally, the diagnosis variable within CEPAS dataset could not be used to define treatment lines due to the possible presence of inaccuracies. For example, aflibercept+FOLFIRI is licenced for second-line treatment of mCRC in Scotland (Scottish Medicine Consortium, 2014). A n entry for aflibercept+FOLFIRI in the prescription name field in CEPAS would result in an automatic entry of (second-line

metastatic colorectal cancer) in the diagnosis field, which might be inaccurate in a case where aflibercept+FOLFIRI was prescribed in the first-line setting. For that reason and following thorough discussions with the lead clinician involved in treating colorectal cancer patients in this study, a number of rules were set to simplify the exposure while acknowledging the treatment intention. Those rules were decided based on 1- the sequence of prescribed drugs, 2- the number of given cycles; and 3- the timing of different regimens and/or drugs. Figure 3.2 and Figure 3.3 represent six different scenarios where treatments required recoding in CEPAS to simplify the exposure and to understand the distribution of various regimens through different lines of treatment. The three scenarios in Figure 3.2 display the situations where treatments were merged into one line of therapy. In contrast, the three scenarios in Figure 3.3 show the situations where a new line of therapy was assumed to be initiated. Recoding the exposures in CEPAS was undertaken before this PhD program was started by Dr TM, the lead data scientist for phase 1 of the CMOP programme.

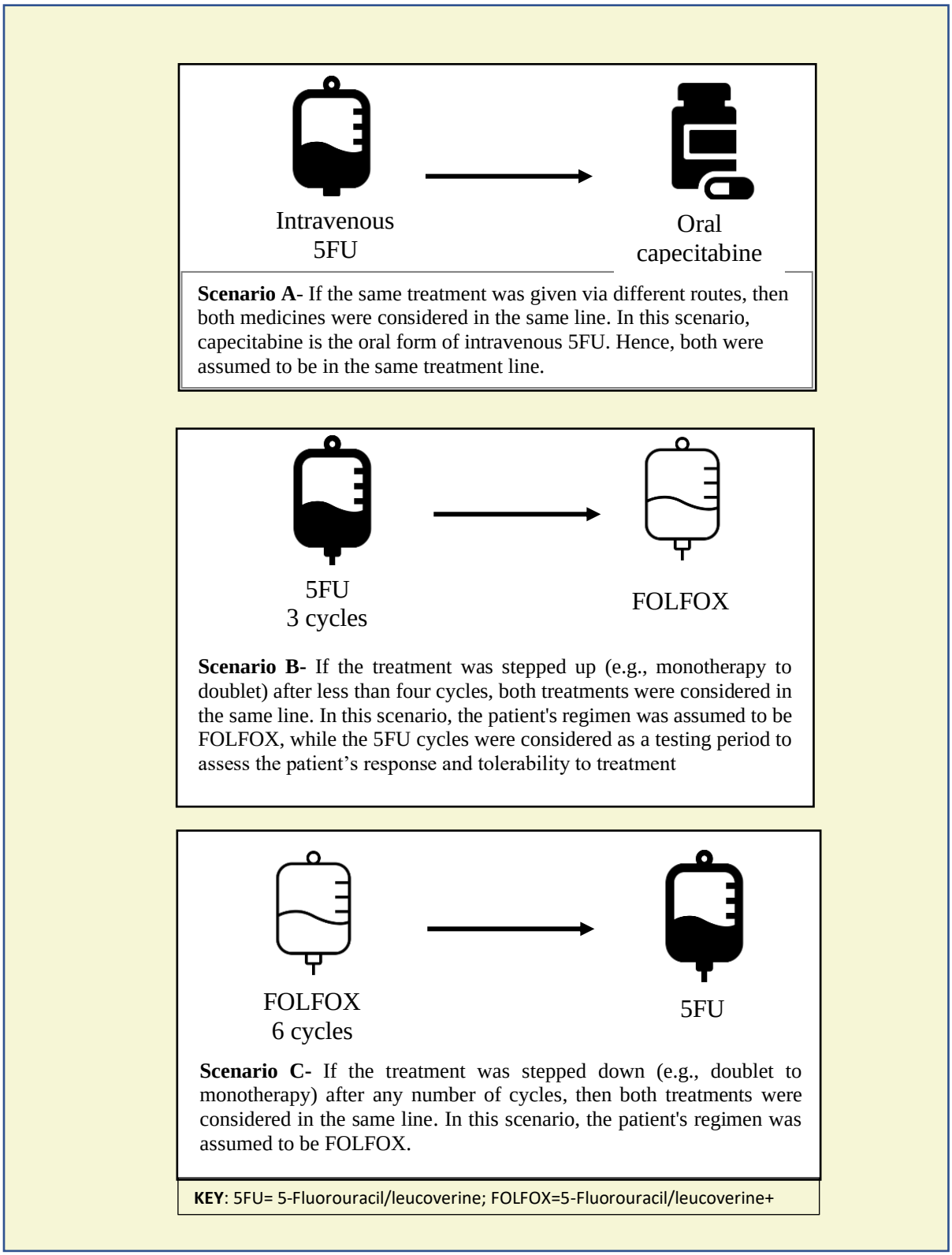


Figure 3.2. Examples of exposure re-coding where treatments were merged into the same line.

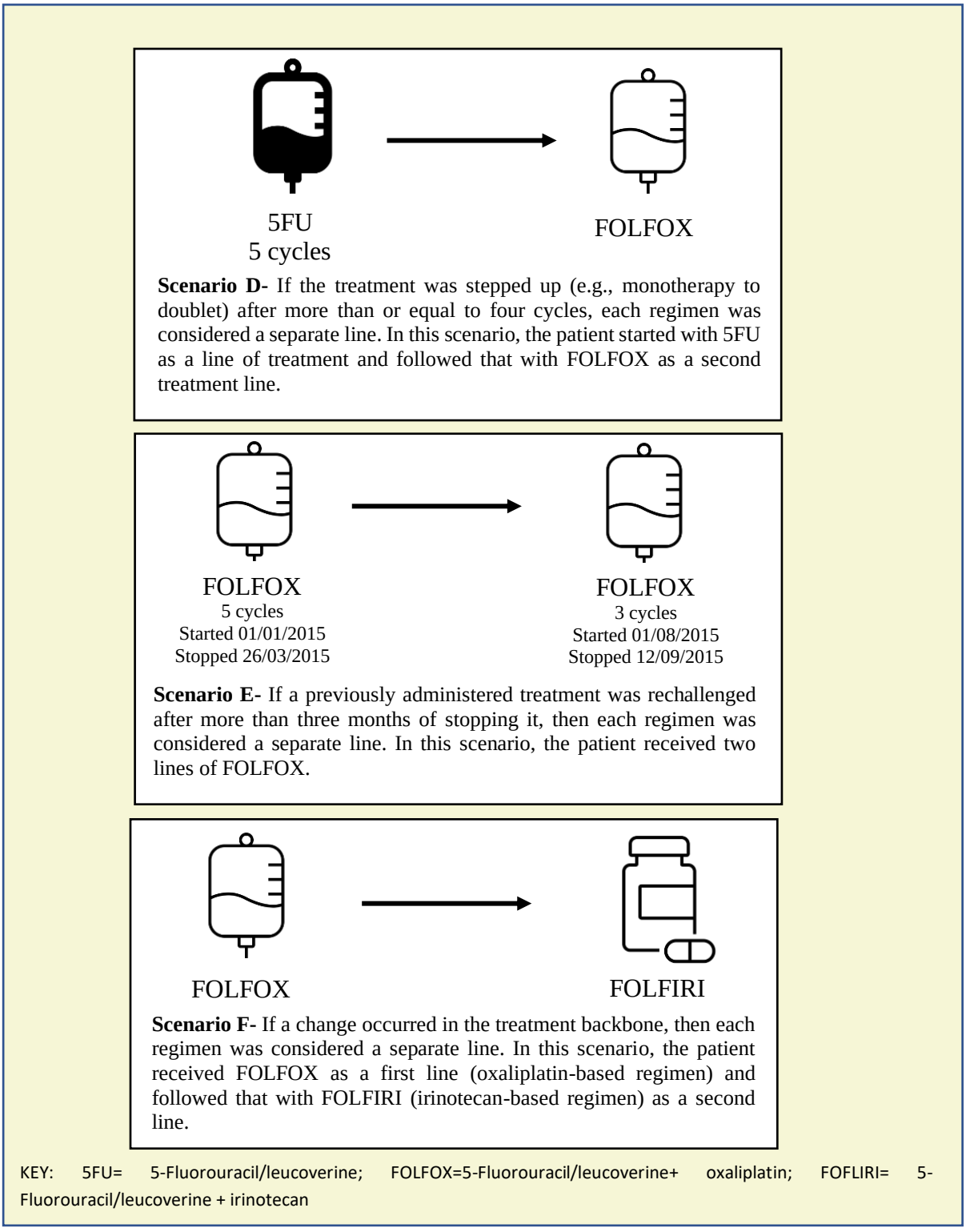


Figure 3.3. Examples of exposure re-coding where a new line of therapy was initiated.

The applied treatment recoding method resulted in a considerable number of SACT regimens, with some of these SACT groups encompassing a small number of patients, which presented a challenge given that the safe haven would not permit the release of any information containing less than five patients. Hence in order to maximize the use of current data and ensure that all SACT regimens were captured, SACT regimens with similar features were recoded into one name. For example, capecitabine is an oral fluoropyrimidine designed to replicate the continuous IV infusion of 5FU to prevent intravenous administration-related problems (Van Cutsem et al., 2004). Therefore, during the analysis and across the thesis chapters (chapter 4, chapter 5, and chapter 6), capecitabine and 5FU were recoded as 5FU. Similarly, both cetuximab+ FOLFOX and cetuximab+ FOLFIRI were recoded as cetuximab+FOLFIRI due to the small number of patients representing the former regimen.

Table 3.2 shows the name of SACT regimens generated from CEPAS datasets (regimen name in CEPAS), the approved SACT name, the recoded name used during the analysis and across this thesis (study name), and finally, the medicines that make up each SACT regimen (description of SACT).

Table 3.2. Renaming SACT regimen during the analysis.

Regimen name in CEPAS	SACT approved name	Study name	Description of SACT
Capecitabine C	Capecitabine	5FU	Capecitabine 1250mg/m^2 BD PO for 14/7
MOD DEGARMONT	5FU/leucovorin	5FU	Leucovorin 350 mg over 2 hours+ 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
MOD DG+ IR PICC	FOLFIRI	FOLFIRII	Irinotecan 180mg/ m^2 over 90 minutes+ leucovorin 350mg over 2hours + 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
OxMDG MET OxMDG metastatic	FOLFOX	FOLFOX	Oxaliplatin 85 mg/m^2 + leucovorin 350mg over 2hours + 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
XELOX MET	XELOX	FOLFOX	Oxaliplatin 130mg/m^2 over 2 hours+ Capecitabine 1000mg/m^2 BD PO for 14/7
AFLIB FOLFIRI C	Aflibercept+ FOLFIRI	Aflibercept+ FOLFIRI	Aflibercept 4mg/kg over 1 hour+ Irinotecan 180mg/ m^2 over 90 minutes+ leucovorin 350mg over 2hours + 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
CET 2 WK IRMDG C CET 2 WK IRMDG P CET IRMDG C1PICC CET IRMDG C2PICC CETUX IRMDG C1 CETUX IRMDG C2+	Cetuximab+ FOLFIRI	Cetuximab+ FOLFIRI	Cetuximab 500mg/m^2 over 1-2 hours + Irinotecan 180mg/ m^2 over 90 minutes+ leucovorin 350mg over 2hours + 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
CET 2 WK OXMDG C CET OXMDG C2PICC	Cetuximab+ FOLFOX	Cetuximab+ FOLFIRI	Cetuximab 500mg/m^2 over 1-2 hours + Oxaliplatin 85mg/m^2 over 2 hours + leucovorin 350mg over 2hours + 5FU 400mg/m^2 over 10 minutes then 2400 mg/m^2 over 46 hours
KEY: SACT= Systemic-anticancer therapy, CEPAS: chemotherapy electronic prescribing system			

In addition to the treatment recoding, SACT regimens were categorised according to their intensity into singlet, doublet and triplet, as illustrated in Table 3.3. This categorisation was performed to allow for better comparability across the different treatments.

Table 3.3. Treatment categorisation based on SACT intensity.

SACT intensity	Description of SACT
Singlet	5-Fluorouracil/leucovorin or Capecitabine
Doublet	5-Fluorouracil/leucovorin or Capecitabine + Oxaliplatin → FOLFOX or XELOX + Irinotican → FOLFIRI
Triplet	5-Fluorouracil/leucovorin + oxaliplatin or irinotecan + Cetuximab or aflibercept or oxaliplatin/irinotican (Cetuximab FOLFIRI) (aflibercept FOLFIRI) (FOLFOXIRI) (Cetuximab FOLFOX)
KEY: SACT= Systemic-anticancer therapy, IV= intravenous	

3.3.2.2 Radiotherapy information

Data regarding radiotherapy treatment details were obtained from CEPAS and ARIA (section 3.2.2 and section 3.2.7, respectively). However, because only a very small number of patients received concurrent radiotherapy treatment (<5 patients), this information could not be released from the Safe Haven and hence was not presented in the results.

3.3.2.3 Primary tumour resection

Data regarding primary tumour resection were drawn from the OPERA (section 3.2.6) dataset in addition to SMR01 (section 3.2.4.2) and SMR06 (section 3.2.4.3). Patients were classified as those who underwent a primary tumour resection (Yes/No). OPCS4 codes (Table 3.4) were used to identify patients who underwent primary colorectal tumour resections (National

Health Service Digital, 2016). Patients who were identified through the OPCS-4 code to have a primary tumour resection were coded “Yes”. For all other patients, it was assumed that no primary tumour resection was performed, so they were coded “No”.

Table 3.4. Examples of OPCS-4 codes and their corresponding descriptions.

OPCS-4 code	Description
H04	Total excision of colon and rectum
H05	Total excision of colon
H09	Excision of left hemicolon
H10	Excision of sigmoid colon
KEY: OPCS-4=Classification of interventions and procedures	

3.3.3 Cancer diagnostic information and tumour-related variables

3.3.3.1 Diagnosis details, Primary tumour location and sidedness

SMR06 was the principal source for affirmation of mCRC diagnosis and hence, patients who had a diagnosis of colon or rectal cancer as defined by ICD-10 codes were included following the identification of the cohort through CEPAS, which captures all SACTs. For patients who had more than one cancer record (i.e., colon and rectum) the incidence date of the earliest diagnosed tumour was used. Patients with diagnoses other than colon or rectal cancer in SMR06 were excluded (e.g., ileum and appendiceal cancer). However, for patients whose diagnosis details were missing from SMR06, other data sources were investigated to compensate for the missing in data in SMR06. Following discussions with the clinicians, it was agreed that one or more of the following datasets was used to identify the diagnosis information as an alternative for SMR06:

1- **NRS** – cause of death identified from ICD-10 codes corresponding to mCRC.
2- **OPERA**- The site of surgery coded by OPCS-4 was used to confirm the diagnosis. For example, an OPCS-4 code of H09 corresponds to the excision of the left hemicolon. This information was used to confirm the diagnosis of colon cancer. It can also be used to identify other variables, such as the primary tumour sidedness, which is the left side in this example. Some of the OPCS-4 codes used to obtain the diagnosis are illustrated in Table 3.4.
3- **ARIA**- the diagnosis information attached to radiotherapy intention as identified from ICD-10 codes.

4- **SMR00/01** – diagnosis from ICD-10 codes corresponding to mCRC and OPCS4 surgical codes related to emergency colorectal cancer surgery.

3.3.3.2 Tumour molecular profile

Data regarding the tumour molecular biomarkers were obtained from the NHS Greater Glasgow and Clyde (NHSGGC) Pathology Department, which uses LIMS (section 3.2.8). Patients were classified according to the tumour molecular biomarker status into patients harbouring mutations in the RAS or BRAF genes and those who were not (i.e., wild RAS tumour). The LIMS extract comprised a considerable number of missing records since assaying mCRC samples for BRAF codon 600 and RAS status mutations has only been made obligatory since July 2015, resulting in missing in data for the first six months of the study (i.e., 1st January 2015 until 30th June 2015).

3.3.3.3 Performance status

Eastern Cooperative Oncology Group performance status (ECOG PS) is one of the most widely used scales to assess patients' overall health. It was first developed in the 1960 (Zubrod et al., 1960) and published in the 1982 (Oken et al., 1982) to measure the patient's level of functioning in terms of their physical and self-care ability as well as the symptoms burden (Oken et al., 1982). The ECOG PS scale otherwise termed the ECOG/WHO scale, utilises a 6-point system. The scale ranges from 0 to 5 where 0 indicates perfect health and 5 indicates death, as shown in Table 3.5. For the study cohort, PS was retrieved from CEPAS and measured at the time of diagnosis and at each cycle of SACT. Recording ECOG PS has been made mandatory since July 2015 across the Scottish cancer networks; hence, missing data is likely to be less for cohorts after July 2015.

In this thesis, due to the small number of patients falling in grade 3 and the lack of patients in categories 4 and 5, patients were categorised into ECOG PS grades 0, 1, and ≥ 2, with PS ≥ 2 including grades 2 and 3.

Table 3.5. The ECOG PS (adopted from *(Oken et al., 1982)*).

ECOG PS (SMR06)	
Grade	**ECOG/WHO PS**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
KEY: SMR06= Scottish cancer registry**;** ECOG= Eastern Cooperative Oncology Group; PS= performance status, WHO= World Health organisation.	

3.3.4 Inflammatory biomarkers and blood cell count parameters

Inflammatory biomarkers and haematological indices are used to assess the prognosis for mCRC. Pre-treatment albumin, neutrophils-to-lymphocyte ratio (NLR), and carcinoembryonic antigen (CEA), with haemoglobin levels, are vital determinants of mCRC prognosis and survival (Riedl et al., 2017).

The values for these variables were obtained from SCI store (section 3.2.5) up to and including 28 days from the index date. Table 3.6 shows the reference ranges for the Inflammatory biomarkers and blood cell count parameter tests used in this thesis.

Albumin levels are commonly used as a surrogate marker to assess the nutritional status of patients with mCRC, with poor nutritional status as indicated by low albumin levels, has been associated with increased treatment-related toxicity, decreased treatment response, and poorer survival outcomes in patients with mCRC (Nazha et al., 2015). On the other hand, Elevated NLR levels have been associated with poorer prognosis in patients with mCRC. High NLR is indicative of increased systemic inflammation, which can promote tumour progression and metastasis. Evidence suggests that patients with higher NLR values at the time of diagnosis or treatment initiation tend to have shorter overall survival and decreased progression-free survival rates (Mazaki et al., 2020). Similarly, elevated levels of Pre-treatment CEA levels in mCRC have been found to have prognostic value. Higher baseline CEA levels are associated with more advanced disease, poorer prognosis, and shorter overall survival (Prager et al., 2014).

Table 3.6. Reference ranges for Inflammatory biomarkers and blood cell count parameter variables.

Inflammatory biomarkers and blood cell count parameters	Reference range	Reference
Albumin	≥ 34 g/L	(He et al., 2018)
Neutrophil-to-lymphocyte ratio (NLR)	≤ 5	(Walsh et al., 2005)
Carcinoembryonic antigen (CEA)	≤5 µg/L	(National Health Service Greater Glasgow and Clyde, 2020a)
Haemoglobin	Male 130 - 180g/L Female 115 - 165g/L	(National Health Service Greater Glasgow and Clyde, 2020c)

3.3.5 Comorbidities

A comorbidity refers to the "co-occurrence of more than one chronic or acute medical condition in one person coexisting with an index condition" (Bayliss et al., 2008). Comorbidities can be either described as an individual comorbidity or by using summary measures such as the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). For this thesis, CCI was used instead of individual comorbidity as it simplifies and standardizes the assessment process, captures the overall comorbidity burden, improves statistical power, and is clinically relevant and widely validated. The CCI was developed as a measure of 1-year mortality of patients through categorising comorbidities, where each category is allocated a weight that ranges between one, representing the least severe comorbidities (e.g., myocardial infarction, cerebrovascular disease) and six, representing the most severe comorbidities (e.g., solid metastatic tumours, acquired immune deficiency syndrome) – depending on its potential effect on mortality. The scores are then summed to calculate the overall score used to estimate patients' 1-year mortality risk. The CCI has been adapted to be used in administrative data using the ICD, 10th revision (ICD-10) (Quan et al., 2005) and Thygesen et al. established the validity of using ICD-10 codes retrieved from administrative databases (Thygesen et al., 2011). Health research widely uses the CCI to estimate the disease burden. Moreover, it has been validated for its capability of predicting mortality in several populations, and it has also been used in disease groups involving cancer patients (Singh et al., 1997, Birim, 2003, Cronin-Fenton et al., 2007, Wildes et al., 2008). For this thesis,

CCI was calculated using ICD-10 codes, which covered five years prior to the index date from SMR00 and SMR01 records. A 5-year period was chosen due to the minimal change in the CCI to mortality for long follow-ups (Fraccaro et al., 2016). Table 3.7 shows the codes and weights used to calculate the CCI. When CCI was calculated, the solid metastatic tumour of interest (i.e., mCRC) was excluded from calculations since CCI measures comorbidities, while mCRC is the condition of interest in the study. The severity of comorbidity was categorised into three distinct grades: no comorbidity, with CCI of 0, mild to moderate comorbidity, with CCI of 1-3, and severe comorbidity with CCI of ≥ 4.

Table 3.7. Weights and ICD-10 codes used to calculate Charlson Comorbidity Index *(Quan et al., 2005)*.

Charlson score (SMR00, SMR01)		
Comorbidity	**CCI weight**	**ICD-10 codes**
Myocardial infarction	1	I21, I22, I25.2
Congestive heart failure	1	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 – I42.9, I43, I50, P29.0
Peripheral vascular disease	1	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	G45, G46, H34.0, I60 – I69
Dementia	1	F00 – F03, F05.1, G30, G31.1
Chronic pulmonary disease	1	I27.8, I27.9, J40 – J47, J60 – J67, J68.4, J70.1, J70.3
Rheumatic disease	1	M05, M06, M31.5, M32 – M34, M35.1, M35.3, M36.0
Ulcer disease	1	K25 – K28
Mild liver disease	1	B18, K70.0 – K70.3, K70.9, K71.3 – K71.5, K71.7, K73, K74, K76.0, K76.2 – K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	1	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with end organ damage	2	E10.2 – E10.5, E10.7, E11.2 – E11.5, E11.7, E12.2 – E12.5, E12.7, E13.2 – E13.5, E13.7, E14.2 – E14.5, E14.7
Hemiplegia or paraplegia	2	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0 – G83.4, G83.9
Moderate or severe renal disease	2	I12.0, I13.1, N03.2 – N03.7, N05.2 – N05.7, N18, N19, N25.0, Z49.0 – Z49.2, Z94.0, Z99.2
Leukaemia, lymphoma, any tumour	2	C00 – C26, C30 – C34, C37 – C41, C43, C45 – C58, C60 – C76, C81 – C85, C88, C90 – C97
Moderate or severe liver disease	3	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5 – K76.7

Metastatic solid tumour	6	C77 – C80
Acquired immune deficiency syndrome	6	B20 – B22, B24
KEY: SMR00= Outpatient Appointments and Attendances; SMR01= General Acute Inpatient and Day Case; CCI= Charlson comorbidity index; ICD= International classification of the diseases		

3.4 Data management

3.4.1 Data access and governance

Complying with the requirements of the Data Protection Act 1998 that dictates the involvement of data controllers and to ensure a legitimate use and access for NHS Scotland health data, the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) and Caldicott Guardians were established to fulfil these functions on a national and regional level, respectively (National Health Service Scotland, 2019). Since this thesis was undertaken in a single NHS health board (i.e., NHS GGC), the Caldicott Guardian approval was obtained to access the linked datasets for purposes unrelated to direct patient care (appendix IV). Additional ethical approval was not required as this project utilises data from administrative systems, which eliminates the need for explicit patient consent. Also, before data access was made, an accredited course in information governance was required to be undertaken; the certificate can be found in appendix IV.

Initial data extraction from the national datasets (i.e., SMR and NRS) was performed by the electronic Data Research and Innovation Services (eDRIS) team. In contrast, CEPAS was extracted by the CMOP team directly and sent to the University of Glasgow safe haven, where all datasets were linked together by the Safe Haven staff through the individual CHI number, which was then removed. An anonymous patient ID was assigned for each patient. Access to this anonymised data was offered through a secure platform hosted by the Robertson Centre for Biostatistics at the University of Glasgow. Access was allowed via a virtual private network (VPN) connection, with the procedure being protected by a password to login into the remote server. NHS GGC Safe Haven does not allow users to upload or download data from or into Safe Haven. The Safe Haven staff uploaded research inputs into a study drive accessible by the user. All results included in chapter 4, chapter 5, and chapter 6 were extracted in tabular and graphical form. They underwent statistical disclosure check by Safe Haven staff before being released to the user, given that no variable category containing less than five patients can be released to reduce the likelihood of identifying the patients.

(National Health Service Greater Glasgow and Clyde, 2020b). The Safe Haven offers a range of software that can be used to handle and analyse the data, including R, SPSS and Stata.

3.4.2 Data structure and content

The Scottish health informatics system is known to be one of the most developed systems in the world, with the health datasets recognised for their high quality. Yet, most of the data in those datasets are collected for administrative purposes such as financial or clinical management purposes. This means that these datasets may comprise many challenges for researchers. One limitation lies in that administrative data may vary in the level of details, completeness and accuracy. For example, coding administrative data may be affected by how ICD-10 codes are applied or how physician recorded entries are interpreted by the medical records clerks (Sarrazin and Rosenthal, 2012, Hashimoto et al., 2014). Missing in data presents another issue with administrative datasets; such an issue can appear in the traditional sense where recoding is incomplete or manifest if a person fails to interact with the service and thus will not be captured by the administrative data. As a result of the pitfalls that might present with the administrative data, preparation steps are needed before analysing the datasets.

The following subsections will highlight the preparation and cleaning process applied to the datasets used for this thesis.

3.4.3 Data preparation and cleaning

Data preparation is the process of transforming raw data into a dataset that can be appropriately analysed. This process is essential in studies that involve administrative data as it provides an opportunity to address the limitations of raw data and reduce the likelihood of bias in subsequent analyses. It requires visual inspection and manual exploration of the data to understand the content and structure of data and recognise problems that need to be resolved. This process also requires extracting relevant data and generating additional variables of interest. The first step of data extraction includes identifying data from the relevant fields within the datasets. The relevant information is stored within the datasets in various formats across different data tables. Raw data may be structured (coded using controlled terminology such as ICD-10), semi-structured (e.g., laboratory results), and unstructured (clinical notes entered as text) (Denaxas et al., 2017). With the variability in data type, different approaches are used to process and recode the data.

Data cleaning is the process of identifying errors and inconsistencies from a dataset to improve the quality of the data (Rahm, 2000). Those errors can be implausible values, miscoded data, missing data, inaccurate or incomplete entries and records duplication. This process involves manual data exploration, screening for potential errors, and deciding whether and how those errors should be corrected, deleted or ignored (Van den Broeck et al., 2005).

The extract from CHI which provided the sociodemographic details, consisted of 27 variables and 309 observations. In contrast, the extract from NRS provided 260 death observations and 38 variables. The complete CEPAS extract, as requested for this study, comprised 47915 observations (prescription) and 30 variables, capturing all SACT prescriptions issued for the patients between January 2015 and December 2016, of which approximately 5021 were prescriptions of treatments of interest. The SMR00/01 extracts, with 49 and 92 variables, respectively, together accounted for an additional 24876 observations (covering all recorded inpatient episodes and outpatient appointments for every cohort member between 2015 and 2016), while the SMR06 extract consisted of 362 observations and 209 variables. The largest dataset was SCI which covered 665514 observations. The molecular pathology dataset contained 235 observations and 11 variables, and OPERA dataset consisted of 547 observations. ARIA extract was the smallest of the datasets, with 33 observations and nine variables.

In this thesis, several steps of data cleaning and preparation were carried out on the ten included datasets (CHI, SMR00, SMR01, SMR06, CEPAS, NRS, SCI-store, ARIA, OPERA, and the clinical pathology dataset) before proceeding with the analysis. Data preparation, cleaning, and analysis for this study were performed using R software version 3.5.0. and the following packages were used: Base R, reshape, tidyverse, and lubridate. Figure 3.4 shows the cleaning process performed for the datasets used in this thesis. The general datasets preparation process involved the following steps:

1- Removing variables and observations with complete missing values (Not Available; NA)
2- Selecting only relevant variables and excluding irrelevant variables, for example, the GP practice code, is not a variable of interest in SMR01, and thus it was eliminated in the cleaning process.

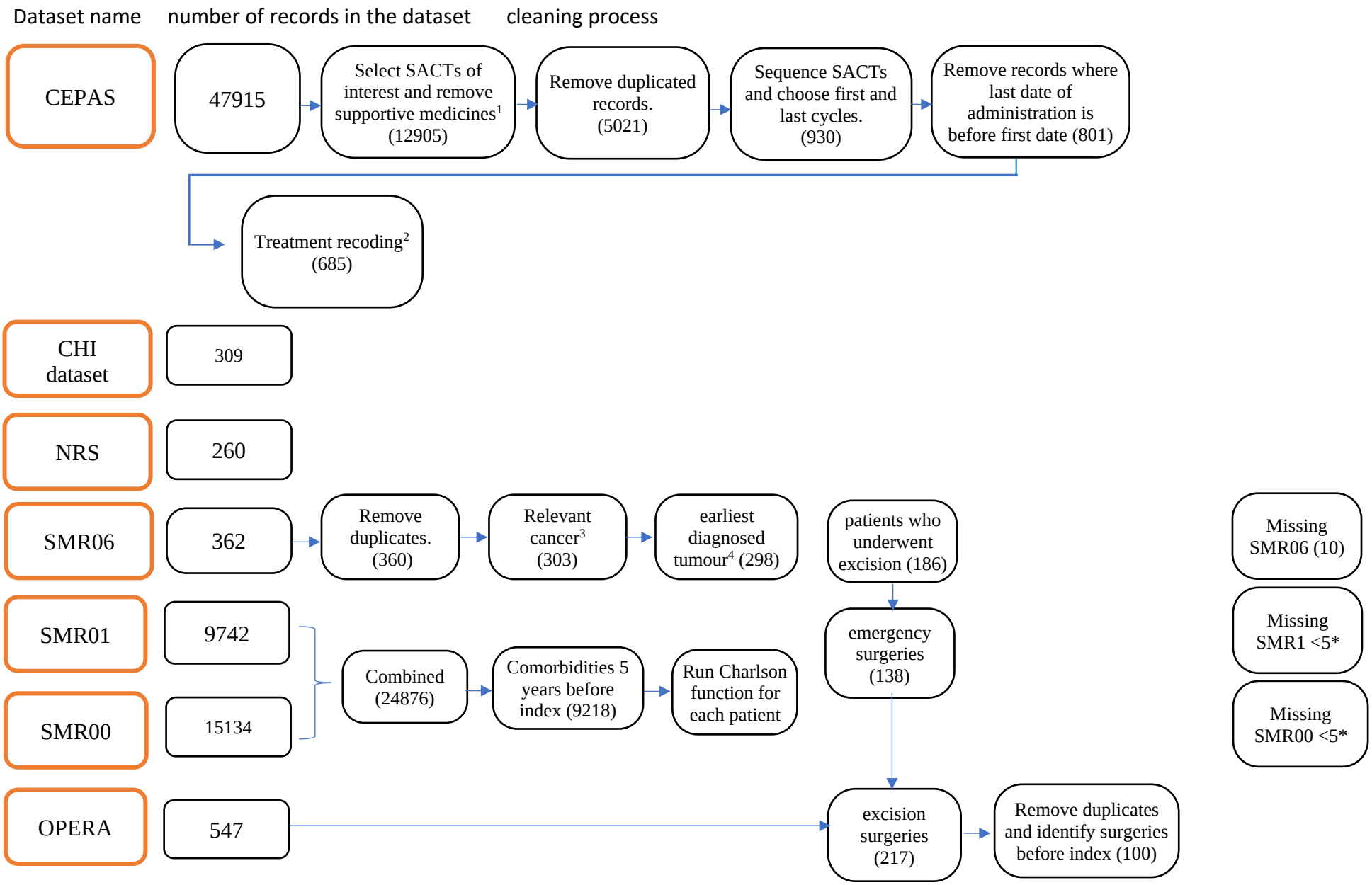
3- Converting data to the appropriate type – datasets were imported into R for analysis as .csv files, which store information as plain text. This, however, results in some limitations when performing the analysis, and, by default, character variables (also called string variables; variables that contain anything other than numbers, e.g., letters or special characters) are converted into factor variables (also referred to as categorical variables) when imported into R. Hence, converting data to the appropriate type was needed for variables that were converted into factor variables but were supposed to be character variables; and for numeric variables, which should have been factor variables or dates. Table 3.8 shows the major examples.

4- Recoding variables – this process was mainly needed for missing data as many different signifiers have been used across the data sets, including spaces and special characters. This step was undertaken to ensure consistency and enable data analysis.

5- Deriving variables was undertaken when a new variable was derived from an existing variable. For example, if a primary tumour location was the rectum, the tumour sidedness would be recoded as the left side.

Table 3.8. Examples for converting data to the appropriate type.

After importing file	After converting data type	Variables
Factor	Character	Drug name, Cause of death
Numeric	Factor	SIMD*, PS
Numeric	Date	Date of birth, diagnosis date, date of SACT prescription, date of death
KEY: SIMD=Scottish Index of Multiple deprivation; PS= performance status; SACT=systemic anticancer therapy		


Dataset name
number of records in the dataset
cleaning process
CEPAS
47915
Select SACTs of interest and remove supportive medicines[1] (12905)
Remove duplicated records. (5021)
Sequence SACTs and choose first and last cycles. (930)
Remove records where last date of administration is before first date (801)
Treatment recoding[2] (685)
CHI dataset
309
NRS
260
SMR06
362
Remove duplicates. (360)
Relevant cancer[3] (303)
earliest diagnosed tumour[4] (298)
patients who underwent excision (186)
Missing SMR06 (10)
SMR01
9742
SMR00
15134
Combined (24876)
Comorbidities 5 years before index (9218)
Run Charlson function for each patient
emergency surgeries (138)
Missing SMR1 <5*
Missing SMR00 <5*
OPERA
547
excision surgeries (217)
Remove duplicates and identify surgeries before index (100)

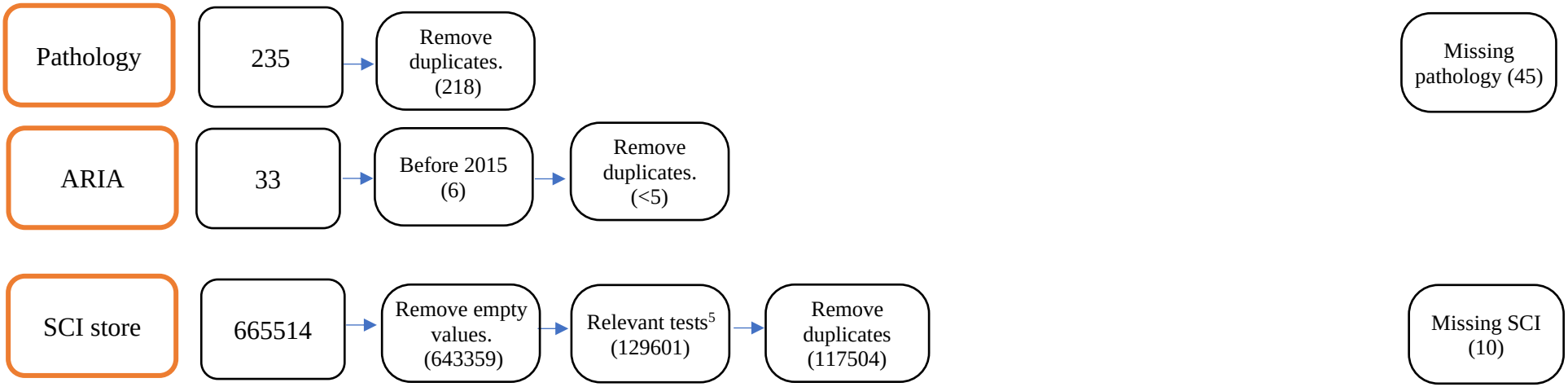


Figure 3.4 Preparation and cleaning of the datasets used in this thesis.

1- Supportive medicines: e.g., dexamethasone, metoclopramide
2- Treatment recoding: further explanation provided in section 3.2.1
3- Relevant cancer: colon cancer or rectal cancer
4- Earliest diagnosed tumour: For patients who had more than one cancer record (i.e., colon and rectum), the incidence date of the earliest diagnosed tumour was used.
5- Relevant tests: haemoglobin, carcinoembryonic antigen, neutrophils -to- lymphocyte ratio, and albumin

KEY: SACT= systemic Anti-cancer treatment; CHI= community health index; NRS= National records of Scotland/death; SMR= Scottish medical records; SCI= Scottish care information; BNF= British National Formulary; *<5: information could not be released from the Safe Haven

4 Chapter 4: Baseline characteristics of metastatic colorectal cancer patients initiating systemic anti-cancer therapy in NHS Greater Glasgow and Clyde.

4.1 Introduction.

The global burden of colorectal cancer (CRC) is expected to increase by 60% by 2030, with more than 2.2 million new cases and 1.1 million deaths (Arnold et al., 2017a). Incidence rates of CRC rise with increasing age; however, in recent years, a rising incidence of CRC has been observed in younger age groups before the age of 50 years. (Favoriti et al., 2016, Siegel et al., 2019). Globally, approximately 25% of patients with CRC present with overt metastatic disease at the time of primary diagnosis, with 40-50% of all CRC patients developing mCRC. This Figure has been stable over the last two decades (Van Cutsem et al., 2014a, van der Geest et al., 2015, Van Cutsem et al., 2014b).

In Scotland, CRC was the third most frequently diagnosed cancer in men and women in 2019 and accounted for the second-highest number of cancer-related deaths in 2018 (Public health information for Scotland, 2021). It has been projected that the incidence of CRC in Scotland will increase by 42.7% between 2008-2012 and 2023-2027 (Public Health Scotland, 2015). Between 2016 and 2018, the incidence of CRC in Scotland was reported to be the highest among the four United Kingdome (UK) countries, with an age-standardised rate (ASR) of 73.7 cases per 100,000 compared to 68.5, 72, and 73.6 cases per 100,000 in England, Wales, and Northern Ireland, respectively (Cancer Research UK, 2021).

The advances in record linkage in Scotland (section 3.1.1) have brought great benefits in understanding patients' characteristics across different diseases and treatments. In Scotland, it has been demonstrated that linked data could serve as a rich source of information to describe cancer patients and their treatment outcomes (Mueller et al., 2022). Moreover, record linkage can provide a deeper characterisation of the patient's needs which is essential to understand the reasons causing disparities in treatments and outcomes. Recently, funding was secured by the COloRECTal Repository (CORECT-R), a programme that aims to quantify the characteristics and variation in CRC in the UK (University of Oxford, 2020) to develop the first national linked colorectal cancer dataset in Scotland that can be used to analyse and

understand variation in CRC patients' characteristics, treatments, and outcomes (Hanna et al., 2021). The published work so far has focussed on the early stages of CRC (Lemmon et al., 2022). Nevertheless, given the global and national increase in the burden of mCRC, it is becoming increasingly important to understand the characteristics of mCRC for several reasons. First, it allows for a better understanding of the patient population, such as their demographics, comorbidities, and disease characteristics, which can help guide treatment selection and treatment outcomes. Second, it can help identify potential disparities in access to cancer care and outcomes, such as differences in treatment utilisation or response based on patient characteristics. This information can help guide interventions to improve treatment outcomes for the patients.

Aims and objectives.

The aims of this chapter are to:

1- Describe the characteristics of mCRC patients initiating first-line mCRC SACT in NHS GGC health board in Scotland,

2- Provide an overview of the thesis population used for subsequent analysis (factors influencing prescribing of first-line mCRC systemic anti-cancer therapy, chapter 5; and treatment pathways and treatment outcomes for mCRC patients, chapter 6) by describing patients' baseline characteristics, including the sociodemographic features, disease characteristics, previous treatment details, and the initial mCRC regimens the patients received, and

3- Describe how the study population was selected for the study.

4.2 Methods.

4.2.1 Study design and cohort identification

This study was designed as a retrospective cohort study from the 1st of January 2015 to the 28th of February 2018, using linked, routinely collected administrative healthcare data in NHS GGC. Patients who initiated mCRC SACT at the Beatson West of Scotland cancer centre in Glasgow between the 1st of January 2015 and the 31st of December 2016 were identified through CEPAS, where all administered SACTs, with their respective indications were captured (section 3.2.2). The Beatson West of Scotland cancer centre is the largest cancer centre in Scotland, covering the West of Scotland cancer network (WoSCAN), with a total covered population of 3,159,940 (Section 3.2.2).

A patient's index date for study inclusion was defined as the date of the first mCRC SACT in the study timeframe between the 1st of January 2015 and the 31st of December 2016 (Figure 4.1).

SACT prescriptions issued during the study period were identified from patients' records within CEPAS using the names of SACT regimens. The treatment recoding process, which was used to simplify exposure and to define SACT lines (section 3.3.2.1), was used to identify treatment lines based on agreed decision rules with the lead clinician. Further details about recoding the SACTs, stratifying them into treatment lines, and categorising SACTs were discussed in section 3.2.2.

Within CEPAS, patients identified to have no prescription for mCRC SACT before the 1st of January 2015 were defined as new mCRC SACT users (incident users). In contrast, patients identified to have mCRC SACT prescriptions before the 1st of January 2015 were defined as prevalent users (Figure 4.1). In pharmacoepidemiological studies, the new user design denotes a cohort of patients who initiate treatment of interest and starts follow-up after treatment initiation (Ray, 2003). In contrast, the prevalent user design includes current (prevalent) users of treatment of interest. And hence, the follow-up starts at different time points in each individual of the study (Suissa et al., 2017). Identifying incident mCRC cases allows for an accurate assessment of the clinical outcomes related to the treatment exposure. It can reduce bias from missing data on prior treatment, which is valuable when different treatments are compared. Also, identifying incident cases minimises inception bias which arises if the patients are not followed from the beginning of the treatment (Lund et al., 2015). In this thesis, only new mCRC SACT users were included in the description of the cohort, assessing the factors influencing the selection of the initial SACT regimen for this cohort of patients (chapter 5) and the treatment pathways and outcomes for new mCRC SACT users (chapter 6).

Patient inclusion and exclusion criteria and the identification method are shown in Table 4.1. Patients who initiated mCRC SACT between 1/1/2015 and 31/12/2016, had no prescription for mCRC SACT before the 1st of January 2015, were diagnosed with mCRC before the index date, and were above 18 years at the index date were included in the study. However, patients were excluded if they initiated mCRC SACT before 1/1/2015 or after 31/12/2016, were prescribed SACT for other cancer diagnoses (e.g., breast cancer), received mCRC SACT

as part of a clinical trial or initiated an adjuvant/ neoadjuvant SACT during the study timeframe due to the potential for these patients to be diagnosed with stage II or III colorectal cancer. The focus of our study was specifically on individuals with metastatic CRC, who initiated first line mCRC SACT. Therefore, to ensure cohort homogeneity, the decision was made to exclude those patients who initiated adjuvant SACT during the study inclusion period (between 1/1/2015 and 31/12/2016), as their disease stage and treatment trajectory deviated from our intended population of interest. However, patients who were identified to be previously (i.e., before 2015) treated with adjuvant/neo-adjuvant SACTs were not excluded, as it was assumed that these patents have progressed to a metastatic stage of the disease by the time of study inclusion period.

Adjuvant therapy is defined as the SACT administered following primary resection of the tumour to reduce the risk of relapse or death by eliminating residual metastatic disease (Saltz, 2010), while neoadjuvant therapy is defined as the chemotherapy or chemoradiation administered before primary tumour resection aiming to downstage the tumour (reduce the size, the extent of metastasis or involvement of lymph nodes) (Bismuth et al., 1996).

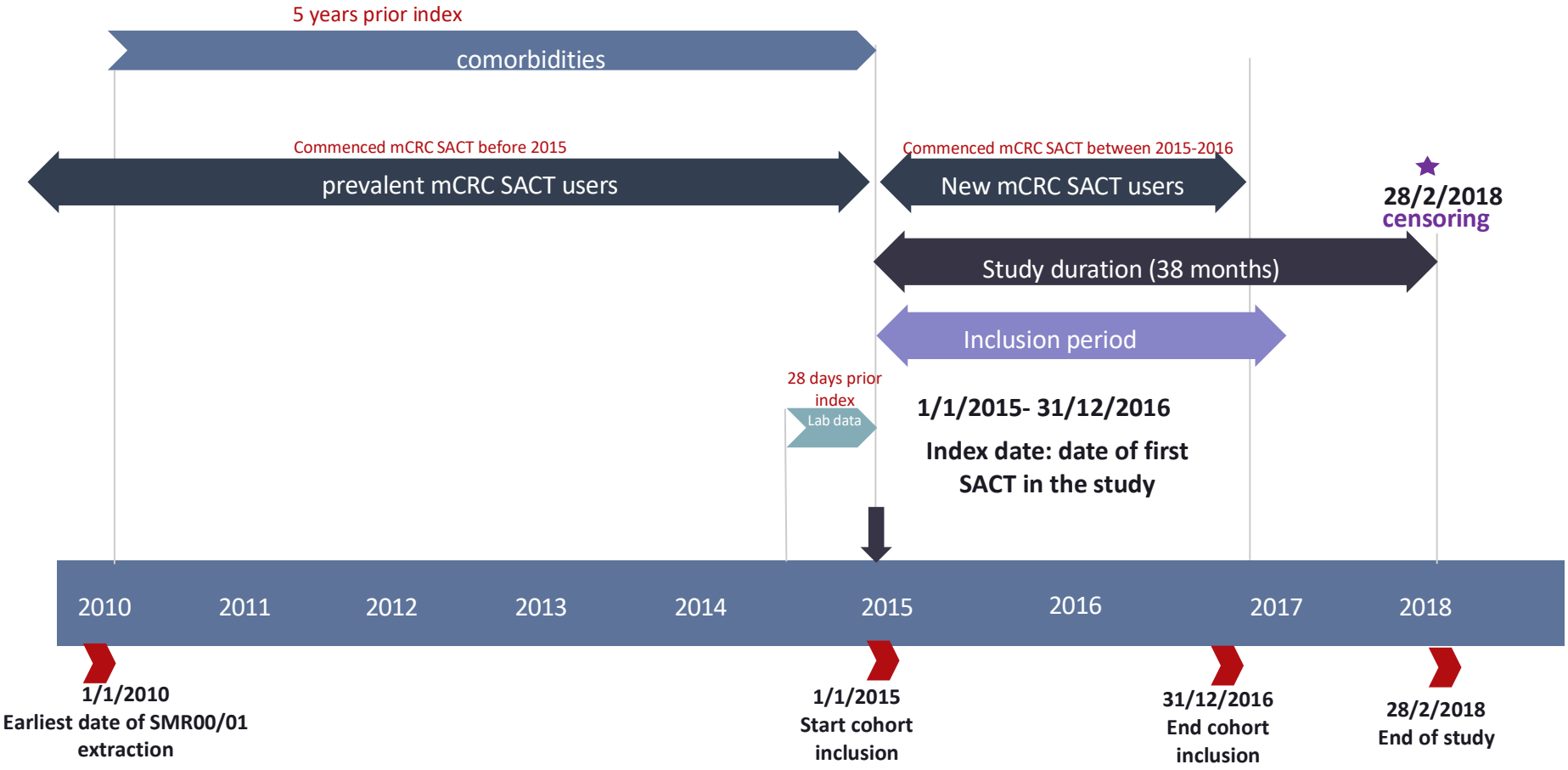


Figure 4.1. The study timeline

Table 4.1. Study population inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion	Identification method
Patients' age	≥ 18 years at index date	< 18 years at index date	Date of index SACT from CEPAS was subtracted from date of birth obtained from CHI database
mCRC diagnosis	ICD-10 code for mCRC: C18, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9, C20, C21.1, C21.8, C78.5, C80, C80.9	Other ICD-10 codes	Primarily: From SMR06 Supplemented from OPERA, NRS, and SMR01
Index SACT date	Between 1/1/2015 and 31/12/2016	Before 1/1/2015 (i.e., prevalent users), After 31/12/2016	Date of first prescription can be identified in CEPAS
SACT	Any oral or injectable mCRC SACT	Adjuvant/ neo adjuvant SACT, SACT as a part of a clinical trial, SACT for another cancer diagnosis	From CEPAS, the diagnosis which each SACT is attached to can provide information about the prescription intention, hence metastatic SACT was selected

KEY: CEPAS= Chemotherapy electronic prescribing system; CHI= Community Health Index; ICD= International Classification of Disease; mCRC= metastatic colorectal cancer; SMR06= Scottish cancer registry; SMR01: SACT= systemic anti-cancer therapy; NRS= National records of Scotland; SMR 00= Scottish medical records Outpatient Appointments and Attendances; SMR01= General Acute Inpatient and Day Case; SMR06= Scottish cancer registry; OPERA= Elective & emergency operations.

4.2.2 Data sources and variables.

Data collected for this thesis were extracted from ten different data sources. The data sources used in this study were described in section 3.2. Table 4.2 provides a summary of the datasets.

Table 4.2 Summary of the datasets used in the study.

Data source	Rational of use	Content	Variables of interest
Community Health Index (CHI) (Section 3.2.1)	CHI number facilitates the linkage of patients' electronic records	Demographic information	Date of birth, gender, SIMD score
Electronic chemotherapy prescribing system (CEPAS) (Section 3.2.2)	Identify the cohort and the SACT regimens	Systemic Anti-Cancer Therapy (SACT)	SACT regimens, date of SACT prescription, performance status
The Scottish Cancer Registry (SMR06) (Section 3.2.4.3)	Identify the diagnosis and the tumour related characteristics	Cancer diagnosis and characteristics of the tumour	Incidence date, tumour sidedness
Scottish Morbidity Records Outpatient Attendance dataset (SMR00) (Section 3.2.4.1)	Identify comorbidities	Episode level data from patients on new outpatient clinic appointments	Clinic speciality, clinic date
Scottish Morbidity Records General/Acute Inpatient and Day Case dataset (SMR01) (Section 3.2.4.2)	Identify comorbidities	Episode level data on inpatient hospital admissions and day case discharges	ICD-10 diagnosis, date, operations, length of stay
Scottish Care Information (SCI store) (Section 3.2.5)	Identify laboratory test results for prognosis and follow-up	Acute phase proteins (CRP, Albumin,) and blood cell count parameters (NLR)	Sample name, date and quantitative value of the tests
Radiotherapy treatment records (ARIA) (Section 3.2.7)	Record radiotherapy information	Radiotherapy treatments	Treatment intent, course start and end date, side of the applied radiation
Elective & emergency operations (OPERA) (Section 3.2.6)	Identify the tumour sidedness and operations carried out	Surgical interventions	Operation date, procedure side
National Records of Scotland (NRS) (Section 3.2.3)	Identify an outcome (death)	Death records	Date of death, cause of death
Molecular pathology (Section 3.2.8)	Identify type of mutation (RAS, BRAF)	Tumour molecular biology	Diagnosis, results
KEY: CHI= community health index; SIMD= Scottish index for multiple deprivation; SACT= systemic ant-cancer therapy; CRP= C-reactive protein; NLR= neutrophils to lymphocytes ratio			

Baseline characteristics refer to the set of sociodemographic, clinical, and other characteristics of the study participants at the beginning of the study before any intervention or treatment is administered. In this thesis, the baseline characteristics were investigated before the administration of index SACT. Sociodemographic characteristics, including gender, age at index SACT and SIMD score, were determined from CHI and NRS (section 3.3.1), while comorbidities were measured from hospital and outpatient clinic records spanning five years prior to the index date (section3.3.5 and Figure 4.1). inflammatory biomarkers were obtained from SCI store up to and including 28 days from the index date (section 3.3.4 and Figure 4.1). Broadly, the variables used to describe the cohort at baseline include sociodemographic characteristics (age, gender, SIMD score), treatment characteristics (baseline SACT and primary tumour resection), tumour characteristics (primary tumour location, tumour sidedness, type of mutation), clinical characteristics (comorbidities and performance status), and Inflammatory biomarkers and blood cell count parameters (CEA, haemoglobin, NLR, and albumin). Table 4.3 presents the variables selected for this study and the coding method. For all variable, missing information were coded as "unknown".

The variables used in this thesis were selected for their relevance and potential impact on the exposure (mCRC SACT) or the outcome (survival), which will be elaborated in greater details in chapter 5 (factors influencing the selection of first-line mCRC SACTs) and chapter 6 (treatment pathways and treatment outcomes for mCRC patients), respectively.

Table 4.3. Variables used to describe the baseline characteristics of mCRC patients and the coding method.

Variable	Coding
Sociodemographic characteristics	
Age at index SACT (Section 3.3.1.1)	Continuous variable Categorical variable (≥ 65, <65)
Gender (Section 3.3.1.1)	Binary (Male, Female)
SIMD (Section 3.3.1.2)	Ordinal categorical (1,2,3,4,5)
Treatment characteristics	
Baseline SACT	Nominal categorical (5FU, FOLFOX, FOLFIRI, cetuximab+FOLFIRI, Aflibercept+ FOLFIRI)
Primary tumour resection (Section 3.3.2.3)	Binary (Yes, No)
Clinical characteristics	
ECOG PS (Section 3.3.3.3)	Ordinal categorical (0,1, ≥ 2)
Comorbidity (CCI) (Section 3.3.5)	Ordinal categorical (0, [1-3], ≥4)
Tumour characteristics	
Primary tumour location (Section 3.3.3.1)	Categorical (colon, rectum, transverse)

Primary tumour sidedness (Section 3.3.3.1)	Nominal categorical (left, right, transverse)
Molecular profile (Section 3.3.3.2)	Nominal categorical (Mutant RAS, Wild RAS, Mutant BRAF)
Inflammatory biomarkers and blood cell count parameters	
Albumin (Section 3.3.4)	Binary (≥ 34, < 34)
CEA (Section 3.3.4)	Binary (≤ 5, > 5)
Haemoglobin (Section 3.3.4)	Binary (Normal, upper, or lower limit of normal)
NLR ((Section 3.3.4)	Binary (≤5, >5)
KEY: SIMD= Scottish index for multiple deprivation; SACT= systemic ant-cancer therapy; ECOG PS= eastern cooperative oncology group performance status; CRP= C-reactive protein; NLR= neutrophils to lymphocytes ratio	

4.2.3 Statistical analysis

Summary statistics were used to describe the baseline characteristics of the patients. Categorical variables were summarised using proportions and frequencies while median and inter-quartile ranges (IQR) or mean and standard deviation (SD) were used to summarise continuous data, as appropriate. Median values were chosen when the data were not normally distributed, and mean values were used when data were normally distributed. The normality of the data was checked using the Shapiro–Wilk test, and data were assumed to be normally distributed when the P value was more than 0.05.

For all the analyses in this chapter, any category containing less than five patients was not presented in the tables or Figures as a part of the University of Glasgow safe haven permission to use the current data. All analyses were carried out using R, and the following packages were used: Base R, dplyr, and lubridate. R code script is presented in appendix VI.

4.3 Results

4.3.1 Overview of the cohort

Between 1/1/2015 and 31/12/2016, a total of 317 patients were identified via CEPAS. Of these, 97 patients were excluded for several reasons as illustrated in Figure 4.2. Hence, 220 new mCRC SACT users (i.e., incident patients) who initiated mCRC SACT regimen between 01/01/2015 and 31/12/2016 were included in the study analysis.

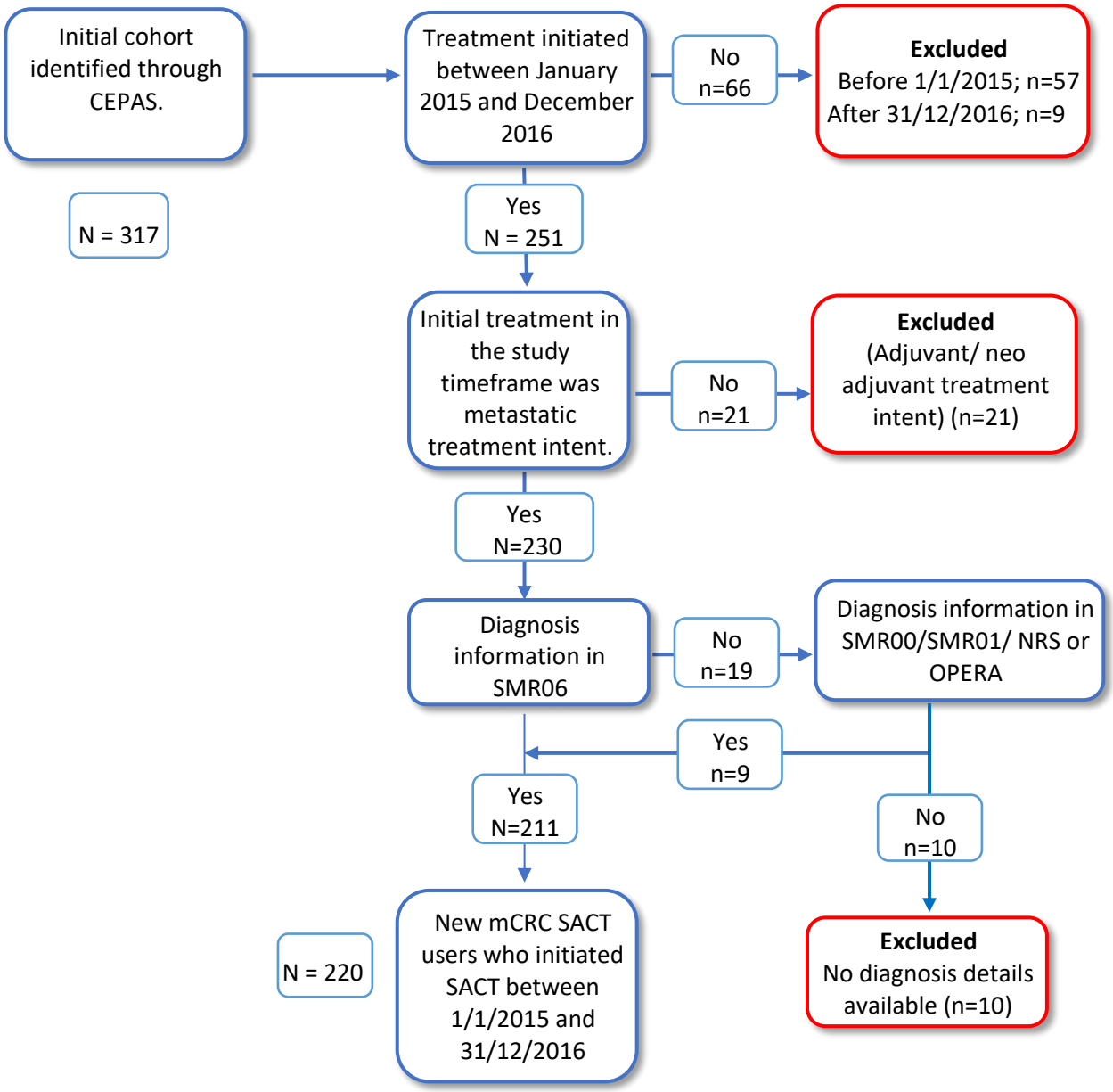


Figure 4.2. Cohort selection criteria flowchart for mCRC patients in NHS GGC initiating systemic anti-cancer treatments for metastatic colorectal cancer between 2015 and 2016.

KEY: CEPAS= chemotherapy electronic prescribing system; SMR06= Scottish cancer registry; SMR 00= Scottish medical records Outpatient Appointments and Attendances; SMR01= General Acute Inpatient and Day Case, OPERA= Elective & emergency operations; NRS= national records of Scotland; mCRC= metastatic colorectal cancer; SACT= systemic ant-cancer therapy

4.3.2 Index SACT distribution

Patients received various SACT regimens at index: the majority of the patients (N=115, 52.3%) were treated with a doublet therapy of FOLFOX, XELOX or FOLFIRI. Table 4.4 shows the distribution of treatment at index date across the patients.

Table 4. 4 Treatment distribution for patients in NHS Greater Glasgow and Clyde health board initiating systemic anti-cancer treatments for metastatic colorectal cancer between 2015 and 2016 (N=220).

Systemic anti-cancer therapy	N=220 (%)
Singlet treatment • *5FU or capecitabine*	**49 (22.3)**
Doublet treatment • *FOLFOX or XELOX* • *FOLFIRI*	**115 (52.3)** *68 (30.9)* *47 (21.4)*
Triplet treatment • *Aflibercept+FOLFIRI* • *Cetuximab+ FOLFIRI or cetuximab+FOLFOX* • *FOLFOXIRI*	**56 (25.4)** 11 (5) 43 (19.5) *
KEY 5FU= Fluorouracil/leucovorin; FOLFOX = Fluorouracil/leucovorin+xaliplatin; FOLFIRI= Fluorouracil/leucovorin + irinotecan; FOLFOXIRI= Fluorouracil/leucovorin+ oxaliplatin+ irinotecan; XELOX= Capecitabine +oxaliplatin. **SACTs containing less than 5 patients were not presented in numbers**	

4.3.3 Baseline characteristics.

The following sections will present the sociodemographic characteristics, tumour characteristics, clinical characteristics, treatment characteristics, inflammatory biomarkers, and blood cell count parameters for mCRC patients initiated mCRC SACTs between 1/1/2015 and 31/12/2016 in NHS GGC. SACTs including less than five patients will not be presented in the tables and Figures, and for any variable containing less than five patients, these characteristics will also not be presented. Since aflibercept+FOLFIRI included 11 patients only, the majority of baseline characteristics will not be presented.

4.3.3.1 Sociodemographic characteristics.

Table 4.5 shows the baseline characteristics for the new mCRC SACT users who initiated treatment between 1/1/2015 and 31/12/2016. Of the 220 patients identified, 105 (47.4%) were female.

For the entire cohort, the median age at index SACT was 66 years (IQR 57-73).

The socioeconomic status was measured via the SIMD score (section 3.3.1.2). For the entire cohort, about one-third of the patients (N= 68, 30.9%) resided in the most deprived areas of the NHS GGC health board areas (rank 1), while 20% (N=44) resided in the least deprived areas (rank 5).

4.3.3.2 Clinical characteristics

Most of the patients included in this study had no comorbidity based on CCI (CCI= zero, N=162, 73.6%) (section 3.3.5). In contrast, 8 (3.6%) patients had severe comorbidities (CCI ≥ 4*).*

At the time of index SACT, 22.7% (N=50) of the patients had an ECOG PS of zero, indicating they were fully active (section 3.3.3.3). In contrast, 6.4% of patients (N=14) had an ECOG PS of 2 or more, implying limited ability for self-care.

4.3.3.3 Tumour characteristics

Out of the 220 patients, 156 (70.9%) patients had primary colon cancer, while 57 (25.9%) patients had primary rectal cancer, with almost similar proportions of the patients across individual SACT regimens had the colon as the primary tumour site.

A total of 175 (79.5%) patients were tested for RAS and BRAF gene mutations. Of these, 81 (36.8%) patients were found to have a mutated RAS gene, whereas 77 (35%) patients had a wild-type RAS, and 17 (7.7%) patients had a mutation in the BRAF gene. Of note, 13 (72.2%) of the patients with a mutated BRAF gene were female, in contrast to 5 (27.8%) male patients (not presented in the table).

4.3.3.4 Inflammatory biomarkers and blood cell count parameters

At the time of index SACT, 50.5% (N= 111) of all patients had anaemia with haemoglobin values less than 115 g/L for females and values less than 130 mg/dL for male patients. Levels

of carcinoembryonic antigen were elevated in 64.1% (N=141) of the patients at the time of index SACT, indicating poor prognosis, while hypoalbuminemia with albumin levels less than 34 mg/dL presented in 53.6% (N=118) of the patients at the index SACT, indicating a worse prognosis. Most patients treated with a singlet SACT had hypoalbuminemia (N= 37, 75.5%). Conversely, less than half of the patients treated with a triplet SACT of cetuximab+FOLFIRI had hypoalbuminemia at index SACT (N= 19, 44.2%). Finally, high neutrophils to lymphocyte ratio, which indicates poor prognosis, was found in 158 (71.8%) of the patients.

Table 4.5 Baseline characteristics for the mCRC patients initiating SACT in NHS Greater Glasgow and Clyde between 2015 and 2016, overall and stratified by SACT (N=220)*

Variable	Full cohort (N=220)	5FU/leucoverine (n=49)	FOFLOX (n= 68)	FOLFIRI (n=47)	Aflibercept+ FOLFIRI (n=11)	Cetuximab+ FOLFIRI (n=43)
Sociodemographic characterisitcs						
Gender						
Female	105 (47.7)	28 (57.1)	36 (52.9)	22 (46.8)	5 (45.5)	12 (27.9)
Male	115 (52.3)	21 (42.9)	32 (47.1)	25 (53.2)	6 (54.5)	31 (72.1)
Age group at diagnosis [years) (%)						
≥ 65	118 (53.6)	43 (87.8)	36 (52.9)	22 (46.8)	*	13 (30.2)
< 65	102 (46.4)	6 (12.2)	32 (47.1)	25 (53.2)	8 (72.7)	30 (69.8)
Median age [years] (IQR)	66 (57-73)	76 (68.8-81)	66.5 (58-72)	66 (54.5-72.8)	64 (55-69)	59 (52.8-65.2)
SIMD score						
1	68 (30.9)	13 (26.5)	25 (36.8)	13 (27.7)	*	14 (32.6)
2	43 (19.5)	15 (30.6)	8 (11.8)	11 (23.4)	*	8 (18.6)
3	25 (11.4)	7 (14.3)	*	9 (19.1)	*	*
4	37 (16.8)	6 (12.2)	10 (14.7)	6 (12.8)	*	11 (25.6)
5	44 (20)	8 (16.3)	19 (27.9)	7 (14.9	*	6 (14)
Unknown	*		*	*)		
Clinical characteristics						
CCI score						
0	162 (73.6)	33 (67.3)	52 (76.5)	34 (72.3)	10 (90.9)	31 (72.1)
1-3	50 (22.7)	12 (24.5)	13 (19.1)	13 (27.7)	*	11 (25.6)
≥ 4	8 (3.6)	*	*	*	*	*
ECOG performance status						
0	50 (22.7)	7 (14.3)	14 (20.6)	10 (21.3)	*	15 (37.2)
1	122 (55.4)	31 (63.2)	37 (54.4)	26 (55.3)	6 (72.7)	22 (55.8)
≥ 2	14 (6.4)	*	7 (10.3)	*	*	*

Variable	Full cohort (N=220)	5FU/leucoverine (n=49)	FOFLOX (n= 68)	FOLFIRI (n=47)	Aflibercept+ FOLFIRI (n=11)	Cetuximab+ FOLFIRI (n=43)
Unknown	34 (15.4)	7 (14.3)	10 (14.7)	10 (21.3)	*	*
Tumour characteristics						
Primary tumour resection						
No	161 (73.2)	35 (71.4)	59 (86.8)	28 (59.6)	7 (63.6)	33 (76.7)
Yes	59 (26.8)	14 (28.6)	9 (13.2)	19 (40.4)	*	10 (23.3)
Primary tumour location						
Colon	156 (70.9)	33 (67.3)	47 (69.1)	34 (72.3)	10 (90.9)	31 (72.1)
Rectum	57 (25.9)	16 (32.7)	16 (23.5)	11 (23.4)	*	12 (27.9)
Unknown	7 (3.2)		5 (7.4)	*		
Tumour sidedness						
Left	130 (59.1)	26 (53.1)	40 (58.8)	25 (53.2)	5 (45.5)	34 (79.1)
Right	67 (30.5)	19 (38.8)	20 (29.4)	14 (29.8)	*	8 (18.6)
Transverse	10 (4.5)	*	*	*	*	*
Unspecified	13 (5.9)		6 (8.8)	6 (12.8)		*
Tumour molecular profile						
Wild RAS	77 (35)	8 (16.3)	16 (23.5)	11 (23.4)	*	39 (90.7)
Mutant RAS	81 (36.8)	16 (32.7)	35 (51.5)	22 (46.8)	7 (63.6)	*
Mutant BRAF	17 (7.7)	*	*	7 (14.9)	*	*
Unknown	45 (20.5)	20 (40.8)	13 (19.1)	7 (14.9)	*	*
Inflammatory biomarkers and blood cell count parameters						
Albumin (g/L)						
< 34	118 (53.6)	37 (75.5)	39 (57.4)	18 (38.3)	*	19 (44.2)
≥ *34*	100 (45.5)	12 (24.5)	28 (41.2)	28 (59.6)	7 (63.6)	24 (55.8)
Unknown	*		*	*		
Carcino embryonic antigen (CEA) (µg/l)						
≤ 5	36 (16.4)	6 (12.2)	7 (10.3)	10 (21.3)	8 (72.7)	10 (23.3)

Variable	Full cohort (N=220)	5FU/leucoverine (n=49)	FOFLOX (n= 68)	FOLFIRI (n=47)	Aflibercept+ FOLFIRI (n=11)	Cetuximab+ FOLFIRI (n=43)
> 5	141 (64.1)	38 (77.6)	49 (72.1)	26 (55.3)	*	22 (51.2)
Unknown	43 (19.5)	5 (10.2)	12 (17.6)	11 (23.4)	*	11 (25.5)
Haemoglobin (g/l)						
Female (115-165) or Male (130-180)	111 (50.5)	22 (44.9)	31 (45.6)	26 (55.3)	7 (63.6)	23 (53.5)
Female (<115 or >165) or Male (<130 or >180)	107 (48.6)	27 (55.1)	37 (57.4)	20 (42.6)	*	20 (46.5)
Unknown	*					
Neutrophil-to-lymphocyte ratio (NLR)						
> 5	158 (71.8)	35 (71.4)	50 (73.5)	31 (66)	11 (100)	31 (72.1)
≤ 5	60 (27.3)	14 (28.6)	17 (25)	15 (31.9)	*	12 (27.9)
Unknown	*					

KEY: ECOG PS= eastern cooperative oncology group performance status, SIMD= Scottish index for multiple deprivation, CCI= Charlson comorbidity index

* Patients treated with FOLFOXIRI were not included in the baseline analysis as N < 5

4.4 Discussion

4.4.1 Summary of key findings

In this study, the baseline sociodemographic, clinical, tumour, Inflammatory biomarkers and blood cell count parameters, and treatment-related characteristics of mCRC patients (new mCRC SACT users) who have initiated mCRC SACT between 1/1/2015 and 31/12/2016 in NHS GGC were described.

A total of 220 new mCRC SACT users were included in the study, with around half of the patients initiated a doublet of FOLFOX or FOLFIRI (N=115, 52.3%, Table 4. 4), while 49 (22.3%, Table 4. 4) patients initiated a singlet of 5FU, 43 (19.5%, Table 4. 4) patients treated initially with cetuximab+FOLFIRI, and 11 (5%, Table 4. 4) patients were treated with aflibercept+FOLFIRI as an initial mCRC SACT.

The cohort comprised slightly more male patients than females (52.3% vs 47.7%) (Table 4.5). The historical notion of the higher incidence of CRC in males compared to females is probably attributed to the possibility of the protective effect offered by the female sex hormones through different mechanisms (Rennert, 2017, Nikolaou et al., 2019). Additionally, our cohort included a slightly higher frequency of patients over 65 years (53.6%, N=118) compared to those less than 65 (46.4%, N=102). In line with the global incidence, Scotland has witnessed a decreased trend for the incidence of CRC among the elderly population since the Scottish Bowel Screening Programme (SBoSP) started to be implemented in 2007 (Steele et al., 2009). Unfortunately, this trend has coincided with an increased trend of incident cases of CRC among younger people, mainly attributed to factors including obesity, smoking, lack of physical exercise, and alcohol consumption (Clark et al., 2020).

Our findings show that mutation in the BRAF gene was detected in 7.7% (N=17, Table 4.5) of the patients, while wild-type RAS tumour was found in 35% (N=77, Table 4.5) of patients. It is, however, important to highlight that 20.5% (N=45, Table 4.5) of the patients were not screened for tumour molecular profile. In Scotland, molecular biomarker testing for patients with CRC was standardised in July 2015. Under this scheme, all patients with CRC are offered testing for several gene mutations, including the RAS gene, which encodes proteins in the EGFR pathway and the BRAF gene (Bouttell et al., 2019). Since the data collection for this study was started in January 2015, while molecular testing was standardised in July of the

same year, this has resulted in six months of testing not being mandatory, resulting in missing data.

Similarly, 15.4% (N=35, Table 4.5) of the values in the ECOG PS were missing for the same reason, as recording the performance status prior to each SACT cycle was made mandatory in Scotland in July 2015. Despite that, more than half of the patients in our study (N=122, 55.4%, Table 4.5) had an ECOG PS grade of 1, implying restriction in physical activity but ambulatory and able to carry out work of a light or sedentary nature (Table 3.5). However, 14 patients (6.4%) had an ECOG PS grade of 2 or more, indicating the capability of self-care but the inability to carry out any work activities (Table 3.5).

Most of the patients were anaemic, had elevated levels of CEA, and had hypoalbuminemia at index SACT (Table 4.5), which predicts a poor prognosis (Susman, 2005, Nazha et al., 2015, Cho et al., 2017, Shibutani et al., 2013).

4.4.2 Comparison with literature

Overall, comparing baseline characteristics among observational studies is challenging, not only because of the variability in each study setting but also due to the variability in the methods for measuring and reporting baseline characteristics, which can make it difficult to compare results across studies or to extrapolate results to other populations. For instance, while almost all studies report sociodemographic characteristics such as age and gender, other baseline characteristics, especially those featuring the disease (e.g., baseline performance status, number, and type of metastatic sites), are not consistently reported across observational studies. For instance, the Scottish cancer registry lacks variables specific to the pattern of metastasis. Hence, the burden of metastasis, including the number of metastatic sites and the location of metastasis, are not captured in our study.

4.4.2.1 Observational studies

The baseline characteristics of mCRC patients who have initiated mCRC SACT in NHS GGC were compared against the characteristics of mCRC patients in the observational studies included in the SR-MA conducted in chapter 2, given that for both settings, patients were initiated on a first-line mCRC SACT. However, it is important to highlight that many observational studies tend to select patients based on specific features, such as age, RAS status, or performance status. For instance, among the studies included in the SR-MA to

which we are comparing our study, many included only elderly patients above the age of 65 years (Stec et al., 2010, Satram-Hoang et al., 2013, Neugut et al., 2019, Meyerhardt et al., 2012a). This, however, resulted in more challenges in comparing our study to other observational studies.

Considering all the patients, regardless of the type of SACT they were treated with, the sociodemographic characteristics of mCRC patients included in this study, with a median age of 66 years and comprising 45.5% females, were comparable to mCRC patients (n=714) included in a prospective observational study conducted in England (Khakoo et al., 2019), where the median age was 66 years (IQR 26-89) and 42.7% female patients. Those Figures were also closely consistent with the demographic characteristics of mCRC patients in other countries such as Australia (median age 69, 42.8% female (McNeill et al., 2021)) and the Netherlands (median age 69, 44% female (Hamers et al., 2021).

When stratifying patients by their index SACT, the median age and the female proportion for the patients in this study were: 5FU (76 years, 57.1%), FOLFOX (66.5 years, 52.9%), FOLFIRI (66 years, 46.8%) (FOLFIRI), cetuximab+ FOLFIRI (59 years, 27.9%), and for aflibercept+ FOLFIRI, the median age for the participants was 64 years with 45.5% of female patients. These findings are broadly comparable with previously published findings of other observational studies. Among 5FU patients, the median age ranged from 73 to 77 years and the proportion of female patients from 40% to 54% (Yoshimatsu et al., 2007, Satram-Hoang et al., 2013, Guo et al., 2020, Varol et al., 2014, Stec et al., 2010). For patients treated with FOLFOX, the median age reported in other observational studies ranged from 54 to 67.3 years, and between 37% to 50% of the patients were female (Lee et al., 2011, Suenaga et al., 2014, Marschner et al., 2015, Nebuloni et al., 2013). For patients treated with FOLFIRI, the median age ranged between 57 to 68 years, with the proportion of female patients between 32% and 44% (Lee et al., 2011, Stec et al., 2010, Marschner et al., 2015). Finally, for patients treated with cetuximab+FOLFIRI, the median age of patients in other observational studies ranged between 57 and 65 years, and the female share ranged between 30% and 47% (Huang et al., 2011, Bai et al., 2016, Yang et al., 2014, Muro et al., 2019). In contrast, patients who were treated with Aflibercept+ FOLFIRI had a median age that ranged between 63 to 65 years, and the female patients accounted for 37% to 45% of the total patients (Chau et al., 2020, Devaux et al., 2019, Fernandez Montes et al., 2017, Fernandez Montes et al., 2019).

Improved ECOG PS values were higher in England than in Scotland, with 42.3% of the patients in the study carried out in England having a performance status value of zero compared to 22.7% of the patients in our study (Khakoo et al., 2019). This may be partially explained by the fact that the entire cohort in our study presented with mCRC at primary diagnosis. In contrast, only 59.4% of the patients in the study in England presented with mCRC at diagnosis (section 3.2.4.3). It has been projected that the stage of cancer diagnosis is a predictor of PS (West and Jin, 2015).

Notably, our study shows a notable difference compared to the published observational studies investigating the outcomes of first-line mCRC SACT regarding the applied therapies (e.g., type of SACT regimen and rates of primary tumour resection).

First, in this study, the utilised SACT included 5FU, capecitabin FOLFOX, XELOX, FOLFIRI, aflibercept+FOLFIRI, and cetuxmab+ FOLFIRI. In contrast, the majority of the observational studies investigating the effectiveness of first-line mCRC SACTs focused on bevacizumab combinations with chemotherapy. For instance, 24 out of 29 studies in the overall survival meta-analysis in this thesis evaluated bevacizumab against other regimens (section 2.3.2). Nevertheless, in England and Scotland, bevacizumab was not approved for the management of mCRC by the National Institute for Health and Clinical Excellence (NICE) in England and the SIGN in Scotland for safety and cost-effectiveness reasons (The National Institute for Health and Care Excellence, 2010, The Scottish Intercollegiate Guidelines Network (SIGN), 2006, Scottish Medicine Consortium, 2006).

Second, the findings of this study show that the rates for primary tumour resection were substantially lower in Scotland (26.8%, Table 4.5) than these in other observational studies, which ranged between 63% to 80.4% in the United States (Houts et al., 2019a, Meyerhardt et al., 2012b, Bendell et al., 2012), 77.2% in France (Bennouna et al., 2017), 87.4% in Germany, and 84% in Japan (Suenaga et al., 2014). However, the findings of this study are similar to those found in a study conducted in England (N=714), where the primary tumour resection rate was 26.8% (Khakoo et al., 2019). A cross-national study comparing the rates of surgical resection for CRC in England, Denmark, Norway, and Sweden found inferior surgical resection rates in England compared to the rest of the countries for two reasons; first, the clinical guidelines for the surgical treatment of CRC varied in their level of specificity with those from England being typically less detailed than those from Denmark, Norway, and

Sweden. Second, it was observed that patients above 75 years were less likely to be offered CRC surgical treatment in England than in the Scandinavian countries (Benitez Majano et al., 2019). The Scottish clinical recommendations for the surgical treatment of CRC are comparable to those in England (National Institute for Health and Care Excellence (NICE), 2020, Scottish Intercollegiate Guidelines Network, 2011b). In light of that, an indirect conclusion can be extrapolated from the findings of the low resection rates in England to the cohort in this study, given the similarity in the surgical resection recommendations between Scotland and England.

4.4.2.2 Clinical trials

Our findings indicated important differences between the patients included in clinical trials and practice settings. In particular, patients included in this study were older, with a higher share of female patients, and poorer performance status compared to clinical trials upon which the approval of the SACTs captured in this study was granted.

Compared to phase III clinical trials, upon which approval for mCRC SACTs was granted, the median age of the participants in this study (66 years) was higher than that reported in the clinical trials, manifesting the classical notion of the underrepresentation of patients > 65 years in cancer clinical trials (Hutchins et al., 1999). The median age in de Gramont 1997 trial (infusional 5FU) was 60.9 years (de Gramont et al., 1997a), while the median age in de Gramont 2000 trial (FOLFOX), Saltz, 2000, and Douillard, 2000 trials (FOLFIRI) was 63 years and 62 years, respectively (de Gramont et al., 2000, Saltz et al., 2000, Douillard et al., 2000). The median age in the (VELOUR) trial (aflibercept+FOLFIRI) was 61 years (Van Cutsem et al., 2012). In contrast, with a median of 61 years, the median age in (CRYSTAL) trial (61 years) (cetuximab+FOLFIRI) was higher than that of the patients in this study (Van Cutsem et al., 2011).

The proportion of female patients was lower in the clinical trials in contrast to this study (N=105, 47.7%, Table 4.5) and ranged from 34% in Saltz 2000 trial (FOLFIRI) (Saltz et al., 2000) to 40.6% in Crystal trial (cetuximab+FOLFIRI) (Van Cutsem et al., 2011). This could be attributed to the fact that the incidence of CRC is higher in males than in females (Bray et al., 2018), in addition to the lower likelihood for female patients to participate in cancer clinical trials, including CRC, compared to male patients (Murthy et al., 2004).

As a result of the strict inclusion and exclusion criteria applied in the clinical trials, the majority of the clinical trials tend to include healthier patients with good performance status, with a value of zero in 44.7%, 43.3%, 39%, 57%, 55.1% for patients who participated in the 5FU, FOLFOX, FOLFIRI, aflibercept+FOLFIRI, and cetuximab+FOLFIRI clinical trials (de Gramont et al., 1997a, de Gramont et al., 2000, Saltz et al., 2000, Van Cutsem et al., 2012, Van Cutsem et al., 2011). In contrast, only 22.7% (N=50) of patients in our study had good performance stats (PS=0).

4.5 Strengths and limitations

This study described the baseline characteristics of patients initiating mCRC SACT. One of the recognised strengths of our study is the utilisation of record linkage to identify the attributes of mCRC patients in NHSGGC, the largest health board in Scotland, with ten different national and regional datasets used to describe the patients' attributes and cover a wide range of different variables. A strength of using electronic record linkage to identify the patients' attributes is that this method enhances the completeness and accuracy of baseline characteristics. Additionally, record linkage can help to minimise missing data and ensure that the data collected on baseline characteristics is accurate, which can increase the statistical power of the study and enhance the precision of the findings. Furthermore, a recognised strength of our study is the inclusion of all mCRC patients initiating mCRC SACT regardless of any specific feature. By this, the risk of selection bias is reduced. Hence, allowing our findings to be more generalisable.

However, this study was limited by database incompleteness and variable missing in data, such as the lack of recording of important variables relevant to the disease of interest (e.g., number of metastatic sites and the site of metastasis). Nevertheless, this issue is inherent to observational studies and not unique to our study.

4.6 Conclusion

Baseline characteristics of patients with mCRC receiving SACT in GGC showed some comparability to other observational studies in terms of sociodemographic characteristics such as age and gender. However, for other characteristics, such as the type of tumour mutation and burden of metastasis, other observational studies varied in the level of reporting these variables. Additionally, many observational studies tend to select patients based on certain features. Therefore, it was difficult to compare the majority of the baseline

characteristics with those of other observational studies. However, a notable difference in the baseline characteristics between our cohort and the cohorts in other observational studies was the rate of primary tumour resection, which was substantially lower in our study compared to the patients included in other observational studies (Table 4.5). Additionally, the type of initial (first-line) mCRC SACT utilised was another difference between our study and the other observational studies. While in Scotland, the doublet FOLFOX, FOLFIRI, or XELOX were the most utilised SACTs, most of the observational studies reported bevacizumab in combination with chemotherapy to be the most commonly utilised SACTs.

In contrast, differences between clinical trial participants and real-world patients, as included in this study, were obvious, especially with regards to performance status; while these differences might have been impacted to a certain extent by data constraints, specific selection criteria as applied in the RCTs have contributed to these differences.

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5 Chapter 5: Factors influencing the selection of first-line metastatic colorectal cancer systemic anti-cancer treatments in NHS Greater Glasgow and Clyde.

5.1 Introduction.

The last 15 to 20 years have witnessed major advances in the management of mCRC, which were accompanied by a global change in clinical management guidelines (Biller and Schrag, 2021). For many years, 5FU remained the only active treatment available for the management of mCRC. However, in the modern era, the rapid licencing of new medicines for mCRC, together with the wide range of potential combinations and sequences available for treating mCRC, presents challenges for clinicians in deciding the optimal treatment plan for their patients. At the same time, the effective selection of therapies in mCRC is a crucial determinant of treatment outcomes. (Van Cutsem et al., 2014b, Golshani and Zhang, 2020).

Optimising a treatment strategy for mCRC patients should rely on three major attributes: first, patient characteristics, such as age, comorbidities, performance status, acceptance of toxicities and expectations; second, tumour characteristics, such as the burden of metastases, the resectability of the primary tumour and the metastasis, and the tumour progression, and; finally, the tumour molecular profile including RAS status, BRAF status, and MSI (section 1.2.3) (De Falco et al., 2020).

Clinical management guidelines (CMGs) are developed, considering the listed factors. For example, the European Society for Medical Oncology (ESMO) guidelines define several factors that determine the treatment selection, including patients' age, performance status, organ function, comorbidities and patient expectations, the tumour RAS/BRAF status, tumour burden and localisation, in addition to treatment-related factors (e.g., toxicity profile, quality of life) (Van Cutsem et al., 2016a). Similarly, In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN*)* develop evidence-based CMG on the national level for NHS Scotland (Miller, 2016). For colorectal cancer, SIGN 126 for the diagnosis and management of colorectal cancer was published in 2011 and revised in 2016 (Scottish Intercollegiate Guidelines Network, 2011b). However, each of the three cancer networks in Scotland publishes its own CMG specific to treatment in the respective cancer

networks to ensure a consistent experience for patients across the region. The WoSCAN, which covers the NHS GGC health board, developed CRC guidance in which the choice of mCRC regimen depends on 1- patients' factors, including age, comorbidities, and performance status; 2- tumour factors, including the molecular profile, the resectability of the primary tumour and the metastasis, and 3- treatment response factors including previous response, the duration of response, and previous toxicity (National Health Service West of Scotland Cancer Network, 2019).

According to the SIGN guideline, all mCRC patients should be offered SACT. The choice of first-line SACT depends on the patient's fitness, comorbidity, and the aim of treatment. Patients with good performance status and adequate organ function should be initially treated with FOLFOX, XELOX, or FOLFIRI. However, patients who cannot endure combination chemotherapy, 5FU or raltitrexed should be considered. Cetuximab, combined with FOLFOX or FOLFIRI, should be considered a first-line treatment for patients with RAS-wild type tumours. The SMC has also approved aflibercept in combination with FOLFIRI to be used in resistant mCRC or mCRC that has progressed despite the use of an oxaliplatin-containing regimen in the first-line (Scottish Medicine Consortium, 2014). The WoSCAN recommendations for the management of mCRC in the 1L settings as guided by the national SIGN 126 guideline is illustrated in Figure 5.1.

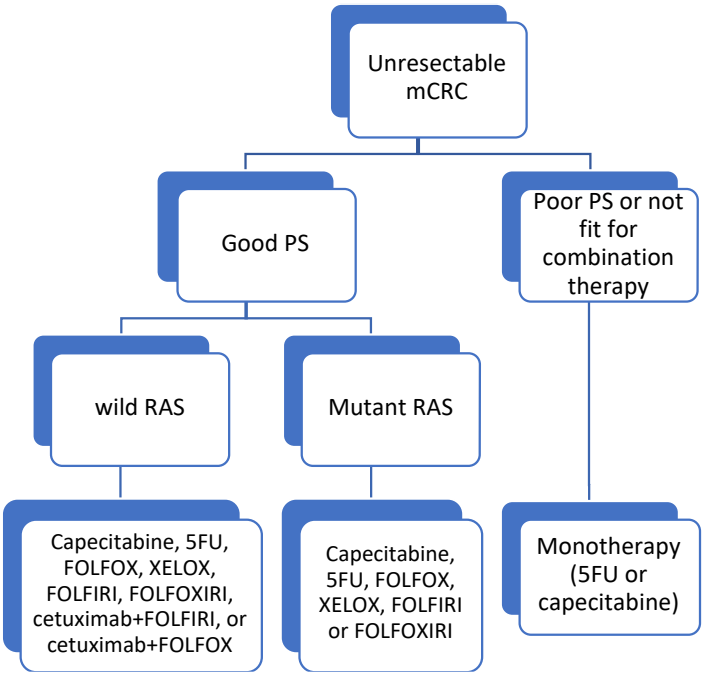

Figure 5.1. WoSCAN recommendations for the management of mCRC in the 1L settings as guided by the national SIGN 126 guideline.

KEY: mCRC= metastatic colorectal cancer, PS= Performance status

The recommendations on optimising the best treatment strategy for the CMGs are evidence-based, principally driven by rigorously conducted randomised controlled trials (Krishnankutty et al., 2012). However, it is now widely accepted by health bodies such as NICE and the FDA that evidence-based practice for drug licencing should embrace other sources such as electronic health records and other sources of RWE (The National Institute for Health and Care Excellence, 2022, Food and Drug administration, 2022). Consequently, RWE is currently used to provide complementary evidence to RCTs to inform regulatory decisions and develop the CMGs.

One of the essential inputs for developing CMGs and health care policies is the factors that influence the prescriber's decision. Therefore, it is important to identify the factors influencing prescribing decisions to help plan a strategy to optimise patient care. In the context of cancer in general, and mCRC in specific, the majority of the research on SACT prescribing decisions has focused on the patients' perception (Bloem et al., 2016, Byrne and Saif, 2019). Nevertheless, there is a paucity of studies focusing on other factors besides the patients' perception that influence the clinician to select the initial, most optimum mCRC SACT.

Aims and objectives.

The aims of this study are:

- To examine the factors associated with prescribing first-line (1L) mCRC SACTs in patients treated in NHS GGC using data from linked health datasets.
- To investigate whether the factors identified from the analysis are consistent with the factors that informed the clinical decisions in the CMGs.

5.2 Methods.

5.2.1 Study design and cohort identification.

This study was designed as a retrospective observational study. The overall study design and cohort identification are explained in section 4.2.1, and an in-depth description of the data sources and variables is provided in sections 3.2 and 3.3, respectively. New mCRC SACT users who initiated metastatic treatment between the 1st of January 2015 and the 31st of December 2016 were included in the study.

The following sections summarise the exposure and the outcome data used in this study and the endpoints. In addition, the statistical methods applied in this study are detailed.

5.2.2 Exposures and outcomes

In this study, the factors identified from the CMGs and the literature to influence the selection of 1L mCRC SACTs, as referred to in section 5.1, were used to select the exposure (i.e., the factors). These factors were mapped into three categories:

1- patient-related factors: age at index SACT (section 3.3.1.1), gender (section 3.3.1.1), deprivation (section 3.3.1.2), and performance status (section 3.3.3.3),
2- tumour-related factors: primary tumour sidedness (section 3.3.3.1) and the tumour molecular profile (section 3.3.3.2),
3- treatment response-related factors, including primary tumour resection (section 3.3.2.3)

Throughout this chapter, the terms exposure and factor will be used interchangeably.

The prescribed SACTs at index (1L mCRC SACTs) were investigated as the outcome. CEPAS, which captures all prescribed SACTs, was used to source the data regarding the prescribed

SACTs. Hence, all mCRC SACTs captured in this study were investigated for their potential association with the exposure (i.e., the factors). However, only FOLFOXIRI was not investigated for its association with the exposure due to the small number of patients falling in this category (N<5).

Table 5.1 summarises the covariates defined as exposure and the outcome extracted from different datasets and the applied coding method.

Table 5.1 Summary of the variables selected in the study to evaluate the association between the selection of first-line mCRC SACT and patient, tumour, and treatment response factors.

Variable	Dataset	Coding
Exposure		
1- Patient-related factors		
Age at index SACT (Section 3.3.1.1)	**CHI** Section 3.2.1) **CEPAS** (Section 3.2.2)	Continuous variable
Gender (Section 3.3.1.1)	**CHI** (Section 3.2.1)	Binary (Male, Female)
SIMD (Section 3.3.1.2)	**CHI** Section 3.2.1)	Ordinal categorical (1,2,3,4,5)
ECOG PS (Section 3.3.3.3)	**CEPAS** (Section 3.2.2)	Ordinal categorical (0,1, ≤ 2)
2- Tumour-related factors		
Primary tumour sidedness (**section 3.3.1**)	**SMR06** (Section 3.2.4.3)	Nominal categorical (left, right, transverse)
Molecular profile (**section 3.3.2**)	**LIMS (**Section 3.2.8)	Nominal categorical (Mutant RAS, Wild RAS, Mutant BRAF)
3- Treatment response-related factors		
Primary tumour resection (**section 3.2.3**)	**OPERA (**Section 3.2.6)) **SMR01 (**Section 3.2.4.2)**,** **SMR06** (Section 3.2.4.3)	Binary (Y, N)
Outcome		
SACT (section 3.3.2.1)	**CEPAS** (Section 3.2.2)	Nominal categorical (5FU, FOLFOX, FOLFIRI, cetuximab+FOLFIRI, Aflibercept+ FOLFIRI)

KEY: CHI= community health index, CEPAS: electronic chemotherapy prescribing system, SACT: systemic anti-cancer therapy, SIMD: Scottish index for multiple deprivation, ECOG PS: Eastern Cooperative Oncology Group performance status, SMR 06: The Scottish Cancer Registry, SMR 01: Scottish Morbidity Records General/Acute Inpatient and Day Case, OPERA: Elective & emergency operations. Y=yes, N=No

5.2.3 Statistical analysis.

A two-step procedure was employed to examine the association of relevant covariates with the selection of each 1L SACT regimen. First, relevant covariates were assessed for their association with the selection of each SACT by performing a univariate multinomial logistic regression (MLR) analysis (Kwak and Clayton-Matthews, 2002). Second, the covariates of statistical significance ($p < 0.05$) in the univariate MLR were subsequently included in the multivariate MLR analysis (Kwak and Clayton-Matthews, 2002). Age and gender were used as priori confounders.

MLR models were used to estimate the odds ratio (OR) and 95% CI between the outcome (SACT) and the exposure at baseline. The OR for the predictor variables refers to the association of each predictor variable (independent variable) with the frequency of each prescribed SACT (dependent variable). The likelihood ratio chi-square test was used to confirm the overall significance of covariates to the model and to test for the goodness-of-fit (Agresti, 1996, Kwak and Clayton-Matthews, 2002). An MLR analysis was used since the categories within the dependent variable (i.e., outcome; SACT) are multiple, discrete, and nominal.

The SACT regimen used as a reference group was FOLFOX, given that it is the standard first-line SACT of choice for the management of mCRC in Scotland (Scottish Intercollegiate Guidelines Network, 2011b). Furthermore, FOLFOX category contained the largest number of patients compared to the other SACT regimen categories.

5.2.4 Assumption of multinomial logistic regression model.

The following are the assumptions that must hold for the MLR estimates to be considered unbiased:

1- The outcome is categorical: the dependent variable in the MLR should be categorical of three or more response categories.

2- Lack of multicollinearity: collinearity occurs when two or more independent variables are highly correlated with each other, resulting in difficulty in determining which predictor variable contributes to the explanation of the dependent variable (Cortina, 1993). Multicollinearity is detected through the variance inflation factor (VIF). The higher the VIF, the more the possibility that collinearity is present. VIF values equal to 1 suggest no correlation between the variables, VIF values > 1 and < 5 suggests a

moderate correlation between the variables, and VIF values more than or equal to 5 suggest the presence of a high correlation between the variables. (Craney and Surles, 2002).

3- The independence of irrelevant alternatives (IIA): this assumption states that the relative likelihood of falling into a certain category rather than the reference category should not change by adding or changing the reference category (McFadden, 1984). Hausman-McFadden test was used to check the IIA assumption, with the null hypothesis of this test being that the probability ratio of every two alternatives depends only on the characteristics of these alternatives (McFadden, 1984, Allison, 2012).

5.2.5 Handling missing data.

The regression model was primarily applied to variables with covariates encompassing different extents of missing data that ranged between complete covariates with no missing data up to 36.7% missing value in a covariate. For this study, the significant missing data existed in two variables, namely, the type of mutation (molecular profile) and performance status, with a percentage of missing data of 20.5% (N=45 observation) and 15.4% (N=34) for each covariate, respectively. Consequently, the primary MLR model contained missing values in the predictor variables, coded as "unknown" and analysed. However, the presence of missing in data might potentially produce biased estimates leading to an invalid conclusion, which was accounted for by two methods, as explained in the next section.

Missing in data was handled according to the type and reason of the missing in data (Kang, 2013).

1- Last observation carried forward (LOCF): this method was used for variables with missing values where a previously observed value existed. This single imputation technique replaces a missing value with a previously observed value (Blankers et al., 2010). For this study, only the missing values for the PS variable were replaced with previously observed variables, whereby in the case of no information at the first index SACT cycle, any value of PS within six months of diagnosis or regardless of the timing of diagnosis was used. While the former restricts the PS to those recorded within six months of the date of diagnosis as recorded in SMR06 and the index date (i.e., date of the first SACT cycle), the latter includes all available information with no

restrictions as to the currency of the data. This method reduced the number of missing in data from 34 (15.4%) missing values to less than five.

For the variables where the LOCF method was not applicable due to a lack of previously observed values, several methods to account for missing in data are proposed in the literature. However, the implementation of any method relies on the type of missing data.
In general, there are three types of missing data according to the mechanism of the missing in data (Rubin, 1976):

- Missing completely at random (MCAR): means that the missing data is distributed randomly across the variable and unrelated to the observed and unobserved (missing) variables.
- Missing at random (MAR): means that missing data is not distributed randomly, and they are related to the observed but not the unobserved data.
- Missing not at random (MNAR): means that missing data is systematically related to the unobserved data.

No definitive test is known to distinguish the type of missing in data. However, Little's MCAR test is a chi-square test used to examine the plausibility of MCAR with a p-value of < 0.05 rejects the null hypothesis (no difference between the means of different missing patterns), hence, providing evidence that the mechanism of missing data is not MCAR (Little, 1988). Little's MCAR test was conducted in this study and showed a p-value of <0.001, which indicates that the missing data in this study is not MCAR. Based on that, the second method was used.

2- Multiple imputations (MI): the MI method accounted for missing in data. This method was used for covariates with overall missing in data of less than 40% (Jakobsen et al., 2017). MI involves replacing missing values with values imputed from the observed data. It aims to allow for uncertainty about the missing in data by generating multiple plausible imputed datasets, which can be later combined to obtain results from them (Sterne et al., 2009). The MI method creates multiple copies of a dataset after imputing the missing values. The imputed values are generated considering the distribution of the missing values across the observed variables. For this study, five imputed datasets with ten iterations for each dataset were used for

MI in which the polynomial logistic regression method was used to model the categorical variables (type of mutation, primary tumour sidedness, SIMD rank, and the remaining missing values for PS after employing the LOCF method). The remaining complete variables with no missing in data (age, gender, primary tumour resection, and CCI) were used as auxiliary variables, which can help to make estimates on incomplete data (Collins et al., 2001).

Table 5.2 summarises the number and frequency of missing in data for each covariate included in this study.

After implementing these two methods, a complete dataset with no missing values in any variable was generated, and a descriptive analysis was carried out similar to the analysis described in section 4.2.3. The full baseline dataset generated following applying the two methods was used to fit an MLR model deemed as sensitivity analysis for the primary regression model containing the missing values to determine the influence of missing in data on the obtained conclusion. The baseline characteristics table generated after applying the LOCF and MI is presented in appendix V.

Table 5.2 The number and frequency of missing in data for variables included in the study.

Variable	Missing observations (out of 220) (N, %)	Method used to handle missing in data
Age	complete	Auxiliary variable in the MI
Gender	complete	Auxiliary variable in the MI
Deprivation (SIMD)	< 5*	Multiple imputations
ECOG PS	34 (15.4)	LOCF then MI
Primary tumour sidedness	13 (5.9)	MI
Primary tumour resection	complete	Auxiliary variable in the MI
Comorbidities (CCI)	complete	Auxiliary variable in the MI
Molecular profile	45 (20.5)	MI

KEY: SIMD= Scottish index for multiple deprivation, ECOG PS = Eastern cooperative oncology group performance status, CCI= Charlson comorbidity index, MI= multiple imputations, LOCF= last observation carried forward.

For all the analysis of this chapter, the FOLFOXIRI SACT category was not analysed for the association with the factors influencing prescribing because this category contained less than five patients, which could result in an inflation of the effect size and confidence interval, hence producing biased estimates.

All the analysis for this study was carried out using R version 3.5.0. The following packages were used: nnet, lmtest, mice and mcar. The analysis R script is presented in appendix VI.

5.3 Results.

This section will present the MLR models' findings to examine the association of patient-related factors, tumour-related factors, and treatment response-related factors with the choice of 1L mCRC SACTs. The primary model with the missing data will be presented as the primary model, while the regression model with missing data accounted for by MI and LOCF will be presented later as a sensitivity analysis for the primary model.

5.3.1 Overview of the cohort.

A total of 220 new mCRC SACT users who initiated 1L mCRC SACT between 1/1/2015 and 31/12/2016 were included in this study. Of these, 49 (22.3%) patients were treated in the 1L setting with 5FU, 68 (30.9%) and 47 (21.4%) patients were treated with an oxaliplatin-based regimen (FOLFOX or XELOX) and irinotecan-based regimen (FOLFIRI), respectively. While 43 (19.5%) patients were treated with the combination of cetuximab+ irinotecan or oxaliplatin-based regimen (cetuximab+FOLFIRI or cetuximab+ FOLFOX), and finally, 11 (5%) patients were treated with aflibercept+FOLFIRI in the 1L settings (Table 4. 4).

The included cohort comprised slightly more male patients than female patients, with a median age of 66 years for the entire cohort. Patients treated initially with 5FU had the highest median age (76 (IQR 68.8-81)), while those treated initially with cetuximab+FOLFIRI had the lowest median age (59 (IQR 52.8-65.2)). Further details regarding the baseline characteristics of the entire cohort and stratified by index SACT are presented in section 4.3.3.

5.3.2 Factors influencing the selection of first-line mCRC SACTs.

Overall, our findings show that age and gender were significantly associated with the selection of 1L mCRC SACTs, with older patients more likely to be prescribed less intensive SACT such as 5FU compared to younger patients, and female patients less likely to be prescribed an intensive therapy such as the triplet regimen cetuximab+FOLFIRI compared to male patients.

Our findings also show that patients harbouring RAS wild-type tumour were significantly more likely to be prescribed cetuximab+FOLFIRI compared to patients with RAS mutant-type tumour. Finally, our analysis shows that patients who had undergone resection of the primary tumour were significantly more likely to be prescribed FOLFIRI or cetuximab+FOLFIRI.

The findings of the univariate MLR are presented in Table 5.3, while the findings of the primary multivariate MLR model are presented in Table 5.4. The multivariate MLR sensitivity analysis models using complete case analysis and multiple imputations are presented in Table 5.5 and Table 5.6, respectively.

The factors identified to be associated with the selection of 1L mCRC SACT were classified into patient-related, treatment-related, and tumour-related factors.

5.3.3 Patients-related factors

This category investigated four factors: the patient's age at index, gender, SIMD score, and the ECOG PS. Overall, both age and gender show a significant association with the selection of 1L mCRC SACTs, with older patients being more likely to be prescribed less intensive therapy compared to younger patients who were more likely to be prescribed more intensive therapy. Also, female patients were less likely to be prescribed more intensive therapy. ECOG PS shows a significant association with the selection of 1L mCRC SACT in the univariate analysis, while it did not display a significant association in the multivariate MLR analysis.

Age was shown to be significantly associated with the choice of 1L mCRC SACT in both the univariate and multivariate models (Table 5.3 and Table 5.4, respectively), with older patients significantly more likely to be prescribed a singlet regimen of 5FU than FOLFOX and younger patients significantly more likely to be prescribed a triplet regimen of cetuximab+FOLFIRI

than FOLFOX. Each one-year increase in age was associated with a 10% increase in the probability of prescribing 5FU (Table 5.4 (OR 1.1, 95% CI 1.05-1.16, P-value <0.001)) and a 7% decrease probability of prescribing cetuximab+FOLFIRI (Table 5.4 (OR 0.93, 95% CI 0.87-0.96, P-value 0.01)). Additionally, gender shows a significant association with the selection of 1L mCRC SACTs in the univariate and multivariate models (Table 5.3 and Table 5.4, respectively). The odds of prescribing a triplet of cetuximab+FOLFIRI rather than FOLFOX was 81% lower in women than in men (Table 5.4 (OR 0.19, 95% CI 0.06-0.59, P-value 0.005)). Moreover, compared to men, women were less likely to be prescribed the triplet of aflibercept+FOLFIRI (Table 5.4, (OR 0.44, 95% CI 0.07-2.3, P-value 0.34)) and more likely to be prescribed 5FU (Table 5.4, (OR 1.30, 95% CI 0.25-3.5, P-value 0.55)). However, the two later associations were not statistically significant. Deprivation, measured by SIMD, did not show an association with the selection of mCRC SACTs in the univariate analysis (Table 5.3). Hence, it was not included in the multivariate analysis model.

Overall, performance status shows a significant association with the selection of 1L mCRC SACTs in the univariate analysis (Table 5.3, (P-value 0.04)), with patients with performance status ≥ 2 (i.e., poor performance status) less likely to be prescribed a triplet regimen of cetuximab+FOLFIRI (Table 5.3, (OR 0.32, 95% CI 1.01-1.15, P-value 0.05)). However, under the adjustment of the rest of the confounders, performance status did not show a significant association with the selection of 1L mCRC SACTs (P-value 0.11).

5.3.4 tumour- related factors

This category explored three factors: type of tumour mutation, tumour sidedness, and comorbidities (measured by CCI). Of these factors, only the type of mutation showed a significant association with the selection of 1L mCRC SACT in the univariate MLR analysis. Thereby, it was included in the multivariate MLR model (Table 5.3, P-value <0.001).

RAS mutation displayed a significant association with the selection of 1L mCRC SACTs. Compared to patients with mutant RAS gene, patients with wild RAS gene were more likely to be prescribed cetuximab+ FOLFIRI rather than FOLFOX ((Table 5.4, OR 65.2, 95% CI 16.1-122.8, P-value <0.001)). On the other hand, compared to patients who harboured a mutation in the RAS gene, patients with mutant BRAF gene were more likely to be prescribed 5FU ((Table 5.4, OR 4.1, 95% CI 0.8-21, P-value 0.08)) and FOLFIRI (Table 5.4, (OR 5.9, 95% CI 0.97-

13.8), P-value 0.07) rather than FOLFOX, yet the association was not significant neither in the univariate nor in the multivariate model.

Primary tumour sidedness did not display an association with the selection of 1L mCRC SACT in the univariate analysis (Table 5.3, P-value 0.69). Hence, this factor was not included in the multivariate model.

Similarly, the presence of comorbidities, measured by CCI, did not show an association with the selection of 1L mCRC SACT in the univariate analysis (Table 5.3, P-value 0.31). Therefore, this variable was not entered into the multivariate model.

5.3.5 Treatment response factors

Within the category of treatment response factors, only one variable existed in our study, which was the primary tumour resection. Resection of the primary tumour was shown to have an association with the prescribing of 1L mCRC SACTs in both the univariate (Table 5.3, P-value 0.001) and multivariate analysis (Table 5.4, P-value <0.001). Compared to patients who did not undergo resection of the primary tumour, those who had the primary tumour resected were 3.64 times (Table 5.4 (OR 3.64, 95% CI 1.64-8.1, P-value 0.001)) and 4.4 times (Table 4 (OR 4.4, 95% CI 1.4-13.8, P-value 0.01)) more likely to be prescribed FOLFIRI and aflibercept+FOLFIRI, respectively, rather than FOLFOX.

Table 5.3 Candidate variables considered in the univariate multinomial logistic regression model for the factors associated with the selection of first-line mCRC SACs and their P-values.

Categories	Reference FOLFOX (n=66)	5FU (n=49)		FOLFIRI (n=47)		Aflibercept+ FOLFIRI (n=11)		Cetuximab+ FOLFIRI (n=47)		Global P-value
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	
Patient-related factors										
Age	**Ref1**	1.11 (1.07 - 1.16)	<0.001	0.99 (0.97-1.03)	0.89	0.98 (0.94-1.03)	0.39	0.94 (0.91-0.97)	<0.001	<0.001
Gender										
Male	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.049
Female	**Ref**	1.18 (0.65-2.48)	0.62	0.78 (0.37-1.64)	0.51	0.72 (0.20-2.66)	0.64	0.34 (0.15-0.78)	0.01	
SIMD score										
1	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.23
2	**Ref**	3.6 (1.21-10.7)	0.02	2.64 (0.85-8.2)	0.09	0.01 (0.01-inf)	0.99	1.78 (0.55-5.8)	0.33	
3	**Ref**	2.7 (0.7-1.01)	0.14	3.46 (0.96-12.5)	0.06	0.01 (0.01-inf)	0.99	1.42 (0.3-6.2)	0.63	
4	**Ref**	1.15 (0.34-3.9)	0.81	1.15 (0.34-3.8)	0.81	3.33 (0.63-17.6)	0.98	1.96 (0/66-5.77)	0.22	
5	**Ref**	0.81 (0.28-2.3)	0.7	0.71 (0.23-2.11)	0.53	1.31 (0.23-7.25)	0.15	0.56 (0.18-1.7)	0.32	
Unknown	**Ref**	0.01 (0.01-inf)	0.99	1.9 (0.11-33)	0.63	8.3 (0.4-20.9)	0.17	0.01 (0.01-inf)	0.99	
ECOG PS										
0	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.04
1	**Ref**	1.78 (0.73-4.31)	0.19	0.88 (0.51-2.45)	0.66	1.1 (0.29-2.66)	0.58	0.62 (0.24-1.13)	0.18	
≥ 2	**Ref**	1.55 (0.42-5.61)	0.56	0.17 (0.02-1.36)	0.1	0.01 (0.01-inf)	0.99	0.32 (1.01-1.15)	0.05	
Unknown	**Ref**	0.01 (0.01-inf)	0.99	1.39 (0.34-5.7)	0.52	1.39 (0.21-9.12)	0.81	0.4 (0.07-2.29)	0.22	
Disease-related factors										
Tumour sidedness										
left	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.69
Right	**Ref**	1.46 (0.65-3.2)	0.3	1.11 (0.48-2.6)	0.81	2.5 (0.6-10.3)	0.2	0.47 (0.18-1.2)	0.11	

Categories	Reference FOLFOX (n=66)	5FU (n=49)		FOLFIRI (n=47)		Aflibercept+ FOLFIRI (n=11)		Cetuximab+ FOLFIRI (n=47)		Global P-value
Transverse	**Ref**	3.1 (0.52-1.8)	0.2	1.6 (0.21-12.1)	0.66	5 (0.3-68)	0.2	0.58 (0.05-6.7)	0.67	
Unknown	**Ref**	0.01 (0.01-inf)	0.99	1.6 (0.46-0.55)	0.4	1.66 (0.15-17.5)	0.67	0.01 (0.01-inf)	0.99	
Molecular profile										
Mutant RAS	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**	<0.001
Wild RAS	**Ref**	1.09 (0.3-3)	0.87	1.09 (0.41-2.3)	0.85	0.62 (0.25-1.34)	0.98	73.2 (22.3-129.1)	<0.001	
Mutant BRAF	**Ref**	2.7 (0.6-11)	0.1	2.7 (0.72-10.6)	0.13	0.01 (0.01-inf)	0.99	2.6 (0.41-8.9)	0.17	
Unknown	**Ref**	3.36 (1.34-11.5)	0.03	0.85 (0.29-2.47)	0.77	0.76 (0.46-3.97)	0.66	2.4 (1.43-103.2)	0.02	
CCI										
0	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.31
(1-3)	**Ref**	1.97 (0.87-4.41)	0.22	1.25 (0.55-2.79)	0.48	0.69 (0.18-2.66)	0.42	1.43 (0.62-3.29)	0.9	
≥4	**Ref**	2.63 (0.56-12.4)	0.35	0.47 (0.05-4.71)	0.6	0.01 (0.01-inf)	0.99	0.59 (0.06-5.87)	0.2	
Treatment response factors										
Primary tumour resection										
No	**Ref**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.001
Yes	Ref	1.9 (0.98-6.1)	0.07	4.4 (1.78-11)	0.001	8.2 (2.8-27.8)	<0.001	1.99 (0.73-5.48)	0.17	

KEY: OR= odds ratio, 95%CI = 95% confidence interval, MLR= multinomial logistic regression, SACT= systemic anticancer therapy, SIMD= Scottish index for multiple deprivation, ECOG PS = Eastern cooperative oncology group performance status, CCI= Charlson comorbidity index, ref= reference group
Global P-value obtained through likelihood ratio test to test the impact of each variable on the selection of SACT

Table 5.4 Association of baseline characteristics with the selection of mCRC SACTs using multivariate multinomial logistic regression models.

Categories	Reference FOLFOX (n=66)	5FU (n=49)		FOLFIRI (n=47)		Aflibercept+ FOLFIRI (n=11)		Cetuximab+ FOLFIRI (n=47)		Global P (MLR)
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	
Patient related factors										
Age	Ref	1.1 (1.05-1.16)	<0.001	0.98 (0.93-1.03)	0.34	0.91 (0.83-0.99)	0.02	0.93 (0.87-0.96)	0.01	<0.001
Gender										
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.04
Female	Ref	1.30 (0.25-3.5)	0.55	0.63 (0.25-1.55)	0.32	0.44 (0.07-2.3)	0.34	0.19 (0.06-0.59)	0.005	
ECOG PS										
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.11
1	Ref	1.13 (0.46-3.3)	0.81	0.77 (0.3-2)	0.6	1.31 (0.28-8.3)	0.77	0.56 (0.19-1.8)	0.34	
≥ 2	Ref	0.83 (0.23-4.2)	0.81	0.1 (0.01-1.15)	0.07	0.01 (0.01-inf)	0.99	0.3 (0.03-3.4)	0.36	
Unknown	Ref	0.01 (0.01-inf)	<.99	1.2 (0.02-2.7)	0.2	0.01 (0.01-inf)	0.99	0.2 (0.02-3.7)	0.2	
Disease related factors										
Molecular profile										
RAS mutant	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	<0.001
RAS wild	Ref	1.34 (0.35-3.07)	0.6	1.2 (0.4-3.54)	0.74	0.64 (0.09-4)	0.66	65.2 (16.1-122.8)	<0.001	
BRAF mutant	Ref	4.1 (0.8-21)	0.08	5.9 (0.97-13.8)	0.07	0.01 (0.01-inf)	<.99	9.1 (0.57-37.6)	0.43	
Unknown	Ref	2.4 (0.7-6)	0.19	0.63 (0.24-1.67)	0.34	0.18 (0.02-1.6)	0.13	10.7 (1.12-22.1)	0.04	
Treatment response factors										
Primary tumour resection										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	<0.001
Yes	Ref	1.92 (0.78-7.6)	0.21	3.64 (1.64-8.1)	0.001	4.4 (1.4-13.8)	0.01	3.9 (0.8-12.8)	0.2	

KEY: OR= odds ratio, 95%CI = 95% confidence interval, MLR= multinomial logistic regression, SACT= systemic anticancer therapy, SACT= systemic anticancer therapy, ECOG PS = Eastern cooperative oncology group performance status, Inf=infinity, ref = reference group
Global P-value obtained through likelihood ratio test to test the impact of each variable on the selection of SACT

Sensitivity analysis

Missing in data was accounted for by performing multiple imputations (Table 5.5). Overall, the significance and direction of association were comparable across all tested variables to the variables included in the primary model with the missing values. However, the magnitude varied across variables with missing values. For example, in the original model, compared to patients who harboured mutant RAS gene, patients with wild RAS gene were 65.2 times more likely to be prescribed cetuximab+FOLFIRI rather than FOLFOX and the association was significant (P-value <0.05). The model performed after accounting for missing in data showed similar significance and direction (P-value <0.05) with 86.9 times more likelihood of selecting cetuximab+ FOLFIRI rather than FOLFOX for patients with wild-RAS tumour.

Table 5.5 The multivariate multinomial logistic regression model after accounting for missing in data by performing the last observation carried forward and multiple imputations of the missing data.

Categories	Reference FOLFOX (n=66)	5FU (n=49)		FOLFIRI (n=47)		Aflibercept+ FOLFIRI (n=11)		Cetuximab+ FOLFIRI (n=47)		Global P (MLR)
	Ref	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	
Patient related factors										
Age	Ref	1.13 (1.06-1.16)	<0.001	0.94 (0.96-1.03)	0.73	0.98 (0.93-1.03)	0.17	0.92 (0.87-0.96)	<0.001	<0.001
Gender										0.049
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Female	Ref	1.14 (0.56-2.7)	0.45	0.81 (0.32-1.37)	0.4	0.91 (0.31-2.6)	0.98	0.23 (0.09-0.59)	0.002	
ECOG performance status										
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
1	Ref	1.19 (0.57-3.88)	0.42	0.84 (0.67-3.4)	0.3	0.8 (0.27-2.4)	0.69	0.58 (0.21-1.57)	0.28	0.17
≥ 2	Ref	1.26 (0.3-5.26)	0.75	0.17 (0.02-1.56)	0.11	0.01 (0.01-0.02)	<0.001	0.24 (0.03-1.79)	0.16	
Disease related factors										
Mutation type										<0.001
Mutant RAS	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Wild RAS	Ref	1.2 (0.31-1.8)	0.26	1.09 (0.49-2.4)	0.65	1.28 (0.42-3.88)	0.99	86.9 (32.9-146.4)	<0.001	
Mutant BRAF	Ref	2.9 (0.83-10.5)	0.2	3.24 (0.99-10.6)	0.06	0.01 (0.01-0.02)	<0.001	17.6 (0.24-76.9)	0.1	
Treatment response related factors										
Primary tumour resection										
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	0.007
Yes	Ref	2.7 (0.88-5.42)	0.2	2.7 (1.62-8.13)	<0.001	4.14 (1.27-1.35)	0.02	1.8 (0.63-5.19)	0.08	

KEY: OR= odds ratio, 95%CI = 95% confidence interval, MLR= multinomial logistic regression, SACT= systemic anticancer therapy, SACT= systemic anticancer therapy, ECOG PS = Eastern cooperative oncology group performance status, Inf=infinity, ref = reference group
Global P-value obtained through likelihood ratio test to test the impact of each variable on the selection of SACT

Assumptions of MLR.

The following assumptions for the MLR were tested for the primary model

1- Independence of irrelevant alternatives given the P-value 0.1, which was generated from the Hausman-McFadden test (hmftest), the assumption of IIA failed to be rejected, and the conclusion is that the MLR model is appropriate.

2- Multicollinearity: The square values for the generalised variance inflation factor across all variables were less than 5, indicating no multicollinearity between the included variables. Table 5.6 shows the squared VIF values for the variables included in the model.

Table 5.6 The squared variance inflated factors for the multicollinearity assumption of the primary multinomial logistic regression model.

Covariates in MLR model	Squared generalized variance inflated factors
Gender	1.06
Age	1.06
Primary tumour resection	1.21
Type of mutation	1.08
Performance status	1.36
SACT line	1.06
KEY: MLR= multinomial logistic regression, SACT= systemic anticancer therapy	

5.4 Discussion.

5.4.1 Summary of the key findings.

This study identified patient, disease, and treatment response-related factors associated with the selection of 1L mCRC SACTs in NHS GGC health board in Scotland between 2015-2016.

Overall, among the patient-related factors, age and gender were significantly associated with the selection of 1L mCRC SACTs, where older patients were more likely to be prescribed less intensive SACTs such as 5FU compared to younger patients. Similarly, female patients were less likely to be prescribed an intensive therapy such as the triplet regimen cetuximab+FOLFIRI compared to males (Table 5.4).

Of the explored tumour-related factors, only RAS status displayed a significant association with the selection of 1L mCRC SACTs, with patients harbouring RAS wild-type tumour being more likely to be prescribed cetuximab+FOLFIRI.

Finally, among the treatment response-related factors, our analysis shows that patients who had undergone resection of the primary tumour were significantly more likely to be prescribed a 1L SACT of either FOLFIRI or aflibercept+FOLFIRI.

Unexpectedly, BRAF status and performance status were not shown to be associated with the choice of 1L mCRC SACT, possibly due to the small sample size representing patients with mutant BRAF and poor performance status. This was manifested by the wide confidence interval but big effect sizes. For example, the analysis showed that patients with a mutant BRAF were 9.1 more times likely to be prescribed cetuximab+FOLFIRI, with the lower bound of the confidence interval being 0.57 and the upper bound of 37.6, indicating a low level of precision for the effect size (i.e., the odds ratio). A similar notion was observed for certain variables where the value of effect size was very small, and the confidence interval ranged between 0.1 to infinity, reflecting how small the sample representing that category. For instance, patients with poor PS (≥ 2) had very small odds of receiving 1L of aflibercept+FOLFIRI (OR = 0.01). The very wide confidence interval (0.01- infinity) indicates the very small sample representing this category (Table 4.5), which, when compared to the reference group, FOLFOX, resulted in a very small ratio and a very wide confidence interval (Table **5.4**).

Compared to FOLFOX, 5FU was more commonly prescribed for elderly patients, and FOLFIRI and Aflibercept+FOLFIRI were more likely to be prescribed for patients who underwent a resection of the primary tumour. In contrast, the triplet combination of cetuximab+FOLFIRI was more commonly prescribed for male, younger patients harbouring RAS wild-type tumours.

The sensitivity analysis carried out to account for missing in data showed similar findings in terms of significance and direction of the association. However, the magnitude of association was different, which is expected given the difference in the sample size between the primary analysis and the analysis conducted following the LOCF and MI of the missing values, which involved replacing missing values with values from the observed data, resulting in increasing the sample size hence, the magnitude of association.

5.4.2 Patient-related factors.

5.4.2.1 Age.

The treatment of elderly patients presents a clinical dilemma for clinicians, particularly since this group of patients is underrepresented in clinical trials, with the majority of the evidence-based treatment decision relying on post hoc analysis for clinical trials, consequently making the selection of the optimum 1L mCRC SACTs for elderly patients challenging with less likelihood of receiving guideline-recommended therapies (Papamichael et al., 2009).

In our study, compared to FOLFOX, older patients were significantly more likely to be prescribed a single agent of 5FU (OR 1.1 (1.05-1.16)) (Table 5.4). This could be attributed to the fact that management of mCRC in the older population is challenging for clinicians due to age-related organ function decline and medical comorbidities, in addition to the special attention that should be paid to the treatment-related toxicities in older patients (Rougier et al., 1998, Millan et al., 2015). This was supported by a pooled analysis of clinical trials, which shows that a single agent of 5FU can be used alone in patients who cannot tolerate the toxicities of combination therapies with an efficacy similar to that of the younger population (Folprecht et al., 2004, Chiara et al., 1998).

In contrast, the findings of this study show that older patients were less likely to be prescribed a triple combination of chemotherapy and targeted therapy (OR 0.93 (0.87-0.96 for cetuximab+ FOLFIRI), (OR 0.91 (0.83-0.99) for aflibercept+FOLFIRI) (Table 5.4), which was expected given the additional toxicities associated with their use (Xie et al., 2020). Although

the introduction of targeted therapies has contributed to the improvement of mCRC outcomes in elderly patients (Tabernero et al., 2014, Cunningham et al., 2013), the concern about their toxicity, including uncontrolled hypertension, stroke, and delayed wound healing, might limit their use in this population (Hershman et al., 2013).

Although age was found to be significantly associated with the selection of 1L mCRC SACT, CCI was not associated with a statistically significant association with the selection of 1L mCRC SACT. The utilisation of the CCI in our study may have contributed to the non-statistically significant findings. By employing a summary measure to capture the overall burden of comorbid conditions, the individual impact of specific comorbidities may have been obscured. The use of a composite index, such as the CCI aims to provide a comprehensive assessment but can result in the loss of granularity and sensitivity to detect significant associations between individual comorbidities and the selection of 1L mCRC SACT. Consequently, the non-statistically significant findings observed in our study could be partially attributed to the limitations of the summary measure in capturing the nuanced effects of individual comorbidities.

5.4.2.2 Gender.

In this study, male patients were more likely to receive more intensive therapy of a combination of chemotherapy and targeted treatment than females (Table 5.4). This difference stems probably from the notion that females are more liable to the toxicities of various anticancer therapies with more risk of developing toxicities due to the interplay between different biological and psychosocial factors (Soldin et al., 2011, Nicolson et al., 2010). For example, several pharmacokinetics analyses reported that females have a lower elimination for 5FU, potentially due to a mutation in the dihydropyrimidine dehydrogenase (DPYD) gene, hence, resulting in more toxicities as the concentration of the drug builds up in the blood (Mueller et al., 2013, Gusella et al., 2006).

Substantial evidence suggests an increased risk of severe mucositis and leukopenia associated with the use of 5FU among female patients compared to their counterparts (Stein et al., 1995, Sloan et al., 2000, Zalcberg et al., 1998, Sloan et al., 2002) while less evidence exists regarding mCRC combination therapy. However, the available data suggests that chemotherapy combinations and chemotherapy+ targeted therapy combinations were significantly associated with more severe toxicities among female patients compared to male

patients, including alopecia, high-grade nausea and vomiting, high-grade diarrhoea, high-grade anaemia, and high-grade neutropenia (Abdel-Rahman, 2019, Wagner et al., 2020). All of these might offer an explanation for the decreased odds of selecting a triplet SACT combination for female patients in our study. However, no safety data is available to confirm this finding.

5.4.2.3 Performance status.

Frailty, in this study measured by ECOG PS, was another factor known to be a strong predictor for SACT selection as patients with poor PS (PS ≥ 2) tolerate SACT poorly and are known to have a poor prognosis (Sargent et al., 2009). Clinical trials tend to exclude frail patients, and evidence for the best treatment for patients with poor PS is still lacking (Travers et al., 2021). However, the classification of a patient as 'fit' or 'unfit' is now used to determine whether or not the patient will be allocated to a more intensive (combination of 2 or 3 SACTs with a targeted treatment) or less intensive treatment approach (Prigerson et al., 2015). For example, the American National Comprehensive Cancer Network (NCCN) and European ESMO guidelines classified the patients according to their eligibility for intensive therapy. The former guideline divides mCRC patients into two groups: “patients appropriate for intensive therapy” and “patients not appropriate for intensive therapy,” based on the presence of comorbidity and the potential SACT tolerability (Messersmith, 2019). In contrast, according to ESMO guidelines, patients are divided into three groups based on the potential resectability of the metastases: “Group 1” intensive treatment approach, “Group 2” intermediate intensive treatment, and “Group 3” not intensive approach (Van Cutsem et al., 2016a). Although the recommended SACT regimens vary between the guidelines in each patient group, mCRC patients with poor performance status usually have poorer tolerability for SACTs. Hence, less intensive therapy is selected for them (Prigerson et al., 2015).

Similar to these global guidelines, the selection of mCRC SACT in Scotland is allocated and conditioned by the patient's performance status (Scottish Intercollegiate Guidelines Network, 2011a). For patients with good performance status and adequate organ function, combination therapy of 5FU/oxaliplatin (FOLFOX), capecitabine and oxaliplatin (XELOX), or 5FU/irinotecan (FOLFIRI) is preferred over a monotherapy of 5FU. In contrast, 5FU remains the SACT of choice for patients with poor performance status (Scottish Intercollegiate Guidelines Network, 2011a). The findings of this study show a significant association of

performance status with the prescribing of 1L mCRC SACTs in the univariate analysis stage (overall P-value 0.04), with patients with poor performance status (PS >2) being more likely to be prescribed a monotherapy of 5FU rather than a doublet of FOLFOX and less likely to be prescribed cetuximab+ FOLFIRI. However, under the adjustment of the rest of the confounders, performance status was not associated with prescribing of mCRC. This is probably because of the small sample representing patients with poor performance status, which limited the ability of the test to detect the differences.

5.4.3 Tumour-related factors.

5.4.3.1 Molecular profile.

The molecular profiling and testing for specific mutations of KRAS and NRAS has been widely accepted in routine practice to allocate patients for treatment with anti-EGFR therapy (Douillard et al., 2010, Bokemeyer et al., 2011, De Roock et al., 2010). The results from several clinical trials have proven the benefit of the addition of anti-EGFR therapy, such as cetuximab to chemotherapy in the 1L settings for patients harbouring wild-type RAS tumour (Heinemann et al., 2014, Venook et al., 2014, Van Cutsem et al., 2011). In our study, patients who presented with a RAS wild-type tumour were significantly more likely to be prescribed cetuximab+FOLFIRI (Table 5.4 OR 65.2 (16.1-122.8)), which is aligned with the current evidence on the management of mCRC with wild-type tumour mutation (Van Cutsem et al., 2016a, Messersmith, 2019). Most of the current approaches to treat mCRC with RAS wild type tumour favour the use of a combination SACT including an anti-EGFR +5FU and irinotecan (FOLFIRI), or an anti-EGFR + 5FU and oxaliplatin (FOLFOX) in the first-line setting as this approach offered improved clinical outcomes in terms of survival and objective response (Van Cutsem et al., 2011, Van Cutsem et al., 2015, Douillard et al., 2013, Douillard et al., 2010).

For patients presenting with a mutation in the BRAF gene (V600E), different therapeutic approaches have been implemented with less consensus across the global guidelines on the optimum treatment strategy. This is due to the mutation's intrinsic resistance to chemotherapy, which warrants more intensive therapeutic strategies with multiple drug combinations (Barras, 2015). Usually, the management of mCRC with BRAF mutant tumour involves the use of the triplet chemotherapy FOLFOXIRI with or without a VEGF, such as bevacizumab depending on the patient's fitness (Van Cutsem et al., 2016a, Messersmith,

2019). In Scotland, during the study timeframe between 2015 and 2016, FOLFOXIRI was the first-line SACT of choice for mCRC patients with V600E BRAF mutation (National Health Service Scotland North, 2021, NHS West of Scotland Cancer Network, 2019). However, patients with BRAF mutation in this study were treated with 5FU, FOLFOX, or FOLFIRI. A possible explanation is that mCRC with BRAF mutations usually arises in older female patients, with often worse performance status at first diagnosis. Hence, a mono or doublet SACT was prescribed instead of a triplet SACT, which is potentially associated with more toxicities (Clancy et al., 2013, Loupakis et al., 2016). Nevertheless, in our study BRAF did not display any significant association with SACT prescribing. This can be attributed to the impact of the small sample representing patients with mutant BRAF (N=17), which might have affected the ability of the test to detect any differences in the association, as explained in the key findings of this section (section 5.4.1).

5.4.4 Treatment response-related factors.

5.4.4.1 Primary tumour resection.

The choice of 1L SACT regimen can be influenced by the treatment goals, which vary according to the clinical scenario. For most mCRC patients, the treatment intent is palliative and not curative. Hence, SACT remains the treatment cornerstone. However, some mCRC patients can benefit from the surgical resection of the primary tumour, which is performed to alleviate tumour-related complications and reduce the likelihood of life-threatening events such as intestinal obstruction, perforation, and bleeding (Eisenberger et al., 2008). Nevertheless, the survival benefit of primary tumour resection has not been proven. (Van Cutsem et al., 2014b, Eisenberger et al., 2008). According to the management guidelines in Scotland, patients with resectable primary tumours and resectable metastasis are offered synchronous surgical resection followed by adjuvant therapy, whereas patients with resectable primary tumours and potentially resectable liver metastases are offered neoadjuvant therapy followed by resection of the primary tumour and the metastases, while patients with unresectable primary tumour and unresectable metastases are offered several options including palliative resection, chemoradiation, or chemotherapy (National Health Service Scotland North, 2021, National Health Service West of Scotland Cancer Network, 2019, Scottish Intercollegiate Guidelines Network, 2011a).

The findings of this study show a significant association between the resection of the primary tumour and prescribing FOLFIRI (Table 5.4, OR 3.64 (95% CI 1.64-8.1))) rather than FOLFOX. Although no specific guideline or body of literature establishes an association between the primary tumour resection and the selection of 1L mCRC SACT following the resection of the primary tumour, this may be explained by the fact that oxaliplatin, which is used as part of the adjuvant therapy following the primary tumour resection, might result in neuropathy that can limit its use again as part of the 1L metastatic regimen. Hence favouring the use of FOLFIRI over FOLFOX in metastatic settings. These results were supported by the findings of a previous retrospective cohort study conducted in Canada (N=22), which explored the selection of palliative oxaliplatin after exposure to adjuvant oxaliplatin, where it was found that the oncologists believe that the use of oxaliplatin in the metastatic settings following its use in the adjuvant setting can be limited by the fact that the disease would become refractory to oxaliplatin, in addition to the persistent neuropathy associated with the use of oxaliplatin (Peixoto et al., 2015a).

Our findings also show a significant association between primary tumour resection and treatment with aflibercept+FOLFIRI in the 1L setting. This finding was unexpected, especially given that aflibercept+FOLFIRI is licenced to be used as a second-line regimen in Scotland following the failure of oxaliplatin-based regimen (Scottish Medicine Consortium, 2014). A possible explanation would be that some patients progress rapidly following primary tumour resection and adjuvant therapy containing oxaliplatin. These patients represent a subset of patients with treatment-resistant tumour, potentially warranting to initiate a second line (2L) of therapy and skipping 1L. For that reason, it was suggested that in our study, primary tumour resection, which involves receiving adjuvant therapy afterwards, was associated with a more likelihood of prescribing aflibercept+FOLFIRI compared to FOLFOX.

5.5 Strengths and limitations.

To our knowledge, this is the first study that utilised record linkage data to explore the factors influencing the selection of 1L mCRC SACTs. This study was strengthened by accounting for the bias introduced by missing data through performing sensitivity analysis regression models. The presence of a wide range of variables from different datasets also strengthened our study.

However, despite the strengths of this study, several limitations exist. This study is limited by the lack of specific data needed to answer the research question, especially information

regarding the potential toxicities of SACTs, which is currently not captured across Scotland. Toxicity data is essential in allocating a treatment for the patient based on a previous response, such as the response in adjuvant settings. Additionally, data regarding health-related quality of life (HRQOL), which is necessary for clinical decision-making, is not collected. Nevertheless, one of the aims of CMOP is to test the feasibility of collecting HRQOL data from the practice to help with the decision-making process, with this work currently progressing (Dunlop et al., 2022). Finally, the small sample in certain variables, such as the BRAF mutation, could have limited the ability of the test to detect the differences between SACT regimens. This problem can be solved by replicating the study on a larger sample to ensure having enough patients across different SACT regimens to allow the statistical test to detect the differences.

5.6 Conclusion.

Our analysis identified an association between the patient's age, gender, harbouring wild-type RAS tumour, and undergoing a primary tumour resection with the selection of 1L mCRC SACTs. Part of the findings of this study is consistent with the recommendations by the national (Scottish) and regional (WoSCAN) CMG for the treatment of mCRC, especially the selection of SACTs based on the patient's age and RAS status. Other factors related to the choice of mCRC SACTs, such as the patient's gender and previous treatment response, were guided by supporting evidence from the clinical trials. In contrast, factors such as the performance status and BRAF mutation, known in the CMGs and in the literature to be predictors for the selection of 1L mCRC SACTs, were not shown to have an association in this study, probably because the sample size representing patients with poor performance status and patients with mutant BRAF was not large enough for the test to detect the differences.

Our findings show that the utilisation of record linkage could serve as an essential and valuable tool to complement the evidence obtained from the clinical trials to allocate patients for treatment. Our study reported the factors influencing the selection of 1L mCRC SACTs in routine practice, which may be helpful in clinical decision-making.

6 Chapter 6: Treatment pathways and outcomes for metastatic colorectal cancer patients initiating systemic anti-cancer therapy in NHS Greater Glasgow and Clyde.

6.1 Introduction.

In line with improvements in the treatment outcomes of CRC globally, Scotland has witnessed a decrease in the mortality rate for CRC by 8% in the last ten years, with a 5-year survival of 55% (Public health information for Scotland, 2021). This has been attributed mainly to three reasons: first, the scaling up of the Scottish Bowel Screening Programme (SBoSP), which resulted in a considerably increased detection of new CRC diagnoses and a significant drop in the number of individuals presenting with late-stage CRC;

second, the increased uptake of molecular profile testing for CRC patients, leading to an improved personalised treatment based on the type of mutation, hence improved survival outcomes (Bouttell et al., 2019), and;

third and most importantly, as a result of the evolving landscape of treatment of mCRC which has increased median overall survival (median OS) from 9 months up to 3 years, especially with the introduction of targeted therapies including the anti-EGFR agents, anti-VEGF agents, and most recently the immune checkpoint inhibitors (section (Petrelli et al., 1989, Douillard et al., 2000, Giacchetti et al., 2000, de Gramont et al., 2000, Saltz et al., 2000, Kohne et al., 2005, Tournigand et al., 2004a, Cunningham et al., 2004, Hurwitz et al., 2004, Kabbinavar et al., 2005, Dienstmann et al., 2015, Sveen et al., 2020).

Despite the advances in screening programs and the treatment of CRC, the mean age-standardised rate (ASR) of survival for CRC patients in Scotland remains inferior to that in the rest of the UK and European countries (De Angelis et al., 2014). Available data suggest that elements of deprivation and remoteness from treatment facilities might be associated with poorer cancer survival in Scotland, with most deprived CRC patients at 21% more risk of death than patients in the least deprived areas (National Health Service Scotland and Macmillan Cancer Support, 2017). It was proposed that factors that may explain the disparities in survival between different socioeconomic groups could include a delayed presentation and disease stage at the time of presentation (National Health Service Scotland and Macmillan Cancer Support, 2017).

Many factors are reported in the literature to impact or predict survival outcomes for mCRC patients; most significantly and consistently reported factors include the performance status and type of SACT regimen (Stillwell et al., 2011). However, a wide range of other patients, tumour, and treatment factors are reported to impact the prognosis of mCRC. These factors include patients' age and gender (Aparicio et al., 2003, Eker et al., 2015, Stillwell et al., 2011), primary tumour resection, primary tumour sidedness, number of metastatic sites (Arnold et al., 2017b, Garcia Alfonso et al., 2018), localisation of metastasis (Garcia Alfonso et al., 2018), tumour molecular profile (Loupakis et al., 2014, Stintzing et al., 2016), along with several clinical and Inflammatory biomarkers and blood cell count parameters such as C-reactive protein, carcinoembryonic antigen, albumin, haemoglobin, neutrophils to lymphocyte ratio, and alkaline phosphatase (Garcia Alfonso et al., 2018, Zacharakis et al., 2010, Eker et al., 2015, Stillwell et al., 2011).

In Scotland, little is known about the impact of different SACT regimens and other patient and disease factors on the survival outcomes for mCRC patients. Furthermore, the increase in available treatment combinations and sequences for mCRC has resulted in challenges for clinicians to decide the optimal treatment sequencing plan for the patients to achieve the best clinical response (Kim and Kim, 2020). The complexity of treatment pathways for mCRC has resulted in a paucity of published studies describing treatment pathways for mCRC in routine practice and the clinical outcomes associated with different treatment pathways.

Real-world data (RWD) is now more readily available to assist in a better understanding of variations in treatment pathways and treatment outcomes in routine practice. Therefore, it is essential to understand the impact of various patient, treatment, and disease characteristics on the clinical outcomes for mCRC patients in Scotland and the clinical outcomes associated with different treatment pathways.

This study aims to investigate the utilisation of RWD using record linkage to describe the treatment pathways and clinical outcomes of the treatment of new mCRC SACT users in the NHS GGC health board in the period between 01/01/2015 to 31/12/2016.

The specific objectives of this study were:

- To determine the clinical outcomes associated with the administration of first-line (1L) SACT regimens for mCRC, including the overall survival and time to initiation of the next SACT regimen (TTNT) as a surrogate for the duration of the clinical benefit.

- To improve the understanding of the complexity of treatment pathways for mCRC patients initiating SACT regimens by developing a Sankey visualisation tool and measuring the median overall survival associated with different treatment pathways.

6.2 Methods.

Details regarding the study design and cohort identification are explained in section 4.2.1. An in-depth description of the data sources and variables is provided in section 3.2 and section 3.3, respectively.

The following sections provide a summary of the study population, the data used in this study, and the endpoints. In addition, the statistical methods applied in this study are described.

6.2.1 Study design and population.

This study was designed as a retrospective observational cohort study from January 1st, 2015, to February 28th, 2018. New mCRC SACT user patients who initiated metastatic treatment between January 1st, 2015, and December 31st, 2016, and were not identified to be prescribed SACT for mCRC previously were included in the study and followed up until death, loss at follow-up, or end of the study on February 28th, 2018, whichever occurred first. Further details about the study population and cohort identification can be found in section 4.2.1.

6.2.2 Exposure and treatment lines.

The first SACT regimen initiated during the study period was defined as the first-line (1L) treatment, and the 1L treatment index date was defined as the starting date of 1L SACT during the study period. For second-line (2L) treatment, the index date was defined as the date when 2L SACT was initiated. Similarly, the date when the third-line SACT was initiated was considered the index date for 3L SACT.

The initiation of a new treatment line was explained in detail in **Error! Reference source not found.**Further details on defining and recoding the exposure are described in section 3.3.2.1.

6.2.3 Study co-variates.

A range of co-variate factors was used for this analysis, as indicated in section 6.1. The prognosis of mCRC is determined by a wide range of prognostic factors identified mainly from

literature for their impact on the disease. These prognostic factors are categorised into the following categories:

- Patient factors, including age at first-line regimen, gender, performance status at index SACT, comorbidities, deprivation level,
- Tumour factors, including tumour sidedness, primary tumour location, and tumour molecular profile,
- Previous treatment, including primary tumour resection,
- Inflammatory biomarkers and blood cell count parameters, including neutrophils to lymphocytes ratio (NLR), baseline albumin, haemoglobin, and carcinoembryonic antigen (CEA).

The list of covariates used in the analysis of survival outcomes (as potential confounders modifying the risk of death), the datasets from which the variables were retrieved, in addition to the applied coding method are presented in Table 6.1.

Table 6.1. Summary of the variables selected in the cox model to evaluate their association with the median OS with the applied coding method.

Variable	Dataset	Coding
SACT (section 3.3.2.1)	**CEPAS** (Section 3.2.2)	Nominal categorical (5FU, FOLFOX, FOLFIRI, cetuximab+FOLFIRI, Aflibercept+ FOLFIRI)
Age at index SACT (Section 3.3.1.1)	**CHI** Section 3.2.1) **CEPAS** (Section 3.2.2)	Continuous variable
Gender (Section 3.3.1.1)	**CHI** (Section 3.2.1)	Binary (Male, Female)
SIMD (Section 3.3.1.2)	**CHI** Section 3.2.1)	Ordinal categorical (1,2,3,4,5)
ECOG PS (Section 3.3.3.3)	**CEPAS** (Section 3.2.2)	Ordinal categorical (0,1, ≤ 2)
Primary tumour resection (section 3.3.2.3)	**OPERA (**Section 3.2.6)) **SMR01 (**Section 3.2.4.2)**,** **SMR06** (Section 3.2.4.3)	Binary (Y, N)
Primary tumour sidedness (section 3.3.3.1)	**SMR06** (Section 3.2.4.3	Nominal categorical (left, right, transverse)
Molecular profile (section 3.3.3.2)	**Molecular pathology (**Section 3.2.8)	Nominal categorical (Mutant RAS< Wild RAS, Mutant BRAF)
Comorbidity (CCI) (section 3.3.5)	**SMR00, SMR01** (section 3.2.4.1, section 3.2.4.2)	Ordinal categorical (0, [1-3], ≥4)
Albumin (section 3.3.4)	**SCI** (section 3.2.5)	Binary (≥ 34, < 34)
CEA (section 3.3.4)	**SCI** (section 3.2.5)	Binary (≤ 5, > 5)

Haemoglobin (section 3.3.4)	**SCI** (section 3.2.5)	Binary (Normal, ULN)
NLR (section 3.3.4)	**SCI** (section 3.2.5)	Binary (≤5, >5)
KEY: CEPAS: electronic chemotherapy prescribing system, SACT: systemic anti-cancer therapy, CHI= community health index, , SIMD: Scottish index for multiple deprivation, ECOG PS: Eastern Cooperative Oncology Group performance status, SMR 06: The Scottish Cancer Registry, SMR 00: Outpatient Appointments and Attendances SMR 01: Scottish Morbidity Records General/Acute Inpatient and Day Case, OPERA: Elective & emergency operations, CCI: charlson comorbidity index, CEA= carcinoembryonic antigen, NLR: Neutrophils to lymphocytes ratio		

6.2.4 Outcomes.

The primary outcome for this study is overall survival (OS), stratified by patients' index SACT. OS is defined as the survival interval from the date of initiation of the 1L SACT regimen (index date) to the time of death, loss at follow-up, or the end of the study period, whichever occurred first. Other secondary outcomes evaluated in this study included the following.

- The pathways across SACT lines, visualised using a Sankey diagram,
- Median OS associated with the treatment pathways identified through the Sankey diagram, which was defined as the survival interval from the date of initiation of the 1L SACT regimen to the time of death, loss at follow-up, or the end of the study period, whichever occurred first.
- Time-to-next-treatment (TTNT), which is defined as the time from initiating the 1L SACT regimen to the initiation of the 2L of therapy as a proxy for the duration of clinical benefit (Chen et al., 2017).

6.2.4.1 Overall survival.

Median OS and survival probability, which is defined as the percentage of individuals surviving a particular disease for a specific time interval. Median OS and survival probability with 95% confidence intervals were estimated using the Kaplan-Meier method for new mCRC SACT users and stratified by the index SACT prescribed for each patient. Moreover, the median follow-up time, defined as the median time from starting index SACT (1L SACT) until death or loss at follow-up, was measured using the reverse Kaplan-Meier method, which was performed by reversing the censor and the event (Shuster, 1991).

6.2.4.2 Secondary clinical outcomes.

Treatment pathways.

Patients' pathways across SACT lines until death, loss at follow-up, or end of the study were described and visualised using a Sankey diagram.

The Sankey diagram is a data visualisation technique that emphasises the flow from one state or time to another using nodes and links. For each state transition, a link flows from its source node (the left side of the diagram) to its target node (the next right node). Also, in a Sankey diagram, the size of each node and the width of each link indicate the number of objects/patients, hence the magnitude of the flow (Lamer et al., 2020).

In this study, an interactive Sankey diagram was designed to illustrate and describe patients' pathways across SACT lines. However, the Figure presented in this thesis is static (not interactive) as Microsoft office word does not support the HTML file extension through which the interactive Sankey diagram was presented.

In addition to visualising treatment pathways using the Sankey diagram, the median OS associated with the identified treatment pathways from 1L to 2L was measured using the Kaplan-Meier method for pathways containing ≥ 5 patients per treatment pathway to determine the survival outcomes associated with different SACT pathways. The median OS associated with treatment pathways from 2L to 3L was not measured due to the small number of patients continuing to 3L treatment.

Time to next treatment.

Time to next SACT treatment (TTNT) was suggested in the literature as a proxy for the durability of clinical benefit, which has shown to be clinically valuable, especially for incurable malignancies (Kim et al., 2019, Chen et al., 2017). TTNT estimates the time between the initiation of treatment and the initiation of the next line of therapy, hence enabling the assessment of the duration of therapeutic benefit.

6.2.4.3 Statistical analysis

Survival analysis

When performing survival analysis in observational studies, presenting crude Kaplan-Meier survival curves can be inadequate due to the influence of other covariates on the outcome.

Hence, it was necessary to carry out an adjusted survival analysis considering the different covariates (Table 6.1). All the variables and covariates were collected at the index date to allow for the identification of potential risk factors for overall survival. For this study, the adjusted median OS was measured for new mCRC SACT users, whereas for the survival analysis of treatment pathways, only crude survival was presented due to the small sample representing patients in various pathways.

Survival was described in terms of median OS, 1-year survival probability (survival time), and survival rate for the entire cohort and stratified by individual SACT. The median OS was calculated as the point in time after initiation of treatment at which 50% of patients were still alive. For each time point when an event happened, survival probability was calculated as the number of patients surviving divided by the number of patients at risk. Whereas survival rate was calculated by dividing the number of patients alive at the end of follow-up by the total number of patients. Patients who were lost to follow-up or were considered "censored" were not counted in the denominator (Dudley et al., 2016). Censoring is the method used to quantify survival time up to the point when a patient does not experience the event of interest and stops being followed up – either because the subject drops out or end of the study period (Lee and Go, 1997).

Moreover, Kaplan-Meier survival graphs were plotted, and the log-rank test was used to calculate the P-value to compare survival across individual SACTs. The log-rank test is a non-parametric test of the null hypothesis (H_0) that no difference exists between the population survival curves by arranging both observed and censored survival times in a rank order (Mantel, 1966). Any difference between the observed and expected is evidence against the $H_{0,}$ and hence, the log-rank test is most likely to detect a difference when the risk of an event (i.e., death) is consistently greater for one group than another and is unlikely to detect a difference when survival curves cross.

To assess the impact of mCRC SACT on the overall survival under the adjustment of different covariates (section 6.2.3), hazard ratios (HRs) were calculated using Cox proportional hazard models (Cox .D. R, 1972). The hazard is the probability that an individual would experience an event at a particular given point in time.

6.2.4.3.1 Univariate Cox regression analysis

A two-step procedure was used to examine the association of different covariates with the hazards of death. First, the association between each study covariate with the overall survival was tested with univariate Cox proportional hazard models. The covariates included are presented in table 6.1. These covariates were chosen based on the literature, suggesting a possible association with mCRC mortality.

6.2.4.3.2 Multivariate Cox regression analysis

The second step of examining the association of different covariates with the hazards of death is to perform a multivariate analysis that allows the impact of a variable to be evaluated under the adjustment of all other variables that may potentially affect the outcome. Multivariate Cox proportional hazards regression is a method of multivariate analysis used to explore differences in survival due to independent variables and distinguishes the individual contributions of covariates on survival, i.e., test whether each factor is an independent risk factor (D. R. Cox, 1972). For this study, the significant variables identified in the univariate analysis, in addition to priori confounders (age and gender) to be significantly associated with OS, were used to select covariates for the final multivariate model. The multivariate models were used to calculate adjusted HRs and 95% CIs of covariates associated with OS. A two-sided $P < 0.05$ was considered significant.

Moreover, after discussions with the statistician, it was agreed that for any variable containing five or fewer missing values, the missing values were not included as a separate category within the primary regression model as this would contribute to infinite estimates and confidence intervals.

For all variables used in the univariate analysis and primary multivariate analysis, missing information were coded as “unknown”.

6.2.4.4 Testing for proportional hazards (PH) assumption for Cox regression

When two groups are compared, and HR is calculated, it is assumed that the hazard ratio between the groups remains constant over time (Breslow, 1975). This applies even if the magnitude of the hazards varies over time, and the constant ratio is known as the hazard ratio. Thus, the mortality rate might differ between the individual SACTs, but the pattern of mortality remains the same. It is crucial to verify that the covariates fulfil the assumption of proportionality because if this assumption is violated, the Cox model is invalid and more

sophisticated analyses are required. The proportional hazards (PH) assumption can be checked using statistical tests such as Schoenfeld residuals which involves calculating the observed rate minus the predicted rate for each covariate over time (Schoenfeld, 1982). This difference between observed and expected for each covariate should remain constant over time and is considered a zero slope. If the residuals vary with time, a non-zero slope indicates a violation of the proportional hazard assumption.

6.2.4.5 Time to next treatment

TTNT was defined as the time from the commencement of the 1L SACT regimen in the study timeframe to the time of commencement of the next SACT in the study (Campbell et al., 2020). Hence, it was Reported only for patients who continued to the subsequent SACT line (2L) and Calculated (in months) from the beginning of the 1L SACT regimen until the beginning of the 2L SACT regimen. Median and interquartile range (IQR) for TTNT stratified by SACT was reported.

6.2.4.6 Handling missing data

To account for the potential bias arising from missing data, the last observation carried forward, and multiple imputations methods were applied for the variables containing missing values. These methods were described in detail in section 5.2.5.

As this study utilises the same cohort and shares several common variables with the study in chapter 5 (factors influencing the prescribing of 1L mCRC SACT regimens), the same methods to account for missing in data and the same generated baseline dataset were used to fit a multivariate Cox model. However, this study uses several additional variables that were not utilised in the study of the factors influencing prescribing of 1L mCRC SACTs, mainly including the Inflammatory biomarkers and blood cell count parameters variables (albumin, CEA, NLR, and haemoglobin). Therefore, the missing values for these variables were obtained through the LOCF method, where the closest value within six months of diagnosis was used to replace the missing value. This method reduced the number of missing values, but a number of missing values remained. Hence, the MI was performed for the remaining missing values, and a final dataset with no missing values was generated. The baseline characteristics table for the dataset generated after LOCF and MI is presented in appendix V.

The number of missing values for the Inflammatory biomarkers and blood cell count parameters variables used specifically for this study is presented in Table 6.2, while the number of missing values of the remaining variables is presented in Table 5.2.

Further details regarding the applied method for LOCF and multiple imputations were provided in section 5.2.5.

The complete baseline dataset generated following the application of these two methods was fitted in a multivariate Cox model deemed as sensitivity analysis for the primary Cox regression model.

Table 6.2 The number and frequency of missing data for Inflammatory biomarkers and blood cell count parameters variables used in survival analysis.

Variable	Number of missing observations before LOCF and MI (out of 220) (N, %)
Albumin	<5
Carcino-embryonic antigen (CEA)	43 (19.5)
Neutrophils to lymphocyte ratio (NLR)	<5
Haemoglobin	<5

KEY: SIMD= Scottish index for multiple deprivation, ECOG = Eastern cooperative oncology group, CCI= Charlson comorbidity index; LOCF = last observation carried forward; MI= Multiple imputations.

All statistical analyses for this study, including the survival outcomes and treatment pathways, were performed using R version 3.5.0/R Studio using the following packages: R base, ggplot2, dplyr, survival, survminer, GTsummary, coxph, and networkD3. R script for this study is provided in appendix VI.

6.3 Results.

This section presents the findings of the survival analysis for 1L and 2L SACT regimens used for new mCRC SACT users, along with the univariate and multivariate Cox regression models for 1L SACT regimens. The model with the missing data is presented as the primary model, and the model fitted after accounting for missing data is presented later as a sensitivity analysis for the primary model. This section also presents the treatment pathways, visualised using a Sankey diagram, along with measuring the time from 1L to 2L as a proxy for clinical benefit. Finally, the crude median OS for treatment sequences identified through the Sankey diagram will be presented for treatment pathways containing more than or equal to 5 patients.

6.3.1 Cohort overview.

A total of 220 new mCRC SACT users who initiated 1L mCRC between 1/1/2015 and 31/12/2016 were included in this study. Of these, 49 (22.3%) patients were treated in the 1L setting with 5FU, 66 (30%) and 47 (21.4%) patients were treated with oxaliplatin-based regimen (FOLFOX or XELOX) and irinotecan-based regimen (FOLFIRI), respectively. While 43 (19.5%) patients were treated with the combination of cetuximab+ irinotecan or oxaliplatin-based regimen (cetuximab+ FOLFIRI or cetuximab+ FOLFOX), and finally, 11 (5%) patients were treated with aflibercept+FOLFIRI in the 1L settings. Further details regarding the baseline SACT are presented in Table 4. 4.

The included cohort comprised slightly more male patients than female patients, with a median age of 66 years for the entire cohort (Table 4.5). A total of 14 patients (6.4%) had a poor performance status before initiating index SACT, while 22.7% (N=50, Table 4.5) of the patients had a good performance status (PS=0). Around one-third (30.5%, N= 67, Table 4.5) of the patients had the primary tumour located in the right side of the colon, and only 26.8% (N=59, Table 4.5) of the entire cohort undergone primary tumour resection. Mutation in the BRAF gene was detected in 7.7% (N=17, Table 4.5) of the patients, while wild-type RAS tumour was found in 35% (N=77, Table 4.5) of the patients. Hypoalbuminemia, elevated levels of carcinoembryonic antigen, haemoglobin levels not within the normal range and elevated levels of neutrophils-to-lymphocytes ratio were found in 53.6%, 64.1%, 48.6%, and

71.8% of the patients, respectively. Further details regarding the baseline characteristics of the entire cohort and stratified by index SACT are presented in section 4.3.3.

6.3.2 Survival analysis

6.3.2.1 Overall survival and survival probability

The median OS from the index SACT date for new mCRC SACT users was 13.3 months (95% CI 10.8-15.4). The survival probability was: 1-year survival 51.8% (95% CI 45.6- 58.9), 2-year survival 28.6% (95% CI 22.7-36), and 3-year survival 13.6% (95% CI 8.3%-22.5). The median follow-up time was 23.5 months (95% CI 20.8-27.9) for the full cohort Table 6.3 shows the median overall survival, the survival rate at 1,2 and 3-year, and the median follow-up for the full cohort and stratified by index SACT.

Table 6.3 Overall survival and survival probability for new mCRC SACT users stratified by SACT regimen.

SACT	N	deaths	Median overall survival(months) (95% CI)	One year survival (%) (95% CI)	Two year survival (%) (95% CI)	Three year survival (%) (95% CI)	Median follow up time (months) (95% CI)
Total	220	161	13.31 (10.81-15.40)	51.81 (45.60-58.90)	28.60 (22.71-36.0)	13.60 (8.30-22.50)	23.50 (20.80-27.90)
5FU/ Capecitabine	49	37	9.57 (7.81-15.41)	40.80 (29.20-57.80)	26.80 (16.50-43.70)	Unreachable	18.82 (16.80-NA)
FOLFOX or XELOX *FOLFIRI*	68 47	55 36	13.36 (10.1-15.6) 10.03 (9.21-18.6)	54.42 (43.80-67.60) 40.41 (28.61-57.20)	23.7 (14.4-39.2) 27.7 (17.1-45)	14.20 (5.90-34.10) 15.80 (7.10-35.40)	24.2 (22.8-NA) 33.6 (22.1-NA)
Aflibercept+FOLFIRI *Cetuximab+ FOLFIRI*	11 43	8 24	13.91 (7.96-NA) 23.72 (13.75-NR)	54.53 (31.81-93.63) 72.11 (60.04-86.81)	unreachable 27.93 (16.21-48.10)	Unreachable Unreachable	21.91 (19.12-NA) 23.90 (18.93-NA)

KEY: N= number of patients; CI= confidence interval; NR= Not reached; SACT = systemic anti-cancer treatment; 5FU= Fluorouracil/leucovorin; FOLFOX = Fluorouracil/leucovorin+ Oxaliplatin; FOLFIRI= Fluorouracil/leucovorin + irinotecan; FOLFOXIRI= Fluorouracil/leucovorin+ oxaliplatin+ irinotecan; XELOX= Capecitabine + Oxaliplatin

The Kaplan Meier curve for the full new mCRC SACT users cohort (N-220) is presented in Figure 6.1, while Figure 6.2 shows the Kaplan Meier curve for the new mCRC SACT stratified by individual SACT (N=218, FOLFOXIRI not included as N < 5 patients). Figure 6.2 shows a non-statistically significant difference in the median overall survival for mCRC SACTs used in the first-line settings with the log rank test (P-value) = 0.05. The Figure also shows the number of patients at different time points. For example, at a 10-month time point, 33 out of 43 patients (76.7%) treated with cetuximab+FOLFIRI were still alive, while at the same time point, 23 out of 49 patients (46.9%) treated with 5FU were still alive.

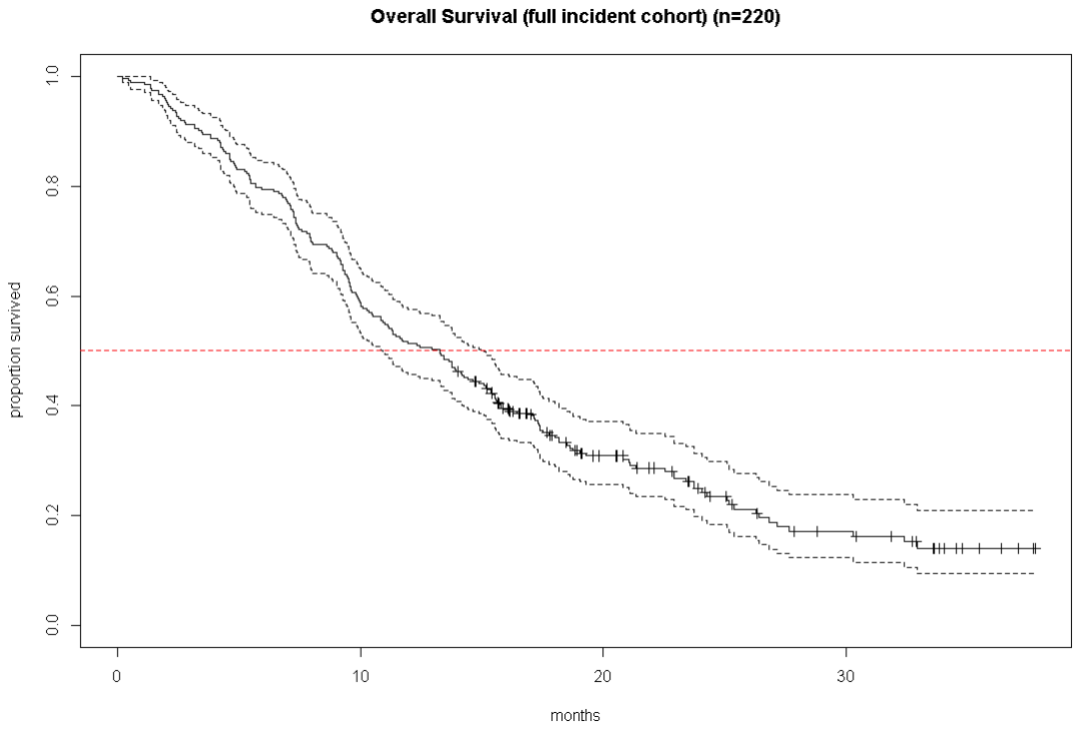

Figure 6.1 Kaplan-Meier curve showing overall survival for the study cohort from index SACT date (N=220).

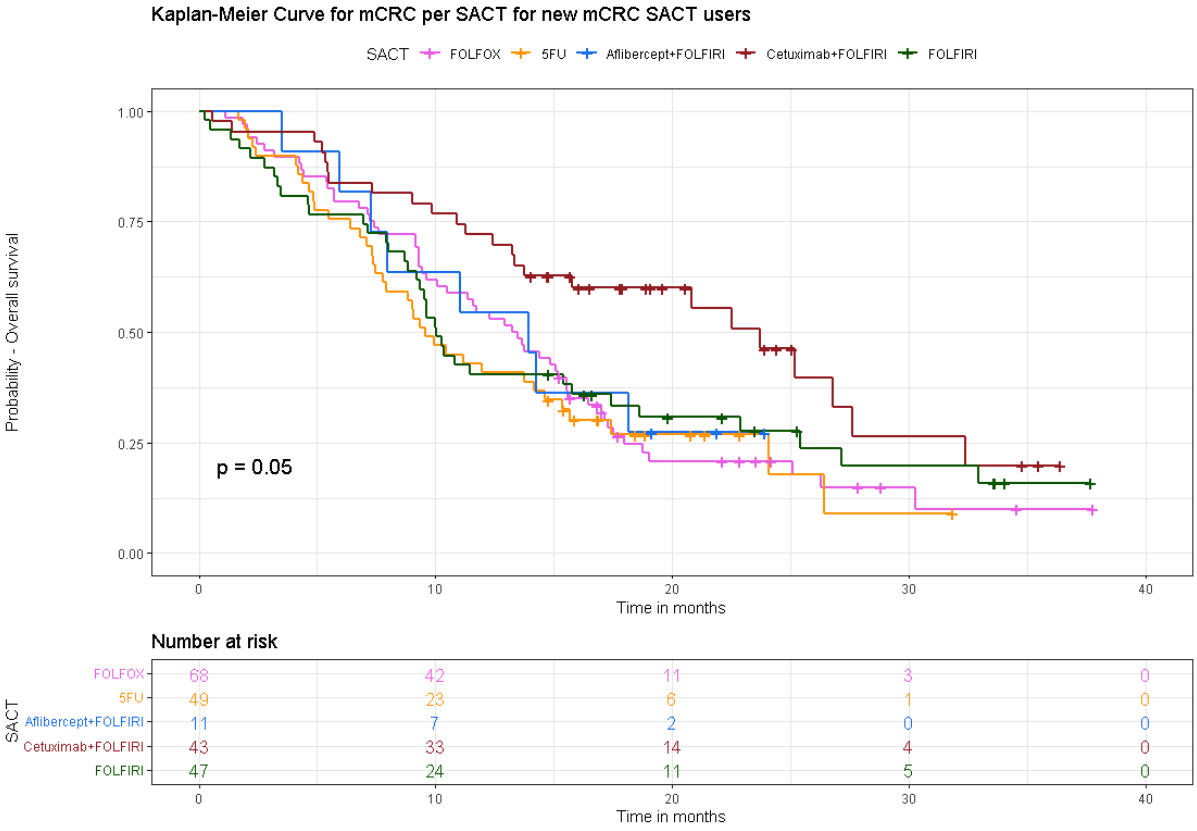

Figure 6.2 Kaplan-Meier survival curves showing overall survival for the index SACT for the new mCRC SACT users (N=218) *

*SACTs with < 5 patients were not presented in this KM curve

6.3.2.2 Univariate analysis

The univariate Cox regression analysis for the study is presented in Table 6.4. The combination of cetuximab+ FOLFIRI as a 1L SACT regimen shows a statistically significant improved OS compared to a singlet of 5FU. However, treatment with a doublet therapy of FOLFOX, FOLFIRI, or XELOX shows no statistically significant difference in OS compared to 5FU. Also, transverse tumour sidedness; BRAF mutant patients; poor PS (≤ 2) at baseline; CEA levels more than 5 µg/L; haemoglobin levels not within the normal range; NLR more than 5; and albumin levels less than or equal to 34 mg/dL were all associated with poorer survival.

Undergoing a primary tumour resection did not display an association with improved survival. Age, gender; SIMD rank; primary tumour location; and Charlson score; did not have a statistically significant impact on OS.

Table 6.4 Candidate variables considered in the univariate Cox regression for the overall survival.

Variable	Categories	Number (220)	Death	Survival rate	Median OS (0.95 LCL - 0.95 UCL)	HR (95% CI)	P-value	Global P-value*
First-line SACT regimen	5FU	49	37	24.5%	9.57 (7.8-15.4)	1		0.05
	FOLFOX	68	55	19.1%	13.36 (10.1-15.6)	0.87 (0.58-1.33)	0.52	
	FOLFIRI	47	36	23.4%	10.03 (9.21-18.6)	0.83 (0.52-1.32)	0.43	
	Cetuximab FOLFIRI	43	24	44.2%	23.72 (13.75-NA)	0.52 (0.31-0.87)	0.01	
	Aflibercept FOLFIRI	11	8	27.3%	13.91 (7.96-NA)	0.81 (0.38-1.73)	0.58	
Gender	Male	115	80	30.4%	15.16 (11.94-18.16)	1		0.08
	Female	105	81	22.9%	10.1 (9.28-13.91)	1.32 (0.97- 1.8)	0.08	
Age group	≥ 65	118	88	25.4%	11.66 (9.57-14.87)	1		0.4
	< 65	102	73	28.4%	14.28 (10.92-17.14)	0.87 (0.63-1.18)	0.362	
Scottish Index for multiple deprivations (SIMD) rank	1	68	52	23.5%	12.78 (9.61-17.4)	1		0.92
	2	43	30	30.2%	14.18 (7.89-26.28)	0.89 (0.57-1.39)	0.60	
	3	25	21	16.0%	10.46 (9.51-15.79)	1.1 (0.66-1.83)	0.71	
	4	37	24	35.1%	12.93 (9.57-NA)	0.86 (0.53-1.4)	0.55	
	5	44	32	27.3%	14.01 (9.97-17.53)	0.94 (0.6-1.45)	0.77	
Tumour sidedness	Left	130	92	29.2%	14.87 (11.71-17.4)	1		0.02
	Right	67	49	26.9%	11.02 (9.34-15.59)	1.17 (0.83-1.66)	0.38	
	Transverse	10	9	10.0%	7.15 (4.9-NA)	2.87 (1.43-5.78)	0.003	
	Unknown	6	4	33.3%	19.74 (5.43-NA)	0.66 (0.24-1.83)	0.43	
	Unspecified	7	7	0.0%	9.64 (6.94-NA)	1.78 (0.82-3.84)	0.14	
Tumour mutation type	Mutant RAS	81	60	25.9%	13.45 (9.44-15.79)	1		0.002
	Mutant BRAF	17	16	5.9%	7.47 (4.64-10.46)	2.6 (1.48-4.56)	0.1	

Variable	Categories	Number (220)	Death	Survival rate	Median OS (0.95 LCL - 0.95 UCL)	HR (95% CI)	P-value	Global P-value*
	Wild RAS	77	51	33.8%	15.79 (13.26-25.10)	0.73 (0.51-1.07)	0.008	
	Unknown	45	34	24.4%	11.18 (7.89-18.62)	0.95 (0.62-1.45)	0.8	
Performance status	0	61	37	39.3%	18.16 (13.65-32.4)	1		<0.001
	1	139	106	23.7%	11.61 (9.61-14.87)	1.71 (1.18-2.5)	0.005	
	≤ 2	15	14	6.7%	5.49 (4.24-9.64)	4.95 (2.63-9.3)	0.000	
	Unknown	5	*	*	15.9 (9.47-NA)	1.18 (0.62-2.22)	0.16	
Charlson comorbidity index	0	162	121	25.3%	12.2 (10.3-14.9)	1		0.28
	1-3	50	34	32.0%	15.1 (10.1-25.4)	0.8 (0.54-1.16)	0.23	
	> 4	8	6	25.0%	10.30 (10.30-NR)	1.17 (0.51-2.70)	0.78	
Primary tumour resection	No	161	117	27.3%	12.90 (10.01-14.90)	1		0.3
	Yes	59	44	25.4%	15.7 (10.3-23.7)	0.82 (0.58-1.17)	0.3	
Tumour primary location	Colon	156	116	25.6%	11.83 (9.93-15.07)	1		0.35
	Rectum	57	40	29.8%	15.53 (11.18-25.16)	0.85 (0.59-1.21)	0.36	
	Unknown	7	*	*	12.90 (5.43-NA)	0.76 (0.41-1.77)	0.85	
Carcino embryonic antigen (CEA)	≤ 5	36	18	50.0%	22.89 (11.28-NA)	1		0.006
	> 5	141	112	20.6%	11.35 (9.61-14.41)	2.05 (1.25-3.17)	0.001	
	Unknown	43	31	27.9%	15.4 (10.1- 25.2)	1.43 (0.81- 2.51)	0.21	
Haemoglobin	Female 115-165 or Male 130-180	111	76	31.5%	15.53 (13.45-23.72)	1		0.001
	Female <115 or >165 or Male <130 or >180	107	84	21.5%	9.87 (8.85-13.26)	1.69 (1.23-2.32)	0.001	
Neutrophil-to-lymphocyte ratio (NLR)	≥ 5	158	112	28.2%	14.23 (11.94-16.45)	1		0.017
	< 5	60	48	22.6%	9.26 (7.24-12.3)	1.53 (1.09-2.15)	0.014	

KEY: HR= hazard ratio, OS= overall survival, UCL= upper confidence level, LCL= lower confidence level, *P-value was calculated through log rank test

6.3.2.3 Multivariate Cox regression analysis.

The association of baseline characteristics with overall survival using multivariate Cox-proportional hazards models is presented in Table 6.5. The multivariate Cox-regression model included priori confounders (age and gender) along with the variables significantly associated with OS in the univariate analyses (Table 6.4). The singlet regimen of 5FU was used as the comparator as it is considered the backbone of mCRC therapy (Biller and Schrag, 2021).

None of the variables entered into the multivariate COX regression model shows an overall statistically significant effect on the model, including first line SACT treatment (global P-value 0.09). However, under the adjustment of the remaining variables, initial treatment with cetuximab+FOLFIRI shows statistically significant reduced hazards of death compared to 5FU (HR 0.4 (0.24-0.85), P-value 0.04). Moreover, Patients who had poorer performance status (≤2) had a statistically significant increased hazard of death compared to patients with good performance status (PS =0) (HR 4.3 (1.52-10.3), P-value 0.001).

Mutation in BRAF gene was associated with an increased hazard of death (HR 1.85 (0.72-4.8), P-value 0.1). However, this increase was not statistically significant, noteworthy, the large confidence interval indicates the small sample in this category (Table 4.5).

Initial treatment with FOLFOX, FOLFIRI, and aflibercept+FOLFIRI shows reduced hazards of death compared to 5FU, however, with a non-statistically significant difference.

Additionally, patients above 65 years, female gender, and tumours originating from the transverse colon, neutrophils to lymphocyte ratio > 5, haemoglobin levels not within the normal range, hypoalbuminemia (>34 g/L), and elevated levels of CEA (>5 μg/l) were all associated with poorer overall survival. However, the impact was not statistically significant (Table 6.5).

For the assumption of the proportionality of the hazards of the model, the global proportional hazard test statistic for the multivariate Cox model was shown to be not significant (P-value 0.057), and therefore the proportionality of the hazards can be assumed, indicating that the ratio of the hazards for any SACT is constant over time.

Table 6.5. Association of baseline characteristics with overall survival using multivariate Cox-proportional hazards models

Variable	Categories	Adjusted HR (95% CI)	P-value	Global P-value
Regimen	5FU	1		0.09
	FOLFOX/ XELOX	0.7 (0.52-1.18)	0.2	
	FOLFIRI	0.93 (0.49-1.22)	0.27	
	Cetuximab+ FOLFIRI	0.4 (0.24-0.85)	**0.04**	
	Aflibercept+ FOLFIRI	0.69 (0.39- 1.13)	0.48	
Age group	< 65	1		0.1
	≥ 65	1.45 (0.93-2.3)	0.1	
Gender	Male	1		0.22
	Female	1.28 (0.84-1.94)	0.22	
Mutation type	Mutant RAS	1		0.09
	Wild RAS	1.3 (0.83-1.69)	0.52	
	Mutant BRAF	1.85 (0.72-4.8)	0.1	
	Unknown	1.1 (0.81-1.25)	0.3	
Tumour sidedness	Left	1		0.11
	Right	1.07 (0.7-1.65)	0.14	
	Transverse	1.81 (0.83-5)	0.09	
	Unknown	1.87 (0.72-4.85)	0.19	
Performance status	0	1		0.25
	1	1.4 (0.87-2.27)	0.6	
	≤ 2	4.3 (1.52-10.30)	**0.001**	
Neutrophil-to-lymphocyte ratio (NLR)	≤ 5	1		0.11
	>5	1.44 (0.91-2.3)	0.11	
Haemoglobin (g/l)	Female 115-165 or Male 130-180	1		0.66
	Female <115 or >165 or Male <130 or >180	1.11 (0.74-1.67)	0.66	
Carcino embryonic antigen (CEA) (µg/l)	≤ 5	1		0.07
	> 5	1.67 (0.95-2.94)	0.07	
Albumin (g/L)	≥ 34	1		0.19
	< 34	1.25 (0.75-1.12)	0.19	

KEY: HR= hazard ratio, OS= overall survival, UCL= upper confidence level, LCL= lower confidence level, global P-value was calculated through log rank test

6.3.2.4 Sensitivity analysis of the multivariate Cox regression

Missing in data was handled through LOCF and multiple imputations methods. The baseline characteristics table for the full new mCRC SACT cohort and stratified by index SACT after addressing the missing in data is presented in appendix VII. after addressing missing in data and obtaining the baseline characteristics without missing data, a multivariate Cox regression analysis was performed (Table **6.6**). Overall, the significance and direction of association were comparable across all tested variables to the variables included in the primary model with the missing values. However, the model shows that patients with a BRAF-mutant type had a statistically significant higher risk of death compared to patients with mutant RAS tumour type HR (2.72 (1.55-4.77), P-value <0.001).

Table 6.6. The COX regression model after accounting for missing in data by performing multiple imputations and last observation carried forward methods.

Variable	Categories	Adjusted HR (95% CI)	P-value	Global P-value
Regimen	5FU	1		0.1
	FOLFOX/ XELOX	0.91 (0.60-1.40)	0.2	
	FOLFIRI	0.97 (0.59-1.61)	0.27	
	Cetuximab+ FOLFIRI	0.48 (0.27-0.96)	**0.04**	
	Aflibercept+ FOLFIRI	0.98 (0.67-1.89)	0.48	
Age group	< 65	1		0.89
	≥ 65	1.02 (0.73-1.45)	0.89	
Gender	Male	1		0.74
	Female	1.05 (0.75-1.5)	0.74	
Mutation type	Mutant RAS	1		0.07
	Wild RAS	1.18 (0.80-1.78)	0.52	
	Mutant BRAF	2.72 (1.55-4.77)	**<0.001**	
Tumour sidedness	Left	1		0.11
	Right	1.05 (0.65-1.69)	0.8	
	Transverse	1.64 (0.79-3.40)	0.18	
Performance status	0	1		0.1
	1	1.42 (0.93-2.13)	0.09	
	≤ 2	3.4 (1.70-6.91)	**<0.001**	
Neutrophil-to-lymphocyte ratio (NLR)	≤ 5	1		0.11
	>5	1.30 (0.89-1.90)	0.11	
Haemoglobin (g/l)	Female 115-165 or Male 130-180	1		0.56
	Female <115 or >165 or Male <130 or >180	1.11 (0.74-1.67)	0.56	
Carcino embryonic antigen (CEA) (µg/l)	≤ 5	1		0.58
	> 5	1.12 (0.73-1.71)	0.58	
Albumin (g/L)	≥ 34	1		0.72
	< 34	1.07 (0.64-1.19)	0.72	

KEY: HR= hazard ratio, OS= overall survival, UCL= upper confidence level, LCL= lower confidence level, global P-value was calculated through log rank test

6.3.3 Secondary outcomes

6.3.3.1 Treatment pathways

Treatment pathways for new mCRC SACT users are illustrated in Figure 6.2. The Figure shows SACT treatment pathways from 1/1/2015 until the patients were deceased, lost at follow-up, or end of the study on 28/02/2018. A total of 46 unique pathways were identified for the new mCRC SACT patients (N=220) across SACT lines as the patients either proceeded to further SACT lines, were deceased, remained on the same SACT, or were lost at follow-up.
The Figure illustrates the flow of patients across SACT lines. The first group of nodes (source nodes) on the left side of the Figure represents the first line regimen (1L) flowing to the subsequent group of nodes, which represent the second line regimen in the study (2L) and then to the third line regimen (3L). For example, the Figure illustrates patients treated with FOLFOX as a 1L regimen (N=68), where these patients would have three different scenarios: 1- die after receiving the 1L regimen (death node on the right side of the Figure) (N=37, 54.4% of the patients who initiated FOLFOX), 2- remain on the same regimen or were lost at follow-up (FOLFOX node on the right side of the Figure) (N=7, 10.3% of the patients who initiated FOLFOX), or 3- proceed to 2L SACT (the next group of nodes) (2L) (N=24, 35.3%), where in this example some of the patients received FOLFIIRI (N=14), aflibercept+FOLFIRI (N=5), or other SACT as a 2L regimen.

A total of 166 (75.5%) patients received only one SACT line; of these, 135 (81.3%) patients were deceased after receiving the 1L SACT, while 31 (18.7%) patients either remained on the same treatment or were lost at follow-up. On the other hand, of the 220 patients who initiated mCRC SACT, 54 (24.5%) patients proceeded to 2L SACT. Of these, 6 (11.1%) and 11 (20.4%) patients had their treatment intensified from a monotherapy (Fluorouracil) to a doublet or triplet SACT (FOLFOX, FOLFIRI, or aflibercept+FOLFIRI), or from a doublet SACT to a triplet SACT (aflibercept+FOLFIRI, cetuximab+FOLFIRI, or FOLFIXIRI), respectively. Moreover, 8 (14.8%) patients had their initial SACT stepped down in the 2L from a triplet to a doublet or from a doublet to a monotherapy. The most common SACT pathways are summarised in Table 6.7. SACT pathways containing less than 5 patients were not reported.

The most commonly prescribed 2L SACT was FOLFIRI (N=19, 35.2%), followed by FOLFOX (N=16, 29.6%). The combination of Aflibercept+FOLFIRI was prescribed for 6 (11.1%) patients, while cetuximab+FOLFIRI was prescribed for 5 (9.3%) patients, and finally, a single agent of cetuximab was prescribed for 6 (11.1%) patients as 2L SACT.

Only 5 (9.3%) of the 54 patients who received a 2L proceeded to a 3L SACT of either FOLFOX, cetuximab, or FOLFOXIRI, while 46 (85.2%) were deceased after receiving the 2L SACT. The remaining patients either continued the same SACT or were lost at follow-up. By the end of the study, 183 patients were deceased.

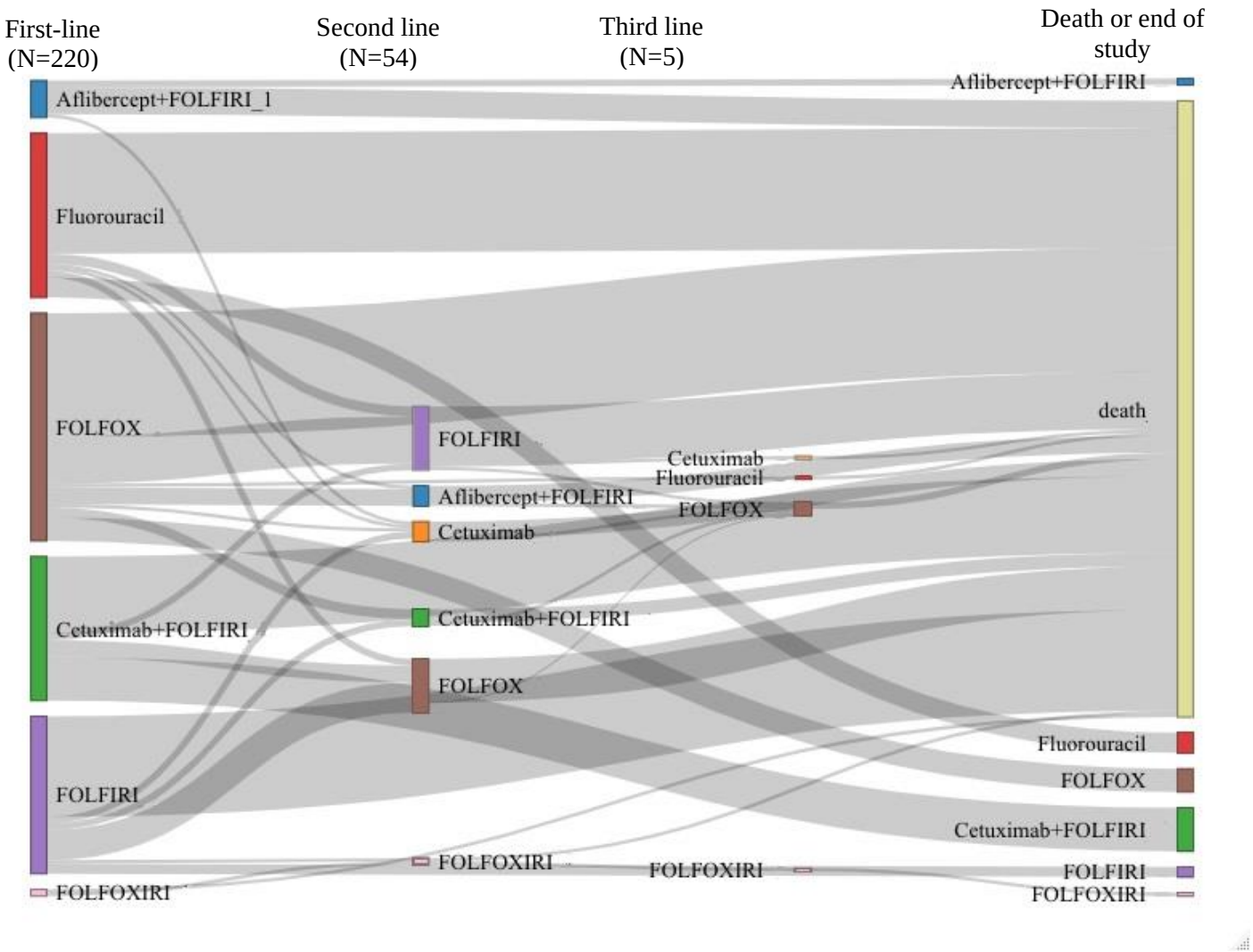

Figure 6.3. Sankey diagram showing the SACT pathways for new mCRC SACT users from 1/1/2015 until death or loss at follow-up (N= 220)

* As a part of the University of Glasgow safe haven permission to use the current data, pathways containing five or less patients were not presented by numbers in the Figure

Table 6.7. The number and frequency of the most common pathways for new mCRC SACT users in the study (N=220)

SACT line	SACT pathway by lines of therapy	N (%)
First-line SACT (N=220)	**First-line SACT**	**220**
	First line SACT to death	**135 (61.4%)[1]**
	FOLFOX to death	37 (27.4)[2]
	FOLFIRI to death	30 (22.2)[2]
	5FU to death	36 (26.7)[2]
	Cetuximab+ FOLFIRI to death	23 (17)[2]
	Aflibercept+ FOLFIRI to death	8 (5.9)[2]
	FOLFOXIRI to death	*
	First line SACT to second line SACT	**54 (24.5)[1]**
	FOLFOX to FOLFIRI	14 (25.9)[3]
	FOLFOX to aflibercept+FOLFIRI	5 (9.3)[3]
	FOLFIRI to FOLFOX	9 (16.7)[3]
	Cetuximab+FOLFIRI to FOLFOX	5 (9.3)[3]
	Other pathways	21 (38.8)[3]
	First-line SACT to loss at follow-up or remain in the same SACT line	**31 (14.1)[1]**
	5FU	6 (19.4)[4]
	FOLFOX	7 (22.6)[4]
	Cetuximab+FOLFIRI	13 (41.9)[4]
	Other SACTs	5 (16.1)[4]
Second-line SACT (N=54)	**Second line SACT**	**54**
	Second line SACT to death	**46 (85.2)[5]**
	FOLFOX to death	13 (28.9)[6]
	FOLFIRI to death	17 (31.5)[6]
	Aflibercept+ FOLFIRI to death	5 (10.9)[6]
	Cetuximab to death	5 (10.9)[6]
	Other pathways to death	6 (13)[6]
	Second line SACT to third line SACT	**5 (9.2)[5]**
	Second line SACT to loss at follow-up or remain in the same line	*
Third line SACT (N=5)	**Third line SACT**	**5**
	Third line SACT to death	*
	Third line SACT to loss at follow-up or remain in the same SACT line	*

KEY: SACT= Systemic anti-cancer therapy; CI= confidence interval, N= number of patients

[1]:denominator is the total sample (N=220); 2: denominator is first line SACT to death patients (N=135); 3: the denominator is first line SACT to second-line SACT patients (N=54); 4: denominator is first-line SACT to loss at follow-up or remain in the same SACT line (N=31); 5: the denominator is second line SACT (N= 54); 6: the denominator is second line SACT to death (N=46)

6.3.3.2 Survival findings for SACT pathways

The median OS for the patients continuing from 1L to 2L, which was measured from the beginning of 1L until death, loss at follow-up, or end of the study is presented in Table **6.8**. For all patients who continued from 1L mCRC SACT to 2L mCRC SACT (N=54), the median overall survival was 13.96 months (95% CI 11.35-17.40). Notably, patients who received FOLFOX in the 1L and continued on FOLFIRI as 2L had similar median overall survival compared to patients treated initially with FOLFIRI and continued on FOLFOX or XELOX as a 2L regimen. On the other hand, patients who received a 1L SACT of cetuximab+FOLFIRI and continued on FOLFOX as the 2L SACT had a median OS of 27.61 months (95%CI 13.32-NA). However, only five patients in our study were treated with this sequence of SACT regimens, and the effect of the small sample is clearly seen in the wide 95%CI.

Table 6.8. The median OS associated with SACT pathways for the patients continuing from first-line to second-line.

SACT pathway (1L to 2L)	Number of patients*	Median overall survival in months (95% CI)
All 1L SACTs to 2L SACTs	54	13.96 (11.35-17.40)
FOLFOX to FOLFIRI	14	10.70 (7.40-19.01)
FOLFIRI to FOLFOX	9	10.80 (9.34-NA)
FOLFOX to aflibercept+FOLFIRI	5	17.3 (15.07-NA)
Cetuximab+FOLFIRI to FOLFOX	5	27.61 (13.32-NA)

KEY: SACT= Systemic anti-cancer therapy, CI= confidence interval
*Pathways containing less than five patients were not presented by numbers in the table as a part of the University of Glasgow safe haven permission to use the current data

6.3.3.3 Time to next treatment (TTNT)

The median TTNT (1L to 2L) is presented in Table **6.9**. For all patients who continued to 2L SACT (N=54), the median time from 1L to 2L was 6.12 months (IQR: 3.1-9.7). When stratified by 1L SACT regimen, the TTNT was reported to be the shortest for patients treated with aflibercept+FOLFIRI in the 1L settings (median TTNT 4 months (IQR 4-4)) and the longest for patients treated with the combination of cetuximab+FOLFIRI as 1L regimen (median TTNT 12.93 (IQR 5.85- 15.25)).

Table 6.9. Time from first line SACT to second-line SACT for new mCRC SACT users (N=220).

SACT	**Number of patients in 1L**	**Number of patients continuing to next SACT regimen**	**Median Time to next treatment in months (IQR)**
Full cohort	220	54	6.12 (3.11-9.70)
5FU/ Capecitabine	**49 (19.5)**	7	6.11 (4.02-7.51)
FOLFOX or XELOX *FOLFIRI*	68 (31) 47 (22.4)	24 14	5.60 (2.22- 9.13) 7.03 (3.26-11.3)
Aflibercept+FOLFIRI *Cetuximab+ FOLFIRI*	11 (7.6) 43 (18.8)	* 7	4.00 (4.00-4.00) 12.93 (5.85-15.25)

KEY: SACT= systemic anticancer therapy, 1L= first-line, IQR= interquartile range
*SACT regimens containing less than five patients were not presented by numbers in the table as a part of the University of Glasgow safe haven permission to use the current data

6.4 Discussion

This retrospective observational study aimed to determine the treatment outcomes for new mCRC SACT users in NHS GGC who initiated mCRC SACT treatment between 1/1/2015 and 31/12/2016, including OS of 1L mCRC SACT, and the time to next SACT treatment. Also, this study aimed to explore treatment pathways by visual depiction using a Sankey diagram and the overall survival associated with the most common SACT pathways.

6.4.1 Summary of key findings

6.4.1.1 Overall survival

The overall survival findings for the new mCRC SACT users in this study were slightly suboptimal. Given that for untreated mCRC patients, the median OS is reported to be approximately nine months with the best supportive care (Rodriguez-Bigas et al., 2003), the median OS for the total cohort in our study was 13.3 months (95% CI 10.8-15.4). However, median OS varied considerably across individual SACTs, with the longest observed median OS being 23.72 months (95% CI 13.75-NA) for patients treated with cetuximab+FOLFIRI as 1L regimen while patients treated with a 5FU monotherapy as 1L regimen had the shortest median OS of 9.57 months (95%CI 7.81-15.41) (Table **6.3**). The multivariate Cox regression model adjusting for the baseline characteristics of the patients shows that the combination of cetuximab+FOLFIRI (HR 0.4 (95% CI 0.24-0.85) (Table 6.5) was significantly associated with less hazards of death compared to 5FU monotherapy. This finding was expected given that 5FU monotherapy is the essential backbone SACT for mCRC, and its use is now limited for patients who cannot endure the toxicity of more intensive therapy (see section 5.3.3). Also, the findings of this study show that initial treatment with doublet therapy of FOLFOX (HR 0.7 (0.52-1.18) or FOLFIRI (HR 0.93 (0.49-1.22) was not associated with a statistically significant improvement in OS compared to monotherapy of 5FU (Table 6.5). 5FU was used as the reference group for the multivariate cox regression since it is considered the backbone therapy for the majority of mCRC SACTs.

The model also shows that poor PS (PS ≥ 2) has a negative impact on the median OS and is associated with more inferior survival outcomes (HR 4.3 (1.52-10.30)) compared to patients with PS= 0. `

The ECOG PS scale indicates an increasing level of disability (Table 3.5). Patients with poor PS (PS ≥ 2) usually experience more adverse events of active treatment compared to

patients with good performance status (Chan et al., 2017, Heedman et al., 2015). Hence, poor performance status is known to predict poorer survival outcomes.

Despite the fact that the primary cox regression model for new mCRC SACT users did not demonstrate a statistically significant impact of BRAF mutation on the OS (HR 1.85 (0.72-4.8), P-value 0.1) (Table 6.5), the model fitted after accounting for data missingness (

Sensitivity analysis of the multivariate Cox regression

Missing in data was handled through LOCF and multiple imputations methods. The baseline characteristics table for the full new mCRC SACT cohort and stratified by index SACT after addressing the missing in data is presented in appendix VII. after addressing missing in data and obtaining the baseline characteristics without missing data, a multivariate Cox regression analysis was performed (Table **6.6**). Overall, the significance and direction of association were comparable across all tested variables to the variables included in the primary model with the missing values. However, the model shows that patients with a BRAF-mutant type had a statistically significant higher risk of death compared to patients with mutant RAS tumour type HR (2.72 (1.55-4.77), P-value <0.001).

Table 6.6) revealed that the presence of a mutation in the BRAF gene was associated with a statistically significant poorer survival (HR 2.72 (1.55-4.77), P-value <0.001) which is consistent with the literature findings on the poor prognosis of BRAF mutation for mCRC patients (Schirripa et al., 2019, Seligmann et al., 2017). This discrepancy between the primary cox regression model and the model fitted after accounting for data missingness is probably due to the large number of missing data in the type of mutation variable (N=45, Table 4.5), which after being accounted for through MI and LOCB resulted in an increased number of patients in the mutant BRAF category (N=17 (Table 4.5) in the primary analysis to N=22 after accounting for data missingness. Hence, the increased number of patients resulted in an increased power that enabled the test to detect the differences and resulted in a statistically significant negative impact of mutant BRAF tumour on overall survival (HR 2.72 (1.55-4.77), P-value <0.001).

It remains debatable whether primary tumour resection has an impact on overall survival for unresectable mCRC patients. Although most of the observational studies have demonstrated a survival benefit for curative primary tumour resection on overall survival for mCRC patients (Michel et al., 2004, Scoggins et al., 1999, Ruo et al., 2003, Tebbutt et al., 2003, Ferrand et al., 2013). Less consistency among the published data exists regarding the survival benefit of palliative resection, which is often performed to reduce the complications of the tumour, such as gastrointestinal obstruction, perforation, or bleeding (Wu et al., 2017). The findings of this study did not identify a statistically significant impact of the primary tumour resection on overall survival (Table 6.5). In our study, data regarding the intention of the surgery was not available. Therefore, it was not clearly defined whether the resection was performed for palliative or curative intention. Hence, the intention of the primary tumour resection was considered an unmeasured confounder that could have contributed to the lack of statistically significant difference between patients who had the resection performed and those who did not undergo the surgical resection. Furthermore, as discussed in section 4.4.2.1, the rates for the primary tumour resection for the patients at baseline in our study were found to be lower compared to the surrounding Scandinavian countries. This difference is important given the potential survival benefit offered by synchronous tumour resection, as reported in the

literature. A study by *Benitez Majano et al*. suggested that the inferior CRC survival in England could be attributed partly to the conservative selection of patients for surgery, as patients >75 years were less likely to be offered curative primary tumour resection surgery in England compared to surrounding Scandinavian countries. (Benitez Majano et al., 2019). Given the comparability among the Scottish and English clinical recommendations for primary tumour resection, it can be concluded that the country-specific management guidelines could possibly impact survival outcomes.

It is also important to highlight that the clinical trials upon which the approval for the SACTs captured in this study included prognostic factors that were not included in our study, mainly encompassing the type of metastases (synchronous vs metachronous metastasis), the metastatic site (liver, lung, peritoneum, etc.), and the number of metastatic sites. These prognostic factors were reported to potentially have an impact on the overall survival (Stillwell et al., 2011). For example, Wang et al. found that lung-only metastasis was considered an independent prognostic factor for better overall survival compared to liver-only metastasis [HR 0.82 (95% CI 0.71-0.94)] (Wang et al., 2020). These factors, along with possible other unmeasured confounders, could possibly have impacted or biased the findings of our study.

6.4.1.2 Secondary outcomes: treatment pathways and TTNT

In this study, the treatment pathways were illustrated through a Sankey diagram, which shows the potential to display the variation in treatment pathways in routine practice. The tool illustrated 46 unique pathways for new mCRC SACT users who initiated a 1L mCRC SACT in NHS GGC until death, loss at follow up or continuing to 2L SACT. The treatment pathways identified using the Sankey diagram were not always aligned with the standard guidelines. For example, the SMC has licenced aflibercept+FOLFIRI to be used in the 2L settings following the failure of a 1L oxaliplatin-based regimen (Scottish Medicine Consortium, 2014). However, in our study, aflibercept+FOLFIRI was used in the 1L setting for 5% of the new mCRC SACT users (N=11) and 6 (11.1%) patients in the 2L settings. Of these, five were treated in the 1L settings with oxaliplatin-based chemotherapy, which complies with the recommendations by the SMC as aflibercept+FOLFIRI is licenced to be used as a 2L regimen following the failure of oxaliplatin-containing regimen (Scottish Medicine Consortium, 2014). Furthermore, cetuximab as a single agent, which the SMC licenced for use as a single agent in patients who

failed oxaliplatin or irinotecan-based therapy (Scottish Medicine Consortium, 2005), was prescribed for 5 (9.3%) patients in the 2L settings. Noteworthy, both FOLFOX and FOLFIRI were predominantly present in the 2L regimens, complying with the SIGN recommendations for prescribing irinotecan-based chemotherapy as 2L following 1L oxaliplatin and vice versa (Scottish Intercollegiate Guidelines Network, 2011b).

Our findings also show that 17 (31.5%) patients who continued to 2L regimen had their 1L SACT regimen intensified from monotherapy (5FU) to doublet (FOLFOX, XELOX, or FOLFIRI) or from a doublet to a triplet (cetuximab+FOLFIRI or aflibercept+FOLFIRI). The intensification of the therapy is potentially associated with the progression of the disease, warranting more intensive approaches (Kim et al., 2015). On the other hand, 8 (14.8%) patients had their 1L SACT regimen stepped down from a triplet or a doublet therapy to a doublet or monotherapy, respectively. This approach is usually associated with intolerability of the SACT regimen or worsening of the patient's performance status following the 1L regimen (Mocellin et al., 2017).

Even though oxaliplatin and irinotecan-based regimens are licenced as first and second-line regimens for mCRC, the optimal sequencing of these regimens remains unclear. Our findings show that patients who received oxaliplatin followed by an irinotecan-based regimen displayed a similar median OS compared to those who received the reverse sequence with a median OS of 10.7 months (7.4-19) for the former sequence and a median OS of 10.8 months (9.34-NA) for the later sequence (Table **6.8**). This finding was supported by previously published findings from observational studies, which reported no statistically significant differences in median OS between the two sequences (Teng et al., 2015).

6.4.2 Comparison with literature

6.4.2.1 Observational studies

Many published real-world studies have reported the survival outcomes for mCRC SACTs in routine practice. Chapter 2 in this thesis reported clinical outcomes, including the overall survival of mCRC patients receiving first-line SACTs in real-world studies.

Marschner et al., 2015 reported a median OS of 26.8 months (95% CI 22.4-31.9) for patients treated with a first-line FOLFOX or XELOX and a median OS of 18.3 months (95% CI 15.1-23.2)

for patients treated with a first-line FOLFIRI or XELIRI, (Marschner et al., 2015), which is longer than the median OS for the patients in our study of 10.03 months (9.21-18.6) (Table **6.3**). This might be attributed to several reasons, including the rate of primary tumour resection, which was reported in 87.4% of patients in Marschner et al., 2015 study compared to 26.8% of the patients in our study. Moreover, whilst the Marschner et al.,2015 cohort comprised patients who presented initially at different stages of CRC at diagnosis before progressing to the metastatic stage, the patients in our study were assumed to have presented at the metastatic stage at the time of diagnosis, which is known to be associated with poor prognosis in contrast to patients presenting with stage I, II, or III CRC (Rosen et al., 2000). Therefore, offering a potential explanation for the shorter OS for our cohort compared to Marschner et al.,2015 cohort.

Fukuchi et al., 2013 reported a median OS of 25.4 months (no confidence interval reported) for patients less than 75 years treated with oxaliplatin-based chemotherapy (i.e, FOLFOX or XELOX) in Japan. However, 72% of the patients in Fukuchi study (N=108) were reported to have undergone primary tumour resection, in contrast to 26.8% of our entire population (Fukuchi et al., 2013).

Furthermore, Satram-Hoang et al.,2013 reported a 3-year survival rate of 68.5% (95% CI 64.2-72.3) (Satram-Hoang et al., 2013) for patients treated with 1L FOLFOX, in contrast to a 3-year survival rate of 14.2% (5.9-34.1) in our study.

Stec et al., who carried out a retrospective observational study of first-line capecitabine versus FOLFIRI for patients with mCRC above the age of 65 years, reported a median OS of 15.4 months (no reported 95% CI) and 19 months (no reported 95% CI) for patients treated with capecitabine and FOLFIRI, respectively (Stec et al., 2010) in contrast to a median OS of 9.2 months (95% CI 7.5-14.6**)** for patients treated with 5FU or capecitabine and a median OS of 10.6 months (95%. CI 9.5-15.4) for patients treated with FOLFIRI in our study. Although Stec et al. cohort restricted the included cohort to elderly patients ≥ 65 years, our cohort seems to have an inferior OS compared to Stec et al. (Table **6.3**). This might be attributed to the fact that Stec et al. included patients whose PS is ≤ 2 in contrast to our cohort, which included patients with PS more than 2.

As demonstrated by the comparison of the findings between our study and other observational studies, a notable gap in median OS can be observed for patients treated with

chemotherapeutic agents (5FU, FOLFOX, FOLFIRI). However, this gap is reduced when the outcomes of our patients treated with ctuximab+ chemotherapy are compared to those of other observational studies. For instance, while in our study, the median OS for patients treated with cetuxmaib+ FOLFOX or ceuxima+ FOLFIRI was 23.72 months (13.75-NA), the median OS in Lam et al. study, which investigated the effectiveness of 1L cetuximab+ fluoropyrimidine chemotherapy, was 25.8 months (18.7-35.6) (Lam et al., 2019). Also, Bai et al. reported a median OS of 28.3 months (22.7–33.9) for patients treated with cetuximab+chemotherapy, which is fairly comparable to our findings (Bai et al., 2016). This comparability could be potentially attributed to the relatively similar characteristics, especially given that the majority of patients treated with cetuximab+ FOLFIRI had wild-RAS tumour and had the lowest median age in our study compared to the remaining SACTs, which is fairly comparable to other observational studies.

Finally, the comparison of survival findings of aflibercept+FOLFIRI between our study and other observational studies could not be established, as, to our knowledge, no previous observational study has performed an evaluation for the effectiveness of aflibercept+ FOLFIRI in the 1L settings.

6.4.2.2 Comparison to clinical trials

Differences in the characteristics between the clinical trials population and observational studies population are inevitable. Details regarding the differences between this study and clinical trials were discussed in section 4.4.2.2.

Compared to the populations of the clinical trials upon which the approval of SACT regimens captured in this study was granted, our cohort included patients with poor PS (PS ≥ 2 (N=15, 6.8%)) and BRAF mutant (N=17, 7.7%) treated in routine clinical settings. However, these factors are recognised as poor prognostic factors, supported by the findings of the multivariate cox models Table 6.6 and Table 6.7). Patients with these characteristics are often excluded from clinical trials. As discussed in chapter 4, the clinical trials upon which the SACTs included in this study were approved mostly included patients with a performance status **≤** 2, with adequate haematological, renal, and hepatic function, and with a median age of less than 65 years (de Gramont et al., 1997a, de Gramont et al., 2000, Saltz et al., 2000, Van Cutsem et al., 2015, Van Cutsem et al., 2012). For example, 43.3% (N=91) of the patients treated with FOLFOX in de Gramont et al., 2000 study had good performance status (PS=0) in contrast to 20.6% (N= 14) patients in our study. The median OS for the patients treated

with FOLFOX in de Gramont et al., 2000 was 16.2 months (no reported 95% CI) compared to a median OS of 13.36 months in our study (Table **6.3**). Moreover, in Saltz et al., 2000, 39% (N=89) of patients treated with FOLFIRI had a good performance status (PS=0) compared to 20.6% (N=14) of the patients treated with FOLFIRI in our study. Saltz et al., 2000 reported a median OS of 14.8 months with FOLFIRI (no reported 95% CI) in contrast to 10.03 months in our study. These differences in the characteristics between this study cohort and the patients included in clinical trials may offer some explanation for the shorter OS for the patients in our study compared to the clinical trial population.

The median OS for the patients treated with cetuximab+FOLFIRI in our study [23.72 months (13.75-NA)] was higher than that reported in the CRYSTAL trial [19.9 months (95% CI 18.5-21.3)] (Van Cutsem et al., 2009). However, when stratified by the type of mutation, the median OS for patients with wild-type RAS mutation CRYSTAL trial was 24.9 months. Considering that 39 (90.7%) patients in our study treated with cetuximab+FOLFIRI had a wild-type RAS mutation, the median OS can be regarded as closely comparable between our study and the CRYSTAL wild-type patients. The comparability between our study and the CRYSTAL trial's findings might stem from the similarity in the patients' baseline characteristics between the two studies, especially the wild-type RAS mutation subgroup in the CRYSTAL trial, such as age [median age 59 years (52-65.5) and 61 (24-79)], and ECOG PS 0-1 [90.3% and 92%] for our cohort treated with cetuximab+FOLFIRI and CRYSTAL wild-type RAS mutation cohort, respectively.

In Scotland, Aflibercept in combination with FOLFIRI is accepted for use for mCRC patients whose disease has progressed after an oxaliplatin-containing regimen (Scottish Medicine Consortium, 2014). In our study, 11 (5%) patients of all new mCRC SACT users were treated with Aflibercept+FOLFIRI in the 1L settings, with a median OS of 13.9 months (95%CI 7.96-NA). The potential reason for selecting aflibercept+FOLFIRI as an initial treatment could be that these patients had their disease progressed rapidly after adjuvant therapy, as discussed in section 5.4.4.1. A post hoc analysis for the phase III VELOUR trial included a cohort of patients who relapsed on or within six months of completing an oxaliplatin-based adjuvant therapy (termed adjuvant rapid relapsers (ARR)) suggested a potential survival benefit from using aflibercept+FOLFIRI following a rapid progression (Van Cutsem et al., 2016b). For these patients included in the post-hoc analysis (N=552), the median OS was 13.8 months, which is

very close to the findings of our study (median OS 13.9). As a result of the rapid progression beyond adjuvant therapy, these patients were deemed to have a poor prognosis, and their inclusion in our cohort might have led to an underestimation of the benefit of 1L mCRC.

However, for patients who were treated with a 2L aflibercept+FOLFIRI in our study (N=6), the median OS was eight months (5.36-NA), which is inferior to the findings of median OS for the patients included in the VELOUR trial, upon which aflibercept+FOLFIRI was approved as a second-line treatment for mCRC (median OS 13.5 months (95% CI 12.5-14.95))(Van Cutsem et al., 2012). It is, however, important to emphasise that a potential reason for this difference could be related to the small sample size in our study representing patients treated with aflibercept+FOLFIRI as a 2L regimen (N=6), which could affect the confidence of this finding.

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6.5 Strengths and limitations

Real-world data is an invaluable source of information about the treatment in real-world clinical practice for patients and their clinicians. Our study reported the treatment pathways and outcomes for the most commonly prescribed SACTs in routine practice for mCRC in Scotland, which can provide useful information for clinical decision-making.

Moreover, despite the fact that the data in our study contained missing values, especially in the molecular profile and the performance status variables, robust statistical methods were implemented to account for missing in data by performing sensitivity analysis cox regression models.

Furthermore, the imbalance between the number of patients receiving each SACT regimen is an inherent limitation of retrospective observational studies. In clinical trials, patients are often stratified in a way that ensures that different baseline characteristics are distributed evenly across arms to confirm that any differences in the outcomes are due to the treatment itself and not due to the differences in the baseline characteristics (confounding bias). In our study, adjusting for these confounders using multivariate cox models ensured that any differences were more likely due to the treatment, not the confounding factors, which can give more confidence regarding the survival estimates.

Moreover, our study was strengthened by investigating patients treated in a first-line setting with aflibercept+ FOLFIRI, which is unique to our study as, to our knowledge, no previous observational study has investigated the treatment outcomes for patients treated with this combination in a 1L setting.

Despite these strengths, our study had several limitations. One of this study's main challenges was defining the exposure, which was complicated by the complex treatment schedules involving several medicines (combinations) with variable sequencing and dosing (stepping up or stepping down), resulting in difficulties in defining and structuring the lines of therapy. Also, despite using robust statistical methods to account for missing in data, our study was limited by the incompleteness of the molecular profile and performance status variables. Also, the unavailability of information such as the burden of metastasis, the site of metastasis, and the type of metastasis, which could be important and potentially other unmeasured confounders, is considered a limitation for our study and warrants a careful interpretation of the findings.

Furthermore, due to the small sample size, the influence on overall survival for further treatment lines could not be investigated under the adjustment of different covariates.
Our analysis was also limited by the small sample size representing patients treated with aflibercept+FOLFIRI as a 1L mCRC SACT, which made extracting specific baseline characteristics that involved several categories (e.g., SIMD score, type of mutation, tumour sidedness) not possible due to restrictions imposed by the university of Glasgow safe haven on releasing data when the number of patients is less than five. This issue has also resulted in wide confidence intervals around the median OS and the estimates from cox regression for all analyses involving aflibercept+FOLFIRI.

Finally, our study was limited by the short follow-up period for a subset of patients. the study included patients from the 1st of January 2015 until the 31st of December 2016, with follow-up until the 28th of February 2018. A minimum duration of 14 months was allowed to capture as many events as possible, which is considered a strength of the study, but at the same time, the follow-up time was limited to 14 months for a small subset of patients. as a result, some of the findings were immature, with a wide or non-reachable confidence interval. For instance, the median OS for patients treated with cetuximab+ FOLFIRI was 23.72 months,

with the upper bound of the confidence interval being unreachable (13.75-NA). Hence, suggesting that there has not been enough time for events to occur.

6.6 Conclusion

The results of this study show that the combination of cetuximab+FOLFIRI offered a survival benefit over 5FU for mCRC patients in NHS GGC, an ECOG PS ≥2 and mutations in the BRAF gene were shown to have a negative impact on survival. Additionally, our findings indicated a consistent trend for the benefits of cetuximab+FOLFIRI as 1L SACT to have the longest median OS and longest TTNT. However, it is important to emphasise that this benefit should be interpreted carefully and has a limited generalisability for all of the mCRC patients treated in 1L settings, as the majority of patients who were treated with cetuximab+FOLFIRI had a wild-type RAS tumour.

The median OS associated with 1L SACT regimens for patients with mCRC in NHS GGC was poorer than the results of the observational studies and clinical trials for chemotherapeutic agents, including 5FU, oxaliplatin-based regimens, and irinotecan-based regimen and comparable to the findings of the observational studies and clinical trials for the combination of cetuximab+FOLFIRI as a 1L SACT.

The exploration of the routine practice data using the Sankey diagram visualising tool may provide a helpful way to better understand the variability and complexity of mCRC treatment in practice and detect atypical pathways.

7 Chapter 7: General discussion

The overall aim of this thesis was to increase evidence generation from clinical practice regarding the use of first-line metastatic colorectal cancer medicines in real-world settings to better inform clinical decisions and optimise clinical outcomes among mCRC patients.

This thesis utilised data obtained from NHS GGC, the largest health board in Scotland to identify: 1- the baseline characteristics of mCRC patients initiating 1L mCRC SACT (chapter 4), 2- the factors that influenced the clinicians to select the 1L mCRC SACTs (chapter 5), 3- the treatment pathways, and 4- treatment outcomes for mCRC patients in NHS GGC (chapter 6). Collectively, and throughout this chapter, the analysis of the data obtained from NHS GGC will be referred to as the fieldwork analysis. Additionally, this thesis was supported by meta-analyses that synthesised evidence from real-world studies on the safety and effectiveness of first-line mCRC SACTs (chapter 2).

7.1 Key findings

In broad terms, over the period 2015 and 2016, a total of 220 patients initiated 1L mCRC SACT in NHS GGC, with approximately half of these treated initially with a doublet therapy consisting of either FOLFOX, FOLFIRI, or XELOX, whereas the remaining patients were treated either with monotherapy of 5FU or triplet therapy of cetuximab+FOLFIRI or aflibercept+FOLFIRI (Table 4. 4). In contrast, our review findings in chapter 2 pointed out that bevacizumab combined with chemotherapy appeared to be the most commonly reported SACT to be used as 1L mCRC SACT in other countries (section 2.3.2).

7.1.1 Baseline characteristics of mCRC patients in NHS GGC.

Overall, the cohort of patients who initiated mCRC SACT in NHS GGC between 2015 and 2016 comprised slightly more male patients than females and a slightly higher frequency of patients over 65 years compared to those less than 65 years. Moreover, 70.9% (N=156) of the patients had the primary tumour located in the colon, 7.7% (N=17) of the patients in the cohort had BRAF mutant tumour, 35% (N=77) had wild RAS tumour, and 6.4% (N=14) had poor performance status (≥2). Furthermore, only 26.8% (N=59) of the patients had resection of the primary tumour. Most of the patients were anaemic, had elevated levels of CEA, and had hypoalbuminemia at baseline (Table 4.5), suggesting a poor prognosis.

Direct comparison of baseline characteristics between our study in NHS GGC and other observational studies was difficult due the differences in data collection methods and the collected variables. However, our study showed some comparability to other observational studies in terms of sociodemographic and clinical characteristics. For instance, our cohort was comparable to the cohorts of other observational studies in terms of the higher frequency of male patients than female patients and the higher frequency of patients presenting with a primary tumour in the colon. Nevertheless, for other characteristics such as age, performance status, and type of tumour mutation, other observational studies varied in the level of reporting these variables. Additionally, many observational studies tended to select patients based on certain features, such as restricting the inclusion to elderly patients or patients with wild-RAS tumour. Therefore, comparing most baseline characteristics with those of other observational studies was difficult. However, a notable difference in the baseline characteristics between our cohort and the cohorts in other observational studies was the rate of primary tumour resection, which was substantially lower in our study compared to the patients included in other observational studies (Table 4.5).

Compared to the populations of clinical trials upon which the approval of the SACTs captured in this study was granted, our patients were older, included a higher proportion of female patients, and had poorer performance status at baseline. For the remaining baseline characteristics such as the type of mutation and primary tumour resection, comparability was difficult due to the variability in the level of reporting these variables.

7.1.2 Treatment pathways and factors influencing the selection of first-line mCRC SACTs.

For the 220 patients who initiated 1L mCRC SACT in NHS GGC between 2015-2016, a total of 46 unique treatment pathways were identified and illustrated through a Sankey diagram (Figure 6.3), where patients either died after receiving 1L SACT, were lost at follow-up, or continued to 2L SACT. Around one-third (N=17, 31.5%) of those who continued to 2L SACT had their treatment intensified, indicating a possibility for disease progression, whereas eight patients (14.8%) had their treatment downgraded, possibly indicating the intolerability of the SACT regimen or worsening of the patient's performance status following the 1L regimen (Table 6.7).

The thesis findings regarding the choice of mCRC SACT showed that the selection of SACT was generally consistent with the national (Scottish) and regional (WoSCAN) CMG recommendations for the management of mCRC. For instance, cetuximab+FOLFIRI was prescribed for the majority of patients who had a wild RAS tumour as recommended by SIGN guideline (Scottish Intercollegiate Guidelines Network, 2011a) (section 5.3.4). Similarly, our findings showed that both FOLFOX and FOLFIRI were predominantly present in the in both 1L and 2L regimens, complying with the SIGN recommendations for prescribing irinotecan-based chemotherapy and oxaliplatin-based chemotherapy as 1L regimen and vice versa as 2L regimen (Scottish Intercollegiate Guidelines Network, 2011a) (section 5.3.4). Nevertheless, the treatment pathways identified were not always aligned with standard guidelines. For example, the use of aflibercept+FOLFIRI in the 1L metastatic settings was unexpected given that this combination is licenced for use across NHS Scotland following the failure of an oxaliplatin-containing regimen in the 1L settings. However, for a subset of mCRC patients who progress rapidly following an adjuvant therapy containing oxaliplatin (e.g., FOLFOX or XELOX), the combination of aflibercept+FOLFIRI was used due to the suggested survival benefits of aflibercept+FOLFIRI in these patients (section 5.3.5).

This thesis identified patient, tumour, and treatment response-related factors associated with the selection of 1L mCRC SACTs in NHS GGC health board in Scotland between 2015-2016. This included patients' age, where older patients were more likely to be prescribed less intensive therapy, such as 5FU, and younger patients were more likely to be prescribed more intensive therapy, such as cetuximab+ FOLFIRI. In addition, the patients' gender appeared to influence the choice of mCRC treatment, with female patients less likely to be administered more intensive therapies such as cetuximab+ FOLFIRI. Unexpectedly, performance status was not found to be associated with the prescribing choices, which was explained by the effect of the small sample size representing patients with poor performance status (Section 5.3.3, Table 5.5).

Tumour-related factors identified to have an impact on the choice of first-line mCRC SACT included the RAS status, with the majority of the patients who harboured a wild RAS tumour being prescribed a combination of cetuximab+FOLFIRI (section 5.3.4). Finally, the choice of first-line mCRC SACT was also influenced by the previous treatment the patients received as a part of CRC management. Patients were more likely to be prescribed FOLFIRI rather than

FOLFOX if they had undergone a resection of the primary tumour, which is preceded by adjuvant therapy, most often encompassing oxaliplatin as part of the regimen. Treatment with FOLFIRI, which consist of 5FU/leucovorin + irinotecan was favoured over the use of FOLFOX, which consists of 5FU/leucovorin + oxaliplatin due to the high potential for neurotoxicity associated with oxaliplatin. Patients who had FOLFOX in adjuvant settings were likely to have developed neurotoxicity (Raymond et al., 1998, Cassidy and Misset, 2002); A finding not only reported in the literature but also confirmed in our non-haematological toxicities meta-analysis (section 2.3.6.4.2). Consequently, FOLFOX use as part of the first-line metastatic treatment could be limited by its toxicity.

7.1.3 Treatment outcomes for mCRC patients

The median OS for mCRC patients treated in NHS GGC between 2015 and 2016 varied across individual 1L SACTs, with the longest observed being 23.72 months for cetuximab+FOLFIRI and the shortest being 9.57 months for 5FU monotherapy (Table **6.3**). The median OS was shown to be influenced by the type of 1L SACT as well as the baseline performance status (Table 6.5). Our fieldwork analysis showed that patients who were initially treated with the combination of cetuximab+FOLFIRI had a statistically significant prolonged median OS compared to 5FU, whereas neither the doublet of FOLFOX or FOLFIRI nor the combination of aflibercept+FOLFIRI displayed a statistically significant different prolonged median OS compared to 5FU (Table 6.5). Furthermore, presenting with a poor performance status at baseline demonstrated a negative prognostic impact on the patients. Moreover, for patients who continued to 2L SACT, our findings indicated that the median OS was comparable between patients who had FOLFOX then FOLFIRI versus those who were initiated on FOLFIRI and continued on FOLFOX (Table **6.8**), whereas a longer median OS was demonstrated for patients who were initiated on cetuximab+ FOLFIRI and continued on FOLFOX (median OS 27.61 months) versus those who had FOLFOX initially then continued on cetuximab+ FOLFIRI (median OS 17.3 months).

Overall, comparing the survival findings of our fieldwork analysis (section 6.3.2) to those in the MA of observational studies (section 2.3.6.1) was challenging due to different SACTs utilised and reported in the observational studies included in the OS MA compared to those utilised in Scotland. While bevacizumab was the most commonly reported SACT to be used as first-line metastatic SACT in combination with other chemotherapeutic agents in the

observational studies investigating the comparative effectiveness and safety of first-line mCRC SACTs, its use in Scotland has not yet been licenced by the SMC.

The findings of the MA pointed to the significant benefit of bevacizumab + chemotherapy compared to chemotherapy alone in the first-line settings of mCRC treatment in terms of improving overall survival (Figure 2.6), progression-free survival (Figure 2.13) and overall response rate (
Figure 2.18). However, the combination was associated with a statistically increased risk of non-haematological toxicities and a non-statistically significant increased risk for haematological toxicity (Figure 2.30 and Figure 2.35, respectively).

In contrast to the findings of our study, which demonstrated the survival benefits of cetuximab+FOLFIRI over 5FU, the findings of the MA did not demonstrate the same finding due to a lack of studies comparing cetuximab+ chemotherapy to chemotherapy alone. The majority of studies investigating the comparative effectiveness of cetuximab+chemotherapy compared this combination to chemotherapy+ targeted treatment, such as bevacizumab. Nevertheless, the findings of the MAs showed that the combination of cetuximab+chemotherapy was associated with an improved overall response rate compared to bevacizumab+ chemotherapy (2.3.6.3.1).

The findings of our field study conducted in NHS GGC agreed with the findings of the OS MA in terms of the lack of survival benefits of any chemotherapeutic agents over each other (e.g., 5FU, capecitabine, FOLFOX, FOLFIRI) (section 6.3.2.3 and section 2.3.6.1).

Furthermore, the findings of the MAs showed that the combination of bevacizumab+ oxaliplatin-based chemotherapy was associated with an increased hazard of disease progression and increased risk of neuropathy compared to bevacizumab+ irinotecan-based chemotherapy (Figure 2.14). The combination of bevacizumab+ irinotecan-based chemotherapy was, however, associated with a significantly higher risk for severe diarrhoea compared to bevacizumab+ oxaliplatin (section 2.3.6.4.2).
Finally, compared to other observational studies, the median OS for the patients initiating mCRC SACT in NHS GGC was inferior to those reported in other countries. This was explained by several reasons; first, it was assumed that all patients in our project presented initially

with metastasis (section 3.2.4.3), which is known as a negative prognostic factor in the context of mCRC, hence, resulting in inferior survival findings. Second, as no strict eligibility criteria were imposed, our cohort included patients who presented initially with poor prognosis, for example, patients with BRAF mutation, patients with poor performance status (ECOG PS ≥ 2), and patients deemed as adjuvant rapid relapsers who received aflibercept+FOLFIRI as a first-line metastatic SACT were all included and considered to have a poor prognosis, thereby, the inclusion of these patients could have resulted in inferior overall survival findings. Finally, the inferior survival findings in NHS GGC could be partly explained by the country-specific management guidelines. For instance, our findings pointed to the lower rate of primary tumour resection in mCRC patients in NHS GGC compared to that reported in other countries. Although the intent of primary tumour resection was not known in our data (palliative or curative intent), the conservative selection of patients into surgical resection could have contributed to the lower survival.

7.2 Strengths and limitations

This thesis has several strengths. First, this thesis provides a comprehensive picture of the use and clinical outcomes of mCRC SACTs in NHS GGC, the largest health board in Scotland covering almost 25% of the entire Scottish population, including the factors that influenced the selection of mCRC SACTs, the treatment pathways for patients initiating mCRC SACT, and the treatment outcomes for these patients including median overall survival and time to initiate next treatment.

Furthermore, this thesis synthesised the effectiveness and safety findings of first-line mCRC SACT findings of observational studies using a Systematic review and meta-analysis approach, which provided a better insight toward the treatment outcomes of mCRC in other countries, and as a result, could be considered useful to improve the practice of mCRC in NHS GGC and in Scotland upon comparing the findings and the reasons underlying these findings.

Additionally, our fieldwork analysis was comprehensive, with no patients being excluded for specific features. Thereby reducing the likelihood of selection bias in the field work analysis and permitting our findings to be generalised for mCRC patients treated in the West of Scotland Cancer Network, which includes three NHS health boards beside NHS GGC (Ayrshire and Arran, Forth Valley, and Lanarkshire), and covers around half of the Scottish population (Table 3.1).

Moreover, this thesis has combined an array of diverse methods and techniques to answer the research questions and to synthesise the evidence from the primary observational study (COX regression and multinomial logistic regression in chapters 5 and 6, respectively) and secondary studies using the random effect meta-analysis in chapter 2. For instance, this thesis attempted to reduce the likelihood of bias arising in the observational type of studies through several techniques, such as the use of cox regression in survival analysis to adjust for confounding bias and the use of multiple imputations and the last observation carried backword technique to account for bias introduced by missing in data. The methods employed in the fieldwork analysis (chapter 5 and chapter 6) can be used as a roadmap for further and future studies in Scotland.

This thesis was further strengthened by the active, intensive engagement with the clinicians, allowing us to obtain valuable insights into the clinical relevance of the work, ensuring that the findings are applicable to real-world situations.

Nevertheless, this thesis has some limitations to be considered. First, missing variables represented a limitation within the fieldwork analysis (chapters 4, 5, and 6) as a number of variables were not available. For instance, the lack of recording information specific to the metastatic pattern, including the onset of metastasis (synchronous versus metachronous) and the burden of metastasis (number of metastatic sites and sites of metastases), had potential implications on both the comparability of the baseline characteristics to other studies and on the findings of treatment outcomes and factors influencing prescribing. Additionally, the stage in which the patients presented with was unknown, and assumptions were made that all patients presented initially with metastasis owing to the fact the Scottish Cancer Registry does not routinely update cancer records (section 3.2.4.3); therefore, patients who progress to stage IV CRC from previous stages were not expected to be captured. Consequently, the analysis of treatment outcomes could have been influenced by unmeasured confounders (such as the stage of disease at presentation and the metastatic pattern), a concern that is not unique to this thesis but frequently encountered in observational studies.

Moreover, as a result of potential inaccuracies in the diagnosis variable in the CEPAS dataset (section 3.3.2.1), determining SACT lines had to rely on a number of assumptions set with the lead oncologist. This, however, could possibly result in potential implications on the

generalisability of the findings. For instance, it was agreed with the lead oncologist to assume that if the SACT was stepped up (e.g., monotherapy to doublet) after less than four cycles, then both SACTs would be considered in the same line (Figure 3.2). However, this rule can vary in practice as different oncologists could implement different treatment strategies, hence, potentially affecting the generalisability of the findings.

Second, database completeness was another challenge in this thesis, especially in the fieldwork analysis. In this thesis, substantial missing in data presented mainly in two covariates within the field analysis: the type of mutation and the ECOG PS. Both variables were important to carry out the analysis of the factors influencing prescribing (chapter 5) and treatment outcomes (chapter 6). However, to account for missing in data, statistical methods were applied in these covariates and to reduce the impact of missing in data on the analysis (section 5.2.3 and section 6.2.4.6).

Third, the small sample size presented as another challenge for the fieldwork analysis, which resulted in two limitations: first, due to the restrictions imposed by the University of Glasgow safe haven on releasing data when the number of patients is less than five, we were unable to extract certain baseline characteristics that involved several categories (e.g., SIMD score, type of mutation, tumour sidedness), especially for SACTs with a small number of patients (e.g., aflibercept+FOLFIRI, where N=11) (Table 4.5). Hence, the comparability of our findings to those reported in other studies was limited by these rules. Second, as a result of the small sample size resulted in amplified effect sizes, especially in the analysis of the factors influencing the selection of SACTs (chapter 5). For instance, the majority of the patients who were treated with cetuximab+ FOLFIRI had a wild-type tumour (N=39 out of 43 patients), while part of the remaining patients treated with cetuximab+ FOLFIRI had mutant RAS tumour (N<5 patients). When the analysis for the factors influencing prescribing of SACT was carried out, the mutant RAS category was set as the reference category. As a result of the very small number of patients with mutant-RAS tumour who were treated with cetuximab+ FOLFIRI (N<5 patients) compared to those with wild-RAS tumour treated with cetuximab+FOLFIRI (N=39), the odds ratio for patients with wild-RAS tumour treated with cetuximab+FOLFIRI was amplified with a large confidence interval (Table **5.4**). This, however, could potentially pose some issues regarding the reliability of the magnitude of effect, but not necessarily the direction or significance of the association (Lin et al., 2013).

In this context, it is important to highlight that access to data for this thesis was made available in early 2020. The COVID-19 pandemic significantly affected data availability for this PhD thesis, preventing the acquisition of additional data. The pandemic disrupted data collection processes as research activities were limited or suspended in various research sites. Additionally, accessing medical records or databases for data extraction was hindered due to diverted resources and personnel prioritizing COVID-19-related activities.

Finally, one of the major limitations of the meta-analysis was the challenge posed by obtaining the effect sizes, especially for the survival outcomes. This problem presented in particular for studies not reporting the effect size, hence, warranting to obtain the effect size indirectly through reconstruction of the Kaplan-Meier curve. For studies with relatively tangled curves, repeating the process more than once was sometimes needed to ensure the accuracy of the output. Additionally, the limited number of studies, particularly within the SACT group comparing bevacizumab+ CT to CT alone in both the haematological and non-haematological toxicity met-analyses has limited our ability to draw a robust conclusion regarding the comparative safety of this SACT group (Figure 2.30 and Figure 2.35).

7.3 Implications of the thesis

7.3.1 Implications for policymakers

The meta-analyses conducted in chapter 2 showed an overall survival, progression-free survival, and overall response benefit for bevacizumab, reinforcing its use in the clinical practice settings for mCRC. In Scotland, bevacizumab combined with fluoropyrimidine-based chemotherapy is not recommended for use in first-line treatment for mCRC patients by the SMC following a submission for Avastin®, the originator of bevacizumab in 2005 and a revision in 2013 for the decision due to concerns regarding the safety of bevacizumab, including the increased risk of elevated blood pressure, thromboembolic events, and bleeding, in addition to the lack of cost analysis provided by Roche, the manufacturer of Avastin (Scottish Medicine Consortium, 2006, The National Institute for Health and Care Excellence, 2010). However, a UK-based population study, sponsored by Roche, the manufacturer of Avastin was published in 2019 to assess the safety and effectiveness of bevacizumab in combination with chemotherapy for mCRC patients in real-world settings across the UK. The study (ACORN) confirmed the safety profile of bevacizumab in

combination with chemotherapy in real-world settings without raising new concerns on these reported by clinical trials and previous population-based studies for most common toxicities of bevacizumab) (Khakoo et al., 2019). Moreover, as of January 2022, the patency of Avastin® has expired in Europe (European Medicines Agency, 2019), allowing for other biosimilars to be rolled out and reducing the cost of the medicine. Hence, given the findings of the ACORN study, which confirmed the safety profile of bevacizumab in combination with chemotherapy in the UK population, and the reduced cost of bevacizumab biosimilars following the expiration of its patency, the findings of our MA can be used as complementary evidence to the currently existing evidence on the advantages offered by bevacizumab and along with a budget impact analysis to inform decision-makers on the benefits of incorporating bevacizumab with chemotherapy as a standard first-line SACT for mCRC patients in Scotland.

Furthermore, our fieldwork analysis findings demonstrated the survival benefits offered by the addition of targeted therapies (e.g., cetuximab) to standard chemotherapy (e.g., FOLFOX or FOLFOIRI). Since our study revealed no statistically significant difference in terms of median OS between the chemotherapeutic agent (5FU, FOLFOX and FOLFIRI - Table 6.5), which was further supported by the findings of the OS MA (Figure 2.6), policymakers should ensure that more patients with mCRC have access to targeted treatments in combination with chemotherapy whenever they are eligible and able to tolerate the treatment.

Additionally, our study identified a substantially lower rate of primary tumour resection among mCRC patients in NHS GGC compared to other observational studies, which could potentially impact treatment outcomes. Policymakers should ensure that primary tumour resection is accessible to patients who need it, regardless of their location or socio-economic status. This includes ensuring that there is adequate funding and staffing for the procedure and that patients have access to trained and experienced surgeons.

7.3.2 Implications for practice

This thesis identified several factors to be taken into consideration when therapeutic choices are discussed with the patients, as well as the treatment outcomes associated with these choices. For patients, it is important to know the outcomes of a particular SACT in terms of its effectiveness and safety, which could be helpful in terms of making informed decisions about their treatment options and allowing the patients to have realistic expectations about

the outcomes. Additionally, healthcare providers can use these findings to evaluate the risk-benefit ratio of different treatments and make informed decisions about which treatments to prescribe based on individual patient factors. For instance, although the CMGs did not define gender as a factor to be considered when the decision regarding certain SACT is made, this thesis identified that gender was an important factor to be considered in the process of treatment decision-making with female patients less likely to be prescribed cetuximab+ FOLFIRI, possibly due to the increased risk of toxicities. However, upon discussing the therapeutic options with female patients, the clinician is expected to highlight that despite the additional survival benefits offered by this combination, this combination could possibly be associated with an increased risk of toxicities. Furthermore, the dissemination of the findings of this thesis can be used to inform colorectal cancer clinicians of the choices of SACTs made by other clinicians, as well as the outcomes associated with these choices. For example, the use of aflibercept+ FOLFIRI was not expected in the 1L settings since it is licenced in Scotland for use after the failure of first-line oxaliplatin-containing regimen. In this thesis, aflibercept+ FOLFIRI was prescribed for those patients who progressed rapidly after adjuvant therapy, which often contains oxaliplatin. And despite the poor prognosis of these patients, the median OS was 13.9 months. Other clinicians may use this finding either to adopt the treatment strategy or to manage the patient's expectations regarding the median OS when the therapeutic options are discussed.

7.4 Future work and recommendations for conducting further research.

This thesis has generated a number of interesting findings with implications and recommendations for practice. Nevertheless, many questions remain to be answered. First, this thesis displayed the complexity of mCRC treatment in clinical practice, where patients can receive more than one treatment line. In this thesis, 75.5% of the patients (N=166) received only one SACT line, whereas 54 (24.5%) patients had more than one SACT line. Statistical analysis with multiple treatment lines is challenging. Nevertheless, crude overall survival for these treatment pathways was obtained (Table **6.8**) despite the need to interpret the findings cautiously, as they were not adjusted for possible confounders due to the small sample size. However, as limiting the survival analysis and treatment outcomes to one SACT line can result in limitations on the generalisability of the findings. Future research can carry

out further analysis to investigate the impact of sequential SACT (i.e., sequential targeted therapy) on outcomes, especially with a larger sample size.

Moreover, in this thesis, identifying treatment outcomes for subsets of patients, including elderly patients > 65 years, those with poor performance status, or patients with mutant BRAF gene was limited by the small sample representing these populations (Table 4.5). Given that a number of new mCRC SACTs, especially targeted treatments and immunotherapies, were recently licenced in Scotland following the end of this study timeframe in 2016, it is important to explore the treatment outcomes for these subsets of patients receiving the newly approved mCRC SACTs. For instance, the combination of encorafenib+ cetuximab was licenced by the SMC in 2021 to be used across NHS Scotland for the management of patients presenting with mutant BRAF mCRC (Scottish Medicine Consortium, 2021). Future research may be conducted to investigate the treatment outcomes of newly licenced medicines such as encorafenib+ cetuximab and other newly licenced mCRC SACTs in real-world settings. for newly licenced mCRC SACTs in Scotland). Additionally, although this project was conducted in NHS GGC, the largest health board in Scotland, replicating the survival analysis and the factors influencing mCRC SACT prescribing nationally across the 14 health boards would be valuable in informing the practice, especially given that the management of mCRC patients might vary across the three Scottish cancer networks, and given the variability in the extent of deprivation across the 14 health boards. Additionally, in contrast to the fieldwork analysis in this thesis which was conducted over two years with 14 months of follow-up, future research could be conducted over a longer duration of time to explore the utilisation trend of mCRC SACTs nationally and visualise the change in prescribing trend from chemotherapies to targeted treatments and finally the immunotherapies.

Second, within this project, we attempted to identify the factors that influence the selection of mCRC SACTs in practice using record linkage. Although quantification of factors influencing the selection of SACTs is essential to understand the association between different patient, disease, and treatment response-related factors with the selection of 1L mCRC SACT, it is necessary to deepen this understanding by supplementing this study with qualitative research, which provides a more in-depth and nuanced understanding of the complex and subjective factors that play a role in decision-making. This includes understanding 1- the patients' perspective, preferences, and values, which can play a role in the decision to prescribe systemic therapy; 2- clinicians' perspective, including their beliefs, attitudes, and

decision-making processes, 3- contextual factors, including the health care system, policies, and cultural norms, and 4-the barriers and facilitators to the prescribing of SACT, such as the availability of treatments. This information can be used to inform policy and practice changes to improve the prescribing of mCRC SACT. Qualitative research methods that can be used to address these gaps include in-depth interviews with clinicians, policymakers, and patients for a detailed exploration of the perspectives and experiences of patients, policymakers, and clinicians. Additionally, focus group meetings can bring together a group of patients or clinicians to discuss their experiences and perspectives on the decision of selected SACT.
Finally, and most importantly,

Finally, in recent years, significant attention has been directed towards investigating the role of emulated targeted trials in generating real-world evidence, particularly in light of advancements in statistical methods aimed at mitigating the biases inherent in observational data. Emulated targeted trials aim to simulate the findings of RCTs using real-world data, while diligently accounting for the inherent limitations associated with observational studies. These trials entail identifying a control group of patients who would have met the eligibility criteria for a hypothetical RCT and subsequently matching them with a treated group of patients who received the targeted therapy. Rigorous statistical methods are then applied to compare the outcomes of these two groups while controlling for potential confounding factors.
The application of emulated targeted trials in the context of mCRC holds substantial promise, as it can furnish invaluable insights into the real-world effectiveness and safety of mCRC, aspects that may not be fully ascertainable through traditional RCTs. Additionally, emulated targeted trials present an opportunity to ameliorate the limitations encountered in observational studies, notably selection bias and confounding, through judicious group selection and matching procedures.
However, it is important to acknowledge that the implementation of emulated targeted trials necessitates specialized statistical analyses, such as propensity score matching, to achieve adequate adjustment and balance for baseline confounders. A potential caveat is that these analyses may entail a reduction in sample size, thereby potentially compromising the efficacy of bias reduction. Consequently, there arises a need for a larger sample size to ensure that emulated target trials are conducted with sufficient statistical power.

In conclusion, the availability of universal healthcare access in Scotland, coupled with comprehensive electronic health records covering the entire population and the exceptional quality and precision of Scottish administrative health data, along with the feasibility of record linkage, augurs well for the feasibility of replicating the analysis of this thesis project at a national level. Employing emulated target trial design methods and assumptions will facilitate the generation of robust real-world evidence from the existing wealth of data.

7.5 Final conclusion

The generation of real-world evidence from real-world data is an important process for improving patient care and advancing the field of cancer. By leveraging real-world evidence, healthcare providers can make informed decisions about the best treatments for their patients. The findings of this thesis show that treatment outcomes and factors influencing prescribing are closely interconnected, as the choice of treatment can impact patient outcomes, and the outcomes of treatment can, in turn, influence prescribing decisions.

In NHS GGC, treatment choices for first-line mCRC were made based on several factors, including patients' age and gender, tumour RAS status, and previous treatment response. However, for more than half of the patients, the initially selected systemic anti-cancer therapy comprised doublet chemotherapy of either FOLFOX, XELOX, or FOLFIRI, while the remaining patients were distributed almost equally between a monotherapy of 5FU and a triplet of cetuximab+ FOLFIRI or aflibercept+ FOLFIRI. The median overall survival for these patients was influenced by the initial mCRC SACT and the performance status. The combination of cetuximab+FOLFIRI demonstrated a statistically significant prolonged median overall survival compared to 5FU.

The results of this thesis also indicated an overall survival, progression-free survival, and overall response rate benefit for bevacizumab in combination with chemotherapy with a statistically increased risk of non-haematological toxicities and a non-statistically significant increased risk for haematological toxicity.

Overall, real-world evidence can help to better understand the impact of systemic anti-cancer therapies of metastatic colorectal cancer, including the effectiveness and safety of different treatments in routine clinical practice, the factors that influence treatment choice,

and the interplay between these factors and treatment outcomes. The findings of this thesis can be used by policymakers to inform the development of treatment guidelines and to allocate resources for the treatment of metastatic colorectal cancer in a more effective and efficient manner.

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9 Appendices

Appendix I.

The search strategy for MEDLINE (OVID)

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 03, 2020
Search Strategy:

#	Searches	Results
1	Epidemiologic Studies/	8182
2	exp Case-Control Studies/	1046179
3	exp Cohort Studies/	1942154
4	Case control.tw.	120801
5	(cohort adj (study or studies)).tw.	192132
6	Cohort analy$.tw.	7561
7	(Follow up adj (study or studies)).tw.	48134
8	(observational adj (study or studies)).tw.	99949
9	Longitudinal.tw.	234492
10	Retrospective.tw.	501907
11	Cross sectional.tw.	332432
12	Cross-Sectional Studies/	314756
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	2898133
14	Colorectal Neoplasms/	83937
15	(metastatic Colorectal Neoplasm or metastatic Colorectal Tumo*r or metastatic Colorectal Carcinoma* or metastatic Colorectal Cancer or Advanced Colorectal Neoplasm or advanced Colorectal Tumo*r or advanced Colorectal Carcinoma* or advanced Colorectal Cancer* or Stage 4 Colorectal Neoplasm or stage 4 Colorectal Tumo*r or stage 4 Colorectal Carcinoma* or stage 4 Colorectal Cancer or Stage IV Colorectal Neoplasm or stage IV Colorectal Tumo*r or stage IV Colorectal Carcinoma* or stage IV Colorectal Cancer* or advanced bowel cancer or advanced bowel carcinoma or advanced colorectal carcinoma).ti,ab.	12005
16	14 or 15	87433
17	treatment outcome/ or disease-free survival/ or progression-free survival/ or response evaluation criteria in solid tumors/	990073
18	(disease free survival or progression-free survival or overall survival or relapse-free survival or objective response rate or DFS or PFS or OS or RFS or effectiveness or safetyor treatment outcome* or healthcare outcome*).mp. [mp=title, abstract, original title, name of substance	695320

	word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
19	((adverse or dangerous or harmful or indirect or injurious or secondary or side or undesirable) adj1 (complication* or consequence* or effect* or event* or impact* or outcome* or reaction*)).ti,ab. or exp "Drug-Related Side Effects and Adverse Reactions"/ or ae.fs.	2195823
20	17 or 18 or 19	3360582
21	(FOLFOX or FOLFIRI or FUFIRI or FOLFOXIRI or IFL or IROX or XELIRI or capecitabine or CAPIRI or CAPEIRI or XELIRI or CAPEOX or CAPOX or XELOX or FUFOL or TEGAFUR or GIMERACIL or OTERACIL or 5FU or leucoverin or folinic acid or oxaliplatin or fluorouracil or irinotecan or Bevacizumab or Regorafenib or Ziv-aflibercept or aflibercept or Cetuximab or Panitumumab or pembrolizumab or Nivolumab or ipilimumab or tegafur uracil or UFT or tegafur gimeracil teracil or S1 or TAS or trifludine tipiracil hydrochloride or Adrucil or Xeloda or UFT or Eloxatin or Camptosar or Avastin or Erbitux or Vectibix or Keytruda or Opdivo or Yervoy or Stivarga or Cyramza or Tomudex or zaltrap).ti,ab.	124167
22	13 and 16 and 20 and 21	2151
23	limit 22 to (english language and humans and yr="1860 - 2019")	1897

Appendix II.

The characteristics of included studies in the review.

Author, year	Comparisons	Total sample	Study design	Data source	setting	Country	Study duration (months)	Funding source
Stec,2010 **(Stec et al., 2010)**	Capecitabine/ FOLFIRI	123	Retrospective cohort	Medical charts	Single centre	Poland	66	The Military Institute of the Health Services
Guo, 2020 **(Guo et al., 2020)**	Capecitabine/ S-1	1066	Retrospective cohort	EMR	Multicentric	China	36	The National Natual Science Foundation of China and Science Foundation of Heilongjiang
Satram-Hoang ,2013 **(Satram-Hoang et al., 2013)**	Capecitabine/ 5FU FOLFOX/ XELOX	4250	Retrospective cohort	SEER registry	Multicentric	USA	84	Genentech
Neugut, 2019 **(Neugut et al., 2019)**	FOLFIRI (± Bevacizumab)/FOLFOX (± Bevacizumab)	3785	Retrospective cohort	SEER registry	Multicentric	USA	96	National Cancer Institute, the Breast Cancer Research Foundation/Conquer Cancer Foundation
Marschner, 2015 **(Marschner et al., 2015)**	Oxaliplatin based CT/ irinotecan-based CT	605	Prospective cohort	TKK registry	Multicentric	Germany	67	The TKK is funded by iOMEDICO
Hammerman,2015 **(Hammerman et al., 2015)**	Bevacizumab + CT/ CT	1739	Prospective cohort	Clalit Health Services' (CHS) administrative database	Multicentric	Israel	48	Non declared
Franchi,2019 **(Franchi et al., 2019)**	Bevacizumab + CT/ CT	480	Observational cohort	population-based cancer registries	Multicentric	Italy	36	Novartis, GlaxoSmithKline, Roche, Amgen, Bristol-Myers Squibb, Roche.

Author, year	Comparisons	Total sample	Study design	Data source	setting	Country	Study duration (months)	Funding source
Houts,2019 **(Houts et al., 2019b)**	Bevacizumab + CT/ CT	373	Retrospective cohort	Vector Oncology Data Warehouse EMR	Multicentric	USA	NR	Genentech
Meyerhardt, 2012 **(Meyerhardt et al., 2012b)**	Bevacizumab + CT/ CT	2526	NR	SEER registry	Multicentric	USA	72	Sanofi-Aventis, Bayer Pharmaceuticals
Razenberg, 2016 **(Razenberg et al., 2016)**	Bevacizumab + CT/ CT	361	Retrospective cohort	Netherlands Cancer Registry (NCR)	Multicentric	Netherlands	60	the Netherlands Organisation for Health Research and Development (ZonMw)
Lee, 2017 **(Lee et al., 2017)**	Bevacizumab + CT/ CT	826	Prospective cohort	TRACC registry	Multicentric	Australia	72	Roche
Suenaga, 2014 **(Suenaga et al., 2014)**	Bevacizumab + FOLFOX/ FOLFOX	213	retrospective cohort	EMR	Single centre	Japan	39	NR
Bendell, 2012 **(Bendell et al., 2012)**	Bevacizumab + FOLFIRI/ Bevacizumab + FOLFOX	1550	prospective cohort	Avastin registry	Multicentric	USA	15	Genentech
Duran,2014 **(Duran et al., 2014)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELOX	409	retrospective cohort	EMR	Multicentric	Turkey	88	NR
Khakoo, 2019 **(Khakoo et al., 2019)**	Bevacizumab + FOLFIRI/ Bevacizumab + FOLFOX Bevacizumab + Capecitabine / Bevacizumab + XELOX	677	prospective cohort	EMR	Multicentric	UK	17	Roche
Uygun, 2013 **(Uygun et al., 2013)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	132	prospective cohort	EMR	Multicentric	Turkey	60	Non declared
Kocakova,2015 **(Kocakova et al., 2015)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	558	retrospective cohort	CORRECT registry	Multicentric	Czech	96	Roche

Author, year	Comparisons	Total sample	Study design	Data source	setting	Country	Study duration (months)	Funding source
Ocvirk, 2011 **(Ocvirk et al., 2011)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	139	retrospective cohort	Medical charts	Single centre	Slovenia	34	Non declared
Bai, 2015 **(Bai et al., 2015)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	175	retrospective cohort	Medical charts	Single centre	China	84	Non declared
Cainap, 2021 **(Cainap et al., 2021)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	151	retrospective cohort	Medical charts	Single centre	Romania	108	BIOGENONCO
Artac, 2016 **(Artac et al., 2016)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	625	retrospective cohort	NR	Multicentric	Turkey	132	Non declared
Stein,2015 **(Stein et al., 2015a)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	1777	Observational cohort	Registry	Multicentric	Germany	42	Hoffman La-Roche
Buchler, 2014 **(Buchler et al., 2014)**	Bevacizumab + FOLFOX / Bevacizumab + XELOX	2191	retrospective cohort	CORRECT registry	Multicentric	Czech	76	Roche, Amgen, and Merck
Cheng, 2015 **(Cheng and Song, 2015)**	Bevacizumab + FOLFOXIRI/ Bevacizumab + XELOXIRI	138	retrospective cohort	NR	Single centre	China	53	Non declared
Yang, 2014 **(Yang et al., 2014)**	Cetuximab+ CT/ Bevacizumab+ CT	158	retrospective cohort	Medical charts	Single centre	Taiwan	84	Non declared
Houts, 2019 **(Houts et al., 2019a)**	Cetuximab+ CT/ Bevacizumab+ CT	400	retrospective cohort	Data warehouse	Multicentric	USA	NR	Genentech
Bai, 2016 **(Bai et al., 2016)**	Cetuximab+ CT/ Bevacizumab+ CT	289	retrospective cohort	Registry	Single centre	China	60	Non declared
Zhou, 2021 **(Zhou et al., 2021)**	Cetuximab+ CT/ Bevacizumab+ CT	620	retrospective cohort	database	Single centre	China	76	the National Key Development Plan for Precision Medicine Research

Author, year	Comparisons	Total sample	Study design	Data source	setting	Country	Study duration (months)	Funding source
Degirmencioglu , 2019 **(Degirmencioglu S, 2019)**	Cetuximab+ CT/ Bevacizumab+ CT	238	retrospective cohort	Medical charts	Multicentric	Turkey	NR	Non declared
Zhou, 2021 **(Zhou et al., 2021)**	Cetuximab+ CT/ Bevacizumab+ CT	620	retrospective cohort	database	Single centre	China	76	the National Key Development Plan for Precision Medicine Research

KEY: CT= chemotherapy; ECOG PS= eastern cooperative group performance status; FOLFOX=5FU/ leucovorin/ oxaliplatinFOLFIRI= 5FU/ leucovorin/ irinotecan; FOLFOXIRI= 5FU/ leucovorin/ oxaliplatin/ irinotecan; NR= Not reported; XELIRI= Capecitabine/ XELIRI; XELOX= Capecitabine/ oxaliplatin; XELOXIRI= Capecitabine / oxaliplatin/ irinotecan; EMR= electronic medical record; NR= not reported

Appendix II.

Sociodemographic and clinical characteristics for the patients enrolled in the included studies.

Author, (year)	Comparisons	Female (%)	Age group (elderly / non-elderly	PS (0-1)/ PS ≥2 (%)	KRAS-wild / KRAS-mutant (%)	Primary location (Colon/rectum /sigmoid) (%)	Primary resection (%)	1 metastasis/ ≥2 metastasis (%)	Metastasis (Liver/ lung/ peritoneum/ lymph nodes) (%)
Stec,2010 **(Stec et al., 2010)**	Capecitabine/ FOLFIRI	35.8	**Elderly**	88.6 / 11.4	NR	39.8/ 28.5/ 31.7	NR	48.8/ 51.2	69.1/ 38.2/ NR
Guo, 2020 **(Guo et al., 2020)**	Capecitabine/ S-1	22.7	Non-elderly	NR	NR	NR	NR	NR	NR
Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	Capecitabine/ 5FU FOLFOX/ XELOX	53.9	**Elderly**	NR	NR	NR	NR	NR	NR
Neugut, 2019 **(Neugut et al., 2019)**	FOLFIRI (± bevacizumab)/ FOLFOX (± bevacizumab)	48.3	**Elderly**	NR	NR	NR	NR	NR	NR
Marschner, 2015 **(Marschner et al., 2015)**	Oxaliplatin based CT/ irinotecan-based CT	36.4	Non-elderly	56/ 11.7	22.6/ 15.7	60.7/39/NR	87.4	NR	48.6/ 16.9/ 11
Hammerman,2015 **(Hammerman et al., 2015)**	Bevacizumab + CT/ CT	51.2	Non-elderly	NR	NR	NR	NR	NR	NR
Franchi,2019 **(Franchi et al., 2019)**	Bevacizumab + CT/ CT	36.4	Non-elderly	NR	NR	75/17.1/7.9	59.4	NR	NR

Author, (year)	Comparisons	Female (%)	Age group (elderly / non-elderly	PS (0-1)/ PS ≥2 (%)	KRAS-wild / KRAS-mutant (%)	Primary location (Colon/rectum /sigmoid) (%)	Primary resection (%)	1 metastasis/ ≥2 metastasis (%)	Metastasis (Liver/ lung/ peritoneum/ lymph nodes) (%)
Houts,2019 **(Houts et al., 2019b)**	Bevacizumab + CT/ CT	27.2	Non-elderly	93.6/ 6.4	0/ **100**	NR	63	NR	72.9/ 35.1 / 17.2
Meyerhardt, 2012 **(Meyerhardt et al., 2012b)**	Bevacizumab + CT/ CT	47	**Elderly**	NR	NR	77.7/ 22.3	75.4	NR	NR
Razenberg, 2016 **(Razenberg et al., 2016)**	Bevacizumab + CT/ CT	59.3	Non-elderly	NR	NR	57.6/ 42.2/ NR	NR	43.5/ 56.5	NR
Lee, 2017a (Lee et al., 2017)	Bevacizumab + CT/ CT	40.9	Non-elderly	84.3/ 15.7	NR	54.3/ 38/ NR	**0**	NR	77.3/ 31.6/ 14.7
Lee, 2017b (Lee et al., 2017)	Bevacizumab + CT/ CT	40.7	Non-elderly	86.9/ 14	NR	71.5/ 24/ NR	**100**	NR	58.5/ 22.2/ 8.8
Suenaga, 2014 **(Suenaga et al., 2014)**	Bevacizumab + FOLFOX/ FOLFOX	47.9	Non-elderly	98.6/ 1.4	36.6/8.9	65.7/ 34.3/ NR	84	34.7/ 65.3	52.6/37.6/ 27.2/ 46.9
Bendell, 2012 **(Bendell et al., 2012)**	Bevacizumab + FOLFIRI/ Bevacizumab + FOLFOX	43.2	Non-elderly	91.6/ 8.4	36.6/ 8.9	76.1/ 23.6/ NR	80.4	NR	NR
Duran,2014 **(Duran et al., 2014)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELOX	39.6	Non-elderly	93.6/ 6.4	NR	NR	NR	NR	55.3/ 13.7. 5.4/ 3.4

Author, (year)	Comparisons	Female (%)	Age group (elderly / non-elderly	PS (0-1)/ PS ≥2 (%)	KRAS-wild / KRAS-mutant (%)	Primary location (Colon/rectum /sigmoid) (%)	Primary resection (%)	1 metastasis/ ≥2 metastasis (%)	Metastasis (Liver/ lung/ peritoneum/ lymph nodes) (%)
Khakoo, 2019 **(Khakoo et al., 2019)**	Bevacizumab + FOLFIRI/ Bevacizumab + FOLFOX Bevacizumab + Capecitabine / Bevacizumab + XELOX	42.7	Non-elderly	91.3/ 8.4	NR	NR	NR	NR	NR
Uygun, 2013 **(Uygun et al., 2013)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	41.7	Non-elderly	90.9/9.1	NR	50.8/ 49.2	61.4	NR	59/ 7.6
Kocakova,2015 **(Kocakova et al., 2015)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	42.8	Non-elderly	60.4/ 0.7	28.3/ 19.4	62.9/ 37.1	86.7	NR	NR
Ocvirk, 2011 **(Ocvirk et al., 2011)**	Bevacizumab + FOLFIRI/ Bevacizumab + XELIRI	38	Non-elderly	100/0	NR	71/29	NR	NR	62/ 7
Bai, 2015 **(Bai et al., 2015)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	36.6	Non-elderly	95.4/ 4.6	NR	63.4/ 36.6	60.5	57.1/ 38.9	32.6/ 10.3/ 28.6/ 7.7

Author, (year)	Comparisons	Female (%)	Age group (elderly / non-elderly	PS (0-1)/ PS ≥2 (%)	KRAS-wild / KRAS-mutant (%)	Primary location (Colon/rectum /sigmoid) (%)	Primary resection (%)	1 metastasis/ ≥2 metastasis (%)	Metastasis (Liver/ lung/ peritoneum/ lymph nodes) (%)
Cainap, 2021 **(Cainap et al., 2021)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	43	Non-elderly	NR	NR	NR	NR	72.8/ 27.2	59/ 12.3/ 15.1/ 5.3
Artac, 2016**(Artac et al., 2016)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	39.2	Non-elderly	83.8/ 15.7	NR	NR	NR	NR	46.9/ 6.4/ 7/ 5.4
Stein,2015 **(Stein et al., 2015a)**	Bevacizumab+ irinotecan-based CT/ Bevacizumab+ oxaliplatin based CT	38	Non-elderly	89/11	NR	NR	NR	68/11	81/ 28
Buchler, 2014 **(Buchler et al., 2014)**	Bevacizumab + FOLFOX/ Bevacizumab + XELOX	36.6	Non-elderly	44.8/ 2.3	NR	60/ 40/	NR	NR	NR
Cheng, 2015 **(Cheng and Song, 2015)**	Bevacizumab + FOLFOXIRI/ Bevacizumab + XELOXIRI	44.9	Non-elderly	100/ 0	NR	73.2/ 26.8/ NR	NR	55/ 45	NR
Yang, 2014 **(Yang et al., 2014)**	Cetuximab+ CT/ Bevacizumab+ CT	38.6	Non-elderly	NR	23.4/ 76.6	60.1/ 39.9	NR	NR	39.8
Houts, 2019 (Houts et al., 2019a)	Cetuximab+ CT/ Bevacizumab+ CT	41.8	Non-elderly	92.5/ 7.5	100/ 0	NR	39	NR	65.3/ 26.8/ 18.3

Author, (year)	Comparisons	Female (%)	Age group (elderly / non-elderly	PS (0-1)/ PS ≥2 (%)	KRAS-wild / KRAS-mutant (%)	Primary location (Colon/rectum /sigmoid) (%)	Primary resection (%)	1 metastasis/ ≥2 metastasis (%)	Metastasis (Liver/ lung/ peritoneum/ lymph nodes) (%)
Bai, 2016 **(Bai et al., 2016)**	Cetuximab+ CT/ Bevacizumab+ CT	34.7	Non-elderly	95.8/ 4.2	NR	63.1/ 36.9	70.1	59/ 41	35.6/ 10.4/ 26.4
Zhou, 2021 (non-mucinous histology) (Zhou et al., 2021)	Cetuximab+ CT/ Bevacizumab+ CT	40.7	Non-elderly	NR	48/ 30.9	NR	67.6	53/ 47	70.8/ 33.9/ 13.2/ 24.8
Zhou, 2021 (mucinous histology) (Zhou et al., 2021)	Cetuximab+ CT/ Bevacizumab+ CT	41.1	Non-elderly	NR	43.3/ 33.3	NR	70.9	51.8/ 48.2	54.6/ 25.5/ 33.3/ 35.9
Degirmencioglu , 2019 **(Degirmencioglu S, 2019)**	Cetuximab+ CT/ Bevacizumab+ CT	35.7	Non-elderly	NR	100/0	34.9/ 37.4 / NA	NR	NR	52.5/ 14.7/ 13.4

KEY: CT= chemotherapy; ECOG PS= eastern cooperative group performance status; FOLFOX=5FU/ leucovorin/ oxaliplatinFOLFIRI= 5FU/ leucovorin/ irinotecan; FOLFOXIRI= 5FU/ leucovorin/ oxaliplatin/ irinotecan; NR= Not reported; XELIRI= Capecitabine/ XELIRI; XELOX= Capecitabine/ oxaliplatin; XELOXIRI= Capecitabine / oxaliplatin/ irinotecan; NR= not reported;

Appendix III.

The brief answers to the signaling questions of the assessment of risk of bias for the studies included in the overall survival meta-analysis.

Study ID	ID 1	ID 2	ID 3	ID 4	ID 5	ID 6	ID 7
Author, year	Stec, 2009	Guo, 2020	Satram-Hoang ,2013a	Neugut, 2019	Marschner, 2015	Hammerman,2015	Franchi,2019
Intervention	Capecitabine	Capecitabine	Capecitabine/ 5-FU	FOLFIRI ± Bevacizumab	Oxaliplatin based CT	Bevacizumab + CT	Bevacizumab + CT
Comparator	FOLFIRI	S-1	FOLFOX/ XELOX	FOLFOX ± Bevacizumab	irinotecan based CT	CT	CT

Bias domain	Signalling questions	Stec, 2009	Guo, 2020	Satram-Hoang ,2013a	Neugut, 2019	Marschner, 2015	Hammerman,2015	Franchi,2019
Bias due to confounding	**1.1.** Is there potential for confounding of the effect of intervention in this study?	Y	Y	Y	Y	Y	Y	Y
	If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered *If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:*	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N	N	N	N	N	N	PY
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, proceed to question 1.3.*	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Proceed to 1.3
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	NA	NA	NA	NA	NA	NA	NI
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)*							
	Questions relating to baseline confounding only							
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	PY	Y	Y	N	Y	Y	Y
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	PN	NI	PN	NA	Y	PN	PY
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	PN	PN	PN	N	PN	PN	PN
	Questions relating to baseline and time-varying confounding							
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA	NA	NA	NA	NA	NA
	1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA	NA	NA	NA	NA	NA	NA
	Risk of bias judgement (see RoB judgement table 1)	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate
Bias in selection of participants into the study	**2.1.** Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PY	PY	PY	PN	PN	NI	PN
	***If N/PN to 2.1:** go to 2.4*	Proceed to 2.2	Proceed to 2.2	Proceed to 2.2	Go to 2.4	Go to 2.4		Go to 2.4
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	PY	PN	PN				
	2.3. If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	PY	PY	PY				
	2.4. Do start of follow-up and start of intervention coincide for most participants?	PY	PY	PY	PY	PY	NI	PY
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?							
	Risk of bias judgement (see RoB judgement table 1)	Serious	Serious	Serious	Moderate	Low	NI	Moderate
Bias in classification of interventions	**3.1.** Were intervention groups clearly defined?	Y	N	N	N	PN	PN	N
	3.2. Was the information used to define intervention groups recorded at the start of the intervention?	Y	Y	Y	Y	PY	PY	PY
	3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 1)	Moderate	Serious	Serious	Serious	Serious	Serious	Serious
Bias due to deviations from intended interventions	**4.1.** Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI	NI	NI	NI	NI	NI	NI
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?							
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6							
	4.3. Were important co-interventions balanced across intervention groups?							
	4.4. Was the intervention implemented successfully for most participants?							
	4.5. Did study participants adhere to the assigned intervention regimen?							
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?							
	Risk of bias judgement (see RoB judgement table 2)	NI	NI	NI	NI	NI	NI	NI
Bias due to missing data	**5.1.** Were outcome data available for all, or nearly all, participants?	N	N	PY	PN	PY	PY	PY
	5.2. Were participants excluded due to missing data on intervention status?	Y	Y	PN	PN	PN	PN	PN
	5.3. Were participants excluded due to missing data on other variables needed for the analysis?	PY	Y	PN	NI	PN	PN	PN
	5.4. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NI	PY	NI	N	NA	NA	NA
	5.5. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NI	NI	NI	NI	NA	NA	NA
	Risk of bias judgement (see RoB judgement table 2)	Serious	Serious	Moderate	Serious	Moderate	Moderate	Low
Bias in measurement of outcomes	**6.1.** Could the outcome measure have been influenced by knowledge of the intervention received?	N	N	N	N	N	N	N
	6.2. Were outcome assessors aware of the intervention received by study participants?	PN	PN	PN	PN	PN	PN	PN
	6.3. Were the methods of outcome assessment comparable across intervention groups?	Y	Y	PY	PY	PY	PY	PY
	6.4. Were any systematic errors in measurement of the outcome related to intervention received?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 2)	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	**Is the reported effect estimate likely to be selected, on the basis of the results, from…**							
	7.1. … multiple outcome measurements within the outcome domain?	PN	PN	PN	PN	PN	PN	PN
	7.2. … multiple analyses of the intervention-outcome relationship?	N	PN	PY	N	N	PY	Y
	7.3. … different subgroups?	N	N	PN	N	N	PY	Y
	Risk of bias judgement (see RoB judgement table 2)	Moderate	Moderate	Serious	Moderate	Moderate	Serious	Serious
Overall bias	**Risk of bias judgement** (see RoB judgement table 3)	Serious	Serious	Serious	Serious	Serious	Serious	Serious

Risk of bias assessment (cohort-type studies)

Study ID		**ID 8**	**ID 9**	**ID 10**	**ID 11**	**ID 12**	**ID 13**	**ID 14**
Author, year		Houts, 2019	Meyerhardt, 2012	Razenberg, 2016	Lee, 2017	Suenaga, 2014	Bendell, 2012	Duran, 2015
Intervention		Bevacizumab + CT	Bevacizumab + CT	Bevacizumab + CT	Bevacizumab + CT	Bevacizumab + FOLFOX	Bevacizumab + FOLFOX	Bevacizumab+ FOLFIRI
Comparator		CT	CT	CT	CT	FOLFOX	Bevacizumab+ FOLFIRI	Bevacizumab+ XELOX
Bias domain	**Signalling questions**	**Houts, 2019**	**Meyerhardt, 2012**	**Razenberg, 2016**	**Lee, 2017**	**Suenaga, 2014**	**Bendell, 2012**	**Duran, 2015**
Bias due to confounding	**1.1.** Is there potential for confounding of the effect of intervention in this study?	Y	Y	Y	Y	Y	Y	Y
	*If **N/PN** to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered* *If **Y/PY** to 1.1: determine whether there is a need to assess time-varying confounding:*	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	PN	PN	PN	PN	PN	PN	PN
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, proceed to question 1.3.*	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	NA	NA	NA	NA	NA		
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)*							
	Questions relating to baseline confounding only							
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	Y	Y	Y	Y	Y	N
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	PN	N	PN	PY	PN	PN	NA
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	PN	PN	PN	PN	PN	PN	PN
	Questions relating to baseline and time-varying confounding							
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	NA	NA	NA	NA	NA		
	1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	NA	NA	NA	NA	NA		
	Risk of bias judgement (see RoB judgement table 1)	Serious	Serious	Serious	Moderate	Moderate	Moderate	Serious
Bias in selection of participants into the study	**2.1.** Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	PN	PN	NI	PY	PN	PY
	***If N/PN to 2.1:** go to 2.4*	Go to 2.4	Go to 2.4	Go to 2.4		Proceed to 2.2	Go to 2.4	Proceed to 2.2
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?					PN		PY
	2.3. If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?					PY		PY
	2.4. Do start of follow-up and start of intervention coincide for most participants?	PY	PY	PY	NI	PY	N	NI
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?						PN	
	Risk of bias judgement (see RoB judgement table 1)	Moderate	Moderate	Moderate	NI	Serious	Serious	Serious
Bias in classification of interventions	**3.1.** Were intervention groups clearly defined?	N	N	N	N	Y	PN	Y
	3.2. Was the information used to define intervention groups recorded at the start of the intervention?	PY	PY	PY	PY	Y	PY	Y
	3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 1)	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate
Bias due to deviations from intended interventions	**4.1.** Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI	NI	NI	NI	PN	PN	NI
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?							
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6							
	4.3. Were important co-interventions balanced across intervention groups?							
	4.4. Was the intervention implemented successfully for most participants?							
	4.5. Did study participants adhere to the assigned intervention regimen?							
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?							
	Risk of bias judgement (see RoB judgement table 2)	NI	NI	NI	NI	Moderate	Moderate	NI
Bias due to missing data	**5.1.** Were outcome data available for all, or nearly all, participants?	Y	Y	Y	Y	Y	Y	Y
	5.2. Were participants excluded due to missing data on intervention status?	PN	PN	PN	PN	PN	PN	PN
	5.3. Were participants excluded due to missing data on other variables needed for the analysis?	PN	PN	PN	PN	PN	PN	PN
	5.4. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?							
	5.5. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?							
	Risk of bias judgement (see RoB judgement table 2)	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in measurement of outcomes	**6.1.** Could the outcome measure have been influenced by knowledge of the intervention received?	N	N	N	N	N	N	N
	6.2. Were outcome assessors aware of the intervention received by study participants?	PN	PN	PN	PN	PN	PN	PN
	6.3. Were the methods of outcome assessment comparable across intervention groups?	PY	PY	PY	PY	PY	PY	PY
	6.4. Were any systematic errors in measurement of the outcome related to intervention received?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 2)	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	**Is the reported effect estimate likely to be selected, on the basis of the results, from...**							
	7.1. ... multiple outcome measurements within the outcome domain?	PN	PN	PN	PN	PN	PN	PN
	7.2. ... multiple analyses of the intervention-outcome relationship?	N	Y	PY	N	N	N	N
	7.3. ... different subgroups?	Y	Y	PN	N	N	N	N
	Risk of bias judgement (see RoB judgement table 2)	Serious	Serious	Serious	Moderate	Moderate	Moderate	Moderate
Overall bias	**Risk of bias judgement** (see RoB judgement table 3)	Serious	Serious	Serious	Serious	Serious	Serious	Serious

Risk of bias assessment (cohort-type studies)

	ID 15	ID 16	ID 17	ID 18	ID 19	ID 20	ID 21
Study ID							
Author, year	Khakoo, 2019a	Uygun, 2013	Kocakova, 2015	Ocvirk, 2011	Bai, 2015	Cainap, 2021	Artac, 2016
Intervention	Bevacizumab+ FOLFIRI	Bevacizumab + FOLFIRI	Bevacizumab + FOLFIRI	Bevacizumab + FOLFIRI	Bevacizumab + Irinotecan-bas	Bevacizumab + Irinote	Bevacizumab + Irinoteca
Comparator	Bevacizumab + FOLFOX	Bevacizumab + XELIRI	Bevacizumab + XELIRI	Bevacizumab + XELIRI	Bevacizumab +Oxaliplatin-bas	Bevacizumab +Oxaliplat	Bevacizumab +Oxaliplat

Bias domain	Signalling questions	Khakoo, 2019a	Uygun, 2013	Kocakova, 2015	Ocvirk, 2011	Bai, 2015	Cainap, 2021	Artac, 2016
Bias due to confounding	**1.1.** Is there potential for confounding of the effect of intervention in this study?	Y	Y	Y	Y	Y	Y	Y
	If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered *If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:*	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	PY	PN	PN	PN	PY	PN	PN
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, proceed to question 1.3.*	Proceed to 1.3	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Proceed to 1.3	Answer 1.4 to 1.6	Answer 1.4 to 1.6
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	N				PN		
	***If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)*	Answer 1.4 to 1.6				Answer 1.4 to 1.6		
	Questions relating to baseline confounding only							
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y	N	Y	N	Y	PN	PY
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y	NA	PN	NA	PY	NA	PY
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	PN	PN	PN	PN	PN	PN	N
	Questions relating to baseline and time-varying confounding							
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?							
	1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?							
	Risk of bias judgement (see RoB judgement table 1)	Moderate	Serious	Moderate	Serious	Moderate	Serious	Moderate
Bias in selection of participants into the study	**2.1.** Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	PY	PN	PY	PN	PY	PN
	***If N/PN to 2.1:** go to 2.4*	Go to 2.4	Proceed to 2.2	Go to 2.4	Proceed to 2.2	Go to 2.4	Proceed to 2.2	Go to 2.4
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?		PY		PY		PY	
	2.3. If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		PY		PY		PY	
	2.4. Do start of follow-up and start of intervention coincide for most participants?	PY	NI	PY	NI	PY	NI	PY
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?		PN		PN		PN	
	Risk of bias judgement (see RoB judgement table 1)	Moderate	Serious	Moderate	Serious	Moderate	Serious	Moderate
Bias in classification of interventions	**3.1.** Were intervention groups clearly defined?	PN	Y	Y	Y	Y	Y	Y
	3.2. Was the information used to define intervention groups recorded at the start of the intervention?	PY	Y	Y	Y	Y	Y	Y
	3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 1)	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias due to deviations from intended interventions	**4.1.** Were there deviations from the intended intervention beyond what would be expected in usual practice?	PN	NI	NI	NI	PN	NI	NI
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?							
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6							
	4.3. Were important co-interventions balanced across intervention groups?							
	4.4. Was the intervention implemented successfully for most participants?							
	4.5. Did study participants adhere to the assigned intervention regimen?							
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?							
	Risk of bias judgement (see RoB judgement table 2)	Moderate	NI	NI	NI	Moderate	NI	NI
Bias due to missing data	**5.1.** Were outcome data available for all, or nearly all, participants?	Y	Y	Y	Y	Y	Y	Y
	5.2. Were participants excluded due to missing data on intervention status?	PN	PN	PN	PN	PN	PN	PN
	5.3. Were participants excluded due to missing data on other variables needed for the analysis?	PN	PN	PN	PN	PN	PN	PN
	5.4. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?							
	5.5. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?							
	Risk of bias judgement (see RoB judgement table 2)	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in measurement of outcomes	**6.1.** Could the outcome measure have been influenced by knowledge of the intervention received?	N	N	N	N	N	N	N
	6.2. Were outcome assessors aware of the intervention received by study participants?	PN	PN	PN	PN	PN	PN	PN
	6.3. Were the methods of outcome assessment comparable across intervention groups?	PY	PY	PY	PY	PY	PY	PY
	6.4. Were any systematic errors in measurement of the outcome related to intervention received?	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 2)	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	**Is the reported effect estimate likely to be selected, on the basis of the results, from...**							
	7.1. ... multiple outcome measurements within the outcome domain?	PN	PN	PN	PN	PN	PN	PN
	7.2. ... multiple analyses of the intervention-outcome relationship?	N	N	N	N	N	PN	PN
	7.3. ... different subgroups?	Y	N	N	N	N	Y	Y
	Risk of bias judgement (see RoB judgement table 2)	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Serious
Overall bias	**Risk of bias judgement** (see RoB judgement table 3)	Serious	Serious	Moderate	Serious	Moderate	Serious	Serious

	Study ID	ID 22	ID 23	ID 24	ID 25	ID 26	ID 27	ID 28	ID 29
	Author, year	Stein,2015	Buchler, 2014	Cheng, 2015	Yang, 2014	Houts, 2019	Bai, 2016	Zhou, 2021	Degirmencioglu , 2019
	Intervention	Bevacizumab + Irinotecan-bas	Bevacizumab + FOLFIOX	Bevacizumab + FOLFOXIRI	Cetuximab+ CT	Cetuximab+CT	Cetuximab+ CT	Cetuximab+ CT	Cetuximab+ CT
	Comparator	Bevacizumab +Oxaliplatin-ba	Bevacizumab + XELOX	Bevacizumab + XELOXIRI	Bevacizumab+CT	Bevacizumab+CT	Bevacizumab+ CT	Bevacizumab+CT	Bevacizumab+CT

Bias domain	Signalling questions	Stein,2015	Buchler, 2014	Cheng, 2015	Yang, 2014	Houts, 2019	Bai, 2016	Zhou, 2021	Degirmencioglu , 2019
Bias due to confounding	**1.1.** Is there potential for confounding of the effect of intervention in this study?	Y	Y	Y	Y	Y	Y	Y	Y
	If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered *If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:*	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2	Proceed to 1.2
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	PN	PN	PN					
	***If N/PN** , answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, proceed to question 1.3.*	Answer 1.4 to 1.6	Answer 1.4 to 1.6	Answer 1.4 to 1.6					
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?								
	***If N/PN** , answer questions relating to baseline confounding (1.4 to 1.6)* ***If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)*								
	Questions relating to baseline confounding only								
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	N	Y	Y	Y	PY	PY	PY	PN
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA	PN	N	PN	PY	PY	PY	NA
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	PN	PN	PN	PN	N	N	N	PN
	Questions relating to baseline and time-varying confounding								
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?								
	1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?								
	Risk of bias judgement (see RoB judgement table 1)	Serious	Serious	Serious	Serious	Moderate	Moderate	Moderate	Serious
Bias in selection of participants into the study	**2.1.** Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	PN	PY	PN	PN	PY	PY	NI
	***If N/PN to 2.1:** go to 2.4*	Go to 2.4	Go to 2.4	Proceed to 2.2	Go to 2.4	Go to 2.4	Proceed to 2.2	Proceed to 2.2	
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?			PY			PN	PN	
	2.3. If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?			PY			PY	PY	
	2.4. Do start of follow-up and start of intervention coincide for most participants?	PY	PY	Y	PY	PY	PY	PY	NI
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?			PN			PN	PN	
	Risk of bias judgement (see RoB judgement table 1)	Moderate	Moderate	Serious	Moderate	Moderate	Serious	Serious	NI
Bias in classification of interventions	**3.1.** Were intervention groups clearly defined?	PN	Y	Y	Y	PN	Y	Y	PN
	3.2. Was the information used to define intervention groups recorded at the start of the intervention?	PY	Y	Y	Y	PY	Y	Y	PY
	3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 1)	Serious	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Serious
Bias due to deviations from intended interventions	**4.1.** Were there deviations from the intended intervention beyond what would be expected in usual practice?	NI	NI	NI	NI	NI	NI	NI	NI
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?								
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6								
	4.3. Were important co-interventions balanced across intervention groups?								
	4.4. Was the intervention implemented successfully for most participants?								
	4.5. Did study participants adhere to the assigned intervention regimen?								
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?								
	Risk of bias judgement (see RoB judgement table 2)	NI	NI	NI	NI	NI	NI	NI	NI
Bias due to missing data	**5.1.** Were outcome data available for all, or nearly all, participants?	Y	Y	Y	Y	PY	Y	Y	Y
	5.2. Were participants excluded due to missing data on intervention status?	PN	PN	PN	PN	Y	PN	PN	PN
	5.3. Were participants excluded due to missing data on other variables needed for the analysis?	PN	PN	PN	PN	Y	PN	Y	PN
	5.4. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?					N		NI	
	5.5. If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?					NI		NI	
	Risk of bias judgement (see RoB judgement table 2)	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	Serious	Moderate
Bias in measurement of outcomes	**6.1.** Could the outcome measure have been influenced by knowledge of the intervention received?	N	N	N	N	N	N	N	N
	6.2. Were outcome assessors aware of the intervention received by study participants?	PN	PN	PN	PN	PN	PN	PN	PN
	6.3. Were the methods of outcome assessment comparable across intervention groups?	PY	PY	PY	PY	PY	PY	PY	PY
	6.4. Were any systematic errors in measurement of the outcome related to intervention received?	PN	PN	PN	PN	PN	PN	PN	PN
	Risk of bias judgement (see RoB judgement table 2)	Low	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	**Is the reported effect estimate likely to be selected, on the basis of the results, from...**								
	7.1. ... multiple outcome measurements within the outcome domain?	PN	PN	PN	PN	PN	PN	PN	PN
	7.2. ... multiple analyses of the intervention-outcome relationship?	PN	N	N	N	N	N	N	N
	7.3. ... different subgroups?	Y	N	N	N	N	N	PY	N
	Risk of bias judgement (see RoB judgement table 2)	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Moderate
Overall bias	**Risk of bias judgement** (see RoB judgement table 3)	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious

The detailed answers to the signalling questions of the assessment of risk of bias for the studies included in the overall survival meta-analysis.

Risk of confounding bias of the included studies

Basic information		Bias due to confounding								
Study ID	**Author Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	inherent by design	no switching involved	Not applicable	adjustment for several confounders was used	confounding domains included age, gender, number of Mets, primary location pre-treatment CEA, **performance status**, regimen. However, the non-significant results in MV analysis were not shown including regimen. Also, resection was not included	the adjustment was only performed for baseline characteristics prior to intervention	Time-varying confounder was not analysed in this study	Not applicable	Serious
ID 2	Guo, 2020 (Guo et al., 2020)	inherent by design	no switching involved	Not applicable	propensity score matching	propensity score matching was performed. However, the variables in which the matching was performed for were not reported in the study	the adjustment was only performed for baseline characteristics prior to intervention	Time-varying confounder was not analysed in this study	Not applicable	Serious
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	inherent by design	no switching involved	Not applicable	adjustment for several confounders was used	confounding variables included treatment, age, sex, race, positive lymph nodes, tumour grade, comorbidity score, geographic region, and income. However, PS and prior resection were not included	the adjustment was only performed for baseline characteristics prior to intervention	adjustment was considered for all important domains	Not applicable	Serious

Basic information		Bias due to confounding								
ID 4	Neugut, 2019 (Neugut et al., 2019)	inherent by design	no switching involved	Not applicable	the study authors did not adjust for potential confounders	Not applicable	no adjustment post intervention was undertaken	the authirs did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 5	Marschner, 2015 (Marschner et al., 2015)	inherent by design	no switching involved	Not applicable	Cox proportional hazards model was used to verify the difference in Kaplan–Meier curves adjusted for potentially confounding variables.	variables are consistent with the pre-determined in the protocol and they are: sex, age at start of treatment, BMI, PS, RAS status, surgery, number of metastatic sites, time form diagnosis to treatment	no adjustment post intervention was undertaken	Time-varying confounder was not analysed in this study	Not applicable	Moderate
ID 6	Hammerman,2015 (Hammerman et al., 2015)	inherent by design	no switching involved	Not applicable	the authors did use an appropriate method which was cox proportional hazards regression.	the authors did not include all important confounders including PS and prior resection	no adjustment post intervention was undertaken	Time-varying confounder was not applicable in this study	Not applicable	Serious
ID 7	Franchi,2019 (Franchi et al., 2019)	inherent by design	participants in both groups switched to different regimens over the course of follow up as stated in the treatment pattern section of the results	NI	the primary endpoint of the study, was calculated by means of the Kaplan-Meier estimator, and the log-rank test was used for testing survival differences between patients starting on B+CT or CT alone. Predictors of OS	the authors did not include all important confounders including PS and liver mets. However, a propensity score matching to account for residual confounders was performed. As stated in the methods section of the study, In this analysis, propensity scores were calculated using, besides the covariates listed above,	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Moderate

Basic information		Bias due to confounding								
					were evaluated by fitting a Cox proportional hazard model.	the following: diabetes, hypertension, cerebrovascular/ischemic heart/respiratory/renl diseases, time to treat (i.e., duration of time between mCRC diagnosis and start of first-line treatment), number of hospitalizations, outpatient services, and drug prescriptions in the 3 years prior to the index date				
ID 8	Houts,2019 (Houts et al., 2019b)	inherent by design	no switching involved	Not applicable	the authors stated that the sample of C patients was likely to be older and have some performance status impairment, factors that may have led to the decision to treat without adding bevacizumab. It is also possible that these "selection" differences accounted for the apparent efficacy advantages of adding B to C. the authors have not used propensity score matching to	covariates included: age, gender, race, BMI), PS, liver metastasis, lung metastasis , stage at diagnosis, chemotherapy backbone. However, prior resection was not accounted for	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Serious

Basic information		Bias due to confounding								
					account for the imbalance in these covariates. however, the authors used cox regression to control for the imbalance and to adjust for the confounders					
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	inherent by design	no switching involved	Not applicable	the study adjusted for potential confounders Also propensity score matching was used to address the confounding	the covariates adjusted for were not reported in the study	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Serious
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	inherent by design	no switching involved	Not applicable	the study adjusted for potential confounders Also propensity score matching was used to address the confounding	age, comorbidity, primary tumor location, adjuvant chemotherapy, time to metastases, period of diagnosed metastases, number of metastases). however, study did not adjust for PS and surgical resection	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Serious
ID 11	Lee, 2017 (Lee et al., 2017)	inherent by design	no switching involved	Not applicable	the authors used an appropriate method which was cox proportional hazards regression.	age, primary resection, ECOG PS, number of metastatic sites, and the addition of bevacizumab to therapy	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Moderate
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	inherent by design	no switching involved	Not applicable	Multivariate analysis of the factors was conducted based on the Cox	treatment, age, ECOG PS, primary site, number of mets, liver involvement. however,	no adjustment post intervention	Time-varying confounder was not	Not applicable	Serious

Basic information		Bias due to confounding								
					proportional hazards model to identify factors associated with PFS and OS.	study did not adjust for surgical resection	was undertaken.	analysed in this study		
ID 13	Bendell, 2012 (Bendell et al., 2012)	inherent by design	no switching involved	Not applicable	A multivariate Cox proportional hazards model was used to assess the effect of first-line chemotherapy with bevacizumab OS outcome, adjusting for potential confounding factors	treatment, age, sex, race, ECOG PS, serum albumin and alkaline phosphatase levels, site of primary tumour, adjuvant therapy, disease-free interval, and history of cardiovascular disease, diabetes, hypertension, or hypercholesterolemia. however, study did not adjust for surgical resection	no adjustment post intervention was undertaken.	Time-varying confounder was not analysed in this study	Not applicable	Serious
ID 14	Duran,2014 (Duran et al., 2014)	inherent by design	no switching involved	Not applicable	the study authors did not adjust for potential confounders	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	inherent by design	one of the study's endpoints was reason for discontinuation of treatment with bevacizumab	reasons for discontinuation included: disease progression, investigator's decision, and Aes. None of which is prognostic for the outcome	A multivariable Cox proportional hazard regression model was used to model OS in terms of baseline and chemotherapy and bevacizumab administration covariates	age, ECOG PS, resection, regimen	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Moderate

Basic information		Bias due to confounding								
ID 16	Uygun, 2013 (Uygun et al., 2013)	inherent by design	no switching involved	Not applicable	the study authors did not adjust for potential confounders	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 17	Kocakova,2015 (Kocakova et al., 2015)	inherent by design	no switching involved	Not applicable	Multivariable Cox proportional hazards model was used to quantify the effect of chemotherapy regimens on survival in the presence of other potential predictive and prognostic factors	treatment, age, gender, primary tumour location, initial stage, number of metastatic sites. however, study did not adjust for PS and surgical resection	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	inherent by design	no switching involved	Not applicable	the study authors did not adjust for potential confounders	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 19	Bai, 2015 (Bai et al., 2015)	inherent by design	one of the study's endpoints was reason for discontinuation of treatment with bevacizumab	reasons for discontinuation included: disease progression, investigator's decision, and Aes. None of which is prognostic for the outcome	The association between potential confounding pre- and on-treatment factors and OS was examined by multivariate Cox proportional hazards regression model	relevant: treatment backbone, maintenance treatment, resection of mets, recurrent mets). PS was not adjusted for	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious

Basic information		Bias due to confounding								
ID 20	Cainap, 2021 (Cainap et al., 2021)	inherent by design	no switching involved	Not applicable	the study used cox regression to estimate HR. however, no reporting for adjustment for potential confounders	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 21	Artac, 2016(Artac et al., 2016)	inherent by design	no switching involved	Not applicable	multivariate Cox proportional hazards models were used to quantify the influence of the treatment regimens on survival in the presence of other potential predictive and prognostic factors. However, there was a need to reconstruct KM curves since the study has not reported the confidence intervals associated with the HR	ECOG PS, mastectomy, age, adverse events, gender , RAS, stage at diagnosis	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Moderate
ID 22	Stein,2015 (Stein et al., 2015a)	inherent by design	no switching involved	Not applicable	ome more limitations must be considered, particularly the bias when selecting patients for specific treatment,	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious

Basic information		Bias due to confounding								
ID 23	Buchler, 2014 (Buchler et al., 2014)	inherent by design	no switching involved	Not applicable	Multivariable Cox proportional hazards model was used to quantify the influence of the considered treatment modalities on survival in the presence of other potential predictive and prognostic factors	treatment, age, gender, primary tumour location, stage, number of Mets- no adjustment for PS and primary tumour resection	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 24	Cheng, 2015 (Cheng and Song, 2015)	inherent by design	no switching involved	Not applicable	Cox proportional-hazards modelling was performed as supportive analyses	only significant values were reported - the effect of treatment on OS was not reported	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 25	Yang, 2014 (Yang et al., 2014)	inherent by design	no switching involved	Not applicable	Cox proportional hazards models were used for univariate and multivariate analyses to determine the independent influence of clinical and pathological factors on survival endpoints	only significant values were reported - the effect of treatment on OS was not reported	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 26	Houts, 2019 (Houts et al., 2019a)	inherent by design	no switching involved	Not applicable	Multivariate Cox regression models were also used to examine OS.	age, gender, race [minority vs. white], body mass index (BMI), number of metastatic sites, performance	no adjustment post intervention	the authors did not adjust for baseline or time varying	Not applicable	Serious

Basic information		Bias due to confounding								
						status. no adjustment for primary tumour resection	was undertaken	confounders		
ID 27	Bai, 2016 (Bai et al., 2016)	inherent by design	no switching involved	Not applicable	In order to estimate the prognostic value of baseline clinicopathological features, Cox proportional hazards models were used in univariate and multivariate analyses and to generate the HR and corresponding 95% confidence intervals (CIs).	gender, primary tumour location, pathological differentiation, number of metastatic sites, peritoneal metastases, backbone chemotherapy, primary tumour resection. However, PS was not adjusted for	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 28	Zhou, 2021 (Zhou et al., 2021)	inherent by design	no switching involved	Not applicable	Cox regression model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI)	age, sex, primary tumour location, number of metastatic sites, sites of Mets, tumour differentiation, primary tumour resection, backbone chemotherapy, RAS status. However, PS was not adjusted for	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	inherent by design	no switching involved	Not applicable	Univariate and multivariate analyses were carried out using Spearman's correlation analysis. This is a	Not applicable	no adjustment post intervention was undertaken	the authors did not adjust for baseline or time varying confounders	Not applicable	Serious

Basic information		Bias due to confounding								
					bivariate evaluation. However, a multivariate evaluation of the effect of different covariates on survival was not demonstrated					

Risk of selection bias of the included studies

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	aged ≥65 years had a good performance status (i.e. WHO 0–2 or Karnofsky ≥80%) and had metastatic CRC (TMN stage IV) confirmed by histopathology with a measurable lesion	patients with better PS are expected to receive intensified therapy whereas patients with poorer PS are expected to receive monotherapy	patients with better PS are expected to have a better survival compared to those with poorer PS	patients in first-line settings	Not applicable	Serious
ID 2	Guo, 2020 (Guo et al., 2020)	"the selection criteria indicated the exclusion of patients who were receiving certain co-interventions. patients were excluded on the following basis treated with immunotherapy or targeted therapy concurrent with chemotherapy; 2) patients with radical surgery or local treatment during chemotherapy; both aspects relate to at or post intervention"	the eligibility criteria are not associated with the intervention	according to the exclusion criteria, patients whose survival was less than 3 months were excluded from the study which leads to overestimating OS	patients in first-line settings	Not applicable	Serious
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	Only patients whose survival time ≥60 days following the date of first-line chemotherapy initiation were included	the eligibility criteria are not associated with the intervention	according to the exclusion criteria, patients whose survival was less less than 60 days were excluded from the study which leads to overestimating OS	patients in first-line settings-	Not applicable	Serious
ID 4	Neugut, 2019 (Neugut et al., 2019)	no indication whether selection was made according to post intervention variables	Not applicable	Not applicable	since patients are newly diagnosed and are in first-line settings. Then probably the start of intervention was used as the start of follow-up. Also, there was no reporting for lead time	Not applicable	Moderate

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
ID 5	Marschner, 2015 (Marschner et al., 2015)	Patients with histologically confirmed colorectal cancer signed informed consent no longer than 4 weeks after the start of systemic neoadjuvant/adjuvant treatment for nonmetastatic or first-line treatment for metastatic/inoperable disease were not included in the study	Not applicable	Not applicable	adjustment for immortal time bias by elimination of patients who did not consent within 4 weeks was used to coincide follow up with time of intervention	Not applicable	Low
ID 6	Hammerman, 2015 (Hammerman et al., 2015)	the study has not provided enough information on the selection and eligibility criteria of the included patients	Not applicable	Not applicable	patients in first-line settings	Not applicable	NI
ID 7	Franchi,2019 (Franchi et al., 2019)	the cohort selection flow chart and details provided in the methods section do not show selection after start of intervention	Not applicable	Not applicable	starting from the index date, all the prescriptions of antineoplastic drugs in the next 21 days (i.e., the plausible duration of a CT cycle, that is, every 14 or 21 days) were selected.	Not applicable	Moderate
ID 8	Houts,2019 (Houts et al., 2019b)	no indication whether selection was made according to post intervention variables. minimal selection criteria used	Not applicable	Not applicable	since patients are newly diagnosed and are in first-line settings. Then probably the start of intervention was used as the start of follow-up. Also, there was no reporting for incretion time	Not applicable	Moderate
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	no indication whether selection was made according to post intervention variables. . minimal selection criteria used	Not applicable	Not applicable	since patients are newly diagnosed and are in first-line settings. Then probably the start of intervention was used as the start of follow-up. Also, there was no	Not applicable	Moderate

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
					reporting for incretion time		
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	no indication whether selection was made according to post intervention variables. . minimal selection criteria used	Not applicable	Not applicable	since patients are newly diagnosed and are in first-line settings. Then probably the start of intervention was used as the start of follow-up. Also, there was no reporting for inception time	Not applicable	Moderate
ID 11	Lee, 2017 (Lee et al., 2017)	the study has not provided enough information on the selection and eligibility criteria of the included patients	Not applicable	Not applicable	Not applicable	Not applicable	NI
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	The study selected patients whose PS is less than or equal 2	Not applicable	Patients whose PS is better are expected to survive longer	since patients are newly diagnosed and are in first-line settings. Then probably the start of intervention was used as the start of follow-up. Also, there was no reporting for incetion time	Not applicable	Serious

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
ID 13	Bendell, 2012 (Bendell et al., 2012)	no treatments, assessments, or exclusions specified by the protocol, including the dose and frequency of bevacizumab or regimens of chemo-therapy (including biologic agents) and the method or frequency of clinical assessments. Notably, no exclusions were made on the basis of the sites of metastasis, the use of concur-rent anticoagulation, or the Eastern Cooperative Oncology Group (ECOG) performance status score	Not applicable	Not applicable	immortal time bias as indicated in the discussion as following: because patients could be enrolled up to 4 months after the initiation of treatment, the timing of enrollment may have affected the inclusion of patients with early progression or death events	immortal time bias was not adjusted for	Serious
ID 14	Duran,2014 (Duran et al., 2014)	Patients were excluded if they had significant cardiovascular, hepatic and renal diseases, hypertension, haemorrhagic diathesis or coagulopathy	Patients who receive bevacizumab are expected to have CV adverse events such as hypertension. Excluding patients with hypertension might bias the outcome	Patients with comorbidities are expected to survive shorter	Not applicable	Not applicable	Serious
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	the eligibility criteria do not indicate the selection of the cohort based on post intervention variables	Not applicable	Not applicable	the following was reported in the study methods: "Bevacizumab had to have been initiated at the same time as the first-line chemotherapy regimen or within 3 months, if delayed administration of bevacizumab was part of the standard of care or resulted from delayed access to bevacizumab"- indicating inception bias	Not applicable	Serious

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
ID 16	Uygun, 2013 (Uygun et al., 2013)	the study selected healthy and fit patients only. Also, the study excluded patients with comorbidities such as cardiovascular diseases or infection	the selection criteria were probably associated with the intervention which is bevacizumab, which is administered for healthy and fit patients with no co existing cardiovascular diseases	the selection criteria included the following: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2,. all of those are prognostics and associated with the outcome	patients in first-line settings	the study did not adjust for selection bias	Serious
ID 17	Kocakova,2015 (Kocakova et al., 2015)	selection bias cannot be excluded as only patients considered medically fit and with good performance status were selected for treatment with bevacizumab-containing combination therapy.	Patients with better PS are eligible to take bevacizumab	Patients whose PS is better are expected to survive longer	patients in first-line settings	Not applicable	Serious
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	the study selected healthy and fit patients only. Also, the study excluded patients with comorbidities such as cardiovascular diseases or infection	the selection criteria were probably associated with the intervention which is bevacizumab, which is administered for healthy and fit patients with no co existing cardiovascular diseases	the selection criteria included the following: patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with adequate hematological and organ function	patients in first-line settings	the study did not adjust for selection bias	Serious
ID 19	Bai, 2015 (Bai et al., 2015)	Patients needed to have an ECOG PS of 0–2, adequate hematologic, liver, and renal function (i.e., neutrophils C1.5 9 109 /l; creatinine clearance C30 ml/min; total bilirubin concentrationB2 times the upper limit of normal; and liver transaminase B2.5 times the upper limit of normal).	patients were selected based on certain characteristics post intervention	patients with the selected criteria are expected to survive longer	patients in first-line settings	Not applicable	Serious

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
ID 20	Cainap, 2021 (Cainap et al., 2021)	the study selected healthy and fit patients only.	the selection criteria were probably associated with the intervention which is bevacizumab, which is administered for healthy and fit patients with no co existing cardiovascular diseases	the selection criteria included the following criteria: histological confirmed CRC, lab tests adequate for chemotherapy: . no medical contraindication to chemotherapy (according to treatment characteristics and recommendations), at least one metastatic site, ECOG PS of 0 to 2,	patients in first-line settings	no adjustment techniques were used to account for selection bias	Serious
ID 21	Artac, 2016(Artac et al., 2016)	the eligibility criteria do not indicate the selection of the cohort based on post intervention variables	Not applicable	Not applicable	patients in first-line settings	Not applicable	Moderate
ID 22	Stein,2015 (Stein et al., 2015a)	minimal patient selection criteria were used and all patients scheduled to be treated with bevacizumab were included in the study; as a result, the population is more likely to be representative of the mCRC patient population eligible for palliative chemotherapy in combination with bevacizumab	Not applicable	Not applicable	patients in first-line settings	Not applicable	Moderate
ID 23	Buchler, 2014 (Buchler et al., 2014)	Selection bias cannot be excluded as fitter patients could have been preferentially allocated to XELOX chemotherapy	Not applicable	capecitabine is associated with more toxicities than 5FU	patients in first-line settings	Not applicable	Serious
ID 24	Cheng, 2015 (Cheng and Song, 2015)	the study selected healthy patients to assess their response to treatment	the selection criteria were probably associated with the intervention which is bevacizumab, which is administered for healthy and fit	the study imposed restrictive inclusion criteria as follow: ECOG PS of 1 or lower, presence of a measurable	The follow up time was measured from the day of first treatment administration to the time of the present analysis	no adjustment techniques were used to account	Serious

Basic information		Bias in selection of participants into the study					
Study ID	**Author Year**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**RoB judgement**
			patients with no co existing cardiovascular diseases	lesion according to WHO criteria.	(for patients still alive) or death for deceased patients.	for selection bias	
ID 25	Yang, 2014 (Yang et al., 2014)	the eligibility criteria do not indicate the selection of the cohort based on post intervention variables	Not applicable	Not applicable	patients in first-line settings	Not applicable	Moderate
ID 26	Houts, 2019 (Houts et al., 2019a)	the eligibility criteria do not indicate the selection of the cohort based on post intervention variables	Not applicable	Not applicable	patients in first-line settings	Not applicable	Moderate
ID 27	Bai, 2016 (Bai et al., 2016)	the eligibility criteria depicted in Figure 1 shows the exclusion of patients with brain metastases and those who underwent surgery or radiotherapy within 6 months	post-intervention variables are not associated with the intervention	patients with brain metastases have poorer survival	patients in first-line settings	no adjustment for selection bias was performed	Serious
ID 28	Zhou, 2021 (Zhou et al., 2021)	Patients were excluded if they were lack of imaging evaluation or complete clinical materials; had underwent local treatment (surgery or radiotherapy) on measurable lesions before the first evaluation; had signet ring cells or undifferentiated components	post-intervention variables are not associated with the intervention	patients who underwent local treatment are expected to have better prognosis	patients in first-line settings	no adjustment for selection bias was performed	Serious
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	no indication whether selection was made according to post intervention variables	Not applicable	Not applicable	patients in first-line settings	Not applicable	NI

Risk *of classification of intervention bias of the included studies*

Basic information		Bias in classification of interventions			
Study ID	**Author Year**	**3.1**	**3.2**	**3.3**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 2	Guo, 2020 (Guo et al., 2020)	information about the treatment was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	Dose selection was at the discretion of the physician and dosing information could not be determined retrospectively from available data within the claims dataset	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 4	Neugut, 2019 (Neugut et al., 2019)	information about the treatment was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 5	Marschner, 2015 (Marschner et al., 2015)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 6	Hammerman,2015 (Hammerman et al., 2015)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data	Serious

				collection which would minimize the bias	
ID 7	Franchi,2019 (Franchi et al., 2019)	he information on chemotherapy (i.e., irinotecan, oxaliplatin, capecitabine, and fluorouracil) of inpatients was not available in our database	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 8	Houts,2019 (Houts et al., 2019b)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 11	Lee, 2017 (Lee et al., 2017)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 13	Bendell, 2012 (Bendell et al., 2012)	Information about the treatment dose, duration, frequency and method of administration was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious

ID 14	Duran,2014 (Duran et al., 2014)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 16	Uygun, 2013 (Uygun et al., 2013)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 17	Kocakova,2015 (Kocakova et al., 2015)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 19	Bai, 2015 (Bai et al., 2015)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study.	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 20	Cainap, 2021 (Cainap et al., 2021)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 21	Artac, 2016(Artac et al., 2016)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate

ID 22	Stein,2015 (Stein et al., 2015a)	information about the treatment was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 23	Buchler, 2014 (Buchler et al., 2014)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 24	Cheng, 2015 (Cheng and Song, 2015)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 25	Yang, 2014 (Yang et al., 2014)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 26	Houts, 2019 (Houts et al., 2019a)	information about the treatment was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious
ID 27	Bai, 2016 (Bai et al., 2016)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 28	Zhou, 2021 (Zhou et al., 2021)	Information about the treatment dose, duration, frequency and method of administration was clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Moderate
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	information about the treatment was not clearly explained in the study	the source of this information is not likely to be affected by the outcome and is likely sufficient to record intervention at start of intervention	the use of medical charts and medical records offer an element of objectivity of the way of data collection which would minimize the bias	Serious

Risk of missing data bias of the included studies

Basic information		Bias due to missing data					
Study ID	**Author Year**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	patients had incomplete data that precluded their objective analysis - out of 214 patients identified to comply with the eligibility criteria, 91 (42%) were excluded from the analysis	patients were excluded from analysis for various reasons	patients had incomplete data that precluded their objective analysis	NI	Na	Serious
ID 2	Guo, 2020 (Guo et al., 2020)	upon propensity score matching, before matching, all the observations with missing values of matching variables would be Eliminated.	after propensity score matching was performed, a significant number of patients were dropped from the outcome analysis	upon propensity score matching, Before matching, all the observations with missing values of matching variables would be eliminated.	the percentages of missing data was calculated and deemed similar between the studies	Na	Serious
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	for the patients who were included in analysis, outcome data were complete	2,811 patients were excluded out of 7061, about 28 % received irinotecan-based therapy, 57 % received other types of chemotherapy, and 15 % received an unknown type of chemotherapy	patients had incomplete data that precluded their objective analysis	NI	NI	Serious
ID 4	Neugut, 2019 (Neugut et al., 2019)	for the patients who were included in analysis, outcome data were complete	missing in data was rather in variables rather in treatment details. However, variables are not essential	NI	missing in data in CCI and in treatment settings was confined to patients who received folfiri not folofx	NI	Moderate
ID 5	Marschner, 2015 (Marschner et al., 2015)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	although there were missing in data in baseline variables such as PS stage at dx, and RAS status, outcome was calculated and missing data	Na	Na	Moderate

Basic information		Bias due to missing data					
Study ID	**Author Year**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**RoB judgement**
				were included in the model as missing			
ID 6	Hammerman,2015 (Hammerman et al., 2015)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 7	Franchi,2019 (Franchi et al., 2019)	for the patients who were included in analysis, outcome data were complete	after the identification of the clean cohort, no patients were excluded from the a based on intervention status	sensitivity analysis was undertaken to account for missing in data in data needed for further analysis. In the study it is stated the following: because information on cancer size, lymph node status and grading was missing in about 24% of cohort patients, a multiple imputation technique (i.e., the fully condition applicable specification) was used to account for missing data	Na	Na	Low
ID 8	Houts,2019 (Houts et al., 2019b)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	there were missing in data in some characteristics such as liver resection. The authors have not performed sensitivity analysis to account for the missing in data	Na	Na	Moderate
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	there were missing in data in some characteristics such as liver resection.	Na	Na	Moderate
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate

Basic information		Bias due to missing data					
Study ID	**Author Year**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**RoB judgement**
ID 11	Lee, 2017 (Lee et al., 2017)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 13	Bendell, 2012 (Bendell et al., 2012)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 14	Duran,2014 (Duran et al., 2014)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 16	Uygun, 2013 (Uygun et al., 2013)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 17	Kocakova,2015 (Kocakova et al., 2015)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	although there was a significant missing in data in PS, which is an important prognostic variable, patients were not excluded from analysis on that basis. The proportion of missing in data between 2 groups was not statistically significant	Na	Na	Moderate

Basic information		Bias due to missing data					
Study ID	**Author Year**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**RoB judgement**
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	for the patients who were included in analysis, outcome data were complete	no patients were excluded based on intervention status	although there was a significant missing in data in PS, which is an important prognostic variable, patients were not excluded from analysis on that basis. The proportion of missing in data between 2 groups was not statistically significant	Na	Na	Moderate
ID 19	Bai, 2015 (Bai et al., 2015)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no exclusions were made on the items of ECOG PS, age, organ function	Na	Na	Moderate
ID 20	Cainap, 2021 (Cainap et al., 2021)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 21	Artac, 2016(Artac et al., 2016)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 22	Stein,2015 (Stein et al., 2015a)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 23	Buchler, 2014 (Buchler et al., 2014)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 24	Cheng, 2015 (Cheng and Song, 2015)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate

Basic information		Bias due to missing data					
Study ID	**Author Year**	**5.1**	**5.2**	**5.3**	**5.4**	**5.5**	**RoB judgement**
ID 25	Yang, 2014 (Yang et al., 2014)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 26	Houts, 2019 (Houts et al., 2019a)	For patients who were alive at final analysis, data on survival were censored at the last contact	screening process Figure shows that a considerable number of patients were excluded as treatment status was not confirmed	screening process Figure shows that a considerable number of patients were excluded as RAS status was not confirmed	70% of initial cetuximab smple vs 24% of initial bevacizumab sample were excluded due to missing data on intervention status. Also, 46.3% of bevacizumab sample vs 3% of cetuximab sample were excluded due to missing data on RAS status	NI	Serious
ID 27	Bai, 2016 (Bai et al., 2016)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate
ID 28	Zhou, 2021 (Zhou et al., 2021)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	according to Figure 1, patients were excluded for lacking of complete material	NI	NI	Serious
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	For patients who were alive at final analysis, data on survival were censored at the last contact	no patients were excluded based on intervention status	no patients were excluded on the basis of missing data needed for analysis	Na	Na	Moderate

Risk of measurement of outcome bias of the included studies

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 2	Guo, 2020 (Guo et al., 2020)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 4	Neugut, 2019 (Neugut et al., 2019)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a sudjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 5	Marschner, 2015 (Marschner et al., 2015)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 6	Hammerman,2015 (Hammerman et al., 2015)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 7	Franchi,2019 (Franchi et al., 2019)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 8	Houts,2019 (Houts et al., 2019b)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 11	Lee, 2017 (Lee et al., 2017)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 13	Bendell, 2012 (Bendell et al., 2012)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 14	Duran,2014 (Duran et al., 2014)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 16	Uygun, 2013 (Uygun et al., 2013)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 17	Kocakova,2015 (Kocakova et al., 2015)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 19	Bai, 2015 (Bai et al., 2015)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 20	Cainap, 2021 (Cainap et al., 2021)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 21	Artac, 2016(Artac et al., 2016)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 22	Stein,2015 (Stein et al., 2015a)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 23	Buchler, 2014 (Buchler et al., 2014)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 24	Cheng, 2015 (Cheng and Song, 2015)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 25	Yang, 2014 (Yang et al., 2014)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 26	Houts, 2019 (Houts et al., 2019a)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 27	Bai, 2016 (Bai et al., 2016)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in measurement of outcomes				
Study ID	**Author Year**	**6.1**	**6.2**	**6.3**	**6.4**	**RoB judgement**
ID 28	Zhou, 2021 (Zhou et al., 2021)		because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	the outcome measured here is overall survival - the occurrence or non-occurrence of death is not a subjective outcome	because data were collected from electronic records are probably the identity of the patients was anonymized, there is a probability that assessors were blinded (outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators)	overall survival was defined similarly for both groups. And the way survival was measured was also similar	the outcome measured is the occurrence of death. The error can arise from wrong reporting of time of death but not necessarily related to intervention	Low

Basic information		Bias in selection of the reported result			
Study ID	**Author Year**	**7.1**	**7.2**	**7.3**	**RoB judgement**
ID 1	Stec, 2009 (Stec et al., 2010)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 2	Guo, 2020 (Guo et al., 2020)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 3	Satram-Hoang ,2013 (Satram-Hoang et al., 2013)	overall survival was solely measured by KM method	the authors reported adjusted, unadjusted and the backwards elimination findings	no subgroup analysis was undertaken	Serious
ID 4	Neugut, 2019 (Neugut et al., 2019)	overall survival was only measured by KM method. The study used the same method to study the effect of different covariates on OS	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 5	Marschner, 2015 (Marschner et al., 2015)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 6	Hammerman,2015 (Hammerman et al., 2015)	KM method was used to measure outcome	the authors provided both adjusted and crude estimates	a sub-analysis was performed to compare outcomes between the cohorts, restricting the results only to patients receiving irinotecan-based protocols in both cohorts. A second sub-analysis was performed among patients in Cohort B, to compare outcomes between oxaliplatin- and irinotecan-based regimens, to evaluate a possible interaction of benefit from bevacizumab therapy and the chemotherapy backbone.	Serious
ID 7	Franchi,2019 (Franchi et al., 2019)	KM method was used to measure outcome	the authors reported the results of the adjusted, crude, before and after sensitivity analysis was performed	separate results were presented according to different subgrouping; the age (<70 years vs. ≥70 years) or surgery (yes vs. no) and then by first-line treatment (B+CT vs. CT alone)	Serious
ID 8	Houts,2019 (Houts et al., 2019b)	only KM method was used to measure outcome	the authors only reported the adjusted HR for OS. They have not reported the unadjusted HR for OS.	the authors conducted subset analyses of OS within each regimen group where patients were divided into those with left- vs. right-sided tumors	Serious

Basic information		Bias in selection of the reported result			
Study ID	**Author Year**	**7.1**	**7.2**	**7.3**	**RoB judgement**
ID 9	Meyerhardt, 2012 (Meyerhardt et al., 2012b)	KM method was used to measure outcome	the authors reported the results of the adjusted, crude, before and after sensitivity analysis was performed	separate results were presented according to different subgrouping; the age (<70 years vs. ≥70 years) or surgery (yes vs. no) and then by first-line treatment (B+CT vs. CT alone)	Serious
ID 10	Razenberg, 2016 (Razenberg et al., 2016)	only KM method was used to measure outcome	the authors only reported the adjusted HR for OS. They have not reported the unadjusted HR for OS.	the authors conducted subset analyses of OS within each regimen group where patients were divided into those with left- vs. right-sided tumors	Serious
ID 11	Lee, 2017 (Lee et al., 2017)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 12	Suenaga, 2014 (Suenaga et al., 2014)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 13	Bendell, 2012 (Bendell et al., 2012)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 14	Duran,2014 (Duran et al., 2014)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 15	Khakoo, 2019 (Khakoo et al., 2019)	only KM method was used to measure outcome	the authors only reported the adjusted HR for OS. They have not reported the unadjusted HR for OS.	the authors conducted subset analyses of OS within each regimen group where patients were divided into those with left- vs. right-sided tumors	Serious
ID 16	Uygun, 2013 (Uygun et al., 2013)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate

Basic information		Bias in selection of the reported result			
Study ID	**Author Year**	**7.1**	**7.2**	**7.3**	**RoB judgement**
ID 17	Kocakova,2015 (Kocakova et al., 2015)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 18	Ocvirk, 2011 (Ocvirk et al., 2011)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 19	Bai, 2015 (Bai et al., 2015)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 20	Cainap, 2021 (Cainap et al., 2021)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	overall survival was compared between standard chemotherapy and double dose chemotherapy	Serious
ID 21	Artac, 2016(Artac et al., 2016)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	the authors conducted subset analyses of OS within each regimen group where patients were divided into those with subgroups within the main groups	Serious
ID 22	Stein,2015 (Stein et al., 2015a)	overall survival was solely measured by KM method	the authors only reported the crude survival analysis	Exploratory post-hoc subgroup analyses were performed to evaluate the effects of different induction and de-escalating maintenance regimens on OS	Serious
ID 23	Buchler, 2014 (Buchler et al., 2014)	overall survival was solely measured by KM method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 24	Cheng, 2015 (Cheng and Song, 2015)	Survival curves were plotted by using the Kaplan-Meier method and compared by using the log-rank test	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate

Basic information		Bias in selection of the reported result			
Study ID	**Author Year**	**7.1**	**7.2**	**7.3**	**RoB judgement**
ID 25	Yang, 2014 (Yang et al., 2014)	The Kaplan–Meier method and log-rank test were used to analyze survival	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 26	Houts, 2019 (Houts et al., 2019a)	Unadjusted OS was calculated using Kaplan–Meier with a log rank test.	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 27	Bai, 2016 (Bai et al., 2016)	Survival curves were plotted by using the Kaplan-Meier method and compared by using the log-rank test	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate
ID 28	Zhou, 2021 (Zhou et al., 2021)	Survival curves were plotted by using the Kaplan-Meier method and compared by using the log-rank test	the authors reported only the results for the full cohort	the study evaluated Survival times according to combined chemotherapy regimens.	Serious
ID 29	Degirmencioglu , 2019 (Degirmencioglu S, 2019)	while PFS and OS were evaluated with Kaplan-Meier method	the authors reported only the results for the full cohort	no subgroup analysis was undertaken	Moderate

Appendix IV.

The permission from the Caldicott Guardian to access the linked datasets.

Application for Caldicott Guardian Approval

NHS
Greater Glasgow and Clyde

NOTE: You must address the 6 Caldicott principles (Appendix A) when submitting this application.

1. Study / Project Title

Cancer Medicines Outcomes Programme – Colorectal cancer
CMOP is a collaborative project between NHS GGC and University of Strathclyde – funded by Scottish Government.

2. Please tick the type of study/project you are undertaking

Audit ☐ Research ☐ Service Improvement ☐ Other ☒
If other, please provide further details:
The Cancer Medicines Outcomes Programme is a collaborative project between NHS Greater Glasgow and Clyde and Strathclyde University. The vision for the project is to create a national clinical effectiveness oncology resource to measure the clinical and patient reported outcomes of cancer medicines used in the real world and provide rapid feedback of findings to inform clinical decision making.
In year two, the aim is to test the connectivity and linkage of current and evolving local and national electronic datasets to determine clinical outcome data for two specified groups of cancer patients; gynaecological cancer (group 1) and colorectal cancer (group 2). This application is for group 2, an application has already been submitted for group 1.

3. Who is providing clinical support for the study / project

Name: Janet Graham
Designation: Consultant Medical Oncologist
Email Address or Telephone Number: janet.graham@ggc.scot.nhs.uk

Name: Jennifer Laskey
Designation: Lead Clinical Effectiveness Pharmacist
Email Address or Telephone Number: Jennifer.laskey@ggc.scot.nhs.uk

4. Details of individual / organisation requesting data

Name: Julie Clarke
Designation: Clinical Effectiveness Pharmacist
Work/University Address: JB Russell House

Contact Number: 0141 201 4795

5. Purpose for which data are to be used (Principle 1)

- To quantify uptake of treatments colorectal cancer for patients within NHS GGC

1

- To compare response of treatments to the pivotal trials (via both individual patient level data retrieval and use of linkage to current local electronic datasets)
- To compare and contrast the quality and quantity of data obtained from individual patient level data retrieval and use of linkage of current local electronic datasets

An application has been submitted to the local NHS GGC Safe Haven for access to electronic data sets (data linkage arm of study). This application is for the individual patient level data retrieval aspect of the study.
A Public Benefit Privacy Panel application will be made to access records for patients residing outwith NHS GGC

6. Which identifiable data items are required? Please detail why these are required. (Principles 2 and 3)

PID Required	√	Justification
CHI Number	x	To identify eligible patients
Forename		
Surname		
DOB	x	To identify age at diagnosis, on initiation of treatment and at death (if applicable)
Age		
Gender	X	To identify gender
Address		
Post code (full)	x	To identify SIMD score
Post code (partial)		
Clinical data	x	To evaluate treatment outcomes
Other (please specify)		

7. Who will have access to this information? (Principle 4)

Internal: Julie Clarke, Kelly Baillie, Christine Crearie, Jennifer Laskey

External: Limited staff within Strathclyde University will have access to anonymised data

8. Storage and use of personal data during the audit/project (Principle 5)

Will you be undertaking any of the following activities at any stage (including the

identification of potential participants)? Please tick as appropriate.

- ☒ Access to Health Record (paper)
- ☒ Access to Health Record (electronic)
- ☐ Sharing of identifiable data with other organisations (provide further detail below)
- ☒ Publication of data (if this could identify individuals provide further detail below)
- ☐ Use of audio/visual recording devices
- ☒ Storage of personal identifiable data on any of the following:
  - ☐ Manual files, including x-rays
  - ☒ NHS Computers
  - ☐ Home or other personal computers
  - ☐ University computer
  - ☐ Private company computer
  - ☒ Laptop computer (or any other mobile device) NHS Laptop
  - ☐ USB Flash Drive

Additional Information:

Data shared with colleagues from University of Strathclyde and any data published will be robustly anonymised.

9. Destruction of Data

How long will the data be held?
Until project is completed and results have been published. Any data held thereafter will have patient identifiers removed

How will the data be destroyed?
Files containing patient identifiable information will be deleted

10. Please provide your organisation's Data Protection Registration Number (if external to NHSGGC)

Note:

- Copies of any other relevant supporting documentation (e.g. ethics approval, patient information leaflet etc.) should be attached to this application
- Appendix A details the Caldicott Principles

Person responsible for the requested data

Name Julie Clarke

Designation Clinical Effectiveness Pharmacist

Signature: ..... Date: 22/3/18

The release of data as described above is: **approved** / ~~**not approved**~~

Caldicott Guardian ..... **Date** 30/04/18

4

Accredited certificate for the course in information governance to access the linked data

This is to certify that:

Haya Yasin

Passed

Research, GDPR and confidentiality Quiz

Date / Time	Student Score	Passing Score	Result
May 29, 2019 10:17 am	77.77	70	Pass

(Click here to print this page)

Appendix V.

Baseline characteristics table generated after applying the last observation carried forward and multiple imputations for the missing values.

Variable	categories	Full cohort (N=220)	5FU/leucoverine (n=49)	FOFLOX (n= 68)	FOLFIRI (n=47)	Aflibercept+ FOLFIRI (n=11)	Cetuximab+ FOLFIRI (n=43)
Gender	Male	115(52.3)	21(42.9)	32(47.1)	25(53.2)	6(54.5)	31(72.1)
	Female	105(47.7)	28(57.1)	36(52.9)	22(46.8)	5(45.5)	12(27.9)
Age group	*≥ 65*	118(53.6)	43(87.8)	36(52.9)	22(46.8)	*(*)	13(30.2)
	< 65	102(46.4)	6(12.2)	32(47.1)	25(53.2)	8(72.7)	30(69.8)
SIMD_2012	1	69(31.4)	13(26.5)	25(36.8)	13(27.7)	*(*)	14(32.6)
	2	43(19.5)	15(30.6)	8(11.8)	11(23.4)	*(*)	8(18.6)
	3	25(11.4)	7(14.3)	5(7.4)	9(19.1)	*(*)	*(*)
	4	38(17.3)	6(12.2)	10(14.7)	7(14.9)	*(*)	11(25.6)
	5	45(20.5)	8(16.3)	20(29.4)	7(14.9)	*(*)	6(14)
Charlson comorbidity index	0	162(73.6)	33(67.3)	52(76.5)	34(72.3)	10(90.9)	31(72.1)
	1	50(22.7)	12(24.5)	13(19.1)	13(27.7)	*(*)	11(25.6)
	2	8(3.6)	*(*)	*(*)	*(*)	*(*)	*(*)
Tumour sidedness	Left	135(61.4)	26(53.1)	42(61.8)	28(59.6)	*()	34(79.1)
	Right	74(33.6)	19(38.8)	23(33.8)	17(36.2)	6(54.5)	8(18.6)
	Transverse	11(5)	*(*)	*(*)	*(*)	*(*)	*(*)
Type of mutation	Mutant RAS	106(48.2)	24(49)	46(67.6)	27(57.4)	8(72.7)	*(*)
	Wild RAS	92(41.8)	16(32.7)	18(26.5)	12(25.5)	*(*)	42(97.7)
	Mutant BRAF	22(10)	9(18.4)	*(*)	8(17)	*(*)	*(*)
Performance status	0	63(28.6)	8(16.3)	19(27.9)	15(31.9)	*(*)	16(37.2)
	1	142(64.5)	36(73.5)	42(61.8)	31(66)	8(72.7)	25(58.1)
	≥ 2	15(6.8)	5(10.2)	7(10.3)	*(*)	*(*)	*(*)
albumin	*< 34*	119(54.1)	37(75.5)	40(58.8)	18(38.3)	*(*)	19(44.2)
	≥ 34	101(45.9)	12(24.5)	28(41.2)	29(61.7)	7(63.6)	24(55.8)

NLR	*≤ 5*	158(71.8)	35(71.4)	50(73.5)	31(66)	11(100)	31(72.1)
	>5	62(28.2)	14(28.6)	18(26.5)	16(34)	*(*)	12(27.9)
CEA	*≤ 5*	47(21.4)	7(14.3)	12(17.6)	11(23.4)	7(63.6)	13(30.2)
	> 5	173(78.6)	42(85.7)	56(82.4)	36(76.6)	8(72.7)	30(69.8)
haemoglobin	0	108(49.1)	21(42.9)	28(41.2)	27(57.4)	*(*)	23(53.5)
	1	112(50.9)	28(57.1)	40(58.8)	20(42.6)	*(*)	20(46.5)
Primary tumour resection	No	161(73.2)	35(71.4)	59(86.8)	28(59.6)	7(63.6)	33(76.7)
	Yes	59(26.8)	14(28.6)	9(13.2)	19(40.4)	*(*)	10(23.3)

Appendix VI.

R code sample used for the meta-analysis and fieldwork analysis

Meta-analysis script

R-code used to process the extracted data points from reconstructed Kaplan-Meier curves and to estimate the Hazard ratio and its corresponding standard error.

```
library(dplyr)
library(ggplot2)
library(gridExtra)
library(readbitmap)
library(IPDfromKM)

###FOLFIRI
S352_FOLFIRI <- read.csv("C:/Users/mhb19110/Desktop/MA- KM curves/MA- KM
curves/PFS/OS 352/S352_FOLFIRI.csv", header=FALSE)

####preprocess raw coordinates to reconstruct IPD
pre_S352_FOLFIRI <- preprocess(dat=S352_FOLFIRI, totalpts=785,maxy=100)
#reconstruct the IPD
est_S352_FOLFIRI <- getIPD(prep=pre_S352_FOLFIRI,armID=0,tot.events=NULL)
head(est_S352_FOLFIRI$IPD)
plot(est_S352_FOLFIRI)
####graph KM curves and cumulative HR
sur <- survreport(ipd1  = est_S352_FOLFIRI$IPD, arms = 1, interval =
10,s=c(0.75,0.5,0.25),showplots=FALSE)
print(sur)
###FOLFOX
S352_FOLFOX <- read.csv("C:/Users/mhb19110/Desktop/MA- KM curves/MA- KM
curves/PFS/OS 352/S352_FOLFOX.csv", header=FALSE)
pre_S352_FOLFOX <- preprocess(dat=S352_FOLFOX, totalpts=3000,maxy=100)
est_S352_FOLFOX <- getIPD(prep=pre_S352_FOLFOX,armID=1,tot.events=NULL)
head(est_S352_FOLFOX$IPD)
plot(est_S352_FOLFOX)
sur1 <- survreport(ipd1  = est_S352_FOLFOX$IPD, arms = 1, interval =
6,s=c(0.75,0.5,0.25),showplots=FALSE)
print(sur1)
survreport(ipd1 = est_S352_FOLFIRI$IPD , ipd2 = est_S352_FOLFOX$IPD, arms = 2,
interval=6,s=c(0.75,0.5,0.25),showplots=TRUE)
### perform the MA for first-line

library(metafor)
library(forestplot)
library(ggplot2)
OS <- read.csv("C:/Users/mhb19110/Desktop/Meta analysis/OS/OS analysis sheet.csv")
```

```
full.model <- rma(Ln.HR.,Vi.HR., data = OS)
summary(full.model)
predict(full.model, transf = exp)
## conducting MA
BevaCT <- read.csv("C:/Users/mhb19110/Desktop/Meta analysis/OS/BevaCT.csv")
full.model <- rma(LnHR, ViHR, data = BevaCT)
summary(full.model)
predict(full.model,transf = exp)

#### Forest plot for OS of first line
full.first <-  read.csv("C:/Users/mhb19110/Desktop/Meta analysis/OS/full-first.csv")
full.first$study_type <- as.factor(full.first$study_type)
OS.model <- rma(Ln.HR., Vi.HR., data = full.first)
summary(OS.model)
predict(OS.model,transf = exp)
res.1 <- rma(Ln.HR., Vi.HR., data = full.first, subset = (study_type == "1"))  ## pooled
estimated for beva group
res.2 <- rma(Ln.HR., Vi.HR., data = full.first, subset = (study_type == "2")) ## pooled estimate
for cetux subgroup
res.3 <- rma(Ln.HR., Vi.HR., data = full.first, subset = (study_type == "3")) ## pooled estimate
for cetux subgroup
res.4 <- rma(Ln.HR., Vi.HR., data = full.first, subset = (study_type == "4")) ## pooled estimate
for cetux subgroup
measure <- rma(Ln.HR., Vi.HR., data = full.first, mods = ~ X.M.E.-1)
summary(measure)
predict(measure,transf = exp)
stype <- rma(Ln.HR., Vi.HR., data = full.first, mods = ~ study_type-1)
summary(stype)
predict(stype,transf = exp)
forest(OS.model, annotate = TRUE, addfit = TRUE, slab = paste(full.first$Author,
full.first$year, sep = ","), atransf = exp,
       xlim = c(-4,4), cex = 0.9, ylim = c(-2, 46), efac = 0.4, yaxs = "i", order =
order(full.first$study_type) ,
       showweights = TRUE, rows = c(42:37,33:27,23:11, 7:2))
text(-4,45,"Author,Year",pos = 4)  ##title of left coloumns
text(4,45, "Weight, HR [95% CI]", pos=2)  ## title of right coloumn
res.OS <- rma(Ln.HR., Vi.HR., data = full.first, mods = ~ study_type-1) # moderator analysis
according to subgroup
text(-4, -1.8, pos=4, cex=0.8, bquote(paste("Test for Subgroup Differences: ",
                              Q[M], " = ", .(formatC(res.OS$QM, digits=2, format="f")), ", df = ",
.(res.OS$p - 1),
                              ", p = ", .(formatC(res.OS$QMp, digits=2, format="f")))))   ## add
results of moderator analysis to FP
op <- par(cex=0.9, font=4)  ## to make title bold
text(-4, c(43,34,24, 8), pos=4, c("CT vs CT","Bevacizumab+CT vs CT", "Bevacizumab+CT Vs
Bevacizumab+CT" , "Cetuximab+CT Vs Bevacizumab+CT" )) # assign subtitles to subgroups
```

```
addpoly(res.1, row=1, col = "Red", cex=1, atransf=exp, mlab="")  # assign and calculate
pooled estimate for each subgroup
addpoly(res.2, row=10, col = "Red", cex=1, atransf=exp, mlab="")
addpoly(res.3, row=26, col = "Red", cex=1, atransf=exp, mlab="")
addpoly(res.4, row=36, col = "Red", cex=1, atransf=exp, mlab="")

text(-4, 1, pos=4, cex=0.75, bquote(paste("RE Model for Subgroup (Q =
",.(formatC(res.4$QE, digits=2, format="f")),
                                ", df = ", .(res.4$k - res.4$p),", p = ",
                                .(formatC(res.4$QEp, digits=2, format="f")), "; ", I^2, " = "
                                ,.(formatC(res.4$I2, digits=1, format="f")), "%")")))

text(-4, 10, pos=4, cex=0.75, bquote(paste("RE Model for Subgroup (Q =
",.(formatC(res.3$QE, digits=2, format="f")),
                                 ", df = ", .(res.3$k - res.3$p),", p = ",
                                 .(formatC(res.3$QEp, digits=2, format="f")), "; ", I^2, " = "
                                 ,.(formatC(res.3$I2, digits=1, format="f")), "%")")))
text(-4, 26, pos=4, cex=0.75, bquote(paste("RE Model for Subgroup (Q =
",.(formatC(res.2$QE, digits=2, format="f")),
                                 ", df = ", .(res.2$k - res.2$p),", p = ",
                                 .(formatC(res.2$QEp, digits=2, format="f")), "; ", I^2, " = "
                                 ,.(formatC(res.2$I2, digits=1, format="f")), "%")")))
text(-4, 36, pos=4, cex=0.75, bquote(paste("RE Model for Subgroup (Q =
",.(formatC(res.1$QE, digits=2, format="f")),
                                 ", df = ", .(res.1$k - res.1$p),", p = ",
                                 .(formatC(res.1$QEp, digits=2, format="f")), "; ", I^2, " = "
                                 ,.(formatC(res.1$I2, digits=1, format="f")), "%")")))

OSmodel.measure <- rma(Ln.HR., Vi.HR., data = full.first, mods = ~ X.M.E.-1)
summary(OSmodel.measure)
funnel(OS.model, level = c(90,95,99), shade = c("white", "grey55", "grey75"), refline = 0,
     xlab = "log(HR)", yaxis ="vinv")
regtest(OS.model)
# no possibility for publication bias
full.first$upperci <- full.first$Ln.HR.+1.96*sqrt(full.first$Vi.HR.)
full.first$lowerci <- full.first$Ln.HR.-1.96*sqrt(full.first$Vi.HR.)
full.first$outlier <-  full.first$upperci < OS.model$ci.lb | full.first$lowerci > OS.model$ci.ub
full.first[full.first$outlier, c("Ln.HR.", "upperci", "lowerci")]

## Fixed effect-test
full.model.2 <- rma(LnHR, ViHR, data = BevaCT, method ="FE")
summary(full.model.2)
## forest plot
forest(full.model, annotate = TRUE, addfit = TRUE, slab = paste(BevaCT$Author,
BevaCT$year, sep = ","), atransf = exp,
     xlim = c(-4,6), cex = 0.9, ylim = c(-2, 9.5), efac = 0.4, yaxs = "i", order =
order(BevaCT$year) , showweights = TRUE )
```

```
text(-4,8,"Author,Year",pos = 4)
text(6,8, "Weight, HR [95% CI]", pos=2)

## moderator analysis according to the trype of ES measurement
model.mod.measure <- rma(LnHR, ViHR, data = BevaCT, mods = ~ M.E-1)
summary(model.mod.measure)

## assess the pooled estimate according to type of measurment
res.m <- rma(LnHR, ViHR, data = BevaCT, subset = (M.E == "M"))
predict(res.m, transf = exp)

res.e <- rma(LnHR, ViHR, data = BevaCT, subset = (M.E == "E"))
predict(res.e, transf = exp)

## funnel plot for overall estimate
funnel(full.model, level = c(90,95,99), shade = c("white", "grey55", "grey75"), refline = 0,
     xlab = "log(HR)", yaxis ="vinv")
# to test for publication bias, we can either do that by visually inspecting the funnel plot or
by undertakin eagers test
regtest(full.model)

# checking for outliers
OS$upperci <- OS$Ln.HR.+1.96*sqrt(OS$Vi.HR.)
OS$lowerci <- OS$Ln.HR.-1.96*sqrt(OS$Vi.HR.)
OS$outlier <-  OS$upperci < full.model$ci.lb | OS$lowerci > full.model$ci.ub
OS[OS$outlier, c("Ln.HR.", "upperci", "lowerci")]

# plotting outliers
ggplot(data = OS, aes(x = Ln.HR., colour = outlier, fill = outlier))+
geom_histogram(alpha = .2) +
geom_vline(xintercept = full.model$b[1]) +
theme_bw()

## cooks distance to measure influential cases in the MA model
x <- cooks.distance(full.model)
plot(x, type = "o", pch = 19, ylab = "cooks distance")

##########################################

BC <- read.csv("C:/Users/mhb19110/Desktop/Meta analysis/OS/BC.csv")
BC$year <-  as.numeric(BC$year)
BC$study_type <- as.factor(BC$study_type)
full <- rma(Ln.HR., Vi.HR., data = BC)
predict(full, transf = exp)
## subgroup analysis according to regimen
mod.regimen <- rma(Ln.HR., Vi.HR., data = BC, mods = ~ study_type-1)
mod.regimen
```

```
res.B <- rma(Ln.HR., Vi.HR., data = BC, subset = (study_type == "1"))  ## pooled estimated
for beva group
res.c <- rma(Ln.HR., Vi.HR., data = BC, subset = (study_type == "2")) ## pooled estimate for
cetux subgroup
```

```
library(reshape2)
library(dplyr)
library(lubridate)
library(survival)

# 1. demographics

cohort_colo <- read.csv("Cohort_Colorectal.csv", stringsAsFactors=FALSE)
names(cohort_colo)[names(cohort_colo) == "SafeHavenID"] <- "ID"

## 2-mCRC demographics
demo_colo <- read.csv(" 01_Demographics_Colorectal.csv", stringsAsFactors=FALSE)
demo <- subset(demo_colo, select=c(SafeHavenID, OBF_DOB, SEX, PCSECTOR,
SIMD_2012_QUINTILE, MARITAL_STATUS_DESC))
demo$OBF_DOB <- as.Date(demo$OBF_DOB, format = "%Y-%m-%d")
demo$SEX <- as.factor(demo$SEX)
names(demo)[1:6] <- c("ID", "DOB", "sex", "postcode", "simd5_2012", "marital_status")

### death records from NRS
death_colo <- read.csv(" 02_Deaths_Colorectal.csv", stringsAsFactors=FALSE)
death <- subset(death_colo, select=c(SafeHavenID, DOD, COD, COD0, COD1, COD2, COD3,
COD4, COD5, COD6, COD7, COD8))
death$DOD <- as.Date(death$DOD, format = "%Y-%m-%d")
is.na(death[3:12]) <- death[3:12] == ""

names(death)[1:12] <- c("ID", "date_death", "cause_death", "other.COD1", "other.COD2",
"other.COD3", "other.COD4", "other.COD5", "other.COD6", "other.COD7", "other.COD8",
"other.COD9")

# 2. cancer registry
SMR6_colo <- read.csv(" 13_SMR06_Colorectal_WOS_GGC.csv", stringsAsFactors=FALSE)
SMR6 <- subset(SMR6_colo, select=c(SafeHavenID, INCIDENCE_DATE,
ICD10S_CANCER_SITE, ICD10S_CANCER_SITE_DESC, ICDO2_ICDO2, ICDO2_ICDO2_DESC,
                        GRADE_CELL_TYPE, STAGE_CLINICAL_T, STAGE_CLINICAL_N,
STAGE_CLINICAL_M, STAGE_PATHOLOGIC_T, STAGE_PATHOLOGIC_N,
                        STAGE_PATHOLOGIC_M, STAGE_COLORECTAL_DESC, SURGERY,
DATE_1ST_SURGERY, REF_TO_RAD, TREATED_WITH_RAD, DATE_1ST_RAD,
                        CHEMO, DATE_1ST_CHEMO, OTHER_THERAPY, TYPE_OTHER_THERAPY,
THERAPY_OBJECTIVES_DESC))
SMR6 <- as.data.frame(SMR6 %>%
                mutate_at(vars(STAGE_CLINICAL_T, STAGE_CLINICAL_N, STAGE_CLINICAL_M,
STAGE_PATHOLOGIC_T, STAGE_PATHOLOGIC_N,
                          STAGE_PATHOLOGIC_M, STAGE_COLORECTAL_DESC,
TYPE_OTHER_THERAPY, THERAPY_OBJECTIVES_DESC), list(as.factor)))
SMR6 <- as.data.frame(SMR6 %>%
                mutate_at(vars(INCIDENCE_DATE, DATE_1ST_SURGERY, DATE_1ST_RAD,
DATE_1ST_CHEMO), list(ymd)))
```

```
is.na(SMR6[8:14]) <- SMR6[8:14] == ""
is.na(SMR6[23]) <- SMR6[23] == ""
SMR6$TYPE_OTHER_THERAPY[SMR6$TYPE_OTHER_THERAPY %in% c("Stent", "stent insert",
"STENT INSERT", "Stent insertion")] <- "stent"
SMR6$TYPE_OTHER_THERAPY[SMR6$TYPE_OTHER_THERAPY %in% c("enteric stent
insertion", "Enteric stent insertion", "Enteric stent insertion ")] <- "Enteric stent"
SMR6 = droplevels(SMR6)

names(SMR6)[1:24] <- c("ID", "date_inc", "ICD10", "ICD10_desc", "ICDO2", "ICDO2_desc",
"grade_cell", "clin_T", "clin_N", "clin_M", "path_T", "path_N", "path_M", "stage_colo",
                "surgery", "date_surgery", "radio_ref", "radio_treated", "date_radio",
"chemo", "date_chemo", "other", "type_other", "intent")

levels(SMR6$stage_colo) = c("distant mets", "not known", "regional positive, apical
negative", "regional positive, apical positive", "tumour invasive, regional negative", "tumour
limited, regional negative")
levels(SMR6$intent) = c("curative", "palliative", "not known")


SMR6 <- as.data.frame(SMR6 %>%
                mutate(primary_site = case_when(ICDO2_desc == "Appendix" ~ "appendix",
                                        ICDO2_desc %in% c("Cecum", "Ascending colon", "Colon,
NOS", "Descending colon", "Hepatic flexure of colon", "Overlapping lesion of colon",
                                                "Sigmoid colon", "Splenic flexure of colon",
"Transverse colon") ~ "colon",
                                        ICDO2_desc %in% c("Anal canal", "Overlapping lesion of
rectum, anus and anal canal", "Rectosigmoid junction", "Rectum, NOS") ~ "rectum",
                                        ICDO2_desc %in% c("Gastrointestinal tract, NOS", "Ileum",
"Intestinal tract, NOS", "Liver", "Small intestine, NOS", "Stomach, NOS") ~ "other GI",
                                        ICDO2_desc == "Unknown primary site" ~ "unknown",
                                        TRUE ~ "other")))

SMR6 <- as.data.frame(SMR6 %>%
                mutate(side = case_when(ICD10 %in% c("C185", "C186", "C187", "C19X",
"C20X", "C211", "C218", "C785") ~ "left",
                                ICD10 %in% c("C180", "C181", "C182", "C183", "D373") ~ "right",
                                ICD10 == "C184" ~ "transverse",
                                ICD10 %in% c("C188", "C189", "D010") ~ "unspecified",
                                ICDO2_desc == "Unknown primary site" ~ "unknown",
                                TRUE ~ "not relevant")))

SMR6_include <- as.data.frame(SMR6 %>% filter(primary_site %in% c("colon", "rectum",
"unknown")))
SMR6_exclude <- as.data.frame(SMR6 %>% filter(primary_site %in% c("appendix", "other",
"other GI")))
SMR6 <- SMR6[!duplicated(SMR6),]
```

```
SMR6_base <- subset(SMR6, SMR6$primary_site %in% c("colon", "rectum", "unknown"),
select =c("ID", "date_inc" , "ICD10", "ICD10_desc", "side", "primary_site"))
SMR6_base <- SMR6_base[!duplicated(SMR6_base$ID),]

SMR6_other.ID <- setdiff(cohort_colo$ID, SMR6_base$ID)
SMR6_other <- subset(SMR6, ID %in% SMR6_other.ID, select=c("ID", "date_inc", "ICD10",
"ICDO2_desc", "primary_site", "side", "clin_T", "clin_N", "clin_M", "path_T", "path_N",
"path_M", "stage_colo","chemo", "date_chemo", "surgery", "date_surgery",
"radio_treated","date_radio"))
SMR6_other <- SMR6_other[order(SMR6_other$ID, SMR6_other$date_inc),]
SMR6_other <- subset(SMR6_other, SMR6_other$primary_site != "other")

SMR6_base.all <- rbind(SMR6_base, SMR6_other)

# SMR6_OP <- subset(SMR6, select=c(ID, surgery, date_surgery, ICD10,ICDO2, ICDO2_desc))


###################### BASELINE DATAFRAME
########################################



# 8. baseline dataframe
cohortID <- unique(chemo_base$ID)
demo_sub <- subset(demo, ID %in% cohortID)
baseline <- merge(demo_sub, chemo_base, c("ID"), all=TRUE)
baseline$cycles.numbers <- ifelse(baseline$cycles < 5,1, ifelse(baseline$cycles >=5 &
baseline$cycles <10,2, ifelse(baseline$cycles >=10 & baseline$cycles <15,3, ifelse
(baseline$cycles >=15 & baseline$cycles <20,4, ifelse(baseline$cycles >=20,5,NA)))))
baseline <- as.data.frame(baseline %>%
                  mutate(REG3 = case_when(treat == "AFLIB" ~ "AFLIB",
                                          treat %in% c("RALTITREXED", "CAP5FU MONO")  ~ "CAP5FU
MONO",
                                          treat %in% c("CET FOLFOX", "CET FOLFIRI") ~ "CET FOLFIRI",
                                          treat == "CETUX" ~ "CETUX",
                                          treat %in% c ("FOLFIRI", "IRINOTECAN") ~ "FOLFIRI",
                                          treat == "XFOX" ~ "XFOX",
                                          treat == "FOLFOXIRI" ~ "FOLFOXIRI")))
                                                 treat %in% c("AFLIB", "CET FOLFIRI", "CET FOLFOX",
"FOLFOXIRI") ~ "triplet")))


surgery_sub <- subset(surgery.all.new, ID %in% cohortID, select=c(ID, date_OP.OPERA,
OPCS4.OPERA,  site.OPERA, site.OPERA, date_OP.SMR1, OPCS4.SMR1, site.SMR1))
baseline <- merge(baseline, surgery_sub, c("ID"), all=TRUE)
```

```
baseline$surgery <- ifelse(baseline$site.OPERA %in% c("abdomen", "colon", "hemicolon",
"liver", "other", "rectum","sigmoid colon") | baseline$site.SMR1 %in% c("abdomen",
"colon", "hemicolon", "liver", "other", "rectum","sigmoid colon"),1,0)

SMR6_base_sub <- subset(SMR6_base, ID %in% cohortID)
## delete the first observation for patient 549 (duplicated, second record relevant to CC and
OPERA)
SMR6_base_sub <- SMR6_base_sub[-c(260),]
SMR6_base_sub <- SMR6_base_sub[!duplicated(SMR6_base_sub$ID),]
### primary site from OPERA or death records for 400,466 and 641. for 433 and 665 primary
site from SMR1 - C19

baseline <- merge(baseline, SMR6_base_sub, c("ID"), all=TRUE)
baseline <- merge(baseline, ECOG.PS, c("ID"), all=TRUE)
dod_sub <- subset(death, ID %in% cohortID, select=c(ID, date_death))
baseline <- merge(baseline, dod_sub, c("ID"), all=TRUE)

lab_sub <- subset(lab, ID %in% cohortID)
baseline <- merge(baseline, lab_sub, c("ID"), all=TRUE)
baseline <- as.data.frame(baseline %>%
baseline$NLR <- ifelse(baseline$value_neu / baseline$value_lym < 5, 0, 1)
baseline$CEA <- ifelse(baseline$value_CEA <= 4.9 , 0 ,1 )
baseline$hemoglobin <- ifelse(baseline$sex == "F" & baseline$value_Haemoglobin > 115 &
baseline$value_Haemoglobin <= 165 , 0, ifelse(baseline$sex == "M" &
baseline$value_Haemoglobin > 130 & baseline$value_Haemoglobin <= 180, 0,1))

baseline <- as.data.frame(baseline %>%
                  mutate(mutation_type = case_when(mutation_type == "mutant BRAF" ~
"mutant BRAF",
                                                   mutation_type== "mutant RAS" ~ "mutant RAS",
                                                   mutation_type == "wild RAS" ~ "wild RAS",
                                                   mutation_type == "failed analysis" ~ "")))
baseline$mutation_type [baseline$mutation_type == ""] <- NA

baseline <- as.data.frame(baseline %>%
                  mutate(PS2 = case_when(PS2 == "0" ~ "0",
                                         PS2== "1" ~ "1",
                                         PS2 %in% c("2", "3")  ~ "2+")))
prevalent <- unique(prior2015$ID)
baseline.prevelant  <- subset(baseline, ID %in% baseline.prevelant)
baseline.incident <- subset(baseline, !ID %in% baseline.incident)
baseline.incident$cond <- "incident"
baseline.prevelant$cond <- "prevelant"
cond <- c("cond")
baseline[cond] <- lapply(cond, function (x) baseline.prevelant[[x]][match(baseline$ID,
baseline.prevelant$ID)])
baseline$cond[is.na(baseline$cond)] <- "incident"
```

Multinomial logstic regression analysis (chapter 5)

```
library(nnet)
library(mlogit)
library(withr)
library(mice)

t est<- subset(reg_new,  select =
                 c("treat",  "REG3",  "sex", "age", "simd5_2012", "charlson2",
                   "PS2", "mutation_type", "primary_site.y", "surg"))
reg_new$REG3 <- as.factor(reg_new$REG3)
reg_new$sex <- as.factor(reg_new$sex)
uni_age <- multinom(REG3 ~ age, data= reg_new, model = TRUE)
summary(uni_age)
exp(coef(uni_age))
# imputation
imp_method = make.method(reg1)
predM = make.predictorMatrix(reg1)
predM[, "ID"] <- 0
 imp_method[c("PS2")]<- "polyreg"
 imp_method[c("mutation_type")] <- "polyreg"
 imp_method[c("simd5_2012")] <- "polyreg"
imp_method[c("charlson2")] <- "polyreg"
 imp_method[c("primary_site.y")]  <- "pol"
 imp_method[c("REG3")] <- ""
 imp_method[c("age")] <- ""
imp_method[c("sex")] <- ""
imp_method[c("surg")]   <- ""
 imp_method[c("cond")]   <- ""

imputed <- mice(reg1, method = imp_method, predictorMatrix = predM, m = 5, print =
FALSE)
imp_sing2 <- complete(reg_single2)
imp_sing2$REG3 <- relevel(imp_sing2$REG3, ref = "XFOX")
imp_sing2$sex <- relevel(imp_sing2$sex, ref = "M")
imp_sing2$mutation_type <- relevel(imp_sing2$mutation_type, ref = "wild RAS")
imp_sing2$charlson2 <- as.factor(imp_sing2$charlson2)
imp_sing2$simd5_2012 <- as.factor(imp_sing2$simd5_2012)

imp_back<- multinom(REG3 ~.  - simd5_2012 - charlson2 - PS2, data= imp_sing2, model =
TRUE)
summary(imp_back)
exp(coef(imp_back))
exp(confint(imp_back))
```

```
z_multiple_imputed <-
summary(imp_back)$coefficients/summary(imp_back)$standard.errors
p_back <- (1- pnorm(abs(z_multiple_imputed),0,1))*2
p_back

imp_back_age <- multinom(REG3 ~. -age , data= imp_sing2, model = TRUE)
anova(imp_back, imp_back_age)

imp_multiple <- mice(reg1, m=5, method = "polyreg", maxit = 20)
data_multiple <- complete(imp_multiple, "repeated", include = TRUE)
data_multiple1 <- data.frame(data_multiple[, 1:6], data[, 2:5])

reg_simd <- subset(reg, simd5_2012 %in% c("1", "2", "3", "4", "5"))
reg_mutation <- subset(reg_simd, mutation_type %in% c("wild RAS", "mutant BRAF",
"mutant RAS"))
reg_PS
reduced_model <- subset(reg, select = c("ID",  "REG3", "sex", "age", "mutation_type",
"surg", "cond"))
reg$REG1 <- as.factor(reg$REG1)
reg$sex <- as.character(reg$sex)
reg[is.na(reg$sex),"sex"] <- "unknown"
reg$sex <- as.factor(reg$sex)
table(reg$simd5_2012,exclude = NULL)
reg$simd5_2012 <- as.character(reg$simd5_2012)
reg[is.na(reg$simd5_2012),"simd5_2012"] <- "unknown"
reg$simd5_2012 <- as.factor(reg$simd5_2012)

back_sex_multi <- multinom(REG3 ~ age+ simd5_2012+charlson2+PS2+surg+
mutation_type + primary_site.y , data= reg, model = TRUE)
summary(back_sex_multi)
z_back_sex <-
summary(back_sex_multi)$coefficients/summary(back_sex_multi)$standard.errors
p_back_sex <- (1- pnorm(abs(z_back_sex),0,1))*2
p_back_sex
anova(back_multi, back_sex_multi)

##IIA test
mydata <- mlogit.data(reg,  choice = "REG3", shape = "wide")
mlogit.model <- mlogit(REG3 ~1, data = mydata, reflevel = "XFOX")
m1 <- mlogit(REG3~1, data = mydata, reflevel = "XFOX")
m2 <- mlogit(REG3~1, data = mydata, reflevel = "XFOX", alt.subset = c("XFOX","AFLIB", "CET
FOLFIRI", "FOLFIRI"))
hmftest(m1,m2)
table(reg$re)
```

```
## reduced model
red_mo <- multinom(REG3 ~1  , data= reduced_model, model = TRUE)
summary(red_mo)
exp(coef(red_mo))
z_red <- summary(red_mo)$coefficients/summary(red_mo)$standard.errors
z_red
p_red <- (1- pnorm(abs(z_red),0,1))*2
p_red

red_mo1 <- multinom(REG3 ~sex   , data= reduced_model, model = TRUE)
summary(red_mo1)
exp(coef(red_mo1))
z_red1 <- summary(red_mo1)$coefficients/summary(red_mo1)$standard.errors
z_red1
p_red1 <- (1- pnorm(abs(z_red1),0,1))*2
p_red1
anova(red_mo1, red_mo)
imp_model <- multinom(REG3 ~sex +age+  mutation_type +surg+  cond   , data= imp_sing,
model = TRUE)
summary(imp_model)
exp(coef(imp_model))
z_imp <- summary(imp_model)$coefficients/summary(imp_model)$standard.errors
z_imp
p_imp <- (1- pnorm(abs(z_imp),0,1))*2
p_imp

#collinearity_test
#assume the dependent variable as contineous - concert to dummy variable- run linear
logistic model then  variance inflation factor
impute3 <- as.data.frame(impute3 %>% mutate(REG4 =case_when(REG3 == "CAP5FU
MONO" ~ 1,
                                        REG3 == "XFOX" ~ 2,
                                        REG3 == "FOLFIRI" ~ 3,
                                        REG3 == "AFLIB" ~ 4 ,
                                        REG3 == "CET FOLFIRI" ~ 5)))
linear <- lm(REG4~ sex+ age+ surg+  mutation_type , data = impute3)
car::vif(linear)

reg2 <- as.data.frame(reg2 %>% mutate(REG4 =case_when(REG3 == "CAP5FU MONO" ~ 1,
                                        REG3 == "XFOX" ~ 2,
                                        REG3 == "FOLFIRI" ~ 3,
                                        REG3 == "AFLIB" ~ 4 ,
                                        REG3 == "CET FOLFIRI" ~ 5)))
full <- lm(REG4~  surg+  mutation_type*sex+ primary_site.y+cond + age* PS2, data = reg2)
car::vif(full)

listwise deletion
```

```
GVIF Df GVIF^(1/(2*Df))
sex          1.024345  1       1.012099
age          1.026870  1       1.013346
surg         1.066220  1       1.032579
mutation_type 1.090852  2       1.021978
original
GVIF Df GVIF^(1/(2*Df))
sex          1.033461  1       1.016593
age          1.062238  1       1.030649
surg         1.210202  1       1.100092
mutation_type  1.297364  3       1.044344
primary_site.y 1.046394  2       1.011402
```

```
####Sankey

library(dplyr)
library(networkD3)
Sankey_inc <-subset (CC2.rec_red2, ID %in% SACTID)  ### obtain the DF
S <- dcast(Sankey_inc, ID ~ number_regimen, value.var= "treat").  ### convert long format
to wide format
names(S) [2:4] <- c("t1", "t2", "t3"). ## change the names of the variables
S <- S[order(S$t1,S$t2,S$t3),]



S <- as.data.frame(S %>% group_by(t1,t2) %>% mutate(seq1=1:n())) ### grouping similar
pathways  for treatment 1 and treatment 2
S <- as.data.frame(S %>% group_by(t1,t2) %>% filter(seq1 == max(seq1))) ### grouping
similar pathways  for treatment 1 and treatment 2 and take the maximum number
S <- as.data.frame(S %>% group_by(t1,t2,t3) %>% mutate(seq2=1:n())) ### grouping similar
pathways  for treatment 1 and treatment 2  and 3 and take the maximum number



links <- data.frame(source = c(paste0(S$tt1,'_1'), paste0(S$tt2,'_2')), target=
c(paste0(S$tt2,'_2'), paste0(S$tt3,'_3')),
                value= c(paste0(S$seq1), paste0(S$seq2))).
### preparing a data frame for the connection – source is treatment 1 and target is
treatment 2

links$source <- as.character(links$source)
links$target <- as.character(links$target)
nodes <- data.frame(S = unique(c(links$source, links$target)))  ## creating a dataframe for
the things to be linked or connected (treatment 1 and treatment 2 ))
links$source <- match(links$source, nodes$S) - 1
```

```
links$target <- match(links$target, nodes$S) - 1
sankeyNetwork(Links = links, Nodes = nodes, Source = 'source', Target = 'target', Value =
'value', NodeID = 'S', fontSize = 12, nodeWidth = 20, sinksRight = FALSE)

saveWidget(p, file = "U:.html", selfcontained = FALSE)
```

```
################### survival script


library(survival)
library(ggplot2)
library(coxphf)
library(survminer)



base2 <- subset(baseline, select=c(ID, DOB, sex, treat, start, stop, date_death, simd5_2012,
age.group , age.group1,
                        REG1, REG2, REG3, surgery, primary_site, side, mutation_type,
other.cancer, years.since.diag, PS2, mGPS, NLR,
                        CEA, hemoglobin, SIS, charlson.x,charlson.2, NSAID_use, PPI_use,
statin_use, antiplatelets_use, antihyper_use
                        , treatment.number.new, charlson2))
baseline <- subset(baseline, !is.na(baseline$start))
baseline$date_death[is.na(baseline$date_death)] <- as.Date("2018-02-28")
baseline$date_death[baseline$date_death > "2018-02-28"] <- as.Date("2018-02-28")
baseline$time_death <- as.numeric(baseline$date_death - baseline$start)/30.4
baseline$event <- ifelse(baseline$date_death == "2018-02-28", 0, 1)
OS <- Surv(baseline$time_death, baseline$event)
summary(survfit(OS~1, baseline))

################
OS<-Surv(baseline$time_death, baseline$event)
summary(survfit(OS~1, baseline))
survfit(OS~1, baseline)
##follow up
summary(baseline$time_death)
##reverse KM for follow up
baseline$event2<-ifelse(baseline$event==0,1,0)
FU<-Surv(baseline$time_death, baseline$event2)
summary(survfit(FU~1, baseline))
```

```
F <- survfit(FU~1, baseline)
summary(FU)
plot(survfit(FU~1,data = baseline), mark.time = TRUE, main= "Overall Survival (n=68)", xlab =
"months", ylab = "proportion survived")
survfit(FU~1,baseline)

###################

summary(OS)
survfit(OS ~ 1, baseline)
survfit(OS ~ treat, baseline)
survfit(OS ~ REG1, baseline)
)
survfit(OS ~ cond, baseline)


v.cox <- coxph(OS~REG3, data = baseline)
summary(v.cox)
cox.zph(v.cox)


plot(survfit(OS~1,data = baseline), mark.time = TRUE, main= "Overall Survival (n=287)", xlab
= "months", ylab = "proportion survived")
survfit(OS~REG1, baseline)
abline(h=0.5,col="red",lty=2)

plot(survfit(OS~REG1,data = baseline), mark.time = TRUE, main= "Overall Survival (by intial
treatment) (n=287)", xlab = "time in months", ylab = "proportion survived", col = 1:3)
legend("topright", legend = unique(base2$REG1), lty = 1,col = 1:3, cex = 0.5)
abline(h=0.5,col="red",lty=2)
legend("topright",levels(baseline$REG1),lty=1,col = 1:7,cex=0.8)

plot(survfit(OS~REG3,data = baseline), mark.time = TRUE, main= "Overall Survival (by intial
treatment) (n=287)", xlab = "months", ylab = "proportion survived", col = 1:3)
legend("topright", legend = unique(baseline$REG3), lty = 1,col = 1:3, cex = 0.5)
abline(h=0.5,col="red",lty=2)

plot(survfit(OS~REG2,data = baseline), mark.time = TRUE, main= "Overall Survival (by intial
treatment) (n=297)", xlab = "months", ylab = "proportion survived", col = 1:3)
legend("topright", legend = unique(base2$REG3), lty = 1,col = 1:3, cex = 0.5)
abline(h=0.5,col="red",lty=2)

z.var <- c("sex", "simd5_2012", "age.group", "primary_site", "side","mutation_type", "PS2",
"mGPS", "NLR", "CEA", "hemoglobin",  "charlson2", "surgery")
for(i in 1:length(z.var)){z.cox <- coxph(OS~get(z.var[i]),z)
z.cox <- summary(z.cox)
sf <- summary(survfit(OS~get(z.var[i]),z))
```

```
z.r <- cbind.data.frame(var=z.var[i],level=levels(z[,z.var[i]]),
                number=sf$n, death=sf$table[,"events"],medianSurv=sf$table[,"median"],
                medianSurvLower=sf$table[,"0.95LCL"],
medianSurvUpper=sf$table[,"0.95UCL"],
                HR=c(1,round(z.cox$conf.int[,"exp(coef)"],2)),
                HRlower=c("",round(z.cox$conf.int[,"lower .95"],2)),
                HRupper=c("",round(z.cox$conf.int[,"upper.95"],2)),
                p=c("",round(z.cox$coefficients[,"Pr(>|z|)"],4)))
if(i==1) z.rr<- z.r else z.rr<-rbind.data.frame(z.rr,z.r)}




dimnames(z.rr)[[1]] <- 1:nrow(z.rr)
z.rr$mediansurvCI <- paste(z.rr$medianSurv, "(" ,z.rr$medianSurvLower, "-",
z.rr$medianSurvUpper, ")",sep="")
```