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Meta-Analysis of Efficiency of Medicines Prescribed in Metastatic Cancer: Focusing on Quality of Life and Life Span

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Abstract

Background: As metastatic malignancies are difficult to cure and manage, they are lethal. Colorectal cancer is one of the most prevalent metastatic malignancies (CRC). Consequently, numerous earlier research has focused on various CRC treatments, which still need to be correlated with CRC patients' life expectancy and quality of life.

Aim: This study's primary objective is to conduct a meta-analysis to examine the efficacy of medications recommended for metastatic cancer regarding the quality of life (QOL) and life expectancy.

Methods: For this investigation, research from 2006 to 2020 focused on treating CRC with various single and combination therapy was chosen. These English-language publications and articles focused on the efficacy outcomes of 5-FU- and capecitabine-based regimens. There were 25 selected papers (ORR=8, OS=7, PFS=7, and TTF=3). The statistical analysis was performed using Stata 13.

Results: The results demonstrated that the efficacy outcomes of both 5-FU-based and capecitabine-based regimens remained debatable. However, 5-FU administered intravenously was more effective and had fewer side effects.

Conclusion: This study indicated that the efficacy of the medicine in treating metastatic cancer is crucial for promoting longevity and quality of life. However, in this instance, 5-FU was more effective than capecitabine at extending patients' lives and enhancing their quality of life.

Keywords:

Metastatic Cancer, Quality of Life, Life Span, Meta-analysis, Colorectal Cancer, 5-FU, Capecitabine

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Introduction

Due to the country's tremendous diversity in lifestyle, culture, geography, foods, and habits, there are few sources of knowledge regarding cancer risk factors in Iraq. According to Abood *et al*.[1], cancer is a prevalently spreading disease in Iraq. Cancer cases documented at the Basra Cancer Control Centre and other affiliated hospitals and laboratories were classified according to gender and age. The data included 100,000 individuals, of whom 2,163 were cancer patients; 6.6% were children, 59% were female, and the remainder were male. The average age of adults was 51 to 19 years, and the average age of children was 6.4 to 4.3 years. The sorts of cancer in each patient varied. In females, breast cancer was the most prevalent form of cancer; in males, lung cancer, urinary bladder cancer, and bronchial cancer were more prevalent; in children, leukemia was the most prevalent.

Cancers are diverse, complex diseases characterized by irregular cell development that can spread to or invade other bodily parts. With 9.6 million recorded deaths in 2018, it is the biggest cause of death on a global scale. Lung, breast, stomach, and colon cancers account for most cancer-related fatalities.[2] Due to the ability of malignant tumors to spread, metastasis

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is the main cause of death among cancer patients. It can also be viewed as the utmost difficulty of cancer research and the most difficult obstacle to efficient cancer management. Metastasis refers to cancer cells migrating throughout the body and forming new clusters in organs other than the one where the main tumor originated. It is commonly recognized that metastasis is a complex, multistep process that almost invariably leads to the death of the patient, despite being extremely inefficient from the cell's standpoint. Tumors spread predominantly through lymphatic systems, blood arteries, and subepithelial surfaces. These three tumor metastasis mechanisms are lymphatic, hematogenous, and trans-coelomic metastases. Carcinomas of the epithelium typically spread via the lymphatic system, with hematogenous metastases emerging later. Sarcomas, or bone and soft tissue malignancies, favor the hematogenous pathway. Trans-coelomic metastasis, in contrast, is a characteristic of a relatively small group of malignancies, including mesotheliomas and ovarian carcinomas.[3] This study will concentrate on the efficacy of medications for metastatic colorectal cancer.

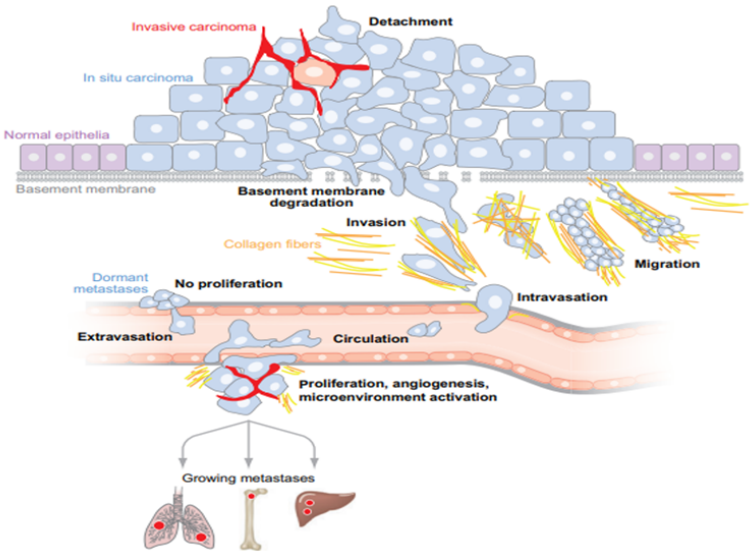


Figure 1: SHOWS THE PRINCIPAL STEPS IN METASTASIS[3]

Colorectal (CRC) cancers are ranked third in incidence and fourth in death among all forms of cancer. It contributes significantly to worldwide death and morbidity. In middle- and low-income countries, colorectal cancer, and mortality incidence are increasing.[4] These rising rates in China contribute to the increasing cancer burden. In both adjuvant and non-adjuvant settings, systemic chemotherapy with intravenous (IV) administration of 5-fluorouracil (5-FU) is the cornerstone of treatment for metastatic colorectal cancer (mCRC). 5-FU is commonly utilized as the cornerstone of chemotherapy and radiation regimens containing oxaliplatin (FOLFOX) or irinotecan (FOLFIRI).[5] Adjuvant 5-FU therapy improves overall survival (OS) and disease-free survival (DFS) in operable "Advanced CRC" and "mCRC" cases. 5-FU is administered via continuous infusion or injection bolus (cIV).[6] Given its greater efficacy and reduced toxicity, cIV 5FU has lately supplanted bolus injection as the recommended treatment method and is currently the gold standard.[7] Oral fluoropyrimidines have been developed to circumvent problems with the intravenous administration of 5-FU. The most commonly encountered fluoropyrimidine treatment is capecitabine, a 5-FU agent that replicates the activity of intravenous 5-FU and stimulates cancer cells preferentially.[8] Several stages II and III randomized controlled trials (RCTs) and observational studies. Cassidy *et al*.[9] investigated the safety and efficacy of oral fluoropyrimidine-based regimens with IV 5-FU regimens in patients with advanced CRC or "mCRC." Recent investigations[10] have demonstrated that despite contradictory evidence suggesting either the superiority or equivalence of one treatment over the other, there is, in reality, a difference between the two regimens.

Numerous cancer treatments exist, and numerous medications are commonly administered to patients in Iraq. The purpose of this study is to determine the impact of various medications on the lifestyles and lifespans of cancer patients. Determining the quality of life of cancer patients and survivors throughout and after cancer recovery treatment necessitates an examination of the effects of various medications on their lives. In addition, in light of the contradicting literature, this meta-analysis provides a comprehensive, in-depth comparison of the Quality of Life and Life Span of cancer patients in Iraq.

Research Question

- What is the efficiency of prescribed medicines in improving the life quality of cancer patients in Iraq?
- How can the medicines cure metastatic cancer and increase cancer patients' and survivors' lives in Iraq?

Methods

For this research investigation, a meta-analysis was undertaken, and previous studies' findings were considered. The search was restricted to randomized controlled trials (RCTs) of metastatic colorectal cancer treatment (CRC). This trial includes regimens based on capecitabine and cIV-5-FU for treating colorectal cancer. Different web databases were chosen to acquire the necessary data for this study. Embase and PubMed were these databases. The selected articles and papers were compiled between 2006 and 2020. English language proficiency is another criterion for selecting papers and articles. For data collection purposes, a list of keywords was generated for online databases. This list contained "5fluorouracil, 5-FU, capecitabine, Xeloda, toxicity, survival, disease progression, colorectal cancer, randomized controlled trial, life span, quality of life, and overall response."

Selection Criteria

This analysis incorporates prior research on treating CRC using 5-FU and capecitabine. The trials with less than 25 patients were included for this purpose. These investigations must incorporate 5-FU administration by bolus injection or hepatic infusion.

Data Extraction

Two researchers contributed to the effective extraction of data; one focused on extraction, while the other effectively rechecked the data. The retrieved data comprised the authors' names, publication year, patients' characteristics, cancer stage, treatment, follow-up, outcomes regarding safety and efficacy, and combination therapy. The effectiveness goals were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease-free survival (DFS), and time to treatment failure (TTF).

Bias Risk Assessment

The reviewers of the current study utilized the Cochrane Collaboration's technique for assessing bias at each stage of the review process. This instrument accurately identified four kinds of discrimination: detection, selection, attribution, and selection bias.

Statistical Analysis

The software Review Manager (RevMan 5.3) and Stata 13 were employed for statistical analysis. Based on the heterogeneity of the included studies, fixed or random models were employed to calculate the summary effects. The statistical heterogeneity was calculated using Cochrane's 2 test, and the significance level was chosen at 10%. Statistical heterogeneity was quantified using the I2 statistic. Guidelines from the "Cochrane Handbook for Systematic Reviews of Interventions"[11] were considered for this aim. When heterogeneity was identified, the random-effects model was utilized, but the fixed-effects model was used when no heterogeneity was observed.

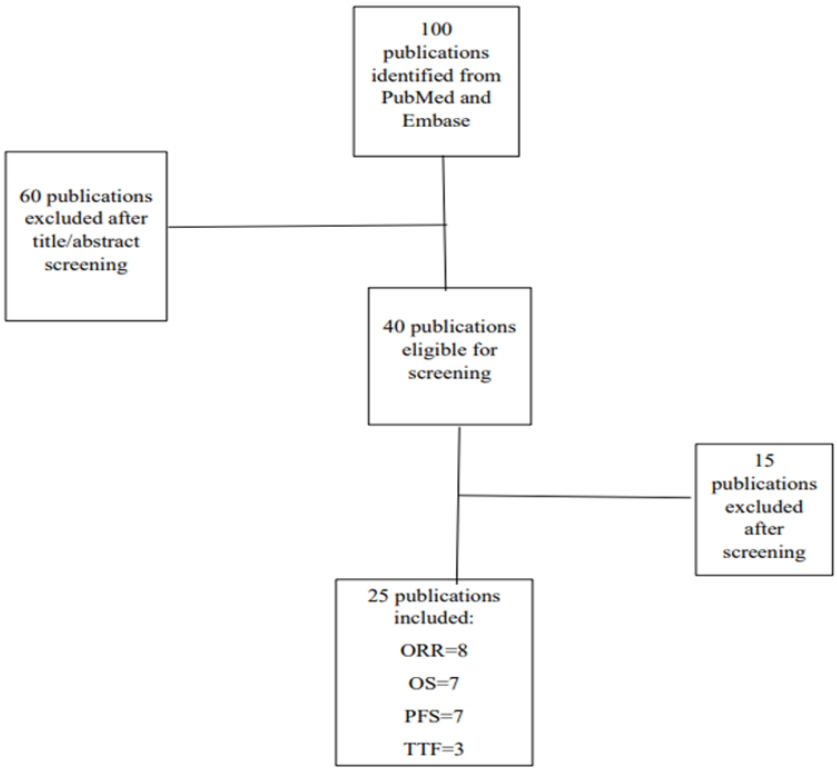


Figure 2: Meta-analysis

Results

Table 1: Characteristics of eligible publication in meta-analysis

Study	Study Design	Indication	Line of treatment/ setting	Patient characteristics Performance status	Age (years)
"Allegra *et al.*[12]"	"Ph III, two-arm, RT, subsequently amended to a 2×2 FD"	"Stage II–III RC"	"Neoadjuvant"	""ECOG, 0-1."	Less than 18
"Cassidy *et al.*[9]"	Ph III, two-arm, RT, subsequently amended to a 2×2 FD	"mCRC"	"First line"	"ECOG, 0-1."	Less than 18
"de Gramont *et al.*[13]"	Ph III, three-arm, open-label, RT	Stage II or III CC	Adjuvant	"ECOG, 0-1."	Less than 18
"Díaz-Rubio *et al.*[14]"	"Ph III, open-label, RT"	"mCRC"	"First line"	"Karnofsky, ≥70"%	Less than 18
"Ducreux *et al.*[15]"	Ph II, open-label, RNCT	"mCRC"	"First line"	ECOG, 0–2	Between 18-75
"Ducreux *et al.*[16]"	"Ph III, open-label, RPAT"	"mCRC"	"First line"	ECOG, 0–2	Less than 18
"Fuchs *et al.*[17]"	"Ph III, open-label, RT"	"mCRC"	"First line"	"ECOG, 0-1."	Less than 18
"Hochster *et al.*[18]"	"ROLT"	"mCRC"	"First line"	"ECOG, 0-1."	Less than 18
"Hochster *et al.*[18]"	"ROLT"	"mCRC"	"First line"	"ECOG, 0-1."	Less than 18
"Köhne *et al.*[19]"	"Phase III, RT," 2×2 FD	"mCRC"	"First line"	WHO, ≤2	Less than 18
"Köhne *et al.*[19]"	"Phase III, RT," 2×2 FD	"mCRC"	"First line"	WHO, ≤2	Less than 18
"Martoni *et al.*[20]"	"Phase II, RT"	"Advanced CRC"	"First line"	"Karnofsky, ≥ 70"	Less than 18
"Pectasides *et al.*[21]"	"Phase III, RT"	Stage II–III CRC	Adjuvant	"ECOG, 0-1."	Not
"Pectasides *et al.*[22]"	"Phase III, RT"	Stage IV "mCRC"	"First line"	ECOG, 0–2	Less than 18
"Porschen *et al.*[23]"	"Phase III, RT"	"mCRC"	"First line"	ECOG, 0–2	Less than 18
"Rothenberg *et al.*[24]"	"Phase III, RT"	"mCRC"	"Second line"	ECOG, 0–2	>18
"Seymour *et al.*[25]"	Randomized trial, 2×2 FD	"mCRC"	"First line"	WHO, ≤ 2	Less than 18
"Souglakos *et al.*[26]"	"Phase II, RT"	"mCRC"	"First line"	ECOG, 0–2	Not
"Skof *et al.*[27]"	"Phase II, RT"	"mCRC"	Neoadjuvant	WHO, ≤ 1	Less than 18

Ph=phase, RT=randomized Trial, FD=factorial design, RC=rectal cancer, RNCT=randomized, non-comparative trial, RPAT=randomized parallel-arm trial, CC=colon cancer, "ROLT"=Randomized, open-label trial

Table 2: Efficacy outcomes

Study	Median FU time (months)	Treatments Cape Regimen	5-FU regimen	Sample size	Efficacy outcomes
Díaz-Rubio *et al.*[14]	17.5	Cape+OX Cape 1000 mg/m2 bid for 14 days plus OX 130 mg/m2 IV infusion on day 1 q3w	"IV 5-FU+OX 5-FU 2250 mg/m2 diluted in saline administered by cIV during 48 h on days 1, 8, 15, 22, 29, and 36, plus OX 85 mg/m2 IV infusion on days 1, 15, and 29 every 6 weeks."	NCape=174 N5-FU=174	ORR OS
Ducreux *et al.*[15]	36	Cape+IRI+bevacizumab IRI 200 mg/m2 IV infusion on day 1, Cape 1000 mg/m2 bid on days 1–14, followed by bevacizumab 7.5 mg/kg IV infusion on day 1 q3w for a maximum of eight cycles After 6 months of chemotherapy and in the absence of disease progression, bevacizumab alone 7.5 mg/kg IV infusion q21 days until disease progression	"IV 5-FU+IRI+bevacizumab 5-FU 400 mg/m2 bolus and 2400 mg/m2 cIV over 46 h plus LV 400 mg/m2 IV infusion plus IRI 180 mg/m2 followed by bevacizumab 5 mg/kg IV infusion on day 1 q2w for a maximum of 12 cycles. After 6 months of chemotherapy, and in the absence of disease progression, bevacizumab alone 7.5 mg/kg IV infusion q21 days until disease progression"	NCape=72 N5-FU=73	ORR PFS
Ducreux *et al.*[16]	18.8	Cape+OX OX 130 mg/m2 IV infusion on day 1 plus Cape 1000 mg/m2 bid on days 1–14 q3w	"OX 100 mg/m2 IV infusion followed by LV 400 mg/m2 IV infusion followed by 5-FU 400 mg/m2 bolus injection, then 5-FU 2400–3000 mg/m2 cIV q2w."	NCape=156 N5-FU=150	ORR PFS OS TTF
Fuchs *et al.*[17]	34	Cape+IRI IRI 250 mg/m2 IV infusion on day 1, Cape 1000 mg/m2 bid on days 1–14 q3w	"IV 5-FU+IRI IRI 180 mg/m2 IV infusion over 90 min, LV 400 mg/m2 IV infusion over 2 h; 5-FU 400 mg/m2 bolus injection then 5-FU 2400 mg/m2 cIV over 46 h q2w"	NCape=145 N5-FU=144	ORR PFS
Köhne *et al.*[19]	14.6	Cape+IRI+placebo IRI 250 mg/m2 IV infusion on days 1 and 22 and Cape 1000 mg/m2 bid on days 1–15 and 22–36, with	cIV 5-FU+IRI+placebo IRI 180 mg/m2 IV infusion on days 1, 15, and 22; FA 200 mg/m2 IV on days 1, 2, 15, 16, 29, and 30; 5-FU	NCape=21 N5-FU=22	ORR PFS OS

Conted...

Table 2: Conted...

		placebo	400 mg/m2 IV bolus, then 600 mg/m2 22-h cIV given after the bolus on days 1, 2, 15, 16, 29, and 30, with a placebo		
Pectasides *et al.*[22]	42	Cape+IRI+bevacizumab Bevacizumab 7.5 mg/kg IV infusion on day 1, IRI 240 mg/m2 IV infusion on day 1, and Cape 1000 mg/m2 on days 1–14 q21 days for six cycles	cIV 5-FU+IRI+bevacizumab Bevacizumab 5 mg/kg IV infusion on day 1, IRI 180 mg/m2 IV infusion on day 1, LV 200 mg/m2 IV infusion on day 1, 5-FU 400 mg/m2 IV bolus on day 1 followed by 5-FU 2400 mg/m2 46-h cIV q14 days for 12 cycles	NCape=143 N5-FU=142	ORR PFS OS
Pectasides *et al.*[21]	74.4	Cape+OX OX 130 mg/m2 IV infusion on day 1 and Cape 1000 mg/m2 bid on days 1–14, q21 days for eight cycles	cIV 5-FU+OX OX 85 mg/m2 IV infusion on day 1, LV 200 mg/m2 IV infusion on day 1 and 5-FU 400 mg/m2 IV bolus on day 1 followed by a 5FU 2400 mg/m2 46-h cIV, q14 days for 12 cycles	NCape=211 N5-FU=197	DFS OS
Rothenberg *et al.*[24]	Not reported	Cape+OX OX 130 mg/m2 IV infusion on day 1, Cape 1000 mg/m2 bid on days 1–15 of a 3-week cycle	cIV 5-FU+OX LV 200 mg/m2/day IV infusion, 5-FU 400 mg/m2/day bolus and 600 mg/m2/day 22-h cIV for two consecutives days q2w, OX 85 mg/m2 IV infusion on day 1	NCape=313 N5-FU=31	PFS OS ORR TTF
Porschen *et al.*[23]	17.3	Cape+OX Cape 1000 mg/m2 bid from days 1 to 14 and OX 70 mg/m2 IV infusion on days 1 and 8	cIV 5-FU+OX OX 50 mg/m2 IV infusion, LV 500 mg/m2, and 5-FU 2000 mg/m2 as a 22-h cIV on days 1, 8, 15, and 22	NCape=241 N5-FU=233	ORR PFS OS TTF

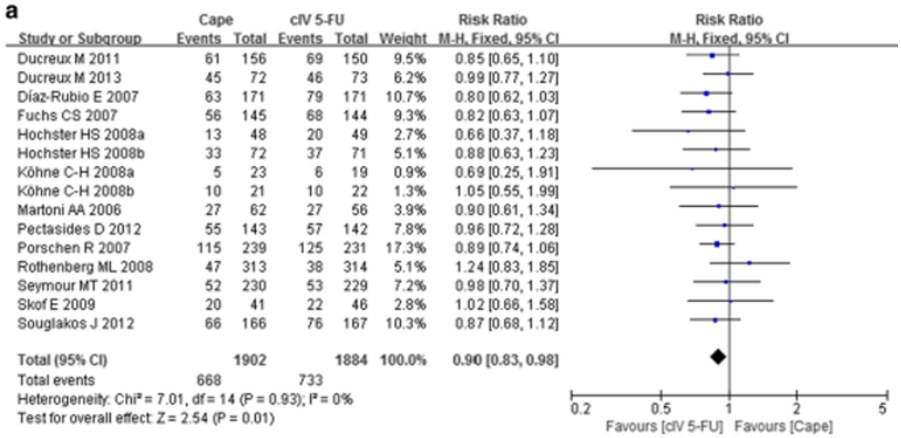
Risk-of-bias assessment

In general, the methodological quality of the included studies was excellent. Six[15, 17, 20, 24, 26, 27] of the evaluated trials[15, 17, 20, 24, 26, 27] failed to explain how the sampling was conducted. While most studies did not reveal any clear concealment of allocation, six studies[9, 13, 14, 16, 23, 28] reported centralized allocation of medicines, which may have introduced bias. In most studies, baseline parameters were comparable between treatment groups, although three trials[15, 18, 19] revealed significant differences. Due to the different administration strategies employed for the comparison groups (oral vs. infusion), we assumed that blinding was impossible in each of the 17 investigations. We suspected bias in the other trials because either the outcome evaluations were conducted by the trial researchers or no information regarding who conducted the evaluations was provided. In most studies, the risk of selective reporting was ambiguous and could not be evaluated.

Efficacy outcomes

• ORR

In 3786 patients, the fixed-effects model meta-analysis (2=7.01, P=0.93, I 2=0.0%) revealed that the cIV-5-FU-based regimens had a considerably higher response rate than the capecitabine-based regimens (RR 0.9; 95% CI 0.83-0.98, P=0.01). (Fig. 3a). When combined with oxaliplatin, cIV-5-FU-based regimens had a significantly higher response rate than capecitabine-based regimens (RR 0.90, 95% CI 0.81-1.00, P=0.04), but when combined with irinotecan, there was no discernible distinction among the two regimens (RR 0.91, 95% CI 0.80-1.03, P=0.13).



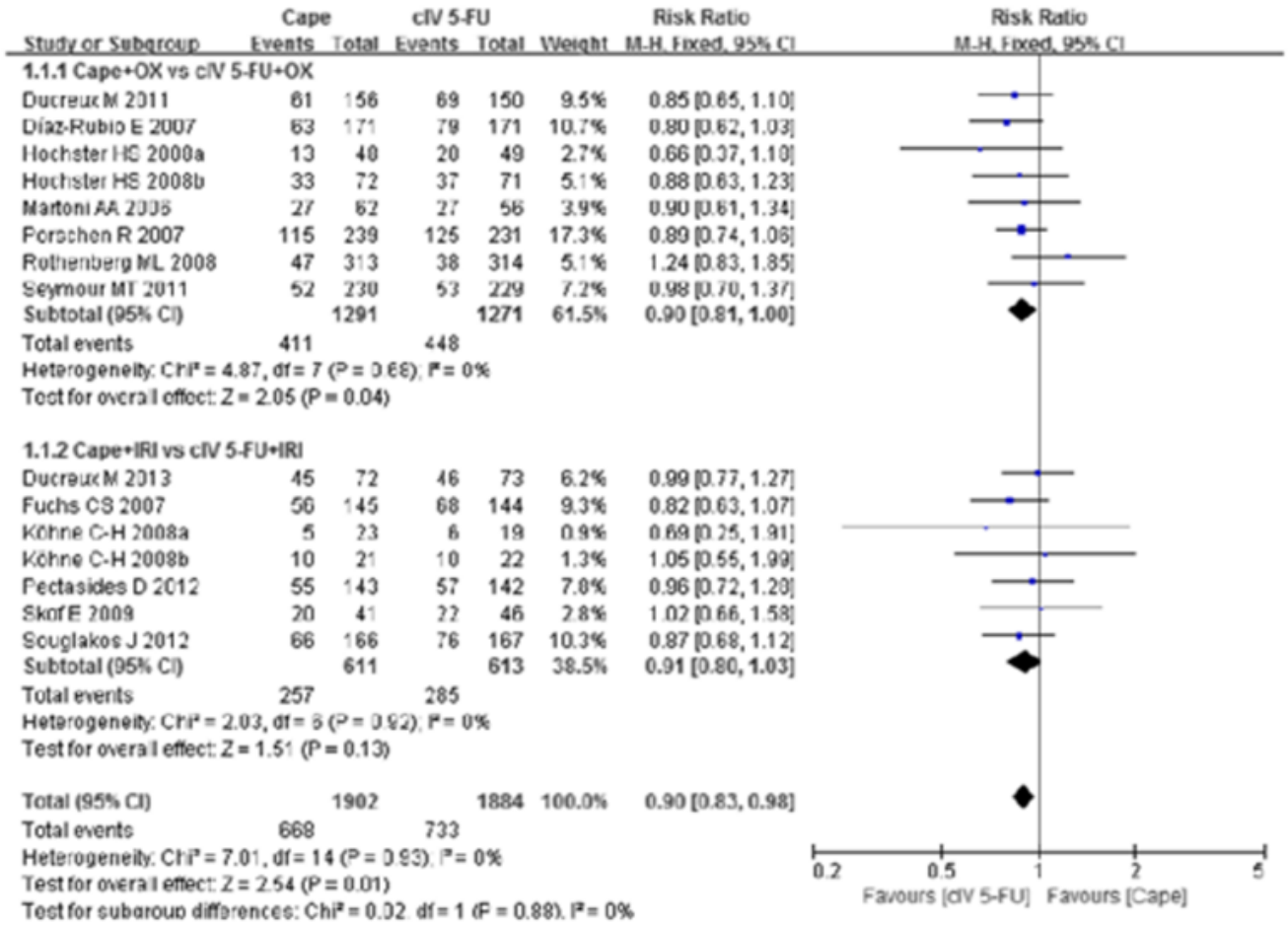
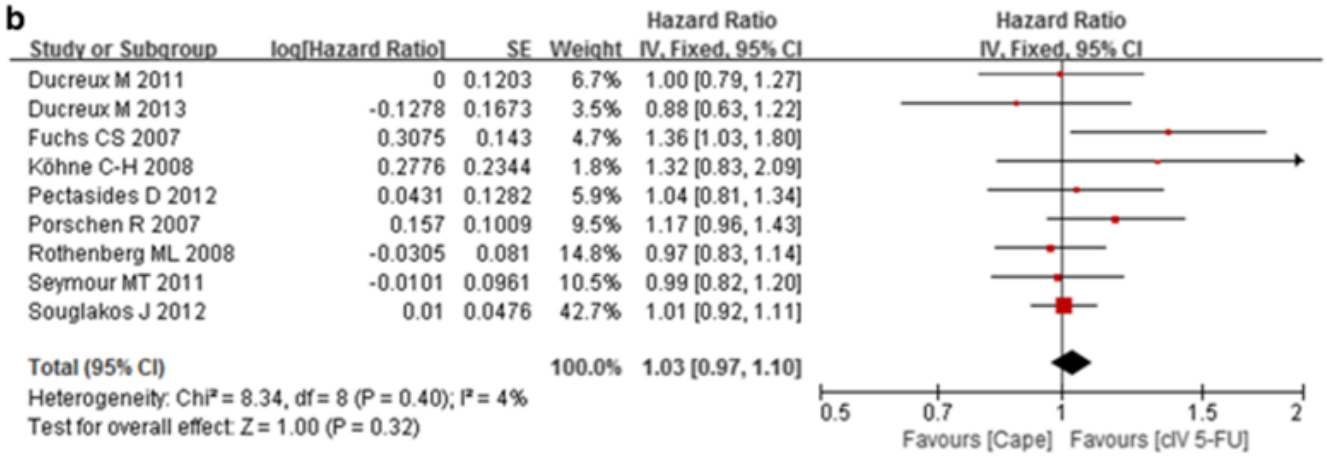


Figure. 3 a

- **PFS and TTF**

In regards to PFS (HR 1.03, 95% CI 0.97-1.10) and TTF (HR 1.05, 95% CI 0.94-1.18, P=0.39), the fixed-effects meta-analyses (PFS: 2=8.34, P=0.40, I 2=4.0%; TTF: 2=3.48, P=0.18, I 2=43.0%) did not reveal any significant differences among the two regimens (Fig. 3b, c). When the two regimens were coupled with oxaliplatin (HR 1.03, 95% CI 0.93-1.15, P=0.55) or irinotecan (HR 1.04, 95% CI 0.96-1.12, P=0.36), the observation held (Fig. 3b, c). Since only a few publications submitted TTF data, no subgroup analyses were carried out for TTF.



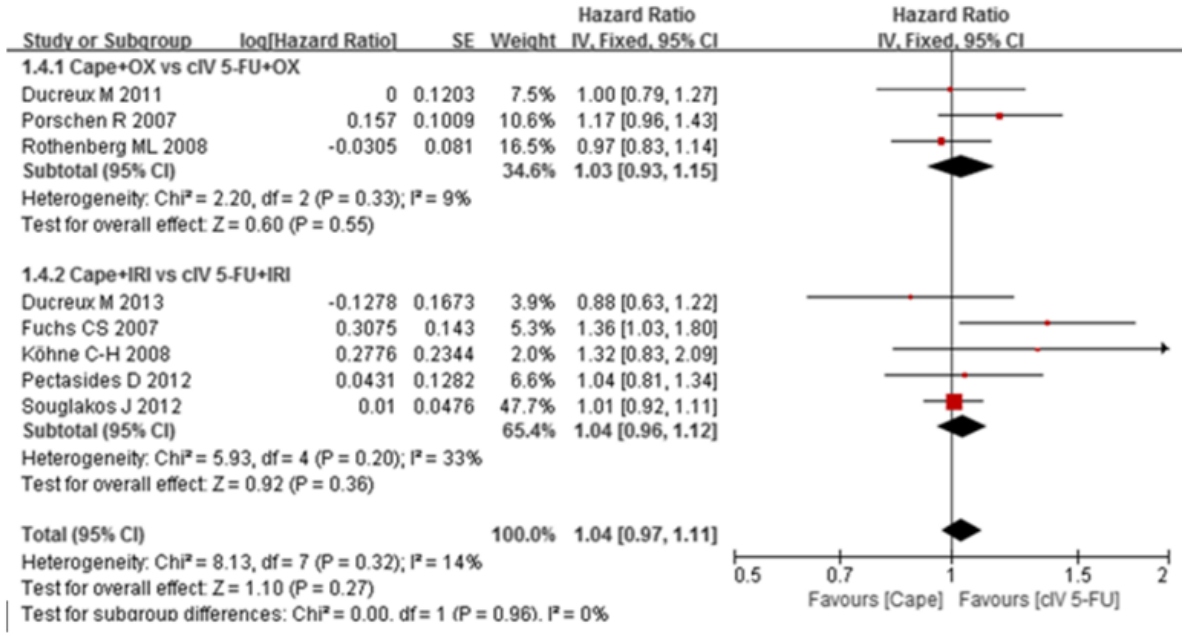


Figure 3b

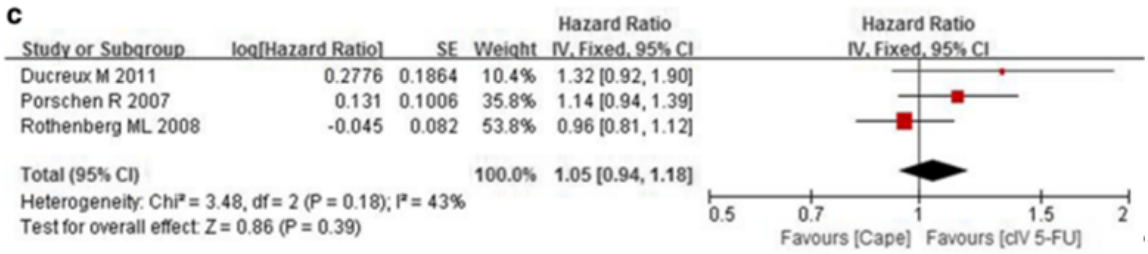
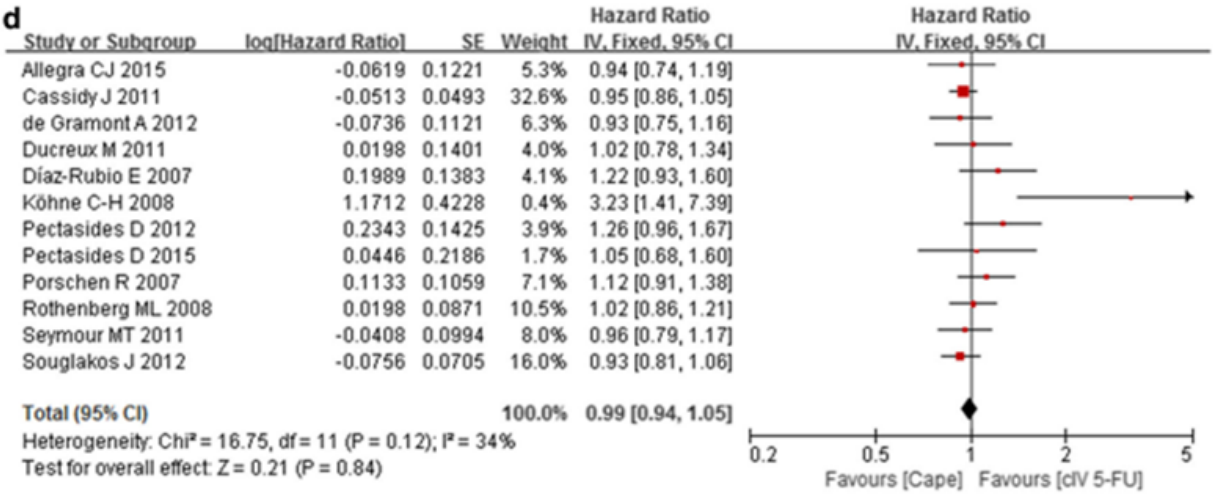


Figure 3c

- **OS**

The fixed-effects meta-analyses (2=16.75, P=0.12, I 2=34.0%) and subgroup analyses in the oxaliplatin-containing regimens (HR 1.00, 95% CI 0.93-1.07, P=0.95) and irinotecan-containing regimens (HR 1.01, 95% CI 0.89-1.14, P=0.86) did not detect any significant difference in OS between the two regimens (Fig. 3d)



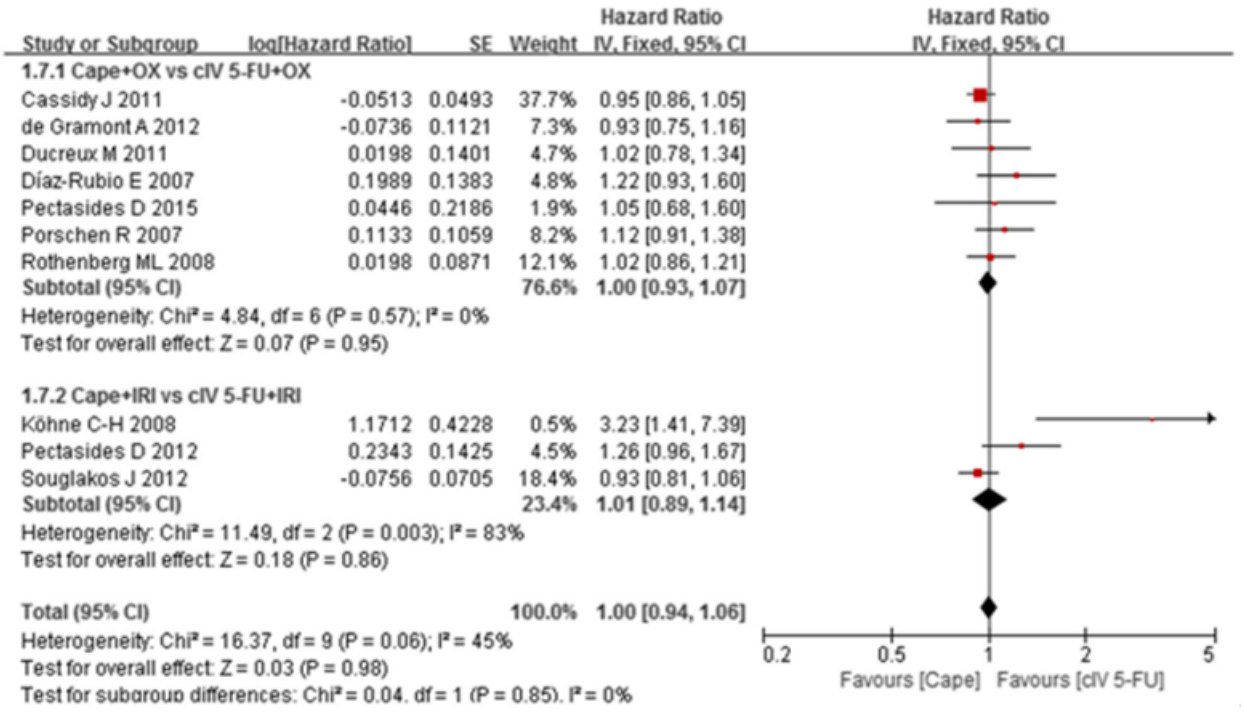


Figure 3d

- **DFS**

The fixed-effects meta-analyses (HR 0.96, 95% CI 0.85-1.08, P=0.50) and none of the studies examining DFS discovered any discernible difference in DFS between the two regimen groups (Fig. 3e).

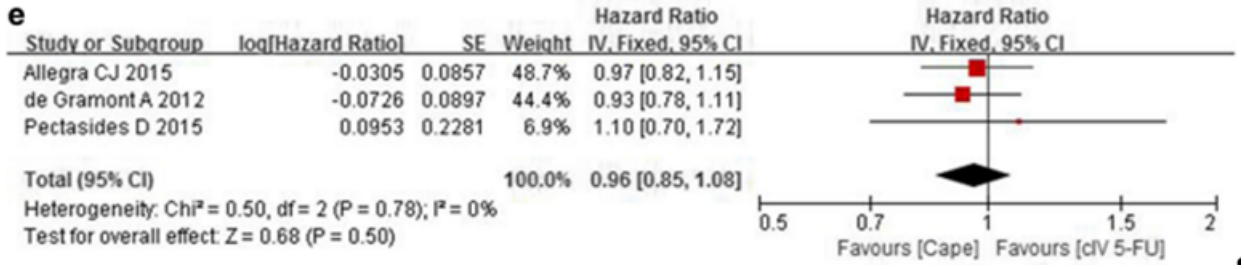


Figure 3e

- **Assessment of publication bias for ORR and OS**

For ORR, there was no evidence of publication bias (P=0.787). Egger's test for OS revealed the possibility of publication bias (P=0.006). Although the effect size remained the same after correction, the "trim-and-fill" method could not identify any appreciable impact of publication bias on it (HR 0.958, 95% CI 0.91-1.01).

Discussion

cIV 5-FU is one of the chemotherapy medicines for CRC that is still often prescribed today. Several meta-analyses have evaluated the efficacy and safety of cIV-5-FU and capecitabine-based regimens. Due to the variability of the inclusion criteria utilized in these meta-analyses, neither regimen was able to demonstrate its superiority. Most prior meta-analyses employed doses of fluoropyrimidines that can be taken orally or nasally as benchmarks.[2, 29, 30] Some of them included studies in which 5-FU injections were only administered as a single dose. Diverse types of research and cancer sites were also considered (RCT vs. observational).

Our investigation of capecitabine, predominantly in cIV 5-FU use in advanced CRC and "mCRC," provides a proportional indication of the most commonly utilized fluorouracil modalities about tumor response, survival, and tolerability profile. However, our meta-analysis contains several papers highlighted in additional

meta-analyses. We demonstrate that 5FU is superior to capecitabine in terms of ORR. Similar outcomes were observed when the agents were used with oxaliplatin, as opposed to when combined with irinotecan. Our findings are consistent with a meta-analysis[2] showing that oral fluoropyrimidine-based regimens had lower response rates than cIV-5-FU-based regimens.

Despite the varied ORRs, our findings suggest that patient survival is equivalent across the two treatment regimes. Comparing PFS in previous meta-analyses yields conflicting results. Although some meta-analyses found that capecitabine-based regimens had a worse PFS[3], other studies reported no significant difference between IV fluoropyrimidines and capecitabine and doxifluridine/S-1 administered orally. Variation in fluoropyrimidine types likely accounts for the difference. Previous research[2] demonstrated that the OS is comparable to this investigation.

The paucity of studies that included DFS and TTF as data sources make it difficult to conclude, despite our meta-analysis revealing no significant difference in DFS and TTF between the two cases. A larger sample of RCTs is necessary to validate these findings. Although neither treatment appeared to offer a survival advantage, patients with largely incurable or possibly curable "mCRC" or those whose primary goal of therapy is to limit the spread of cancer may benefit from the improved ORR of cIV 5-FU.[10]

Importantly, our meta-analysis extensively analyzes the safety outcomes of the two regimens, enabling a better understanding of their tolerance profile. Diarrhea is one of the most common adverse effects (AEs) associated with fluoropyrimidines, which reduces the quality of life and medication adherence.[31] Combinations of fluoropyrimidine and irinotecan are known to exacerbate severe diarrhea. Investigations have indicated that the combination of capecitabine and irinotecan can produce more severe toxicity or even death.[17, 19]

Compared to cIV-5-FU regimens containing capecitabine are associated with a 1.7-fold greater frequency of G- 3/4 diarrhea. The danger was significantly increased when irinotecan was included. Iacovelli *et al*.[32] investigated the incidence of grade 3/4 diarrhea in patients receiving capecitabine/cIV 5FU to treat colorectal, gastrointestinal, or breast cancer. The incidence of severe diarrhea in CRC patients treated with capecitabine was up to 17%, which was significantly higher than the incidence found with cIV 5-FU; the RR value increased to 2.35 percent when capecitabine and irinotecan were administered simultaneously.

In addition, a meta-analysis was performed to evaluate patients with rectal cancer[2], and a comparison between a variety of fluoropyrimidines that can be administered orally and cIV 5-FU[29] revealed an increased incidence of diarrhea. It has been proven that the chemotherapy regimen and the timing of administration affect the incidence of chemotherapy-induced diarrhea.[33] Given that fluoropyrimidines have previously been associated with an increased risk of diarrhea[33, 34], we hypothesize that the higher incidence of diarrhea associated with capecitabine may be attributable to the drug's daily delivery schedule, as opposed to cIV 5-FU's frequently more extended schedule. In the two RCTs that comprised our meta-analysis and utilized daily doses of cIV 5-FU[12, 20], there was no significant difference in diarrhea incidence between the two regimens. Additionally, Allegra *et al*.[12] shown that reducing the frequency of administration of both drugs from seven to five days per week significantly reduced diarrhea of grades 3-5 in both groups.

We also observed an increase in the likelihood of additional category 3/4 GI adverse events. Patients receiving capecitabine had a 1,3-fold greater risk of vomiting or nausea than those receiving cIV 5-FU; the risk was even greater when capecitabine and irinotecan were combined, indicating the extreme toxicity of this combination once again. Recent meta-analyses[2] showed that capecitabine was related to an increased risk of GI adverse events, which our findings supported.

Hand-foot syndrome, which occurs five times more frequently with capecitabine than with cIV 5-FU, is a common and dose-limiting adverse effect of capecitabine. In addition, capecitabine regimens have been linked to a roughly twofold increased risk of thrombocytopenia of grade 3/4 severity. A meta-analysis comparing capecitabine with oxaliplatin versus cIV 5- FU with oxaliplatin as first-line chemotherapy for "mCRC" yielded comparable results. In contrast, capecitabine plus oxaliplatin was associated with a higher incidence of grade 3/4 thrombocytopenia and hand-foot syndrome. Other meta-analyses[2, 30] have consistently associated oral fluoropyrimidines and capecitabine with increased hand-foot syndrome risk.

We demonstrated that cIV-5-FU-based regimens were associated with a higher incidence of grade 3/4 neutropenia and stomatitis than capecitabine-based regimens. We hypothesize that the concomitant administration of bolus 5-FU and cIV 5-FU in the majority of the studies included in our meta-analysis was associated with an increased risk of neutropenia. This is supported by the findings of the Meta-analysis Group in Cancer[13], which revealed more severe hematologic damage in patients treated with bolus 5FU compared to cIV 5-FU. The incidence of neutropenia did not differ between the two patient groups in studies that did not involve the administration of a 5-FU bolus.[20, 25]

Our data indicate that, despite capecitabine's apparent ease of administration, it has a poor assimilation rate that may decrease patient quality of life. Therefore, this should be prudently evaluated, especially when pharmacological therapies are required. Although fluoropyrimidines are frequently poorly tolerated, we could not clearly explain the increased incidence of adverse events (AEs), notably gastrointestinal (GI) AEs, associated with capecitabine compared to cIV 5-FU.

In terms of categorical characteristics, renal function, and median age, the patient populations in all the included studies were comparable, except in one study,[25] in which a slightly larger population was recorded without affecting the direction of the results. As a result, we cannot associate any patient-centric characteristic with this research. In addition, no study has analyzed capecitabine toxicity risk variables using a multivariable approach. To appreciate this discrepancy's fundamental concept, additional investigation is required.

Conclusion

Due to its increasing tumor response and toxicity profile, our meta-analytical research demonstrates that cIV 5-FU is currently the most effective and safest form of fluorouracil administration. As evidenced by the pooled RCTs, we believe these results can be used to guide clinical practice in treating CRCs, taking into account tolerability and effectiveness benefit.

Limitations and Delimitations

We believe that various variables may have influenced the results of our meta-analytical investigation. First, our data were collected from previously published accounts of the research, which is not the most reliable source of information for meta-analytical research methods. Individual patient data can be used to get more solid conclusions. Second, there was much heterogeneity in the treatment strategies for timing and combined therapy among the included trials.

Reduced adherence to medication in both groups, dose and treatment schedule alterations due to increased toxicity, and other circumstances can obscure the actual effectiveness of the impact on a larger scale. Utilizing various toxicity indicator tests as evaluation criteria and toxicity level organization methodologies may have affected the toxicity indicator. In the future, meta-lapse approaches may be used to validate our findings further while considering potential confounders.

References

1. Abood RA, Abdahmed KA, Mazyed SS. Epidemiology of Different Types of Cancers Reported in Basra, Iraq. Sultan Qaboos Univ Med J 2020;20:e295-e300. https://doi.org/10.18295/squmj.2020.20.03.008
2. Zou XC, Wang QW, Zhang JM. Comparison of 5-FU-based and Capecitabine-based Neoadjuvant Chemoradiotherapy in Patients With Rectal Cancer: A Meta-analysis. Clin Colorectal Cancer 2017;16:e123-e39. https://doi.org/10.1016/j.clcc.2017.01.009
3. Bacac M, Stamenkovic I. Metastatic cancer cell. Annu Rev Pathol 2008;3:221-47. https://doi.org/10.1146/annurev.pathmechdis.3.121806.151523
4. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683-91. https://doi.org/10.1136/gutjnl-2015-310912
5. Chen W, Zheng R, Zhang S, Zeng H, Zuo T, Xia C, *et al.* Cancer incidence and mortality in China in 2013: an analysis based on urbanization level. Chin J Cancer Res 2017;29:1-10. https://doi.org/10.21147/j.issn.1000-9604.2017.01.01
6. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. Bmj 1993;306:752-5. https://doi.org/10.1136/bmj.306.6880.752
7. Piedbois P, Rougier P, Buyse M, Pignon J, Ryan L, Hansen R, *et al.* Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16:301-8. https://doi.org/10.1200/jco.1998.16.1.301
8. Schüller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, *et al.* Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291-7. https://doi.org/10.1007/s002800050043
9. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, *et al.* XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011;105:58-64. https://doi.org/10.1038/bjc.2011.201
10. Van Cutsem E, Hoff PM, Harper P, Bukowski RM, Cunningham D, Dufour P, *et al.* Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 2004;90:1190-7. https://doi.org/10.1038/sj.bjc.6601676
11. Deeks JJ, Higgins JPT, Altman DG, Group CSM. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2019. p. 241-84. https://doi.org/10.1002/9781119536604.ch10
12. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, *et al.* Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial. J Natl Cancer Inst 2015;107:djv248. https://doi.org/10.1093/jnci/djv248
13. de Gramont A, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, *et al.* Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012;13:1225-33. https://doi.org/10.1016/s1470-2045(12)70509-0
14. Díaz-Rubio E, Tabernero J, Gómez-España A, Massutí B, Sastre J, Chaves M, *et al.* Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 2007;25:4224-30. https://doi.org/10.1200/jco.2006.09.8467
15. Ducreux M, Adenis A, Pignon JP, François E, Chauffert B, Ichanté JL, *et al.* Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). Eur J Cancer 2013;49:1236-45. https://doi.org/10.1016/j.ejca.2012.12.011
16. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, *et al.* Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer 2011;128:682-90. https://doi.org/10.1002/ijc.25369
17. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, *et al.* Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-86. https://doi.org/10.1200/jco.2007.11.3357
18. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, *et al.* Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008;26:3523-9. https://doi.org/10.1200/jco.2007.15.4138
19. Köhne CH, De Greve J, Hartmann JT, Lang I, Vergauwe P, Becker K, *et al.* Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. Ann Oncol 2008;19:920-6. https://doi.org/10.1093/annonc/mdm544

20. Martoni AA, Pinto C, Di Fabio F, Lelli G, Rojas Llimpe FL, Gentile AL, *et al*. Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). Eur J Cancer 2006;42:3161-8. https://doi.org/10.1016/j.ejca.2006.08.034
21. Pectasides D, Karavasilis V, Papaxoinis G, Gourgioti G, Makatsoris T, Raptou G, *et al*. Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer. BMC Cancer 2015;15:384. https://doi.org/10.1186/s12885-015-1406-7
22. Pectasides D, Papaxoinis G, Kalogeras KT, Eleftheraki AG, Xanthakis I, Makatsoris T, *et al*. XELIRI-bevacizumab versus FOLFIRI-bevacizumab as first-line treatment in patients with metastatic colorectal cancer: a Hellenic Cooperative Oncology Group phase III trial with collateral biomarker analysis. BMC Cancer 2012;12:271. https://doi.org/10.1186/1471-2407-12-271
23. Porschen R, Arkenau HT, Kubicka S, Greil R, Seufferlein T, Freier W, *et al*. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol 2007;25:4217-23. https://doi.org/10.1200/jco.2006.09.2684
24. Rothenberg ML, Cox JV, Butts C, Navarro M, Bang YJ, Goel R, *et al*. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 2008;19:1720-6. https://doi.org/10.1093/annonc/mdn370
25. Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, *et al*. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet 2007;370:143-52. https://doi.org/10.1016/s0140-6736(07)61087-3
26. Souglakos J, Ziras N, Kakolyris S, Boukovinas I, Kentepozidis N, Makrantonakis P, *et al*. Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC). Br J Cancer 2012;106:453-9. https://doi.org/10.1038/bjc.2011.594
27. Skof E, Rebersek M, Hlebanja Z, Ocvirk J. Capecitabine plus Irinotecan (XELIRI regimen) compared to 5-FU/LV plus Irinotecan (FOLFIRI regimen) as neoadjuvant treatment for patients with unresectable liver-only metastases of metastatic colorectal cancer: a randomised prospective phase II trial. BMC Cancer 2009;9:120. https://doi.org/10.1186/1471-2407-9-120
28. Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, *et al*. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet 2011;377:1749-59. https://doi.org/10.1016/s0140-6736(11)60399-1
29. Chionh F, Lau D, Yeung Y, Price T, Tebbutt N. Oral versus intravenous fluoropyrimidines for colorectal cancer. Cochrane Database Syst Rev 2017;7:Cd008398. https://doi.org/10.1002/14651858.cd008398.pub2
30. Zhang L, Xing X, Meng F, Wang Y, Zhong D. Oral fluoropyrimidine versus intravenous 5-fluorouracil for the treatment of advanced gastric and colorectal cancer: Meta-analysis. J Gastroenterol Hepatol 2018;33:209-25. https://doi.org/10.1111/jgh.13845
31. Kripp M, Wieneke J, Kienle P, Welzel G, Brade J, Horisberger K, *et al*. Intensified neoadjuvant chemoradiotherapy in locally advanced rectal cancer -- impact on long-term quality of life. Eur J Surg Oncol 2012;38:472-7. https://doi.org/10.1016/j.ejso.2012.02.002
32. Iacovelli R, Pietrantonio F, Palazzo A, Maggi C, Ricchini F, de Braud F, *et al*. Incidence and relative risk of grade 3 and 4 diarrhoea in patients treated with capecitabine or 5-fluorouracil: a meta-analysis of published trials. Br J Clin Pharmacol 2014;78:1228-37. https://doi.org/10.1111/bcp.12449
33. Kornblau S, Benson AB, Catalano R, Champlin RE, Engelking C, Field M, *et al*. Management of cancer treatment-related diarrhea. Issues and therapeutic strategies. J Pain Symptom Manage 2000;19:118-29. https://doi.org/10.1016/s0885-3924(99)00149-9
34. Uddin D, Khan M, Habib S. Oral Capecitabine Compared With Intravenous Fluorouracil Plus Leucovorin in Patients With Metastatic Colorectal Cancer. TAJ: Journal of Teachers Association 2012;25:17-25. https://doi.org/10.3329/taj.v25i0.37552