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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

Capecitabine Versus Continuous Infusion Fluorouracil for the Treatment of Advanced or Metastatic Colorectal Cancer: a Meta-analysis

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Opinion statement

Nowadays, systemic chemotherapy with intravenous (IV) 5-fluorouracil (5-FU) remains the most commonly prescribed treatment for metastatic colorectal cancers (CRC), in combination with other cytotoxic drugs. 5-FU can be administered through a bolus injection or continuous infusion (cIV), with the latter becoming the preferred administration method and standard of care in recent years. Oral fluoropyrimidines were developed to overcome challenges associated with the IV administration of 5-FU, among which capecitabine has become the most widely used one. However, although capecitabine and other oral fluoropyrimidine-based regimens are more convenient to administer, their efficacy and safety in comparison with IV 5-FU are not well understood. Results from recent randomized controlled trials, observational studies, and meta-analyses have been inconsistent. Safety, in particular, remains controversial. Our review, a first comprehensive meta-analysis comparing the efficacy and safety of cIV 5-FU with capecitabine, the two most widely used fluorouracil modalities in CRC, showed that cIV 5-FU-based regimens are associated with greater response rates compared with capecitabine-based regimens, with no difference in progression-free survival, time to treatment failure, overall survival, or disease-free survival between the two. Furthermore, cIV 5-FU-based regimens showed an improved safety profile compared with capecitabine-based regimens.

Our findings suggest that cIV 5-FU remains a more effective and safer modality of fluorouracil administration than capecitabine, thus providing supporting evidence to guide clinical practice in the management of colorectal cancer.

Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality worldwide, ranking third among all cancers in terms of incidence, and fourth in terms of cancer-related mortality. CRC incidence and mortality rates are increasing in low- and middle-income countries [1]. In China, these rising rates [2, 3] are contributing to the growing burden of cancer in the country.

Systemic chemotherapy with intravenous (IV) administration of 5-fluorouracil (5-FU) has been the mainstay of treatment for metastatic CRC (mCRC) in the neoadjuvant and adjuvant settings [4•, 5•, 6•], most commonly as the backbone of combination chemotherapy with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) [7–9]. 5-FU-based chemotherapy improves overall survival (OS) and disease-free survival (DFS) in the adjuvant setting, in inoperable advanced CRC and mCRC [7, 10–12].

5-FU is administered through a bolus injection or continuous infusion (cIV). Recently, cIV 5FU has become the preferred administration method over bolus injection and is considered standard of care, given its superior efficacy and lower toxicity [13]. Oral fluoropyrimidines have been developed to overcome challenges associated with the IV administration of 5-FU. Capecitabine, the most widely used oral fluoropyrimidine agent [14], is a 5-FU prodrug that mimics the activity of IV 5-FU, with preferential activation at the level of the cancer cells [15]. Several phase II and III randomized controlled trials (RCTs) and observational studies have compared the efficacy and safety of oral fluoropyrimidine-based regimens with IV 5-FU regimens in advanced CRC or mCRC, but results have been inconclusive, with some studies proving equivalence of the two regimens [16–27] and others demonstrating superiority of one over the other [28, 29].

Tolerability is a major challenge with fluoropyrimidines and may be affected by the administration route, dosage, and pharmacokinetics of the drug and patient variability. Studies comparing the safety of IV 5-FU and capecitabine present conflicting results. While some have described capecitabine as safe or safer than IV 5-FU [16, 17, 30], others have reported excessive toxicity with capecitabine when combined with oxaliplatin (XELOX) or irinotecan (XELIRI), specifically increased severe gastrointestinal (GI) adverse events (AEs) and hand–foot syndrome, which resulted in treatment discontinuation [23, 25, 29], dose reductions [21, 25], and even study termination [28].

In summary, although capecitabine offers more convenient administration, uncertainty remains regarding its efficacy and tolerability compared with IV 5-FU. Also, despite capecitabine's preferential activation at the level of the tumor cells and it remaining intact while passing through the intestine, the associated increased risk of severe GI AEs is disputable.

Several meta-analyses have been published recently comparing regimens based on IV 5-FU and oral fluoropyrimidines [31••, 32–36]; however, studies varied in terms of oral fluoropyrimidine backbone, cancer type, IV 5-FU delivery method, and combination therapy. Specifically, there has been no comprehensive meta-analysis comparing the efficacy and safety of cIV 5FU with capecitabine in CRC. Given that they are the most widely used fluorouracil modalities, we conducted this meta-analysis to compare chemotherapy regimens that use cIV 5-FU or capecitabine as backbone. Moreover, this meta-analysis provides a comprehensive, detailed, comparative review of safety outcomes of the two regimens in view of the conflicting literature.

Methods

Literature search strategy

The electronic databases PubMed and Embase were searched for articles published between January 1, 1998 and September 15, 2017. The search

was restricted to RCTs, reported in English, comparing capecitabine-based regimens with cIV-5-FU-based regimens for the treatment of CRC in neo-adjuvant or adjuvant settings and locally advanced metastatic disease. We used the following search strategy: intervention keywords: '5fluorouracil' OR '5-FU' OR 'capecitabine' OR 'xeloda' OR 'xelox' OR 'folfox' OR 'folfiri' OR 'capox' OR 'folfoxiri' OR 'xeloxiri' OR 'xeliri'; indication keywords: 'colorectal cancer' OR 'colon cancer' OR 'rectal cancer'; outcomes keywords: 'efficacy' OR 'safety' OR 'overall response' OR 'survival' OR 'disease progression' OR 'adverse events' OR 'toxicity'; study design keywords (limited to title, abstract): 'randomized' OR 'randomized' OR 'random' OR 'randomly' OR 'randomized controlled trial.'

Study selection criteria

We included capecitabine and cIV 5-FU treatments administered as single agents or in combination with any other cytotoxic agent(s) (e.g., irinotecan, oxaliplatin) or targeted therapies (e.g., bevacizumab, cetuximab). No restrictions for inclusion were made on drug dose, administration frequency, treatment duration, or tumor stage. Studies were excluded if they were published as abstracts, < 25 patients were included, age was an eligibility criterion, 5FU was administered through hepatic arterial infusion or as a single bolus injection only, or combined chemotherapy included nitroglycerin or hyroxyurea. For 2×2 factorial design trials, whereby more than one head-to-head comparison was performed, we only included comparisons that assessed a capecitabine-based regimen against a cIV-5-FU-based regimen.

Data extraction

One reviewer extracted the data and a second performed an independent data check, with any discrepancies resolved by a third. The data extracted for each trial were first author's name, publication year, number of enrolled patients, patient characteristics, tumor stage, type of treatment administered (combined or monotherapy), type of combination therapy, line of treatment, follow-up time, and reported efficacy and safety outcomes.

The following outcomes were considered as efficacy endpoints in our analysis and were abstracted and analyzed: objective response rate (ORR), progression-free survival (PFS), OS, DFS, and time to treatment failure (TTF). For the safety analysis, AEs of interest included grade 3/4 diarrhea, dehydration, anorexia, hand–foot syndrome, mucositis, stomatitis, cardiovascular AEs, neuropathy and neurotoxicity, neutropenia, lethargy/fatigue, vomiting, nausea, thrombocytopenia, leukopenia, anemia, asthenia, serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) increase, constipation, fever, alopecia, abdominal pain, allergic reaction, and infection.

Assessment of risk of bias

The risk of bias in each trial was assessed by two reviewers independently based on the Cochrane Collaboration's 'risk-of-bias' tool; any differences were resolved between the two reviewers by consensus. The tool considers four types of bias: selection, performance, detection, and attribution bias [37].

Statistical methods

Statistical analyses were performed with Stata 13, and forest plots were generated using Review Manager software (RevMan 5.3) [38].

For time-to-event outcomes, we extracted hazard ratios (HRs) and their 95% confidence intervals (CIs) directly from reports of studies where possible, or estimated them indirectly from Kaplan–Meier survival curves using the method described by Tierney et al. [39]. For studies in which CIs for effect estimates were not reported as 90, 95, or 99% for input into Review Manager, indirect variance estimation was used to determine the standard error of the natural logarithm of the reported HR se(lnHR).

For dichotomous outcomes, we expressed effect estimates as relative risks (RRs) with 95% CIs. We calculated the RR using the number of participants who experienced a specific event as the number of 'events' and the total number of participants assessable for that event as the 'total.' When only the percentage of participants who experienced an event was reported, we used this percentage and the number of participants in the assessable population to calculate the number of 'events.'

When study authors presented efficacy data for both 'per protocol' and 'intention-to-treat' (ITT) populations (as defined in the study report), we used results for the ITT population, with safety data extracted from that population.

Summary-effect estimates were calculated using random or fixed-effects models, depending on the heterogeneity of the included studies. Statistical heterogeneity was calculated using Cochrane's χ^2 test for heterogeneity, with the significance level set at 10%. We quantified statistical heterogeneity using the I^2 statistic, with the interpretation guided by the Cochrane Handbook for Systematic Reviews of Interventions [40]. When substantial heterogeneity was observed, the pooled estimate was calculated based on the random-effects model, while a fixed-effects model was used when no significant heterogeneity was detected.

Subgroup analyses were performed to explore the robustness of the findings across oxaliplatin- versus irinotecan-based therapies.

Publication bias was assessed whenever ≥ 10 studies were included for a certain outcome. We used funnel plots and Egger's test for publication bias [41], with a 5% significance level. When potential publication bias was detected, the 'trim-and-fill' method [42] was used to determine the impact of publication bias on effect size, and an effect size adjusted for publication bias.

Results

Literature search results

The search strategy described previously yielded 2480 potentially evaluable publications, of which 2460 were excluded after title/abstract screening. After reviewing the full-text reports of the remaining 20 RCTs, three trials were excluded, and 17 relevant RCTs were finally included (Fig. 1).

Characteristics of included studies

Most of the included trials had two arms, while a minority had a 2 × 2 factorial design and therefore had four arms. Altogether, we included 23 head-to-head comparisons of cIV-5FU-based regimens with capecitabine-based regimens for

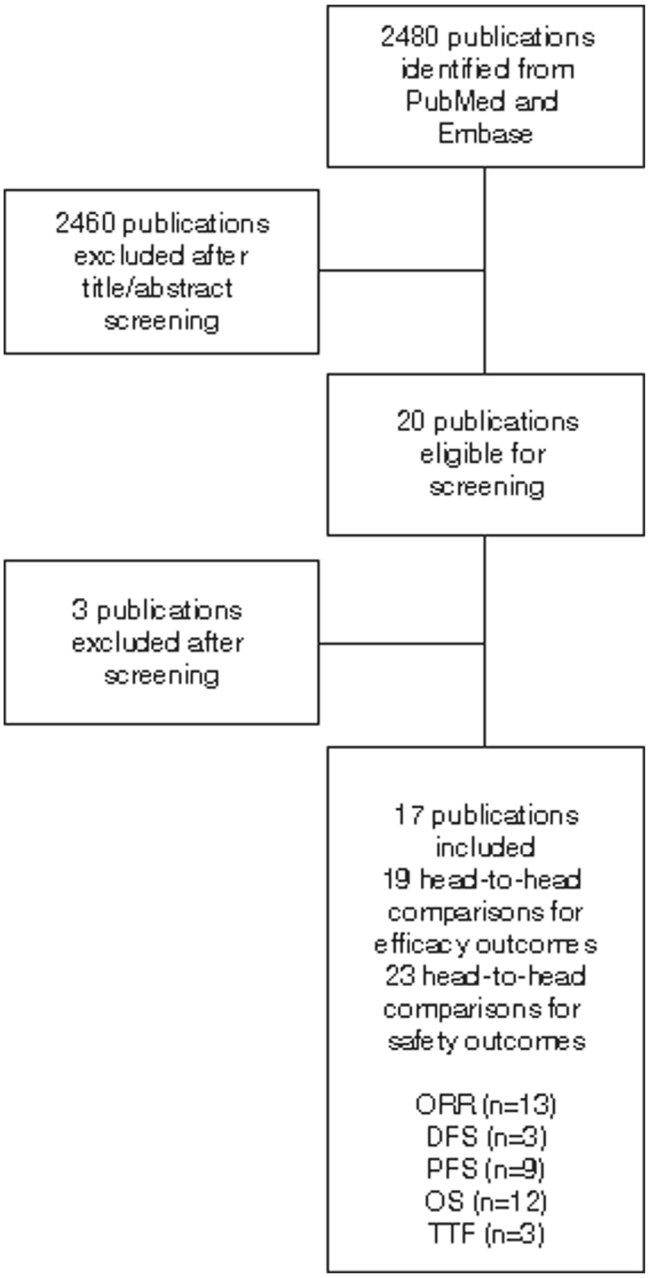


Fig. 1. Study flow diagram. *DFS* disease-free survival, *n* number of studies, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *TTF* time to treatment failure.

10,105 randomized patients.

In all included trials but one, cIV 5-FU and capecitabine were given in combination with either oxaliplatin or irinotecan.

In the majority of trials, cIV 5-FU was preceded by bolus administration, and six trials included bevacizumab as targeted therapy in combination with chemotherapy [23, 25–27, 43, 44].

Table 1 presents the characteristics of the included trials.

Table 1. Characteristics of eligible publications included in the meta-analysis

Study	Study design	Indication	Line of treatment/setting	Patient characteristics	
				Performance status	Age (years)
Allegra CJ 2015 [45]	Phase III, two-arm, randomized trial, subsequently amended to a 2 × 2 factorial design	Stage II–III rectal cancer	Neoadjuvant	ECOG, 0–1	≥ 18
Cassidy J 2011 [27]	Phase III, two-arm, randomized trial, subsequently amended to a 2 × 2 factorial design	mCRC	First line	ECOG, 0–1	≥ 18
de Gramont A 2012 [43]	Phase III, three-arm, open-label, randomized trial	Stage II or III colon cancer	Adjuvant	ECOG, 0–1	≥ 18
Díaz-Rubio E 2007 [22]	Phase III, open-label, randomized trial	mCRC	First line	Karnofsky, ≥ 70%	≥ 18
Ducreux M 2013 [26]	Phase II, open-label, randomized, non-comparative trial	mCRC	First line	ECOG, 0–2	18–75
Ducreux M 2011 [19]	Phase III, open-label, randomized parallel-arm trial	mCRC	First line	ECOG, 0–2	≥ 18
Fuchs CS 2007 [29]	Phase III, open-label, randomized trial	mCRC	First line	ECOG, 0–1	≥ 18
Hochster HS 2008a [44]	Randomized, open-label trial	mCRC	First line	ECOG, 0–1	≥ 18
Hochster HS 2008b [44]	Randomized, open-label trial	mCRC	First line	ECOG, 0–1	≥ 18
Köhne C-H 2008a [28]	Phase III, randomized trial, 2 × 2 factorial design	mCRC	First line	WHO, ≤ 2	≥ 18
Köhne C-H 2008b [28]	Phase III, randomized trial, 2 × 2 factorial design	mCRC	First line	WHO, ≤ 2	≥ 18
Martoni AA 2006 [46]	Phase II, randomized trial	Advanced CRC	First line	Karnofsky, ≥ 70	≥ 18
Pectasides D 2015 [47]	Phase III, randomized trial	Stage II–III CRC	Adjuvant	ECOG, 0–1	Not
DFS					
OS					
Pectasides D 2012 [23]	Phase III, randomized trial	Stage IV mCRC	First line	ECOG, 0–2	≥ 18
Porschen R 2007 [48]	Phase III, randomized trial	mCRC	First line	ECOG, 0–2	> 18
Rothenberg ML 2008 [18]	Phase III, randomized trial	mCRC	Second line	ECOG, 0–2	≥ 18
Seymour MT 2011 [49]	Randomized trial, 2 × 2 factorial design	mCRC	First line	WHO, ≤ 2	Not
ORR					
PFS					

Table 1. (Continued)

Study	Study design	Indication	Line of treatment/setting	Patient characteristics	
				Performance status	Age (years)
OS					
Souglakos J 2012 [25]	Phase II, randomized trial	mCRC	First line	ECOG, 0–2	≥ 18
Skof E 2009 [24]	Phase II, randomized trial	mCRC	Neoadjuvant	WHO, ≤ 1	18–75

Study	Median FU time (months)	Treatments Cape regimen	5-FU regimen	Sample size	Efficacy outcomes
Allegra CJ 2015 [45]	Not reported	Cape + radiation + OX Cape 825 mg/m^2 bid 7 days a week + radiation therapy *After protocol amendment* OX 50 mg/m^2 IV infusion weekly × 5 during radiation therapy, Cape 825 mg/m^2 bid 5 days a week	IV 5FU + radiation + OX 5-FU 225 mg/m^2 per day cIV 7 days a week + radiation therapy *After protocol amendment* OX 50 mg/m^2 IV infusion weekly × 5 during radiation therapy, 5-FU 225 mg/m^2 per day cIV 5 days a week	N_{Cape} = 785 $N_{5\text{-}FU}$ = 782	OS DFS
Cassidy J 2011 [27]	Not reported	Cape + OX + bevacizumab/placebo Cape 1000 mg/m^2 bid for 2 weeks in a 3-week cycle. OX 130 mg/m^2 IV infusion on day 1 Bevacizumab 7.5 mg/kg every third week or placebo	IV 5-FU + OX + bevacizumab/placebo LV 200 mg/m^2/day IV infusion followed by IV 5-FU bolus 400 mg/m^2/day and 600 mg/m^2/day in a 22-h cIV for two consecutive days q2w OX 85 mg/m^2 IV infusion on day 1, bevacizumab 5 mg/kg every second week or placebo	N_{Cape} = 1017 $N_{5\text{-}FU}$ = 1017	OS
de Gramont A 2012 [43]	48.5	Cape + OX + bevacizumab Bevacizumab 7.5 mg/kg IV infusion followed by OX 130 mg/m^2 IV infusion on day 1 q3w and Cape 1000 mg/m^2 bid q3w for eight cycles (24 weeks) Bevacizumab 7.5 mg/kg IV infusion on day 1 q3w for a further 24 weeks (eight cycles)	IV 5-FU + OX + bevacizumab Bevacizumab 5 mg/kg IV infusion on day 1 followed by OX 85 mg/m^2 IV with LV 200 mg/m^2 IV infusion, followed by 5-FU 400 mg/m^2 bolus then 600 mg/m^2 in a 22-h cIV On day 2, LV 200 mg/m^2 IV infusion, 5-FU 400 mg/m^2 bolus then 600 mg/m^2 in a 22-h cIV, with cycles repeated q2w for 12 cycles (24 weeks) Bevacizumab 7.5 mg/kg on day 1 q3w for a further 24 weeks (eight cycles)	N_{Cape} = 1145 $N_{5\text{-}FU}$ = 1155	OS DFS
Díaz-Rubio E 2007 [22]	17.5	Cape + OX Cape 1000 mg/m^2 bid for 14 days plus OX 130 mg/m^2 IV infusion on day 1 q3w	IV 5-FU + OX 5-FU 2250 mg/m^2 diluted in saline administered by cIV during 48 h on days 1, 8, 15, 22, 29, and 36, plus OX 85 mg/m^2 IV infusion on days 1, 15, and 29 every 6 weeks	N_{Cape} = 174 $N_{5\text{-}FU}$ = 174	ORR OS
Ducreux M 2013 [26]	36	Cape + IRI + bevacizumab IRI 200 mg/m^2 IV infusion on day 1, Cape 1000 mg/m^2 bid on days 1–14 followed by	IV 5-FU + IRI + bevacizumab 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 cIV over 46 h plus LV 400 mg/m^2 IV infusion plus IRI 180 mg/m^2	N_{Cape} = 72 $N_{5\text{-}FU}$ = 73	ORR PFS

Table 1. (Continued)

Study	Median FU time (months)	Treatments Cape regimen	5-FU regimen	Sample size	Efficacy outcomes
		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	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		
Ducreux M 2011 [19]	18.8	Cape + OX OX 130 mg/m^2 IV infusion on day 1 plus Cape 1000 mg/m^2 bid on days 1–14 q3w	IV 5-FU + OX OX 100 mg/m^2 IV infusion followed by LV 400 mg/m^2 IV infusion followed by 5-FU 400 mg/m^2 bolus injection then 5-FU 2400–3000 mg/m^2 cIV q2w	N_{Cape} = 156 $N_{5\text{-}FU}$ = 150	ORR PFS OS TTF
Fuchs CS 2007 [29]	34	Cape + IRI IRI 250 mg/m^2 IV infusion on day 1, Cape 1000 mg/m^2 bid on days 1–14 q3w	IV 5-FU + IRI IRI 180 mg/m^2 IV infusion over 90 min, LV 400 mg/m^2 IV infusion over 2 h; 5-FU 400 mg/m^2 bolus injection then 5-FU 2400 mg/m^2 cIV over 46 h q2w	N_{Cape} = 145 $N_{5\text{-}FU}$ = 144	ORR PFS
Hochster HS 2008a [44]	15–18.5	Cape + OX OX 130 mg/m^2 IV infusion on day 1 and Cape 1000 mg/m^2 orally bid on days 1–15 q3w	cIV 5-FU + OX OX 85 mg/m^2 IV infusion with LV 350 mg IV over 2 h plus FU 400 mg/m^2 IV bolus and 2400 mg/m^2 cIV over 46 h q2w	N_{Cape} = 48 $N_{5\text{-}FU}$ = 49	ORR
Hochster HS 2008b [44]	15–18.5	Cape + OX + bevacizumab Same as above + bevacizumab 7.5 mg/kg IV infusion q3w	cIV 5-FU + OX +bevacizumab Same as above + bevacizumab 5 mg/kg IV infusion q2w	N_{Cape} = 72 $N_{5\text{-}FU}$ = 71	ORR
Köhne C-H 2008a [28]	14.6	Cape + IRI + celecoxib IRI 250 mg/m^2 IV infusion on days 1 and 22 and Cape 1000 mg/m^2 bid on days 1–15 and 22–36 with celecoxib 800 mg: 2 × 200 mg bid	cIV 5-FU + IRI + celecoxib IRI 180 mg/m^2 IV infusion on days 1, 15 and 22; FA 200 mg/m^2 IV on days 1, 2, 15, 16, 29 and 30; 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 22hour cIV given after the bolus on days 1, 2, 15, 16, 29, and 30, with celecoxib 800 mg: 2 × 200 mg bid	N_{Cape} = 23 $N_{5\text{-}FU}$ = 19	ORR PFSOS
Köhne C-H 2008b [28]	14.6	Cape + IRI + placebo IRI 250 mg/m^2 IV infusion on days 1 and 22 and Cape 1000 mg/m^2 bid on days 1–15 and 22–36, with placebo	cIV 5-FU + IRI + placebo IRI 180 mg/m^2 IV infusion on days 1, 15, and 22; FA 200 mg/m^2 IV on days 1, 2, 15, 16, 29, and 30; 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 22-h cIV given after the bolus on days 1, 2, 15, 16, 29, and 30, with placebo	N_{Cape} = 21 $N_{5\text{-}FU}$ = 22	ORRPFSOS
Martoni AA 2006 [46]	Not reported	Cape + OX OX 130 mg/m^2 IV infusion Cape 1000 mg/m^2 bid on days 1–14	cIV 5-FU + OX Dexamethasone 20 mg in 100 mL of saline IV, granisetron 3 mg in 100 mL of saline IV, OX 130 mg/m^2 in 500 mL of 5% glucose solution IV and 5-FU 250 mg/m^2 daily cIV on days 1–14	N_{Cape} = 62 $N_{5\text{-}FU}$ = 56	ORR
Pectasides D 2015 [47]	74.4	Cape + OX OX 130 mg/m^2 IV infusion on	cIV 5-FU + OX OX 85 mg/m^2 IV infusion on day 1, LV 200 mg/m^2 IV infusion on day 1 and 5-FU 400 mg/m^2 IV bolus on day 1	N_{Cape} = 211 $N_{5\text{-}FU}$ = 197	DFS OS

Table 1. (Continued)

Study	Median FU time (months)	Treatments Cape regimen	5-FU regimen	Sample size	Efficacy outcomes
		day 1 and Cape 1000 mg/m^2 bid on days 1–14, q21 days for eight cycles	followed by a 5FU 2400 mg/m^2 46-h cIV, q14 days for 12 cycles		
Pectasides D 2012 [23]	42	Cape + IRI + bevacizumab Bevacizumab 7.5 mg/kg IV infusion on day 1, IRI 240 mg/m^2 IV infusion on day 1, and Cape 1000 mg/m^2 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/m^2 IV infusion on day 1, LV 200 mg/m^2 IV infusion on day 1, 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 46-h cIV q14 days for 12 cycles	N_{Cape} = 143 $N_{5\text{-}FU}$ = 142	ORR PFS OS
Porschen R 2007 [48]	17.3	Cape + OX Cape 1000 mg/m^2 bid from days 1 to 14 and OX 70 mg/m^2 IV infusion on days 1 and 8	cIV 5-FU + OX OX 50 mg/m^2 IV infusion, LV 500 mg/m^2, and 5-FU 2000 mg/m^2 as a 22-h cIV on days 1, 8, 15, and 22	N_{Cape} = 241 $N_{5\text{-}FU}$ = 233	ORR PFS OS TTF
Rothenberg ML 2008 [18]	Not reported	Cape + OX OX 130 mg/m^2 IV infusion on day 1, Cape 1000 mg/m^2 bid on days 1–15 of a 3-week cycle	cIV 5-FU + OX LV 200 mg/m^2/day IV infusion, 5-FU 400 mg/m^2/day bolus and 600 mg/m^2/day 22-h cIV for two consecutive days q2w, OX 85 mg/m^2 IV infusion on day 1	N_{Cape} = 313 $N_{5\text{-}FU}$ = 314	PFS OS ORR TTF
Seymour MT 2011 [49]	Not reported	Cape + OX Group C: Cape 1000 mg/m^2 bid on days 1–15. The cycle was repeated q21 days Group D: OX 104 mg/m^2 IV infusion and Cape 800 mg/m^2 bid on days 1–15 q21 days	cIV 5-FU + OX Group A: Levofolinate 175 mg IV infusion, 5-FU 320 mg/m^2 IV bolus, and 5FU 2240 mg/m^2 46h cIV. The cycle was repeated q14 days Group B: Levofolinate 175 mg/m^2 and OX 68 mg/m^2 by concurrent IV infusion, 5-FU 320 mg/m^2 IV bolus, and 5-FU 1920 mg/m^2 46-h cIV infusion q14 days	N_{Cape} = 229 $N_{5\text{-}FU}$ = 230	ORR PFS OS
Souglakos J 2012 [25]	32	Cape + IRI + bevacizumab Cape 2000 mg/m^2 on days 1–14, IRI 250 mg/m^2 IV infusion on day 1, and bevacizumab 7.5 mg/kg IV infusion q3w	cIV 5-FU + IRI + bevacizumab IRI 180 mg/m^2 IV infusion on day 1, FA 200 mg/m^2 IV infusion on days 1 and 2, and 5-FU 400 mg/m^2 IV bolus on day 1 and 600 mg/m^2 as a 22-h cIV on days 1 and 2, plus 5 mg/kg bevacizumab on day 1, q2w	N_{Cape} = 166 $N_{5\text{-}FU}$ = 167	ORR OS PFS
Skof E 2009 [24]	17	Cape + IRI IRI 250 mg/m^2 IV infusion on day 1 and Cape 1000 mg/m^2 bid from days 2 to 15, q21 days	cIV 5-FU + IRI IRI 180 mg/m^2 IV infusion, 5-FU 400 mg/m^2 IV bolus, LV 200 mg/m^2 IV infusion, 5-FU 2400 mg/m^2 46-h cIV on day 1, q14 days	N_{Cape} = 41 $N_{5\text{-}FU}$ = 46	ORR

5-FU 5-fluorouracil, *bid* twice a day, *Cape* capecitabine, *cIV* continuous infusion, *CRC* colorectal cancer, *DFS* disease-free survival, *ECOG* Eastern Cooperative Oncology Group, *FA* folinic acid, *IRI* irinotecan, *IV* intravenous, *LV* leucovorin, *mCRC* metastatic colorectal cancer, *ORR* objective response rate, *OS* overall survival, *OX* oxaliplatin, *q* every, *q2w* every 2 weeks, *q3w* every 3 weeks, *TTF* time to treatment failure

Risk-of-bias assessment

The methodological quality of the included studies was acceptable overall. All the included trials applied randomization; however, six [18, 24–26, 29, 46] did not describe the randomization method. Six trials [19, 22, 27, 43, 48, 49] reported central allocation of treatments, while most did not report any clear concealment of allocation, which could have potentially introduced some selection bias. Baseline characteristics were comparable between treatment arms in most studies, although three trials [26, 28, 44] presented some differences in baseline characteristics. All 17 studies were open label; however, we presumed that blinding was not possible because of the different administration routes (oral vs infusion) of the comparison groups. Two studies [18, 19] reported a blinded review of tumor response by an independent review committee, and for a third study [27], the outcome was judged not likely to be influenced by lack of blinding. For the other studies, either the outcome assessments were performed by the trial investigators or no information on who made the assessments was provided; we therefore suspected detection bias in these trials. The risk of reporting bias was unclear in most of the studies and could not be evaluated. The qualities of the included trials are presented in Fig. 2.

Efficacy outcomes

ORR

The fixed-effects model meta-analysis ($\chi^2 = 7.01$, $P = 0.93$, $I^2 = 0.0\%$) showed a significantly greater response rate in cIV-5-FU-based regimens than in capecitabine-based regimens (RR 0.9; 95% CI 0.83–0.98, $P = 0.01$) in 3786 patients (Fig. 3a). Subgroup analyses demonstrated a significantly greater response rate in cIV-5-FU-based regimens compared with capecitabine-based regimens when combined with oxaliplatin (RR 0.90, 95% CI 0.81–1.00, $P = 0.04$), while no significant difference between the two regimens was detected when combined with irinotecan (RR 0.91, 95% CI 0.80–1.03, $P = 0.13$) (Fig. 3).

PFS and TTF

The fixed-effects meta-analyses (PFS: $\chi^2 = 8.34$, $P = 0.40$, $I^2 = 4.0\%$; TTF: $\chi^2 = 3.48$, $P = 0.18$, $I^2 = 43.0\%$) did not show any significant difference between the two regimens in terms of PFS (HR 1.03, 95% CI 0.97–1.10, $P = 0.32$) or TTF (HR 1.05, 95% CI 0.94–1.18, $P = 0.39$) (Fig. 3b, c). The observation remained valid in subgroup analyses, with no difference in PFS between the two regimens when combined 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, $P = 0.36$) (Fig. 3b, c). No subgroup analyses were performed for TTF as very few studies reported TTF data.

OS

The fixed-effects meta-analyses ($\chi^2 = 16.75$, $P = 0.12$, $I^2 = 34.0\%$) did not demonstrate any significant difference in OS between the two regimens (HR 0.99, 95% CI 0.94–1.05, $P = 0.84$), nor did subgroup analyses in 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, $P = 0.86$) (Fig. 3d).

DFS

None of the studies analyzing DFS found any significant difference in DFS between the two regimen groups, nor did the fixed-effects meta-analyses (HR 0.96, 95% CI 0.85–1.08, $P = 0.50$) (Fig. 3e).

Assessment of publication bias for ORR and OS

No publication bias was detected for ORR ($P = 0.787$). For OS, Egger's test indicated the potential presence of publication bias ($P = 0.006$). Nevertheless, the 'trim-and-fill' method did not detect any substantial impact of publication bias on effect size as it remained the same after adjustment (HR 0.958, 95% CI 0.91–1.01).

Safety outcomes

Grade 3/4 GI AEs, such as diarrhea (RR 1.68, 95% CI 1.34–2.10, $P < 0.001$), vomiting (RR 1.30, 95% CI 1.08–1.56, $P = 0.006$), and nausea (RR 1.34, 95% CI 1.14–1.59, $P < 0.001$), were more frequent with capecitabine-based regimens than with cIV-5-FU-based regimens. Additionally, patients on capecitabine-based regimens had > 5-fold increased risk (RR 5.46, 95% CI 4.01–7.43, $P < 0.001$) of developing grade 3/4 hand–foot syndrome over patients on cIV 5-FU. Grade 3/4 thrombocytopenia (RR 1.62, 95% CI 1.07–2.44, $P = 0.02$) and dehydration (RR 2.33, 95% CI 1.58–3.45, $P < 0.001$) were also more frequent in capecitabine-based regimens; however, grade 3/4 neutropenia (RR 0.34, 95% CI 0.23–0.49, $P < 0.001$) and stomatitis (RR 0.51, 95% CI 0.30–0.88, $P = 0.01$) were more frequent in cIV-5FU-based regimens. No significant differences were found between the two regimens in grade 3/4 neuropathy and neurotoxicity, lethargy/fatigue, leukopenia, anorexia, cardiovascular events, mucositis, infection, allergic reaction, abdominal pain, alopecia, fever, constipation, and SGOT or SGPT increase.

Importantly, subgroup analyses showed an inflated effect size when treatment was combined with irinotecan. Specifically, the RR (95% CI) of developing diarrhea when treated with capecitabine plus irinotecan increased to 2.37 (1.80–3.14) compared with cIV 5-FU plus irinotecan; the risk of nausea increased to 1.62 (1.00–2.62), that of vomiting to 1.87 (1.11–3.16), and that of dehydration to 3.28 (1.54–6.96).

In treatments combined with oxaliplatin, grade 3/4 diarrhea, nausea, hand–foot syndrome, thrombocytopenia, and dehydration were still significantly more frequent in capecitabine-based regimens than in cIV-5-FU-based regimens, while neutropenia still occurred more frequently in cIV-5-FU-based regimens when combined with oxaliplatin or irinotecan.

A summary of safety outcomes meta-analyses and corresponding subgroup meta-analyses is presented in Table 2.

Assessment of publication bias for safety outcomes

Egger's test for all safety outcomes was not significant, and no publication bias was detected.

Discussion

Today, cIV 5-FU remains one of the most extensively prescribed chemotherapy agents in CRC. Several meta-analyses have been conducted to evaluate the

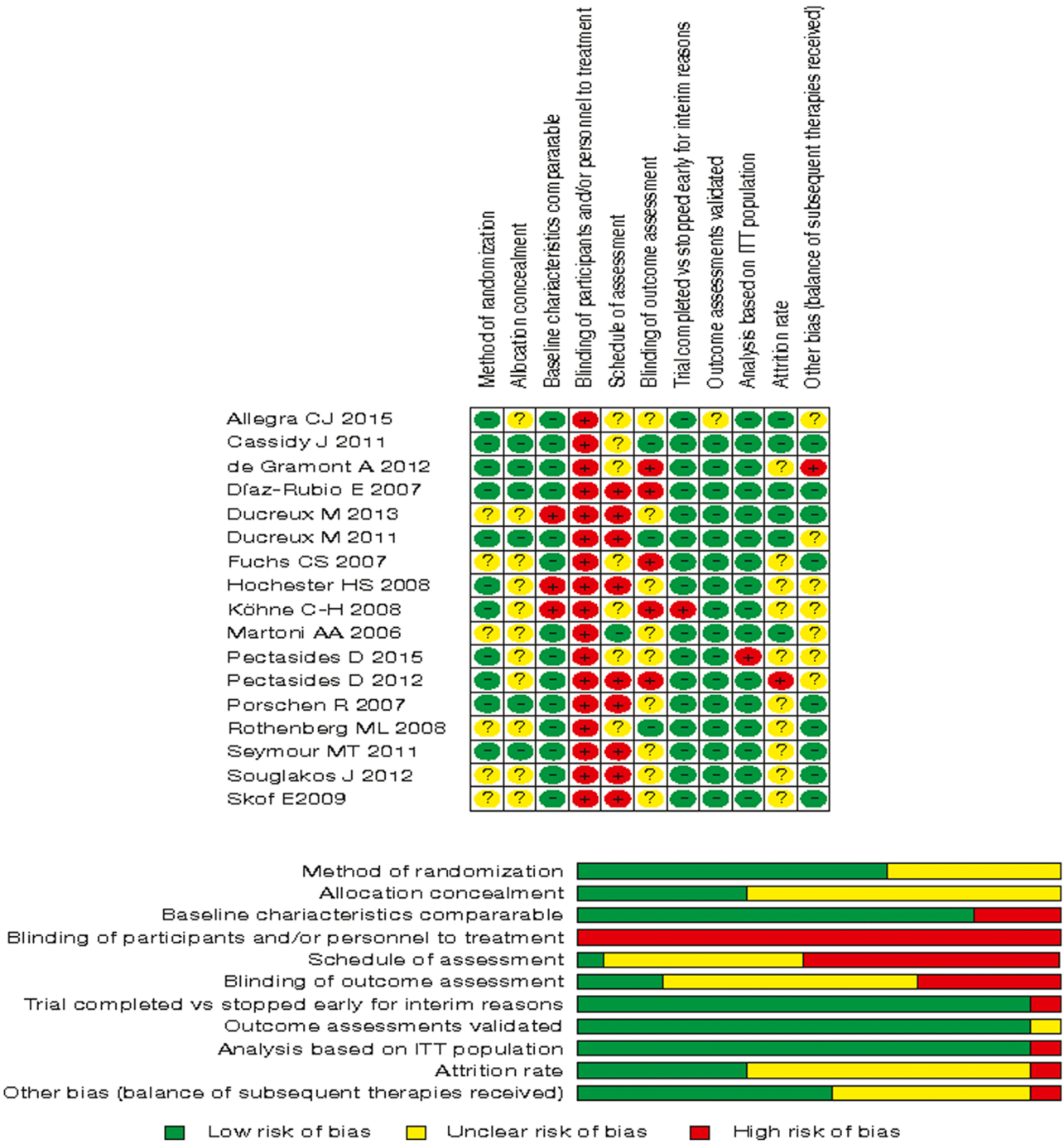


Fig. 2. Risk-of-bias summary and graph. *ITT* intention to treat.

efficacy and safety of cIV-5-FU- and capecitabine-based regimens. However, these meta-analyses were heterogeneous in terms of study inclusion criteria, and superiority could not be demonstrated by either regimen. Most of these meta-analyses included several oral fluoropyrimidines as comparators [31••, 32–34],

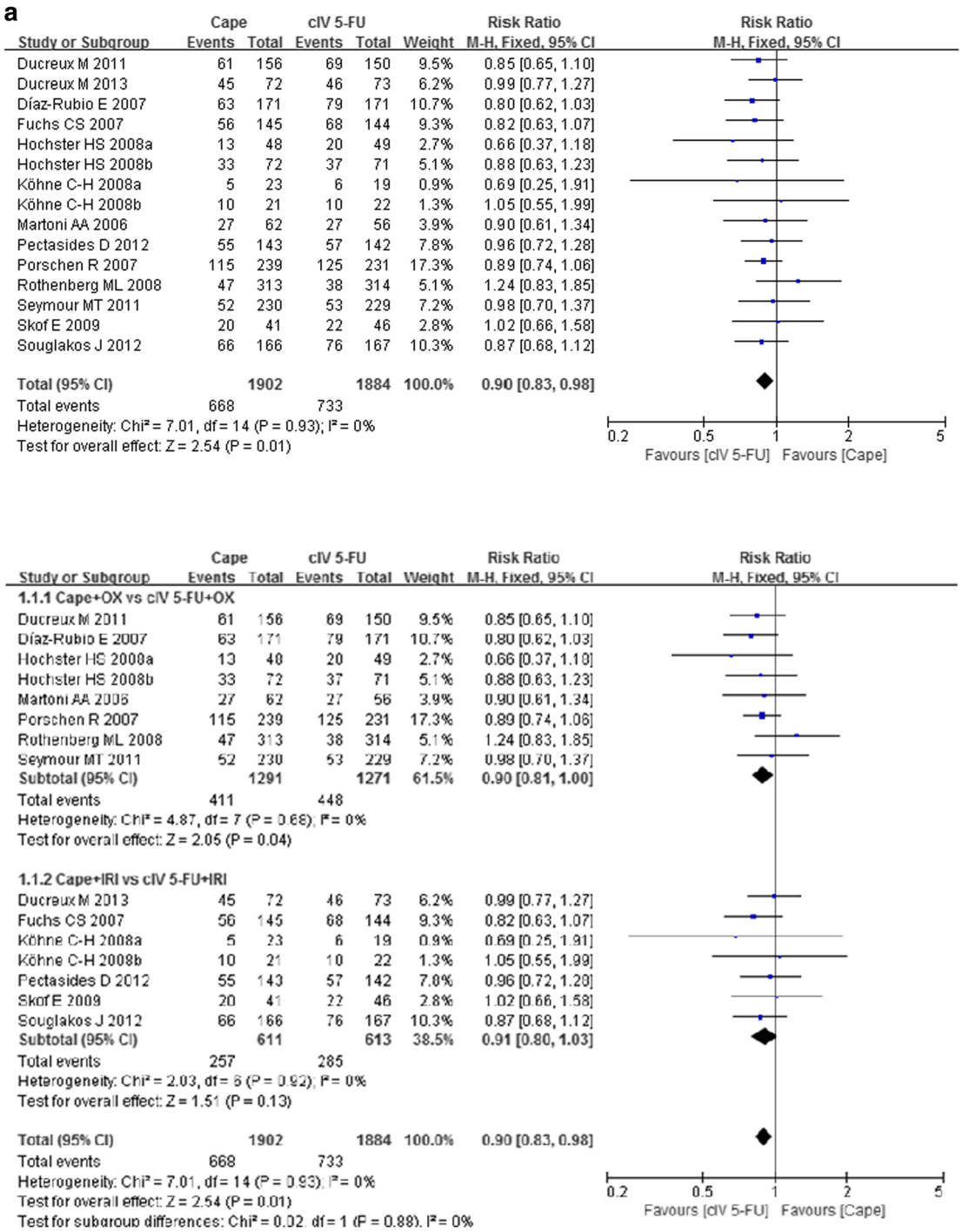
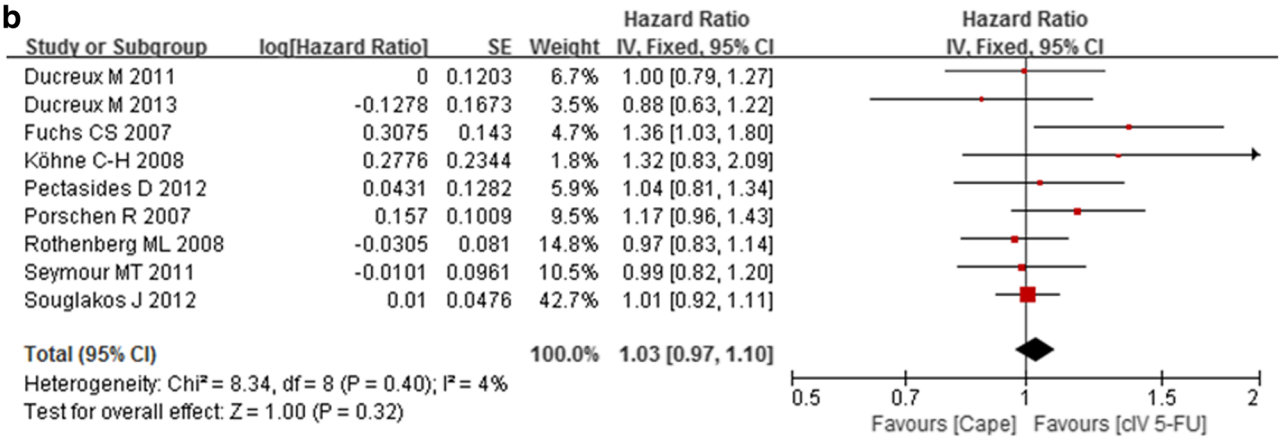
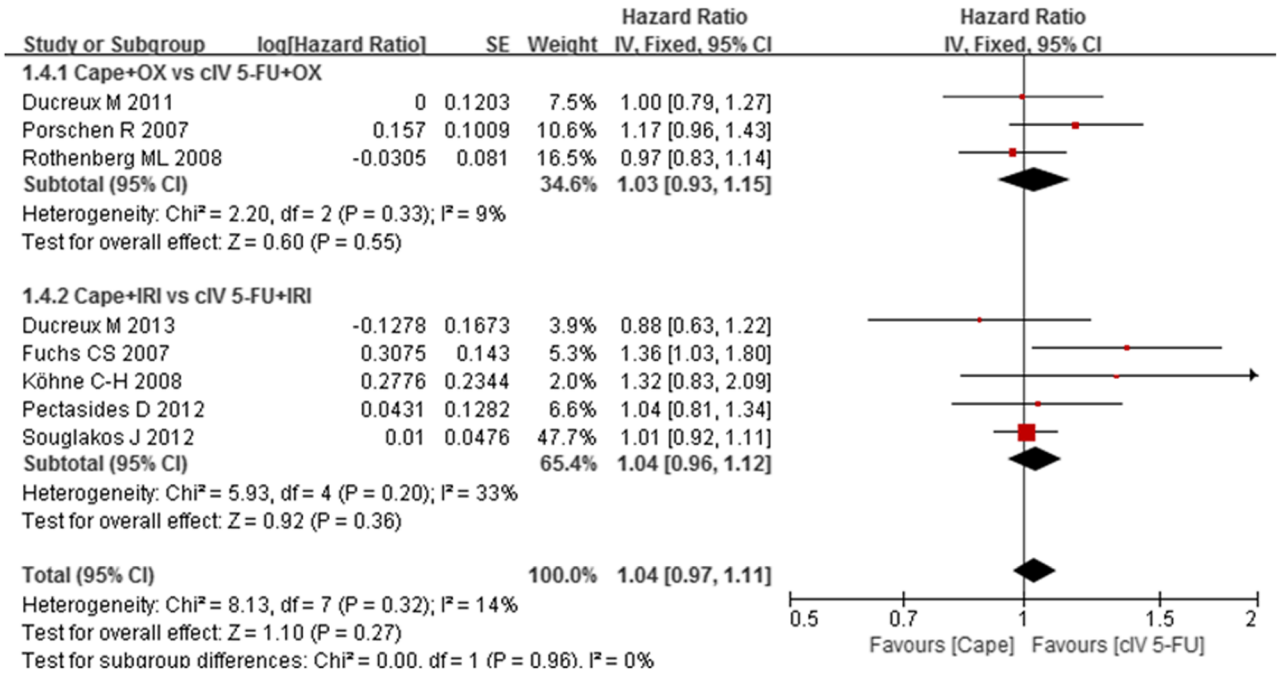


Fig. 3. Forest plots and statistics for **a** ORR, **b** PFS, **c** TTF, **d** OS, and **e** DFS meta-analyses and subgroup analyses (for ORR, PFS, and OS). *5-FU* 5-fluorouracil, *Cape* capecitabine, *CI* confidence interval, *cIV* continuous infusion, *df* degrees of freedom, *DFS* disease-free survival, *IRI* irinotecan, *InV* inverse variance, *M-H* Mantel–Haenszel, *ORR* objective response rate, *OS* overall survival, *OX* oxaliplatin, *PFS* progression-free survival, *SE* standard error, *TTF* time to treatment failure.

b





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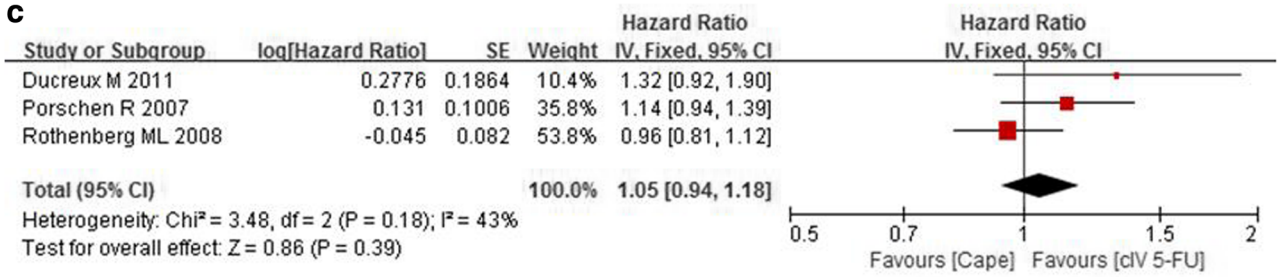

Fig. 3. continued.

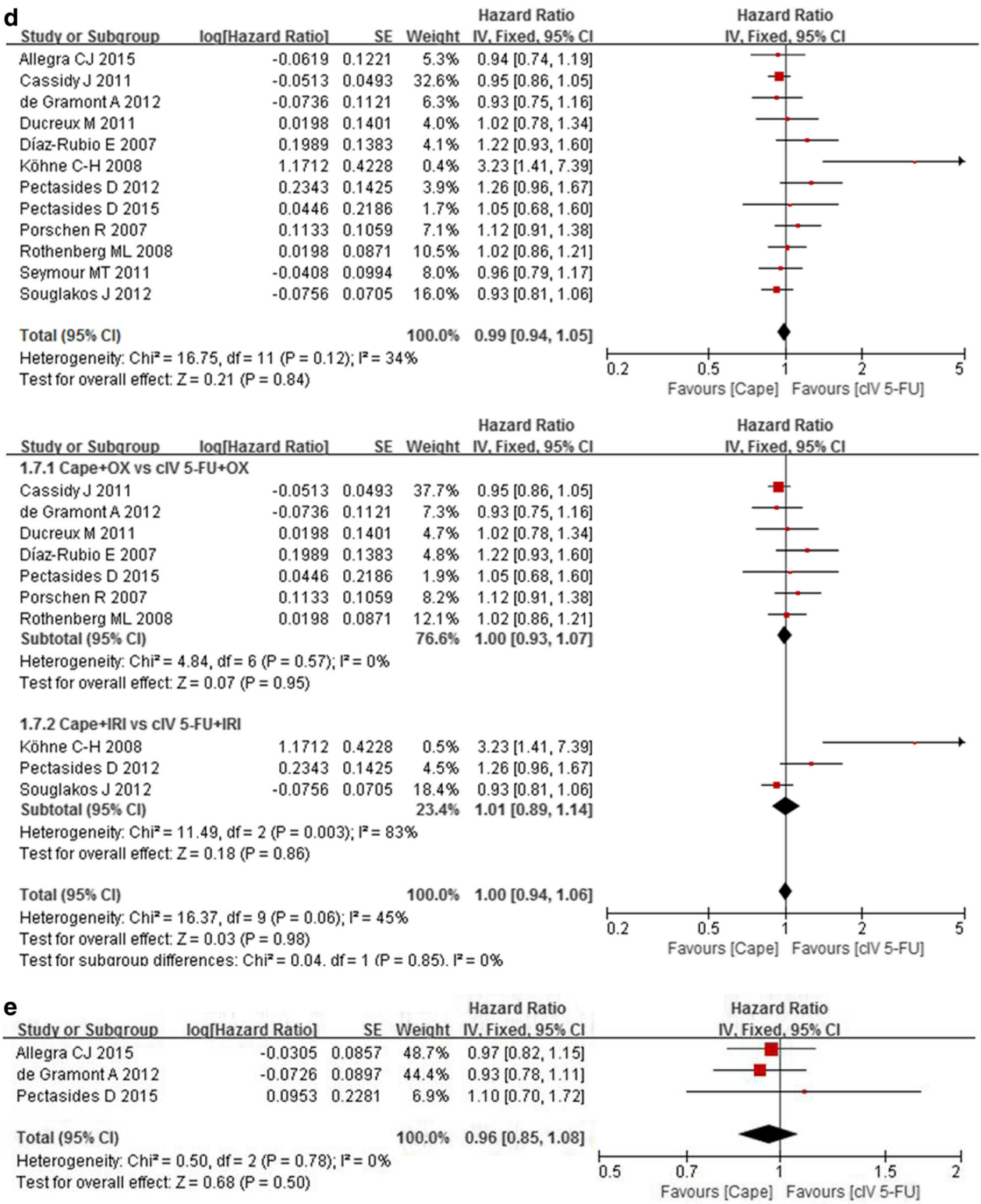

Fig. 3. continued.

and some included studies in which IV 5-FU was administered solely as a bolus injection [31••, 34]. Studies also differed in terms of cancer sites and type of studies included (RCT vs observational).

Though our meta-analysis included many of the articles featured in other meta-analyses, our review is the first to compare capecitabine with cIV 5-FU in advanced CRC and mCRC, providing a comparative overview of the most commonly used fluorouracil modalities in relation to tumor response, survival, and tolerability profile. We demonstrated that cIV 5FU is superior to capecitabine in terms of ORR. Similar findings were obtained for the agents in combination with oxaliplatin, but not with irinotecan. Our observation is consistent with a meta-analysis [34] that reported lower response rates with oral fluoropyrimidine-based regimens compared with cIV-5-FU-based regimens.

Despite the ORR difference, our results suggest that patient survival is similar between the two therapies. PFS comparisons in previous meta-analyses are conflicting. Although some meta-analyses reported shorter PFS for capecitabine-based regimens [34, 35], others did not find any significant difference between oral and IV fluoropyrimidines when capecitabine, doxifluridine, or S-1 was used [31••]. The inconsistency is probably due to the differences in the types of fluoropyrimidines. In this study, OS was similar in both groups, a finding consistent across several others [31••, 32, 33, 50].

Although our meta-analysis showed no significant difference in DFS and TTF between the two groups, it was difficult to draw any conclusion given the small number of trials reporting DFS and TTF data. These results need to be confirmed by a larger sample of RCTs.

While no survival advantage was evident with either agent, the improved ORR with cIV 5-FU might help achieve treatment goal, especially for patients with initially unresectable or potentially resectable mCRC, or for those whose treatment goal is disease control [6•].

Importantly, our meta-analysis presents a comprehensive comparative review of the safety outcomes of the two regimens, enabling a better understanding of their tolerability profile.

Diarrhea is one of the most common AEs reported with fluoropyrimidines, resulting in quality-of-life deterioration and poor treatment compliance [51]. Severe diarrhea is also known to worsen with fluoropyrimidine–irinotecan combinations; some trials reported increased toxicity, even death, with the capecitabine–irinotecan combination [28, 29].

Our analysis showed that capecitabine-based regimens are associated with a 1.7-fold increased risk of grade 3/4 diarrhea over cIV-5-FU-based regimens; the risk was even more pronounced when irinotecan was added. Iacovelli et al. [52] reviewed the incidence of grade 3/4 diarrhea in patients treated with capecitabine or cIV 5FU for colorectal, gastric, and breast cancer. In patients with CRC, incidence of severe diarrhea was 17% in the capecitabine group, significantly higher than that reported for cIV 5-FU (RR = 1.46, $P < 0.0001$); RR increased to 2.35 when capecitabine was combined with irinotecan. The increased risk of diarrhea was also described in a meta-analysis that included patients with rectal cancer [33], and in another that compared several oral fluoropyrimidines with cIV 5-FU [31••]. The frequency of chemotherapy-induced diarrhea has been shown to be related to the chemotherapy regimen and the administration schedule [53]. Given that fluoropyrimidines have long been associated with increased occurrence of diarrhea [53], we hypothesize that the increased

Table 2. Summary of safety outcomes meta-analyses

Outcome (grade 3–4)	Trials reporting outcome	Model assumptions	Relative risk (95% CI) Reference group 5-FU	Subgroup analysis Relative risk (95% CI) Reference group 5-FU	
				Combined with oxaliplatin	Combined with irinotecan
Diarrhea	[18, 19, 22–29, 43, 44, 46, 48, 49]	Random effects	1.68 (1.34–2.10)[c]	1.49 (1.14–1.96)[a]	2.37 (1.80–3.14)[c]
Dehydration	[29, 44, 45]	Fixed effects	2.33 (1.58–3.45)[c]	1.89 (1.07–3.33)[a]	3.28 (1.54–6.96)[a]
Anorexia	[18, 22, 23, 26, 49]	Fixed effects	1.60 (0.92–2.80)	1.53 (0.77–3.04)	1.58 (0.42–5.94)
Hand–foot syndrome	[18, 19, 22–29, 43–46, 49]	Fixed effects	5.46 (4.01–7.43)[c]	5.55 (3.94–7.81)[c]	5.27 (2.13–13.00)[b]
Mucositis	[22, 23, 25]	Fixed effects	0.55 (0.23–1.33)	0.47 (0.15–1.41)	0.75 (0.17–3.32)
Stomatitis	[18, 19, 27, 46, 49]	Fixed effects	0.51 (0.30–0.88)[a]	NA	NA
Cardiovascular events	[23, 25, 28]	Fixed effects	1.24 (0.56–2.75)	NA	NA
Neuropathy and neurotoxicity	[19, 22, 23, 27, 43, 44, 46, 48, 49]	Fixed effects	0.94 (0.84–1.06)	NA	NA
Neutropenia	[18, 19, 22–27, 29, 43, 44, 46, 48, 49]	Random effects	0.34 (0.23–0.49)[c]	0.24 (0.17–0.33)[c]	0.70 (0.57–0.86)[b]
Lethargy/fatigue	[18, 23–26, 44, 45, 49]	Fixed effects	1.22 (0.94–1.57)	1.11 (0.81–1.53)	1.01 (0.55–1.86)
Nausea	[18, 19, 22–29, 43–45, 48, 49]	Fixed effects	1.34 (1.14–1.59)[c]	1.26 (1.05–1.52)[a]	1.62 (1.00, 2.62)
Vomiting	[18, 19, 22–24, 26–29, 43, 45, 48, 49]	Fixed effects	1.30 (1.08–1.56)[a]	1.20 (0.98–1.46)	1.87 (1.11–3.16)[a]
Thrombocytopenia	[18, 19, 22, 23, 25, 44, 46, 49]	Fixed effects	1.62 (1.07–2.44)[a]	1.67 (1.06–2.62)[a]	1.26 (0.44–3.58)
Leukopenia	[22, 23, 26, 44]	Fixed effects	0.74 (0.44–1.24)	0.52 (0.25–1.10)	1.09 (0.51–2.33)
Anemia	[19, 22, 23, 25, 26, 44, 46, 49]	Fixed effects	0.75 (0.42–1.35)	0.76 (0.38–1.52)	1.00 (0.27–3.67)
Asthenia	[18, 19, 22]	Fixed effects	0.76 (0.52–1.11)	NA	NA
SGOT/SGPT increase	[22, 23, 46]	Fixed effects	1.34 (0.45–4.00)	0.97 (0.26–3.58)	2.98 (0.31–28.26)
Constipation	[18, 22, 23, 26]	Fixed effects	0.61 (0.26–1.47)	0.63 (0.25–1.61)	0.51 (0.05–5.47)
Fever	[19, 22, 23]	Fixed effects	0.98 (0.32–2.99)	0.62 (0.16–2.33)	4.96 (0.24–102.39)
Alopecia	[19, 22, 23, 25]	Fixed effects	1.54 (0.92–2.59)	NA	NA
Abdominal pain	[18, 22, 44–46]	Fixed effects	1.01 (0.66–1.55)	NA	NA
Allergic reaction	[22, 23]	Fixed effects	2.06 (0.58–7.27)	1.91 (0.48–7.58)	2.98 (0.12–72.44)
Infection	[23, 26]	Fixed effects	0.77 (0.19–3.07)	0.93 (0.06–14.83)	0.72 (0.14–3.58)

5-FU 5-fluorouracil, *CI* confidence interval, *NA* not applicable (analysis not performed), *SGOT* serum glutamic oxaloacetic transaminase, *SGPT* serum glutamic pyruvic transaminase

[a] $P < 0.05$

[b] $P < 0.001$

[c] $P < 0.0001$

incidence of diarrhea with capecitabine specifically could be related to the daily administration schedule of the drug, compared with the commonly more protracted schedule for cIV 5-FU. In the two RCTs included in our meta-analysis that adopted a daily administration schedule for cIV 5-FU [45, 46], no significant difference in diarrhea incidence could be detected between the two regimens. Also, Allegra et al. [45] demonstrated that modifying the administration schedule of both agents from 7 to 5 days a week resulted in a significant decrease in grade 3–5 diarrhea in both groups.

We also observed an increased risk of other grade 3/4 GI AEs. Patients treated with capecitabine had a 1.3-fold increased risk of experiencing vomiting or nausea over treatment with cIV 5-FU; the risk was more pronounced when capecitabine was combined with irinotecan, demonstrating again the excessive toxicity associated with this combination. Our results were comparable to those of other meta-analyses reporting an increased risk of GI AEs with capecitabine [31••, 32, 35].

Another common and dose-limiting toxicity associated with capecitabine is hand–foot syndrome, which appeared to be five times more common with capecitabine compared with cIV 5-FU. Furthermore, there was an almost two-fold increased risk of grade 3/4 thrombocytopenia associated with capecitabine regimens. A meta-analysis comparing capecitabine plus oxaliplatin with cIV 5-FU plus oxaliplatin as first-line treatment for mCRC reported similar findings, with a higher incidence of grade 3/4 thrombocytopenia and hand–foot syndrome with capecitabine plus oxaliplatin [36]. The increased risk of hand–foot syndrome with oral fluoropyrimidines in general, and capecitabine specifically, was also a recurrent finding in other meta-analyses [32, 33].

We demonstrated that the incidence of grade 3/4 neutropenia and stomatitis was higher in patients treated with cIV-5-FU-based regimens than in those treated with capecitabine-based regimens. We suggest that the increased risk of neutropenia could have been associated with the concomitant use of bolus 5-FU administration with cIV 5-FU in most of the studies included in our meta-analysis. This is supported by the findings of the Meta-analysis Group in Cancer [13], which demonstrated increased hematologic toxicity in patients treated with bolus 5FU compared with cIV 5-FU. Importantly, studies that did not include 5-FU bolus administration did not report any difference in neutropenia incidence between the two treatment groups [22, 46, 48].

Our results prove that, although capecitabine seems more convenient in terms of administration, it exhibits an unfavorable tolerability profile that is likely to impede patients' quality of life; therefore, its use should be carefully examined, especially when combination therapy is required. Although tolerability is a challenge with fluoropyrimidines in general, we could not fully explain the increased occurrence of AEs—especially GI AEs—associated with capecitabine compared with cIV 5-FU. We could not associate any patient-related factor to this observation, as the enrolled patient populations were homogeneous in terms of baseline characteristics, specifically renal function and median age, across all included studies except one [8] which enrolled a slightly older population without having any impact on the direction of the results. In addition, none of the studies explored factors associated with capecitabine toxicity in multivariable analyses. Further investigations are needed to understand the underlying mechanism for this difference.

We believe that several factors might have affected our meta-analysis results. Firstly, our data were derived from published reports of the included articles, which does not represent the most reliable source of data for meta-analyses. The use of individual patient data would have provided more robust conclusions. Secondly, there was a high degree of heterogeneity in study treatment regimens among the included studies with regard to schedule and combined therapy. In addition, increased toxicity could have resulted in dose and treatment-schedule modification, as well as poor adherence to treatment in both groups, which could have masked the true efficacy effect size. Finally, the use of different toxicity-assessment criteria and approaches for toxicity management could have affected toxicity manifestation. Meta-regression methods could be considered in future to further confirm our findings while controlling for potential covariates.

Conclusions

In conclusion, our meta-analysis suggests that cIV 5-FU remains a more effective and safer modality of fluorouracil administration, owing to its improved tumor response and toxicity profile. We believe that these results present as supporting evidence to guide clinical practice in CRC management while giving careful consideration to tolerability and efficacy advantage, as demonstrated from pooled RCTs.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare they have conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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