

Oral Tegafur-Uracil Combination plus Leucovorin versus Other Fluoropyrimidine Agents in Colorectal Cancer: A Systematic Review and Meta-Analysis

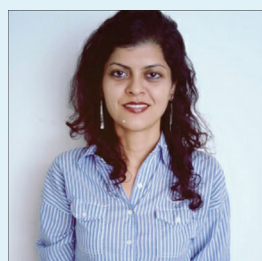
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Abstract



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Background Systemic fluoropyrimidines, both oral and intravenous, are an integral part of colorectal cancer (CRC) management. They can be administered either with curative or palliative intent.

Objectives This article examines the literature to analyze the efficacy and safety of the oral fixed-dose combination of uracil and tegafur (UFT)/leucovorin (LV) compared with other fluoropyrimidine agents, with an intention to implement the findings into the current treatment algorithms for CRC.

Methods An exhaustive systematic literature search was performed for prospective studies using PUBMED, Cochrane Library, and EMBASE database. Studies which met eligibility criteria were shortlisted and grouped into chemotherapy given for curative or palliative intent.

Results Eight trials were shortlisted involving 4,486 patients for the analysis. There was no difference between UFT/LV and other fluoropyrimidines in the primary endpoints—disease-free survival (hazard ratio [HR] 1.01; 95% confidence interval [CI] 0.90–.15; $p = 0.81$) and progression-free survival (HR 0.87; 95% CI 0.66–.66; $p = 0.35$) for curative and palliative intent CRC patients, respectively. In secondary analyses, there was no significant difference observed between UFT and other fluoropyrimidines in overall survival in CRC patients with curative intent (HR 1.04; 95% CI 0.88–1.23; $p = 0.63$) and palliative intent (HR 1.02; 95% CI 0.97–1.06; $p = 0.42$). In the safety analysis, we found significantly lesser patients on UFT/LV had stomatitis/mucositis (odds ratio [OR] 0.20; 95% CI 0.05–0.85; $p = 0.03$), fever (OR 0.46; 95% CI 0.29–0.71; $p < 0.001$), infection (OR 0.42; 95% CI 0.24–0.74; $p < 0.01$), leukopenia (OR 0.04; 95% CI 0.00–0.95; $p = 0.05$), febrile neutropenia (OR 0.03; 95% CI 0.00–0.24; $p = 0.001$), and thrombocytopenia (OR 0.14; 95% CI 0.02–0.79; $p = 0.03$) compared with other fluoropyrimidines.

Keywords

- ▶ uracil-tegafur
- ▶ colorectal cancer
- ▶ 5-fluorouracil
- ▶ meta-analysis
- ▶ systematic review

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Conclusion Oral UFT/LV is equally efficacious to other fluoropyrimidines, especially intravenous 5-fluorouracil, in the management of early as well as advanced CRC patients. Importantly, UFT/LV has a superior safety profile compared with other fluoropyrimidines in terms of both hematological and nonhematological adverse events.

Introduction

Globally, colorectal cancer (CRC) is the second leading cause of death due to neoplasm.¹ According to Globocan data of 2018, in India, an estimated 27,605 people were diagnosed with colon cancer and it accounted for 19,548 deaths.² The survival rates have significantly improved in the last two decades because of better treatment options such as surgery, radiotherapy, chemotherapy, and combination of both (radiotherapy and chemotherapy).³ If the cancer is detected in early stages (stage I–III), treatment is done with curative intent and therapy options includes neoadjuvant intravenous 5-fluorouracil (5-FU) therapy, followed by total mesorectal excision, and adjuvant intravenous 5-FU and oxaliplatin therapies.^{4,5} On the contrary, if the cancer is detected in the late stage—inoperable advanced or metastatic disease—management is done with palliative intent by adopting chemotherapy approach with the popular drug intravenous 5-FU.^{4,5} 5-FU is widely used in the treatment of solid malignancies.

Historically, intravenous 5-FU has been widely used in the treatment of CRC; however, the use of oral preparation has been limited due to unpredictable pharmacokinetics and gastrointestinal-related adverse events.⁶ To overcome the pharmacokinetic pitfall, 5-FU is combined with leucovorin (LV), which results in a more stable complex because of inhibition of thymidylate synthase enzyme leading to better efficacy.^{7,8} Moreover, research into biomodulation of oral 5-FU has led to the development of uracil and tegafur (UFT), a fixed-dose combination of tegafur and uracil, in 1:4 proportions.⁹ Tegafur is a prodrug of 5-FU, which results in prolonged action and release, while uracil provides a better toxicokinetic profile for the combination.¹⁰ Patients prefer oral over intravenous preparation due to ease of administration, given that oral administration is not inferior to intravenous preparation.^{11,12} The oral formulation, UFT, was approved in advanced CRC by the Japanese regulatory authority based on a multicenter randomized trial.¹³ UFT is approved in > 50 countries for various cancers. In India, the Central Drugs Standard Control Organization has approved UFT in 2007 for CRC. Currently, four brands of UFT are marketed in India, namely Luporal (Lupin), Uracel (Celon Labs), BDFucil (BDR Pharmaceuticals), and Tegafi (Intas).¹⁴

In the context of meta-analysis relevant to UFT, a 2009 study identified five randomized clinical trials and addressed the research question whether UFT/LV combination was noninferior to intravenous preparation.¹⁵ The analysis showed that UFT/LV was equal in efficacy to intravenous 5-FU, with a hazard ratio (HR) of 1.01 (95% confidence interval [CI] 0.91–1.12) for overall survival (OS). However,

superiority was demonstrated in terms of better toxicokinetic profile, especially hematologic adverse events. Additionally, a Cochrane meta-analysis revealed that different oral preparations of 5-FU compared with intravenous formulation had similar efficacy, but a better hematological adverse event profile.¹⁶ Nevertheless, after 2009, large randomized clinical trials have compared the efficacy and safety of UFT/LV with other systemic fluoropyrimidine compounds, in the subgroup of elderly patients and those with advanced metastatic disease.^{17,18} Further, Chen et al conducted a meta-analysis by comparing the efficacy and safety of S-1 (tegafur, gimeracil, and oteracil potassium) to capecitabine and found difference in efficacy between the two oral agents.¹⁹ To the best of our knowledge, till date, no meta-analysis has comprehensively compared UFT/LV with other fluoropyrimidines including intravenous 5-FU, oral agents such as capecitabine, or the combination. Therefore, it is prudent to conduct systematic review to analyze the efficacy and safety of oral UFT/LV compared to other fluoropyrimidines, with an intention to implement the findings into the current treatment algorithms for CRC.

Methods

Given that this was a systematic review and meta-analysis, the study was exempt from ethics committee review and approval.

Search Strategy

The search was performed on July 29, 2020, in the electronic databases, namely, “PUBMED” – U.S. National Library for Medicine, “CENTRAL” – Cochrane Central Registry for Clinical Trials, and “EMBASE” – Elsevier database for drug development using following keywords: “tegafur uracil” AND “colorectal cancer” OR “colon cancer” OR “rectal cancer” and the search was limited to clinical trials and meta-analysis. No other filters were applied. For the initial search, abstracts and publications from non-English language were included. The literature search and systematic review has been conducted and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement guidelines²⁰. “Cochrane Handbook for Systematic Reviews of Interventions” was used as an overarching guidance document.²¹

Eligible Criteria and Study Selection

All prospective studies including randomized controlled trials and observational studies, which compared oral UFT/LV with any other fluoropyrimidine agent (both oral and intravenous formulations) conducted on patients

diagnosed (confirmed by histopathological or cytological finding) with colon cancer, rectal cancer, or CRC, irrespective of stage (stage I, II, or III, i.e., early operable, and for palliative intent; stage III/IV—late, inoperable) at diagnosis or line of treatment (first-, second-, or third-line therapy), adjuvant/neoadjuvant status, pre- or postradiotherapy were included in the analysis. There was no restriction based on drug dosage, frequency of administration, the strength of the underlying formulation, and duration of treatment. If the studies used tegafur or uracil with other active pharmaceutical ingredients, such as gimeracil and oteracil potassium, we excluded them as they would confound the outcomes related to our objectives. Further, if the studies assessed other interventions (e.g.: radiotherapy vs. placebo) as their primary objective, and if UFT/LV were only part of the comedication in each arm, we excluded such studies from our analysis. Single-arm, genome studies, and dose-finding studies were excluded from our analysis. Trials that reported results in the form of abstracts, case reports, meta-analysis, case series, letter to editors, and non-English language publications were later excluded from the analysis.

Types of Outcome Measures

Disease-free survival (DFS), progression-free survival (PFS), OS, and objective response rate (ORR) were used to assess the efficacy of the comparators used. Safety findings concerning \geq grade 3 adverse events were also assessed.

Primary Objectives

Patients of CRC treated with curative intent:

1. DFS, defined as the time from randomization until death or disease recurrence, as defined in the protocol of the contributory studies, whichever occurred first.

Patients of CRC treated with palliative intent (inoperable, advanced, and metastatic):

1. PFS: we followed a similar definition for those patients who were treated with curative intent, except for the fact that these patients had advanced disease.

Secondary Objectives

Patients of CRC treated with curative intent:

1. OS, defined as the time from randomization until death.
2. The occurrence of grade \geq 3 adverse events: judged according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)²² or as per other available criteria defined in the study.

Patients of CRC treated with palliative intent (inoperable, advanced, metastatic):

1. OS.
2. ORR: response adjudicated as complete response or partial response based on Response Evaluation Criteria in Solid Tumours.²³
3. The occurrence of grade \geq 3 adverse events: judged according to NCI CTCAE²² or as per other available criteria defined in the study.

Data Collection and Analysis

Selection of Studies

Two reviewers (S.V. and V.P.) conducted the initial search and the studies were evaluated for inclusion and exclusion based on a simple checklist. If any disagreements were encountered, the issue was resolved by S.P., who had the final say in the inclusion of the studies.

Data Extraction Management

As part of the essential information required for the studies, the following parameters were tabulated: the first name of the author along with the year of publication, country/region in which clinical trial was performed, disease status/stage, line of treatment, the total number of patients screened, gender, comparators used in the study, European Cooperative Oncology Group (ECOG)/Karnofsky Performance Status,²⁴ and the available outcome measures.

If multiple publications reported the results of the same study, only those publications with the most comprehensive and updated information were used. Information extracted was restricted only to published material in the public domain. However, depending on the requirement additional information was obtained from the supplementary material of the publication for estimating bias or outcome measures.

Risk of Bias and Quality Assessment

We used the Cochrane “risk of bias” tool for assessing bias in the included studies.²⁵ It consisted of seven domains, namely, random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and “other bias.” Additionally, a 5-point Jadad scale²⁶ was used to assess the quality of data relevant to the study. According to the scale, “0” represented poor methodology in the study, whereas “5” represented optimal study methodology. For quality assessment, a score of 4/5 we termed as “high quality,” 2/3 was “moderate quality,” and 1 was “low-quality” evidence. The entire risk and quality assessment were performed independently by S.V. and V.P., and any disagreement was resolved by X.X.

Statistical Analysis

When evaluating outcomes, if the total number of subjects assessed in the outcome measures were not available, we used the total number of patients randomized to that group as the denominator. Time-to-event analysis such as DFS, PFS, and OS were reported as HR (95% CI), which, if available, was directly taken up from the publication report. For ORR and adverse events, dichotomous variables, odds ratio (OR) (95% CI) was used for reporting. For missing data, we did not use any imputation method. The pooled estimate was computed using the generic inverse-variance method for time-to-event outcomes and the Mantel-Haenszel method for dichotomous outcomes.

Statistical heterogeneity was assessed using chi-square test. To quantify heterogeneity, I^2 statistic was applied and as

per standard practice heterogeneity was defined in the following manner: 0 to 40% might not be important, 30 to 60% represents moderate heterogeneity, 50 to 90% substantial heterogeneity, and 75 to 100% considerable heterogeneity.

Results

Search and Study Results

In our initial search using the keywords mentioned in the methodology section we have retrieved 639 articles across the three databases. After removing duplicates, and thorough screening by looking at the titles and abstracts, finally eight eligible articles/trials found to meet the selection criteria (→ Fig. 1).^{17,18,27-32} Out of the eight trials, half of them used chemotherapy with curative intent and the other half used chemotherapy with palliative intent.

All the trials were randomized studies except the Kim et al study,²⁷ which was initially randomized but later patients were given a choice to choose their intervention and therefore qualified as an observational cohort study. We included this study in the final analysis as it qualified predefined eligibility criteria. Overall, eight included studies accounted for 4,486 patients (i.e., 2,986 patients with curative intent,

while 1,500 patients with palliative intent). The sample size for each with curative intent ranged from 122 to 1,101 and that of palliative intent had a range of 67 to 817 patients. The curative intent studies for CRC used UFT/LV in neoadjuvant and adjuvant settings, either accompanying resection or with radiotherapy. All the palliative intent chemotherapy studies administered the medication UFT/LV as part of the first-line management. Only, two studies, Douillard et al's³⁰ and Carmichael et al's³¹ studies were global trials, whereas the rest of the trials were country-specific trials. Irrespective of the intent for the intervention, the median age of the patients was in the range of 56.2 to 77 years. The Kroep et al study¹⁸ enrolled patients in the elderly age group and, therefore, was the only trial with age-specific criteria. The gender distribution and ECOG 0/1 performance status were well balanced across all the studies. Additionally, intravenous 5-FU/LV was the comparator arm in all studies except the Kroep et al study,¹⁸ which used capecitabine as a comparator (→ Table 1).

Assessment of Bias and Quality of Evidence

The randomization method and concealment of allocation for treatment was adequately described in 50% of the studies.^{17,18,29,32} Three studies employed an unspecified method

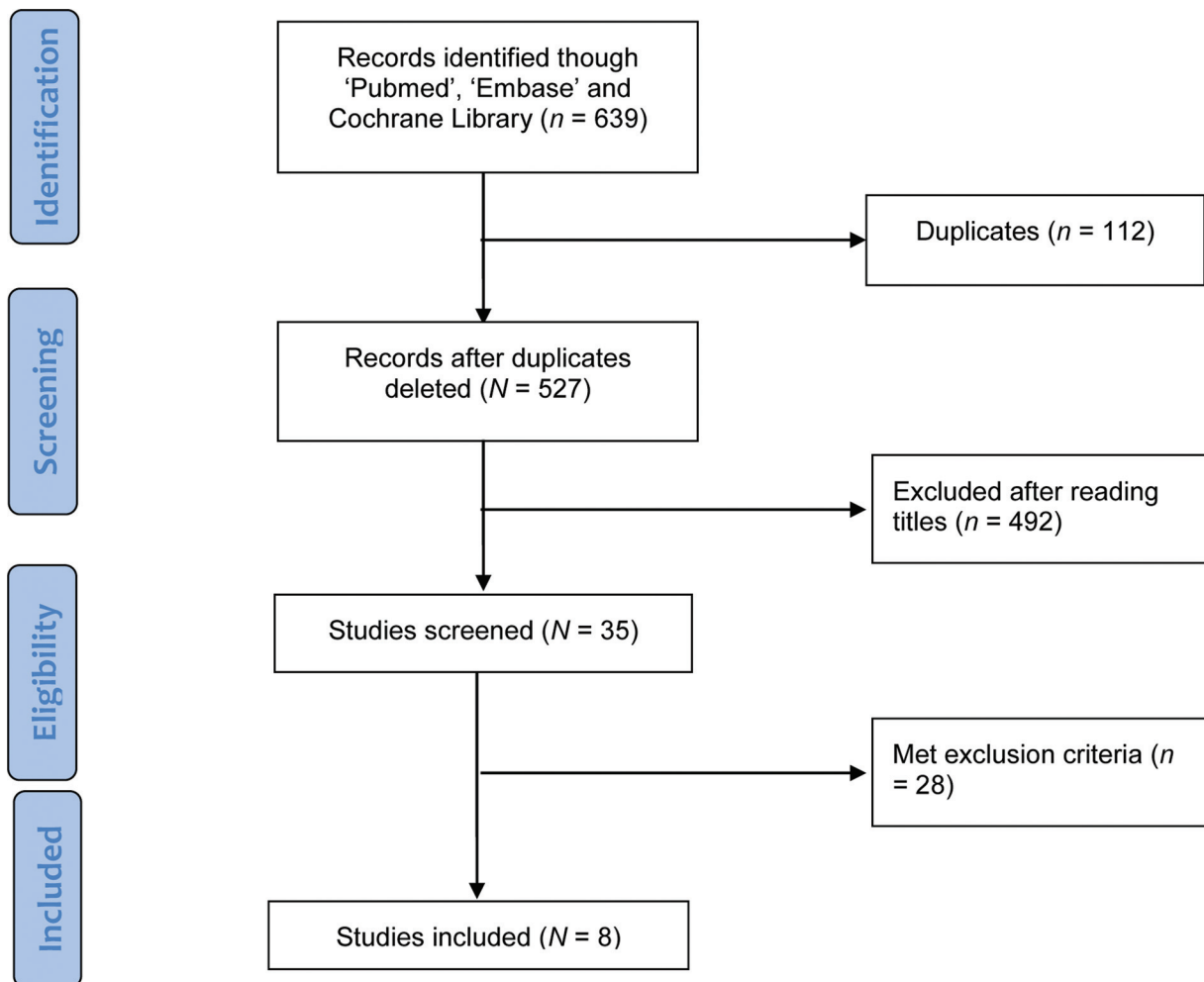


Fig. 1 CONSORT flow diagram.

Table 1 Baseline characteristics of the included studies

	Author	Country	Cancer stage	Line of treatment	Sample size	Mean age	Male	ECOG 0/1	Comparator to UFT/LV	Outcomes assessed
Studies with curative intent (Stage II/III; operable)	Kim et al 2003 ²⁷	Korea	Adenocarcinoma who have undergone curative resection Duke's B2 or C1	Adjuvant therapy following resection	122	56.2	43%	68%	IV 5-FU/LV	Grade \geq 3 AEs
	Lembersky et al 2006 ²⁸	USA	Stage II/III adenocarcinoma of the colon	Adjuvant	1608	58.3% (\geq 60 y)	51.60%	NA	IV 5-FU/LV	DFS, OS, Grade \geq 3 AEs
	de la Torre et al 2008 ²⁹	Spain	T3 or T4 rectal adenocarcinoma, with or without nodal metastasis, or any T stage tumors with nodal metastasis	Neoadjuvant with radiotherapy background	155	65	74%	100%	IV 5-FU/LV	DFS, OS, Grade \geq 3 AEs
Studies with palliative intent (Stage IV; inoperable, advanced metastatic)	Shimada et al 2014 ¹⁷	Japan	Stage 3 colon cancer	Adjuvant	1101	61	54%	NA	IV 5-FU/LV	DFS, OS, Grade \geq 3 AEs
	Douillard et al 2002 ³⁰	Multiple countries U.S., U.K.	Metastatic nonsurgical patients	First-line therapy	816	64	61%	93%	IV 5-FU/LV	OS, ORR (WHO criteria, modified), Grade \geq 3 AEs
	Carmichael et al 2002 ³¹	Multinational: NA, Europe, AZ, NZ	Metastatic adenocarcinoma	First-line therapy	380	61	67%	86%	IV 5-FU/LV	PFS, OS, ORR, Grade \geq 3 AEs
	Nogué et al 2005 ³²	Spain	Metastatic/unresectable, first-line	First-line therapy	237	67	62%	81%	IV 5-FU/LV	OS, ORR Grade \geq 3 AEs
	Kroep et al 2015 ¹⁸	Netherlands	Elderly patients with advanced colorectal cancer	First-line therapy	67	77	54%	87%	Capecitabine	PFS, OS, ORR, Grade \geq 3 AEs

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; DFS, disease-free survival; ECOG, European Cooperative Oncology Group; IV, intravenous; LV, leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; UFT, uracil and tegafur fixed-dose combination; WHO, World Health Organization.

to randomize the patients.^{28,30,31} None of the studies mentioned “double-blind” in the methodology section and other parts of the manuscript and, thereby, all the studies had a performance bias. The dropouts and reason for study withdrawal were mentioned in five trials.^{18,27,29–31} Further, we could not ascertain the availability of the protocol for six studies.^{27–32} Risk assessment for the bias are mentioned in ▶Table 2 and ▶Fig. 2. As per the 5-point Jadad scale, seven studies^{17,18,28–32} were classified under “moderate-quality evidence” and only one study, that is, the Kim et al study²⁷ was downgraded to “low quality” evidence, due to lack of randomization. In terms of specific scoring, three studies received a score of “3,”^{17,29,32} whereas four studies received a score of “2”^{18,27,30,32} and the Kim et al study²⁷ was given a score of “1.”

Primary Endpoint Analysis

For the primary endpoint, DFS, with respect to the curative intent of CRC, the pooled HR was 1.01 (95% CI 0.90–1.15; $p=0.81$), indicating no difference between UFT and intravenous 5-FU (▶Fig. 3). We could perform the analysis only with the Lembersky et al,²⁸ de la Torre et al,²⁹ and Shimada et al studies.¹⁷ All studies showed consistent results without any statistical heterogeneity as corroborated by an I^2 of 0%. The Lembersky et al study²⁸ contributed to 53.6% weight in the overall analysis due to the high sample size of 1,608.

In the context of the primary endpoint analysis of CRC studies involving palliative intent, there was no significant difference between UFT and intravenous 5-FU in PFS; HR for the pooled analysis was 0.87 (95% CI 0.66–1.66; $p=0.35$). The analysis was performed using the Carmichael et al study,³¹ which contributed to 79.6% of the weightage in the overall analysis, and the Kroep et al study.¹⁸ The statistical heterogeneity was deemed as unimportant ($I^2=20%$) by the authors.

Secondary Endpoint Analysis

Similar to the primary event analysis, in the secondary analyses no significant difference in OS was found between UFT and other fluoropyrimidines in CRC patients with curative intent (HR 1.04; 95% CI 0.88–2.3; $p=0.63$) and palliative intent (HR 1.02; 95% CI 0.97–1.06; $p=0.42$). In secondary analysis only three studies^{17,28,29} were included in the curative intent category and remaining four studies^{18,30–32} were included in the palliative intent category. Additionally, no heterogeneity was observed in the studies of curative intent, but moderate heterogeneity ($I^2=47%$) was seen in the palliative intent studies. Further, we also examined the ORR in the palliative intent studies. A HR of 1.17 (95% CI 0.74–1.85; $p=0.50$) in ORR indicated that there was no difference between UFT and other fluoropyrimidines. The detailed description of the secondary endpoint analysis is given in ▶Fig. 4.

Safety Analysis

Analysis of the curative intent studies showed significantly lesser patients on UFT/LV had leukopenia (OR 0.10; 95% CI 0.02–0.42; $p<0.01$) compared with intravenous 5-FU. Although the difference noticed was not statistically significant,

Table 2 Risk of bias assessments in the included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Studies with curative intent (Stage II/III; operable)	Kim et al 2003 ²⁷						
	?	?	R	R	?	?	?
	Lembersky et al 2006 ²⁸	G	R	R	G	?	?
	de la Torre et al 2008 ²⁹	G	R	R	G	?	?
	Shimada et al 2014 ¹⁷	G	R	R	?	G	?
Studies with palliative intent (Stage IV; inoperable, advanced metastatic)	Douillard et al 2002 ³⁰	G	R	R	G	?	G
	Carmichael et al 2002 ³¹	?	R	R	G	?	G
	Nogué et al 2005 ³²	G	R	R	R	?	G
	Kroep et al 2015 ¹⁸	G	?	?	G	G	?

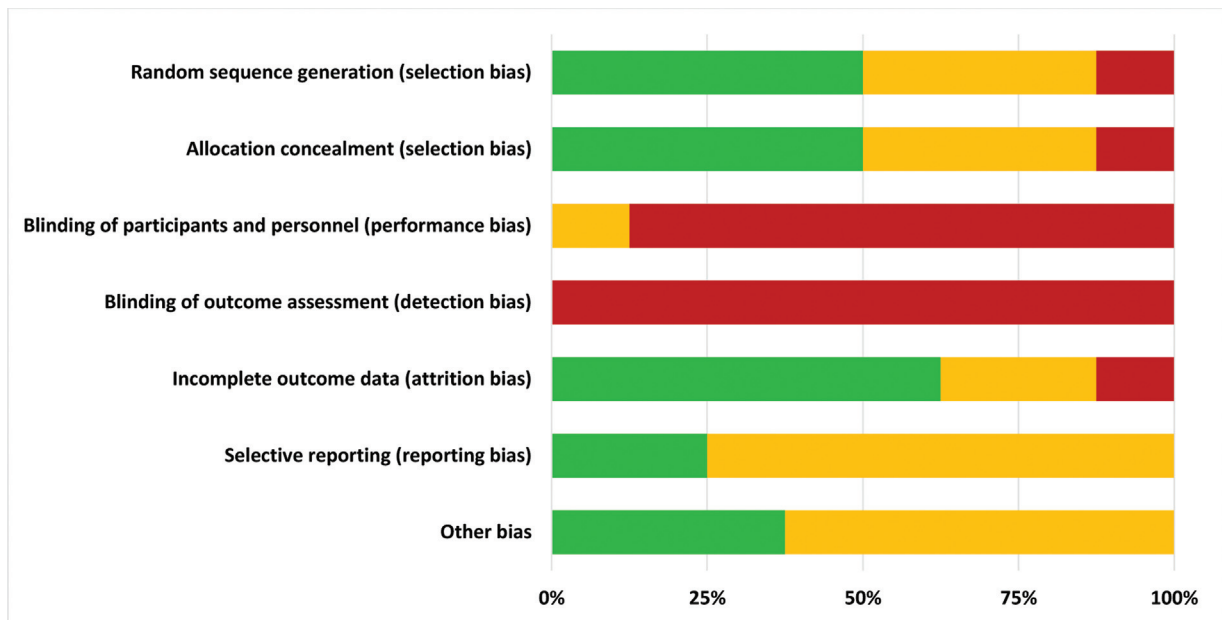


Fig. 2 Summary of risk of bias in the analysis.

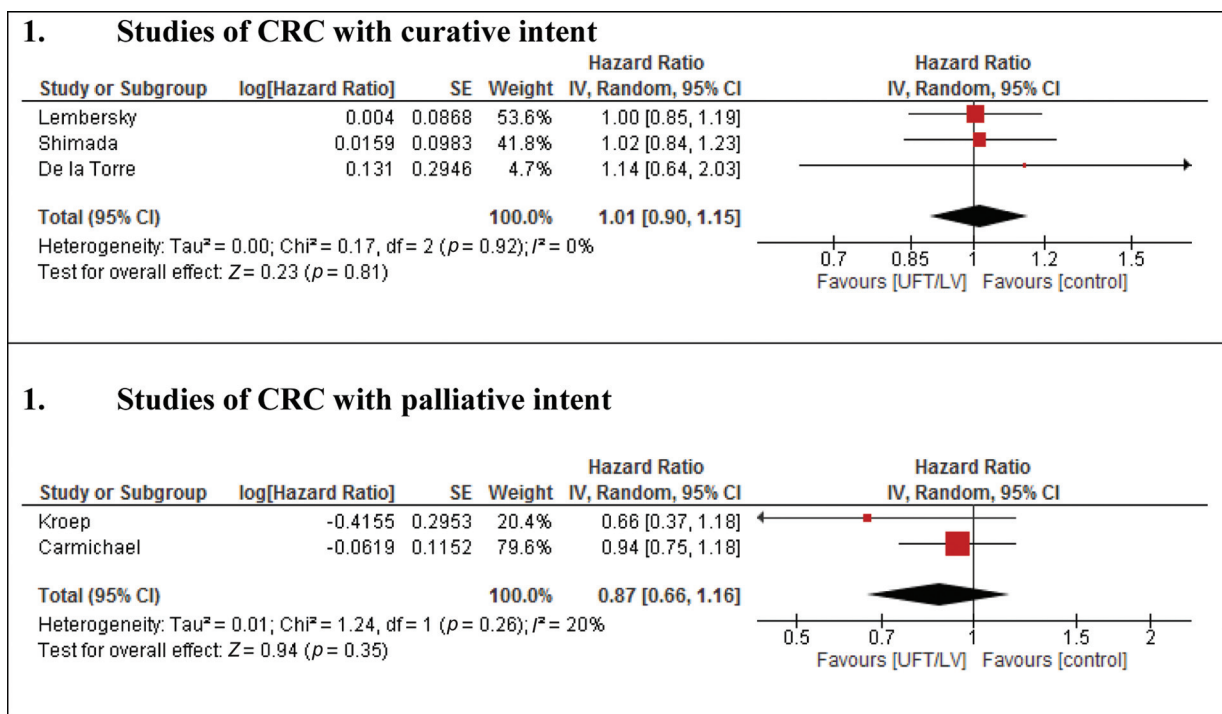


Fig. 3 Primary endpoint analysis.

numerically fewer patients on UFT/LV had developed stomatitis/mucositis, nausea/vomiting, fever, infection, anemia, and hyperbilirubinemia compared with the intravenous 5-FU. On the contrary, significantly more patients on UFT reported increased alanine transaminase levels (OR 12.87; 95% CI 4.60–35.98; $p < 0.001$) compared with intravenous 5-FU. Details related to all adverse events are elucidated in [Supplementary Fig. S1](#) (available online only). With respect to palliative intent studies, we found significantly lesser

patients on UFT/LV had stomatitis/mucositis (OR 0.20; 95% CI 0.05–0.85; $p = 0.03$), fever (OR 0.46; 95% CI 0.29–0.71; $p < 0.001$), infection (OR 0.42; 95% CI 0.24–0.74; $p < 0.01$), leukopenia (OR 0.04; 95% CI 0.00–0.95; $p = 0.05$), febrile neutropenia (OR 0.03; 95% CI 0.00–0.24; $p = 0.001$), and thrombocytopenia (OR 0.14; 95% CI 0.02–0.79; $p = 0.03$) compared with other fluoropyrimidines. Statistical heterogeneity between studies was variable, that is, I^2 range of 0 to 81%. Moreover, nausea/vomiting was numerically more in patients

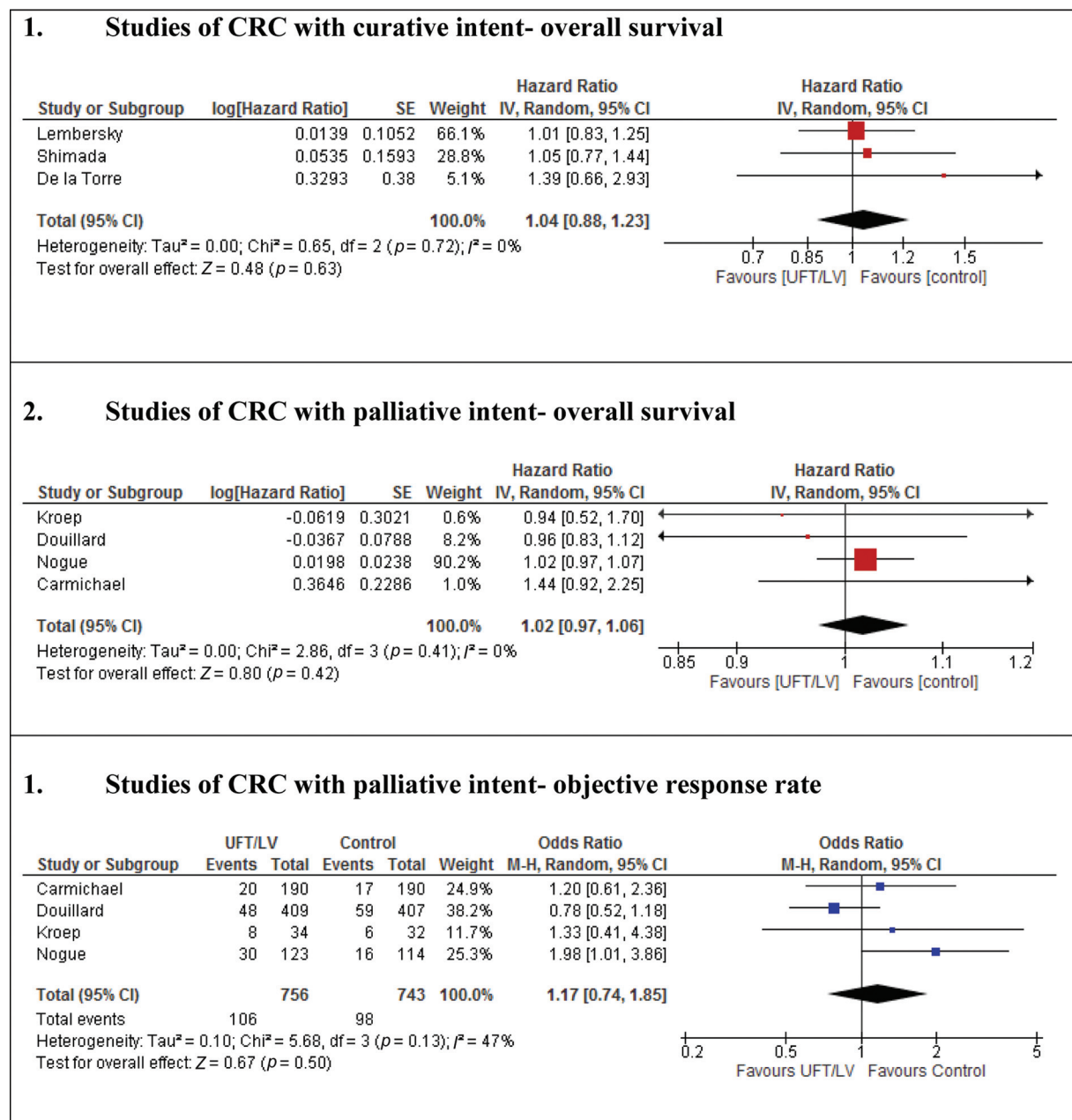


Fig. 4 Secondary endpoint analysis.

on UFT/LV but statistically nonsignificant difference was noticed compared with other fluoropyrimidines. The detailed description of safety analysis of colorectal cancer studies with palliative intent is given in **Supplementary Fig. S2** (available online only).

Discussion

The National Comprehensive Cancer Network recommends fluoropyrimidine-based chemotherapy for the management of CRC, both as an adjuvant and neoadjuvant therapy.^{4,5} As the objectives varied based on the different stages of cancer, we have analyzed and bifurcated the results based on the intent of chemotherapy. The main findings of our study are: (1) UFT/LV has shown equivalent efficacy (DFS and PFS) with

other fluoropyrimidines when used as chemotherapy agent in CRC patients with curative or palliative intent; (2) OS in UFT/LV and other fluoropyrimidines is comparable in all CRC patients irrespective of the intent of chemotherapy. Additionally, analysis of ORR suggests that UFT/LV and other fluoropyrimidines are comparable, when chemotherapy is given with a palliative intent; (3) Irrespective of the intent of chemotherapy, UFT/LV has a superior safety profile in comparison to other fluoropyrimidines, as fewer hematological adverse events, such as anemia, leukopenia, thrombocytopenia, and febrile neutropenia, and nonhematological adverse events, such as stomatitis/mucositis and infections, were observed in the UFT/LV group.

Historically, intravenous 5-FU have shown 22% risk reduction (DFS) in early-stage CRC patients.³³⁻³⁶ Our meta-

analysis shows that UFT/LV resulted in a nonsignificant DFS (HR 1.01; 95% CI 0.90–1.15; $p = 0.81$) compared with intravenous 5-FU (the historical comparator). There was no heterogeneity observed in the analysis, and two studies (Lembersky et al²⁸ and Shimada et al¹⁷) which contributed to 95% of the weightage in the overall analysis. The Cochrane review conducted in 2017¹⁶ showed that oral formulations of fluoropyrimidines were more efficacious compared with the intravenous preparations with a HR of 0.93 (95% CI 0.87–1.0). However, the included studies in the Cochrane analysis¹⁶ combined multiple oral drugs including capecitabine in the oral group as opposed to only UFT/LV in our analysis.

In advanced, inoperable CRC, our study has shown that UFT/LV is equivalent to other fluoropyrimidines in PFS (HR 0.87; 95% CI 0.66–1.66; $p = 0.35$). Previously, intravenous 5-FU had demonstrated a 5-month PFS (risk reduction of 62%) when chemotherapy was initiated early, before the appearance of symptoms, and therefore a similar advantage is expected with UFT/LV.³⁷ In our analysis we did not observe a PFS benefit. One of the reasons could be because of the heterogeneity in the included studies. Contrary to the results of our study, the Cochrane analysis¹⁶ which included 24 trials showed a 6% PFS advantage in favor of the intravenous 5-FU group. However, in comparison to our study, one needs to consider the significant heterogeneity in the study design and the differences in the oral fluoropyrimidines that were used in the included studies. Nevertheless, based on our analysis, we can conclude that UFT/LV is comparable to other fluoropyrimidines in early as well as advanced CRC.

Our study revealed that OS is comparable between UFT/LV and other fluoropyrimidines, in both early (HR 1.04; 95% CI 0.88–1.23; $p = 0.63$) and advanced CRC patients (HR 1.02; 95% CI 0.97–1.06; $p = 0.42$). The Cochrane meta-analysis¹⁶ findings are consistent with our study results. For curative intent studies, the OS HR was 0.92 (95% CI 0.84–1.00), and for the palliative intent studies, the OS HR was 1.02 (95% CI 0.99–1.05). In the Cochrane meta-analysis¹⁶ although a tendency toward statistical significance was seen in OS for the curative intent studies, the included trials, as stated earlier, had clinical heterogeneity since they grouped the results of different oral formulations into a single category. Furthermore, Bin et al¹⁵ showed that in a meta-analysis of four CRC trials, irrespective of the intent of chemotherapy, UFT/LV was comparable to intravenous 5-FU (HR 1.01; 95% CI 0.91–1.13). Additionally, the ORR was also comparable between UFT/LV and intravenous 5-FU, both in our study as well the Bin et al study.¹⁵ Taking into consideration the previous literature and the results of our study, we can conclude that UFT/LV has comparable efficacy to other fluoropyrimidines, irrespective of the CRC stage.

Adverse events related to fluoropyrimidine compounds are well documented.³⁸ They include hematological, such as anemia, and nonhematological adverse events, such as hand-foot-mouth syndrome and stomatitis.³⁸ Although we have bifurcated the adverse events based on the early and advanced stage of CRC, we intend to discuss the adverse events in terms of the overall class effect associated with UFT/LV compared with other fluoropyrimidine agents. The hemato-

logical adverse events are a result of myelosuppression³⁹ with fluoropyrimidine compounds leading to anemia, leukopenia, neutropenia, and thrombocytopenia. Our study has shown that UFT/LV is associated with significantly lesser hematological adverse events compared with other fluoropyrimidine compounds. Similar conclusions were drawn from the meta-analysis by Chen et al,¹⁹ Bin et al,¹⁵ and the Cochrane review.¹⁶ Carmichael et al,³¹ Lembersky et al,²⁸ de la Torre et al,²⁹ and Shimada et al's studies¹⁷ jointly contributed to >50% weightage in our safety analysis.

An indirect consequence of myelosuppression is that it renders the patient more prone to infection, besides its associated symptoms such as fever and febrile neutropenia. Our study shows that UFT/LV is superior to other fluoropyrimidines in terms of indirect toxicities as a result of myelosuppression. Moreover, most importantly, UFT/LV is superior to other fluoropyrimidines in terms of nonhematological toxicities such as stomatitis/mucositis. This condition is debilitating as it results in increased hospitalization days⁴⁰ and patients usually present with redness, edema, and ulceration of the gastrointestinal tract leading to decreased intake and ingestion of oral foods and would require parenteral nutritional support. Further, it is noteworthy to mention that in previous reviews^{15,16} UFT/LV was associated with an increase in hand-foot-mouth syndrome, which was not found in our analysis.¹⁶ Although UFT/LV demonstrates superiority in adverse event profile compared with other fluoropyrimidines, we need to factor in the clinical heterogeneity in dosage, consider the dietary folate intake and genetic polymorphism between individuals, and interpret the results accordingly. Nonetheless, it is reasonable to conclude that UFT/LV has a superior safety and tolerability profile compared with other fluoropyrimidines.

In the last decade, intravenous 5-FU, given either as a bolus or continuous regimen, was considered as standard therapy for early- and late-stage CRC patients. The oral formulation, UFT/LV, has comparable efficacy to other fluoropyrimidines, especially continuous infusion of intravenous 5-FU. Besides, UFT has demonstrated a high antiangiogenic effect in murine models compared with intravenous 5-FU, and this effect has been attributed to higher and sustained blood levels of UFT and its metabolites (γ -hydroxybutyric acid and γ -butyrolactone).⁴¹ With the superiority in adverse events, both hematological and non-hematological, more clinicians are likely to accept UFT/LV as a standard fluoropyrimidine in CRC patients having early- and late-stage disease. In a developing country like India, besides the convenience of intake, the cost of therapy plays a pivotal role in patient decision making, especially when alternatives are available.

Our study updates the Bin et al meta-analysis¹⁵ by adding two trials. Despite of the advantage, our study has its share of limitations. First, all studies included in the analysis were unblinded studies. As the gold standard criterion of double-blind was not followed, it would have resulted in the bias of the outcome assessments. Second, in some cases, we could not factor in the endpoint for all the objectives, either

because those specific outcomes were not assessed in the studies or confidence limits for the outcomes were not reported clearly. Third, background therapy such as radiation and second/third-line therapy following primary treatment failure would have led to some confounding of the results, especially the OS analysis and adverse events. Lastly, only one study was included, which compared UFT/LV to capecitabine, thus, one needs to exercise caution in concluding comparison with all other fluoropyrimidines in general. However, the Chen et al meta-analysis,¹⁹ which included four comparator trials with capecitabine arrived at a similar conclusion as our study.

Regardless of the limitations, future studies on the mechanistic pathways underpinning the superior safety and tolerability profile of UFT/LV compared with other fluoropyrimidines are warranted. As cancer treatment algorithms are becoming selective based on gene signatures,^{4,5,42} more research in this direction is the need of the hour, as one needs to ascertain the group of patients who would benefit the most from UFT/LV. Moreover, in the context of biological therapy positioning itself at the forefront of CRC management,^{4,5} it is essential to study the impact of biologics when used in combination with fluoropyrimidine compounds.

Conclusion

Oral UFT/LV is equally efficacious to other fluoropyrimidines, especially intravenous 5-FU, in the management of early as well as advanced CRC patients. Importantly, UFT/LV has a superior safety profile compared with other fluoropyrimidines in terms of both hematological and nonhematological adverse events.

Earlier Presentation

None.

Conflict of Interest

None declared.

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