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A multicenter retrospective study evaluating the effect of proton pump inhibitors on adjuvant tegafur-uracil/leucovorin efficacy for stage II–III colorectal cancer

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We hypothesized that there is reduced efficacy of fluorinated pyrimidines, such as capecitabine, caused by low active folic acid levels induced by vitamin B_{12} deficiency, due to proton pump inhibitors (PPIs), and that this can be recovered by the administration of leucovorin (LV). Thus, we retrospectively analyzed the effects of PPIs on adjuvant tegafur–uracil (UFT) plus LV for stage II/III colorectal cancer (CRC). Patients newly diagnosed with stage II/III CRC who underwent curative surgery and received adjuvant UFT/LV therapy between January 2013 and June 2018 were included. The primary endpoint was the difference in relapse-free survival (RFS) between the PPI and non-PPI groups. Data from 396 eligible patients were evaluated, 84 of whom received PPIs. There were 93 relapse events and 57 deaths across the groups. RFS rates at 5 years were 73.8% (95% confidence interval [CI], 62.9–81.9%) and 77.1% (95% CI, 72.0-81.4%) in the PPI and non-PPI groups, respectively. Cox regression analysis showed no significant differences in RFS between the PPI and non-PPI groups (hazard ratio, 1.16; 95% CI, 0.72–1.87; *P* = 0.539). Our findings suggest that the concomitant use of PPIs does not significantly reduce the efficacy of adjuvant UFT/LV treatment for patients with stage II/III CRC.

Keywords Colorectal cancer, Proton pump inhibitors, Tegafur uracil plus leucovorin, Reduced folic acid, Adjuvant chemotherapy

Abbreviations

5-FU	5-Fluorouracil
CRC	Colorectal cancer
CI	Confidence interval
HR	Hazard ratio
LV	Leucovorin
OS	Overall survival
PPI	Proton pump inhibitor
RFS	Relapse-free survival
UFT	Tegafur–uracil

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Colorectal cancer (CRC) is the third most common cancer worldwide in terms of incidence, and the second most common cancer in terms of mortality, according to the GLOBOCAN database[1]. Although surgery remains the only curative treatment for CRC, the Japanese Society for Cancer of the Colon and Rectum has reported recurrence rates of 15.0% and 31.8% in patients with stage II and stage III CRC, respectively[2]. Postoperative adjuvant chemotherapy reduces disease recurrence, improves overall survival, and is recommended for patients with stage II–III CRC[2]. Chemotherapies based on fluorinated pyrimidines, such as capecitabine, tegafur–uracil (UFT) plus leucovorin (LV), and intravenous 5-fluorouracil (5-FU), are commonly used[2]. Capecitabine and tegafur are oral prodrugs of 5-FU.

Proton pump inhibitors (PPIs) specifically block H+/K+-adenosine triphosphatase, termed the "proton pump," which plays a role in the final production step of gastric acid; consequently, treatment with PPIs results in decreased gastric acid production[3]. These agents are widely used to treat conditions in older adults such as peptic ulcers, nonsteroidal anti-inflammatory drug-induced gastroduodenal ulcer prevention, functional dyspepsia, gastrointestinal bleeding prevention, and non-erosive reflux disease[3,4]. Additionally, an association between PPIs and CRC incidence has been reported[5]. Consequently, as most patients with CRC are elderly, many patients diagnosed with CRC may be taking PPIs.

Recent studies have reported that PPIs reduce the efficacy of adjuvant capecitabine or adjuvant capecitabine + oxaliplatin therapies in patients with CRC[6–8]. However, coadministration of rabeprazole, a PPI, was reported to have no effect on the pharmacokinetics of capecitabine or its metabolites[9]. In contrast, coadministration of esomeprazole led to an 18.9% increase in the area under the plasma concentration-time curve of capecitabine and an extension of its half-life[10]. Therefore, since the mechanism of drug interaction cannot be explained by pharmacokinetics and remains controversial, workarounds are required in clinical settings[11,12].

The reduced form of folic acid is a modulator of 5-FU, and this theory is useful for developing 5-FU based regimens such as 5-FU + LV + oxaliplatin and 5-FU + LV + irinotecan[13]. A previous study reported that patients receiving adjuvant 5-FU with higher serum folate levels showed a tendency toward lower rates of recurrence and significantly lower mortality than those receiving adjuvant 5-FU with lower serum folate levels[14]. Therefore, folic acid plays a key role in adjuvant 5-FU-based chemotherapy. However, long-term usage of PPIs is associated with an increased risk of vitamin B_{12} deficiency; vitamin B_{12} is necessary to activate folic acid[15]. Thus, we hypothesized that there is reduced efficacy of fluorinated pyrimidines caused by low active folic acid levels induced by vitamin B_{12} deficiency, due to PPIs, and that this can be recovered by the administration of LV, which is the reduced form of folic acid. In fact, as no significant effects on 5-FU + LV + oxaliplatin-treated patients with early-stage CRC were shown, regimens based on LV may represent a useful alternative to capecitabine[16].

The JCOG0205 and NSABP C-06 trials have confirmed the non-inferiority of adjuvant UFT/LV to intravenous 5-FU/LV for CRC[17,18]; as such, adjuvant UFT/LV is one of the recommended regimens. It is the only regimen based on oral LV in Japanese guidelines as well as Pan-Asian adapted ESMO Clinical Practice Guidelines, which describe recommendations adapted for the treatment of localized colon cancer in Asian patients[2,19]. In this study, we retrospectively analyzed the effects of PPIs on the efficacy of adjuvant UFT/LV therapy in patients with stage II–III CRC to confirm the hypothesis. If this hypothesis is confirmed, the present study could present an option in clinical practice for patients for whom concomitant PPIs may decrease adjuvant capecitabine efficacy, and thus serve to help researchers to verify drug-interaction mechanism between capecitabine and PPIs.

Results

Patient characteristics

A flowchart of the participant recruitment process is shown in Fig. 1. In total, 662 patients met the inclusion criteria, and 84 patients were excluded when adjuvant UFT/LV treatment begun. The primary reasons for exclusion were insufficient information ($n = 10$), history of treatment with fluorinated pyrimidines for CRC ($n = 42$), and receipt of any adjuvant chemotherapy for CRC, except UFT/LV ($n = 20$). The data of 578 patients were evaluated using the sensitivity analysis. Moreover, 182 patients were excluded after initiation of adjuvant UFT/LV treatment, primarily because they received more than 140 days of adjuvant UFT ($n = 125$), or developed other carcinomas following adjuvant chemotherapy ($n = 37$). Finally, the data from 396 patients were included in the main analysis. The baseline patient characteristics in the main analysis are shown in Table 1. The median age of the patients was 68.0 years (interquartile range, 62.0–74.0 years); 200 (50.5%) were males, 120 (30.3%) had right-sided colon cancer, and 76 (19.2%) had stage II CRC. The PPIs used included esomeprazole (23 [27.4%]), omeprazole (2 [2.4%]), lansoprazole (36 [42.9%]), rabeprazole (22 [26.2%]), and vonoprazan (1 [1.2%]).

Endpoints

In this study, the median duration of follow-up was 5.71 years (interquartile range, 4.95–7.08 years). There were 93 relapse events and 57 deaths in across both groups. As shown in Fig. 2, relapse-free survival (RFS) rates at 5 years were 73.8% (95% confidence interval [CI], 62.9–81.9%) and 77.1% (95% CI, 72.0-81.4%) in the PPI and non-PPI groups, respectively. Overall survival (OS) rates at 5 years were 86.0% (95% CI, 76.1–92.0%) and 88.0% (95% CI, 83.7–91.2%) in the PPI and non-PPI groups, respectively.

Table 2 shows the results of the Cox regression and inverse probability of treatment weighting analyses. It was considered that the proportional hazards assumption was not violated (Chi-square test $P = 0.645$). The Cox regression analysis showed no significant difference in RFS (hazard ratio [HR], 1.16; 95% CI, 0.72–1.87; $P = 0.539$) and OS (HR, 1.13; 95% CI, 0.62–2.06; $P = 0.697$) between the PPI and non-PPI groups. The inverse probability of treatment weighting analysis also revealed that coadministration of PPIs was not associated with RFS (HR, 1.05; 95% CI, 0.64–1.71; $P = 0.847$) and OS (HR, 1.05; 95% CI, 0.58–1.91; $P = 0.865$). Stage III high-risk was a factor for decreased RFS (HR, 2.68; 95% CI, 1.33–5.38; $P = 0.006$). No factors which associated with

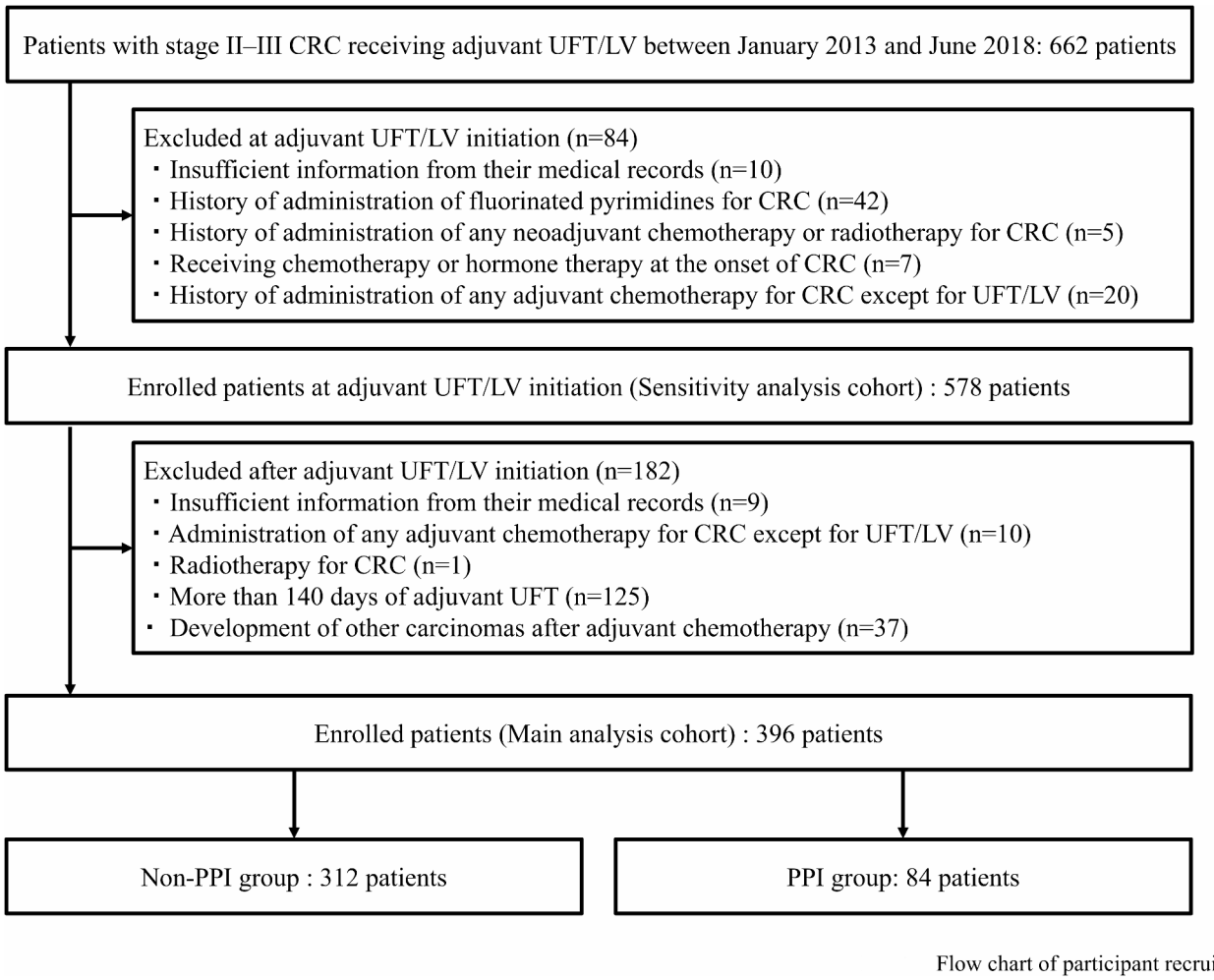

Fig. 1. Flow chart of participant recruitment. *UFT/LV* tegafur–uracil plus leucovorin, *CRC* colorectal cancer, *PPI* proton pump inhibitor.

Factors		ALL ($n=396$)	Non-PPI group ($n=312$)	PPI group ($n=84$)	*P* value
Age (years)	Median [IQR]	68.0 [62.0, 74.0]	68.0 [61.0, 74.0]	68.0 [63.0, 74.0]	0.765
Sex	Female	196 (49.5%)	157 (50.3%)	39 (46.4%)	0.527[a]
	Male	200 (50.5%)	155 (49.7%)	45 (53.6%)	
BSA (m^2)	Median [IQR]	1.56 [1.43, 1.70]	1.54 [1.43, 1.70]	1.58 [1.44, 1.72]	0.137
Primary site	Right-sided colon	120 (30.3%)	88 (28.2%)	32 (38.1%)	0.080[a]
	Others	276 (69.7%)	224 (71.8%)	52 (61.9%)	
Stage	II	76 (19.2%)	61 (19.6%)	15 (17.9%)	0.345[a]
	III low-risk	186 (47.0%)	151 (48.4%)	35 (41.7%)	
	III high-risk	134 (33.8%)	100 (32.1%)	34 (40.5%)	

Table 1. Baseline patient characteristics. [a]Chi-square test, other: Mann–Whitney *U* test. *PPI* proton pump inhibitor, *BSA* body surface area, *IQR* interquartile range.

decreased OS were identified. The subgroup analysis revealed that no factors were associated with RFS or OS in the PPI and non-PPI groups (Fig. 3). Analysis of interaction terms in the regression model revealed that PPI effects did not significantly differ across subgroups.

The results of sensitivity analysis are presented in Supplementary Table 1 and Supplementary Fig. 1. Overall, the RFS rates at 5 years were 78.8% (95% CI, 70.5–85.1%) and 80.4% (95% CI, 76.4–83.8%) in the PPI and non-PPI groups, respectively, while the respective OS rates at 5 years were 87.3% (95% CI, 79.8–92.1%) and 89.1% (95% CI, 85.8–91.7%). Cox regression analysis revealed no significant difference in RFS (HR, 1.04; 95% CI, 0.67–1.61; $P=0.862$) and OS (HR, 0.97; 95% CI, 0.57–1.65; $P=0.919$) between the PPI and non-PPI groups. The

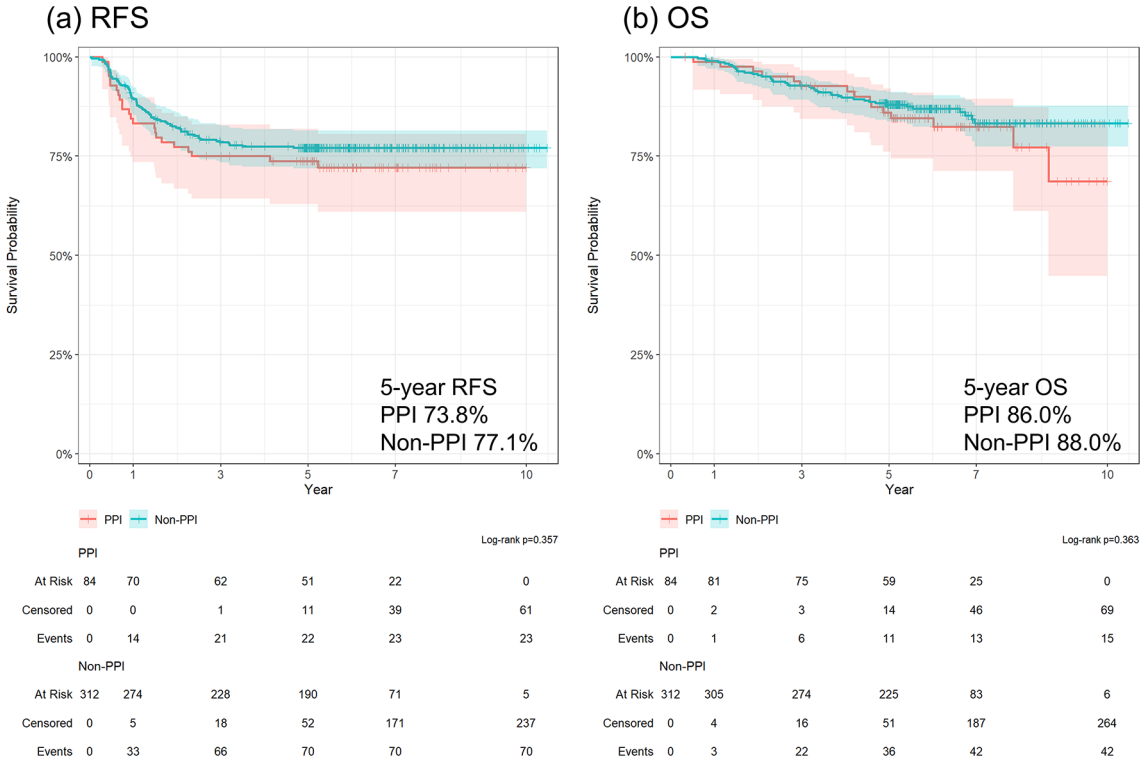

Fig. 2. Kaplan–Meier curves for RFS (**a**) and OS (**b**) according to the absence or presence of PPIs in the main analysis. *RFS* relapse-free survival, *OS* overall survival, *PPI* proton pump inhibitor.

inverse probability of treatment weighting analysis further revealed that the coadministration of PPIs was not associated with RFS (HR, 0.91; 95% CI, 0.58–1.43; $P = 0.676$) and OS (HR, 0.97; 95% CI, 0.57–1.64; $P = 0.897$).

Discussion

The present study retrospectively showed that coadministration of PPIs did not have negative effects on adjuvant UFT/LV treatment in patients with stage II–III CRC. These results were consistent with our expectations, and this is the first study to investigate whether the coadministration of PPIs affects the efficacy of adjuvant UFT/LV treatment in patients with stage II–III CRC.

As shown in Fig. 1, the primary reasons for exclusion at adjuvant UFT/LV initiation were insufficient information, fluorinated pyrimidines, and any adjuvant chemotherapy. Exclusion of these patients was necessary as they had a large impact on UFT/LV efficacy. The main reasons for exclusion after initiation of adjuvant UFT/LV were the administration of adjuvant UFT for more than 140 days and development of other carcinomas. As UFT duration and development of other carcinomas had a large impact on UFT/LV efficacy or therapeutic strategy, those were also excluded. Sensitivity analysis indicated a similar tendency to the main analysis. Therefore, we surmised that these exclusions following the initiation of adjuvant UFT/LV had little impact on this analysis.

For eligible patients without PPI administration in the main analysis, the 5-year RFS and 5-year OS rates were 77.1% and 88.0%, respectively. Conversely, the 5-year disease-free survival and 5-year OS rates in the JCOG0205 trial, which also evaluated the non-inferiority of UFT/LV treatment in stage III CRC, were 73.6% and 87.5%, respectively[17]. Although there were differences between RFS and disease-free survival, different percentages of older patients, and no patients with stage II CRC, the results of this study were approximately the same as those of JCOG0205[17].

In this study, the Cox regression analysis showed no significant difference in RFS (HR, 1.16; 95% CI, 0.72–1.87) and OS (HR, 1.13; 95% CI, 0.62–2.06) between the PPI and non-PPI groups. A previous study showed that concomitant PPIs resulted in a much larger decrease in the efficacy of adjuvant capecitabine monotherapy in terms of RFS (HR, 2.48) and OS (HR, 2.58) than adjuvant UFT/LV therapy in this study[8]. Therefore, compared with capecitabine, the concomitant use of PPIs may not be associated with a decrease in the efficacy of adjuvant UFT/LV therapy. Additionally, stage III high-risk was only a factor for decreasing RFS, which is consistent with a previous report[8]. Although there were few events and some variations, the tendency of PPIs to not significantly decrease UFT/LV efficacy was generally consistent in the subgroup analysis for RFS and OS.

UFT consists of uracil and tegafur and has been developed as a 5-FU prodrug[20]. One of the cytotoxic mechanisms of 5-FU involves fluorouridine monophosphate, which is the active metabolite of 5-FU that can form a complex with thymidylate synthase[20]. Stabilization of the binding of fluorouridine monophosphate to thymidylate synthase requires an adequate concentrations of reduced folate, which is converted from folic acid using vitamin B_{12} as a coenzyme[21]. This mechanism may explain why patients receiving adjuvant 5-FU

Variables		Multivariable analysis		IPTW	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
(a) RFS					
PPIs	No	–		–	
	Yes	1.16 (0.72–1.87)	0.539	1.05 (0.64–1.71)	0.847
Age (10-year intervals)		1.07 (0.86–1.32)	0.568		
Sex	Female	–			
	Male	1.09 (0.72–1.65)	0.693		
Primary site	Right-sided colon	–			
	Others	1.11 (0.70–1.76)	0.651		
Stage	II	–			
	III low-risk	1.61 (0.80–3.25)	0.180		
	III high-risk	2.68 (1.33–5.38)	0.006		
RDI (10% intervals)		1.04 (0.96–1.12)	0.335		
(b) OS					
PPIs	No	–		–	
	Yes	1.13 (0.62–2.06)	0.697	1.05 (0.58–1.91)	0.865
Age (10-year intervals)		1.24 (0.92–1.67)	0.165		
Sex	Female	–			
	Male	1.34 (0.78–2.31)	0.293		
Primary site	Right-sided colon	–			
	Others	0.79 (0.46–1.37)	0.407		
Stage	II	–			
	III low-risk	0.84 (0.36–1.96)	0.692		
	III high-risk	2.09 (0.94–4.62)	0.069		
RDI (10% intervals)		0.99 (0.90–1.09)	0.874		

Table 2. Multivariable Cox proportional hazards model and IPTW analyses of the effect of coadministration of PPIs on RFS (a) and OS (b) in the main analysis. *IPTW* inverse probability of treatment weighting, *RFS* relapse-free survival, *OS* overall survival, *CI* confidence interval, *HR* hazard ratio, *PPI* proton pump inhibitor, *RDI* relative dose intensity.

with higher serum folate levels showed a tendency toward lower recurrence rates than those receiving adjuvant 5-FU with lower serum folate levels[14]. In contrast, long-term usage of PPIs is associated with an increased risk of deficiency of vitamin B_{12} [15,22]. This could be explained by the decrease in stomach acid due to PPIs and inactivation of pepsin, a proteolytic enzyme that separates vitamin B_{12} from food to absorb vitamin B_{12}[22].

Based on the above, we hypothesized that the reduced capecitabine efficacy was caused by low levels of active folic acid induced by vitamin B_{12} deficiency due to PPIs. If this theory holds true, the addition of LV could lead to an increase in the intracellular concentration of reduced folate without vitamin B_{12}, thereby stabilizing the fluorouridine monophosphate/enzyme complex and recovering the antitumor effect of PPIs[20]. In fact, as a single dose of oral leucovorin increases the plasma levels of 5-methyltetrahydrofolate several dozen times, daily administration of oral leucovorin may be able to recover reduced folic acid due to vitamin B_{12} deficiency[23]. In support of this hypothesis, Wong et al. reported that PPIs had a significant negative effect on the 3-year RFS of capecitabine + oxaliplatin-treated patients but no significant effects on 5-FU + LV + oxaliplatin-treated patients with early stage CRC[16]. Similarly, in this study, adjuvant UFT/LV efficacy was thought to be unassociated with PPIs because of the administration of oral LV.

Folic acid is mainly absorbed through a proton-coupled folate transporter, which is mainly expressed in the small intestine[24]. In a low-pH environment, the proton-coupled folate transporter shows high activity[25]. Because PPIs lead to decreased gastric acid production, they may prevent the absorption of LV via the proton-coupled folate transporter. However, as there is also a reduced folate carrier 1 in the intestine, which can absorb reduced folic acid optimally at a pH of 7.4[26], LV is absorbed via the receptor under PPI therapy. These mechanisms may explain why PPIs hardly affected adjuvant UFT/LV therapy in patients with stage II–III CRC in this study.

This study has several limitations. First, as the number of patients with PPIs ($n = 84$), relapse events ($n = 93$), and deaths ($n = 57$) was small, the statistical power may be low. Second, because this study was retrospective, information bias could not be excluded. Thus, although we performed multivariable analyses to decrease the effects of potential confounding factors, unmeasured confounders, such as baseline nutritional status or vitamin B_{12} levels, could not be adjusted for. Third, as the study population is predominantly Japanese, the generalizability of the findings to other ethnic groups or healthcare systems was limited. Fourth, the coadministration of PPIs was determined based on prescription history or medications brought to the hospital; and consequently, if PPIs were prescribed at other hospitals, their use during UFT administration could not have been tracked. Additionally, as this study did not include information regarding PPI duration, dosage, or timing, we were unable to determine whether specific PPI treatment regimens affected UFT/LV efficacy. Finally, as our hypothesis on LV

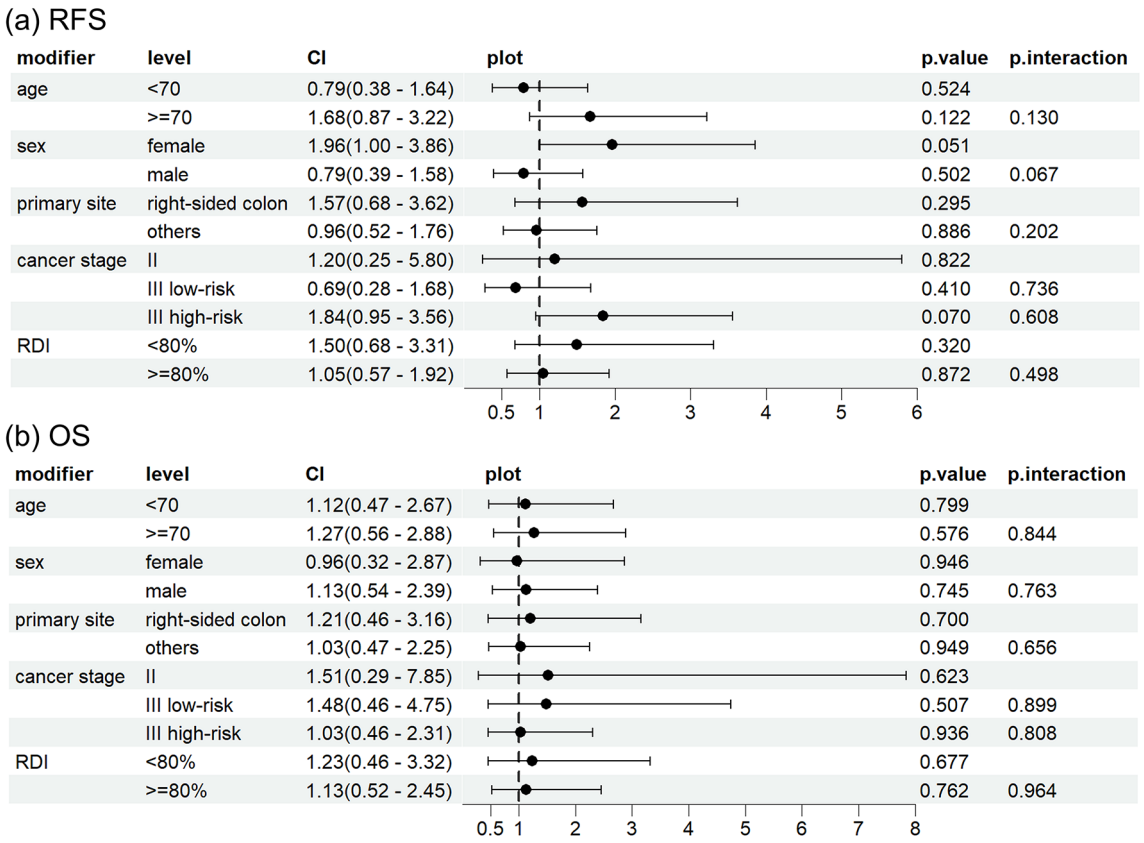

Fig. 3. Subgroup analysis for RFS (**a**) and OS (**b**). *RFS* relapse-free survival, *OS* overall survival, *PPI* proton pump inhibitor, *RDI* relative dose intensity, *CI* confidence interval.

compensating for reduced folate levels was not directly supported by the experimental data, further investigation is required to examine our hypothesis and apply the concomitant use of LV and capecitabine.

In conclusion, the findings of this study suggest that concomitant use of PPIs does not reduce the efficacy of adjuvant UFT/LV treatment in patients with stage II–III CRC. Therefore, we propose that clinicians should avoid the usage of PPIs during adjuvant capecitabine. However, if PPI usage is unavoidable, adjuvant UFT/LV should be used instead of adjuvant capecitabine in patients with stage II–III CRC treated with PPIs.

Methods

Study design and participants

Seven institutions, including university and community hospitals in Japan, participated in this retrospective observational study. This study was conducted in accordance with the standards set by the Declaration of Helsinki and approved by the Human Subjects Review Committee at Osaka Metropolitan University (No. 2023-049). Permission to conduct this study was obtained from each facility. The need for informed consent was waived by the Human Subjects Review Committee at each hospital, and the participants were free to opt out if they no longer wished to participate.

The information necessary for this study was collected from the medical records of each institution. Patients were included in the study if they were aged ≥ 20 years, were newly diagnosed with stage II–III CRC, had undergone curative surgery, and had received adjuvant UFT/LV therapy between January 2013 and June 2018. The basic treatment schedule was five courses of UFT/LV (The regimen comprised 300 mg/m^2/day UFT plus 75 mg/day LV on days 1–28 every 5 weeks, according to package insert in Japan; if this went smoothly, it took 168 days to complete the treatment), however, there was an allowance for modification of treatment schedule depending on toxicity profile. The clinicopathological data were reclassified based on the TNM Classification of Malignant Tumors, 8th edition of the Union for International Cancer Control.

The exclusion criteria were as follows: (1) refusal to allow for use of medical records; (2) insufficient or missing data from medical records; (3) history of previous administration of fluorinated pyrimidines for CRC, before the investigation period; (4) history of administration of any adjuvant chemotherapy for CRC, except for UFT/LV; (5) history of prior administration of any neoadjuvant chemotherapy or radiotherapy for CRC; (6) radiotherapy for CRC; (7) receiving > 140 days of adjuvant UFT therapy; (8) receiving any anticancer drugs or hormone therapy when CRC was diagnosed; and (9) development of other malignancy after adjuvant UFT/LV therapy.

Data collection

The following data were collected from patients' medical records: age, sex, body surface area (BSA), cancer stage, primary tumor site, UFT/LV dose, PPI use, and date of recurrence and/or death after adjuvant UFT/LV therapy. The primary site was classified into the right-sided colon (cecum, ascending colon, and transverse colon), left-sided colon (descending colon, sigmoid, and rectosigmoid junction), and rectum. Concomitant use of PPIs was defined by the assumption of ≥20% overlap of PPI administration on the day of UFT/LV therapy from their prescription history or medications brought in at the last admission to a hospital. The end date of the follow-up period was June 30, 2023.

If the period until final administration of UFT was ≤168 days, the relative dose intensity of UFT was calculated as 100 × [actual total dosage (mg)]/[standard dosage (mg/day) × 140 days]. If the period until final administration was >168 days, the relative dose intensity of UFT was calculated as 100×168 × [actual total dosage (mg)]/{period until final administration (days) × [standard dosage (mg/day) × 140 days]}. Standard UFT dosage was 300 mg/day with BSA < 1.17 m^2, 400 mg/day with BSA 1.17–1.49 m^2, 500 mg/day with BSA 1.50–1.83 m^2, and 600 mg/day with BSA > 1.83 m^2.

RFS was defined as the time from the date of UFT/LV therapy initiation to the date of CRC recurrence, or death due to any cause. Patients were censored in the RFS analysis on the date of the last follow-up if they were alive and without CRC recurrence at the time of the last medical visit. OS was defined as the time from the date of UFT/LV therapy initiation to the date of death due to any cause. Patients who were alive were censored on the date of the last follow-up in the OS analysis.

Statistical analysis

Baseline characteristics were summarized using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. The Mann–Whitney *U* test and the Chi-square test were used to compare these variables between PPI groups (yes vs. no).

The primary and secondary endpoints were the RFS and OS, respectively. The Cox proportional hazards model was used to compare differences between the two groups. The test for proportional hazards assumption was used to check whether the assumption was satisfied. Potential explanatory variables concerning patient background, including concomitant use of PPIs (yes vs. no), age (10-year intervals), sex (male vs. female), primary site (right-sided colon vs. others [left-sided colon and/or rectal]), cancer stage (III high-risk [T4, N2, or both cancers] vs. III low-risk [T1, T2, or T3 and N1 cancers] vs. II), and relative dose intensity (10% intervals), were included as independent variables in the multivariable model, in accordance with a previous report[8]. To account for indication bias due to the lack of randomization, propensity score-adjusted analyses using the inverse probability of treatment weighting method based on the stabilized weights were performed. The probability for concomitant use of PPIs was estimated for each patient using a logistic regression model with age, sex, primary site, cancer stage, and relative dose intensity as independent variables. The estimated probability from this model is the propensity score. The HRs and 95% CIs were calculated. The robustness of the conclusions was evaluated using sensitivity analyses. The main analysis and sensitive analysis did not perform imputation methods for missing data.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R (version 4.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

Data availability

The data supporting the findings of this study are available on request from the corresponding author after approval from the ethics committees. The data are not publicly available since they contain information that could compromise the patients' privacy.

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Author contributions

MT and Katsuyuki Takahashi contributed to the study conception and design. MT, DF, KI, HY, KY, HA, NY, TH, TK, MS, Kanako Tsukada, YT, YK, and SN contributed to the data collection. MT, Katsuyuki Takahashi, Kanae Takahashi and KH performed the statistical analyses. All authors contributed to the interpretation of the results. MT wrote the initial draft of the manuscript. Katsuyuki Takahashi, Kanae Takahashi, and TO participated in manuscript editing. All the authors critically reviewed and approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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