

Original Article

Adjuvant Chemotherapy for Stage III Colorectal Cancer: A Single-center Retrospective Study of Treatment-related Outcomes and Adverse Effects

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Key Words

Stage III colorectal cancer;
Adjuvant chemotherapy;
Survival;
Adherence

Purpose. This study is aimed to evaluate the efficacy and tolerance to commonly used adjuvant regimens for stage III colorectal disease, in a single-center Taiwanese cohort.

Methods. This retrospective study analyzed 672 patients with stage III CRC treated between 2015 and 2020 at Kaohsiung Veterans General Hospital. Patients were divided into colon ($n = 362$) and rectal cancer ($n = 87$) cohorts. The adjuvant chemotherapy regimens included mFOLFOX, UFUR, and capecitabine. Disease-free survival (DFS), 6-month completion rate, and adherence (completion rate minus early recurrence rate) were evaluated. Subgroup analyses were performed for colon and rectal cancer, TNM stage, and age. Propensity score matching analysis was performed to adjust for potential confounders between groups.

Results. In colon cancer, DFS did not significantly differ across regimens; but stage IIIA patients receiving mFOLFOX or capecitabine had better DFS than those receiving UFUR ($p = 0.021$). Among patients aged 70 years or younger, capecitabine showed superior adherence among the three regimens (capecitabine: 95.2%, mFOLFOX: 88.9%, UFUR: 70.0%, $p = 0.000$), and apparently better DFS than UFUR ($p = 0.040$). Propensity score-matched analysis revealed no statistically significant differences between regimens.

In rectal cancer, no significant differences were observed in DFS or adherence to the regimens. However, UFUR was most widely used to treat patients with rectal cancer (87.0%, 65.3%, and 53.3% for stage IIIA, IIIB, and IIIC disease, respectively).

Conclusions. Overall, the regimens demonstrated comparable efficacy. Capecitabine showed the highest treatment adherence, likely due to multiple contributing factors. mFOLFOX remains a suitable option for patients with advanced stage III disease. UFUR continues to play a role in rectal cancer and palliative care due to reimbursement policy.

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Colorectal cancer (CRC) is one of the most diagnosed cancers and one of the leading causes of

cancer-related deaths worldwide. In 2018, more than 1 million new cases of colorectal cancer (CRC) were di-

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agnosed and over 500,000 patients died of colorectal cancer.¹

Among all stages of colorectal cancer, most non-screening-detected cancers are stage III.² Some reports state that stage III colorectal cancer can account for up to 70% of non-screening-detected cancers.³ This emphasizes the importance of adequately treating stage III CRC.

In the National Comprehensive Cancer Network (NCCN) guideline for colon cancer, patients with resectable colon cancer should be treated with primary radical surgery followed by adjuvant chemotherapy.^{4,6} 5-FU-based adjuvant chemotherapy up to 6 months for stage III colon cancer was reported to provide a 30% reduction in recurrence rate and an approximately 22% to 32% reduction in mortality in the first 2 years.⁷

The NCCN guideline suggests total neoadjuvant therapy for locally advanced rectal cancer (clinical T3-T4 or positive local lymph node metastasis) followed by radical surgery. This strategy provides a chance for tumor downstaging, sphincter preservation, and better local control, and may also reduce the necessity of adjuvant chemotherapy (total neoadjuvant therapy).^{8,9} However, if locally advanced cancer is still present on pathology after radical therapy, adjuvant therapy for up to 6 months should be administered with regimens including concurrent chemoradiotherapy and oxaliplatin-based adjuvant chemotherapy.^{4,10-14}

Although the efficacy of adjuvant chemotherapy regimens has been demonstrated in clinical trials conducted in Western countries, real-world practice is often influenced by a range of medical and nonmedical factors that may impact treatment outcomes. Therefore, we aimed to compare the results of adjuvant therapy for stage III CRC in recent years using our institutional data and present drug adherence issues, which may help us suggest specific strategies for specific populations, resulting in better outcomes.

Materials and Method

Patients

We retrospectively reviewed 2015 to 2020 patient

data from the Cancer Registry Database provided by the Cancer Center of Kaohsiung Veterans General Hospital.

We divided our data into 2 sections: (1) colon cancer and (2) rectal cancer because each type follows different NCCN guidelines.

In the colon cancer group, we enrolled patients who underwent primary radical surgery and were pathologically diagnosed with stage III colon cancer; therefore, adjuvant chemotherapy was prescribed (those who received neoadjuvant therapy were excluded).

In the rectal cancer group, we recruited patients who underwent radical surgery followed by adjuvant therapy, regardless of whether perioperative radiotherapy was performed.

Treatments

Concerning adjuvant regimens, we enrolled only 3 regimens: mFOLFOX, UFUR (Uracil-Tegafur), and capecitabine. These are the major regimens used at our hospital. Although perioperative chemoradiotherapy (CRT) is recommended for patients with rectal cancer, some patients refused CRT but were still included in the study.

Outcomes

The primary outcome measure was disease-free survival (DFS). DFS was calculated from the date of radical surgery (pathologically free margins) to the date of local recurrence or distant metastasis. Secondary outcomes included the completion rate of the 6-month adjuvant therapy, reasons for incomplete chemotherapy, and adherence to each regimen. Adherence was defined as the completion rate minus the early recurrence rate. Early recurrence was defined as disease progression or recurrence during the 6 months of adjuvant treatment.

Statistical analysis

Statistical analyses were performed using SPSS 26th edition. Kaplan-Meier analysis with the log-rank test was used for survival analysis. Nonparametric sta-

tistics (Kruskal-Wallis one-way analysis) were used for continuous variables, e.g., age. Pearson's chi-square test was used for descriptive variables, e.g., gender and drug adherence.

Further analyses, including Cox regression and propensity score matching, were performed in the colon cancer cohort. Univariate and multivariate Cox regression were performed to identify factors affecting survival. Propensity score matching (1:1 nearest-neighbor matching without replacement, caliper = 0.01) was performed to reduce allocation bias. The covariates included age, sex, and pathologic stage (IIIA, IIIB or IIIC). Matching was conducted using SPSS 26th edition. After matching, Kaplan-Meier survival analysis was used to compare disease-free survival between groups.

Results

Of the 672 initial patients, 362 were assigned to the colon cancer group and 87 to the rectal cancer group.

Colon cancer

In colon cancer group, the average follow up duration is 1447.67 days and the median is 1393.50 days. Most of the 362 recruited patients received mFOLFOX as adjuvant chemotherapy. However, in stage IIIA disease, more than half of the patients were treated with capecitabine (56.8%), whereas mFOLFOX (64.1%) was the most used regimen for stage IIIC disease. Patients receiving mFOLFOX were younger (median = 60), whereas patients receiving UFUR were generally older (median = 76 years). Furthermore, capecitabine had the highest completion rate for the 6-month chemotherapy regimen (92.5%), whereas UFUR had a much lower completion rate (65.6%). In the analysis of adherence, capecitabine was the highest (94.6%) and UFUR was the lowest (68.9%) for the 6-month adjuvant treatment (Table 1).

In the analysis of DFS for each regimen, several subcategories were made: (1) all patients with stage III colon cancer versus those who completed the 6-month adjuvant therapy (Figs. 1 and 2), (2) patients

Table 1. Patient characteristics grouped by regimen used (colon cancer)

	Overall	mFOLFOX	UFUR	Capecitabine	<i>p</i> value
Colon, n (%)	362 (100%)	165 (45.6)	64 (17.7)	133 (36.7)	
Age (years), median [range]	64 [24-88]	60 [24-83]	76 [43-88]	65 [37-88]	0.000 ^c
Gender, n (%)					0.098 ^d
Male	199 (55.0)	100 (60.6)	35 (54.7)	64 (48.1)	
Female	163 (45.0)	65 (39.4)	29 (45.3)	69 (51.9)	
Stage, n (%)					0.000 ^d
IIIA	44 (100)	13 (29.5)	6 (13.6)	25 (56.8)	
IIIB	240 (100)	102 (42.5)	43 (17.9)	95 (39.6)	
IIIC	78 (100)	50 (64.1)	15 (19.2)	13 (16.7)	
Completion issue, n (%)					0.000 ^d
Completion, n (%)	301 (83.1)	136 (82.4)	42 (65.6)	123 (92.5)	
Incomplete reasons					
Intolerance to drug	24 (6.6)	13 (7.9)	7 (10.9)	4 (3.0)	
Severe comorbidity	8 (2.2)	2 (1.2)	5 (7.8)	1 (0.8)	
Loss to follow up	6 (1.7)	0 (0.0)	4 (6.3)	2 (1.5)	
Stoma/wound issue	4 (1.1)	1 (0.6)	3 (4.7)	0 (0.0)	
Early recurrence ^a	19 (5.2)	13 (7.9)	3 (4.7)	3 (2.3)	
Adherence ^b , %	87.8	89.5	68.9	94.6	0.000 ^d

^a Early recurrence: recurrence or progression during the 6-month chemotherapy course.

^b Adherence = (N of subgroup – N of all incomplete reasons) / (N of subgroup – N of early recurrence) * 100%.

^c Kruskal-Wallis one-way analysis.

^d Pearson's chi-square test.

with colon cancer in pathological stages IIIA, IIIB, and IIIC (Figs. 3, 4 and 5), (3) patients with colon can-

cer in low-risk stage III and high-risk stage III (Figs. 6 and 7), (4) patients with stage III colon cancer who

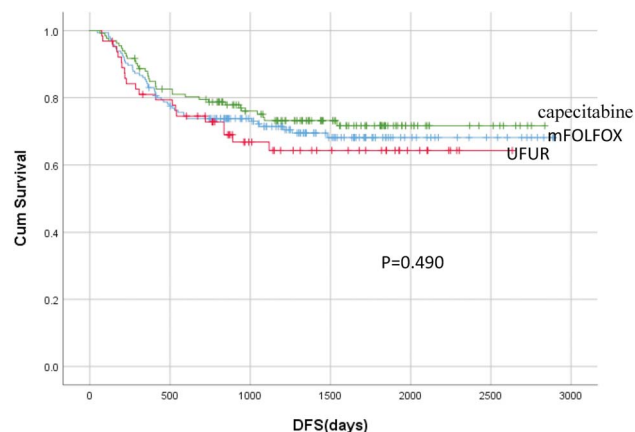


Fig. 1. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer.

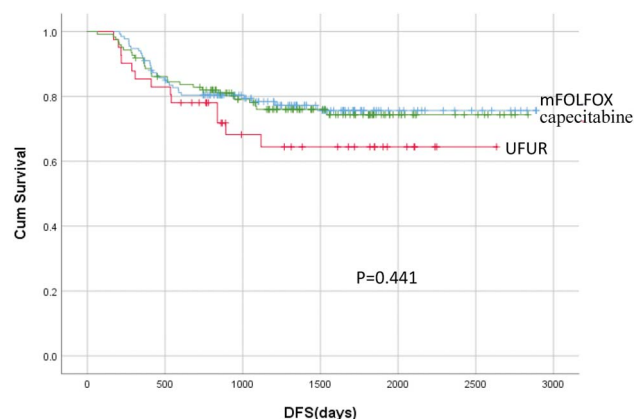


Fig. 2. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer and completed 6-month chemotherapy.

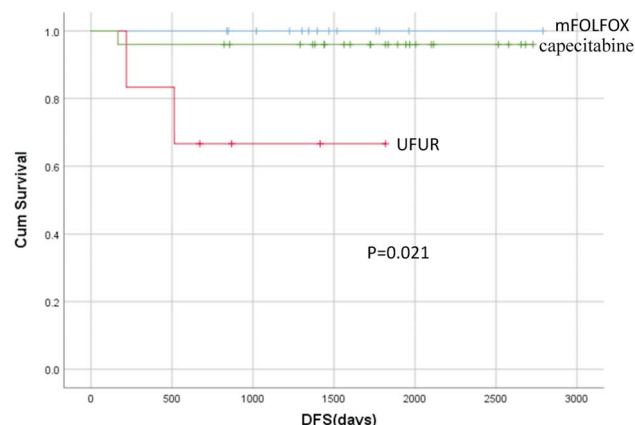


Fig. 3. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIA colon cancer (significant statistical difference was found between mFOLFOX and UFUR, $p = 0.029$; between capecitabine and UFUR, $p = 0.034$).

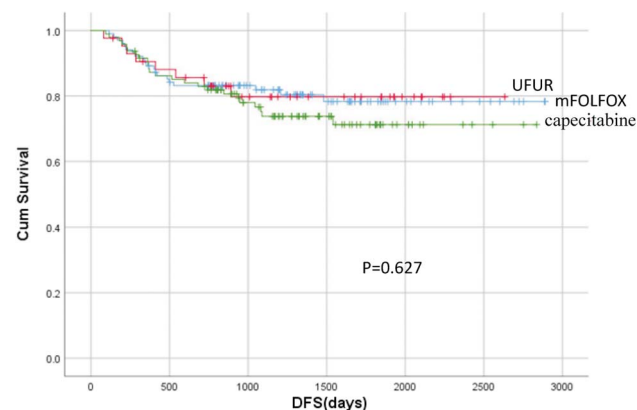


Fig. 4. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIB colon cancer.

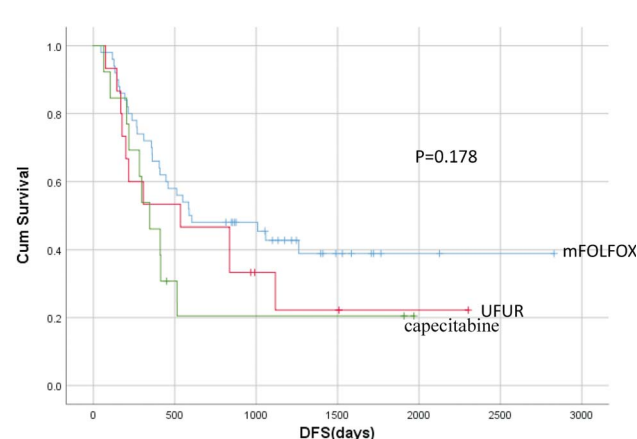


Fig. 5. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIC colon cancer.

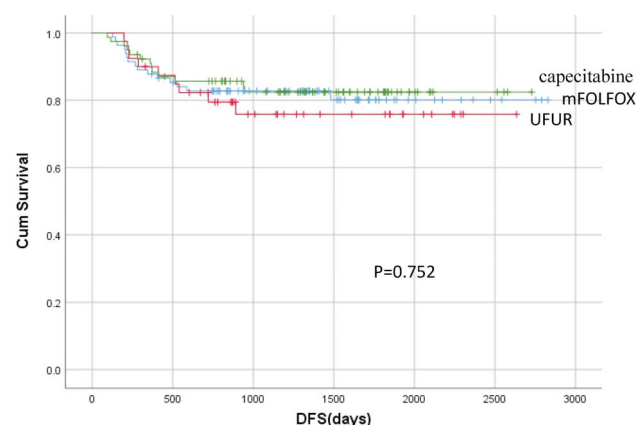


Fig. 6. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with low-risk stage III colon cancer.

aged 70 years or younger versus same patients but restricted to those who completed 6-month adjuvant therapy (Figs. 8 and 9), and (5) patients with stage III colon cancer who is older than 70 years versus same patients but restricted to those who completed 6-month adjuvant therapy. (Figs. 10 and 11). Among these sub-categories, significant difference was found only in the stage IIIA cohort (mFOLFOX vs. UFUR, $p = 0.029$; capecitabine vs. UFUR, $p = 0.034$) and in patients with stage III colon cancer aged ≤ 70 years (capecitabine vs. UFUR, $p = 0.040$).

The adherence to each regimen within each subgroup was also assessed. In the group aged 70 years or

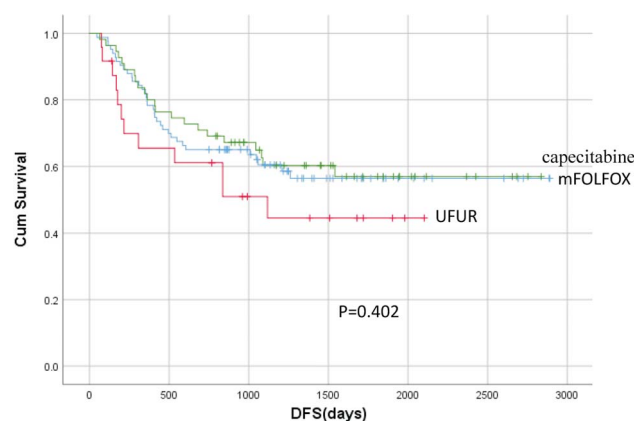


Fig. 7. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with high-risk stage III colon cancer.

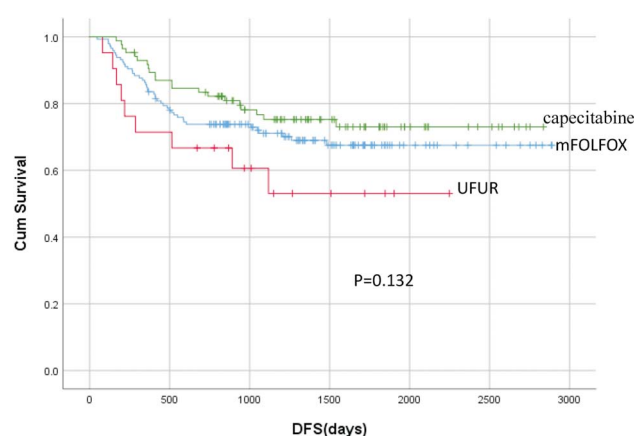


Fig. 8. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer and age ≤ 70 years old (statistical difference between each other: capecitabine to mFOLFOX, $p = 0.275$; capecitabine to UFUR, $p = 0.040$; mFOLFOX to UFUR, $p = 0.176$).

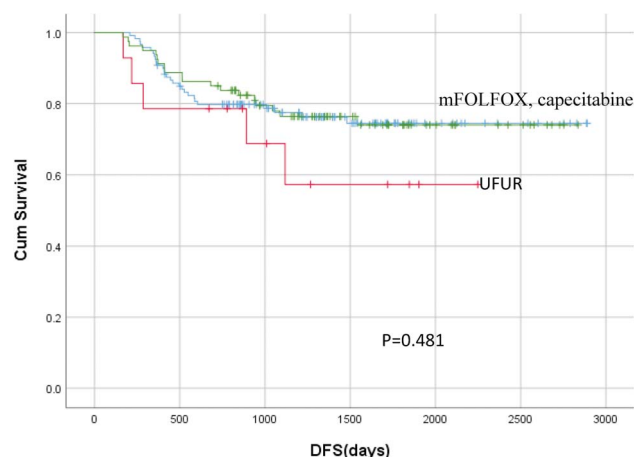


Fig. 9. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer, age ≤ 70 years old and completed 6-month chemotherapy.

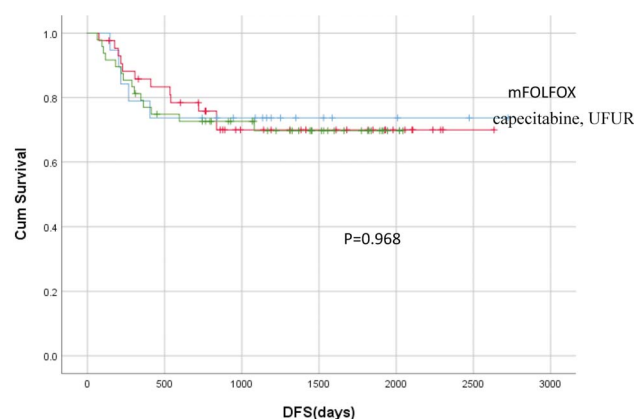


Fig. 10. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer and age > 70 years old.

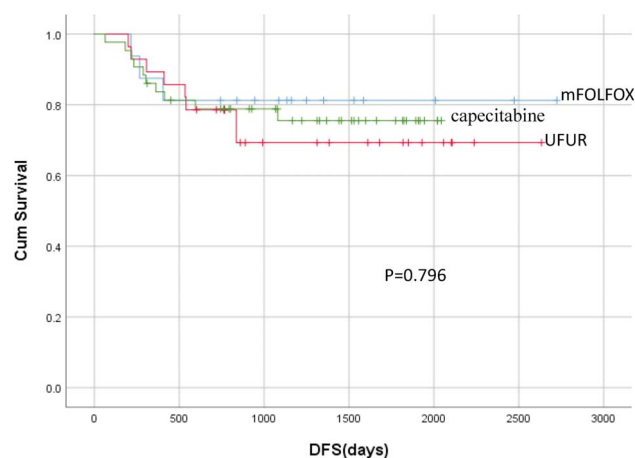


Fig. 11. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III colon cancer, age > 70 years old and completed 6-month chemotherapy.

Table 2. Adherence to each regimen, subgrouped by age

	All colon	mFOLFOX	UFUR	Capecitabine	<i>p</i> value
Adherence ^a of age ≤ 70, n/n (%)	214/239 (89.5)	120/135 (88.9)	14/20 (70.0)	80/84 (95.2)	0.000
Adherence ^a of age > 70, n/n (%)	87/104 (83.7)	16/17 (94.1)	28/41 (68.3)	43/46 (93.5)	0.081

^a Adherence = (N of subgroup – N of all incomplete reasons) / (N of subgroup – N of early recurrence) * 100%.

p values were calculated using Pearson's chi-squared test.

older, the difference in adherence of each regimen was statistically significant (88.9%, 70.0%, and 95.2%, *p* = 0.000), showing capecitabine was highest in adherence, followed by mFOLFOX, then UFUR. In contrast, in the subgroup of patients aged less than 70 years, the difference in adherence to each regimen was not statistically significant because mFOLFOX and capecitabine had the same level of adherence. (94.1% and 93.5%) (Table 2).

Cox regression analysis was performed in patients with stage III colon cancer aged 70 years or younger. In univariate Cox regression analysis, UFUR versus capecitabine within the regimen variable (HR = [2.224], 95% CI = [1.017-4.865], *p* = 0.045) and pathologic stage (HR varies by stage, *p* = 0.000) were significantly associated with disease-free survival (Table 3). In multivariate analysis, only pathologic stage (HR varies by stage, *p* = 0.003) remained significant (Table 4).

Pairwise regimen comparisons using propensity score matching showed no significant differences in the Kaplan-Meier curves (*p* = 0.942, 0.784, and 0.346, respectively; Figs. 12-14). Further analysis of disease-free survival after propensity score matching be-

tween UFUR and capecitabine in patients aged ≤ 70 years with stage III colon cancer using the Kaplan-Meier method also revealed no statistical significance (*p* = 0.462; Fig. 15).

Rectal cancer

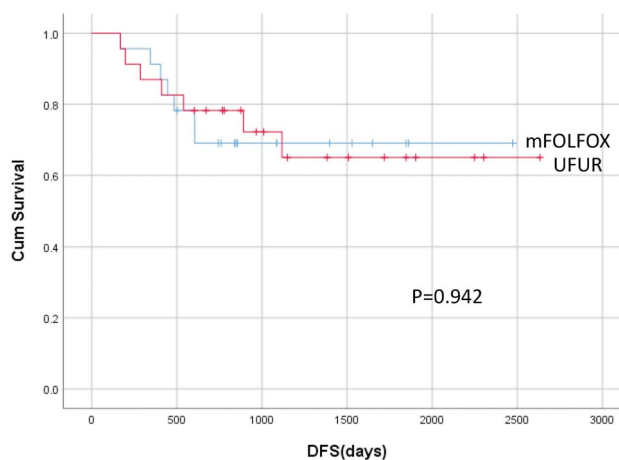
In this group, the average follow up duration is 1440.17 days and the median is 1399.00 days. Among the 87 recruited patients, most received UFUR as

Table 4. Multivariate Cox regression analysis of disease-free survival in patients aged ≤ 70 years with stage III colon cancer receiving different adjuvant regimens

Variable	Hazard ratio (95% CI)	<i>p</i> value
Regimen		
UFUR vs. capecitabine	1.231 (0.513-2.950)	0.642
Age (per year increase)	0.988 (0.947-1.030)	0.568
Gender (male vs. female)	2.112 (0.983-4.535)	0.055
Stage		
General		0.003
IIIA vs. IIIC	0.102 (0.025-0.420)	0.002
IIIB vs. IIIC	0.268 (0.105-0.682)	0.006

Table 3. Univariate Cox regression analysis of disease-free survival in patients aged ≤ 70 years with stage III colon cancer receiving different adjuvant regimens

Variable	Hazard ratio (95% CI)	<i>p</i> value
Regimen		
mFOLFOX vs. UFUR	0.612 (0.299-1.254)	0.180
mFOLFOX vs. capecitabine	1.335 (0.793-2.245)	0.277
UFUR vs. capecitabine	2.224 (1.017-4.865)	0.045
Age (per year increase)	1.017 (0.989-1.044)	0.235
Gender (male vs. female)	1.018 (0.644-1.610)	0.939
Stage		
General		0.000
IIIA vs. IIIC	0.083 (0.025-0.270)	0.000
IIIB vs. IIIC	0.251 (0.157-0.402)	0.000

**Fig. 12.** Kaplan-Meier curves for disease-free survival in stage III colon cancer after propensity score matching: mFOLFOX vs. UFUR (23 vs. 23 cases).

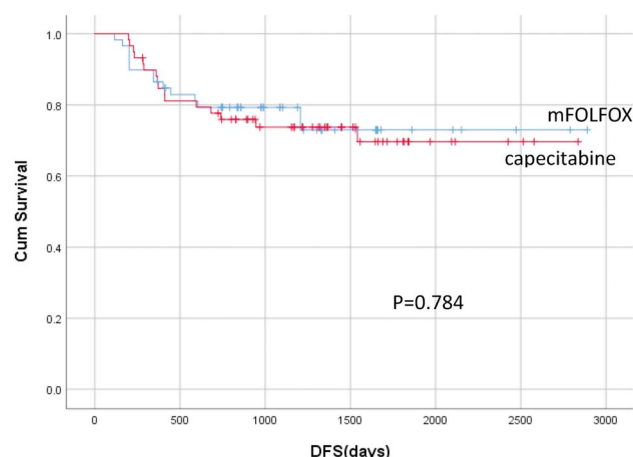


Fig. 13. Kaplan-Meier curves for disease-free survival in stage III colon cancer after propensity score matching: mFOLFOX vs. capecitabine (59 vs. 59 cases).

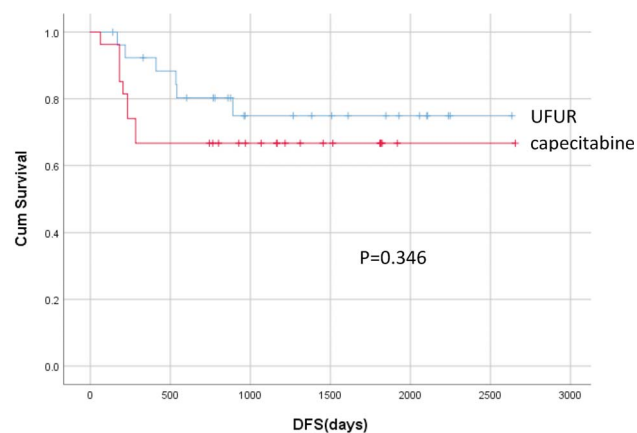


Fig. 14. Kaplan-Meier curves for disease-free survival in stage III colon cancer after propensity score matching: UFUR vs. capecitabine in stage III colon cancer (27 vs. 27 cases)

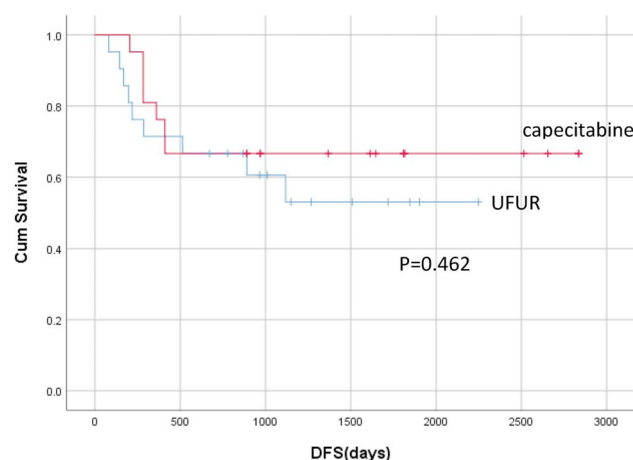


Fig. 15. Kaplan-Meier curves for disease-free survival after propensity score matching between UFUR and capecitabine in patients aged ≤ 70 years with stage III colon cancer (21 vs. 21 cases).

adjuvant chemotherapy, regardless of the cancer stage (87.0, 65.3%, and 53.3%). Patients treated with mFOLFOX tended to be younger (median = 55 years), whereas those receiving capecitabine were older (median = 69 years). Adherence to mFOLFOX, UFUR, and capecitabine showed no statistically significant differences (84.2, 79.3, and 83.3%, $p = 0.796$) (Table 5).

In the analysis of DFS associated with each regimen, we analyzed the following subcategories: (1) all patients with stage III rectal cancer versus those who completed the 6-month adjuvant therapy (Figs. 16 and 17), and (2) patients with rectal cancer in pathological stage IIIA, IIIB, and IIIC (Figs. 18-20). Neither of the above results was statistically significant.

Discussion

This study compared the disease-free survival (DFS) outcomes among patients with stage III cancer receiving different adjuvant chemotherapy regimens: mFOLFOX, UFUR, and capecitabine. The findings demonstrated patterns of efficacy and tolerability, with several subgroup differences.

DFS outcomes in patients with colon cancer

There was no statistically significant difference in DFS across the 3 regimens, either in all stage III cases or in the stage III patients who completed 6 months of chemotherapy ($p = 0.490$ and 0.441 , respectively). However, when stratified by TNM substage, a significant difference was noted in stage IIIA patients ($p = 0.021$), where mFOLFOX and capecitabine demonstrated superior DFS compared with UFUR ($p = 0.029$ and 0.034 , respectively). No significant differences were observed in stage IIIB ($p = 0.627$) or IIIC ($p = 0.178$). These findings suggest that mFOLFOX and capecitabine may be particularly related to better outcomes for patients with early-stage (IIIA) disease, although the small sample sizes (mFOLFOX, $n = 13$; UFUR, $n = 6$; capecitabine, $n = 25$) warrant cautious interpretation.

In the other staging categories stratified by low- or

Table 5. Patient characteristics grouped by regimen (rectal cancer)

	Overall	mFOLFOX	UFUR	Capecitabine	<i>p</i> value
Rectum, n (%)	87 (100)	21 (24.1)	60 (69.0)	6 (6.9)	
Age (years), median [range]	62 [31-88]	55 [40-72]	63.5 [31-88]	69 [56-78]	0.017 ^c
Gender, n (%)					0.276 ^d
Male	49 (56.3)	13 (61.9)	31 (51.7)	5 (83.3)	
Female	38 (43.7)	8 (38.1)	29 (48.3)	1 (16.7)	
Stage, n (%)					0.194 ^d
IIIA	23 (100)	2 (8.7)	20 (87.0)	1 (4.3)	
IIIB	49 (100)	14 (28.6)	32 (65.3)	3 (6.1)	
IIIC	15 (100)	5 (33.3)	8 (53.3)	2 (13.3)	
Completion issue, n (%)					0.786 ^d
Completion, n (%)	67 (77.0)	16 (76.2)	46 (76.7)	5 (83.3)	
Incomplete reasons					
Intolerance to drug	10 (11.5)	3 (14.3)	6 (10.0)	1 (16.7)	
Severe comorbidity	5 (5.7)	0 (0.0)	5 (8.3)	0 (0.0)	
Lost to follow up	1 (1.1)	0 (0.0)	1 (1.7)	0 (0.0)	
Stoma/wound issue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Early recurrence ^a	4 (4.6)	2 (9.5)	2 (3.3)	0 (0.0)	
Adherence ^b , %	80.7	84.2	79.3	83.3	0.796 ^d

^a Early recurrence: recurrence or progression during the 6-month chemotherapy course.

^b Adherence: same calculation method as completion rate but early recurrence was excluded.

^c Kruskal-Wallis one-way analysis.

^d Pearson's chi-square test.

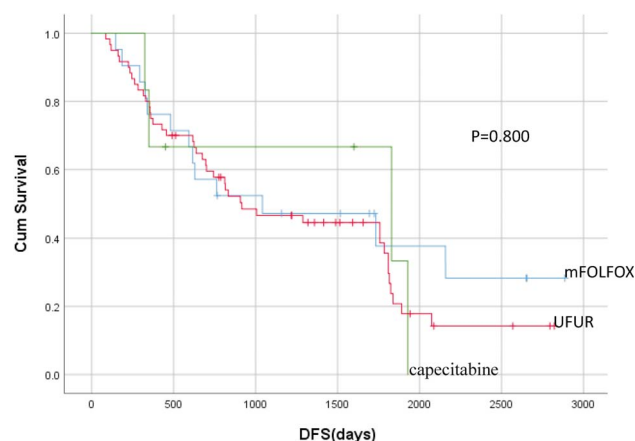


Fig. 16. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III rectal cancer.

high-risk stage III disease, there was no difference in DFS in the 3 regimens.

Chemotherapy discontinuation reasons and adherence

According to the NCCN guidelines, the non-inferiority of 3 versus 6 months FOLFOX has not been

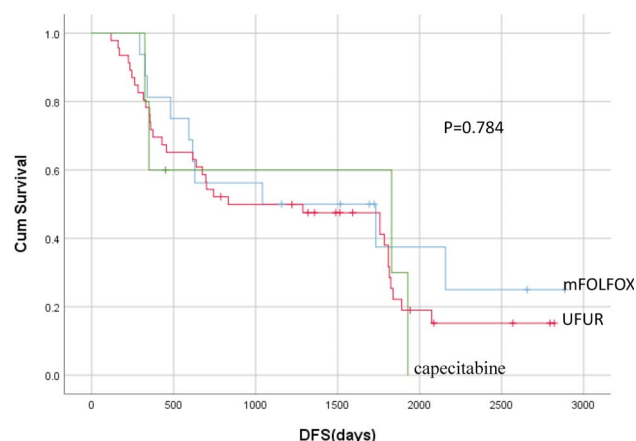


Fig. 17. Kaplan-Meier curves for disease-free survival after receiving different regimens, patients with stage III rectal cancer and completed 6-month chemotherapy.

proven for overall stage III disease. It was only proven that for patients with colon cancer staged as high-risk stage III colon cancer (T4, N1-2 or any T, N2), 6 months of FOLFOX was superior to 3 months of FOLFOX in terms of DFS.¹⁵ Therefore, we uniformly recommended that all patients with stage III colon cancer complete a full 6-month course. This uniform

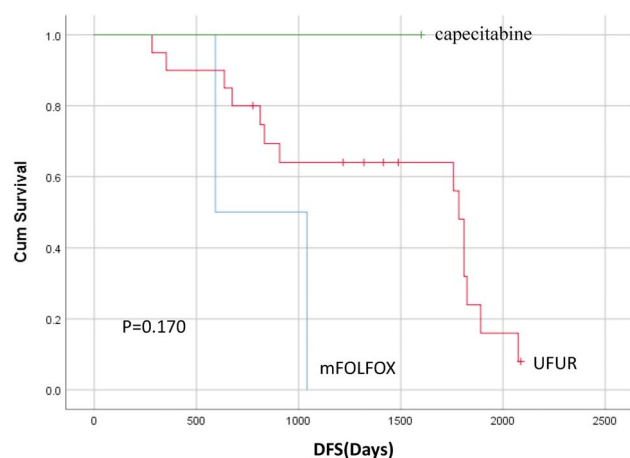


Fig. 18. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIA rectal cancer.

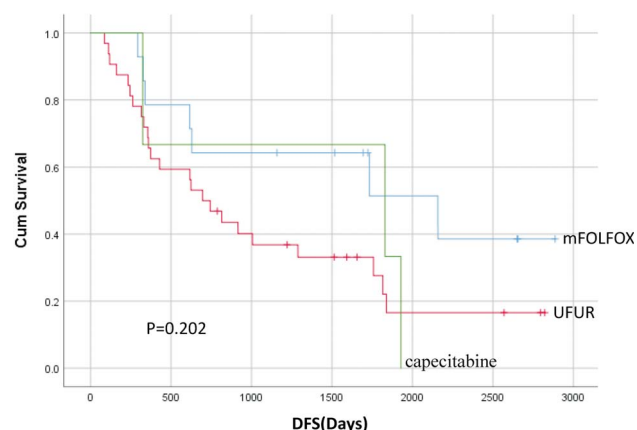


Fig. 19. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIB rectal cancer.

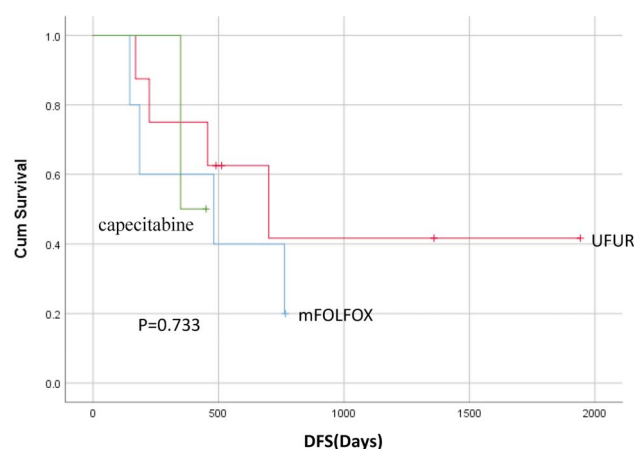


Fig. 20. Kaplan-Meier curves for disease-free survival after receiving different regimens, patient with stage IIIC rectal cancer.

approach to all 3 regimens (mFOLFOX, UFUR, and capecitabine) allowed the proportion of patients completing 6 months of chemotherapy to serve as a proxy for treatment adherence.

Previous studies have shown that the 6-month completion rate of mFOLFOX for stage III colon cancer varies from 59% to 78%.¹⁶⁻¹⁸ In comparison, the 6-month completion rate of mFOLFOX for stage III colon cancer was 82.4% in our study, indicating a non-inferior quality. In this study, we analyzed the reasons for the cessation of chemotherapy in colon cancer and found significant differences across the regimens ($p = 0.000$). The most common reason for this was patient intolerance, which includes adverse effects and allergic reactions. Other reasons include comorbidities (e.g., myocardial infarction and stroke), loss of follow-up, stoma-related complications, and disease progression.

Disease progression is the only factor that should not be considered a part of adherence, as it reflects tumor biology rather than drug-patient interactions. Including disease progression in adherence calculations could lead to double counting of its impact when analyzing DFS. Therefore, they were excluded from the adherence assessment.

Age distribution differences and confounding effects

Age distribution differed significantly among the 3 regimen groups ($p = 0.000$, Table 1). The patients who received UFUR were significantly older than those who received mFOLFOX or capecitabine. Given the known influence of age on DFS, these demographic imbalances may act as confounding factors, highlighting the importance of adjustment and stratification in future analyses.

Age-stratified efficacy and the impact of adherence

Previous studies have not proven the benefit of adding oxaliplatin to 5-FU/leucovorin in patients over 70 years of age.¹⁹ Therefore, using age 70 years as a stratification cutoff appears to be clinically reasonable.

The efficacy of adjuvant chemotherapy regimens appears to vary across different age groups, particularly among patients aged 70 years or younger. In this younger subgroup, capecitabine demonstrated significantly superior disease-free survival (DFS) than UFUR ($p = 0.040$), suggesting that treatment outcomes may be associated with the choice of regimen. However, when the analysis was restricted to patients who completed the full 6-month course of chemotherapy, thereby eliminating the confounding effect of adherence, no significant differences in DFS were observed among the three regimens ($p = 0.481$ for ≤ 70 years; $p = 0.968$ for > 70 years). These findings imply that differences in adherence, rather than intrinsic regimen efficacy, may account for the observed variations in DFS.

Historically, mFOLFOX has been shown to be superior to 5-FU/leucovorin in patients with stage III colon cancer.^{4,5} Capecitabine has been reported to provide equivalent efficacy to bolus 5-FU/leucovorin,⁶ while UFUR, as an oral fluoropyrimidine, is considered pharmacologically similar in terms of efficacy and safety to intravenous 5-FU/leucovorin.²⁰ Based on these data, mFOLFOX was expected to yield the most favorable DFS, or at least comparable results to those of the other 2 regimens. However, in a stratified subgroup of patients aged ≤ 70 years, capecitabine appeared to offer the best DFS. (Statistically significant when compared with UFUR but not significant when compared with mFOLFOX.) This finding may be associated to many factors including treatment adherence, as discussed in subsequent sections.

Propensity score matching and Cox regression in colon cancer

In this study, we found that under certain conditions (such as age and cancer stage), the efficacy of regimens may differ among patients. However, there are inherent biases in regimen selection by physicians and patients. Therefore, we applied propensity score matching to balance patient characteristics and minimize these biases. Although mFOLFOX, as a combined regimen, was expected to demonstrate superior efficacy compared with single-agent UFUR or capecitabine, no statistically significant difference was ob-

served after propensity score matching.

In the stratified subgroup of patients aged ≤ 70 years, capecitabine was found to be significantly superior to UFUR. However, after propensity score matching, this statistical significance disappeared. In univariate Cox regression, UFUR versus capecitabine was significantly associated with disease-free survival, but this association was not observed in multivariate Cox regression. These findings suggest that the previously observed difference in efficacy between UFUR and capecitabine in patients aged ≤ 70 years is likely attributed to other confounding factors.

DFS and adherence in rectal cancer

In contrast to colon cancer, patients with rectal cancer showed no significant differences in disease-free survival (DFS) across different chemotherapy regimens, regardless of whether they completed the full 6-month course ($p = 0.800$ and 0.784 , respectively). Subgroup analysis according to pathological stage (IIIA, IIIB, and IIIC) also revealed no significant differences ($p = 0.170$, 0.202 , and 0.733 , respectively). These findings suggest that the choice of adjuvant chemotherapy may have a more limited impact on DFS in rectal cancer or that the sample size was insufficient to detect meaningful differences.

The small sample size ($N = 87$) limited the number of parameters that could be analyzed. We did not stratify patients with rectal cancer by age (e.g., using 70 years as a cutoff), nor did we assess adherence by age subgroup. Generally, in rectal cancer, UFUR appears to be used in relatively younger patients and demonstrates better adherence than that in the colon cancer cohort. This result likely reflects a policy-driven pattern rather than a purely clinical rationale, which will be discussed later.

Sociological and the policy factors influencing chemotherapy adherence

There are several confounding factors that influence the regimen a patient ultimately chooses, such as age, comorbidities, self-care ability, family support, national health insurance policy, doctor preferences,

and patient preferences. Although not directly, “medication adherence” may reflect the final combination of these factors.

Our colorectal surgeons rarely used the CAPEOX regimen in patients with colorectal cancer. By interviewing the attending surgeons in our CRS department, we found they all encouraged the use of mFOLFOX for patients as much as possible. Only when a patient is deemed unsuitable for an intravenous regimen — due to various reasons — is an oral regimen considered instead. Such reasons include advanced age and frailty, multiple comorbidities, limited self-care ability, inadequate family support or patient’s personal consideration. When an oral regimen is chosen, the decision between capecitabine and UFUR is often based on the surgeon’s personal preference. Some attending surgeons prefer capecitabine, others prefer UFUR, some use both almost equally.

The primary advantage of UFUR and capecitabine is their oral administration, whereas FOLFOX requires intravenous delivery and minor surgery for venous port implantation. When the potential survival benefit of FOLFOX is not clearly communicated, patients may favor oral agents owing to cosmetic concerns (female) and greater convenience (not yet retired) in daily life. This preference is supported by 2 findings: (1) a higher proportion of female patients receiving capecitabine and a lower female proportion receiving mFOLFOX in patients aged 70 years or younger ($p = 0.014$) (Table 6), and (2) a higher adherence rate to capecitabine compared to mFOLFOX in patients aged 70 years or younger ($p = 0.000$) (Table 2).

In contrast, UFUR demonstrated the lowest adherence rate, likely because it is more commonly prescribed with palliative intent. In Taiwan, the National Health Insurance (NHI) reimburses capecitabine for up to 8 cycles (approximately 6 months) as adjuvant therapy, while UFUR can be used for up to 2 years.²¹ As a result, older and more frail patients may be more likely to receive UFUR as adjuvant treatment. This inference is supported by the older age distribution among patients receiving UFUR, the higher incidence of severe comorbidities and loss of follow-up in this group, and the low number of patients receiving UFUR in the subgroup aged 70 years or younger.

In the subgroup of patients aged older than 70 years with colon cancer, adherence to mFOLFOX and capecitabine appeared to be the same. A reasonable interpretation might be that oncologists already carefully filtered the patients who looked healthier and had better family support to receive mFOLFOX because it warrants frequent hospital visits and may be more uncomfortable in the first several days after intravenous drug delivery. This perspective is supported by the surprisingly low number of patients receiving mFOLFOX in subgroups aged older than 70 years (Table 2).

The NHI in Taiwan does not reimburse oxaliplatin or capecitabine as adjuvant therapy in patients with stage III rectal cancer. This reimbursement policy led to a predominance of UFUR use in this population, accounting for 69.0% of patients with pathological stage III rectal cancer.

Although clinical guidelines recommend concurrent radiotherapy with oral chemotherapy as the standard adjuvant treatment, only a small proportion (23.3%) of patients in this cohort received concurrent radiotherapy. This was largely due to patients’ reluctance to endure the adverse effects of radiotherapy.

Moreover, the oncological stage appears to influence the selection of chemotherapeutic regimens. In stage IIIA rectal cancer, the majority of patients (87.0%) received UFUR. In contrast, among patients with stage IIIC disease, the use of UFUR was lower (53.3%) and mFOLFOX was used more frequently (33.3%) than early stage III. These findings suggest that oncologists may be more likely to recommend mFOLFOX to patients with advanced rectal cancer, possibly because of its superior efficacy according to previous studies.

Conclusion

In general, mFOLFOX, UFUR, and capecitabine

Table 6. Proportion for genders of patient receiving different regimens

Age ≤ 70 years	Male	Female	<i>p</i> value
mFOLFOX, n (%)	88 (60.3)	58 (39.7)	0.014
Capecitabine, n (%)	37 (43.5)	45 (56.5)	

demonstrated comparable efficacies in patients with stage III colorectal cancer. Differences in outcomes among the treatment regimens may not only reflect the intrinsic efficacy of the drugs, but also be associated with the impact of medication adherence and other factors examined in this study.

For younger patients (aged ≤ 70 years) with stage III colon cancer, capecitabine showed superior performance compared to UFUR and comparable performance to mFOLFOX. In this cohort, capecitabine also showed the highest drug adherence. This result should be interpreted as the influence of multiple confounding factors, as demonstrated by the findings from Cox regression and propensity score matching. In contrast, for more advanced stage III colon cancer, mFOLFOX remains the preferred regimen, which is supported by previously established evidence of its efficacy. UFUR plays an important role in the treatment of rectal cancer and is frequently used for palliative purposes. Its continued use is supported by its non-inferior efficacy and the current reimbursement policies that make it broadly accessible.

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原 著

第三期大腸直腸癌的輔助化學治療：單中心回顧性研究，著重於治療相關療效與不良反應

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目的 本研究旨在評估單一醫學中心中，常見輔助化療的療效及治療耐受性。

方法 本回溯性研究分析了 2015 年至 2020 年間在高雄榮民總醫院接受治療的 672 名第三期大腸直腸癌患者。篩選後，患者依癌別分為大腸癌 (362 人) 與直腸癌 (87 人) 兩組。所使用的輔助化療為 mFOLFOX、UFUR 或 capecitabine 中其中一項。評估的指標包括無病存活率 (DFS)、六個月化學治療療程完成率與藥物依從性 (定義為六個月療程完成率扣除早期復發者)。另針對癌別 (大腸或直腸癌)、TNM 分期及年齡等進行分組分析。使用傾向分數配對分析來減少混雜因子 (confounding factors)。

結果 在大腸癌部分，各化療藥物在無病存活率上並無顯著差異，但在第三 A 期患者中，接受 mFOLFOX 或 capecitabine 治療者的無病存活率明顯優於接受 UFUR 者 ($p = 0.021$)。年齡 70 歲以下的患者對 capecitabine 依從性最佳 (capecitabine: 95.2%, mFOLFOX: 88.9%, UFUR: 70.0%, $p = 0.000$)，且使用 capecitabine 的患者無病存活率亦明顯優於 UFUR ($p = 0.040$)。傾向分數配對分析則顯示各治療方案之間無統計上顯著差異。

在直腸癌部分，三種方案在無病存活率與藥物依從性方面均無顯著差異。但 UFUR 在直腸癌治療中使用最為廣泛 (在第三 A、三 B 與三 C 期中使用率分別為 87.0%、65.3% 與 53.3%)。

結論 整體而言，各種治療藥物顯示出相近的療效。Capecitabine 的治療依從性最高，這可能和多種因素有關。mFOLFOX 因其有效性適合用於較晚期的第三期大腸癌病患。UFUR 則因給付政策因素，仍在直腸癌及緩和治療中扮演重要角色。

關鍵詞 第三期大腸直腸癌、輔助性化學治療、存活率、藥物依從性。