

Original Article

Adjuvant Therapy in Stage IIb and IIc Colorectal Cancer: An Eight-year Cohort Study at Taichung Veterans General Hospital

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Key Words

Stage II colorectal cancer;

Adjuvant chemotherapy;

Oral chemotherapy

Purpose. Tumor staging of colorectal cancer plays a significant role in both treatment and prognosis. At present, T4 tumors without lymph node metastasis are considered high-risk Stage II, for which adjuvant chemotherapy (C/T) is recommended. However, there is no consensus on the optimal C/T regimen. Therefore, we collected patient data from Taichung Veterans General Hospital over the past decade to conduct further research.

Methods. Between 2010 and 2018, a total of 5,760 newly diagnosed colorectal cancer patients were treated at our hospital. We focused on patients with pathologic Stage IIb and IIc disease (T4a-bN0M0). Patients diagnosed with colorectal cancer who had received neoadjuvant chemoradiotherapy were excluded. Ultimately, 132 patients were included in this study. A multivariate Cox regression analysis was conducted to identify the independent risk factors for overall survival.

Results. A total of 132 patients were included in the study: 38 of them did not receive adjuvant C/T, while 94 patients did undergo adjuvant C/T. These 94 patients were further divided into two groups: 69 in the oral Tegafur-Uracil group and 25 in the FOLFOX group. The 10-year disease free survival rates for the adjuvant C/T group and the non-adjuvant C/T group were 55.7% and 28.0%, respectively, with a p -value < 0.001 . The 10-year overall survival rates for the Tegafur-Uracil group and the FOLFOX group were 53.8% and 57.8%, respectively, with a p -value of 0.559.

Conclusion. Based on our data, patients with locally advanced Stage II colorectal cancer may benefited from adjuvant C/T, indicating that the use of FOLFOX may not be strictly necessary.

[J Soc Colon Rectal Surgeon (Taiwan) 2026;37:202-210]

Data from the Taiwan National Health Insurance Administration indicates that both the incidence and mortality rates of colorectal cancer have shown a continuous upward trend over the years, with the disease remaining the most prevalent form of cancer in Taiwan over the past 15 years. The treatment of colorectal cancer is staged according to the American Joint

Committee on Cancer (AJCC) TNM system, with corresponding treatments recommended based upon the different stages. Patients diagnosed with pathologic Stage I do not require adjuvant chemotherapy (C/T), while those who have reached Stage III are advised to undergo adjuvant C/T. The treatment approach for Stage II patients, however, remains a topic of discus-

Received: June 11, 2025.

Accepted: July 31, 2025.

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sion.¹ Currently, decisions regarding the administration of C/T are based upon both clinical and pathological risk assessments.

Since 2010, under the seventh edition of the AJCC staging system (AJCC-7),² T4 lesions have been further classified as either T4a (tumor penetrates the surface of the visceral peritoneum) or T4b (tumor directly invades or is histologically adherent to other organs or structures). Studies have confirmed that use of the AJCC-7 staging system has improved predictive capabilities for the prognosis of colorectal cancer.³ According to the National Comprehensive Cancer Network (NCCN) guidelines, observation, together with either adjuvant intravenous (IV) C/T or adjuvant oral C/T for pT4N0M0 tumors is indicated. Our team became curious about the long-term prognosis for patients diagnosed with colorectal cancer when the postoperative pathology has revealed a patient with a T4N0M0 tumor who has been given a strategy of observation or adjuvant C/T. We also posed questions regarding the difference in long-term prognosis between treatment involving either adjuvant IV C/T or adjuvant oral C/T in pT4N0M0 patients.

Materials and Methods

This study is a retrospective analysis of a prospective database. The colorectal cancer registry at Taichung Veterans General Hospital has prospectively collected and quality-audited data since January 2010. We requested access to the dataset in 2023. To ensure that all included patients had a minimum potential follow-up of five years — an essential criterion for reliable analyses of overall and disease-free survival — we closed case accrual on December 31, 2018. This resulted in an eight-year cohort spanning from 2010 to 2018. The inclusion criteria encompassed all newly diagnosed and curatively operated colorectal cancer patients from the years 2010 to 2018, with postoperative pathology reports indicating T4a-bN0 and no clinical evidence of distal metastasis being reported. Patients receiving preoperative neoadjuvant therapy were excluded, as well as those with synchronous double primary cancer, postoperative complications leading

to death, a history of previous malignancy, incomplete medical records, and patients who did not return for postoperative follow-up. Patients with R2 resection (macroscopic residual tumor peri-operation) were also excluded. A total of 132 patients were ultimately included in this study.

Data were collected regarding patient characteristics, primary tumor side, high-risk pathological features (poor differentiation, perineural invasion, fewer than 12 lymph nodes harvested, lymphovascular invasion, positive resection margin), and high-risk clinical features (colonic obstruction, colonic perforation). Dates of disease progression and sites of recurrence were documented based upon formal reports issued by radiologists. Sites of tumor recurrence were recorded based upon imaging and colonoscopy reports and included the liver, lung, peritoneum and local recurrence.

Patients were categorized into two groups: adjuvant C/T and non-adjuvant C/T. Furthermore, patients who received adjuvant C/T were divided into two subgroups: oral 5-FU (5-Fluorouracil) and standard mFOLFOX6 (5-Fluorouracil, leucovorin and oxaliplatin) treatment. Oral 5-FU refers to a combination of Tegafur 100 mg and Uracil 224 mg (trade name: UFUR). The initial dose was 2 tablets administered twice daily. Prior to 2018 our hospital did not undergo the practice of using the regimen of Oral 5-FU + Oxaliplatin. Main outcomes included overall survival (OS) and disease free survival (DFS). OS was defined as death during follow-up, while DFS was defined to the time interval from the date of surgery to the date of the first documented recurrence of the disease, or death from any cause.

Statistical analysis

Chi-square tests were used to compare the differences in characteristics between the groups. Cox proportional hazard regression was employed to assess the impact of various factors on OS. Variables with a univariate p -value < 0.20 were entered into a multivariable Cox proportional-hazards model to identify independent prognostic factors. A two-sided p -value < 0.05 in the multivariable analysis was considered

statistically significant. OS and DFS were estimated using the Kaplan-Meier method from the time of surgery, while the log-rank test was used to compare the statistical differences between survival outcomes within the groups.

Results

A total of 132 patients were included in the study, with 94 patients receiving adjuvant C/T and 38 pa-

tients not receiving adjuvant C/T. The median follow-up, calculated using the reverse Kaplan-Meier method, was 83 months (IQR 64-110). There were no differences between the two groups in terms of gender distribution, BMI, BSA, primary tumor site (left or right colon) or risk features. However, patients who received adjuvant C/T were of a younger age, had a lower Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS Scale) and also a more advanced T stage (Table 1).

The 10-year overall survival rates for adjuvant

Table 1. Patient characteristics

	No adjuvant therapy	Oral 5-FU	FOLFOX	<i>p</i> value
Number	38	69	25	
Age	78.5 (59.0-86.0)	64.0 (55.0-73.0)	54.0 (42.5-58.5)	< 0.001**
Gender				0.872
Female	14 (36.8%)	29 (42.0%)	10 (40.0%)	
Male	24 (63.2%)	40 (58.0%)	15 (60.0%)	
BMI	22.2 (19.2-24.7)	22.9 (20.2-24.9)	22.9 (21.0-25.2)	0.554
BSA	1.6 (1.5-1.7)	1.6 (1.5-1.8)	1.7 (1.6-1.8)	0.391
ECOG				0.007**
0	2 (5.3%)	11 (15.9%)	0 (0.0%)	
1	15 (39.5%)	32 (46.4%)	19 (76.0%)	
2-3	21 (55.3%)	26 (37.7%)	6 (24.0%)	
Site				0.741
Left	24 (63.2%)	41 (59.4%)	17 (68.0%)	
Right	14 (36.8%)	28 (40.6%)	8 (32.0%)	
Poor differential				0.259
No	35 (92.1%)	62 (89.9%)	25 (100.0%)	
Yes	3 (7.9%)	7 (10.1%)	0 (0.0%)	
Lympho/vascular invasion				0.474
No	35 (92.1%)	58 (84.1%)	21 (84.0%)	
Yes	3 (7.9%)	11 (15.9%)	4 (16.0%)	
Obstruction				0.131
No	27 (71.1%)	52 (75.4%)	23 (92.0%)	
Yes	11 (28.9%)	17 (24.6%)	2 (8.0%)	
< 12 lymph nodes examined				--
No	38 (100.0%)	69 (100.0%)	25 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Perineural invasion				0.663
No	27 (71.1%)	49 (71.0%)	20 (80.0%)	
Yes	11 (28.9%)	20 (29.0%)	5 (20.0%)	
Perforation				0.093
No	36 (94.7%)	60 (87.0%)	25 (100.0%)	
Yes	2 (5.3%)	9 (13.0%)	0 (0.0%)	
Margins positive				0.819
No	32 (84.2%)	57 (82.6%)	22 (88.0%)	
Yes	6 (15.8%)	12 (17.4%)	3 (12.0%)	
T stage				0.001**
T4a	21 (55.3%)	57 (82.6%)	12 (48.0%)	
T4b	17 (44.7%)	12 (17.4%)	13 (52.0%)	

Chi-square test or Kruskal-Wallis test. Median (IQR) * $p < 0.05$, ** $p < 0.01$.

C/T and non-adjuvant C/T were 54.0% and 32.6%, respectively, with a p -value of < 0.001 (Fig. 1). The 10-year disease free survival rates for adjuvant C/T and non-adjuvant C/T were 55.7% and 28.0%, respectively, with a p -value of < 0.001 (Fig. 2). In multivariate analysis, there appeared to be a difference be-

tween adjuvant C/T and non-adjuvant C/T (p -value = 0.003) (Table 2) in overall survival (OS), as well as a difference between age (p -value = 0.002).

Of the 94 adjuvant C/T patients, 25 received IV C/T while 69 received oral C/T. The 10-year overall survival rates for IV C/T and oral C/T were 57.8% and

	Total	Death	Censored		Survival rate				p for log rank
			n	%	1y	3y	5y	10y	
Adjuvant C/T									
No	38	25	13	(34.2%)	66.1%	48.9%	41.6%	32.6%	< 0.001
Yes	94	33	61	(64.8%)	96.6%	80.9%	71.7%	54.0%	

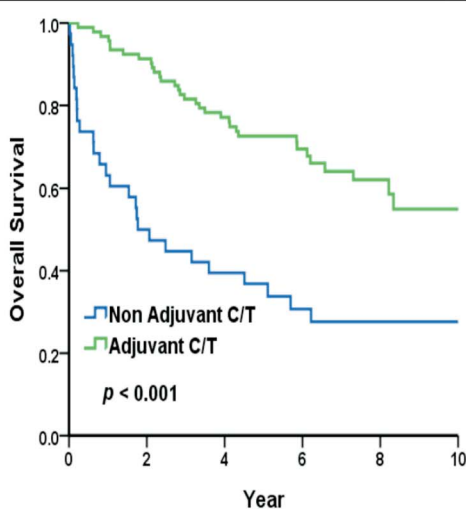


Fig. 1. Overall survival.

	Total	Progression/Death	Censored		Survival rate				p for log rank
			n	%	1y	3y	5y	10y	
Adjuvant C/T									
No	38	27	11	(28.9%)	50.0%	36.8%	34.2%	28.0%	< 0.001
Yes	94	35	59	(62.8%)	87.0%	72.9%	68.4%	55.7%	

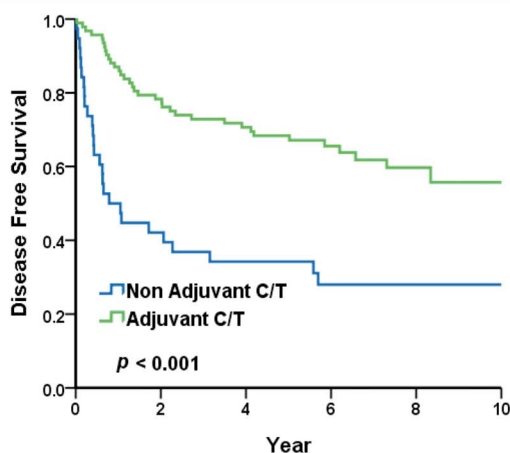


Fig. 2. Disease free survival.

Table 2. Cox regression – overall survival

	Univariate			Multivariable		
	Hazard ratio	95% CI	<i>p</i> value	Hazard ratio	95% CI	<i>p</i> value
Age	1.05	(1.03-1.07)	< 0.001**	1.03	(1.01-1.06)	0.002**
Gender						
Female	Reference			Reference		
Male	1.56	(0.91-2.67)	0.108	1.52	(0.83-2.78)	0.170
BMI	0.92	(0.85-1.00)	0.053	0.93	(0.85-1.01)	0.083
ECOG						
0	Reference			Reference		
1	0.99	(0.34-2.88)	0.981	0.90	(0.30-2.66)	0.849
2-3	3.14	(1.11-8.84)	0.030*	2.59	(0.81-8.33)	0.110
Site						
Left	Reference			Reference		
Right	1.67	(1.00-2.78)	0.048*	1.14	(0.63-2.05)	0.671
Adjuvant C/T						
No	Reference			Reference		
Yes	0.31	(0.19-0.52)	< 0.001**	0.41	(0.23-0.74)	0.003**
Poor differential						
No	Reference			Reference		
Yes	1.86	(0.84-4.10)	0.123	1.58	(0.67-3.76)	0.299
lympho/vascular invasion						
No	Reference					
Yes	1.29	(0.67-2.50)	0.441			
Obstruction						
No	Reference			Reference		
Yes	1.66	(0.95-2.91)	0.078	0.88	(0.44-1.79)	0.732
Perineural invasion						
No	Reference					
Yes	0.82	(0.45-1.49)	0.517			
Perforation						
No	Reference					
Yes	1.69	(0.72-3.93)	0.225			
Margins positive						
No	Reference					
Yes	0.76	(0.36-1.60)	0.468			
Stage						
T4a	Reference			Reference		
T4b	1.57	(0.93-2.63)	0.089	1.03	(0.52-2.03)	0.928

Cox proportional hazard regression. * $p < 0.05$, ** $p < 0.01$.

53.8%, respectively, with a p -value of 0.559 (Fig. 3). The 10-year disease free survival rates for IV C/T and oral C/T were 59.4% and 53.0%, respectively, with a p -value of 0.726 (Fig. 4).

Discussion

Our data analysis unveiled compelling insights

which revealed that adjuvant C/T not only offered statistical significance in 10-year OS when compared with non-adjuvant C/T (54.0% vs. 32.6%, $p < 0.001$) but also in 10-year DFS (55.7% vs. 28.0%, $p < 0.001$) (Figs. 1&2). Notably, within this retrospective study, there was no statistical significance seen in 10-year OS and 10-year DFS between the IV adjuvant C/T and oral adjuvant C/T. Therefore, we can draw the result that adjuvant C/T offers a better prognosis for Stage

Treatment	Total	Death	Censored		Survival rate				p for log rank
			n	%	1y	3y	5y	10y	
IV C/T	25	8	17	(68.0%)	100.0%	87.5%	79.2%	57.8%	0.559
Oral C/T	69	25	44	(63.8%)	95.6%	79.4%	70.3%	53.8%	

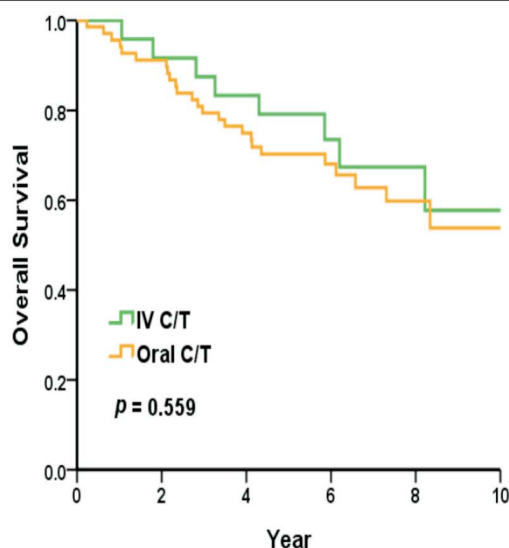


Fig. 3. Overall survival between IV C/T (FOLFOX) and oral C/T (5-FU).

Treatment	Total	Progression/Death	Censored		Survival rate				p for log rank
			n	%	1y	3y	5y	10y	
IV C/T	25	9	16	(64.0%)	95.8%	75.0%	70.8%	59.4%	0.726
Oral C/T	69	26	43	(62.3%)	83.9%	72.1%	67.5%	53.0%	

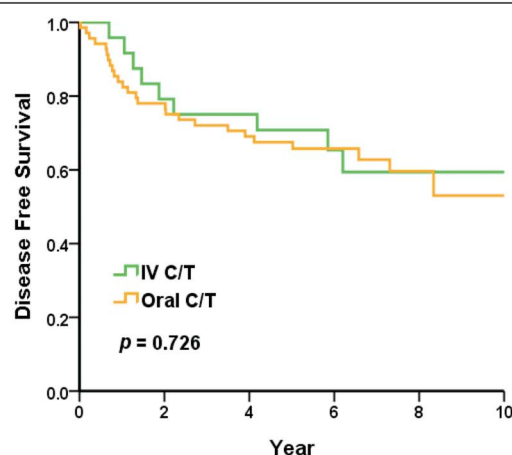


Fig. 4. Disease free survival between IV C/T (FOLFOX) and oral C/T (5-FU).

IIb and IIc colorectal cancer patients. However, when choosing the optimum adjuvant C/T regimen, there is no difference between the IV form and oral form.

In Stage II colorectal cancer, the choice to proceed with adjuvant therapy following surgery depends hea-

vily on a comprehensive evaluation of risk. Clinical practitioners employ various strategies to accurately assess the potential risks linked to this stage of the disease. Traditionally, these predictions have been based on both clinical and pathological features.⁴⁻⁶ How-

ever, as our understanding better evolves over time, additional concerns such as tumor budding,⁷⁻⁹ collagen factors,¹⁰ immunoscores,¹¹ inflammation index ratio,^{12,13} and the concentration of circulating tumor DNA (ctDNA) as measured by next-generation sequencing (NGS), have all gained significance in regards to the risk assessment process.¹⁴ To better deal with pathological T4 tumors, clinical practitioners may prescribe adjuvant C/T to patients according to any high-risk pathological and clinical features seen, as well as each patient's current medical condition, along with any other concerns which may apply.

Older patients generally have shorter life expectancies and a higher likelihood of underlying comorbidities. These factors may contribute to physicians' decisions to withhold adjuvant C/T in this population. Such circumstances inevitably introduce selection bias, which may have influenced the outcomes of our study. While the use of propensity score matching (PSM) could potentially improve the reliability of the results, a substantial imbalance in the number of patients who received adjuvant C/T versus those who did not was observed in our study. Applying PSM under these conditions would have resulted in the exclusion of a large number of cases, thereby reducing statistical power and limiting the robustness of the findings. Nevertheless, our results are consistent with previous studies. According to Yujin Lee et al.,¹⁵ among elderly patients with stage II high-risk colorectal cancer, adjuvant C/T did not significantly improve recurrence-free survival or overall survival compared to patients who did not receive adjuvant C/T. These findings support our observation that patients who did not receive adjuvant C/T were, on average, older — suggesting that advanced age may influence both clinical decision-making and potential therapeutic benefit.

T4 tumors in Stage II colorectal cancer have long been considered a high-risk factor for disease recurrence, and its outcome in patients is similar to that seen in T3N1 colorectal cancer.¹⁶ The administration of adjuvant therapy to patients diagnosed with Stage II local advanced colorectal cancer is universally undisputed. Previous articles have argued that not all risk factors have the same impact, and that T4 tumors, in fact, benefit more from adjuvant therapy.¹⁷ In our

data, it was revealed that there was no statistically significant difference in either OS or DFS regarding the administration of adjuvant IV C/T or oral C/T (Fig. 3, p -value = 0.559; Fig. 4, p -value = 0.726). According to ISAO ITO et al.,¹⁸ oral regimen achieved equivalent efficacy to the IV regimen in patients with stage II colorectal cancer, while improving their postoperative quality of life. Additionally, considering the potential residual neurotoxic side effects from oxaliplatin, it may be reasonable to consider either intravenous infusions of 5-FU or oral 5-FU alone according to our study.

This study has several limitations. First, its single-center retrospective design introduces inherent risks of selection bias and unmeasured confounding. Although treatment decisions were made through a multidisciplinary team (MDT) approach, inter-physician variability in clinical judgment may have influenced patient management. Furthermore, while two dedicated cancer case managers monitored patient progress, the extended study duration of over a decade may have resulted in inconsistencies in data collection timing and methodology, potentially affecting the validity of the findings.

Conclusion

Based on our data, patients with locally advanced Stage II colorectal cancer clearly benefited from adjuvant C/T. However, when compared with adjuvant IV C/T or oral C/T, there was no difference seen in either OS or DFS. Therefore, we can draw the result that the use of FOLFOX may not be strictly necessary.

Sources of Financial Support

There are no conflicts of interest to declare.

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原 著

第二期 B 與 C 期結腸直腸癌的輔助性治療： 臺中榮民總醫院八年期世代研究

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目的 大腸直腸癌的腫瘤分期在治療與預後中扮演著關鍵角色。根據現行標準，無淋巴結轉移的 T4 腫瘤被歸類為高風險第二期，建議接受輔助性化學治療。然而，關於最佳化療方案尚未有共識。因此，我們蒐集了臺中榮民總醫院過去十年的病患資料，進行進一步的研究。

方法 於 2010 年至 2018 年間，本院共治療了 5,760 位新診斷的大腸直腸癌病患。本研究僅納入病理分期為 IIb 與 Iic (T4a-bN0M0) 的病患。曾接受新輔助性同步化學放射治療的結腸直腸癌病患則排除在外。最終共有 132 位病患納入本研究，並進行多變項 Cox 回歸分析，以找出影響整體存活率的獨立危險因子。

結果 本研究共納入 132 位病患，其中 38 位未接受輔助性化學治療，94 位接受了輔助性化療。這 94 位病患進一步分為兩組：69 位為口服 Tegafur-Uracil 組，25 位為 FOLFOX 組。10 年疾病無病生存期在接受輔助性化療組與未接受組分別為 55.7% 與 28.0%， p 值 < 0.001 。10 年整體存活率在口服 Tegafur-Uracil 組與 FOLFOX 組分別為 53.8% 與 57.8%， p 值為 0.559。

結論 根據我們的數據顯示，局部晚期第二期結腸直腸癌病患或許可從輔助性化療中受益，但使用 FOLFOX 並非絕對必要。

關鍵詞 第二期大腸直腸癌、輔助性化學治療、口服化療藥。