Original Article

Impact of Chemotherapy Cycles on pT1 Node-positive Colorectal Cancer Patient's Outcome

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Purpose. pT1 colorectal cancers have certain risks of lymph node metastasis. The optimal duration of adjuvant chemotherapy in pT1N+ colon cancer remains a controversial topic. This study aimed to investigate whether there is a survival difference between patients with pT1 node positive colorectal cancers who received FOLFOX chemotherapy for 6-8 cycles compared to those who received 10-12 cycles.

Methods. We conducted a retrospective cohort study including patients with pT1N+ colorectal cancer who underwent adjuvant FOLFOX chemotherapy between 2010 to 2020. Survival outcomes were analyzed using Kaplan-Meier survival curves and Cox proportional hazards models.

Results. A total of 57 patients met the inclusion criteria, with 29 receiving 6-8 cycles of FOLFOX and 28 receiving 10-12 cycles. Five-year disease-free survival rates were comparable. Our analysis revealed no statistically significant difference in overall survival (OS) and disease-free survival (DFS) between the two groups. Subgroups analysis of disease-free survival.

Conclusion. In patients with pT1N+ colon cancer, there was no significant difference in survival outcomes between those who received 6-8 cycles of FOLFOX chemotherapy and those who received 10-12 cycles. These findings suggest that a shorter course of adjuvant FOLFOX chemotherapy may be as effective as a longer course in this patient population. Further prospective studies are warranted to validate these results and refine treatment recommendations.

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Key Words
pT1 colorectal cancers;
Lymph node metastasis;
Duration of adjuvant chemotherapy

Colorectal cancer is an important disease that was the most common type of cancer in Taiwan in 2020.[1] Approximately 10%-15% of lymph node metastasis cases are pT1 node-positive colorectal cancers. The risk factors include poor histological differentiation, submucosal invasion depth, lymphovascular invasion, perineural invasion, carcinoembryonic antigen (CEA) level > 5 ng/dL, and high tumor budding (> 10/high-power field).[2-4]

Six months of chemotherapy with FOLFOX (flu-

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orouracil [5-FU], leucovorin, and oxaliplatin) is considered the standard treatment for stage III colon cancer, based on the results of the MOSAIC trial.[5] However, long-term oxaliplatin-based therapy can cause serious adverse effects, such as peripheral neurotoxicity. Based on this premise, the IDEA collaboration was established with the aim of reducing the toxicity of adjuvant therapy. The study concluded that 3 months of adjuvant therapy was noninferior to 6 months of oxaliplatin-based chemotherapy for stage III colon cancer in terms of disease-free survival and neurotoxicity, especially in the low-risk and CAPOX (capecitabine and oxaliplatin) prescription groups. However, no studies have investigated the optimal duration of chemotherapy for pT1 node-positive colorectal cancer.

This study investigated the optimum duration of FOLFOX chemotherapy cycles for pT1N+ colorectal cancer. Specifically, we explored the pivotal question of whether a chemotherapy regimen lasting 6-8 cycles or an extended course of 10-12 cycles can significantly influence patient outcomes and disease progression. By clarifying this critical aspect, we hope to furnish clinicians with a robust reference point that would facilitate informed treatment decisions for this distinct subgroup of patients with colorectal cancer.

Methods and Materials

We conducted a retrospective cohort study of all patients with pT1 colorectal cancer registered in the medical database of Taipei Veterans Hospital and Chi Mei Medical Center from January 2010 to December 2020. The inclusion criteria were patients with pathologically proven adenocarcinoma and T1-positive lymph nodes indicating T1 node-positive colorectal cancer. The exclusion criteria were those who underwent preoperative irradiation; received a diagnosis of synchronous colorectal cancers; exhibited a histological type other than adenocarcinoma; and received capecitabine (Xeloda) for treatment instead of an intravenous 5-FU-based regimen. All surgical resections were performed with curative intent. Tumor invasion and lymph node status were defined according to the (5) American Joint Committee 8th edition on Cancer classification system. (6) According to a previous study conducted at our hospital,[11] which reported that a minimum of 8 cycles of FOLFOX is necessary for optimal overall survival and that 7 cycles are sufficient for improving disease-free survival in stage III colon cancers, we concluded that 8 cycles is a cutoff value. However, since no patients in our study received 9 cycles of chemotherapy, we divided our patients into two groups: those receiving 6-8 cycles and those receiving 10-12 cycles of FOLFOX. The primary outcome of interest was disease-free survival. The chemotherapy regimen evaluated was mFOLFOX6. The treatment dose would be reduced or omitted accordingly, depending on the emergence of neurotoxicity during the clinical course. Postoperative routine follow-up was performed at the outpatient department. Tumor markers, such as CEA and CA-199, were evaluated every 3-6 months, whereas colonoscopy was performed every 3-5 years starting from 1 year postoperatively. Computed tomography (CT), including chest and liver assessment, was performed every 6-12 months within the first 3 years postoperatively. Further imaging assessments, such as MRI, was considered if are suspicious liver lesions were noted, or local recurrence were detected on CT.

Statistical analysis

Descriptive statistics were employed to characterize patient demographics and clinical characteristics. Continuous variables were compared using the Mann-Whitney *U*-test or Kruskal-Wallis test. Categorical variables were compared using the chi-square test. Disease-free survival and overall survival were assessed using Kaplan-Meier survival analysis. The risk factors were determined using the Cox proportional hazards model and multivariate logistic regression analysis. Statistical significance was established using appropriate tests, with p-values < 0.05 indicating statistical significance. All analyses were performed using the Medcalc statistical software package and SPSS version 25.

Results

In total, 574 cases of pathological stage T1 colorectal cancer surgically treated at Taipei Veterans General Hospital were retrieved from the database. Two cases were excluded for inadequate data or lack of follow-up; 9 for undergoing regimens other than FOLFOX; 6 for not undergoing any chemotherapy, and 1 for synchronous tumors. Consequently, a final total of 57 pT1 node-positive cases were analyzed (Fig. 1). Table 1 presents the patient demographic data. (1) Of the 57 patients, only one had N2a lymph node status and was therefore included in the > N1a group. The number of patients with > N1a status was comparable between the two groups. (4) Patients with N1c status were excluded from this study. (2) During

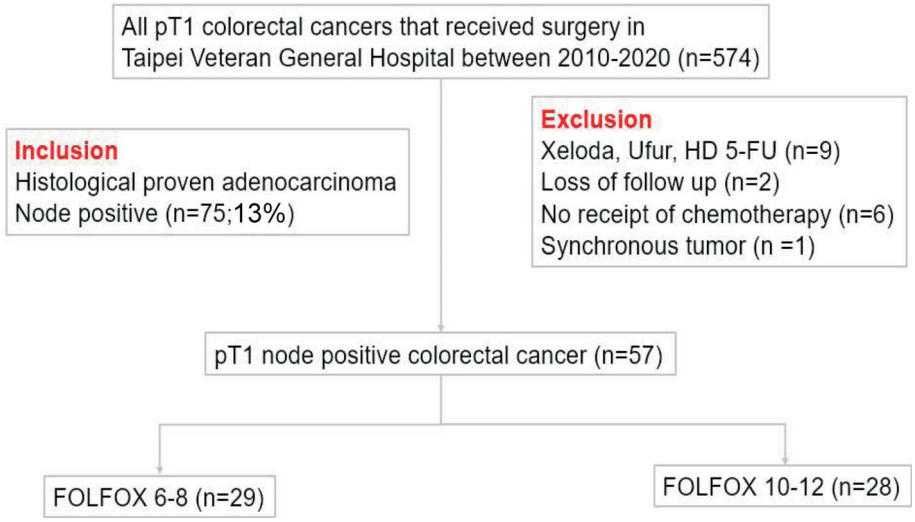

Fig. 1. Flowchart of patient selection. ** No. 9 courses of chemotherapy administered.

Table 1. Patient characteristics

	FOLFOX (6-8) (N = 29)	FOLFOX (10-12) (N = 28)	*p* value
Gender			0.087
Male	9 (31%)	15 (54%)	
Female	20 (69%)	13 (46%)	
Age (SD)	65.24 (12.4)	68.04 (11.7)	0.386
ASA			0.886
I	5 (17%)	6 (21%)	
II	20 (69%)	19 (68%)	
III	4 (14%)	3 (11%)	
Location			0.079
Colon	19 (66%)	24 (86%)	
Rectum	10 (34%)	4 (14%)	
Lymph node status			0.554
N1a	18 (62%)	18 (64%)	
> N1a	11 (38%)	10 (36%)	
LVI			0.840
Yes	9 (31%)	8 (29%)	
No	20 (69%)	20 (71%)	
PNI			0.309
Yes	0 (0%)	1 (3%)	
No	29 (100%)	27 (97%)	
Pre-op CEA, ng/dl (SD)	2.23 (1.34)	2.62 (1.55)	0.324

the 5-year follow-up period, each group had two patients who died. Additionally, three patients experienced recurrence after 6-8 cycles of chemotherapy, while six patients experienced recurrence after 10-12 cycles. In the 6-8 cycle group, two patients developed lung metastasis and one had a local recurrence. In the 10-12 cycle group, there were four cases of lung metastasis, one case of liver metastasis, and one case with both liver and lung metastasis. (3) Furthermore, two patients in the 6-8 cycle group suffered from anastomosis leakage within three months post-operation, which was managed with immediate diversion colostomy. The 5-year disease-free survival was 87% for 10-12 cycles and 84% for 6-8 cycles. No significant difference was observed in overall survival and disease-free survival between the two treatment durations (Fig. 2). (1) The similarity in overall survival and disease-free survival between the two groups may be attributed to both groups being classified as stage IIIA according to AJCC staging 8th edition. Cox regression model showed no specific risk factors of disease-free survival in both univariate and multivariate analysis except the American Society of Anesthesiologists physical status score (ASA) (Table 2).

Discussion

Colorectal cancer is a significant public health concern threatening the nation. Patients with pT1

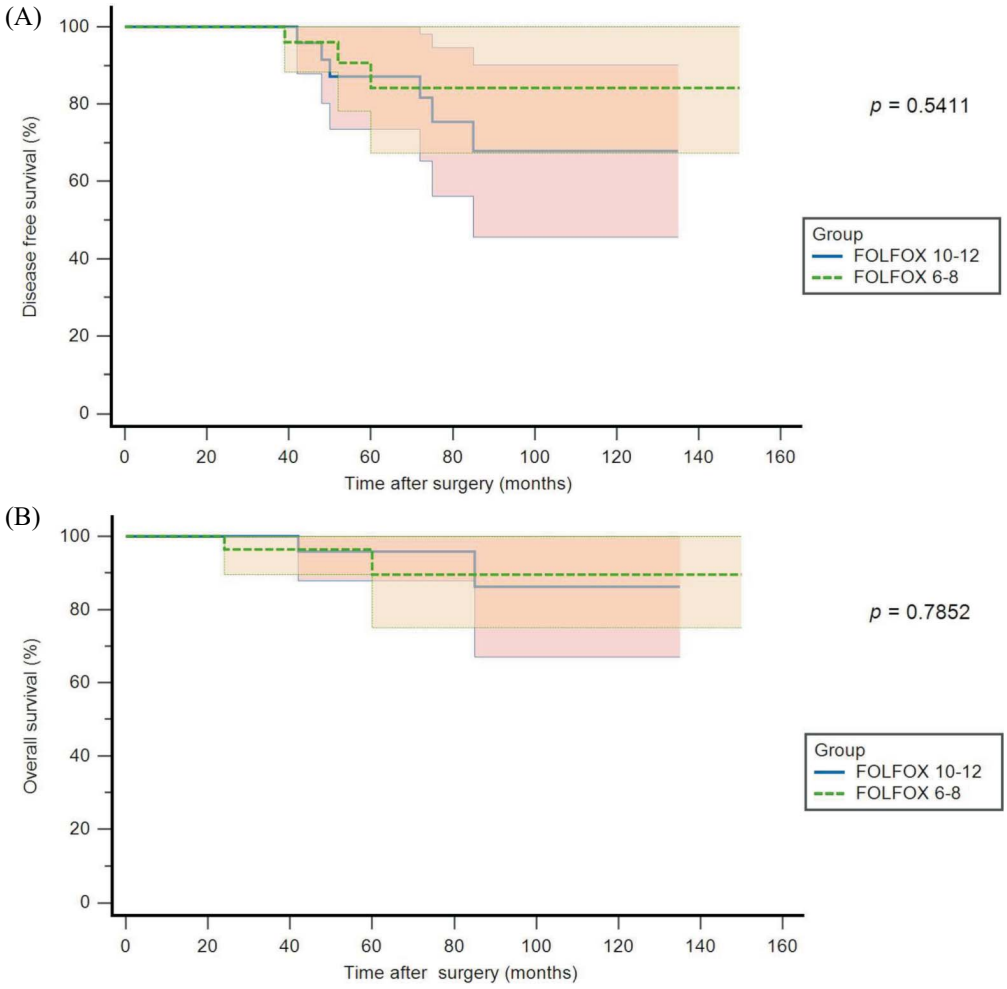

Fig. 2. (A) Disease free survival between FOLFOX 6-8 group and FOLFOX 10-12 group. (B) Overall survival between FOLFOX 6-8 group and FOLFOX 10-12 group.

Table 2. Univariate and multivariate Cox regression models of disease-free survival

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (< 60/≥ 60)	0.620 (0.114-3.376)	0.580		
Gender (M/F)	2.052 (0.534-7.893)	0.296	2.017 (0.530-7.674)	0.303
ASA (I-II/III)	0.129 (0.029-0.563)	0.006	0.113 (0.021-0.596)	0.010
LVI	2.249 (0.517-9.789)	0.280		
N stage (N1a/> N1a)	3.005 (0.764-11.81)	0.115	0.233 (0.029-1.893)	0.173
Colon/rectum	0.543 (0.114-2.591)	0.444	0.611 (0.146-2.556)	0.500
Pre-op CEA (< 3/≥ 3)	0.576 (0.122-2.721)	0.486		
FOLFOX (6-8/10-12)	0.661 (0.175-2.494)	0.541		

node-positive colorectal cancers represent a unique subset within stage III colorectal cancer. Lymph node involvement, even at the early T1 stage, indicates a higher risk of disease progression. The proportion of lymph node metastasis in T1 disease is approximately 10%-15%.[6]

FOLFOX is considered the standard therapy for stage III colorectal cancers after radical surgery. Novel treatment strategies for pT1-node-positive colorectal cancers have not yet been explored. Few studies have provided collective evidence about the most effective chemotherapy regimens for this subpopulation. Yan et al.[7] found that a 5-FU-based chemotherapy regimen significantly improved cancer-specific survival and overall survival among patients with T1N+ colon cancer, confirming the role of adjuvant chemotherapy in T1N+ disease. Asvin et al.[8] reported that adjuvant chemotherapy prolongs long-term survival in patients undergoing chemotherapy, although no specific chemotherapy regimen was proposed.

Several studies have investigated the effects of the duration of adjuvant therapy on oncological outcomes in stage II and III colorectal cancers. Tsai et al.[9] suggested that a minimum of 8 cycles of FOLFOX is necessary for optimal overall survival, whereas 7 cycles was reportedly sufficient for improving disease-free survival for stage III colon cancers. In contrast, Kumar et al.[10] found no significant difference in oncological outcomes between > 10 cycles and < 10 cycles of FOLFOX adjuvant therapy among patients with stage III colon cancers. A randomized phase III ACHIEVE-2 trial involving 514 participants with stage II colon cancers with high-risk features revealed that a shorter duration of FOLFOX adjuvant chemotherapy (3-month arm vs. 6-month arm) did not adversely affect the 3-year disease-free survival rate.[11] A recent meta-analysis proposed that a tailored treatment strategy could be implemented for specific cancer populations that could benefit from a shorter treatment duration and fewer adverse effects.[14] The present study found that a shorter duration of chemotherapy is beneficial in patients with pT1 node-positive colorectal cancers. Grothey et al. found that a 3-month FOLFOX regimen was not superior to a 6 months one in terms of disease-free survival. Furthermore, we found no significant difference in disease-free survival between the two treatment durations.[12]

No significant covariates were found between the shorter- and longer-interval treatment groups except for the American Society of Anesthesiologists physical status score. Patients with low comorbidity status seemed more able to complete longer cycles of chemotherapy due to a better physical condition. Recurrence was higher with 10-12 cycles of treatment, with distant metastasis occurring more frequently in the lungs than in the liver. One local recurrence was observed in a patient with rectal cancer.

Our study has some limitations. First, given the small sample size in the present study, the impact of the length of chemotherapy on survival outcomes must be interpreted cautiously. Second, colon and rectal cancers were evaluated equally in the study. However, these two cancer types are distinct disease entities with varied biological characteristics. Studies have consistently demonstrated that rectal cancer is more prone to lymph node metastasis.[13,14] Thus, not distin-

guishing between the two may limit the generalizability of our results. Finally, patients who received XELOX were excluded, which may have potentially introduced bias, considering this population represent a basic distribution of treatment modalities in treatment protocols for colon cancer. Future investigations need to address these limitations, investigate larger, more diverse cohorts, and consider the nuanced differences between rectal and colon cancers to provide a more comprehensive understanding of the relationship between chemotherapy duration and survival outcomes in pT1N+ colorectal cancer.

Conclusion

Shortening the duration of adjuvant chemotherapy from 10-12 cycles to 6-8 cycles may help reduce peripheral neuropathy induced by oxaliplatin in patients with pT1 node-positive colorectal cancer.

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原　著

化療次數對 pT1N+ 大腸直腸癌病人治療預後的影響

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目的　pT1 結直腸癌存在一定的淋巴結轉移風險。對於 pT1N+ 結腸癌患者，輔助化療的最佳持續時間仍然是一個有爭議的話題。本研究旨在探討接受 6-8 個周期 FOLFOX 化療的 pT1N+ 結直腸癌患者與接受 10-12 個周期化療的患者之間是否存在生存差異。

方法　我們進行了一項回顧性研究，納入了 2010 年至 2020 年間接受輔助 FOLFOX 化療的 pT1N+ 結直腸癌患者。使用 Kaplan-Meier 生存曲線和 Cox 比例風險模型分析生存結果。

結果　共有 57 名患者符合納入標準，其中 29 名接受了 6-8 個周期的 FOLFOX 化療，28 名接受了 10-12 個周期的化療。五年無病生存率相當。我們的分析顯示，兩組之間的總體生存率 (OS) 和無病生存率 (DFS) 沒有統計學上的顯著差異。次分析顯示無病生存率沒有顯著差異。

結論　在 pT1N+ 結腸癌患者中，接受 6-8 個周期 FOLFOX 化療與接受 10-12 個周期化療的患者在生存結果上沒有顯著差異。這些發現表明，較短療程的輔助 FOLFOX 化療在這種患者群體中可能與較長療程同樣有效。進一步的前瞻性研究是必要的，以驗證這些結果並完善治療建議。

關鍵詞　pT1 大腸直腸癌、淋巴結轉移、化療週期。