Original Article

Impact of Delayed Cycles of Adjuvant FOLFOX Chemotherapy in Patients with Stage III Colon Cancer: A Single-center, Retrospective Study

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Key Words
Stage III colon cancer;
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Adjuvant chemotherapy;
Treatment delays;
Cancer substaging

Purpose. To investigate whether prolonging the duration of adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy beyond 24 weeks influences survival outcomes in patients with stage III colon cancer.
Methods. This retrospective study analyzed data from 102 patients with stage III colon cancer who underwent curative resection and completed 12 cycles of adjuvant FOLFOX chemotherapy at Kaohsiung Veterans General Hospital (Kaohsiung City, Taiwan) between 2006 and 2016. Patients were stratified into 4 groups according to treatment duration: 24-28 weeks (n = 29); 29-32 weeks (n = 22), 33-36 weeks (n = 32); and > 36 weeks (n = 19). Primary outcomes included overall survival (OS), disease-free survival (DFS), and recurrence. Secondary analysis examined outcome differences among the cancer substages (IIIa, IIIb, and IIIc).
Results. There were no statistical differences in five-year OS rates among the 4 duration groups (69.0%, 77.3%, 68.8%, and 78.9%, respectively) (p = 0.800), nor in five-year DFS rates (72.4%, 81.8%, 78.1%, and 68.4%, respectively) (p = 0.359). Subgroup analysis revealed significant prognostic stratification according to tumor substage, with DFS rates of 100%, 83.9 %, and 47.6% for patients with stage IIIa, IIIb, and IIIc disease, respectively (p < 0.001).
Conclusion. Prolongation of adjuvant FOLFOX chemotherapy beyond the standard 24-week timeframe did not significantly compromise survival outcomes in patients with stage III colon cancer who completed all 12 prescribed cycles. These findings suggest that moderate delays in chemotherapy were not associated with statistically significant differences in survival outcomes in this cohort; however, prospective studies are needed to confirm clinical acceptability. Provided the complete therapeutic regimen was completed, tumor substaging remains the strongest prognostic factor for survival.

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Colon cancer remains a significant global health issue and currently ranks as the second leading cause of cancer-related mortality in the United States, with an estimated 152,810 new cases and approximately

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53,010 deaths projected to occur in 2024.[1] Stage III colon cancer, defined by regional lymph node involvement, poses a significant clinical challenge due to its aggressive nature and high recurrence potential. Approximately 40%-50% of patients diagnosed with stage III disease experience recurrence even after curative-intent surgical resection, highlighting the critical importance of effective adjuvant therapy in improving patient outcomes.[2,3] The current National Comprehensive Cancer Network (NCCN) guidelines advocate adjuvant chemotherapy as a standard component of postoperative management for patients with stage III colon cancer to reduce the risk for recurrence and enhance survival.[4]

The standard adjuvant chemotherapy protocol recommended for patients with stage III colon cancer is the folinic acid, fluorouracil (FU), and oxaliplatin (i.e., "FOLFOX").[5-8] Adherence to the timely initiation of chemotherapy, specifically within 8 weeks post-surgery, has been strongly correlated with improved survival outcomes. Studies have consistently demonstrated inferior overall survival (OS) in patients who experienced delays beyond this critical period.[9] One study reported a three-year OS rate of 80.98% in patients initiating chemotherapy after 8 weeks, compared with 89.62% in those treated earlier ($p = 0.008$).[9] Additional research has further emphasized this risk, revealing that delays between 9 and 12 weeks post-surgery increased the hazard ratio (HR) for mortality (HR 1.222), with even greater delays correlating with progressively worse outcomes.[10] The causes of delayed chemotherapy initiation are multifactorial and involve patient-specific conditions (e.g., postoperative recovery, comorbidities, and adverse effects), treatment-related issues (e.g., hematological toxicity), and systemic challenges such as hospital resource limitations.[11]

Despite the established benefits of completing adjuvant FOLFOX chemotherapy, treatment cycles are frequently delayed for various patient, treatment, and logistical reasons.[11,12] The clinical impact of extending treatment beyond the standard 24 weeks due to such delays remains unclear, complicating decisions regarding the balance between treatment completion and potential adverse consequences.

The present study, therefore, investigated whether prolonging the total duration required to complete 12 cycles of FOLFOX therapy beyond 24 weeks influenced survival outcomes, regardless of the timing of chemotherapy initiation in patients with stage III colon cancer, hypothesizing that such delays could negatively affect OS and disease-free survival (DFS) differently across disease substages.

Methods

Study design and population

This retrospective study included patients diagnosed with stage III colon cancer who underwent surgical resection followed by adjuvant chemotherapy at the Kaohsiung Veterans General Hospital (Kaohsiung City, Taiwan) between January 2006 and December 2016. Patients with rectal or appendiceal cancer and those who did not complete 12 full cycles of FOLFOX chemotherapy were excluded. The final cohort comprised 102 patients who completed the full FOLFOX regimen. It is important to note that the interval between surgery and chemotherapy initiation was not analyzed in this study; our focus was on the total treatment duration for completing all 12 cycles. The treatment duration groups (24-28, 29-32, 33-36, and > 36 weeks) were chosen based on common clinical practice patterns observed in our institution, where treatment delays of 2-4 weeks per cycle were frequently encountered. These intervals were selected to reflect real-world delays while allowing for group comparability in size.

Data collection

Patient demographic information, including age and sex, clinical and pathological staging (IIIa, IIIb, and IIIc), dates of surgery and chemotherapy cycles, and follow-up outcomes (recurrence and survival status), was collected from hospital medical records and electronic health databases. Treatment duration was categorized into 4 groups based on the time required to complete 12 chemotherapy cycles:24-28, 29-32, 33-36, and > 36 weeks.

Outcome measures

The primary outcomes of interest included OS, DFS, and five-year survival rates analyzed across the 4 defined chemotherapy duration groups. Secondary outcomes included differences in DFS among cancer substages (i.e., IIIa, IIIb, and IIIc). Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause or last follow-up. Disease-free survival (DFS) was defined as the time from the date of surgery to the first documented recurrence of colon cancer, death from any cause, or last follow-up, whichever occurred first. Patients without an event at the time of analysis were censored at the date of last follow-up.

Statistical analysis

Survival estimates were calculated using the Kaplan-Meier method and compared across groups using log-rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware tests. Recurrence rates between the duration groups were compared using Pearson's chi-squared and likelihood ratio tests. Differences with $p < 0.05$ were considered to be statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the patients

A total of 726 patients were diagnosed with pathological stage III colon cancer at the Kaohsiung Veterans General Hospital between 2006 and 2016 (Fig. 1). After excluding 140 patients who did not undergo adjuvant chemotherapy and 482 who underwent chemotherapy regimens other than FOLFOX, had rectal or appendix cancers, incomplete chemotherapy cycles, or missing data, a final cohort of 102 eligible patients was identified for analysis. The mean (± SD) age of the study population was 57.32 ± 11.49 years, with a slight female predominance (57.8% female, 42.2% male) (Table 1). Patients were stratified into 4 groups based on the duration required to complete 12 cycles

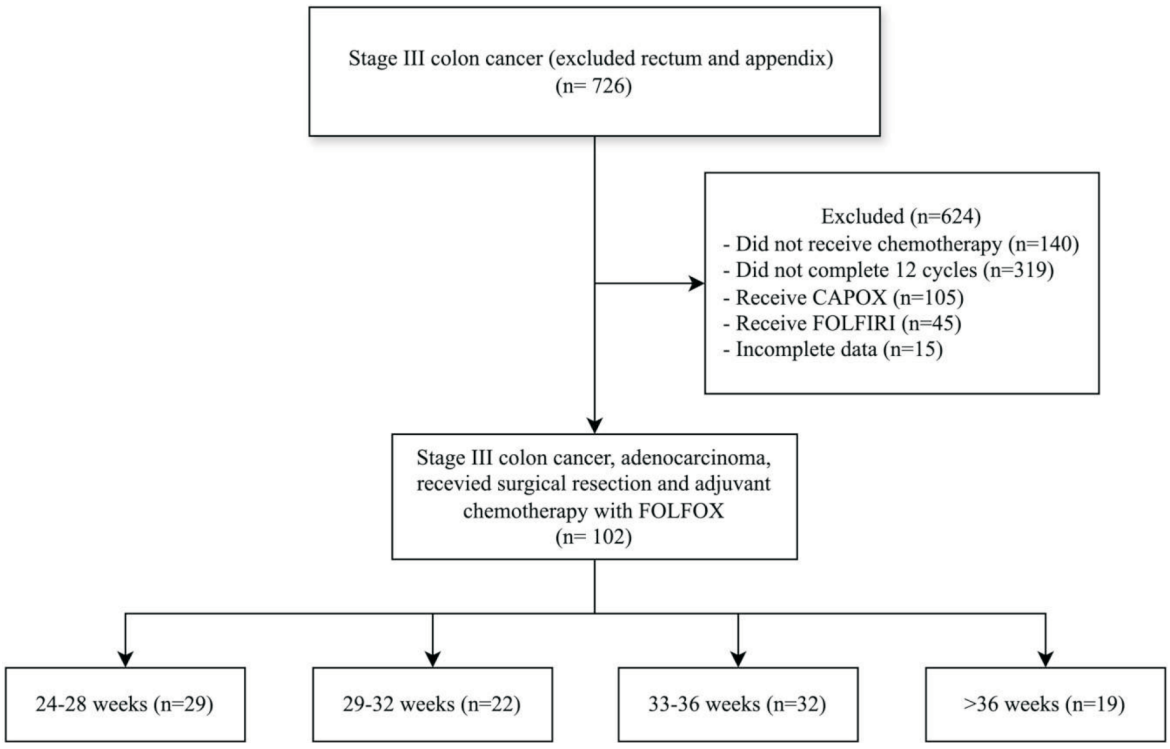

Fig. 1. Flow-diagram illustrating the patient selection process.

Table 1. Baseline characteristics of all patients

Variables	Total (N = 102)	24-28 weeks (N = 29)	28-32 weeks (N = 22)	32-36 weeks (N = 32)	> 36 weeks (N = 19)	*p*-value
Age (years), mean (SD)	57.32 (11.49)	57.10 (11.67)	56.73 (11.18)	56.25 (12.71)	60.16 (9.67)	0.687
Gender, *n* (%)						0.855
Men	43 (42.2%)	14 (48.3%)	8 (36.4%)	13 (40.6%)	8 (42.1%)	
Women	59 (57.8%)	15 (51.7%)	14 (63.6%)	19 (59.4%)	11 (57.9%)	
Substage						0.468
IIIa	12 (11.8%)	3 (10.3%)	2 (9.1%)	3 (9.4%)	4 (21.1%)	
IIIb	62 (60.8%)	16 (55.2%)	15 (68.2%)	18 (56.2%)	13 (68.4%)	
IIIc	28 (27.4%)	10 (34.5%)	5 (22.7%)	11 (34.4%)	2 (10.5%)	
Tumor location						0.939
Left	67 (65.7%)	18 (62.1%)	14 (63.6%)	22 (68.8%)	13 (68.4%)	
Right	35 (34.3%)	11 (37.9%)	8 (36.4%)	10 (31.3%)	6 (31.6%)	
T stage						0.647
T1	4 (3.9%)	1 (3.5%)	1 (4.5%)	1 (3.1%)	1 (5.2%)	
T2	8 (7.9%)	2 (6.9%)	1 (4.5%)	1 (3.1%)	4 (21.1%)	
T3	76 (74.5%)	23 (79.3%)	17 (77.3%)	25 (78.1%)	11 (57.9%)	
T4	14 (13.7%)	3 (10.3%)	3 (13.7%)	5 (15.7%)	3 (15.8%)	
N stage						0.156
N1	59 (57.8%)	13 (44.8%)	15 (68.2%)	17 (53.1%)	14 (73.7%)	
N2	43 (42.2%)	16 (55.2%)	7 (31.8%)	15 (46.9%)	5 (26.3%)	
LN examined (median)	20	20	18	20	16	
LN positive (median)	4	4	2	3	2	

of FOLFOX therapy: 24-28 weeks (n = 29 [28.4%]); 29-32 weeks (n = 22 [21.6%]); 33-36 weeks (n = 32 [31.4%]); and > 36 weeks (n = 19 [18.6%]). In terms of tumor substage distribution, 12 patients (11.8%) were classified as stage IIIa, 62 (60.8%) as stage IIIb, and 28 (27.4%) as stage IIIc.

Survival analysis

Survival analysis was performed to evaluate OS among the four chemotherapy duration groups using the Kaplan-Meier method (Fig. 2). Over a median follow-up of 60 months, the five-year OS rates among the groups were distributed as follows: 72.4% (24-28 weeks); 81.8% (28-32 weeks); 78.1% (32-36 weeks); and 78.9% (> 36 weeks). 25 death events (24.5%) were recorded among the entire cohort of 102 patients. The estimated mean OS across all groups was 52.57 months (95% confidence interval [CI] 49.86-55.27 months). No statistically significant differences in survival were detected among the groups according to log-rank (Mantel-Cox, $p = 0.810$), Breslow (Generalized Wilcoxon, $p = 0.805$), or Tarone-Ware ($p = 0.810$) tests. The

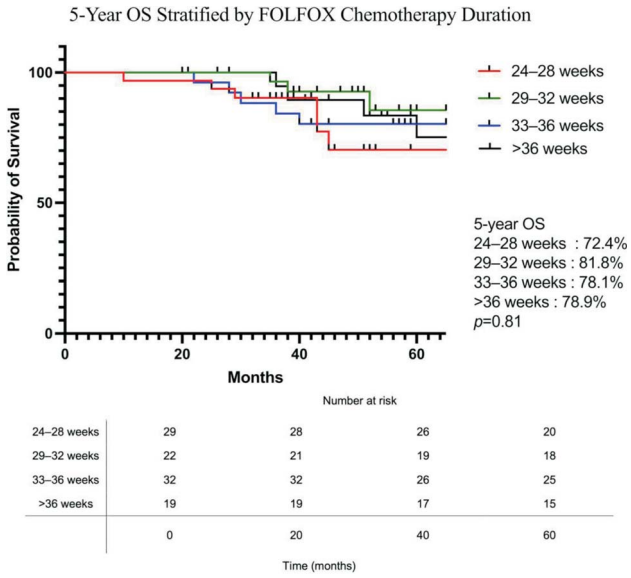

Fig. 2. Five-year overall survival (OS) stratified according to duration of FOLFOX (i.e., folinic acid, fluorouracil, and oxaliplatin) chemotherapy in patients with stage III colon cancer.

Kaplan-Meier survival curves exhibited similar survival distributions among all chemotherapy duration groups.

Recurrence analysis

Kaplan-Meier analysis was also used to assess DFS, focusing on recurrence events among the 4 chemotherapy duration groups (Fig. 3). Recurrence was documented in 28 (27.5%) patients within the total cohort during the follow-up period. The corresponding five-year DFS rates were 69.0% in the 24-28 weeks' group, 77.3% in the 29-32 weeks' group, 68.8% in the 33-36 weeks' group, and 68.4% in the group with chemotherapy duration > 36 weeks. No statistically significant differences in recurrence rates or DFS among the 4 duration groups were observed when analyzed using the log-rank (Mantel-Cox, $p = 0.362$), Breslow (Generalized Wilcoxon, $p = 0.479$), or Tarone-Ware ($p = 0.432$) tests. The Kaplan-Meier recurrence curves exhibited overlapping trends, indicating that prolonged chemotherapy beyond the recommended 24 weeks did not significantly affect DFS outcomes.

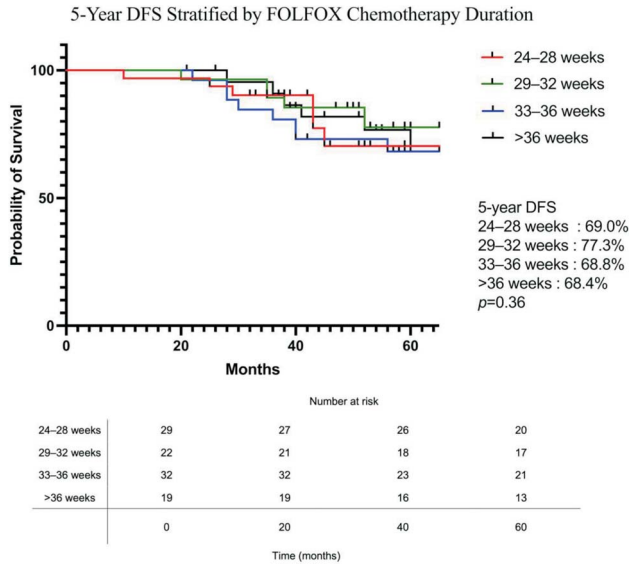

Fig. 3. Five-year disease-free survival (DFS) stratified according to duration of FOLFOX (i.e., folinic acid, fluorouracil, and oxaliplatin) chemotherapy in patients with stage III colon cancer.

Subgroup analysis according to disease stage

Subgroup survival analysis according to tumor substage demonstrated significant differences in both five-year OS and DFS among patients with stage IIIa, IIIb, and IIIc disease (Fig. 4). The five-year OS rates for stage IIIa, IIIb, and IIIc disease were 100%, 85.5%, and 46.7%, respectively, and for five-year DFS were 100%, 83.9%, and 32.1%. No mortality events were recorded among the 12 patients with stage IIIa disease during follow-up, while 9 deaths (14.5%) occurred among the 62 with stage IIIb and 15 deaths (53.3%) among the 28 stage IIIc disease. The Kaplan-Meier survival curves revealed significant differences across the 3 substages, as confirmed by the log-rank (Mantel-Cox, $p < 0.001$), Breslow (Generalized Wilcoxon

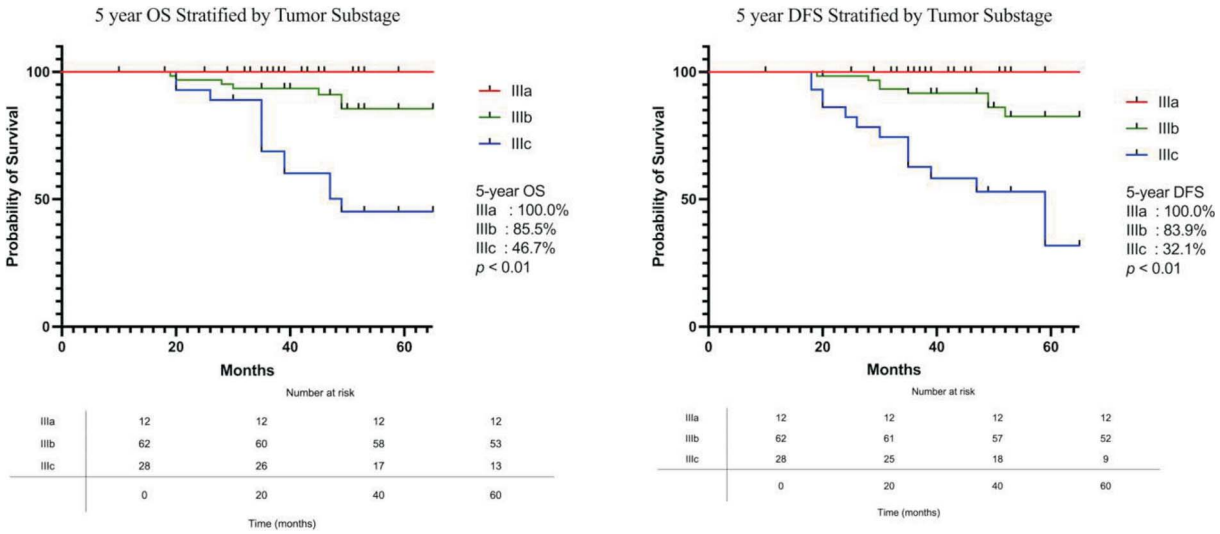

Fig. 4. Five-year overall survival (OS) and five-year disease-free survival (DFS) stratified according to tumor substage in patients with stage III colon cancer.

test, $p < 0.001$), and Tarone-Ware ($p < 0.001$) tests.

Further analysis of recurrence patterns revealed 10 recurrence events (16.1%) in patients with stage IIIb disease and 19 recurrences (57.9%) in patients with stage IIIc disease. Kaplan-Meier analysis of DFS revealed significantly inferior outcomes in stage IIIc than those in stage IIIb (log-rank, $p < 0.001$; Breslow, $p \leq 0.001$; Tarone-Ware, $p \leq 0.001$) (Fig. 4). These findings highlight the following: prognostic heterogeneity within stage III disease and emphasized the markedly poorer survival and higher recurrence risk associated with stage IIIc tumors.

Discussion

The present single-center retrospective study assessed the effect of prolonged adjuvant FOLFOX chemotherapy on the survival outcomes of patients with stage III colon cancer who completed all 12 cycles. Among 102 eligible patients, no statistically significant differences in five-year OS or DFS were observed across the 4 chemotherapy duration groups (i.e., 24-28, 29-32, 33-36, and > 36 weeks). The five-year OS rates were 72.4%, 81.8%, 78.1%, and 78.9%, respectively ($p = 0.810$). The five-year DFS rates were 69.0%, 77.3%, 68.8%, and 68.4%, respectively ($p = 0.362$). These findings suggest that delays in completing the full FOLFOX regimen beyond the conventional 24-week timeframe may not significantly compromise survival provided all 12 cycles are completed. This may offer reassurance in clinical scenarios in which temporary delays are unavoidable due to patient comorbidities, hematological toxicity, and/or institutional limitations.[13]

The established standard of care for adjuvant chemotherapy in stage III colon cancer is a six-month course of FOLFOX based on evidence from multiple pivotal trials.[14-16] The MOSAIC trial demonstrated that adding oxaliplatin to 5-FU/leucovorin improved the three-year DFS rate from 73% to 78% and increased the six-year OS rate by approximately 6% in patients with stage III disease.[5] Other studies, such as the NSABP C-07 trial, reinforced these findings, leading to the global adoption of 12 cycles (6 months) of FOLFOX as the standard regimen.[17] Earlier studies also concluded that extending fluoropyrimidine-based chemotherapy beyond 6 months conferred no additional benefit. For example, the GERCOR C96.1 trial revealed no significant difference in the efficacy between 6 and 9 months of 5-FU/leucovorin.[18]

Findings of our study align with this body of evidence by demonstrating that extending the duration of chemotherapy beyond 6 months due to delays between cycles did not adversely affect survival or recurrence outcomes as long as the full regimen was completed. These observations are clinically relevant because treatment interruptions are frequently unavoidable due to postoperative complications, hematological toxicities, or institutional factors.[19-22] Thus, although timely completion of adjuvant chemotherapy remains ideal, our data suggest that moderate prolongation may be tolerated without significant detriment.

Importantly, no large, randomized trial has evaluated extending FOLFOX beyond 6 months, largely due to concerns over cumulative toxicity, particularly oxaliplatin-induced peripheral neuropathy.[23] In the MOSAIC trial,[5] approximately 12% of patients developed grade 3 neurotoxicity by the end of treatment, and persistent grade 1-2 symptoms were reported in up to 50% of patients 1 to 2 years post-treatment. The IDEA collaboration,[24] comprising > 12,000 patients across 6 phase III trials, sought to evaluate whether shortening therapy (to 3 months) could maintain efficacy while reducing toxicity. While the pooled results narrowly missed demonstrating non-inferiority overall, subgroup analyses supported three-month CAPOX (i.e., capecitabine and oxaliplatin) as a reasonable option for low-risk patients (T1-3, N1), whereas high-risk patients (T4 and/or N2) benefited from the full 6 months of FOLFOX.

Conversely, extending the therapy beyond 6 months has not demonstrated a clear benefit. A Japanese study (JFMC37-0801)[25] comparing 6 versus 12 months of capecitabine without oxaliplatin noted only a modest improvement in OS (five-year, 87.6% vs. 83.2%, $p = 0.0124$) without a significant DFS gain, and the regimen excluded oxaliplatin-related neurotoxicity. As such, the current NCCN, European Society for Medical Oncology ("ESMO"), and American Society of Clinical Oncology ("ASCO") guidelines recommend

6 months of adjuvant FOLFOX for high-risk patients with stage III disease and explicitly discourage routine extension beyond this timeframe due to the lack of evidence supporting survival benefits and the increased risk for toxicity.[8,26,27]

Subgroup survival analysis demonstrated significant prognostic stratification among the colon cancer substages. Stage IIIa patients exhibited 100% DFS during follow-up, whereas progressively diminishing rates were observed in patients with stage IIIb (83.9%) and stage IIIc (47.6%) disease ($p < 0.001$). This prognostic gradient is consistent with the established literature and highlights the heterogeneity of stage III disease.

The observed stratification aligned with the AJCC Sixth Edition data, which reported five-year survival rates of 83.4%, 64.1%, and 44.3% for patients with stage IIIa, IIIb, and IIIc disease, respectively.[28] Similarly, a Japanese multicenter study (n = 5919) reported five-year cancer-specific survival rates of 96.5%, 88.5%, and 66.6%, respectively.[29]

Substantial outcome differences across substages have important clinical implications. First, they invalidated the non-stratified risk assessments for patients with stage III disease. Second, they support tailored approaches to adjuvant therapy duration, as demonstrated in the IDEA trial, which suggested that lower-risk patients (T1-3N1) may achieve comparable outcomes with shorter treatment courses.[30] Finally, these results underscore the necessity for molecular and genetic characterization of each substage to refine risk assessment and treatmen tselection. Future research should identify biological signatures explaining the outcome disparities between substages and potentially reveal novel therapeutic targets for high-risk stage IIIc disease, in which recurrence rates remain elevated despite standard adjuvant therapy.

Strengths and limitations

The present study had several methodological strengths. First, complete follow-up data over a median of 60 months enabled a robust analysis of long-term outcomes in patients with stage III colon cancer. Second, our homogeneous cohort, comprising only patients who completed all 12 FOLFOX cycles, facilitated a focused assessment of timing effects rather than dose effects. Additionally, comprehensive subgroup analysis according to tumor substage (i.e., IIIa, IIIb, and IIIc) provides clinically relevant prognostic information that aligns with the previous literature. Finally, our real-world clinical setting reflects the practical challenges of adjuvant chemotherapy administration, thus enhancing the applicability of our findings to daily oncology practice. There were, however, several limitations that warrant consideration when interpreting these results. The single-center retrospective design potentially introduced selection bias, thus limiting generalizability to other populations or healthcare settings. Our relatively small sample size (102 patients) reduced the statistical power to detect subtle differences between the chemotherapy duration groups. Furthermore, stratifying the small cohort into four duration-based subgroups reduced statistical power and may have increased the risk of Type II error, potentially obscuring small but clinically relevant differences between groups. Including only patients who completed all 12 cycles may have introduced selection bias by excluding those with treatment-limiting toxicity, comorbidities, or early recurrence. This likely resulted in a healthier cohort with better treatment tolerance, potentially inflating survival outcomes and limiting generalizability to the broader stage III colon cancer population. Additionally, we did not assess the time interval between surgery and the initiation of chemotherapy, which has been shown in prior studies to impact survival outcomes. Our analysis focused solely on treatment duration and completion time. Furthermore, we did not analyze the reasons for treatment delays or comprehensively assess treatment-related toxicities, particularly cumulative neurotoxicity, which remains a significant concern with prolonged oxaliplatin exposure. The retrospective design limited our ability to determine the causes of chemotherapy delays, as documentation of factors like neutropenia, neuropathy, or logistical issues was often incomplete. This precluded analysis of how these factors may have influenced survival outcomes. Additionally, the distribution of tumor substages (IIIa, IIIb, IIIc) was uneven among the chemotherapy duration groups, with nota-

bly fewer stage IIIc patients in the > 36-week group. While this difference was not statistically significant ($p = 0.468$), the clinical relevance remains given the small sample size and the strong impact of substage on survival outcomes. This imbalance may have confounded the comparison of OS and DFS across groups.

Conclusion

This single-center retrospective study demonstrated that prolongation of adjuvant FOLFOX chemotherapy beyond the standard 24-week timeframe did not significantly impact OS or DFS in patients with stage III colon cancer who completed all 12 prescribed cycles, with comparable five-year mortality and disease recurrence rates across all duration groups ($p = 0.800$ and $p = 0.359$, respectively). Our subgroup analysis confirmed significant prognostic stratification among tumor substages, with stage IIIa patients exhibiting 100% DFS compared with progressively worse outcomes in patients with stage IIIb (83.9%) and stage IIIc (47.6%) disease ($p < 0.001$), indicating that, within the limitations of this retrospective study, moderate delays in chemotherapy administration were not associated with significant differences in survival outcomes. However, due to potential confounding and limited statistical power, these findings should be interpreted with caution, and prospective studies are needed to determine whether such delays are clinically acceptable. Despite methodological limitations, including the single-center design and relatively small sample size, these results have meaningful clinical implications for optimizing adjuvant chemotherapy administration in real-world settings. However, future multi-institutional prospective studies with larger cohorts and detailed toxicity assessments are warranted to validate these findings and potentially identify biological signatures explaining outcome disparities between substages.

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第三期大腸癌病患 FOLFOX 輔助化療延遲之影響：單一中心回溯性研究

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目的　探討 FOLFOX 輔助化療時間延長是否影響第三期大腸癌病患的生存結果。

方法　回顧分析 2006 至 2016 年間 102 位接受根除手術並完成 12 療程 FOLFOX 化療的第三期大腸癌病患，依治療完成時間分為四組 (24-28 週、29-32 週、33-36 週、> 36 週)。主要觀察指標為五年總生存率 (OS)、無病生存率 (DFS) 及復發率，並進行次期分組分析 (IIIa、IIIb、IIIc)。

結果　四組間五年總生存率與無病生存率無統計差異 (OS: 72.4%, 81.8%, 78.1%, 78.9%, $p = 0.810$; DFS: 69.0%, 77.3%, 68.8%, 68.4%, $p = 0.362$)。分期分析顯示預後與次期有關：IIIa 五年無病生存率為 100%，IIIb 為 83.9%，IIIc 僅 32.1% ($p < 0.001$)。

結論　若最終完成 12 療程，FOLFOX 治療延長超過 24 週並不顯著影響 OS 與 DFS，適度延遲在臨床上可接受。腫瘤分期仍為預後最重要因素。

關鍵詞　第三期結腸癌、FOLFOX 化療、輔助性化學治療、治療延遲、癌症分期次型分析。