Original Article

Comparison of the Clinical Outcomes between Direct Surgery and Neoadjuvant Therapy in Clinical Stage III cT4a Colorectal Cancer Patients: A Retrospective Analysis at a Single Center

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Key Words
Colorectal cancer (CRC);
Disease-free survival (DFS);
Overall survival (OS);
Neoadjuvant therapy;
cT4a stage

Purpose. The aim of the study is to compare the clinical outcome between direct-to-surgery (DTS) and neoadjuvant therapy (NCT) in patients of clinical stage III colorectal cancer (CRC) with cT4a stage.
Methods. From February 2016 to December 2020, 72 patients with cT4 stage of clinical stage III colon cancer were screened, and among these, 46 patients met the criteria and were enrolled into the study. Finally, 42 patients with cT4a of clinical stage III CRC including 20 patients with direct surgery and 22 patients with neoadjuvant therapy were analyzed and their clinicopathologic characteristics were collected. We retrospectively analyzed the recurrence rate, disease-free survival rates (DFS), overall survival rates (OS) and other clinical outcomes.
Results. The median follow-up of our study was 53 months. We demonstrated that it was not significant differences between direct surgery and neoadjuvant therapy in patients with cT4a of stage III CRC in early relapse (p = 0.349), recurrence (p = 0.588), DFS (p = 0.585) and OS (p = 0.649). It is noteworthy that early relapse (11.5% vs. 25%) and recurrence rates (23.1% vs. 35%) were numerically lower in the neoadjuvant therapy group but were not statistically significant. However, the NCT group showed a significantly lower rate of perineural invasion (p = 0.035).
Conclusions. Whether DTS or NCT for patients with cT4a of clinical stage III CRC had better outcome still remains unclear. Our findings suggest potential trends favoring neoadjuvant chemotherapy in selected patients, but no definitive survival advantage was demonstrated. Although no definitive survival advantage was demonstrated, the association with reduced perineural invasion and recurrence suggests potential clinical benefit. Further prospective studies are warranted to clarify its role in this specific patient population.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2026;37:125-133*]

Received: May 14, 2025. Accepted: July 10, 2025.
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Colon cancer remains one of the most prevalent malignancies worldwide as a leading cause of cancer-related mortality.[1] The prognosis of colorectal cancer is closely related to tumor stage at diagnosis, with T4 tumors, characterized by invasion through the visceral peritoneum or into adjacent organs, posing significant challenges in surgical management and long-term outcomes.[2,3] According to the American Joint Committee on Cancer (AJCC) 8th edition, T4 disease is subclassified into T4a (penetration of the visceral peritoneum) and T4b (direct invasion of adjacent structures), each with distinct prognostic implications.[4]

Standard treatment for locally advanced colon cancer typically involves curative resection followed by adjuvant chemotherapy.[5] However, patients with T4 tumors are at higher risk for margin-positive resections, peritoneal dissemination and distant recurrence.[6] In recent years, neoadjuvant chemotherapy (NCT) has emerged as a potential strategy to improve resectability and long-term oncologic outcomes. The FOxTROT trial demonstrated that preoperative chemotherapy is feasible and could lead to significant tumor downstaging and reduced circumferential margin involvement in high-risk colon cancers with benefits such as tumor downstaging, reduced margin involvement and potentially improved survival.[1] Moreover, retrospective analyses, including those using large national datasets, have suggested a survival advantage of NCT, particularly in T4b colon cancers with multi-visceral involvement.[2,6]

Despite these findings, the role of NCT in T4a colon cancer remains unclear, as most studies have focused on either broader T3-T4 groups or specifically on T4b tumors.[3,6] Limited data are available regarding the efficacy of NCT in stage III T4a patients who could well benefit from earlier systemic treatment but lack robust evidence to guide clinical decision-making.

This study aims to evaluate and compare the clinical outcomes of patients with clinical stage III T4a colon cancer who received neoadjuvant chemotherapy versus those who underwent direct surgery followed by adjuvant therapy. In order to elucidate this clinical question, we analyzed survival outcomes, recurrence patterns, and pathological characteristics to clarify the potential benefits of preoperative treatment in this specific and under-investigated subgroup.

Materials and Methods

Patients and study design

This retrospective cohort study included patients diagnosed with clinical stage III T4a colon adenocarcinoma between February 2016 to December 2020, using data derived from Kaohsiung Medical University Chung-Ho Memorial Hospital. Inclusion criteria were age ≥ 18 years and confirmed diagnosis of T4a colon cancer based on preoperative clinical radiological staging. Clinical T4a staging was defined by preoperative contrast-enhanced computed tomography as tumor invasion through the visceral peritoneum without direct extension into adjacent organs (T4b). Patients were categorized into two groups according to treatment strategy: those who received neoadjuvant chemotherapy (NCT) followed by curative-intent surgery, and those who underwent upfront surgery without preoperative treatment (direct-to-surgery, DTS). Patients with metastatic disease, T4b tumors or those who received neoadjuvant chemotherapy but did not receive surgery due to morbidity or mortality were excluded.

Patients in the NCT group received oxaliplatin-based chemotherapy regimens such as modified FOLFOX (mFOLFOX), typically administered over a 6- to 8-week period prior to surgery. Postoperative adjuvant chemotherapy was given at the discretion of the multidisciplinary colorectal cancer team and applied to both groups according to national treatment guidelines. For the DTS group, patients proceeded directly to surgery followed by adjuvant chemotherapy. Treatment allocation was non-randomized and determined by multidisciplinary tumor board consensus or treating physician judgment.

Clinicopathologic investigation

The clinicopathological factors were determined according to the TNM classification of malignant tumors prescribed by the AJCC 8th edition. Variables

collected included sex, clinical lymph node stage (cN), primary lesion site, neoajuvant radiotherapy, pre- and post-treatment carcinoembryonic antigen (CEA) level, harvested lymph node, perineural invasion (PNI), lympho-vascular invasion (LVI) and microsatellite instability (MSI) status. Early relapse was defined as local recurrence or distant metastases occurrence within 12 months postoperatively.

Efficacy measurement

DFS was defined as the time from the date of enrollment until the first documentation of relapse, regardless of the patient's treatment status; OS was defined as the time from the date of enrollment until the date of death or the last date of follow-up.

Statistical analysis

The analyses included patients who completed surgical intervention and were not lost to follow-up. Continuous variables are presented as the mean ± standard deviation, and dichotomous variables as numbers and percentages. All statistical analyses were performed using SPSS v27.0.1 (SPSS, Chicago, IL, USA). The clinicopathological characteristics of the two groups were compared using Pearson's chi-square test while DFS and OS were evaluated using the Kaplan-Meier method, and the log-rank test was used to compare time-to-event distributions. Statistical significance was set to $p < 0.05$.

Results

Study population and disposition

Between February 2016 to December 2020, 72 patients with a diagnosis of clinical stage III with T4 colorectal cancer were screened. Twenty-six patients with clinical T4b were excluded. There were 46 patients to be divided into NCT group (numbers: 46) and DTS group (numbers: 20). In the NCT group, four patients died due to morbidity or other causes and did not proceed to surgery. Finally, the eligible 42 eligible patients (NCT: 22 patients; DTS: 20 patients) with clinical stage III T4a colon cancer were retrospectively enrolled and analyzed. The CONSORT diagram is shown in Fig. 1.

Efficacy outcomes

The database for the final analysis was locked on January, 2025. At the cut-off time for analysis, the median follow-up time was 53 months [interquartile range (IQR), 35~72 months]. Comparison of the baseline demographic and tumor characteristics between the two groups are listed in Table 1. No significant differences were observed in gender, clinical lymph node stage, tumor sidedness, pre-operation and post-operation CEA levels, tumor grade, lympho-vascular invasion (LVI), or microsatellite instability (MSI) status. However, perineural invasion (PNI) was significantly lower in the NCT group compared to the DTS group (9.1% vs. 40%, $p = 0.035$). For cN stage, among NCT group, cN1 and cN2 was 23% and 77%; among DTS group cN1 and cN2 was 40% and 60%. It was not statistically significant. For treatment efficacy (DFS and OS), it also did not reach statistically significant. Similarly, no significant correlation was found between preoperative and postoperative carcinoembryonic antigen (CEA) levels. Recurrence or overall survival in the two groups also did not reach statistically significant. In this study, cN stage and carcinoembryonic antigen (CEA) levels did not affect clinical outcome whether in NCT or DTS group.

Survival outcomes

Median follow-up duration was 53 months. Kaplan-Meier analysis revealed no statistically significant difference in disease-free survival (DFS) between groups ($p = 0.585$; Fig. 2A). Similarly, overall survival (OS) did not significantly differ between the two groups ($p = 0.649$; Fig. 2B).

Recurrence and early relapse

Early relapse within 12 months occurred in 3 patients (11.5%) in the NCT group and 5 patients (25%)

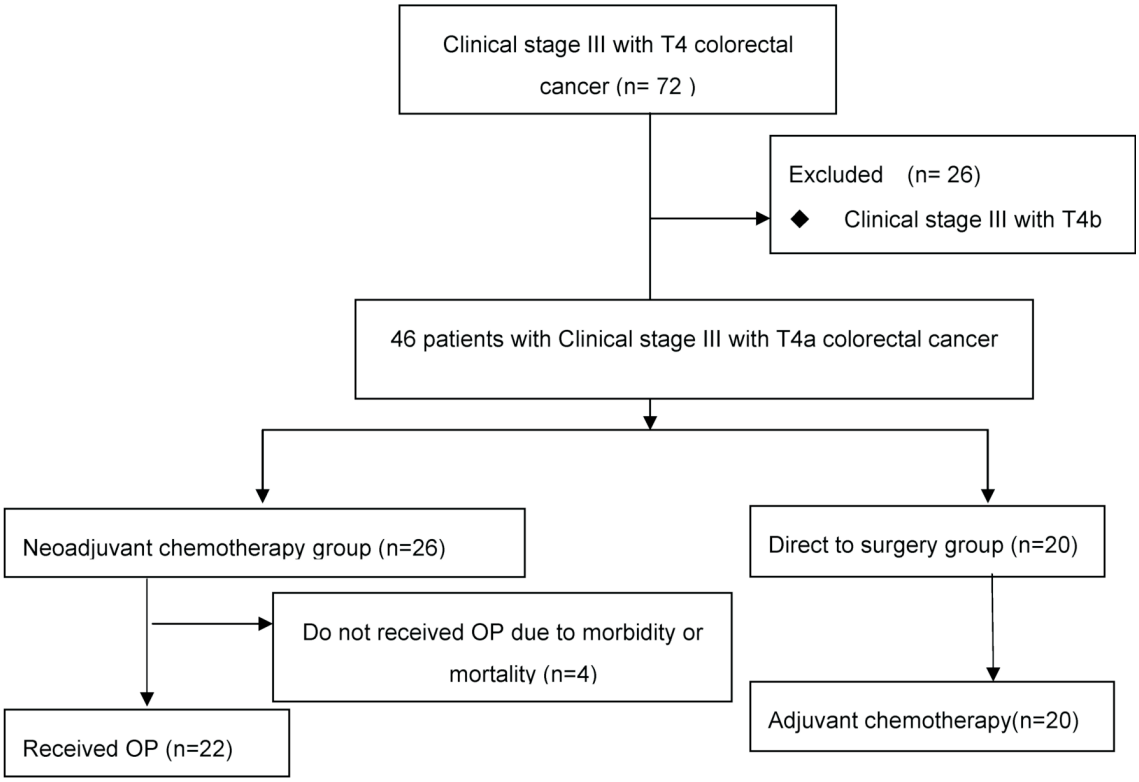

Fig. 1. CONSORT diagram of this study. The final enrolled patients for analysis were 42 patients. Collection was from February 2016 to December 2020, and database was locked for final analysis on January 2025. Median follow-up time was 53 months (IQR: 35~72 months).

in the DTS group ($p = 0.349$). Recurrence occurred in 6 patients (27.3%) in the NCT group and 7 patients (35%) in the DTS group ($p = 0.588$). Although no statistically difference, numerically lower recurrence and early relapse rates were observed in the NCT group (in Table 1).

Discussion

Our retrospective single-center analysis aimed to evaluate the impact of neoadjuvant chemotherapy on patients with clinical stage III T4a colon cancer. However, we did not observe a statistically significant survival benefit with NCT. Both disease-free survival (DFS) and overall survival (OS) were comparable between the NCT group and DTS group but the NCT group seemed to be better than the DTS group in 3-year DFS and 3-year OS (DFS: 81% vs. 62%; OS: 90% vs. 79% respectively). Despite that, we did observe a lower rate of early relapse and total recurrence in the NCT group, and notably, a significantly reduced incidence of perineural invasion (PNI). Since PNI is a known adverse prognostic factor in colon cancer, its reduction may suggest a potential biological benefit of preoperative treatment beyond survival outcomes. This aligns with our hypothesis that NCT may have an impact on micrometastatic disease or adverse histopathological features.[13-15]

The FOxTROT trial, the largest prospective randomized study on NCT in colon cancer to date, demonstrated significant tumor downstaging, improved R0 resection rates and favorable histological responses in patients with radiologically staged high-risk T3 or T4 tumors. However, the FOxTROT pilot phase included relatively few T4a cases and excluded T4b disease, limiting its direct applicability to our patient population.[1]

In a comprehensive meta-analysis, Jung et al. confirmed improved margin-negative resection and 5-

Table 1. Clinical features of enrolled patients with cT4a stage III colorectal cancer

	Total (n = 42)	NCT group (n = 22)	DTS group (n = 20)	*p*-value†
Baseline	n	n (%)	n (%)	
Pre-OP variates				
Gender				0.662
Male	28	14 (63.6)	14 (70)	
Female	14	8 (36.4)	6 (30)	
cN stage				0.227
cN1	13	5 (22.7)	8 (40)	
cN2	29	17 (77.3)	12 (60)	
Location				0.554
Right side	19	9 (40.9)	10 (50)	
Left side	23	13 (59.1)	10 (50)	
Pre OP CEA				0.14
≥ 5	18	7 (31.8)	11 (55)	
< 5	23	15 (68.2)	8 (40)	
N/A	1	0	1 (5)	
Post-OP variates				
Type				0.221
Adenocarcinoma	36	19 (86.4)	17 (85)	
Mucinous/other	4	1 (4.5)	3 (15)	
N/A	2	2 (9.1)	0	
Grade				0.385
MD	36	18 (81.8)	18 (90)	
PD	4	2 (9.1)	2 (10)	
N/A	2	2 (9.1)	0	
Post-OP CEA				0.249
≥ 5	4	1 (3.8)	3 (15)	
< 5	38	21 (80.8)	17 (85)	
LVI				0.238
Yes		6 (27.3)	9 (45)	
No	25	14 (63.6)	11 (55)	
N/A	2	2 (9.1)	0	
PNI				0.035*
Yes	10	2 (9.1)	8 (40)	
No	30	18 (81.8)	12 (60)	
N/A	2	2 (9.1)	0	
MSI status				0.256
High	5	2 (9.1)	3 (15)	
Low	32	16 (72.7)	16 (80)	
N/A	5	4 (18.2)	1 (5)	
Early relapse				0.349
Yes	8	3 (11.5)	5 (25)	
No	34	19 (73.1)	15 (75)	
Relapse				0.588
Yes	13	6 (23.1)	7 (35)	
No	29	16 (61.5)	13 (65)	
Survival				0.881
Yes	34	18 (81.8)	16 (80)	
No	8	4 (18.2)	4 (20)	

Note. Data are given as no. (%) except where otherwise noted.

NCT, neoadjuvant chemotherapy; DTS, direct to surgery.

Preoperative variates: gender, clinical lymph node stage (cN), right side (cecum, ascending and transverse colon); left side (descending, sigmoid colon and rectum); pre-OP carcinoembryonic antigen (CEA).

Postoperative variates: type, grade, post-OP CEA (carcinoembryonic antigen), perineural invasion (PNI), lymphovascular invasion (LVI), microsatellite instable (MSI) status.

Early relapse was defined as local recurrence or distant metastases occurrence within 12 months postoperatively.

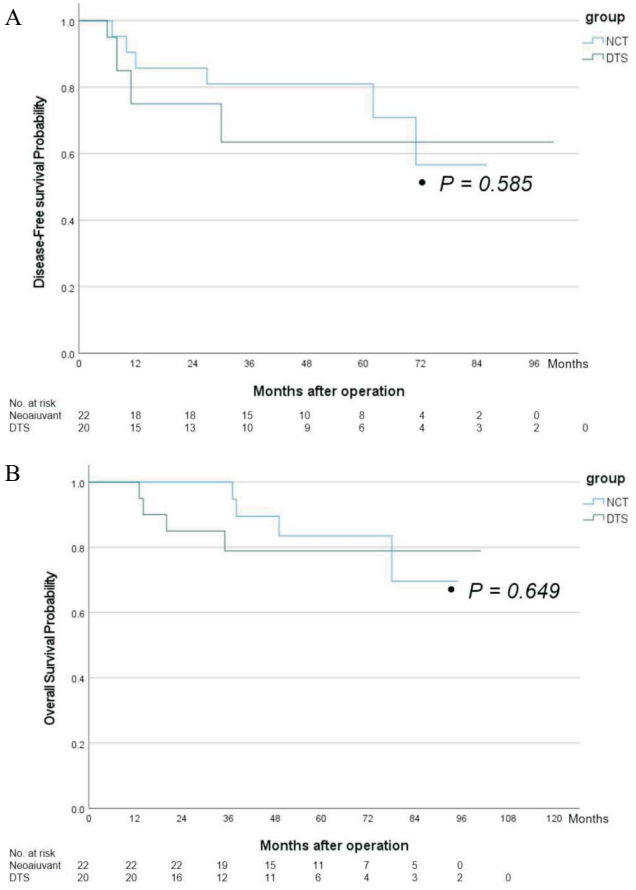

Fig. 2. Cumulative disease-free survival (DFS) rates and overall survival (OS) rates of the 42 enrolled patients with cT4a stage III CRC, obtained using the Kaplan-Meier method. Differences in DFS and OS were analyzed using the log-rank test. The results demonstrated that (A) The DFS didn't significantly differ between the two groups ($p = 0.585$). (B) The OS did not significantly differ between the two groups ($p = 0.649$).

year OS in patients receiving neoadjuvant therapy with no increase in perioperative morbidity, although with considerable heterogeneity across studies.[6]

Notably, our study is among the first to specifically examine the impact of NCT on stage III T4a colon cancer, a group often underrepresented in prior trials. While our results do not show statistically significant differences in survival, the observed trends and histopathological findings are aligned with existing evidence suggesting a potential role for NCT in reducing micrometastatic disease and adverse pathological features.

Several limitations should be acknowledged. The retrospective design and relatively small sample size limit the statistical power and introduce potential selection bias.[18,19] Therefore, it may be insufficient to detect moderate effect differences in assessing the survival rates and increasing the risk of type II error in this study. Additionally, patient performance status and comorbidities, molecular characteristics such as *KRAS* and *BRAF* genes, which may influence response to chemotherapy, were not consistently available. While baseline characteristics were compared using chi-square tests, unmeasured confounders such as ECOG performance status or comorbidities could not be fully accounted for. We acknowledge that the absence of propensity score adjustment is a limitation due to relative sample size. Future multicenter studies with larger cohorts should consider such adjustments to reduce selection bias. Given that stage III T4a colon cancer represents a distinct subgroup often underrepresented in clinical trials, our findings provide preliminary insight into the potential role of NCT in this population. Further prospective studies with larger sample sizes and more patient baseline data are warranted to validate these results and better define the patients who may benefit from preoperative chemotherapy. Such trials should incorporate stratification by molecular subtypes and use robust risk-adjusted models.

Conclusions

In conclusion, although our study did not demonstrate a survival advantage for neoadjuvant chemotherapy in T4a colon cancer, the reduced perineural invasion and trends toward lower recurrence support its potential benefit in selected patients. In light of accumulating evidence from larger studies and national databases, the integration of neoadjuvant strategies in the treatment of locally advanced colon cancer deserves further investigation. These preliminary findings underscore the need for further prospective, multi-institutional studies better to define the role of neoadjuvant therapy in this population.

Acknowledgements

This work was supported by grants through funding from the National Science and Technology Council (MOST 111-2314-B-037-070-MY3, NSTC 112-2314-B-037-050-MY3, NSTC 113-2321-B-037-006, NSTC 113-2314-B-037-057) and the Ministry of Health and Welfare (MOHW113-TDU-B-222-134014) and funded by the health and welfare surcharge of on tobacco products, and Kaohsiung Medical University Hospital (KMUH112-2R37, KMUH112-2R38, KMUH 112-2R39, KMUH112-2M27, KMUH112-2M28, KMUH112-2M29, KMUH113-3R31, KMUH113-3R32, KMUH113-3R33, KMUH113-3M58, KMUH113-3M59, KMUH-S11303, KMUH-SH11309, KMUH-SH11327), Kaohsiung Medical University Research Center Grant (KMU-TC113A04) and National Tsing Hua University-Kaohsiung Medical University Joint Research Project (NTHU-KMU-KT114P008). In addition, this study was supported by the Grant of Taiwan Precision Medicine Initiative and Taiwan Biobank, Academia Sinica, Taiwan, R.O.C.

Authors' Contributions

All authors contributed equally to the writing of the manuscript. All authors also reviewed any revisions that were made and provided their final approval of the manuscript.

Consent for Publication

Written informed consent was obtained from the patients for the treatment. In addition, written informed consent was obtained from the patients' family for publication of this case report and any accompanying images.

Competing Interests

The authors declare that they have no competing interests.

Sources of Financial Support

Nil.

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原　著

臨床分期第三期，腫瘤分期 T4a 的結直腸癌患者直接接受手術治療與接受術前輔助性化學治療之相關臨床預後結果比較 — 單一機構回顧性分析

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目的　本研究旨在比較臨床分期為第三期、腫瘤分期為 cT4a 之結直腸癌 (CRC) 患者接受直接手術與接受術前輔助性化學治療的臨床結果差異。

方法　自 2016 年 2 月至 2020 年 12 月，共篩選出 72 位臨床分期為第三期、腫瘤為 cT4 期的結直腸癌患者。經過篩選後，46 位符合條件的患者納入研究。最終，共有 42 位臨床分期為第三期且為 cT4a 期的結直腸癌患者被納入分析，其中包括 20 位接受直接手術治療的患者與 22 位接受術前輔助性化學治療的患者。我們收集患者的臨床病理資料，並回顧性分析其復發率、無病存活率 (DFS)、總存活率 (OS) 以及其他臨床結果。

結果　本研究的中位追蹤時間為 53 個月。結果顯示，直接手術組與術前輔助性化學治療組在早期復發率 ($p = 0.349$)、整體復發率 ($p = 0.588$)、無病存活率 (DFS, $p = 0.585$) 及總存活率 (OS, $p = 0.649$) 之間並無統計上的顯著差異。值得一提的是，雖然統計上未達顯著差異，術前輔助性化學治療組在早期復發率 (11.5% 對 25%) 與整體復發率 (23.1% 對 35%) 方面皆低於直接手術組。此外，術前輔助性化學治療組的神經周圍侵犯率亦顯著較低，並達到統計學意義 ($p = 0.035$)。

結論　對於臨床分期為第三期且腫瘤為 cT4a 期的結直腸癌患者而言，目前尚無法明確判定直接手術或接受術前輔助性化學治療何者能帶來較佳的臨床預後。然而，術前輔助性化學治療與較低的神經周圍侵犯率及復發率之間的關聯，顯示其可能具有潛在的臨床效益。建議未來進一步進行前瞻性研究，以釐清新輔助治療在此特定病人族群中的臨床角色。

關鍵詞　結直腸癌 (CRC)、無病存活率 (DFS)、總存活率 (OS)、術前輔助性化學治療、cT4a 期別。