Original Article

Impact of Neoadjuvant Chemotherapy on Disease-free, Overall, and Liver-free Survival in Patients with Colorectal Cancer with Liver Metastases

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Key Words
Colorectal cancer liver metastases (CRLM);
Neo-adjuvant chemotherapy (NACT);
Overall survival (OS);
Disease free survival (DFS);
Liver-free survival (LFS)

Purpose. This study aims to evaluate the impact of NACT versus upfront liver metastasectomy on overall survival (OS), disease-free survival (DFS), and liver-free survival (LFS) in patients with resectable CRLM.
Methods. A retrospective cohort study analyzed 188 patients who underwent CRLM resection at Chang Gung Memorial Hospital (2017-2020). Patients were categorized into NACT and non-NACT groups. Primary outcomes were OS and DFS; secondary outcomes included LFS. Statistical analysis utilized Kaplan-Meier methods and Cox proportional hazards models.
Results. The non-NACT group exhibited significantly better OS and DFS compared to the NACT group ($p = 0.029$ and $p = 0.041$, respectively). Median DFS was longer in the non-NACT group (24.9 ± 28 vs. 17.2 ± 22 months, $p = 0.041$). The 1-, 2-, and 3-year DFS rates were higher in the non-NACT group. However, baseline differences in preoperative hepatic markers suggest chemotherapy-related liver injury in the NACT group may contribute to poorer outcomes.
Conclusions. While NACT aids in tumor downsizing and resectability, it may lead to hepatic injury and delayed surgery, negatively affecting survival. Upfront surgery appears to offer superior survival outcomes in resectable CRLM, emphasizing the need for patient-specific treatment strategies.
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Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide. A similar trend has been observed in Taiwan.[1,2] Risk factors for CRC include age > 50 years, family history of CRC, previous CRC or polyp history, westernized diet habits such as consumption of red and processed meat, high body mass index (BMI), sedentary lifestyle, excessive alcohol, and tobacco consumption, and a low-fiber diet.[2]

As CRC symptoms are atypical and difficult to detect, 25% of patients present with distant metastases at diagnosis.[3] Additionally, approximately 25% of the remaining patients progress to stage IV during subsequent follow-up.[4] Due to the anatomy of venous drainage, the liver is the most frequent site of distant metastases after regional lymph nodes. The incidence of synchronous colorectal liver metastases (CRLM) is approximately 26.5% among newly diagnosed CRC

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cases.[5] Moreover, 40% of patients with stage IV CRC develop liver metastases either at diagnosis or during disease progression.[6]

Management of CRLM has been constantly improving, aided by the development of new and effective chemo/targeted therapeutic agents and the co-option of multidisciplinary team (MDT) management. Radical liver metastasectomy remains the only curative treatment, achieving a 5-year survival rate of up to 58% for resectable cases.[7] However, approximately 50-75% of patients with CRLM who undergo metastasectomy experience recurrence, and 80% of recurrences occur within 2 years post-metastasectomy.[8] It is crucial for MDTs to select patients suitable for liver resection. In general, if patients can achieve R0 resection while maintaining adequate liver function, MDTs consider those CRLM cases resectable. Therefore, the primary challenge in treating CRLM is selecting patients who can achieve R0 resection and minimizing intrahepatic recurrence.

Recent studies[9,10] have increasingly focused on the benefits of neoadjuvant chemotherapy (NACT) for CRLM. Advantages of NACT include downstaging liver tumors, converting unresectable CRLM to resectable cases, increasing negative resection margin rates, and addressing potential recurrence from micro-metastases. However, drawbacks include chemotherapy-associated liver injury and reduced hepatic functional reserve.

There is ongoing debate about whether NACT or upfront liver metastasectomy offers better survival benefits. In 2022, Hirokawa et al. reported significantly worse overall survival (OS) in the NAC group compared to the upfront surgery group.[11] Conversely, Wei Liu et al. demonstrated that preoperative chemotherapy improved metastasis resectability and OS compared to upfront surgery.[12] Given these conflicting findings, this study aims to evaluate whether NACT or upfront liver metastasectomy impacts OS, disease-free survival (DFS), or liver-free survival in patients with CRLM.

Materials and Methods

This retrospective cohort study aimed to evaluate the benefits of NAC before liver metastasectomy in patients with CRLM. Patients diagnosed with adenocarcinoma of the colon or rectum, aged ≥ 18 years, and who received CRLM metastasectomy at Chang Gung Memorial Hospital (Keelung or Linkou branches) between January 2017 and December 2020 were included. Exclusion criteria comprised patients with secondary cancers, adenocarcinoma of non-colorectal origin, inability to achieve R0 resection, incomplete medical records, or follow-up of < 12 months after metastasectomy. A total of 188 patients were included in the study.

Participants were divided into the NACT and non-NACT groups based on MDT discussions prior to treatment initiation according to guideline of 2006[13] and further systematic review published in 2021.[14] The NACT regimen included anti-vascular endothelial growth factor (anti-VEGF) or anti-epidermal growth factor receptor (anti-EGFR) agents combined with mFOLFOX6 as the chemotherapy backbone. Patients in NACT groups would bring surgical intervention into discussion after four to six times of chemotherapy.

Demographic data collected included age, BMI, active smoking status, comorbidities (hypertension, diabetes, cardiovascular disease, secondary cancer, end-stage renal disease), tumor characteristics (pathological T and N status), regimen of NACT, biochemical data pre-operatively (including albumin, total bilirubin, carcinoembryonic antigen [CEA], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and hemoglobin [Hb]), and tumor burden score. The primary endpoints were DFS and OS after metastasectomy. The secondary endpoint was liver-free survival.

Continuous data were presented as mean and standard deviation, while categorical data were presented as frequency and percentage. Comparisons were performed using the chi-square test and independent t-test for categorical and continuous variables, respectively. Survival analysis was conducted using the Kaplan-Meier method, log-rank tests, and Cox proportional hazards models. All statistical analyses were performed using SPSS software, version 20 (IBM SPSS Version 25.0; IBM Corp., Armonk, NY, USA). All p-values were two-sided, and values < 0.05 were considered statistically significant.

Results

Patients were categorized into the NACT (n = 97) or the upfront metastasectomy group (non-NAC, n = 91) groups based on MDT discussions prior to treatment. No significant differences in demographic data were observed between the two groups (Table 1). In the NACT group, 38 patients received anti-vascular endothelial growth factor (anti-VEGF) therapy, and 39 received anti-epidermal growth factor receptor (anti-EGFR) therapy based on their RAS gene mutation status.

Preoperative differences were significant between the groups. The NACT group had significantly lower pre-operative carcinoembryonic antigen (CEA) levels (25.73 ± 53.28 ng/mL vs. 74.44 ± 215.34 ng/mL, p = 0.038) but higher CEA levels at diagnosis (283.89 ± 841.86 ng/mL vs. 74.63 ± 219.66 ng/mL, p = 0.023). Alkaline phosphatase (ALK-P) levels were slightly higher in the NACT group (89.32 ± 37.65 U/L vs. 78.31 ± 34.67 U/L, p = 0.05). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly elevated in the NACT group (p = 0.003 and $p < 0.001$, respectively), while total bilirubin level was no difference between groups (p = 0.226). Additionally, Hb levels were higher in the NACT group than in the non-NAC group (12.64 ± 1.52 g/dL vs. 12.02 ± 2.29 g/dL, p = 0.032). No significant differences were observed in other parameters, such as albumin and tumor burden score (p = 0.95 and p = 0.141, respectively) (Table 2).

Post-operative data between the non-NAC and NACT groups showed no statistically significant differences. Post-operative CEA levels were comparable between the non-NACT (10.16 ± 27.99 ng/mL) and the NACT groups (11.17 ± 38.64 ng/mL, p = 0.84), which was also observed with albumin levels (3.43 ± 0.68 g/dL vs. 3.40 ± 0.57 g/dL, p = 0.992). AST and ALT levels were higher in the NACT group (p = 0.266 and p = 0.099, respectively); however, these differences were not statistically significant. Total bilirubin levels (p = 0.223) and Hb levels (p = 0.577) were also similar between groups. Lastly, the length of hospital stay was similar in both the non-NAC (12.35 ± 8.15 days) and NACT (11.65 ± 9.50 days) groups with p value = 0.588 (Table 3).

Primary tumor stage, lymph node status, and positive liver resection margin rates were similar between the two groups. The R0 resection rates after metastasectomy were significantly lower in the NACT group (39.2%) compared to the non-NAC group (54.9%), with a p-value of 0.04.

In the non-NAC group, 70 patients achieved negative margins after liver metastasectomy; however, only 51 were considered to have R0 resection. This was because patients in the non-NAC group who did not achieve R0 resection had synchronous metastases to other solid organs or distal lymph nodes at the time of liver metastasectomy.

During 3-year follow-up period, among the total 188 cases, 60 patients experienced only liver metastasis. Additionally, 28 patients had both liver and lung metastases, while 12 patients had both liver metastasis and peritoneal carcinomatosis. Other cases involving liver metastasis with additional metastasis were found in the adrenal gland, lymph nodes, and anastomosis site. In contrast, among patients without liver recurrence, the most common recurrence site was lung, with 27 cases. Othersites including peritoneum, lymph nodes, and bone. The recurrence rates in the non-NAC

Table 1. Patient demographic data

	No NAC (n = 91)	NAC (n = 97)	p value
Gender			0.883
Male	54 (59.3)	56 (57.7)	
Female	37 (40.7)	41 (42.3)	
Age (years old)	59.24 ± 12.98	58.59 ± 11.31	0.712
BMI	24.02 ± 3.73	23.55 ± 3.61	0.383
Hypertension	36 (39.6)	24 (24.7)	0.041
Type 2 diabetes mellitus	20 (22.0)	16 (16.5)	0.36
Coronary artery disease	4 (4.4)	3 (3.1)	0.714
End stage renal disease	1 (1.1)	0 (0)	0.484
T stage			0.626
1	0 (0)	1 (1.0)	
2	1 (1.1)	1 (1.0)	
3	52 (57.1)	61 (62.9)	
4	38 (41.8)	34 (35.1)	
N stage			0.342
0	10 (11.0)	18 (18.6)	
1	42 (46.2)	40 (41.2)	
2	39 (42.9)	39 (40.2)	

Table 2. Biochemistry data

	No-NAC	NAC	*p*-value
Pre-operative			
CEA (ng/mL)	74.44 ± 215.34	25.73 ± 53.28	0.038
CEA while first diagnosis	74.63 ± 219.66	283.89 ± 841.86	0.023
ALK-P (IU/L)	78.31 ± 34.67	89.32 ± 37.65	0.05
Albumin (g/dL)	4.09 ± 0.74	4.09 ± 0.50	0.95
AST (IU/L)	23.91 ± 9.42	29.62 ± 16.04	0.003
ALT (IU/L)	17.81 ± 10.38	28.04 ± 23.23	< 0.001
Total bilirubin (mg/dL)	0.30 ± 0.54	0.22 ± 0.41	0.226
Hemoglobin (g/dL)	12.02 ± 2.29	12.64 ± 1.52	0.032
Tumor burden score	4.70 ± 3.05	5.49 ± 4.15	0.141
Post-operative			
CEA (ng/mL)	10.16 ± 27.99	11.17 ± 38.64	0.84
Albumin (g/dL)	3.43 ± 0.63	3.40 ± 0.57	0.992
AST (IU/L)	195.47 ± 294.32	271.23 ± 560.71	0.266
ALT (IU/L)	180.84 ± 267.50	301.56 ± 644.29	0.099
Total bilirubin (mg/dL)	0.86 ± 2.02	1.15 ± 1.16	0.223
Hemoglobin (g/dL)	11.08 ± 1.92	11.23 ± 1.73	0.577
Hospital stay (days)	12.35 ± 8.15	11.65 ± 9.50	0.588

Abbreviations: CEA, carcinoembryonic antigen; ALK-P, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin.

and NACT groups were similar (78% and 80.4%, respectively). In addition, 56 patients (61.5%) in the non-NAC group and 68 (70.1%) in the NACT group died within 3-years of follow-up. The mean survival duration for the non-NAC and NACT groups were 45.44 ± 27.7 and 37.31 ± 22.82 months, respectively ($p = 0.029$), while DFS for the non-NAC and NACT groups were 24.9 ± 28 and 17.2 ± 22 months, respectively ($p = 0.041$). In primary outcomes, the non-NAC group demonstrated better OS and DFS than the NACT group (Table 3).

The median DFS was significantly longer in the non-NAC group than in the NACT group (24.9 ± 28 vs. 17.2 ± 22 months, $p = 0.041$). Similarly, the 1-, 2-, and 3-year DFS rates were higher in the non-NAC group (58.2%, 26.4%, and 1.7%, respectively) compared to the NACT group (32.9%, 20.6%, and 17.5%, respectively), with p values < 0.05 (Table 4). In contrast to DFS, OS showed a significant difference at the 2-year mark; however, no significant differences at the 1- and 3-year time points.

Table 3. Primary outcomes

	No NAC (n = 91)	NAC (n = 97)	*p* value
Positive margin	21 (23.1)	31 (32.0)	0.194
R0 resection	50 (54.9)	38 (39.2)	0.04
Recurrence	71 (78.0)	78 (80.4)	0.722
Expire	56 (61.5)	68 (70.1)	0.223
Disease free survival (months)	24.9 ± 28	17.2 ± 22	0.041
Overall survival (months)	45.5 ± 27.7	37.3 ± 22.8	0.029

Table 4. Disease free survival and overall survival in 1, 2 and 3 years follow up

	No-NAC	NAC	*p* value
DFS			
1 years	53 (58.2%)	32 (32.9%)	0.001
2 years	24 (26.4%)	20 (20.6%)	0.021
3 years	18 (19.7%)	17 (17.5%)	0.044
OS			
1 years	82 (90.1%)	83 (85.5%)	0.341
2 years	71 (78.0%)	60 (61.9%)	0.015
3 years	46 (50.5%)	49 (50.5%)	0.585

Discussion

NACT for resectable CRLM remains a topic of debate, with studies highlighting its advantages and limitations. The primary objectives of NACT include

tumor downsizing, evaluation of tumor biological behavior, and reduction of postoperative recurrence risk. However, its role in managing initially resectable CRLM is not universally accepted. Among the advantages, NACT has been shown to effectively reduce tumor size and provide critical insights into tumor biology, thereby guiding subsequent treatment strategies.[1] Additionally, NACT facilitates the evaluation of histological and pathological responses, with strong histological responses being associated with improved survival outcomes. Predictive factors for favorable histological responses include combining chemotherapy with targeted therapies.[2] Furthermore, achieving a pathological complete response has been identified as a significant predictor of tumor reduction and survival improvement.[3]

Conversely, NACT poses risks, including adverse effects and potential delays in surgical intervention, which may limit the window for curative treatment. Therefore, striking a balance between the therapeutic benefits of NACT and its potential to cause hepatic injury is critical.[1,15]

In our study, the non-NAC group demonstrated significantly longer median survival than the NAC group, consistent with the results reported by Burasakarn et al.[4] Additionally, the 1-, 2-, and 3-year DFS rates were higher in the non-NAC group than in the NACT group (Fig. 1), aligning with findings by Famularo et al.[5] However, in terms of OS, only the 2-year OS rate was significantly better in the non-NAC group, with no significant differences observed in the 1- or 3-year OS rates (Fig. 2). Liver-specific recurrence-free survival analysis revealed a trend toward poorer outcomes in the NACT group at both 1- and 3-year follow-ups (Fig. 3). Drawing on findings from breast cancer recurrence patterns, patients with delayed recurrence at metastatic sites following curative-intent treatment exhibited significantly better survival than

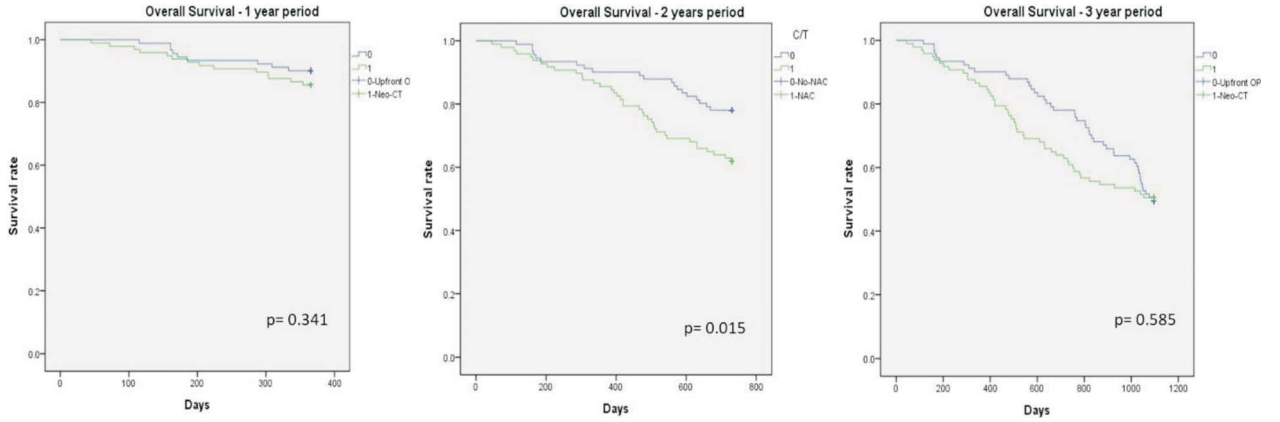

Fig. 1. Overall survival in non-NAC and NACT groups in 1, 2 and 3 years follow up.

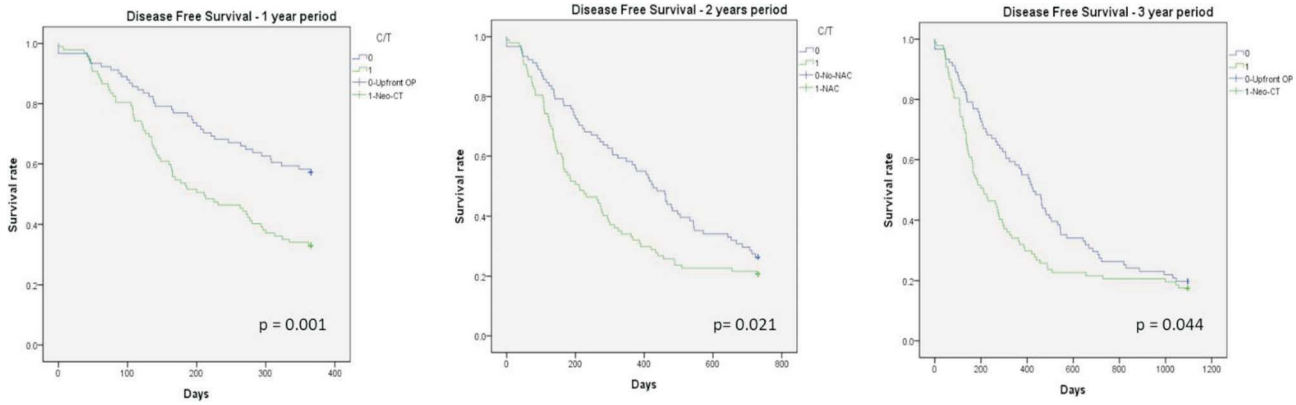

Fig. 2. Disease free survival in non-NAC and NACT groups in 1, 2 and 3 years follow up.

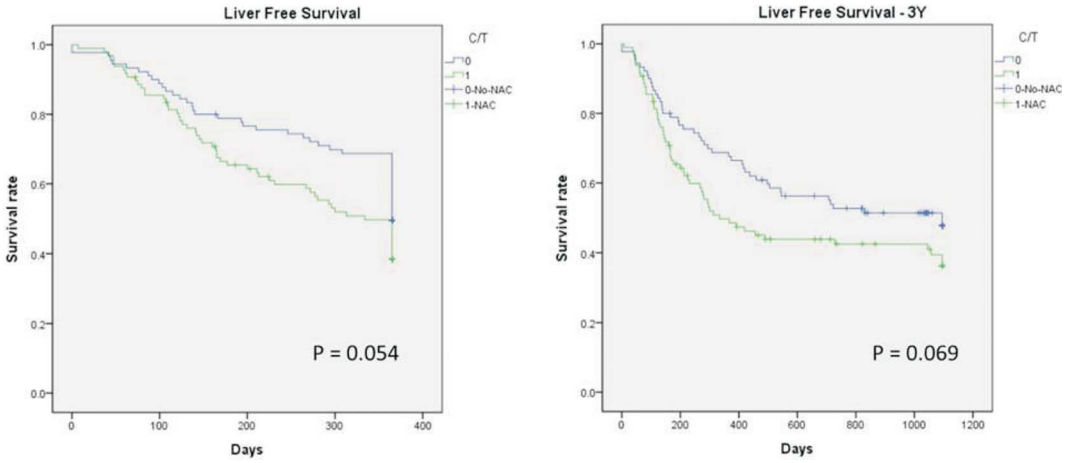

Fig. 3. Liver free survival in non-NAC and NACT groups in 1 and 3 years follow up.

those with early recurrence.[6,7] These findings suggest that tumors in the non-NAC group may exhibit more favorable biological behavior, characterized by less aggressive micro-metastases. Upfront surgery to reduce tumor burden may enhance subsequent treatment efficacy by removing visible liver lesions, decreasing tumor burden, improving systemic therapeutic agent penetration into residual micro-metastases, and restoring systemic immune function — both critical for successful systemic therapy.[9,10]

Although NACT facilitates liver tumor downsizing and enables liver metastasectomy, its associated adverse effects, such as chemotherapy-induced hepatic injury, may negatively affect OS despite achieving curative liver resection. Baseline differences between the NACT and non-NAC groups were also observed preoperatively. Elevated AST and ALT in the NACT group were associated with poorer OS, potentially reflecting chemotherapy-induced hepatic injury or more aggressive liver metastases. Recent studies on the prognostic risk factors of CRLM have identified elevated levels of lactate dehydrogenase, AST, and ALT as markers of poor outcomes.[11,12,16] These findings may partially explain the poor survival outcomes observed in the NACT group.

Limitation

This study has limitations, including its retrospective nature and reliance on single-center data, which may limit generalizability. While tumor burden scores in the NACT and non-NAC groups were comparable and below the threshold of 10,[17] patients deemed suitable for direct surgery during MDT discussions were likely considered to have relatively less severe diseases. This inherent bias could have influenced the outcomes, reducing the generalizability of the findings. Additionally, the retrospective design may introduce confounding factors that were not accounted for, such as differences in patient demographic data, lifestyles, or treatment protocols. These factors should be carefully considered when interpreting the findings.

Future research should focus on identifying patients who fall into the borderline resectable category to assess whether NACT can significantly enhance OS or DFS. Concentrating on this subgroup will allow studies to better evaluate the potential benefits of NACT in cases with uncertain surgical outcomes, providing targeted, evidence-based guidance for treatment decisions.

Conclusion

In conclusion, while NACT offers potential benefits, such as tumor downsizing and insights into tumor biology, its role in resectable CRLM remains controversial. Our findings indicate that patients undergoing upfront surgery without NACT demonstrate superior survival outcomes, likely due to tumor removal with less aggressive biological behavior and the enhanced efficacy of subsequent systemic therapies. However,

the adverse effects of NACT, including chemotherapy-induced hepatic injury and delayed surgical intervention, may negatively impact survival despite facilitating resectability. These results highlight the importance of careful patient selection for NACT and the need to tailor treatment strategies to optimize long-term outcomes.

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原　著

術前輔助性化學治療使用對大腸直腸癌合併肝轉移病患之無病生存期、總生存期及無肝轉移生存期的影響

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目的　本研究旨在評估接受術前輔助性化學治療與直接進行肝轉移切除手術對於可切除之大腸直腸癌肝轉移患者的總生存期、無病生存期和肝無病生存期的影響。

方法　本回溯性研究分析了 188 名於長庚紀念醫院 (2017-2020 年) 接受肝轉移切除手術的患者，並將其分為化學治療組 (NACT) 和優先進行手術組 (Non-NAC)。主要研究結果包括總生存期及無病生存期；次要研究結果為肝無病生存期。統計分析採用 Kaplan-Meier 方法和 Cox 比例風險模型。

結果　與化學治療組相比，優先進行手術組 (Non-NAC) 的總生存期及無病生存期顯著更高 ($p = 0.029$ 和 $p = 0.041$)。優先進行手術組的肝無病生存期中位數較長 (24.9 ± 28 vs. 17.2 ± 22 個月，$p = 0.041$)。此外，優先進行手術組的 1 年、2 年和 3 年 DFS 率均高於化學治療組。然而，術前肝臟指數之差異表明，化學治療組的化療相關肝損傷可能導致更差的結果。

結論　雖然術前輔助性化學治療有助於腫瘤縮小和提高可切除性，但可能因肝損傷和延遲手術而對生存率產生負面影響。對於可切除的大腸直腸癌合併肝轉移，直接進行轉移切除手術可能提供更好的生存結果，強調需要針對患者制定個性化的治療策略。

關鍵詞　大腸直腸癌合併肝轉移、術前輔助性化療、無病生存期、總生存期、無肝轉移生存期。