Original Article

Adjuvant Chemotherapy Has a Limited Benefit in Terms of Recurrence-free Survival and Overall Survival in Colon Cancer with Solitary Lymph Node Metastasis: A Propensity Score Matching Analysis

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Key Words
Adjuvant chemotherapy;
Stage III colon cancer;
Solitary lymph node metastasis;
Survival analysis;
Propensity score matching

Background. Although current guidelines support adjuvant chemotherapy for stage III colon cancer, its therapeutic effects have not been proven in colon cancers with solitary node metastasis (SLNM). This study focuses on recurrence free survival (RFS) and overall survival (OS) in colon cancer with SLNM with or without adjuvant chemotherapy.
Methods. We retrospectively studied 273 patients who had colon cancer with SLNM who received curative resection between 2004 and 2015. Clinicopathological factors, RFS and OS were compared between those who underwent adjuvant chemotherapy and those who did not. A propensity score match (PSM) of ratio 1:1 propensity score match was then used to diminish the selection bias between the groups.
Results. The adjutant chemotherapy and non-adjuvant chemotherapy groups represented 78.7 and 21.3% of the sample size, respectively. The non-chemotherapy group were of a older age, had more comorbidities, and poorer performance status (all at $p < 0.001$) as well as had a higher rate of tumor obstruction or perforation ($p = 0.002$). Before PSM, RFS did not significantly differ between the groups whereas OS was significantly higher in the adjuvant chemotherapy group ($p < 0.001$). Moreover, after PSM, both RFS ($p = 0.591$) and OS ($p = 0.992$) did not significantly differ between the groups.
Conclusions. The survival benefit of adjuvant chemotherapy was limited in colon cancer with SLNM after propensity score matching.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2021;32:150-158*]

The treatment and prognosis of colon cancer has been determined through the TNM (tumor, node, and metastasis) staging system based on the 8th edition manual of the American Joint Committee on Cancer.[1] Surgical resection has been the usual priority for the treatment of colon cancer. Although adjuvant chemotherapy plays an important role in high-risk stage II and III diseases, the survival paradox contrary to stages exists between stage IIb/IIc (pT4N0) and stage IIIa (pT1-2N1a), even with the administration of ad-

Received: May 24, 2021. Accepted: August 12, 2021.
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juvant chemotherapy.[2-4]

Current guidelines recommend adjuvant chemotherapy in all types of stage III cancers. The combined use of 5-fluorouridine (5-FU) and leucovorin has been adopted as the backbone of the chemotherapeutic regimen since 1990.[5] With the addition of oxaliplatin, the 5-year disease-free and overall survival significantly improved in stage III diseases.[5,6] Among all the lymph node-positive colon cancers, solitary lymph node metastasis (SLNM, N1a in TNM staging) has been considered as a distinct subgroup of favorable prognosis in a previous study based on the Surveillance, Epidemiology, and End-Results (SEER) database. The prognosis of pT1-2 cancer with SLNM was comparable to stage IIa disease whereas the prognosis of pT3-4 cancer with SLNM was better than stage IIc.[7] Furthermore, certain studies have demonstrated that epicolic and pericolic lymph nodes have the highest probability for lymph node metastasis.[8] A previous report also revealed the low incidence of pericolic lymph node metastasis at more than 10 cm from the primary tumor.[9] These observations present the features of a loco-regional disease presence in colon cancers with SLNM.

To our knowledge, there have been only two studies that attempted to demonstrate the efficacy of adjuvant chemotherapy in colon cancer with SLNM. Yeom et al. compared survival as the primary endpoint, there was a severe selection bias that existed between the chemotherapy and non-chemotherapy groups[10] while Lin et al. compared the overall survival – but with unadjusted differences between ages.[11]

In this study, we aimed to study the efficacy of adjuvant chemotherapy using a propensity score that matched for stage III colon cancer with SLNM.

Material and Methods

Study design

This was a retrospective study that included patients with pathologically confirmed stage III colon cancer with SLNM at the Division of Colon & Rectal Surgery, Taipei Veterans General Hospital between 2004 and 2015. All selected patients received either open or laparoscopic resection of curative intent. After specimen retrieval, mesocolic tissue was labeled as pericolic and intermediate/main groups by the surgeons at back table according to anatomy of feeding vessels. Our pathologist specialized in colorectal pathology then examined primary tumor and regional lymph node labeled by the surgeons. Patients with pre-operative chemoradiotherapy, rectal cancer, non-adenocarcinoma pathology, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, as well as synchronous and metachronous colon cancers were excluded. The clinicopathological factors such as age, sex, body mass index (BMI), performance status (PS), the American Society of Anesthesiologists (ASA) score, preoperative carcinoembryonic antigen (CEA) levels, tumor sidedness, tumor size, presence of any obstruction or perforation, cell differentiation, pathological T stage, lymphovascular invasion (LVI) and pattern of lymph node metastasis (pericolic or intermediate/main) were collected from the patient database of the hospital. Survival data were collected from the in-hospital medical record and the National Death Registry. The study population was divided into two groups based on those who received adjuvant chemotherapy (adjuvant C/T (+)) and those who did not (adjuvant C/T (-)). All patients were first followed up every 3 months for 2 years after the surgery, than the next 3 to 5 years for every 6 months and then annually after 5 years. Surveillance was based on the National Comprehensive Cancer Network's recommendation: CEA every 3 to 6 months for 2 years, then every 6 months for 5 years; chest/abdominal CT scan every 6 to 12 months for 5 years; colonoscopy at 1 year after surgery, and every 3 years if no advanced adenoma was detected. Chemotherapy was decided based on clinical judgment or patient choice.

The main outcome measured the 5-year recurrence-free survival (RFS) and overall survival (OS). Recurrence was defined as the presence of clinical evidence of local flare-up or distant metastasis through either colonoscopy or imaging modalities of CT, MRI and PET scan. All recurrence cases were discussed at multi-disciplinary meetings comprised radiologists, surgeons, medical oncologists and radiation

oncologists, and possible choices of salvage treatment were advised according to patient condition. Each patient received treatment after discussion with physician. Survival was defined as the interval between surgery and the latest follow-up or death. The latest review on survival status was December 20, 2020.

Propensity score matching

We performed propensity score matching to minimize selection bias and potential confounding while comparing the chemotherapy and non-chemotherapy groups. The propensity score was calculated based on binary logistic regression that included age, BMI, PS, ASA score, follow-up months, the approach of surgery and the presence of any obstruction or perforation. The groups were matched with a 1:1 ratio using a caliper width as 0.1 of the standard deviation of the propensity score.

Statistical analysis

Categorical variables are reported in numbers with percentages and compared using the X^2 test. Continuous variables were reported as mean with range and compared using the Student's *t*-test. Survival analysis was compared using the Kaplan-Meier survival curve and log-rank test. After propensity score matching, categorical variables were compared using McNemar's test or marginal homogeneity test; continuous variables were compared using paired *t*-test; survival analysis was compared with a stratified log-rank test. All the analysis were conducted using the SPSS software (Version 25.0, IBM Corp., Armonk, NY). Statistical significance was defined as a 2-tailed p value of < 0.05.

Results

Patient characteristics

Between 2004 and 2015, 273 patients who had stage III colon cancer with SLNM underwent curative resection. A total of 215 (73.8%) patients received adjuvant chemotherapy while 58 (21.2%) patients did not. The baseline demographics are shown in Table 1. The mean age (63.6 vs. 77.7, $p < 0.001$), proportion of performance status > 2 (1.9% vs. 24.1%, $p < 0.001$), proportion of ASA score ≥ III (9.3% vs. 32.8%, $p < 0.001$), an open approach of surgery (54.4% vs. 69%, $p = 0.047$) and proportion of obstruction or perforation (8.8% vs. 24.1%, $p = 0.002$) were significantly higher in the adjuvant C/T (-) group, while mean BMI (24.1 vs. 22.9, $p = 0.022$) and follow-up period (71.1 vs. 39.1, $p < 0.001$) were significantly lower. However, both groups did not differ significantly in sex, tumor sidedness, tumor size, preoperative CEA level, T stage, cell differentiation, LVI, lymph node counts

Table 1. Baseline characteristics

Variables	Before PSM			After PSM		
	Adjuvant C/T (+) (n = 215)	Adjuvant C/T (-) (n = 58)	*p*	Adjuvant C/T (+) (n = 44)	Adjuvant C/T (-) (n = 44)	*p*
Male (%)	111 (51.6)	38 (65.5)	0.059	26 (59.1)	27 (61.4)	0.999
Age (range)	63.6 (28-91)	77.7 (38-93)	< .001	74.1 (42-91)	75.8 (38-93)	0.375
Mean BMI (range)	24.1 (15.9-35.6)	22.9 (15.5-32.2)	0.022	23.1 (15.9-35.3)	23.1 (16.6-36.2)	0.998
ECOG PS (%)			< .001			
≤ 2	211 (98.1)	44 (75.9)		40 (90.9)	40 (90.9)	0.999
> 2	4 (1.9)	14 (24.1)		4 (9.1)	4 (9.1)	
ASA score (%)			< .001			0.607
I/II	195 (90.7)	39 (67.2)		34 (77.3)	31 (70.5)	
III/IV	20 (9.3)	19 (32.8)		10 (22.7)	13 (29.5)	
Median F/U, months (range)	69 (1-192)	39 (0-153)	< .001	40 (2-139)	39 (0-153)	0.793

BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; ASA: American Society of Anesthesiologists; F/U: follow-up.

and location of lymph node metastasis (Table 2).

Oncological outcome

Of the 273 patients, 58 showed recurrence of cancer. The pattern of recurrence was similar between the groups (Table 3). The proportion of supportive care was higher during the treatment for recurrence in the adjuvant C/T (-) group (58.3% vs. 15.2%, $p < 0.001$). Moreover, the 5-year RFS was similar ($p = 0.601$). While the 5-year OS (77.7% vs. 52.6%, $p < 0.001$) was significantly higher in the adjuvant C/T (+) group.

Table 2. Clinicopathological characteristics

Variables	Before PSM			After PSM		
	Adjuvant C/T (+) (n = 215)	Adjuvant C/T (-) (n = 58)	*p*	Adjuvant C/T (+) (n = 44)	Adjuvant C/T (-) (n = 44)	*p*
Approach of surgery (%)			0.047			0.999
Open	117 (54.4)	40 (69)		28 (63.6)	27 (61.4)	
Laparoscopic	98 (45.6)	18 (31)		16 (36.4)	17 (38.6)	
Tumor sidedness (%)			0.077			0.999
Right	87 (40.5)	31 (53.4)		28 (63.6)	27 (61.4)	
Left	128 (59.5)	27 (46.6)		16 (36.4)	17 (38.6)	
Tumor size, mm (range)	45.5 (4-160)	50.7 (10-150)	0.162	54.5 (10-140)	51.1 (10-150)	0.593
Pre-OP CEA > 5 ng/ml (%)	73 (39.7)	23 (34)	0.420	20 (45.5)	17 (38.6)	0.148
Obstruction/perforation (%)	19 (8.8)	14 (24.1)	0.002	7 (15.9)	8 (18.1)	0.999
T stage (%)			0.115			0.239
I/II	37 (17.2)	4 (6.9)		2 (4.6)	4 (9.1)	
III	152 (70.7)	44 (75.9)		32 (72.7)	31 (70.5)	
IV	26 (12.4)	10 (17.2)		10 (22.7)	9 (20.4)	
Differentiation (%)			0.896			0.754
Well/moderate	194 (90.2)	52 (89.7)		37 (84.1)	39 (88.6)	
Poor/MUC	21 (9.8)	6 (10.3)		7 (15.9)	5 (11.4)	
LVI (%)	51 (23.7)	11 (19)	0.443	7 (15.9)	8 (18.1)	0.999
Mean LN counts (range)	19.8 (4-44)	19.2 (4-38)	0.651	19.8 (8-42)	19.5 (4-38)	0.865
LN sampling < 12 (%)	30 (14)	7 (12.1)	0.710	3 (6.8)	4 (9.1)	0.999
Pattern of LN metastasis (%)			0.376			0.344
Pericolic	183 (85.1)	52 (89.7)		36 (81.8)	40 (90.9)	
Intermediate/main	32 (14.9)	6 (10.3)		8 (18.2)	4 (9.1)	

CEA: carcinoembryonic antigen; MUC: mucinous adenocarcinoma; LVI: lymphovascular invasion; LN: lymph node.
Pericolic LN: lymph nodes confined within marginal artery; Intermediate LN: lymph node along major trunk of mesocolic feeding arteries; Main LN: lymph nodes at root of major mesocolic feeding arteries.

Table 3. Recurrence rate, pattern and salvage treatments

Variables	Before PSM			After PSM		
	Adjuvant C/T (+) (n = 215)	Adjuvant C/T (-) (n = 58)	*p*	Adjuvant C/T (+) (n = 44)	Adjuvant C/T (-) (n = 44)	*p*
Recurrence number (%)	46 (21.4)	12 (20.7)	0.907	16 (36.3)	8 (18.1)	0.115
Pattern (%)			0.186			0.178
Local ± distant	2 (4.3)	2 (16.7)		1 (6.3)	2 (25)	
Distant	44 (95.7)	10 (83.3)		15 (93.7)	6 (75)	
Treatment of recurrence			< .001			0.322
Supportive treatment	7 (15.2)	7 (58.3)		3 (18.7)	6 (75)	
Chemo ± target therapy	16 (34.8)	5 (41.7)		10 (62.5)	2 (25)	
Resection or RFA						
W/chemo ± target therapy	19 (41.3)	0		2 (12.5)	0	
W/O chemo ± target therapy	4 (8.7)	0		1 (6.3)	0	

RFA: radiofrequency ablation; W/: with; W/O: without.

Propensity score matching

After propensity score matching, a total of 88 patients were included, 44 in each group. Age, BMI, PS, ASA score, follow-up duration, the approach of surgery and presence of obstruction and perforation did not statistically differ between the groups after paired analysis. Other clinicopathological factors such as sex, tumor sidedness, tumor size, preoperative CEA level, T stage, cell differentiation, LVI, lymph node counts and location of lymph node metastasis remained comparable.

Regarding oncological outcomes, the rate, pattern and treatment of recurrence had a comparable distribution. The 5-year RFS (45.2% vs. 47.5%, $p = 0.591$, Fig. 1) and OS (49.7% vs. 50%, $p = 0.992$, Fig. 2) did not significantly differ after propensity score matching with log-rank test stratified on matched pairs.

Discussion

This study focuses on survival efficacy of the administration of adjuvant chemotherapy in stage III colon cancer with SLNM. In this study, the 5-year OS were significantly higher in the adjuvant C/T (+) group

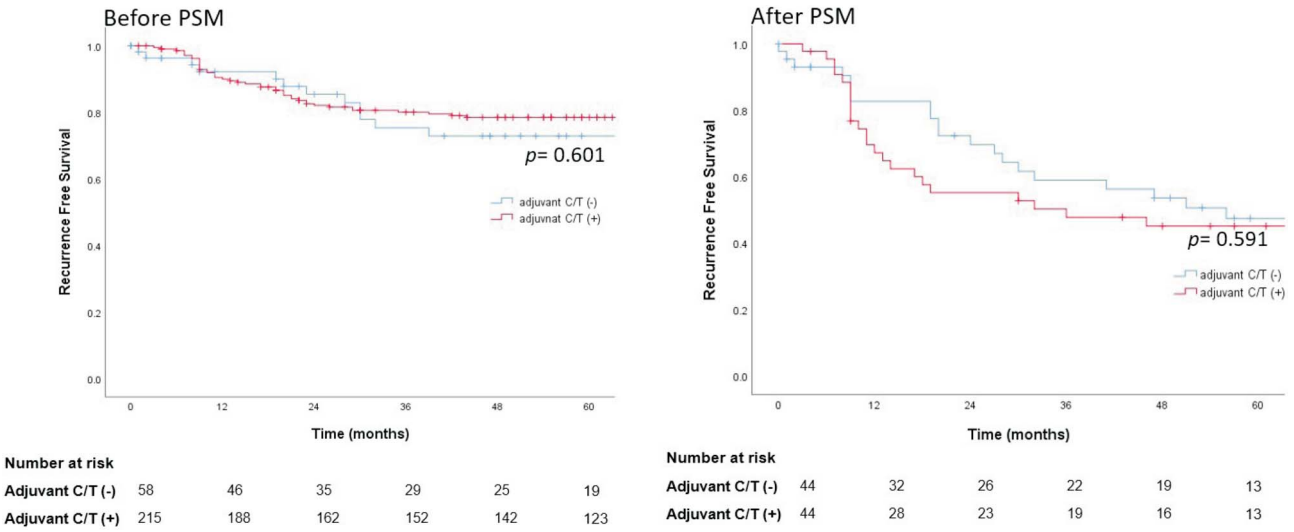

Fig. 1. Recurrence-free survivals according to the use of adjuvant chemotherapy.

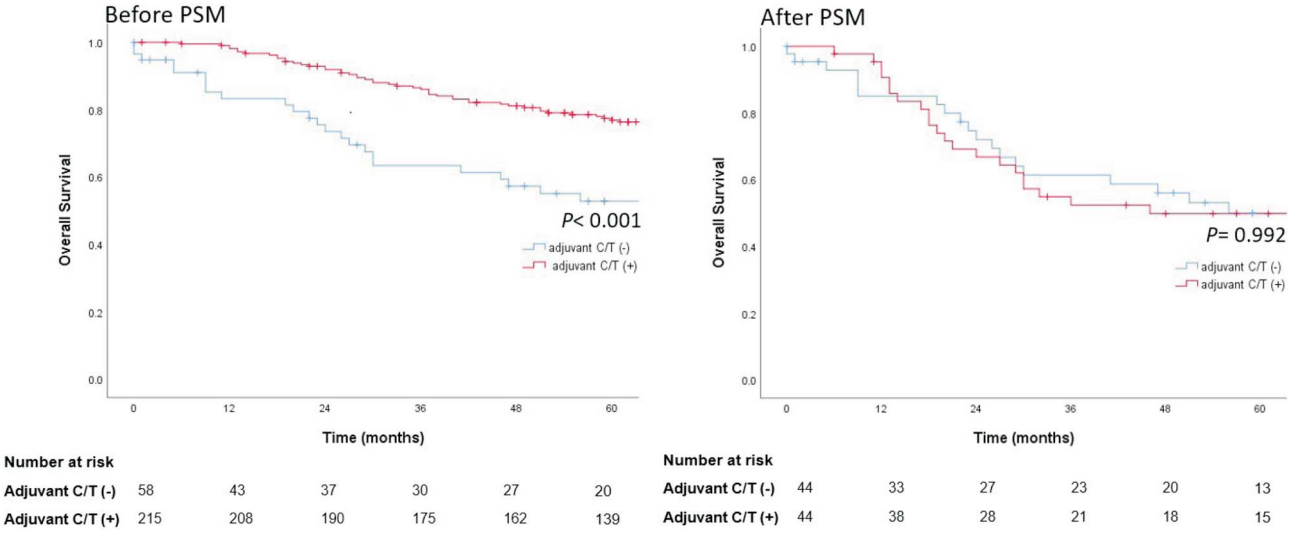

Fig. 2. Overall survival according to the use of adjuvant chemotherapy.

before matching, this may be due to younger age and fewer comorbidities. These differences remarkably affected the survival rates. In addition, more patients in the adjuvant C/T (+) group received aggressive salvage treatment, such as resection of metastasis or radiofrequency ablation, which led to better OS after the cancer recurrence. Moreover, the rate of recurrence was similar between the groups. Hence, we considered the improved OS to be strongly correlated with age and comorbidity differences at baseline.

Apart from OS, which is prone to be affected by baseline characteristics, RFS is an alternative endpoint in evaluating efficacy of adjuvant chemotherapy. The rate of RFS was similar before matching. In multivariate Cox regression before matching, chemotherapy did not notably affect RFS (HR: 0.73, p = 0.249, data not shown) as well as OS (HR: 0.61, p = 0.074, data not shown). Even after propensity score matching, RFS and OS were not still significantly influenced by the administration of adjuvant chemotherapy. In our study, 5 types of adjuvant chemotherapies were administered to our population: 5FU plus oxaliplatin (FOLFOX) (n = 126); capcitabine plus oxaliplatin (XELOX) (n = 9); 5FU plus leucovorin (n = 37); capcitabine (Xeloda) (n = 6) and tegafur/uracil (Ufur) (n = 37). The RFS stratified in different regimens did not found any regimen yielded better survival than adjuvant C/T (-) group. Those regimens were than classified into 5FU-based and oxaliplantin-based therapies. In those who received oxaliplatin-based therapy, 135 of 214 (63%) patients had received it before matching, while 19 of 44 patients (43%) received it after matching. The alteration in regimens may also lead to insignificant difference in RFS and OS. In addition, treatment duration may vary according to patient conditions and regimens. The mean treatment duration was 5.28 months with standard deviation of 1.9 months. (5.05 in oxaliplatin-based therapy and 5.65 in 5FU-based therapy individually) We considered the heterogeneity of different durations in our population was limited in extent.

A few previous studies have investigated colon cancer with SLNM. In an earlier study based on the Yorkshrine population, 480 patients had colorectal cancer with SLNM in which adjuvant chemotherapy was beneficial for survival.[12] However, the study included both colon and rectal cancers, which may comprised different preoperative treatment modalities. In addition, the major outcome was the discriminability of the prognostic model and not survival. Moreover in another study, Yeom et al. had studied 281 patients and concluded that OS had improved in the adjuvant chemotherapy group.[10] Furthermore, Lin et al. included 363 patients with colon cancer with SLNM and found that adjuvant chemotherapy failed to alter the OS.[11] The population in these studies were younger than our patients and the follow-up period was not provided. Moreover, the selection bias at the baseline was not balanced. Better survival may result from selection bias with younger age and better health status in the adjuvant chemotherapy group.

Several prognostic factors in colon cancer have been proposed, such as neutrophil-to-lymphocyte ratio,[13,14] platelet-to-lymphocyte ratio[15-17] and the lymph node ratio (positive lymph node over harvested lymph node)[18,19] especially in stage III colon cancer. To date, adjuvant chemotherapy has been suggested for all stage III colorectal cancers. Despite those prognostic factors predicts outcome, the predictive factor of adjuvant chemotherapy in clinical practice is still lacking. In real world, it was difficult to identify which patients may be potential responders to the adjuvant chemotherapy. One of the promising factors was the immunoscore that predicted FOLFOX response from recent literatures.[20,21] Circulating tumor cells (CTCs), as another marker being proposed, was associated with tumor recurrence and the persistence of CTCs may reflect tumor resistance to adjuvant chemotherapy.[22,23] In the future, the decision to administer adjuvant chemotherapy should be tailored and individualized based on different markers other than clinicopathological parameters.

This study had several limitations. Firstly, the retrospective design included a selection bias between adjuvant and non-adjuvant chemotherapy. Secondly, the small number and shorter duration of follow-up in the non-adjuvant chemotherapy group led to a bias for recurrence and survival. Although we adopted the propensity score matching to eliminate baseline differences, the loss of samples may contribute to under-

powered results. Also, the small numbers after matching restricted further regression analysis and may not fully represent our original population. Thirdly, the adjuvant chemotherapy group included different regimens and treatment periods, which were not included in our analysis.

Despite these differences, our study included the most available clinicopathological factors and attempted to reduce bias and confounding factors by means of propensity score matching. Further studies on large scale and workups on pathological and molecular factors should be conducted in the future to verify our findings.

Conclusion

The efficacy of adjuvant chemotherapy for stage III colon cancer with SLNM remains limited in terms of recurrence-free and overall survival. Further studies with larger sample sizes and identification of markers associated with response to chemotherapy are necessary.

Acknowledgement

The authors would like to thank all colleagues who contributed to this study. We are grateful to Prof. Jiang for his collaboration during preliminary investigations.

Sources of Financial Support

Not applicable.

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原　著

評估輔助化學治療在單一淋巴結轉移大腸癌病患之存活效益 – 一個傾向分數配對分析研究

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前言　目前第三期大腸癌術後皆建議施行輔助性化學治療，但化學治療實際效益在單一淋巴結轉移大腸癌病患中尚未明瞭。本研究探討並比較化學治療與否對單一淋巴結轉移大腸癌病患在無復發存活與總體存活之差異。

材料與方法　本研究回顧單一醫學中心 2004 至 2015 年病例，統計 273 名單一淋巴結轉移大腸癌病患之臨床與病理因子，並根據化學治療與否比較無復發存活與總體存活率差異。為消除化學治療與否組間選樣偏差，研究使用 1:1 傾向分數配對 (propensity score matching) 比較存活差異。

結果　273 名病患中接受與未接受化學治療病例分別佔總樣本數之 78.7% 與 21.3%。未接受化學治療病例平均年齡較長、體能狀態 (performance status) 較差、美國麻醉醫學會分級 (ASA score) 較高 (p 值皆 < 0.001) 與術前出現腫瘤阻塞或破裂比例較高 (p = 0.002)。在傾向分數配對前之無復發存活曲線與接受輔助化學治療與否無統計顯著性但接受化學治療病例總體存活曲線顯著優於未接受化學治療病例 (p 值 < 0.001)。傾向分數配對後接受化學治療與否對於無復發存活 (p = 0.591) 與總體存活曲線 (p = 0.992) 皆無顯著性影響。

結論　本研究顯示輔助性化學治療對於單一淋巴結轉移大腸癌病例在無復發存活與總體存活率改善之侷限。

關鍵詞　輔助化學治療、第三期大腸癌、單一淋巴結轉移、存活分析、傾向分數配對。