Original Article

Adjuvant Chemotherapy on Cancer Relapse in Stage IIIA Colon Cancer

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Key Words
Stage IIIA colon cancer;
Adjuvant chemotherapy;
Time-to-relapse;
Overall survival

According to the seventh edition of the AJCC staging system, a 5-year survival paradox exists between colon cancer stages IIB and IIIA (72.2% and 83.4%, respectively). Owing to pericolic lymph node metastasis, patients with stage IIIA colon cancer have a relatively low risk of cancer relapse. Pericolic lymph node metastasis has a limited range in stage IIIA and can be completely resolved through surgery. Therefore, we investigated the effect of adjuvant chemotherapy on 5-year time-to-relapse (TTR) of stage IIIA colon cancer patients. Overall, 215 patients with stage IIIA colon cancer who underwent cancer resections between 1995 and 2016 were analyzed. Among these patients, 137 (63.7%), 76 (35.3%), and 2 (0.9%) patients had N1a (one lymph node), N1b (two to three lymph nodes), and N2a (four to six lymph nodes) lymph node metastasis, respectively. Two groups were compared: adjuvant chemotherapy (resection with chemotherapy; n = 166) and cancer-resection-only (n = 49). The cancer-resection-only group had significantly more patients with comorbidities than the adjuvant chemotherapy group. The physical score of the American Society of Anesthesiologists (≥ 3) was significantly higher in the cancer-resection-only group than in the adjuvant group (40.8% vs. 19.0%, p = 0.007). However, the 5-year TTR rate did not differ significantly between the adjuvant chemotherapy and cancer-resection-only groups (91.8% vs. 93.3%, p = 0.809). Cox regression analysis indicated that the T2 stage was the only factor with a significant TTR difference between the groups (p = 0.030). Moreover, no survival difference was observed in overall survival between the adjuvant chemotherapy and cancer-resection-only groups for stage IIIA patients with T1 status (95.4% vs. 91.0%; p = 0.311) or those who were younger than 65 years old (95.0% vs. 90.1%; p = 0.370). Patients with stage IIIA colon cancer had favorable outcomes; meanwhile, adjuvant chemotherapy did not improve the 5-year TTR.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2025;36:274-287*]

Colorectal cancer is the third most prevalent and second most fatal cancer worldwide, according to 2022 data from Global Cancer Statistics (GLOBOCAN).[1] The clinical decisions of most physicians treating colorectal cancer are based on the cancer stage according to the tumor staging system. In the past four decades, the tumor (T), lymph node (N), and metastasis (M) staging system (TNM) stratification for colorectal cancer has been progressively revised to improve outcome predictions for patients in each stage.

Received: January 24, 2025. Accepted: May 23, 2025.
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In the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, stage II colon cancer was separated into stages IIA and IIB, and stage III colon cancer was separated into stages IIIA, IIIB, and IIIC.[2,3] Stage IIIA colon cancer was defined as a "tumor lesion invading submucosa (T1) or muscularis propria (T2) with N1 status and without distant metastasis". In the seventh edition of the AJCC staging system, N2 was subdivided into N2a (metastasis in four to six lymph nodes) and N2b (metastasis in seven or more lymph nodes), and colon cancer T1N2aM0 was also considered stage IIIA colon cancer (Table 1).[4] According to the sixth edition of the AJCC staging system, the survival rates of patients with stages I, IIA, IIB, IIIA, IIIB, IIIC, and IV colon cancer in the Surveillance, Epidemiology, and End Result Program (SEER) database were 93.2%, 84.7%, 72.2%, 83.4%, 64.1%, 44.3%, and 8.1%, respectively. The survival paradox between stages IIB and IIIA colon cancer has been evident since the sixth edition of the AJCC staging system was published.

Most lymph node metastases are observed in the pericolic region in colon cancer patients, which is usually within 10 cm distal to the tumor site.[5] Meanwhile, cancer invasion risk in the lymphatic drain system tends to be low in the presence of a solitary metastatic lymph node. Thus, the prognostic effect of postoperative adjuvant chemotherapy is potentially con-

Table 1. AJCC staging system for colorectal cancer

Stage	5th edition	6th edition	7th edition
I	T1N0M0	T1N0M0	T1N0M0
	T2N0M0	T2N0M0	T2N0M0
II	T3/T4N0M0		
IIA		T3N0M0	T3N0M0
IIB		T4N0M0	T4aN0M0
IIC			T4bN0M0
III	Any T N1M0		
IIIA		T1N1M0	T1N1/1cM0
		T2N1M0	T2N1/1cM0
			T1N2aM0
IIIB		T3N1M0	T3N1/1cM0
		T4N1M0	T4aN1/1cM0
			T1N2bM0
			T2N2bM0
			T2N2aM0
			T3N2aM0
IIIC		T1N2M0	T4aN2aM0
		T2N2M0	T3N2bM0
		T3N2M0	T4aN2bM0
		T4N2M0	T4bN2M0
			T4bN1M0
IV	Any T, any N, M1		
IVA		Any T Any N M1	Any T Any N M1a
IVB			Any T Any N M1b

T stage: T1 = tumor invading submucosa; T2 = tumor invading muscularis propria; T3 = tumor growth through the muscularis propria and into the subserosa; T4 = tumor penetration over visceral peritoneum with or without adjacent organ invasion (T4a: tumor through the visceral peritoneum; T4b: tumor has grown into other nearby tissues or organs).
N stage: N0 = no regional lymph node metastasis; N1 = one to three nodes metastases (N1a: metastasis in 1 regional node; N1b: metastasis in 2-3 nodes; N1c: there are nodules made up of tumor cells found in the structures near the colon that do not appear to be lymph nodes); N2 = four or more nodes metastases (N2a: metastasis in 4-6 nodes; N2b: metastasis in 7 or more nodes).
M stage: M0 = no distant metastasis; M1 = presence of distant metastasis (M1a: the cancer has spread to 1 other part of the body beyond the colon or rectum; M1b: the cancer has spread to more than 1 part of the body other than the colon or rectum).

troversial because surgical resection may be sufficient for this stage of colon cancer if only one lymph node metastasis occurs. In previous studies, patients with T1 or T2 colon cancer have a lower prevalence of lymph node metastasis and distant metastasis than those with T3 or T4 colon cancer.[6] Although considerable evidence supports the use of postoperative chemotherapy for treating stage III colon cancer, conclusions regarding the effect of adjuvant chemotherapy on survival outcomes in patients with stage IIIA colon cancer remain inconsistent. The risk of cancer relapse in stage IIIA colon cancer patients who do not receive adjuvant chemotherapy can potentially remain low owing to pericolic lymph node metastasis, which has a limited range in stage IIIA status and can be completely resolved through surgery. Therefore, this study hypothesized that stage IIIA colon cancer patients get limited benefits from adjuvant chemotherapy after curative colon cancer surgery. Hence, we aimed to determine the effect of adjuvant chemotherapy on the prognosis and survival outcomes of stage IIIA colon cancer patients.

Materials and Methods

Patient selection

According to a study comparing the survival outcomes of colon cancer stages I-III based on the sixth and seventh editions of the AJCC staging system, the seventh edition of the AJCC staging system has not eliminated discrepancies in the SEER-based cohort of survival outcomes between patients with colon cancer stages II and IIIA.[7] The present study reassigned patients with colon cancer to a stage according to the seventh edition of the AJCC staging system. Meanwhile, the eighth edition of the AJCC staging system is irrelevant to our study as it only includes a new IVC stage. Moreover, since our patients were selected before the release of the eighth edition, we decided to maintain the use of the sixth and seventh editions of the AJCC staging system for simplicity.

Initially, 3378 patients with pathologic colon cancer stage III who underwent curative surgical resection at the Linkou branch of Chang Gung Memorial Hospital between 1995 and 2016 were enrolled. Among these patients, those with stage IIIA were selected for analysis. Participants were excluded if they had (a) other forms of stage III colon cancer, including stages IIIB and IIIC; (b) double cancer; (c) no curatively radical resection. Finally, 215 stage IIIA colon cancer patients were selected and divided into two groups: an adjuvant chemotherapy (AC) group (77.2%), comprising 166 patients who received surgical resection followed by postoperative adjuvant chemotherapy, and a cancer-resection-only (CRO) group (22.8%), consisting of 49 patients who received curative cancer resection only. The Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol.

Patient follow-up

Follow-up data for survival analysis were collected retrospectively from medical records or through interviews with patients. Meanwhile, patient follow-ups were performed through a clinical examination or identification of tumor markers (e.g., carcinoembryonic antigen, CEA) once every 3 months for the first 5 years after cancer surgery and once every 6 months thereafter. Moreover, patients underwent whole-body computer tomography scanning every year. A colonoscopy was performed 1 year after cancer surgery and then once every 2 or 3 years. All cancer relapses during follow-up, including distant metastasis or local recurrence, were identified solely through imaging or imaging followed by pathological examination (e.g., biopsy or resection).

Adjuvant chemotherapy regimens

For postoperative adjuvant chemotherapy in the present study, (a) 5-fluorouracil plus leucovorin (FL), (b) capecitabine, (c) tegafur 100 mg/uracil 224 mg (UFUR), and (d) oxaliplatin-based regimens were used.

The FL regimen was applied biweekly. This regimen involved intravenous administration of bolus infusion (400 mg/m^2 over 10-15 min on the day of leucovorin treatment) and continuous infusion (1200

mg/m^2/day (total dose of 2400 mg/m^2) on the day of 5-fluorouracil bolus treatment and the following day) of fluorouracil over 46 hours.[8,9] Capecitabine was administered at 1250 mg/m^2 twice daily for 14 days; the patient was allowed to rest for 7 days before beginning the next cycle.[9] A total daily UFUR dose of 400 mg was administered twice daily for 28 consecutive days every 5 weeks. A total daily folinic acid dose of 30 mg (15 mg/tablet) was administered twice daily for 28 consecutive days every 5 weeks.[10,11] The oxaliplatin-based regimen was applied biweekly: oxaliplatin was intravenously administered (85 mg/m^2 over 2 h on day 1) before the FL regimen was used.[12]

Overall, 54 (32.5%) patients in the AC group received an oxaliplatin-based regimen, 28 (16.9%) received FL infusion, 23 (19.9%) received oral UFUR, and 51 (30.7%) received oral capecitabine.

Survival follow-up and statistical analysis

This study used Pearson's chi-square test to compare categorical characteristics between the AC and CRO groups. The survival difference was estimated using the Kaplan-Meier method, and the log-rank test was used to perform a comparison. Overall survival (OS) was the interval between cancer diagnosis dates and any-cause death. Time-to-relapse (TTR) was defined as the period from curative surgery to cancer relapse. Our primary endpoint was a 5-year TTR, and the secondary endpoint was a 10-year OS. Confounders were controlled for using a multivariate Cox regression model. All statistical analyses were performed using SPSS version 17 (SPSS, Chicago, IL, USA). All *p*-values were two-tailed, and a value < 0.05 indicated statistical significance.

Results

Patient clinicopathological characteristics

Of the 215 patients in the study cohort, 111 (51.6%) were men. Solitary (N1a), two to three (N1b), and four to six (N2a) lymph node metastases were observed in 137 (63.7%), 76 (35.3%), and 2 (0.9%) patients, respectively. The mean ± standard deviations of the ages of the patients in the AC and CRO groups were 61.0 ± 11.6 (range: 30-88) and 69.4 ± 12.8 (range: 34-94) years, respectively ($p < 0.001$).

The clinicopathological characteristics of the patients in the AC and CRO groups are detailed and compared in Tables 2 and 3. No difference was observed between the two groups except concerning patient age, preoperative CEA, number of examined lymph nodes, TNM N-stage, and comorbidities. Compared with the AC group, the CRO group had significantly higher rates of comorbidities, including hypertension, cerebrovascular accident (CVA), diabetes mellitus (DM), and chronic kidney disease (CKD). Furthermore, the American Society of Anesthesiologists (ASA) scores for cancer surgery were higher in the CRO group than in the AC group.[13]

Survival and related prognostic factors

The 215 included patients had mean, median, and maximum follow-up periods of 99.7, 94, and 305 months, respectively. No significant difference was observed in the mean ± standard deviation follow-up interval between the AC and CRO groups (101.7 ± 48.0 vs. 93.2 ± 62.1 months; $p = 0.314$; Table 2). Of the 16 patients with cancer relapse, 13 (7.8%) were in the AC group, and 3 (6.1%) were in the CRO group; however, no significant difference was noted between the two groups ($p = 0.689$). Of the nine patients who underwent resection for cancer relapse, eight patients were in the AC group, and one patient was in the CRO group. Finally, four of these nine patients were disease-free after undergoing a metastasectomy.

The 5-year TTR did not significantly differ between these two groups (91.8% and 93.3% in the AC and CRO groups, respectively; $p = 0.809$; Fig. 1). Moreover, the 5-year TTR for different chemotherapy regimens were similar in the AC group (91.6% in FL/UFUR/capecitabine and 92.1% in the oxaliplatin-based regimen; $p = 0.935$). Univariate analysis revealed that the pathologic T stage was statistically significant and was the sole prognostic factor for 5-year TTR. Two coefficients, histology grade, and perineural invasion, exhibited no statistical convergence

Table 2. Clinicopathologic characteristics of two groups (undergoing and not undergoing adjuvant chemotherapy) with stage IIIA colon cancer

Characteristic	With adjuvant C/T (N = 166, 100%)	Without adjuvant C/T (N = 49, 100%)	*p* value
Age (y)			< 0.001
< 65	99 (59.6)	17 (34.7)	
≥ 65	67 (40.4)	32 (65.3)	
Sex			0.923
Female	80 (48.2)	24 (49.0)	
Male	86 (51.8)	25 (51.0)	
CEA (ng/mL)			0.006
< 5	148 (89.2)	36 (73.5)	
≥ 5	18 (10.8)	13 (26.5)	
NLR			0.266
≥ 2.87	29 (19.5)	12 (27.3)	
< 2.87	120 (80.2)	32 (72.7)	
Cancer location			0.591
Right side	40 (24.1)	10 (20.4)	
Cecum	8 (4.8)	1 (2.0)	
Ascending	14 (8.4)	3 (6.1)	
Transverse (+ hepatic flexure)	18 (10.8)	6 (12.2)	
Left side	126 (75.9)	39 (79.6)	
Splenic flexure	1 (0.6)	2 (4.1)	
Descending	21 (12.7)	5 (10.2)	
Sigmoid	100 (60.2)	30 (61.2)	
Rectosigmoid	4 (2.4)	2 (4.1)	
Histology type			0.361
Adenocarcinoma	159 (95.8)	45 (91.8)	
Mucinous type	1 (0.6)	0	
Signet ring cell	6 (3.6)	4 (8.2)	
Histology grade			0.509
Well	32 (19.3)	13 (26.5)	
Moderate	122 (73.5)	32 (65.3)	
Poorly	12 (7.2)	4 (8.2)	
LV invasion			0.504
Presence	69 (41.6)	23 (46.9)	
Perineural invasion			0.149
Presence	13 (7.8)	1 (2.0)	
Examined LN (n)			0.045
< 12	29 (17.5)	15 (30.6)	
≥ 12	137 (82.5)	34 (69.4)	
TNM-T stage			0.229
T1	63 (38.0)	14 (28.6)	
T2	103 (62.0)	35 (71.4)	
TNM-N stage			0.029
N1a	98 (59.0)	39 (79.6)	
N1b	66 (39.8)	10 (20.4)	
N2a	2 (1.2)	0 (0.0)	
Regimens of C/T			NA
5-FU/LV	28 (16.9)	0	
mFOLFOX6	50 (30.1)	0	
XELOX	4 (2.4)	0	
UFUR	23 (19.9)	0	
Capecitabine	51 (30.7)	0	
Regimen groups			NA
Fluoropyrimidine	112 (67.5)	0	
Oxaliplatin	54 (32.5)	0	
Cancer relapse			0.689
Relapse	13 (7.8)	3 (6.1)	
No relapse	153 (92.2)	46 (93.9)	
Relapse-free (m) (mean ± SD)	97.2 ± 50.1	90.9 ± 63.6	0.468
Total follow-up (m) (mean ± SD)	101.7 ± 48.0	93.2 ± 62.1	0.314

y: year; m: month; C/T: chemotherapy; CEA: carcinoembryonic antigen; LV: lymphovascular; NLR: neutrophil to lymphocyte ratio; LN: lymph node; TNM: tumor (T), lymph node (N), and metastasis (M) staging system; T1: tumor invading submucosa; T2: tumor invading muscularis propria; N1a: metastasis in 1 regional node; N1b: metastasis in 2-3 nodes; N2a: metastasis in 4-6 nodes.

(Table 4). Since only one significant prognostic factor was noted in the univariate Cox regression model, further multivariate analysis was not performed to determine the TTR of each patient.

A significantly longer 10-year OS was observed in the AC group than in the CRO group (94.3% vs. 79.3%, respectively; $p < 0.001$; Fig. 1). A univariate analysis revealed that adjuvant chemotherapy, old age (≥ 65 years), high ASA score (≥ 3), abnormal preoperative CEA level (≥ 5 ng/mL), tumor invasion (T2 stage), and high neutrophil-to-lymphocyte ratio (≥ 2.87) were statistically significant factors influencing OS in stage IIIA cancer patients, which was a parameter set in one of our previous research projects.[31,32] Multivariate analysis revealed that old age, T2 stage, and postoperative adjuvant chemotherapy were independent prognostic factors for 10-year OS (Table 5). Finally, we further analyzed the effect of adjuvant chemotherapy on OS in stage IIIA colon cancer patients for different age and T-stage groups. The AC group had significantly greater OS than the CRO group for patients with T2 stage and those who were ≥ 65 years old (Figs. 2 and 3). However, no survival difference was observed between the AC and CRO groups for patients with T1 stage (T1 stage, 95.4% vs. 91.0%; $p = 0.311$) or those who were < 65 years old (age < 65, 95.0% vs. 90.1%; $p = 0.370$).

Table 3. Comorbidity and anesthesia risk in two groups (undergoing and not undergoing adjuvant chemotherapy) with stage IIIA colon cancer

Characteristic	With adjuvant C/T (N = 166, 100%)	Without adjuvant C/T (N = 49, 100%)	*p* value
ASA score			0.007
1	42 (25.3)	6 (12.2)	
2	91 (54.8)	23 (46.9)	
≥ 3	33 (19.0)	20 (40.8)	
Hypertension	62 (37.3)	30 (61.2)	0.003
Heart disease	21 (12.7)	10 (20.4)	0.174
CVA	4 (2.4)	5 (10.2)	0.017
Asthma	6 (3.6)	1 (2.0)	0.585
DM	21 (12.7)	17 (34.7)	< 0.001
Peptic ulcer	13 (7.8)	7 (14.3)	0.172
Hepatitis	18 (10.8)	5 (10.2)	0.899
Liver cirrhosis	2 (1.2)	1 (2.0)	0.661
CKD	16 (9.8)	12 (24.5)	0.007
ESRD and H/D	1 (0.6)	2 (4.1)	0.070

C/T: chemotherapy; ASA score: Physical Status Classification System by American Society of Anesthesiologists; CVA: cerebrovascular accident; DM: diabetes mellitus; CKD: chronic kidney disease; ESRD: end-stage renal disease; H/D: hemodialysis.

Discussion

T and N stages are key factors in the AJCC staging system for colorectal cancer. However, colorectal cancer with positive metastatic lymph nodes is considered more invasive than that with negative metastatic

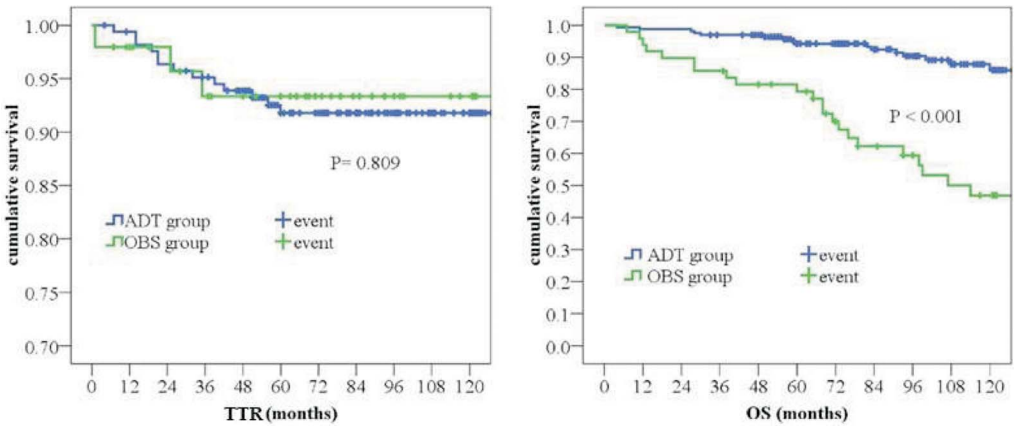

Fig. 1. Postoperative adjuvant chemotherapy (AC group) does not significantly improve 5-year TTR in stage IIIA colon cancer; however, a significantly longer 10-year OS was observed in the adjuvant chemotherapy group (AC group) than in the cancer-resection-only group (CRO group).

Table 4. Univariate COX proportional hazards models for 5-year TTR

Characteristic	Patient number	5-y TTR (%)	Univaiate HR (95% CI)	*p* value
Age (y)				
< 65	116	91.1	1	
≥ 65	99	93.4	0.720 (0.262-1.982)	0.525
Sex				
F	104	93.1	1	
M	111	91.2	1.195 (0.445-3.209)	0.724
ASA score				
1	48	95.8	1	
2	114	89.8	2.442 (0.541-11.017)	0.246
3	53	93.7	1.445 (0.241-8.646)	0.687
CEA (ng/mL)				
≥ 5	31	92.6	1	
< 5	184	92.0	1.152 (0.262-5.069)	0.852
NLR				
≥ 2.87	41	89.0	1	
< 2.87	152	93.0	0.614 (0.192-1.958)	0.410
Cancer location				
Right colon	50	95.7	1	
Left colon	165	91.0	2.078 (0.472-9.145)	0.333
Histology type				
Others	11	90.0	1	
Adenocarcinoma	204	92.2	0.743 (0.098-5.627)	0.773
Histology grade*				
Poorly	16	100.0		
Well/moderate	199	91.5	No convergence in the coefficient	
LV invasion				
Absence	123	93.0	1	
Presence	92	91.0	1.372 (0.515-3.656)	0.527
Perineural invasion*				
Absence	201	91.5		
Presence	14	100.0	No convergence in the coefficient	
Examined LN				
< 12	44	90.6	1	
≥ 12	171	92.5	0.830 (0.268-2.574)	0.747
TNM-T stage				
T1	78	98.7	1	
T2	137	88.2	9.401 (1.241-71.198)	0.030
TNM-N stage				
N1a	137	92.9	1	
Over N1a	78	90.7	1.358 (0.506-3.646)	0.544
Adjuvant C/T				
Yes	166	91.8	1	
No	49	93.3	0.857 (0.244-3.007)	0.809
Regimens				
Fluoropyrimidine	112	91.6	1	
Oxaliplatin	54	92.1	0.952 (0.293-3.093)	0.935

y: year; TTR: time-to-relapse; N: number; ASA score: Physical Status Classification System by American Society of Anesthesiologists; CEA: carcinoembryonic antigen; LV: lymphovascular; NLR: neutrophil to lymphocyte ratio; LN: lymph node; TNM: tumor (T), lymph node (N), and metastasis (M) staging system; T1: tumor invading submucosa; T2: tumor invading muscularis propria; N1a: metastasis in 1 regional node; Over N1a: includes N1b (metastasis in 2-3 nodes) and N2a (metastasis in 4-6 nodes); C/T: chemotherapy. * No convergence in the coefficient.

Table 5. Univariate and multivariate COX proportional hazards models for 10-year OS

Characteristic	N	5-y OS (%)	Univaiate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age (y)						
< 65	116	95.4	1		1	
≥ 65	99	85.6	5.796 (2.555-13.145)	< 0.001	2.672 (1.061-6.728)	0.037
Sex						
F	104	90.2	1			
M	111	91.4	1.456 (0.764-2.776)	0.254		
ASA score						
1	48	95.8	1		1	
2	114	91.7	3.788 (0.874-16.409)	0.075	1.833 (0.390-8.602)	0.443
3	53	81.8	11.630 (2.710-49.914)	0.001	2.946 (0.598-14.516)	0.184
CEA (ng/mL)						
≥ 5	31	86.7	1		1	
< 5	184	91.6	0.462 (0.225-0.948)	0.035	1.074 (0.468-2.463)	0.866
NLR						
≥ 2.87	41	77.1	1			
< 2.87	152	93.8	0.451 (0.227-0.898)	0.024	0.787 (0.372-1.664)	0.531
Cancer location						
Right colon	50	90.2	1			
Left colon	165	90.6	1.616 (0.677-3.857)	0.280		
Histology type						
Others	11	81.8	1			
Adenocarcinoma	204	91.4	0.917 (0.221-3.809)	0.905		
Histology grade						
Poorly	16	86.1	1			
Well/moderate	199	90.6	0.606 (0.215-1.707)	0.343		
LV invasion						
Absence	123	91.6	1			
Presence	92	89.8	1.025 (0.544-1.932)	0.938		
Perineural invasion						
Absence	201	90.2	1			
Presence	14	100.0	0.045 (0.000-17.055)	0.307		
Examined LN						
< 12	44	90.7	1			
≥ 12	171	91.0	0.573 (0.294-1.116)	0.101		
TNMT-stage						
T1	78	96.1	1		1	
T2	137	87.2	3.039 (1.272-7.259)	0.012	3.577 (1.245-10.276)	0.018
TNMN-stage						
N1a	137	90.2	1			
Over N1a	78	91.9	0.753 (0.381-1.487)	0.414		
Adjuvant C/T						
Yes	166	94.3	1		1	
No	49	79.3	4.964 (2.635-9.351)	< 0.001	3.244 (1.584-6.643)	0.001
Regimens						
Fluoropyrimidine	112	94.5	1			
Oxaliplatin	54	93.5	0.910 (0.292-2.834)	0.871		

y: year; TTR: time-to-relapse; N: number; ASA score: Physical Status Classification System by American Society of Anesthesiologists; CEA: carcinoembryonic antigen; LV: lymphovascular; NLR: neutrophil to lymphocyte ratio; LN: lymph node; TNM: tumor (T), lymph node (N), and metastasis (M) staging system; T1: tumor invading submucosa; T2: tumor invading muscularis propria; N1a: metastasis in 1 regional node; Over N1a: N1b (metastasis in 2-3 nodes) and N2a (metastasis in 4-6 nodes); C/T: chemotherapy.

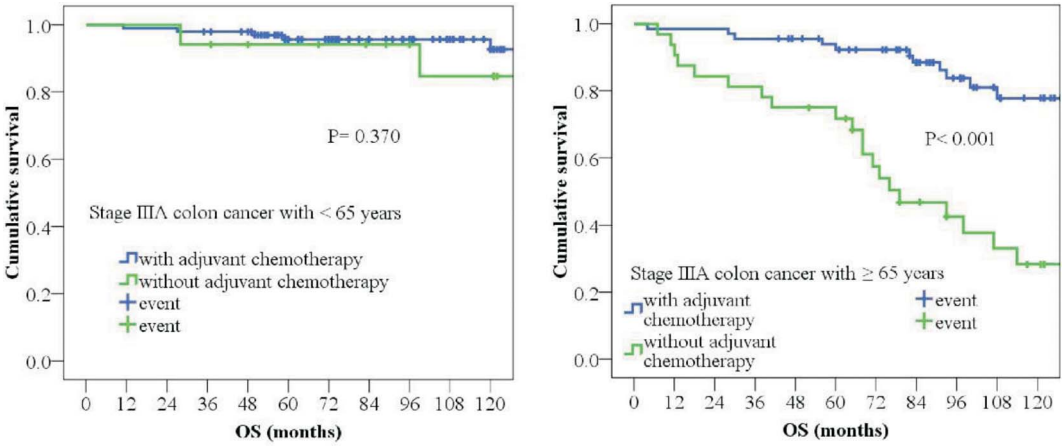

Fig. 2. The adjuvant chemotherapy (AC) group exhibited a significantly greater OS than the cancer-resection-only (CRO) group for patients aged ≥ 65 years; however, no survival difference was observed between the two groups for patients aged < 65 years.

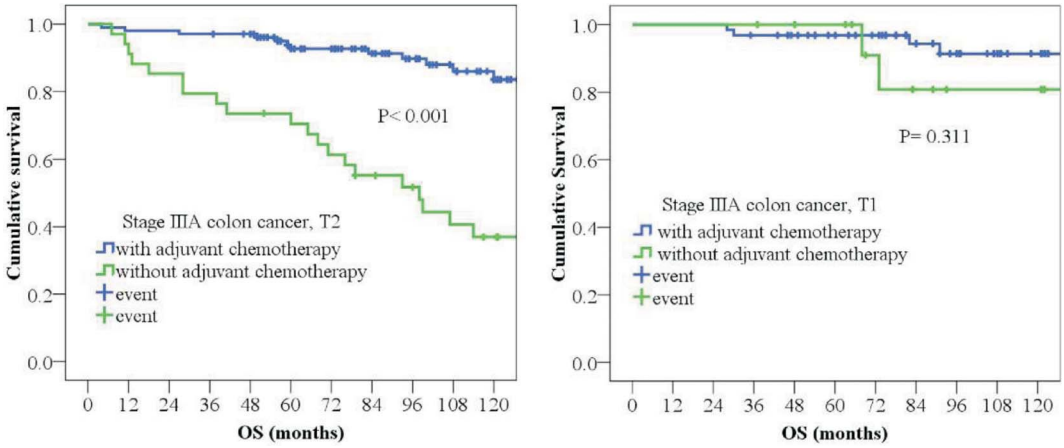

Fig. 3. The adjuvant chemotherapy (AC) group had a significantly greater OS for stage IIIA colon cancer with T2 stage than the cancer-resection-only (CRO) group; however, no survival difference was observed between the two groups for patients with T1.

lymph nodes. Postoperative adjuvant chemotherapy, either the FL regimen only or FL combined with oxaliplatin, has been demonstrated to reduce the risks of cancer relapse and death in patients with stage III colon cancer.[14-16] According to the AJCC treatment guidelines for stage III colon cancer, most patients with stage III colon cancer undergo postoperative adjuvant chemotherapy after curative surgery. However, limited evidence is available regarding the effect of adjuvant chemotherapy on survival in patients with stage IIIA colon cancer compared with those with stages IIIB and IIIC because stage IIIA colon cancer accounts for only 5%-11% of all stage III diseases in both the National Cancer Database and a single-institution database.[17,18] In this present study, 6.4% (215/3378) of our patients with stage III colon cancer had a status representative of stage IIIA.

The use of postoperative adjuvant chemotherapy for treating colon cancer with solitary lymph node metastasis was supported in a study of 281 patients with colon cancer who had solitary lymph node metastasis. Yeom et al.[19] reported that 5-year OS was significantly better in the postoperative chemotherapy group, but 5-year disease-free survival was similar between the chemotherapy and observation groups. The number of metastatic lymph nodes among the patients

in our study was higher than that in the study by Yeom et al. because stage IIIA colon cancer in our patients involved the metastasis of one to six lymph nodes (Table 1). Our results reveal a significant association between postoperative adjuvant chemotherapy and improved 10-year OS, indicating that adjuvant chemotherapy does not significantly affect 5-year TTR. Moreover, the effects of different chemotherapy regimens on TTR and OS in the AC group did not significantly differ. In 2020, Kim et al.[18] conducted the largest study on this controversial topic of the effect of adjuvant chemotherapy on RFS in patients with stage IIIA colon cancer. Kim found that postoperative adjuvant chemotherapy may not improve the RFS of patients.

The controversy regarding the effect of postoperative adjuvant chemotherapy on TTR and OS in stage IIIA colon cancer patients may result from various causes. First, stage IIIA colon cancer is composed of T1 and T2 stages. Our previous studies have revealed an association between different pathologies of the T stage and lymph node metastasis at the apical location. The rates of inferior mesentery artery (IMA) node metastasis in different T-stages were 0% (T1), 1.0% (T2), 2.6% (T3), and 4.3% (T4).[20] In the distribution of metastatic lymph nodes, Yeom et al.[19] documented that 85.1%, 13.5%, and 1.4% of stage III colon cancer with solitary lymph node metastasis were in the pericolic or epicolic, intermediate, and apical sites, respectively. Lymph node metastasis at the apical site poses a risk for patients with stage III colon cancer because patients with IMA node metastasis exhibit a high incidence of tumor relapse. However, IMA node metastasis is rare in patients with stage IIIA colon cancer because of the associated lower T stage. In the present study, only one patient had lymph node metastasis at the apical site (1 of 138 stage IIIA cancers with T2 stage). Most lymph node metastases only involved the pericolic region and were usually within 10 cm distal to the tumor site.[5] In other words, the region of lymph node metastasis in stage IIIA colon cancer is limited; thus, complete surgical resection is easily accomplished.

Second, the tumor invasive level (T stage), both T1 and T2, is lower in patients with stage IIIA colon cancer than in those with stages IIIB or IIIC. The tumor invasion depth was highly correlated with nodal involvement and the rates of extramural venous invasion, poor differentiation, and distant metastasis.[21] The depth of tumor invasion in T4 of the TNM stage was considered an independent factor for hepatic metastasis.[22] Even stage II colon cancer, which is locally advanced due to its T4 level, has been considered a risk factor requiring adjuvant chemotherapy.[23,24] Therefore, the survival paradox between colon cancer stages IIB and IIIA has been evident since the publication of the sixth edition of the AJCC staging system.

Tumor deposits are another marker used to investigate survival in stage III colon cancer after surgery. Tumor deposit rates were reported to be only 6.1% and 7.4% in the T1 and T2 stages, respectively, but 18.6% and 29.8% in the T3 and T4 stages, respectively.[25] Negtegaal et al.[26] noted an association between tumor deposits and extramural vascular invasion. Patients with stage IIIA colon cancer might have a lower incidence of cancer relapse, probably due to less invasiveness in the vascular route.

Finally, univariate and multivariate Cox regression models revealed that TTR was affected by a single independent factor: the T2 status of stage IIIA colon cancer. In contrast, a multivariate analysis showed that OS was affected by three independent factors: old age (≥ 65 years), T2 stage, and postoperative adjuvant chemotherapy. The differences in these independent factors were apparent between TTR and OS. The T2 stage could be used for predicting TTR and OS in stage IIIA colon cancer; however, adjuvant chemotherapy implementation was probably associated with physiological factors and the age of the patients. In the present study, patients in the CRO group tended to have hypertension, CVA, DM, CKD, and a high ASA score (≥ 3) in cancer surgery. All these comorbidities could influence the decision of the patient, family, and doctors to administer adjuvant chemotherapy.

The effect of adjuvant chemotherapy on OS was significant in patients with stage IIIA colon cancer with T2 status and in those who were > 65 years old. Conversely, the 10-year OS was similar in the AC and CRO groups for patients with T1 status and those aged < 65 years. Thus, older patients or those with many comorbidities might not have received postop-

erative adjuvant chemotherapy. Although colon cancer stage during diagnosis is a crucial determinant of oncological outcomes, comorbidities increase the complexity of cancer treatment and further affect patient survival.[27] This could explain the findings in this study, whereby older patients who did not receive adjuvant chemotherapy had worse 10-year OS but no significant difference in 5-year TTR. Future randomized control trials may be needed to provide definite answer for the origin of such discrepancy. However, no survival difference was noted in patients < 65 years old between those who did and did not receive adjuvant chemotherapy.

This study had some limitations. First, selection bias may have occurred because of the retrospective study design and because data were procured from a single institution. The data collection period or follow-up months for both arms was extensive. However, differences in the treatment strategy and staging system affected survival outcomes during the follow-up period; nonetheless, the detailed effects of these changes could not be analyzed in the present study. Second, we did not have microscopic data, e.g., tumor deposits, to support our findings. Additionally, the present study did not have data regarding tumor molecular subtypes, including microsatellite instability-high (MSI/dMMR) tumors, RAS, and *B-Raf* (*BRAF*) gene mutations. Although MSI/dMMR is a positive prognostic factor for stage II colon cancer after curative resection, the prognostic impact of MSI/dMMR status remains controversial in patients with stage III colon cancer who have received postoperative adjuvant chemotherapy.[28-30] Finally, the small sample size and size imbalance between the AC and CRO groups in this study are common challenges in stage IIIA colon cancer studies because of the relative rarity of this stage. Therefore, a large-scale multicenter study is warranted in future studies to evaluate the effect of adjuvant chemotherapy on the survival outcomes of patients with stage IIIA colon cancer.

Conclusions

Patients with stage IIIA colon cancer had relatively favorable outcomes. The present results suggest that postoperative adjuvant chemotherapy does not improve TTR at this stage. Improved OS is attributable to adjuvant chemotherapy and a relatively good physiological condition. Meanwhile, patients with poor physiological conditions may have a low likelihood of receiving adjuvant chemotherapy and a high risk of death due to their comorbidities.

Acknowledgments

We thank the Chang Gung Medical Foundation of Linkou for helping with data collection through their Cancer Registry. Wallace Academic Editing edited this manuscript.

Funding

No funding was received for this study.

Conflicts of Interest/Competing Interests

All authors declare no conflicts of interest.

Availability of Data and Material

Except in exceptional cases, such as identifiable data, the raw data supporting our findings can be shared and made available to other researchers upon reasonable request. These researchers can easily reanalyze the data, which we ensured would involve user-friendly software. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

CCC and HYH had full access to all the data in the study and were responsible for data integrity and data

analysis accuracy. Study concept and design: YHK and CCC. Data acquisition: all authors. Drafting of the manuscript: YHK and HYH. Critical revision of the manuscript for crucial intellectual content: CCC and YHK. Statistical analysis: YHK and JFY. Administrative, technical, and material support: CCC and JMC. Study supervision: CCC and YHK.

Ethics Approval

When patients received colorectal cancer treatment, their clinical and pathological data were collected prospectively in the Department of Colon and Rectal Surgery tumor registry. We obtained ethics approval from the Institutional Review Board of Chang Gung Memorial Hospital for accessing the tumor registry. IRB No.: 202301050B0. Further follow-up data for survival analysis were collected retrospectively from medical records or interviews. The informed consent requirement was waived since this study was a retrospective analysis.

Consent for Publication

This does not apply to this section because our report has no recognizable information.

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原　著

術後輔助化學治療對第 IIIA 期結腸癌復發率及存活率影響之分析

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根據美國癌症聯合委員會 (AJCC) 第七版分期系統，結腸癌第 IIB 期與第 IIIA 期患者的五年存活率存在矛盾 (分別為 72.2% 與 83.4%)。第 IIIA 期結腸癌患者因僅發生結腸周邊淋巴結轉移，癌症復發風險相對較低。此階段淋巴結轉移範圍有限，可透過手術完全清除。因此，本研究探討輔助性化療對第 IIIA 期結腸癌患者五年復發時間 (TTR) 的影響。研究分析 1995 至 2016 年間接受腫瘤切除的 215 名第 IIIA 期結腸癌患者。其中 137 人 (63.7%) 為 N1a (單一淋巴結轉移)、76 人 (35.3%) 為 N1b (二至三顆淋巴結轉移)、2 人 (0.9%) 為 N2a (四至六顆淋巴結轉移)。比較兩組治療方式：輔助化療組 (手術合併化療，n = 166) 與單純手術組 (n = 49)。單純手術組患者合併症比例顯著高於輔助化療組，且美國麻醉醫學會 (ASA) 生理狀態評分 ≥ 3 分者比例顯著較高 (40.8% vs. 19.0%, p = 0.007)。然而，兩組間五年復發時間 (TTR) 無顯著差異 (91.8% vs. 93.3%, p = 0.809)。Cox 回歸分析顯示，僅 T2 分期為影響組間復發時間的顯著因素 (p = 0.030)。此外，針對 T1 分期患者 (95.4% vs. 91.0%, p = 0.311) 或年齡低於 65 歲族群 (95.0% vs. 90.1%, p = 0.370)，輔助化療組與單純手術組的整體存活率亦無顯著差異。研究顯示第 IIIA 期結腸癌患者預後良好，而輔助性化療未能顯著改善五年復發時間。

關鍵詞　第三期 A 階段結腸癌、輔助性化療、復發時間、整體存活率。