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Original Article

Survival of Adjuvant Chemotherapy Among Elderly Patients with Stage II Colon Cancer

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SUMMARY

Background: There have been few previous studies regarding survival and predictive factors for elderly patients with stage II colon cancer who also undergo surgery. This study examined the effects of adjuvant chemotherapy (AC) on long-term survival among elderly patients with stage II colon cancer who underwent surgery.

Methods: This was a survival analysis study with a retrospective design. We reviewed the records of 98 elderly patients with adenocarcinoma of the colon who underwent a surgical intervention with curative intent from 2006 to 2013 at a teaching hospital in southern Taiwan. Some of those 98 patients also received AC, while others did not. The distant metastasis rates (DM rates), disease-free survival (DFS), deaths as a result of various causes, and overall survival (OS) rates of these two groups were studied.

Results: The patients treated with AC did not exhibit better recurrence rates, DM rates, DFS, or OS rates than the patients who did not receive AC (the no-AC patients). In terms of 5-year OS, there was no significant difference between the AC and no-AC patients ($p = 0.398$). Patients from whom the number of lymph nodes retrieved <12 exhibited significantly poorer OS A significant predictor of poorer DFS was a higher pathologic T stage. Moreover, patients treated with FOLFOX4 had not better outcomes than patients treated with 5-fluorouracil in terms of DFS and OS.

Conclusion: Our results indicated no significant difference in OS between elderly patients who received AC and those who did not.

1. Introduction

Cancer is an important global health issue, and colon cancer in particular is among the diseases with the greatest impact on health worldwide. Moreover, colon cancer is the cancer with the highest prevalence in Taiwan. A total of 15,140 people in Taiwan were newly diagnosed with colon cancer in 2013, and the number of new cases is increasing every year.[1] In 2013, 5265 people in Taiwan died from colorectal cancer.[1]

Clinical trials have not demonstrated that adjuvant chemotherapy (AC) improves the survival rates of patients with age-unspecified resected stage II colon cancer. Nevertheless, patients may receive this treatment despite its lack of proven benefit.[2] As such, the use of AC for stage II patients remains controversial, and the identification of reliable prognostic factors to aid in therapeutic decision making is crucial.[3] For stage II colon cancer, the effects of chemotherapy in general are still debated, and it is unclear whether the benefits of adjuvant therapy are consistent even across different patient subsets.[4] An increased lymph node harvest is recommended to improve survival rates, because a relationship between the number of lymph nodes retrieved from the surgical specimen and patient survival has been established. Similarly, tumors located in the sigmoid have been found to be associated with improved survival in stage II colon cancer.[5] These findings suggest that harvesting higher numbers of lymph nodes (L.N.) may have a therapeutic effect and may enhance survival.[6–8] Previous studies have also shown that age, sex, tumor site, TNM stage, lymphatic and

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vascular invasion, and presurgery carcinoembryonic antigen (CEA) levels > 5 ng/ml significantly affect prognosis, with the number of metastatic lymph nodes being an independent prognostic factor regardless of the examined number of L.N.[9,10] Patients with poorly differentiated histological grade cancer have been reported as having a significantly increased risk of death.[11,12] In another previous study, elderly patients were found to have experienced significantly higher hematological neutropenia and thrombocytopenia toxicity than younger patients.[13]

Nonetheless, even though colon cancer is one of the most common causes of cancer death in Taiwan, there have been few previous studies regarding survival and prognostic factors for elderly patients with stage II colon cancer who have undergone surgery. Therefore, this study examined how AC affects the outcomes of elderly patients with stage II colon cancer. We determined the effects of various prognostic factors on colon cancer survival rates and conducted an exploration of the role of oxaliplatin-based chemotherapy.

2. Materials and methods

2.1. Subjects

This retrospective study was conducted using data collected from 2006 to 2013. We retrospectively reviewed the records of 1994 consecutive patients diagnosed with colon cancer who had undergone curative resection surgery at a single medical center in southern Taiwan. Overall, 194 of these patients had stage II disease, and of these 194 patients, a total of 98 were over the age of 70. Those patients were stratified into two groups: an AC group and a non-adjuvant chemotherapy (no-AC) group. Any patients with microscopic positive margins, grossly positive resected margins, or residual disease after resection, as well as any patients with distant metastasis who only underwent local excision, were excluded. The follow-up time for all included patients was continued until December 31, 2013, or until the data cutoff date of December 31, 2013.

The chemotherapy regimen was developed from the National Comprehensive Cancer Network (NCCN) guideline.[14] In the AC group, the patients received 5-fluorouracil (5-FU)-based AC, and of these patients, 16 received FOLFOX4 (5-FU + oxalipatin) treatment and 28 received 5-FU treatment.

The 5-FU treatment was adopted from the de Gramont regimen. It consisted of 200 mg/m^2 of leucovorin administered as a 2-h infusion followed by IV infusion of 400 mg/m^2 of 5-FU and then IV continuous 600 mg/m^2 of 5-FU is infused over 22 h on Day 1–2. This treatment was also repeated on a bi-weekly basis over a total of 24 weeks.

The FOLFOX4 treatment consisted of oxaliplatin (Eloxatin) 2 h infusion plus de-Gramont 5-FU regimen. 85 mg/m^2 of IV oxaliplatin was administered over 2 h concurrent with the leucovorin only on Day 1. This treatment was repeated on a bi-weekly basis over a total of 24 weeks. All the drugs were administered in a 5% dextrose solution.

2.2. Data collection

The collected data for each patient included gender, Charlson comorbidity index score (CCI), pathological grading, pathologic T stage, tumor location, presurgery serum CEA level, perineural invasion, number of L.N. retrieved, cause of death, type of recurrent, and disease-free survival (DFS). Based on International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD-9), the CCI selected 19 diseases and weighted scores with each comorbidity after adjusting for relative risk.[15] Then a value for each disease was calculated to attain overall scores. The DFS was defined as the time from the first day of surgery to the first event of either evidence of recurrent any site or all the end points to overall survival (OS).

Among the included patients, some received AC while others did not. The follow-up time for each patient was defined as the interval between the date of diagnosis and the date of death, the date of the last contact with the patient or the patient's family members, or the data cutoff date of December 31, 2013. Survival was defined as the time from the date of diagnosis to the date of death or to the last follow-up for a censored patient. This study was approved by the institutional review board of Chi Mei Medical Center, Taiwan.

2.3. Analysis

All the data were analyzed using SPSS software (ver. 20.0). The associations between categorical variables were analyzed by using Pearson's χ^2 test, and continuous variables were analyzed by using *t*-test. Survival analysis, DFS analysis, and the univariate analysis were performed by using the Kaplan-Meier method and a log-rank test followed by a Cox proportional hazards regression model. Categorical variables showing significant association with patient survival were then placed in a multivariate Cox regression model to calculate adjusted hazard ratios along with their 95% confidence interval. The differences between groups were considered significant when the relevant p value was less than or equal to 0.05.

3. Results

3.1. Subject characteristics

The average age of the subjects was 75.88 (standard deviation = 3.96) years. Table 1 lists the patient characteristics. There were significant differences between the two groups in terms of pathologic grading and pathologic T stage.

3.2. Treatment outcomes

3.2.1. Cancer recurrence

All the patients were evaluated for treatment outcomes during the follow-up period. Nineteen patients were found to have a recurrence of cancer; fourteen of those patients were in the no-AC group and five of those patients were in the AC group. The rate of recurrence in the AC group was lower than that of the no-AC group, but the difference was not significant ($\chi^2 = 3.29$, $p = 0.070$). The types of cancer recurrence were divided into distant metastasis (DM) and local relapse. Fourteen patients had proven DM during the follow-up period, including five patients (11.4%) in the AC group and nine patients (16.7%) in the no-AC group. There was no significant difference between these DM rates ($\chi^2 = 0.56$, $p = 0.456$) for the two groups. With regard to local relapse, no case of local relapse occurred in the AC group, while five patients in the no-AC group suffered from a local relapse ($\chi^2 = 4.29$, $p = 0.038$).

3.2.2. Disease-free survival (DFS)

The median disease-free survival (DFS) of the AC group was longer than that for the no-AC group (40.00 months vs. 34.00 months).

Table 1
Patients characteristics between two groups of AC and no-AC (N = 98).

Variables	N (%)	Adjuvant Chemotherapy		*p*-value
		Yes (%)	No (%)	
No. of patients	98	44 (44.9)	54 (55.1)	
Gender				0.987
Male	58 (59.2)	26 (59)	32 (59.3)	
Female	40 (40.8)	18 (41)	22 (40.7)	
Charlson score				0.661
0–1	8 (8.1)	3 (6.8)	5 (9.2)	
2^{+}	90 (91.9)	41 (93.2)	49 (90.8)	
Pathologic grading				0.014[a]
Well differentiated	19 (19.4)	7 (15.9)	12 (22.2)	
Moderate differentiation	30 (30.6)	8 (18.2)	22 (40.7)	
Poor differentiation	49 (50.0)	29 (65.9)	20 (37.0)	
pT stage				
pT3	45 (45.9)	30 (55.6)	15 (34.1)	0.034[a]
pT4	53 (54.1)	24 (44.4)	29 (65.9)	
Tumor location				0.340
A-colon	2 (2)	2 (4.5)	0 (0)	
Cecum	14 (14.3).	5 (11.4)	9 (16.7)	
S-colon	74 (75.5)	32 (72.7)	42 (77.8)	
T-colon	4 (4.1)	2 (4.5)	2 (3.7)	
D-colon	4 (4.1)	3 (6.8)	1 (1.9)	
Presurgery serum CEA level				0.920
<5	82 (83.6)	37 (84)	45 (83.3)	
≥5	16 (16.4)	7 (16)	9 (16.7)	
Perineural invasion				0.821
Yes	5 (5.1)	2 (4.5)	3 (5.5)	
No	93 (94.9)	42 (95.5)	51 (94.5)	
Number of L.N. retrieved				0.663
<12	29 (29.5)	14 (31.8)	15 (27.7)	
≥12	69 (70.5)	30 (68.2)	39 (72.3)	

[a] $p \leq 0.05$.

3.2.3. Cause of death

As of the data cutoff date, 12 patients in the AC group and 10 patients in the no-AC group had died. In the AC group, one patient had died from a cancer-related cause, while 11 patients had died from treatment-related factors, including four patients with pneumonia, two patients with acute myocardial infraction (AMI), one patient with liver failure, three patients with port-A infection, and one patient with grade IV diarrhea. In the no-AC group, three patients had died from a cancer-related cause, while seven patients had died from operative factors, including six patients with infection and one patient with AMI. four patients out of six with infection died as a consequence of pneumonia, and two patients died as a consequence of operative wound infection. The causes of death were not significantly different between the two groups (cancer-related cause: $\chi^2 = 0.67$, $p = 0.411$; treatment-related factor: $\chi^2 = 2.34$, $p = 0.132$, respectively).

3.3. Survival analysis

3.3.1. Overall survival

In terms of 5-year OS, however, there was no significant difference between the AC and no-AC groups (75.3% vs. 79.2%, $p = 0.398$) (Fig. 1). That said, no survival benefit for AC treatment was observed among these elderly patients with stage II colon cancer.

3.3.2. Disease-free survival

In terms of 5-year DFS, there was no significant difference between the AC and no-AC groups. The patients who received AC did not exhibit significantly better DFS than the patients who did not (77.9% vs. 64.4%, $p = 0.127$) (Fig. 2).

3.3.3. Univariate analysis of overall and DFS survival

Univariate analysis showed that the pathologic T stage and the number of L.N. retrieved were significant factors affecting OS (Table 2). The patients with pathologic T4 stage had a significantly poorer overall survival compared to those with pathologic T3 stage ($p = 0.004$), and patients whose L.N. retrieved ≥12 had better survival than those whose L.N. retrieved <12 ($p < 0.001$). The univariate analysis showed that the pathologic grading ($p < 0.001$) and pathologic T stage ($p = 0.035$) significantly affected DFS.

3.3.4. Multivariate analysis for overall and disease-free survival

The Cox-proportional regression model was used to calculate hazard ratios (HRs) (95% CI) in terms of the pathologic T stage and number of L.N. retrieved for OS, as well as in terms of the pathologic T stage and the pathologic grading for DFS. Patients whose L.N. retrieved ≥12 improved the OS, when comparing to the reference group (L.N. retrieved <12) (HR: 0.23; 95% CI: 0.09–0.59). A high pathologic T stage was significantly associated with poorer DFS. Specifically, a high pathologic T stage was associated with an HR of 7.01 (95% CI: 1.89–26.0) compared with a low pathologic T stage. Table 3 shows these results.

3.3.5. Survival analysis for AC group

In the AC group, all the colon cancer patients received 5-FU-based AC, and of these patients, 16 received FOLFOX4 (5-FU + oxalipatin) treatment and 28 received 5-FU treatment. According to a multivariate analysis, the HRs for FOLFOX4 treatment compared with 5-FU treatment were 11.67 (95% CI: 2.54–53.59, $p = 0.002$) for OS and 11.77 (95% CI: 2.54–54.48, $p = 0.002$) for DFS (Table 4). The patients who received 5-FU treatment had better outcomes than the patients treated with FOLFOX4 in terms of OS and DFS.

4. Discussion

The results of our study indicate that there was no significant difference between the AC group and the no-AC group, both of which consisted of elderly patients with stage II colon cancer, in terms of 5-year OS ($p = 0.398$) and DFS ($p = 0.127$). Similarly, a previous study found that patients with stage II cancer who accepted AC exhibited no survival benefit from the AC.[16] In fact, AC treatment has even been found to be a negative factor for OS for colon cancer patients.[17]

The risks and benefits of AC for stage II disease have not been clearly defined in elderly patients. The decision to offer adjuvant therapy for stage II disease needs to be individualized to the circumstances of each specific patient and should be balanced against the possible risks of treatment-related toxicity.[4] Relatedly, the result of this study were consistent with those of a prior report which found that stage II colon cancer patients without high-risk features should not receive AC.[18]

The prognosis for a local relapse in the no-AC group was worse than the prognosis for a local relapse in the AC group. The AC treatment could prevent local relapse ($p = 0.04$), but treatment-related factors were major causes of death. The causes of death were diverse. Eighteen patients out of the 22 (81.81%) who died did so as a consequence of treatment, and 11 of those had received AC. Of course, it is unsurprising that surgery and chemotherapy would have some harmful effects. Perhaps further studies could be conducted to explore the other factors relating to quality of life, fatigue, side effects, etc.

We found that stage II disease was based on consensual prognostic factors (pT4), similar recent studies, and the depth of tumor

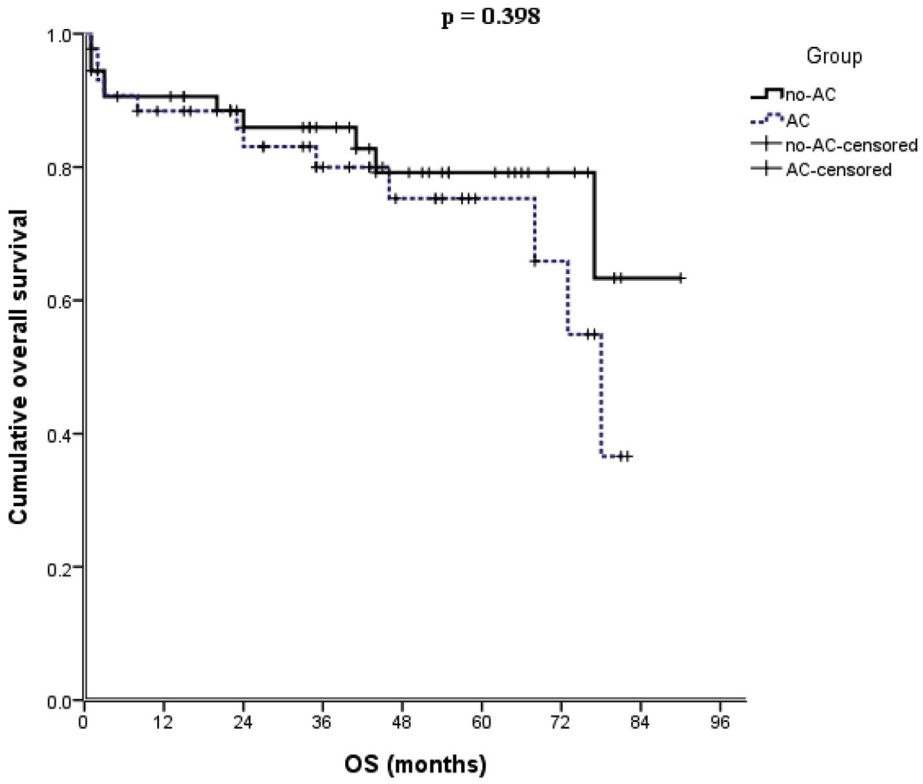

Fig. 1. Overall survival of AC patients vs no-AC patient.

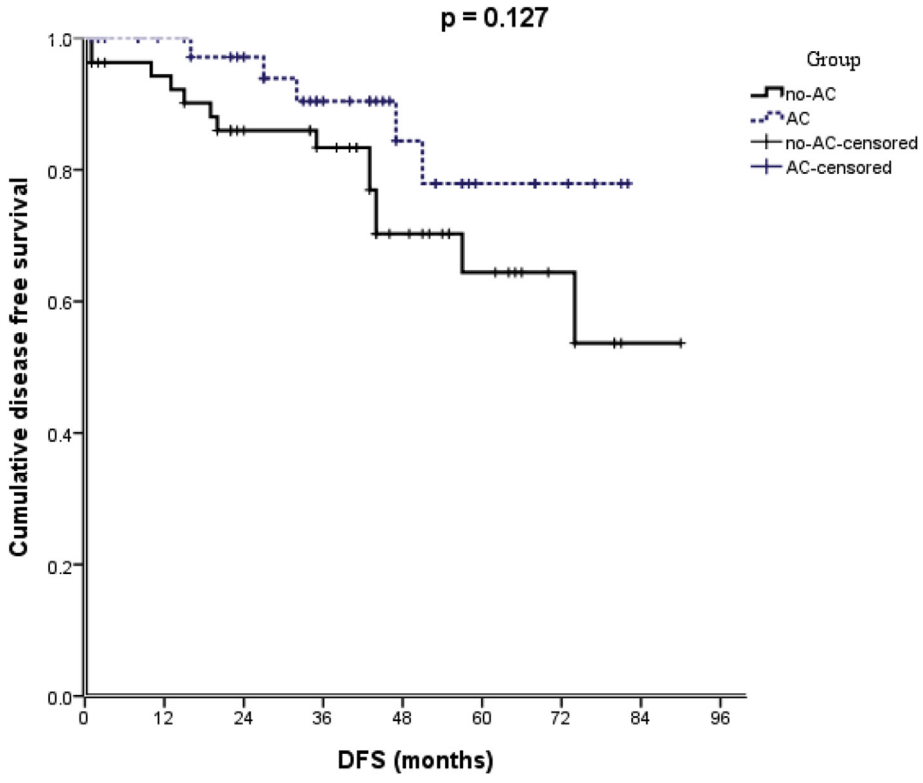

Fig 2. DFS in recurrent of AC group vs no-AC group.

invasion may prominently affect the prognosis of stage II patients after radical resection.[2,6,17] Patients from whom the number of L.N. retrieved $\geq$12 had better survival than those from whom the number of L.N. retrieved <12 ($p < 0.001$). This result was the same

Table 2
Univariable analysis of overall and DFS (N = 98).

Variables	n	Overall survival		Disease free survival	
		Survival %	*p*-value	Survival %	*p*-value
Gender			0.223		0.524
Male	58	83.6		67.0	
Female	40	69.6		86.8	
Charlson score			0.717		0.949
0-1	8	87.5		85.7	
2+	90	76.7		74.7	
Pathologic grading			0.706		<0.001[c]
Well differentiated	19	89.5		60.2	
Moderate differentiation	30	75.6		54.2	
Poor differentiation	49	73.6		94.1	
pT stage			0.004[b]		0.035[a]
pT3	45	92.9		62.6	
pT4	53	66.8		87.6	
Tumor location			0.175		0.857
A-colon	2	100		82.5	
Cecum	14	92.9		70.2	
S-colon	74	74.9		100	
T-colon	4	25.0		0	
D-colon	4	100		100	
Presurgery serum CEA level			0.140		0.110
<5	82	80.5		70.9	
≥5	16	60.2		100	
Perineural invasion			0.918		0.322
Yes	5	80.0		100	
No	93	77.4		74.3	
Number of L.N. retrieved			<0.001[c]		0.562
<12	29	53.2		77.8	
≥12	69	88.1		74.1	

[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.

as that of a previous study.[6–8] More specifically, it has previously been found that if the number of L.N. retrieved is at least 21, then that could increase OS.[8] That said, further research should be conducted to determine the optimal number of harvested lymph nodes. Histology grading has also previously been found to be predictive of treatment outcomes,[7] a finding which was also consistent with the results of the present study. The pathologic grading ($p < 0.001$) and the pathologic T stage ($p = 0.035$) significantly affected DFS. In other words, the characteristics of a tumor, especially the pathologic T stage, effectively decided the DFS.

In the present study, we found that elderly patients who received AC exhibited roughly the same OS as patients who received no AC. This finding was similar to those of a recent study which included adjuvant trials that compared 5-FU to combinations with irinotecan or oxaliplatin in stage II/III colon cancer.[19] Furthermore, that study found that among all the outcome measures, OS was statistically and significantly improved among young patients but not in elderly patients.[19] Even though chemotherapy in the adjuvant and metastatic setting clearly offers a survival benefit, elderly patients are frequently underrepresented in standard clinical trials that evaluate new cancer treatments, and markedly fewer trials are conducted that address the different risks and aims of treatment in the elderly population.[13,16] In addition, we also found a statistically significant high hazard (in terms of OS or DFS) from the addition of oxaliplatin to 5-FU as an adjuvant treatment, which suggests that ensuring the effectiveness of adjuvant therapy continues to be challenging, especially for elderly patients with stage II disease. In our hospital, the regimen of AC for stage II colon cancer was not standardized for elderly patients. Rather, the specific treatment administered depended on the given patient's physical and psychological status, as well as professional assessments. After all, chemotherapy has highly adverse effects,[20,21] and elderly patients are more fragile than younger groups. As such, an elderly patient's overall fitness for AC should always be considered.

Statistically significant benefits in terms of OS and DFS were not found for the addition of FOLFOX4 to 5-FU as an adjuvant treatment for elderly patients with stage II colon cancer. These findings were also consistent with those of a previous study of elderly colon cancer patients.[22] It thus appears that FOLFOX4 regimens could not decrease the risk of mortality for stage II colon cancer.

In conclusion, the results of this study indicated that whether the elderly patients investigated received AC or not, there was no significant difference in OS or DFS. As such, it is hoped that this elderly-specific clinical study will provide important clues and information regarding the treatment of this specific population.

Table 3
Cox-proportional regression model for pathologic T stage, grading and number of lymph nodes removed (N = 98).

Variables	Overall survival			Disease free survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Pathologic grading						0.247
Well differentiated				1	Referent	
Moderate differentiation				1.68	0.34–8.34	
Poor differentiation				0.68	0.14–3.29	
pT stage			0.074			0.004[a]
pT3	1	Referent		1	Referent	
pT4	3.15	0.90–11.12		7.01	1.89–26.0	
Number of L.N. retrieved			0.002[a]			
<12	1	Referent				
≥12	0.23	0.09–0.59				

[a] $p \leq 0.01$.

Table 4
Different regimens of Cox-proportional regression model in AC group (N = 44).

Variables	Overall survival			Disease free survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Regimen			0.002[a]			0.002[a]
5FU	1	Referent		1	Referent	
FOLFOX4	11.67	2.54–53.59		11.77	2.54–54.48	

[a] $p \leq 0.01$.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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