

Original Article

Use of Adjuvant Chemotherapy for Extremely Elderly Patients with Stage III Colorectal Cancer

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Key Words

Extremely elderly patient;
Colorectal cancer;
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Purpose. Although tumor resection surgery followed by adjuvant chemotherapy is the primary treatment for stage III colorectal cancer, the optimal protocol for patients aged ≥ 80 years remains unclear. Our study aimed to evaluate the long-term outcomes of adjuvant chemotherapy after tumor resection surgery in extremely elderly patients.

Methods. We retrospectively examined patients aged ≥ 80 years, who were diagnosed with stage III colorectal cancer following tumor resection surgery between 2009 and 2013 at the Taipei and Taichung Veterans General Hospital. Normally distributed data are presented as mean and assessed using Chi-square tests. We calculated 5-year overall survival by using the log-rank test. Multivariable proportional hazards regression analysis was used to determine independent risk factors for overall mortality.

Results. In total, 213 patients were analyzed and divided into two groups: complete ($n = 71$) or incomplete adjuvant chemotherapy ($n = 142$). The group of complete adjuvant chemotherapy had better 5-year overall survival (52.4% vs. 35.2%, $p = 0.003$). The timing of initial adjuvant chemotherapy after surgery was 6.86 weeks in average. Multivariate analysis showed that the independent prognostic factors were TNM stage and the receiving of complete adjuvant chemotherapy, or not ($p = 0.006$; $p = 0.001$).

Conclusion. Nearly half of the extremely elderly patients with stage III colorectal cancer didn't complete adjuvant chemotherapy. Those who received complete adjuvant chemotherapy showed higher overall survival in our study.

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Colorectal cancer is one of the most commonly diagnosed malignancies in developed countries.¹ According to the report from World Health Organization (WHO),² approximately 1.80 million individuals were diagnosed with colorectal cancer in 2018, and approximately 0.86 million patients died from colorectal cancer. In Taiwan, colorectal cancer is the most common cancer in males and second-most common cancer in females; additionally, it is the third leading

cause of cancer-related deaths.³ In 2016, there were 19,279 newly diagnosed cases of colorectal cancer in Taiwan, and the number of cases has annually increased since 2002.³ There were 5,722 deaths from colorectal cancer in Taiwan in 2016. According to the National Cancer Intelligence Network in the UK, most patients with colorectal cancer were aged > 70 years (approximately 60%).⁴ Therefore, the importance of treatment plans specifically designed for elderly pa-

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tients is increasing.

The survival benefit for younger patients with stage III colon cancer treated with 5-fluorouracil (5-FU)-based adjuvant chemotherapy is well-established.⁵ More recently, a report showed an equal benefit of 5-FU-based adjuvant chemotherapy for selected elderly patients with stage III colon cancer.⁶ Although adjuvant chemotherapy is recommended for patients with stage III colon cancer, a smaller proportion of elderly individuals with stage III colon cancer receive adjuvant chemotherapy.⁷ Reasons for this disparity include frailty, additional comorbidities, and the diminished life expectancy of extremely elderly patients. The survival benefit of adjuvant chemotherapy for patients with stage III colorectal cancer aged ≥ 80 years remains unclear; this study was designed to evaluate the benefits of chemotherapy in this elderly population.

Materials and Methods

We retrospectively examined 222 extremely elderly patients aged ≥ 80 years, who were treated at two hospitals, from January 2009 to December 2013. We included patients diagnosed with stage III colorectal cancer after tumor resection surgery at the Taipei Veterans General Hospital and the Taichung Veterans General Hospital. We divided the patient cohort into two groups according to the completeness of their adjuvant chemotherapy regimen (i.e., complete versus incomplete adjuvant chemotherapy groups). We defined complete adjuvant chemotherapy as receiving at least six courses of adjuvant chemotherapy or more than six months of adjuvant chemotherapy without interruption. The incomplete adjuvant chemotherapy group included patients who never received adjuvant chemotherapy and those who received fewer than six courses of chemotherapy. We excluded patients with in-hospital mortality from the analysis. In-hospital mortality was defined as death during hospitalization for tumor resection surgery.

Data were collected for all patients, including age, sex, comorbidities, ASA classification prior to surgery, tumor location, the type of surgery, pathological TNM staging, in-hospital mortality, the duration of

follow-up, and the final cause of death. Statistical analyses were conducted with IBM SPSS Statistics version 20. Normally distributed data are presented as mean and examined with chi-square tests. The survival time was defined as the time from surgery to death or latest follow-up day. We calculated overall 5-year survival for both groups and compared the results using the log-rank test. Multivariable proportional hazards regression analysis was used to determine independent risk factors for death of extremely elderly patients with stage III colorectal cancer, treated with or without adjuvant chemotherapy. *p* values less than 0.05 were considered statistically significant.

Results

Patients

We analyzed 222 extremely elderly patients (aged ≥ 80 years) who underwent tumor resection surgery and were diagnosed with stage III colorectal cancer. There were 136 patients from Taipei Veterans General Hospital and 86 from Taichung Veterans General Hospital. We excluded 9 cases of in-hospital mortality and evaluated the remaining 213 patients. There were 87 patients who did not receive any adjuvant chemotherapy. There were 126 patients who received at least one course of adjuvant chemotherapy. Of the 126 cases, 68 patients underwent at least six courses of adjuvant chemotherapy, or more than 6 months of chemotherapy without interruption. There were 31 patients receiving oxaliplatin-based chemotherapy and 37 patients receiving 5-Fluorouracil (5-FU)/Leucovorin or capecitabine. There were 58 patients who did not complete adjuvant chemotherapy, and the reasons for incomplete treatment are summarized in Table 1. One patient had the chemotherapy regimen changed from oral uracil-tegafur (UFUR) to oxaliplatin-based chemotherapy because of recurrence. There were two patients changed regimens from oxaliplatin-based chemotherapy to UFUR because of intolerable side effects, but went on to receive at least 6 months of additional treatments. These 3 patients were included in the complete chemotherapy group. The remaining

Table 1. Analysis of adjuvant chemotherapy in patients with stage III colorectal cancer aged > 80 years (n = 213)

No adjuvant chemotherapy	87
Completed adjuvant chemotherapy (≥ 6 courses/months)	68
Incomplete adjuvant chemotherapy (< 6 courses/months)	58
Lost to follow-up	20
Refused by patient or family	20
Documented side effects	6
Change regimen because of recurrence	2
Change regimen because of side effects	4
Unknown	6

cases who received fewer than six courses of adjuvant chemotherapy, and those who never received adjuvant chemotherapy were included in the incomplete chemotherapy group. Males comprised 63.38% of the incomplete chemotherapy group and 76.06% of the complete chemotherapy group ($p = 0.054$). Histological examinations revealed that most patients had moderately-differentiated adenocarcinoma (Table 2). Most patients were diagnosed with stage IIIB colorectal cancer (73.24% in the incomplete chemotherapy group and 78.87% in the complete chemotherapy

Table 2. Characteristics of patients with stage III colorectal cancer aged > 80 years according to adjuvant chemotherapy administration (n = 213)

	Incomplete adjuvant chemotherapy (n = 142)	Complete adjuvant chemotherapy (n = 71)	<i>P</i>
Age [years (range)]	85.17 (80-99)	83.05 (80-91)	0.069
Male	90 (63.38%)	54 (76.06%)	0.054
ASA score [n(%)]			
0-2	45 (31.69%)	27 (38.03%)	0.265
> 2	97 (68.31%)	44 (61.97%)	
Tumor location [n (%)]			
Right colon	54 (38.03%)	15 (21.13%)	0.216
Left colon	52 (36.62%)	41 (57.75%)	
Rectum	36 (25.35%)	15 (21.13%)	
Histology [n (%)]			
Adenocarcinoma	133 (93.66%)	69 (97.18%)	0.245
Mucinous adenocarcinoma	7 (4.93%)	2 (2.82%)	
Signet cell carcinoma	1 (0.70%)	0	
Mixed adenoneuroendocrine carcinoma	1 (0.70%)	0	
Grade of differentiation			
Well	2 (1.41%)	0	0.523
Moderate	118 (83.10%)	65 (91.55%)	
Moderate to poor	13 (9.15%)	2 (2.82%)	
Poor	9 (6.34%)	4 (5.63%)	
T [n (%)]			
1	1 (0.70%)	1 (1.40%)	-
2	16 (11.27%)	2 (2.82%)	
3	103 (72.54%)	54 (76.06%)	
4a	12 (8.45%)	8 (11.27%)	
4b	10 (7.04%)	6 (8.45%)	
N [n (%)]			
1	100 (70.42%)	50 (70.42%)	-
2	42 (29.58%)	21 (29.58%)	
Stage [n (%)]			
IIIA	14 (9.86%)	2 (2.82%)	-
IIIB	104 (73.24%)	56 (78.87%)	
IIIC	24 (16.90%)	13 (18.31%)	
Emergent operation	24 (16.90%)	9 (12.68%)	0.424
Causes of emergent operation (n)			
Perforation	4	1	-
Obstruction	22	9	
Minimally invasive surgery [n (%)]	44 (30.99%)	23 (32.39%)	0.836

group). There was no significant between-group difference for the percentage of emergent procedures and minimally invasive surgery (Table 2).

The mean duration between surgery and initial adjuvant chemotherapy was 6.86 weeks. The mean duration was 6.19 weeks in the complete adjuvant chemotherapy group and 7.80 weeks in the incomplete group.

Survival outcomes

Five-year overall survival was significantly better in those who received complete adjuvant chemotherapy ($52.4 \pm 6.6\%$) than in those who received incomplete adjuvant chemotherapy ($35.2\% \pm 4.6\%$; $p = 0.003$) (Fig. 1). Multivariate proportional hazards regression analysis revealed that the independent prognostic factors were TNM stage and the receiving of complete adjuvant chemotherapy, or not (Table 3).

Discussion

Previous studies about clinical decision making

Table 3. Multivariate survival analysis for patients with stage III colorectal cancer aged > 80 years (n = 213)

	Hazard ratio (95% CI)	<i>p</i>
Gender	1.375	0.147
ASA		
0-2	1.000	0.757
> 2	1.062	
Tumor location		
Right colon	1.000	0.588
Left colon	1.227	
Rectum	0.979	
TNM stage		
IIIA	1.000	0.006
IIIB	1.090	
IIIC	1.304	
Emergent operation	1.006	0.470
Complete adjuvant chemotherapy	0.465	0.001

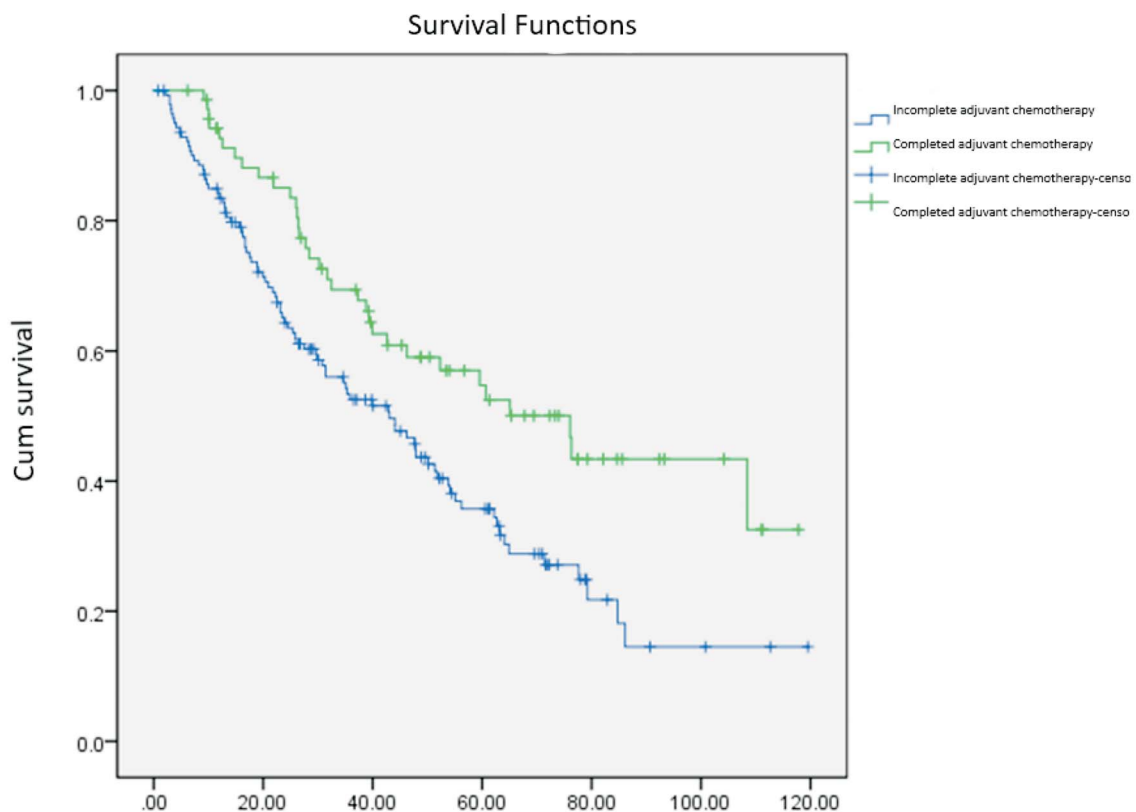


Fig. 1. Overall survival in patients with stage III colorectal cancer aged ≥ 80 years according to adjuvant chemotherapy (n = 213) ($p = 0.003$).

regarding chemotherapy demonstrate that elderly patients are more unwilling to receive adjuvant chemotherapy because of side-effect-related concerns, including potential negative effects on quality of life.^{8,9} We found that approximately 40% of patients with stage III colorectal cancer aged ≥ 80 years did not receive adjuvant chemotherapy after tumor resection surgery. For those who had ever received adjuvant chemotherapy, more than 40% discontinued treatment before finishing six courses or six months of chemotherapy. The most common reasons for discontinuing adjuvant chemotherapy were loss to follow-up at OPD and treatment refusal (either patient or family). No major complications were documented and fewer than 5% of the patients who received adjuvant chemotherapy in our study changed the regimen for any reason.

In our study, the characteristics of the patients in the complete adjuvant chemotherapy group were similar to those in the incomplete adjuvant chemotherapy group. There were no significant between-group differences with respect to ASA score, tumor location, TNM staging, emergent operation, or minimally invasive surgery. The most common reason for emergent surgery was intestinal obstruction. In our study, only 5 patients who received emergent surgery presented with colonic perforations.

In 1990, 5-FU-based adjuvant chemotherapy was found to reduce the rate of recurrence compared with surgery only for stage III colorectal cancer.¹⁰ The MOSAIC trial and NSABPC-07 revealed a better overall survival rate with the addition of oxaliplatin for patients with stage III colorectal cancer. Sanoff et al. reported that 5-FU-based adjuvant chemotherapy showed a significant survival benefit compared with surgery only in a cohort study with 5489 patients aged ≥ 75 years with stage III colorectal cancer.¹¹ However, for elderly patients aged ≥ 80 years, there was limited evidence of the benefit of adjuvant chemotherapy.

A previous study showed that, for every 4-week delay in chemotherapy, there is a 14% decrease in overall survival.¹² According to NCCN guideline version 1.2018,^{13,14} adjuvant chemotherapy should be administered as soon as the patient is able to medically tolerate it. In our study, the mean duration of administering adjuvant therapy was less than 8 weeks. Only 5

patients in our study had initial adjuvant chemotherapy after more than 100 days of surgery.

In our study, patients with stage III colorectal cancer aged ≥ 80 years who completed adjuvant chemotherapy had better overall survival than those with incomplete adjuvant chemotherapy or surgery only. The 5-year survival rate of the complete adjuvant chemotherapy group was $52.4 \pm 6.6\%$. The multivariable proportional hazards regression analysis also showed similar results.

Our study had several limitations. First, this study was retrospective; patient cohort from two medical centers was limited. Second, owing to the small cohort size, the survival benefit between the different chemotherapy regimens was difficult to evaluate. Also, the influence of neoadjuvant chemoradiotherapy was difficult to show in our study due to limited case number. There were only 4 rectal cancer patients who received neoadjuvant chemoradiotherapy. Two of them were concluded in complete adjuvant chemotherapy group, and the other two cases were in incomplete adjuvant chemotherapy. Third, we were unable to assess the influence of different tumor locations. This may also have been caused by the small patient cohort. Finally, data pertaining to microsatellite instability, gene mutation, and protein expression were not included. With the rapid progression in the management of colorectal cancer, further evaluations are needed to determine more specific and personalized treatment plans.

Conclusions

For patients with stage III colorectal cancer, tumor resection surgery with adjuvant chemotherapy is the standard treatment. However, fewer patients with stage III colorectal cancer aged ≥ 80 years receive adjuvant chemotherapy. Our study showed an overall survival benefit for patients with stage III colorectal cancer aged ≥ 80 years who received more than six courses of adjuvant chemotherapy. Future studies should analyze the effects of MSI, gene presentation, and protein expression in these extremely elderly patients.

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原 著

術後化學治療於第三期結腸直腸癌之 極老年患者的分析

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第三期結腸直腸癌的治療方法目前以腫瘤切除手術合併術後化學治療為主，但對於年齡大於八十歲患者的最佳治療方法仍未確定。本研究旨在評估術後化學治療對於接受腫瘤切除手術後確診為第三期結腸直腸癌患者的療效。這項回顧性研究收錄 2009 年至 2013 年間在台北榮民總醫院及台中榮民總醫院接受結腸直腸癌腫瘤切除手術的老年患者。正態分佈數據以平均值表示，並用 chi-square 檢驗進行檢驗。兩組病患五年存活率以 log-rank test 表示，死亡率相關因子也進行多變相分析。共收錄 222 名老年患者，排除 9 位發生術後一個月內死亡病患，其餘病患分為完成術後化療，及未接受或未完成術後化療兩組，分別有 71 位及 142 位。研究顯示完成術後化學治療病患有較高的整體存活率 (52.4% vs. 35.2%, $p = 0.003$)。病患平均於術後 6.86 周開始接受化學治療。多變項分析顯示 TNM 分期及是否完成術後化療為獨立預測因子 ($p = 0.006$; $p = 0.001$)。將近一半的八十歲以上第三期大腸直腸癌患者無法完成術後化療療程。完成化療療程在八十歲以上病患可見較高整體存活率。

關鍵詞 老年人、結腸直腸癌、術後化學治療。