Original Article

Adjuvant Chemotherapy for Stage III Colorectal Cancer in Elderly Patients

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Key Words
Colorectal cancer;
Adjuvant chemotherapy;
Elderly patient

Background. Adjuvant chemotherapy is a standard treatment for stage III colorectal cancer patient under curative surgery. Since the toxicity of chemotherapy, the benefit of chemotherapy has been doubtful for elderly patients. This study evaluates the survival benefit of adjuvant chemotherapy in elderly patients.
Methods. A total of 448 stage III colorectal cancer patients receiving curative surgery from April 2004 to December 2007 were enrolled. The primary outcome was post-operative disease-free survival (DFS) and overall survival (OS). The toxic effects measured during adjuvant chemotherapy include neutropenia, thrombocytopenia, anemia and infection event.
Results. There were 241 patients younger than 70 and 207 patients older than 70. In the younger group, the 5-year disease-free survival (DFS) was slightly higher in the patients with adjuvant chemotherapy (5-year DFS: 62.1% vs. 33.3%, $p = 0.095$), and the 5-year overall survival (OS) was significantly higher (5-year OS: 77.9% vs. 50.0%, $p = 0.026$). However, in the older group, the 5-year OS was significantly higher in the adjuvant chemotherapy group (64.6% vs. 40.9%, $p = 0.013$), but the 5-year DFS showed no difference (55.6% vs. 49.8%, $p = 0.668$). The frequency of hematologic toxicity, such as anemia and neutropenia, was significantly higher in the older patients with intravenous chemotherapy.
Conclusion. The effect of adjuvant chemotherapy in elderly patients with colorectal cancer was equivocal. Careful patient selection is necessary. Increased hematologic adverse events were observed in elderly patients with intravenous chemotherapy; close monitoring is necessary to avoid severe adverse events.
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Colorectal cancer is the most common cancer in Taiwan currently, with the highest occurrence among cancers since 2006. In total, 14,087 new cases were registered in the database of Ministry of Health and Welfare in 2011.[1] Colorectal cancer is also the third most common cause of cancer death in Taiwan.[2] The chance of colorectal cancer increases with age after 40 years old.[3] The improvement in life expectancy of the general population has increased the number of elderly patients with colorectal cancer. Currently, the median age of colorectal cancer patients in Taiwan is 66 years old.

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Adjuvant chemotherapy with regimen of Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX) is considered a standard treatment for the patients of stage III colorectal cancer because of the improvement of disease free survival. The effect has been established through randomized trials.[4,5] According to previous research, adjuvant chemotherapy is as effective in elderly patients as in young patients.[6-9] On the other hand, acceptable adverse effects of the chosen regimen are inevitable. Elderly patients received less adjuvant chemotherapy than younger patients because the possibility of toxicity increases with age.[10] However, limited data is available about the risk and benefit of specific regimens for elderly patients.[11-14] The purpose of this single institute study is to compare the safety and efficacy of adjuvant chemotherapy in patients who are younger and those older than 70 years old.

Materials and Methods

Patients and clinical findings

As a retrospective study, 502 TNM stage III colorectal cancer patients who underwent curative surgery at the Taipei Veterans General Hospital from April 2004 to December 2007 were initially enrolled in this study. The following duration ranged from 4 to 107 months, and the median was 62.40 months. Before surgery, surveillance procedures, including colonoscopy and computed tomography from the abdominal cavity to the pelvis were performed. Patients excluded from this study included 26 rectal cancer patients who received preoperative chemoradiotherapy, 7 patients who had liver or lung metastasis within 3 months, and 21 patients who had follow-up less than one year. All clinical characteristics were recorded. The disease stage and important pathological features of the tumors were recorded according to the Tumor Node Metastasis classification system of the American Joint Committee on Cancer and International Union Against Cancer.[15] After surgery, the patients were monitored every 3 months in the first 2 years and every 6 months thereafter. Imaging studies including chest radiography, abdominal ultrasonography and computed tomography were performed at least every 6 months. Follow-up colonoscopy was performed 6 months to 1 year after the surgery and every 1 to 2 years thereafter.

Chemotherapy

According to the status of adjuvant chemotherapy, the patient was classified as 1) patients who received fluorouracil (5-FU) based intravenous chemotherapy, including the regimen of **5-fluorouracil plus Leucovorin** or **FOLFOX4**, 2) patient who received oral chemotherapy, including **Xeloda** (oral Capecitabine) or **U-fur plus Folica**, 3) patients who did not receive any adjuvant chemotherapy. These patients were assessed before starting each 2-week cycle and the chemotherapy would be delayed if neutrophils decreased to less than 1,500 cells/cumm or platelets decreased to less than 100,000 cells/cumm or when significant nonhematologic toxicity was detected.

Study purpose

The primary outcome of the analyses was disease-free survival (DFS) and overall survival (OS) from the date of surgery. The disease-free survival was calculated from the date of operation to disease recurrence. The overall survival was calculated from the date of operation to death of patient. The toxic effects monitored during adjuvant chemotherapy included 1) neutropenia, if the absolute neutrophil count was less than 1500/cumm, 2) thrombocytopenia, if the platelet count was less than 75,000/cumm, 3) Anemia, if Hemoglobin was less than 10 g/dL; 4) infection events, if there were any infection episode during the interval of chemotherapy, mandatory admission or intravenous antibiotics therapy.

Statistical analysis

All data was recorded as a standard data form and was analyzed with SPSS. (version 16.0 for Windows, SPSS, Chicago, IL, USA). Quantitative values were compared with t-test for independent groups. The survival curves were constructed with the Kaplan-Meier method and the survival differences were compared

with the log-rank test. Hazard ratios (OR) and 95% confidence intervals (CI) were calculated. The level of statistical significance was set at $p < 0.05$. All reported p values are two-tailed.

Results

A total of 448 stage III colorectal cancer patients who underwent curative-intent surgery were enrolled in this study. The patient population was composed of 241 patients aged younger than 70 years old (range, 27-69 years; median, 58 years) and 207 patients aged older than 70 years old (range, 70-94 years; median, 77 years). In the younger group, 201 (83.4%) patients received intravenous chemotherapy, 32 (13.3%) patients received oral chemotherapy, and only 8 (3.3%) patients did not receive any adjuvant chemotherapy. In the older group, 114 (55.2%) patients received intravenous chemotherapy, 40 (19.3%) patients received oral chemotherapy, and 53 (25.5%) patients did not receive adjuvant chemotherapy. Obviously, more patients did not receive adjuvant chemotherapy in the older group. The clinical characteristics are listed in Table 1.

According to the univariate analysis (Table 2), in the younger group, the 5-year disease-free survival (DFS) was slightly higher in the patients with adjuvant chemotherapy (5-year DFS: 62.1% vs. 33.3%, $p = 0.095$), and the 5-year overall survival (OS) was significantly higher (5-year OS: 77.9% vs. 50.0%, $p = 0.026$) (Fig. 1).

In the older group, the 5-year OS in patients receiving chemotherapy was 64.6 %, which was significantly higher than in patients without adjuvant chemotherapy (40.9%, $p = 0.013$); however, the 5-year DFS of the older group did nott reach statistical significance. (55.6% vs. 49.8% of the control group, $p = 0.668$) (Fig. 1).

The rate of adverse events for patients with intravenous chemotherapy or oral chemotherapy is listed in Table 3, according to different age groups. Older patients with oral chemotherapy did not report more adverse events than the younger group. However, among the patients receiving intravenous chemotherapy, the frequency of neutropenia (15.7% vs. 8.4%; $p = 0.038$) and anemia (21.1% vs. 8.5%; $p = 0.003$) was significantly higher in the older group.

Discussion

The improvement in life expectancy of the general population has resulted in a higher number of elderly patients with colorectal cancer. It is more challenging for clinical physicians to select appropriate treatment modality for elderly patients. It is necessary to find a balance between the risk and the advantage of adjuvant chemotherapy for elderly patients. The primary care physicians may hesitate about recommending

Table 1. Clinical characteristics of stage III colorectal cancer patients receiving curative resection according to age group

	Number	Age < 70 y/o	Age ≧ 70 y/o	*p*-value
Patients, n		241	207	
Age (yr)		58 (27-69)	77 (70-94)	
Gender				
Male	271	121 (50.2%)	150 (72.5%)	< 0.001
Female	177	120 (49.8%)	57 (27.5%)	
Location				
Colon	290	152 (63.1%)	138 (66.7%)	0.381
Rectum	158	89 (36.9%)	69 (33.3%)	
Chemotherapy				
No chemotherapy	61	8 (3.3%)	53 (25.5%)	< 0.001
IV chemotherapy	315	201 (83.4%)	114 (55.2%)	
Oral chemotherapy	72	32 (13.3%)	40 (19.3%)	

n = the number of individuals examined.

Table 2. Univariate analysis for 5-year disease-free survival (DFS) and overall survival (OS)

Variable	Number	5-year DFS (%)	*p* *	Hazard ratio (95% CI)	*p* **
Age < 70 y/o					
No Chemotherapy	8	33.3	0.095	1.0	0.145
Chemotherapy	233	62.1		0.475 (0.193-1.170)	
Age ≧ 70y/o					
No Chemotherapy	53	49.8	0.668	1.0	0.671
Chemotherapy	154	55.6		0.900 (0.554-1.461)	

*Log-rank test.

Variable	Number	5-year OS (%)	*p* *	Hazard ratio (95% CI)	*p* **
Age < 70 y/o					
No Chemotherapy	8	50.0	0.026	1.0	0.068
Chemotherapy	233	77.9		0.333 (0.120-0.923)	
Age ≧ 70y/o					
No Chemotherapy	53	40.9	0.013	1.0	0.019
Chemotherapy	154	64.6		0.566 (0.359-0.894)	

*p**: log-rank test.
*p***: cox-regression test.

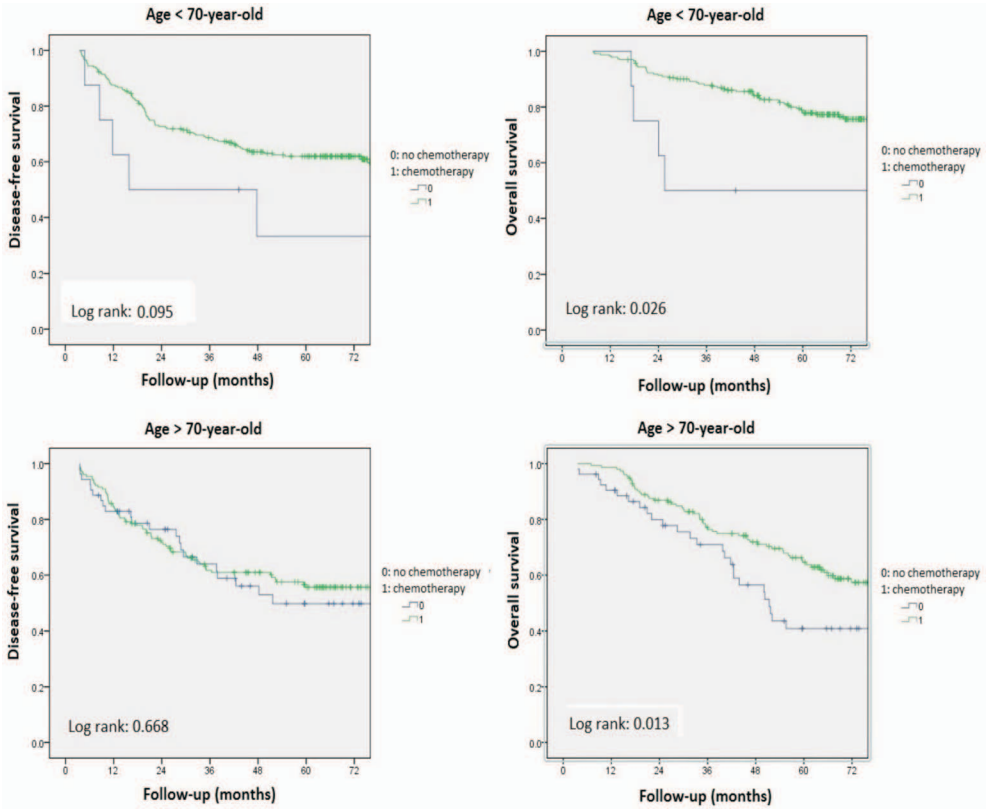

Fig. 1. Comparison of disease-free survival and overall survival according to chemotherapy and different age group.

chemotherapy for elderly patients for some reasons, such as the patient's rejection or major concomitant diseases. In our study, 53 patients (25.5%) did not receive adjuvant therapy in the older group, and 40 pa-

Table 3. Frequency of patients treated with FOLFOX4 who experienced NCI-CTCAE all grade adverse events

Adverse events	Patients received IV chemotherapy (N = 315)			Patients received oral chemotherapy (N = 72)		
	Age < 70 N = 201 (100%)	Age ≧ 70 N = 114 (100%)	*p value	Age < 70 N = 32 (100%)	Age ≧ 70 N = 40 (100%)	*p value
Neutropenia	16 (8.4%)	18 (15.7%)	0.038	0 (0.0%)	2 (5.0%)	0.499
Thrombocyto-penia	17 (8.5%)	6 (5.3%)	0.371	0 (0.0%)	2 (5.0%)	0.499
Anemia	17 (8.5%)	24 (21.1%)	0.003	2 (6.3%)	7 (17.5%)	0.282
Infection	9 (4.4%)	7 (6.1%)	0.596	1 (3.1%)	0 (0.0%)	0.444

* p value: Fisher exact test (two-tailed).

tients (19.3%) chose oral chemotherapy as an alternative. In contrast, only 8 patients (3.3%) did not receive adjuvant therapy in the younger group.

In our study, adjuvant chemotherapy remained effective in the younger group, with the improvement of overall survival and disease free survival. However, in the older group, the benefit of adjuvant chemotherapy was not as significant as that in the younger group in terms of disease-free survival. The improvement of overall survival in elderly patients may be due to selection bias. The patients who received adjuvant chemotherapy generally were in better condition and performance status. Therefore these people could endure the whole course of adjuvant therapy and even the salvage therapy, in the event of disease recurrence. The salvage chemotherapy or surgery of metastatic site for recurrent patients also could prolong overall survival of patients. On the other hand, Sargent D. et al. stated that the probability of death without recurrence of cancer was strongly associated with age.[16] There were 14 patient (6.8%) died without detectable cancer in the older group, whereas those younger than 70 years old had only one (0.4%) death without detectable cancer. Death of older patients was probably due to causes other than cancer, before disease recurrence occurred.

Oral chemotherapy is recommended for patients who are hesitative of or unable to tolerate intravenous chemotherapy. It remains effective in prolonging survival and even has the potential to replace 5-FU/LV as a standard adjuvant treatment in some study.[10] In fact, the subgroup of oral chemotherapy showed better results (5-year DFS: 79.8% vs. 59.2%, $p = 0.025$; 5-year OS: 85.6% vs. 76.7%, $p = 0.167$) than those of intravenous chemotherapy in the younger patients. However, there was an obvious selection bias in that the physicians tend to choose oral chemotherapy for low-risk stage III patients, such as those with scant metastatic lymph node numbers or without any specific pathological characteristics. The result of intravenous chemotherapy in the older group was slightly better than that of oral chemotherapy, but the difference was not statistically significant. A pooled analysis from Goldberg RM. et al. stated that FOLFOX4 maintains its efficacy and safety ratio in selected elderly patients with colorectal cancer. Its judicious use should be considered without regard to the patient's age.[5] The difference between intravenous chemotherapy and oral chemotherapy was not obvious in our study, which may be attributable to the limited number of patients in each subgroup.

The second concern is whether adjuvant chemotherapy will induce severe adverse events in elderly patients. Overall, the analysis showed similar adverse effect patterns in the two age groups. Hematologic adverse events, especially anemia and neutropenia were slightly more common in the older group with intravenous chemotherapy. Regular monitoring of blood routine data and prolonged interval of chemotherapy for intolerable patients would be necessary.

The major limitation of this study is the limited number of patients in each subgroup. Second, this retrospective analysis was based on medical records and some clinical information and the data was not completely detailed. Some patients received an incomplete course of chemotherapy, which may interfere with the result of adjuvant chemotherapy, but the information was not available in our database. There was also no detailed data of comorbidity or performance status of the patients. Thus, there could be selection bi-

ases when assigning patients to the adjuvant chemotherapy group or other alternatives.

Conclusion

The effect of adjuvant chemotherapy in elderly patients with colorectal cancer was equivocal as it may not be suitable for every patient. Through careful patient selection, the elderly patients can reach the same treatment effect as the younger patients. Increased hematologic adverse events were observed in elderly patients with intravenous chemotherapy. However, these events were detectable and could be avoided by close monitoring.

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原　著

輔助性化學治療在第三期大腸直腸癌老年病患之分析

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目的　輔助性化學治療在術後的第三期大腸直腸癌病患已是標準治療。由於化學治療本身有毒性，對老年病患是否有益令人存疑。這項研究評估輔助性化學治療在老年病患的存活效益。

方法　從 2004 年 4 月至 2007 年 12 月，共 448 位接受過治癒性手術的第三期大腸直腸癌病患。研究的主要目標是無病存活率及整體存活率，並評估病患接受輔助性化學治療期間所發生的副作用，包括嗜中性球低下、血小板低下、貧血及感染事件。

結果　共計 241 位年紀在 70 歲以下的病患，以及 207 位年長於 70 歲的病患。在年輕的病患方面，接受過輔助性化學治療者的五年無病存活率較高 (62.1% vs. 33.3%, p = 0.095)，五年整體存活率明顯較好 (77.9% vs. 50.0%, p = 0.026)。在年長者這組，接受輔助性化學治療者的五年整體存活率明顯較佳 (64.6% vs. 40.9%, p = 0.013)，但五年無病存活率無顯著差異 (55.6% vs. 49.8%, p = 0.668)。接受輔助性化學治療的老年病患發生血液學方面副作用，如貧血及嗜中性球低下者的頻率明顯較高。

結論　輔助性化學治療在老年大腸直腸癌病患的效益仍有疑義，需要慎選病患。老年病患在血液學方面相關的副作用較高，必須密切監測以避免嚴重副作用。

關鍵詞　大腸直腸癌、輔助性化學治療、老年病患。