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The efficacy of oxaliplatin combination adjuvant chemotherapy for elderly patients with stage III colorectal cancer

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ABSTRACT

Now we are facing to aging society. We aimed to determine the long-term outcomes receiving adjuvant chemotherapy among elderly patients with stage III colorectal cancer. Elderly patients ($\geqq 65$ years, n=91) diagnosed as stage III colorectal cancer and received adjuvant chemotherapy were retrieved from the database and classified into two groups according to whether the patient received monotherapy (n=65) or doublet therapy(n=26). Recurrence-free survival and overall survival were compared between the groups. To balance the essential variables, we conducted propensity score matching. After one-to-one propensity score matching, each group consisted of 22 patients. No significant difference was detected by comprehensive geriatric assessment 7. Overall survival was significantly longer in the monotherapy group. Adverse events occurred more frequently in the doublet therapy group. Monotherapy may improve the long-term outcome of elderly patients while the adverse events were less frequent.

Keywords: colorectal cancer, elderly, adjuvant chemotherapy, prognosis, adverse events

INTRODUCTION

Colorectal cancer is the third commonest cancer in the world with over 1,800,000 new cases in 2018[1]. National Comprehensive Cancer Network guideline recommends adjuvant chemotherapy for stage III colorectal cancer patients after curative resection to prevent recurrence and to improve prognosis[2]. Although an oxaliplatin-containing doublet therapy for 6 months has been recommended as the standard of care (category1), there are other treatment options such as fluorouracil-based monotherapy for 6 months and a combination of capecitabine and oxaliplatin for 3 month (category2)[3]. Under such circumstances, doublets may not be suitable for the vulnerable elderly patients[4,5]. Moreover, a benefit for the addition of oxaliplatin to fluorouracil in patients aged 70 years and older has not been proven[6-8], while some observational studies

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based on large database demonstrated efficacy of monotherapy[4,9,10]. However, elderly patients often receive the doublet in Japan possibly because of the recommendation regardless of age in the Japanese Society for Cancer of the Colon and Rectum guideline 2019[11].

Given that Japan is a fast aging society, identification of optimal treatment strategy for the elderly is mandatory from the view point of safety, quality of life and health care cost. In the current study, we explored value of monotherapy as an adjuvant treatment for the elderly patients with stage III colorectal cancer through comparison of the long-term outcome of between patients who received monotherapy and those treated by the doublet at a community hospital.
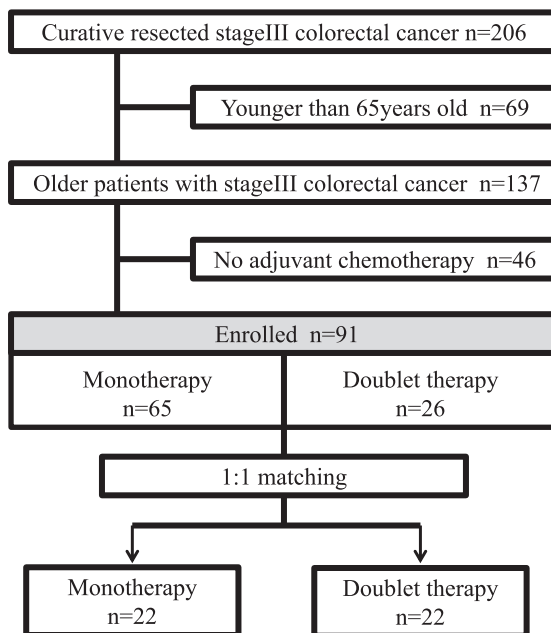
MATERIALS AND METHODS

Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This observational study was approved by the Institutional Review Board of Tosei general hospital (approval number 699-1). Consent of this study was in opt-out form.

Selection of patients

A flow-chart of this study is shown in Fig 1. Two hundred and six patients were diagnosed with stage III colorectal cancer at Tosei general hospital (Department of surgery) between April 2008 and 2016 March. Of these, 137 patients aged over 65 were selected for the current study because World Health Organization defines people over 65 years old as the elderly. Patients who did not receive adjuvant chemotherapy were excluded (n=46), and the remaining 91 patients

Curative resected stageIII colorectal cancer n=206

Younger than 65years old n=69

Older patients with stageIII colorectal cancer n=137

No adjuvant chemotherapy n=46

Enrolled n=91

| Monotherapy n=65 | Doublet therapy n=26 |

1:1 matching

| Monotherapy n=22 | Doublet therapy n=22 |

Fig. 1 Study design

were classified into two groups according to whether they received monotherapy (n=65) or oxaliplatin-containing doublet therapy (n=26).

We used the propensity score matching to balance in essential variables for the comparison analysis. Propensity score were estimated using a logistic regression model based on age, sex, performance status and Union for International Cancer Control (UICC) stage. One-to-one matching was performed and the result of matching was used for subsequent analysis.

Patients management

A routine screening including physical examination and blood biochemistry was provided on the day or the day before administration of chemotherapy during the treatment, based on which treatment modification such as dose reduction or withdrawal was conducted. Follow up examinations by enhanced computed tomography (chest and abdominal cavity) and measurements of blood biochemistry and serum tumor markers was performed every 3 months.

Comparisons between groups

Preoperative background data included demographics, age, performance status, pathology, T factor, N factor, UICC stage and comprehensive geriatric assessment (CGA) 7. CGA7 was conducted at discharge after colorectal resection. CGA7 includes following categories; vitality, instrumental activities of daily living, cognitive function (repeat or reproduction), basic activities of daily living (bath and restroom) and emotion.

Statistical analysis

To compare the two groups, we used a chi-square test and Mann-Whitney's test. Survival curves were drawn using Kaplan-Meier method. Differences of survival between two groups were assessed with Cox hazard model. All analysis were performed by Easy R12. $P < 0.05$ represents statistically significant difference.

RESULTS

Patients background

The mean age was 70±10.6 (standard deviation, SD) years, and the female: male ratio was 1.2:1. The median follow-up duration was 56.5months. Before propensity score matching, 65 and 26 patients had been classified into the monotherapy group and doublet groups, respectively. There were significant differences between the two groups in age and distribution of UICC stage (Table 1). After one-to-one propensity score matching, both groups consisted of 22 patients and the age and distribution of UICC stage were well-balanced between the groups (Table 1). Undifferentiated pathological type was significantly more frequent in the doublet therapy group (Table 2). There was no significant difference in the CGA7 score between the two groups (Table 2).

Treatment background

There was no significant difference in the relative dose intensity (RDI) of fluorouracil between the two groups. The RDI of oxaliplatin in the doublet group was 0.56. Completion rate of adjuvant chemotherapy was higher in the monotherapy group although the difference did not reach statistical significance (Table 3).

Long-term outcomes

Fourteen patients (32%) had relapsed within 3 years. The recurrence rate was 0%, 28% and

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Table 1 Patient characteristics before and after propensity score matching

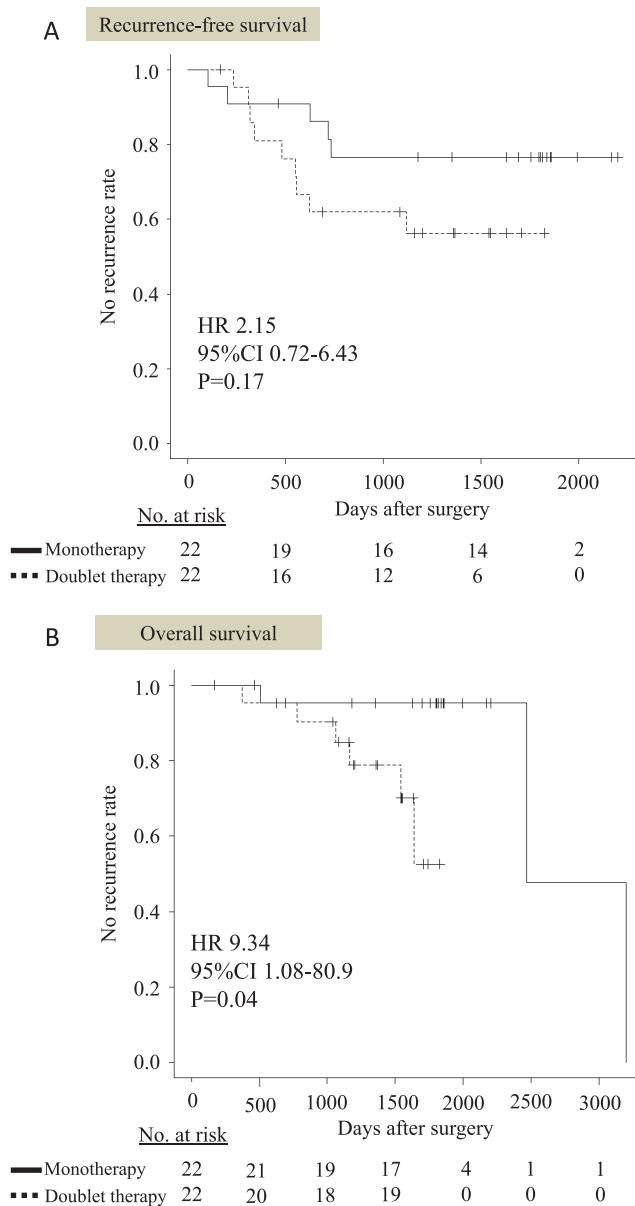| Characteristic	Unmatched comparison			Matched comparison		
	Mono-therapy group (n=65)	Doublet therapy group (n=26)	P value	Mono-therapy group (n=22)	Doublet therapy group (n=22)	P value
Age (years), mean±SD	75±4.6	70±4.2	<0.01*	71±3.6	71±4.3	1.0
Sex (male/female)	39/26	11/15	0.12	10/12	10/12	1.0
PS (0/1)	55/10	23/3	0.63	19/3	19/3	1.0
UICC stage						
A	11 (17%)	2 (8%)	0.03*	3 (14%)	2 (9%)	0.84
B	48 (74%)	16 (73%)		16 (73%)	16 (73%)	
C	6 (9%)	8 (31%)		3 (14%)	4 (18%)	

PS: Performance status

Table 2 Patients' demographics and pre-chemotherapeutic clinical characteristics

	Monotherapy (n=22)	Doublet therapy (n=22)	P value
Age (years), mean±SD	71±3.6	71±4.3	0.83
Sex (male/female)	10/12	10/12	1.00
Pathology (well to mod/poorly to signet)	21/1	16/6	0.04*
T factor			
pT1/0	1 (5%)	0 (0%)	0.79
pT2	2 (10%)	2 (10%)	
pT3	11 (50%)	11 (50%)	
pT4	8 (36%)	9 (41%)	
N factor			
pN1	17 (77%)	15 (68%)	0.50
pN2	5 (23%)	7 (32%)	
UICC stage			
A	3 (14%)	2 (9%)	0.84
B	16 (73%)	16 (73%)	
C	3 (14%)	4 (18%)	
CGA7 problem (yes/no)			
Vitality	0/22	0/22	1.00
Instrumental ADL	3/19	1/21	0.61
Cognitive function (repeat)	2/20	0/22	0.49
Basic ADL (bath)	2/20	1/21	1.00
Basic ADL (restroom)	0/22	1/21	1.00
Cognitive function (reproduction)	2/20	0/22	0.49
Emotion	1/21	0/22	1.00

Table 3 Chemotherapeutic course

	Monotherapy (n=22)	Doublet therapy (n=22)	P value
Relative dose intensity of fluorouracil	0.86	0.79	0.24
Relative dose intensity of Oxaliplatin	–	0.56	–
Completion rate of adjuvant chemotherapy	82%	68%	0.30

Oxaliplatin for elderly patients

71% in stage IIIA, B and C, respectively. The recurrence rate stratified by the treatment groups was 23% (5 patients) and 41 % (9 patients) in the monotherapy group and the doublet group, respectively. One case of the doublet group underwent resection of the recurrent lesion. There was no significant difference in recurrence-free survival between the treatment groups (Fig 2A). On the other hand, 11 patients had died during follow-up period. All patients died from cancer recurrence except one case in the monotherapy group. The difference in overall survival between the treatment groups was statistically significant (Fig 2B).

A Recurrence-free survival

HR 2.15
95%CI 0.72-6.43
P=0.17

No. at risk

Monotherapy	22	19	16	14	2
Doublet therapy	22	16	12	6	0

B Overall survival

HR 9.34
95%CI 1.08-80.9
P=0.04

No. at risk

Monotherapy	22	21	19	17	4	1	1
Doublet therapy	22	20	18	19	0	0	0

Fig. 2 Prognosis of patients who underwent adjuvant chemotherapy for stage III colorectal cancer according to treatment
**Fig. 2A:** Disease-free
Fig. 2B: Overall survival

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Adverse Events

There were no differences in the frequency of Grade 3/4 adverse events between the two groups (Table 4). However, the frequency of all adverse events (Grade1 to 4) was higher in the doublet group (Fig 3).

Table 4 Frequency of G3 to 4 adverse events

	Monotherapy (n=22)	Doublet therapy (n=22)	P value
Hematologic			
Anemia	0 (0%)	0 (0%)	1.00
Neutropenia	0 (0%)	2 (9%)	0.10
Thrombocytopenia	0 (0%)	2 (9%)	0.10
Non-hematologic			
Appetite loss	0 (0%)	1 (5%)	0.23
Vomiting	0 (0%)	0 (0%)	1.0
Diarrehea	1 (5%)	0 (0%)	0.23
Liver disfunction	0 (0%)	0 (0%)	1.00
Renal disfunction	0 (0%)	0 (0%)	1.00
Peripheral neuropathy	0 (0%)	1 (5%)	0.23
Hand-foot syndrome	1 (5%)	0 (0%)	0.23
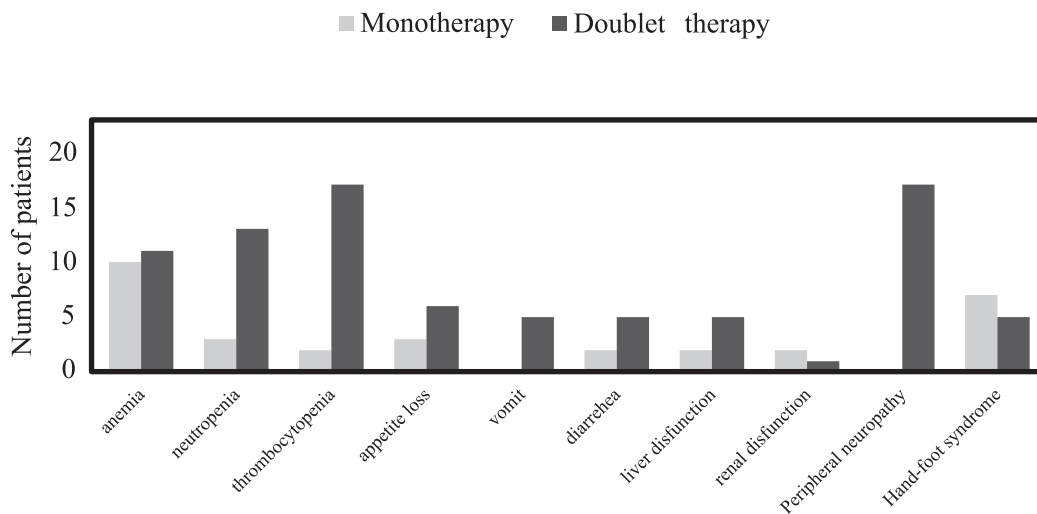
Fig. 3 Frequency of all adverse events according to treatment

DISCUSSION

We evaluated the long-term outcomes of elderly patients with stage III colorectal cancer receiving adjuvant chemotherapy. After propensity score matching, we showed significant difference in overall survival between patients receiving the monotherapy and the doublet therapy. Aging is rapidly progressing globally. The definition of elderly patients may differ according to the

organization, sometimes depending on each malignant tumor. World Health Organization defines people over 65 years old as elderly, and we chose to use this criteria for the current study. In our hospital, 88% of patients with malignant tumors are aged over 65 years old. Although the two treatment groups were well-matched in several relevant parameters after propensity score matching, patients who underwent monotherapy had been significantly older in the unmatched population. This suggests that the physicians may have had tendency to select monotherapy for the elderly patients. Nevertheless, we found that the monotherapy was superior in terms of overall survival. This result is similar to other large clinical trials[4,13]. The frequency of any adverse events was significantly higher in the doublet therapy. Although we sometimes focus on only grade 3/4 adverse events in clinical trials, even grade 1or 2 adverse events could be substantial problems, especially for the elderly patients, and efforts should always be made to minimize the occurrence of adverse events. Moreover, RDI of oxaliplatin was lower in our study than in other clinical trials[14-16]. Several clinical trials exploring adjuvant chemotherapy using oxaliplatin-containing regimens were conducted between 2004 and 2011. Capecitabine plus oxaliplatin has been widely used in our hospital after establishment of its efficacy because of simplicity to administrate at the out-patient clinic. Our study is an observation study of patients who were treated between 2008 to 2016. The doublet therapy was more frequently performed in the latter half (p<0.01). However, RDI of oxaliplatin was the similar in the earlier and latter half (0.54 and 0.56, respectively), indicating that the physicians consistently fail to administrate oxaliplatin at sufficient dose intensity to the elderly patients even after some experience with the treatment. These findings indicate the monotherapy is more suitable to elderly patients.

Recurrence rate is different in stage IIIA, IIIB and IIIC[17]. The effect of oxaliplatin has been anticipated to be larger in stage IIIC. Nevertheless, National Comprehensive Cancer Network guideline does not recommend the doublet therapy to elderly patients[18], and this decision is based on sufficient body of evidence. On the other hand, Japanese Society for Cancer of the Colon and Rectum guideline recommends the doublet therapy (evidence level A)[11]. This decision may have been a driving force in our institution to use the doublet regardless of the age, especially for the stage IIIC patients, although there were cautionary notes that care should be taken when administering the doublet therapy to the elderly patients. The current study indicates, however, that a monotherapy may be more practical for the elderly patients even if the patient suffers from Stage IIIC disease.

On the other hand, the doublet therapy may be beneficial to selected elderly patients who can tolerate the treatment. It is our future task to find ways to identify elderly patients who can benefit from the doublets. One way of selecting fit patients may be the use of CGA. CGA can pick up problems behind the daily medical examination according to assess following factors: functional status (activities of daily living and instrumental activities of daily living); cognitive function; psychological status; nutritional status; comorbidity; polypharmacy and social support[19-21]. Results led from CGA help a decision making of a treatment for physicians, patients and their family. It is shown that there is a correlation between CGA problems and occurrence of adverse events or completion rate of planned chemotherapy[19,20,22]. National Comprehensive Cancer Network and task force of international society of geriatric oncology have recommended a geriatric assessment for elderly patients before starting chemotherapy[23,24]. Patients recruited in this study underwent CGA7 by nurses at the time of discharge after colorectal resection. Although CGA7 may not be sufficient for comprehensive geriatric assessment, its simplicity allowed us to use it routinely for patients with over 65 years of age. In our study, 80% of patients with any problems on CGA7 were given monotherapy. We consider it is necessary to spread any geriatric assessment tools in clinical practice to select a suitable regimen.

This study has limitations, such as a limited number of patients and potential selection biases

due to the retrospective nature even after propensity score matching. In this study, only patients who underwent adjuvant chemotherapy were analyzed. Frail patients who had poor performance status or severe comorbidity were considered to be unfit to adjuvant chemotherapy and underwent surgery only. The objective assessment for quality of life will make deeper discussion about this topic.

CONCLUSION

Long-term outcomes were comparable between elderly patients with stage III colorectal cancer receiving the monotherapy and those receiving the doublet therapy. Our findings indicate the monotherapy may be more suitable for the elderly patients, both oncologically and from the view point of safety and quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest for the present study.

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