Title	Association between social background and implementation of postoperative adjuvant chemotherapy for older patients undergoing curative resection of colorectal cancers, sub-analysis of the HiSCO-04 study
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Relation	

Title: Association between social background and implementation of postoperative adjuvant chemotherapy for older patients undergoing curative resection of colorectal cancers, sub-analysis of the HiSCO-04 study

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Abstract

Purpose: Adjuvant chemotherapy is recommended following colorectal cancer resection based on risk of recurrence. In older patients, treatment decisions should consider recurrence rates and tolerability, as well as functional prognosis, residual disease, and social factors. This study aims to investigate factors, including social background, influencing implementation of postoperative adjuvant chemotherapy in older patients undergoing curative resection for colorectal cancer.

Methods: This multi-institutional prospective cohort study included 15 institutions belonging to the Hiroshima Surgical study group for Clinical Oncology. We analyzed 159 older patients aged ≥ 80 years, who underwent curative resection for stage III colorectal cancer between December 2013 and June 2021, as sub-analysis of the HiSCO-04 study.

Results: In total, 62 (39.0%) patients underwent postoperative adjuvant chemotherapy. Four factors were significantly associated with its implementation: performance status < 2, Charlson Comorbidity Index < 2, prognostic nutritional index < 40, and presence of a spouse or siblings as lifestyle supporters. No significant difference was found in the backgrounds between complete and incomplete postoperative adjuvant chemotherapy patients.

Conclusion: Performance status, Charlson Comorbidity Index, nutritional status, and presence of a spouse or siblings as lifestyle supporters are possible factors influencing the implementation of postoperative adjuvant chemotherapy in older patients. To select appropriate treatment options, including postoperative adjuvant chemotherapy, it is essential to consider physical condition and comorbidities of older patients, thoroughly explain the situation to their families, and establish a support system to enhance understanding of the available treatment options.

Ethics statements

This study was conducted in accordance with the guidelines of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and was approved by the institutional review board of Hiroshima University Hospital (approval number: Epd-893,approval day: August 7, 2014). All patients provided written informed consent after the purpose and investigational nature of the study was explained to them. The institutional review board and ethics committee of each participating center reviewed and approved the protocol. This study was registered with the Japan Registry of Clinical Trials (jRCTs061180087).

Keywords: colorectal cancer, older patients, postoperative adjuvant chemotherapy, social backgrounds

Statement & Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions: Tomoaki Bekki and Manabu Shimomura drafted the manuscript. Hideki Ohdan revised the manuscript substantially. All authors cooperated in the collection of cases and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Introduction

The number of older patients with cancer is increasing, and it is predicted that by 2030, approximately 70% of all new cancer cases will be diagnosed in individuals aged ≥ 65 years [1]. Colorectal cancer (CRC) is the most commonly diagnosed gastrointestinal cancer worldwide, accounting for approximately 10% of all new cases [2]. Therefore, incidence of CRC is predicted to be significantly influenced by aging populations.

The treatment approach for stage III CRC involves surgical resection followed by postoperative adjuvant chemotherapy (ACT). However, evidence on safety and efficacy of postoperative ACT in older patients with stage III CRC is lacking. Regarding fluoropyrimidine monotherapy, patients > 70 years of age appear to exhibit overall survival (OS) and recurrence-free survival (RFS) rates similar to those in patients ≤ 70 years of age [3]. However, combining 5-fluorouracil (5-FU) with oxaliplatin does not appear to be an effective treatment option for patients ≥ 70 years of age [4, 5]. Recently, uracil-tegafur/leucovorin (UFT/LV) was found to be a safe postoperative ACT in CRC patients aged ≥ 80 years at HiSCO-03 study, although adequate feasibility was not achieved [6]. The accompanying HiSCO-04 study revealed that patients who completed the treatment protocol experienced improvements in postoperative disease-free survival (DFS), whereas those who did not complete treatment showed poorer outcomes [7]. Based on the findings of these studies, the assessment of the condition to successfully complete ACT is significant importance for older patients. Another study investigated doctor-related factors determining decision-making for ACT in older patients with stage III colon cancer [8]. Selection of treatment strategies for older patients, including surgery and chemotherapy, should be approached cautiously, considering physical fitness and nutritional status.

Social background, including family composition and presence of supportive friends for outpatient visits and psychological care, plays a vital role in older patients continuing cancer treatment, although its actual impact remains unclear. Further, an association between social support and cancer prognosis has been observed, primarily in breast and colorectal cancers [9-11].

This study aimed to investigate the influence factors, including patient social backgrounds, such as residential status and presence of lifestyle supporters, associated with implementation of postoperative ACT in older patients who underwent curative resection of CRC, as accompanying the HiSCO-04 study.

Materials and Methods

Study Population

Between December 2013 and June 2018, 214 patients ≥ 80 years of age with Stage III CRC, who underwent initial R0 curative resection at 15 institutions belonging to the Hiroshima Surgical study group of Clinical Oncology,

were enrolled in this study, as sub-analysis of the HiSCO-04 study. These patients were the same as those enrolled in our previous study (HiSCO-04 study), where we investigated the relationships between pre- and postoperative residential status, lifestyle support, and implementation of postoperative ACT, as accompanying study. Of the older patients who requested postoperative ACT, those whose organ function and performance status (PS) were maintained were considered eligible. Patients deemed ineligible for postoperative ACT, owing to general condition, presence of dementia, or double cancers, as well as those with unknown lifestyle support, were excluded from analysis. As all patients who received ACT had been discharged, 159 patients who were discharged were included in the analysis (Fig. 1). Patients were divided into two groups based on the reception of postoperative ACT. We investigated the influencing factors, including patient background (body mass index, PS), Charlson comorbidity index (CCI), prognostic nutritional index (PNI), tumor factors, and social background factors such as residential status and availability of lifestyle supporters for implementing the ACT. The study was conducted in accordance with the Declaration of Helsinki guidelines (Fortaleza, Brazil, October 2013). Written informed consent was obtained from each participating patient for their data to be used for study purposes.

Adjuvant chemotherapy

After surgery for CRC, the treating physician determined the indications for ACT, considering pre-existing medical conditions, complications, and general health status. Patients determined to have an indication for ACT were educated about its importance and adverse events, and it was administered to those who requested it. In most cases, patients who did not meet the exclusion criteria for clinical trials received UFT/LV therapy. ACT included 57 patients who were treated with UFT/LV. Of the rest, two patients were treated with capecitabine, two with 5-FU, LV, and oxaliplatin (FOLFOX), one with S-1, and two with UFT alone. UFT (300mg with body surface area (BSA) < 1.17 m^2, 400mg with BSA 1.17–1.49 m^2, 500mg with BSA 1.50–1.83 m^2, 600mg with BSA > 1.83 m^2) and LV (75 mg/body) were administered orally in three divided doses (every 8h) > 1h before or after meals for 28 consecutive days, followed by a 7-day rest. Five courses (25 weeks) were administered. Adjuvant chemotherapy was initiated within eight weeks of surgery. This study commenced before the results of the IDEA trial [12] was published. Six months of anticancer oral therapy was planned for almost all patients, and there were no patients who had three months of postoperative chemotherapy planned.

Definition of social background

The social backgrounds of the discharged patients (living situation, lifestyle supporters) were investigated. Living situation involved whether the patients lived alone, while lifestyle supporters were individuals who offered

various forms and degrees of assistance.

Statistical analysis

Nominal variables were expressed as numbers (%). Univariate analysis was conducted using the chi-squared test or Fisher's exact test for nominal variables. A multivariate logistic regression model was used to analyze impact of independent variables on implementation of postoperative ACT. All variables were included in the first model and stepwise selection using the Akaike Information Criterion (AIC) was performed to identify the most influential variables for implementation of postoperative ACT. Where AIC is used for model selection, different variables may be chosen for univariate and multivariate analyses. In this study, model selection was based on the AIC, and the chosen model was determined to have the best prediction accuracy. Statistical significance was set at $P < 0.05$. significant. Calculations were performed using JMP v14 (SAS Institute, Cary, NC, USA).

Results

Residential Status and Lifestyle Supporters among Registered Patients

Older patients may be difficult to discharge home depending on their family support because of their low postoperative fitness due to surgical invasion and complications. Therefore, this study investigated how many older patients could be discharged home after surgery and aimed to identify the living situations and lifestyle supporters of those who could be discharged. Table 1 compares the patients' pre- and postoperative residential statuses. Of the 196 (91.6%) patients residing at home before surgery, 181 (84.6 %) were discharged back home. Table 2 summarizes the social backgrounds of the patients who were discharged home (n=181), including living situations and lifestyle supporters. Among them, 53 (29.3%) lived alone, whereas 124 (68.5%) lived with spouses, partners, or children. In terms of lifestyle support, 38 (21.0%) patients had a partner or sibling and 141 (77.9%) had a child or grandchild. Many older patients who were discharged home had a housemate, and almost all (98.9%) had at least one lifestyle supporter.

Influencing factors for implementation of postoperative adjuvant chemotherapy for older patients after CRC resection in univariate and multivariate analysis

Next, we investigated the factors that influence the implementation of postoperative ACT in older patients. Table 3 shows the relationship between postoperative residential status and ACT implementation. All 64 patients

who underwent postoperative ACT were discharged home ($P < .0001$). Table 4 summarizes the background characteristics of patients in the ACT versus non-ACT groups after CRC resection. Overall, 62 (39.0%) patients (all but two whose lifestyle supporters were unknown) and 97 (61.0 %) patients were included in the ACT and non-ACT groups, respectively. None of the patients received preoperative chemoradiotherapy for rectal cancer. Compared with the non-ACT group, the proportion of patients with PS < 2 ($P = 0.0030$), CCI < 2 ($P = 0.0348$) were higher in the ACT group, and a lower proportion of patients with PNI < 40 ($P = 0.0114$). The proportion of patients with spouses or siblings as lifestyle supporters was higher in the ACT group, whereas the proportion of patients with children or grandchildren as lifestyle supporters ($P = 0.0357$) was higher in the non-ACT group. Implementing postoperative ACT did not appear to significantly influence living situations ($P = 0.5907$). In multivariate analysis, the following factors were identified as influencing implementation of postoperative ACT: PS < 2 (odds ratio [OR] = 7.223; 95% confidence interval [CI] = 1.55–33.6, $P = 0.0118$, CCI < 2 (OR = 2.349; 95% CI = 1.01–5.48, $P = 0.0482$), PNI ≥ 40 (OR = 3.290; 95% CI = 1.22–8.88, $P = 0.0187$), and spouse or siblings as lifestyle supporters (OR = 2.535; 95% CI = 1.09–5.87, $P = 0.0300$). Table 5 presents the factors influencing the completion of postoperative ACT. A total of 33 (53.2%) patients completed postoperative ACT, and no significant differences were observed in background.

Discussion

This study investigated the factors influencing implementation of postoperative ACT in older patients who underwent CRC resection. Several reasons for not recommending postoperative ACT have been provided by surgeons and oncologists, including age, comorbidity, surgical complications, living alone, patient or family refusal, and social circumstances [8, 13]. This study revealed that PS, CCI, PNI, and the patient's relationship with a lifestyle supporter were influential in implementing postoperative ACT among older patients; this was consistent with previous studies. Recently, the number of older cancer patients has been increasing, with 38.7% of CRC cases involving patients between 70 and 80 years of age, and 17.5% involving patients > 80 years of age [14]. Many older patients exhibit poor performance status, comorbidities, and malnutrition, emphasizing the need for careful consideration when deciding to administer postoperative ACT. Therefore, older patients are less likely to receive postoperative ACT than younger patients [14-16].

Indeed, patients aged 70 years are often excluded from studies investigating the effectiveness of postoperative ACT, and its efficacy in these patients is controversial. While the benefits of fluorouracil-based postoperative ACT in older patients have been confirmed [3], the benefits of adding oxaliplatin to fluorouracil in

this procedure remain unclear [4, 5, 15, 17]. The aforementioned studies defined older patients as those over 70 or 75 years of age, and very few studies on postoperative ACT in patients over 80 years of age exist. Our HiSCO-04 trial demonstrated that patients over 80 years of age who completed the prescribed ACT regimen exhibited improved postoperative DFS, whereas those who did not complete treatment showed poorer outcomes [7]. Additionally, a recent study revealed that patients ≥ 70 years of age who did not complete ACT exhibited inferior OS compared with those who completed treatment [16].

Discontinuation of postoperative ACT in older CRC patients is primarily attributed to side effects [16, 18]. Lund et al. reported that age is a risk factor for side effects of postoperative ACT [19]. Several studies have indicated that chemotherapeutic regimens containing oxaliplatin lead to increased side effects [20-22]. In fact, in the present study, the impact of side effects of the anticancer drugs (76.7%) was the most common reason for the discontinuation of postoperative ACT. Given the potential impact of ACT discontinuation on postoperative prognosis, the selection and introduction of chemotherapy regimens for older patients should be approached cautiously, considering comorbidities and performance status. In this study, we observed that older patients, as well as those with poor performance status, and malnutrition, were less likely to receive postoperative ACT. This can be the result of a careful assessment of the patient's ability to tolerate ACT.

Social support is recognized as a determinant of prognosis in older patients with cancer, and adequate social support has been associated with favorable outcomes in CRC [10, 11]. Furthermore, social support influences completion of chemotherapy [18]. Generally, this refers to relationships with close relatives or friends who have the potential to assist patients during their illness [23]. Older patients find it difficult to implement postoperative undergo cancer therapy without external support. One study showed that patients who did not have someone to accompany them to the doctor were less likely to have severe grade non-hematological toxicity compared with those who did [24]. Support from family or friends enables older patients with cancer to attend outpatient appointments, and provides them with emotional support during treatment. However, it is crucial to acknowledge the substantial emotional burden faced by cancer patients' families [25, 26]. Therefore, cooperation of family and friends it of utmost importance; in addition, they should possess a comprehensive understanding of the details of postoperative ACT in older patients with cancer.

Among older patients with cancer, familial refusal has been reported to contribute to non-implementation of ACT [8]. In this study, the presence of children or grandchildren was identified as a negative influencing factor on implementation of postoperative ACT in older patients, although it did not affect completion. This result suggests that children or grandchildren may oppose the implementation of postoperative ACT, potentially

preventing older patients who could benefit from ACT from receiving it. Another possibility is that older patients who lack a supportive individual who understands treatment may have accepted physician-recommended adjuvant chemotherapy without a comprehensive understanding. Additionally, the concept of life expectancy must be considered when implementing postoperative ACT in older patients. To prevent situations in which eligible older patients do not undergo ACT, sufficient explanations of ACT and potential adverse events should be provided to the patients as well as their families, to establish appropriate treatment strategies. In the absence of a supportive and understanding individual, it is crucial to establish a support system that assists older patients in better understanding their treatment.

This study had several limitations. First, this was a prospective study with a relatively small sample size. Additionally, it serves as a sub-analysis of a previous study, which limits the number of social background factors examined compared with previous studies. Another limitation is that only living situation and lifestyle supporters were examined as social backgrounds.

Conclusions

PS, CCI, nutritional status, and patient's relationship with lifestyle support may influence the implementation of postoperative ACT among older patients with CRC. To select appropriate treatment options, including postoperative ACT, it is necessary to consider the physical fitness and comorbidities of older patients, provide adequate explanations to their families, and establish a support system to deepen their understanding of treatment.

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Figure legends

Fig. 1: Flowchart of the study design

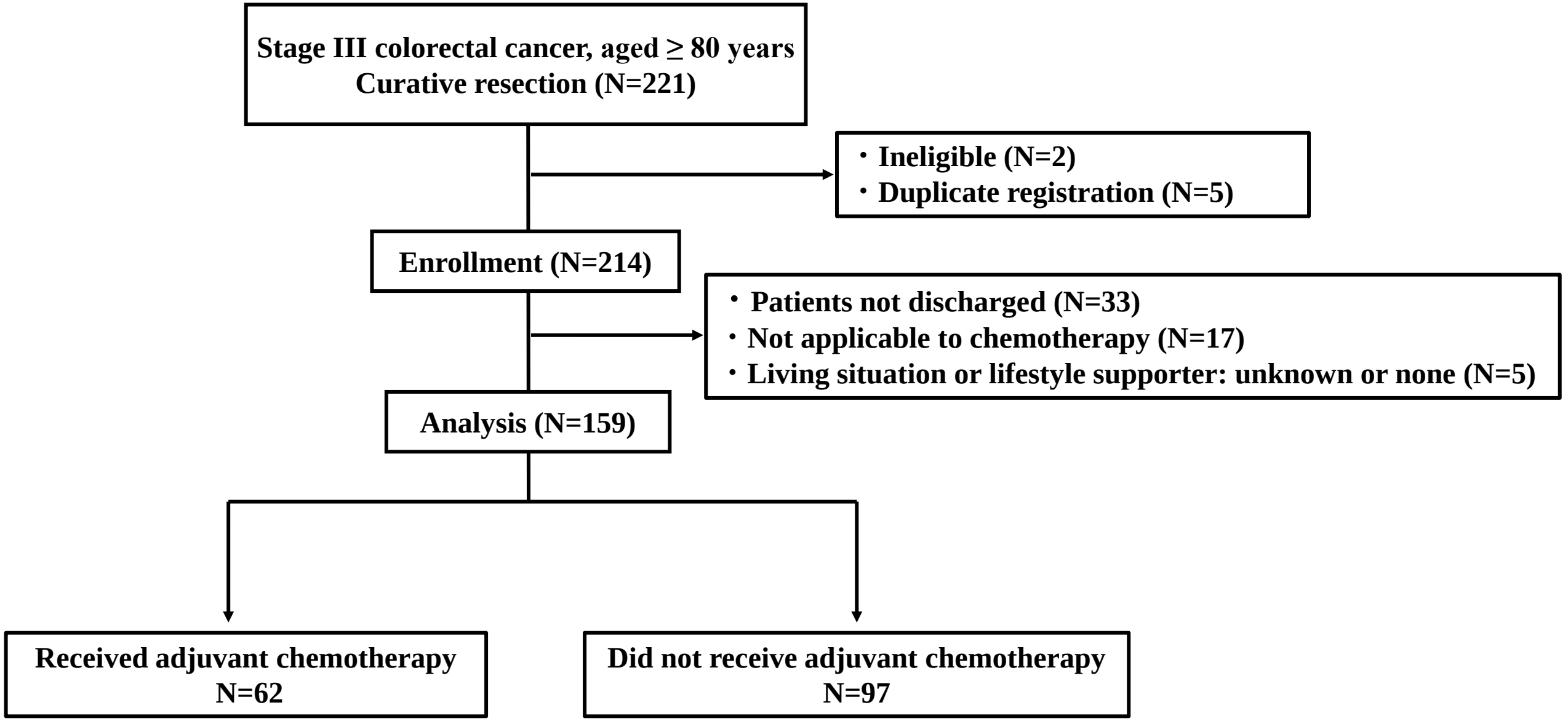
Stage III colorectal cancer, aged ≥ 80 years
Curative resection (N=221)
・Ineligible (N=2)
・Duplicate registration (N=5)
Enrollment (N=214)
・Patients not discharged (N=33)
・Not applicable to chemotherapy (N=17)
・Living situation or lifestyle supporter: unknown or none (N=5)
Analysis (N=159)
Received adjuvant chemotherapy
N=62
Did not receive adjuvant chemotherapy
N=97

Table 1. Comparison of preoperative and postoperative patient residential status

Characteristics	Patients (n = 214)
Preoperative residential status	
Home	196 (91.6%)
Assisted-living residence	14 (6.54%)
Hospital	3 (1.40%)
Unknown	1 (0.05%)
Postoperative residential status	
Home	181 (84.6%)
Assisted-living residence	22 (10.3%)
Death	3 (1.4%)
Unknown	8 (3.7%)

Qualitative variables were expressed as numbers (%).

Table 2. Social background details of discharged patients

Characteristics	Patients (n = 181)	
Living situation		
Alone	53 (29.3%)	
Living with someone	124 (68.5%)	
	*Details of roommate:	
	Spouse or siblings	56 (30.9%)
	Children or grandchildren	65 (35.9%)
	Unknown	3 (1.66%)
Unknown	4 (2.21%)	
Lifestyle supporter		
Spouse or siblings	38 (21.0%)	
Children or grandchildren	141 (77.9%)	
Unknown	1 (0.55%)	
None	1 (0.55%)	

Qualitative variables were expressed as numbers (%).

Table 3. Relationship between postoperative residential status and implementation of adjuvant chemotherapy

Characteristics	ACT group (n = 64)	Non-ACT group (n = 150)	*P*-value
Postoperative residential status			
Home	64 (100%)	117 (78.0%)	< .0001
Others	0 (0.00%)	22 (14.7%)	
Death	0 (0.00%)	3 (2.0%)	
Unknown	0 (0.00%)	8 (5.3%)	

Qualitative variables were expressed as numbers (%). Abbreviations: ACT, adjuvant chemotherapy.

Table 4. Characteristics of patients treated with and without postoperative adjuvant chemotherapy.

Variables	ACT group (n=62)	Non-ACT group (n=97)	Univariate *P*-value	Multivariate OR	95% CI	95% CI
Sex (M/F)	33:29	40:57	0.1390			
BMI (kg/m^2) ≥ 25	7 (11.3%)	18 (18.6%)	0.2196			
< 25	55 (88.7%)	79 (81.4%)				
PS < 2	60 (96.8%)	78 (80.4%)	**0.0030**	**7.223**	**1.55–33.6**	**0.0118**
≥ 2	2 (3.2%)	19 (19.6%)				
CCI < 2	51 (82.3%)	65 (67.0%)	**0.0348**	**2.349**	**1.01–5.48**	**0.0482**
≥ 2	11 (17.7%)	32 (33.0%)				
PNI ≥ 40	56 (90.3%)	71 (74.0%)	**0.0114**	**3.290**	**1.22–8.88**	**0.0187**
< 40	6 (9.7%)	25 (26.0%)				
Tumor location: right	25 (40.3%)	48 (49.5%)	0.3037			
left	25 (40.3%)	38 (39.2%)				
rectum	12 (19.4%)	11 (11.3%)				
Stage: IIIa	11 (17.7%)	15 (15.5%)	0.8975			
IIIb	42 (67.8%)	69 (71.1%)				
IIIc	9 (14.5%)	13 (13.4%)				
pT ≥ 3	53 (85.5%)	83 (85.6%)	0.9884			
< 3	9 (14.5%)	14 (14.4%)				
pN ≥ 2	15 (24.2%)	23 (23.7%)	0.9446			
< 2	47 (75.8%)	74 (76.3%)				
Histology: well or moderate	56 (90.3%)	82 (84.5%)	0.2932			

others	6 (9.7%)	15 (15.5%)				
Postoperative complications (+)	15 (24.2%)	19 (19.6%)	0.4896			
(–)	47 (75.8%)	78 (80.4%)				
Living situation: alone	21 (33.9%)	28 (29.8%)	0.5907			
with family	41 (66.1%)	66 (70.2%)				
Lifestyle supporter: spouse or siblings	19 (30.7%)	16 (16.5%)	**0.0357**	**2.535**	**1.09–5.87**	**0.0300**
children or grandchildren	43 (69.3%)	81 (83.5%)				

Bold variables are considered statistically significant ($P < 0.05$). Qualitative variables were expressed as numbers (%). Abbreviations: ACT, adjuvant chemotherapy; M, male; F, female; BMI, body mass index; PS, performance status; CCI, Charlson Comorbidity Index; PNI, prognostic nutritional index.

Table 5. Comparison of patient characteristics between complete and incomplete groups after postoperative adjuvant chemotherapy.

Variables	Complete group (n=33)	Incomplete group (n=29)	*P*-value
Sex (M/F)	19:14	14:15	0.4640
BMI (kg/m^2) ≥ 25	5 (15.2%)	2 (6.9%)	0.3055
< 25	28 (84.8%)	27 (93.1%)	
PS ≥ 2	0 (0.0%)	2 (6.9%)	0.1251
< 2	33 (100%)	27 (93.1%)	
CCI < 2	29 (87.9%)	22 (75.9%)	0.2165
≥ 2	4 (12.1%)	7 (24.1%)	
PNI < 40	3 (8.8%)	28 (22.6%)	0.0895
≥ 40	31 (91.2%)	96 (77.4%)	
Tumor location: right	12 (36.3%)	13 (44.8%)	0.6753
left	15 (45.5%)	10 (34.5%)	
rectum	6 (18.2%)	6 (20.7%)	
Stage: IIIa	4 (12.1%)	5 (17.2%)	0.6688
IIIb	24 (72.7%)	18 (62.1%)	
IIIc	5 (15.2%)	6 (20.7%)	
pT ≥ 3	29 (87.9%)	24 (82.8%)	0.5680
< 3	4 (12.1%)	5 (17.2%)	
pN ≥ 2	8 (24.2%)	7 (24.1%)	0.9924
< 2	25 (75.8%)	22 (75.9%)	
Histology: well or moderately	30 (90.9%)	26 (89.7%)	0.8677
others	3 (9.1%)	3 (10.3%)	
Postoperative complications (+)	6 (18.2%)	9 (31.0%)	0.2384
(–)	27 (81.8%)	20 (69.0%)	
Living situation: alone	12 (36.4%)	19 (31.0%)	0.6582
with family	21 (63.6%)	20 (69.0%)	
Lifestyle supporter: spouse or siblings	10 (30.3%)	9 (31.0%)	0.9503
children or grandchildren	23 (69.7%)	20 (69.0%)	

Bold variables are considered statistically significant ($P < 0.05$). Qualitative variables were expressed as numbers (%). Abbreviations: ACT, adjuvant chemotherapy; M, male; F, female; BMI, body mass index; PS, performance status; CCI, Charlson Comorbidity Index; PNI, prognostic nutritional index.