Cancer Management and Research

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ORIGINAL RESEARCH

Impact of Adjuvant Chemotherapy on the Prognosis in Elderly Patients with Stage II and III Colorectal Cancer: A Retrospective Multicenter Study

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Purpose: The objective of this retrospective multicenter study was to evaluate the efficacy of adjuvant chemotherapy (adCTx) following curative resection in patients aged ≥70 years with colorectal cancer (CRC) and to compare the outcomes of monotherapy versus combination chemotherapy.

Methods: Data from 1183 patients with stage II or III CRC who underwent surgery at five Hallym University-affiliated hospitals in Korea between 2012 and 2022 were retrospectively analyzed. Patients were divided into two groups based on adjuvant chemotherapy status (adCTx (+) vs adCTx (-)). Those receiving adCTx were further stratified into 5-fluorouracil (5-FU) monotherapy or 5-FU plus oxaliplatin combination therapy. Multivariable Cox regression was used to estimate adjusted hazard ratios (HRs) for overall survival (OS) and recurrence-free survival (RFS).

Results: Of the 1183 patients, 555 received adCTx and 628 did not. Patients in the adCTx (+) group showed significantly better 5-year OS (88.6% vs 75.7%, P < 0.001) and RFS (66.5% vs 58.6%, P < 0.001). In multivariable analysis, adCTx was independently associated with improved OS (HR 0.33, 95% CI 0.23–0.48, P < 0.001) and RFS (HR 0.59, 95% CI 0.47–0.76, P < 0.001). Among patients receiving chemotherapy, there was no significant difference in OS or RFS between monotherapy and combination therapy. In stage II patients with high-risk factors, adCTx (+) was associated with better OS (P = 0.002) and RFS (P = 0.006), but the number of agents did not provide additional benefit.

Conclusion: In this study of patients aged ≥70 years with stage II or III CRC, adjuvant chemotherapy was associated with improved OS and RFS. No significant differences in oncologic outcomes were observed between monotherapy and combination therapy. These findings suggest a potential benefit of adjuvant chemotherapy in selected elderly patients; however, prospective randomized studies are needed to confirm these results.

Keywords: colorectal cancer, elderly, adjuvant chemotherapy, combination therapy

Introduction

According to the United Nations Fund for Population Activities, the global population aged ≥65 years doubled from 5.5% in 1974 to 10.3% in 2024, and it is projected to increase further to 20.7% by 2074.[1] In parallel with this global trend, Korea has rapidly transitioned into a super-aged society; according to Statistics Korea, individuals aged ≥65 years account for approximately 21% of the total population, and those aged ≥70 years represent approximately 13%.[2] With the rapid increase in the elderly population, the incidence of colorectal cancer (CRC) is rising because of its greater prevalence in older adults.[3,4] The significantly worse prognosis and survival rates of CRC in elderly patients than in younger patients are major concerns.[5–7]

https://doi.org/10.2147/CMAR.S589756
Received: 17 December 2025
Accepted: 18 April 2026
Published: 27 April 2026

Elderly patients have distinct clinical characteristics, including a higher prevalence of comorbidities and sarcopenia, both of which are associated with increased postoperative morbidity and mortality[8,9] These features are closely related to frailty, a multidimensional syndrome reflecting reduced physiologic reserve and increased vulnerability to stressors.[10] In addition, age-related decline in organ function, particularly hepatic and renal function that are essential for drug metabolism,[7] together with impaired functional status and decreased performance capacity, may limit tolerance to systemic chemotherapy[11] Furthermore, older patients face substantial competing mortality risks from non-cancer causes, which may influence overall survival outcomes and complicate the assessment of treatment benefit.[12] Consequently, clinicians often approach intensive chemotherapy cautiously in this population, and elderly patients with CRC are less likely to receive adjuvant treatment.[13,14]

Several large-scale randomized controlled trials (RCTs) have demonstrated that adjuvant chemotherapy (adCTx) consisting of 5-fluorouracil (5-FU) after curative resection improves the survival and prevents the recurrence of CRC.[15] Subsequent RCTs of patients with advanced-stage CRC have demonstrated that the addition of agents such as oxaliplatin[16,17] to 5-FU/leucovorin improved overall survival (OS) and recurrence-free survival (RFS) compared with prior treatment regimens. However, some of those clinical trials limited the age of patients to <75 years,[16] and the proportion of elderly patients was low, ranging from 14% to 22% in several studies.[16–18] Although randomized controlled trials provide high-level evidence, elderly patients enrolled in such trials often represent a relatively selected population, which may limit generalizability to routine clinical practice.[15,18]

Previous studies have reported conflicting results regarding the efficacy of adCTx in elderly patients with CRC. Some studies found that patients who received adCTx had better OS and disease-free survival (DFS) than patients who did not.[19–21] However, other studies found no differences in the oncologic outcomes between patients who did or did not receive adCTx.[22–24] Additionally, some studies reported that 5-FU combined with oxaliplatin or irinotecan achieved superior oncologic outcomes compared with 5-FU-based monotherapy,[20,25,26] but other studies found no significant difference in the oncologic outcomes between combination therapy and monotherapy.[18,27–29]

Although treatment recommendations for elderly patients vary slightly among guidelines,[30–32] therapeutic decisions in this population are often individualized based on physiological reserve and organ function rather than chronological age alone. For example, oxaliplatin may be considered in selected patients aged ≥70 years with preserved liver and renal function, whereas monotherapy may be preferred in more vulnerable individuals. Therefore, determining the most appropriate adjuvant chemotherapy regimen for elderly patients remains clinically challenging.

The objective of this study was to investigate the efficacy of adCTx following curative resection in patients aged ≥70 years with CRC. The study also sought to compare the outcomes of monotherapy vs combination chemotherapy to identify the most appropriate adCTx for elderly patients.

Methods

Medical records of patients with stage II or III CRC who underwent curative resection at five Hallym University-affiliated hospitals in Korea (Dongtan Sacred Heart Hospital, Chuncheon Sacred Heart Hospital, Gangnam Sacred Heart Hospital, Gangdong Sacred Heart Hospital, and Hallym Sacred Heart Hospital) between January 2012 and December 2022 were retrospectively reviewed. In this study, elderly patients were defined as those aged ≥70 years. Although 65 years is frequently used as a general demographic threshold, several CRC studies have also defined elderly patients as those aged ≥70 years.[23–26] Therefore, this cutoff was selected to ensure comparability with prior oncologic literature and to focus on an older population more likely to demonstrate age-related differences in treatment tolerance and outcomes. Patients with synchronous or prior CRC, incomplete medical records, a history of neoadjuvant chemoradiotherapy, or histological diagnoses other than adenocarcinoma (eg., lymphoma, gastrointestinal stromal tumor, or sarcoma) were excluded. The study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB HDT 2024–08-015) and complied with the Declaration of Helsinki. The Institutional Review Board waived the need to obtain informed consent because of the retrospective nature of the study. All patient data were anonymized prior to analysis, and confidentiality of patient information was strictly maintained throughout the study.

The characteristics, perioperative outcomes, and pathologic characteristics were retrieved from the patients' medical records. The patient characteristics were age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA)

score, comorbidities, tumor location, and presence of obstruction/perforation. The perioperative outcomes were emergency surgery, minimally invasive surgery, length of postoperative hospital stay, and complications. The pathologic characteristics included the histological grade of the cancer, tumor size, number of harvested lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), and the Tumor–Node–Metastasis (8^{th} edition) classification.[33] The severity of postoperative complications was categorized according to the Clavien–Dindo classification, where grade ≥3 complications were considered to be severe.[34] First, patients were divided into two groups according to receipt of adjuvant chemotherapy [adCTx (+) vs adCTx (−)], and oncologic outcomes were compared. Among patients who received chemotherapy, further stratification was performed into 5-FU monotherapy and oxaliplatin-based combination therapy groups to compare prognoses. According to the NCCN guidelines, high-risk features include obstruction, perforation, poor differentiation, T4 stage, <12 harvested lymph nodes, LVI, or PNI.[35] Therefore, a subgroup analysis was performed in patients with stage II CRC with any high-risk features to assess oncologic outcomes according to receipt of adjuvant chemotherapy and the number of chemotherapy agents (monotherapy vs combination therapy).

The decision to commence chemotherapy should be primarily based on the consent of the patient and their family. However, even after obtaining consent, the final decision to administer chemotherapy is made by the attending physician according to the patient's overall clinical condition. If selected, chemotherapy should be started within 6 weeks after surgery.

The long-term oncological outcomes were evaluated in terms of OS and RFS. OS was defined as the interval from the date of surgery to the date of death from any cause, with patients alive at last follow-up censored at that time. RFS was defined as the interval from the date of tumor resection to the date of first documented recurrence (local or distant) or death from any cause, with patients without an event censored at last follow-up. These definitions are consistent with commonly accepted survival endpoints in adjuvant trials.[36]

The primary endpoint of this study was to compare the 5-year oncological outcomes (ie., OS and RFS) after surgery according to the use of adCTx. The secondary endpoints were to identify independent risk factors associated with the oncologic outcomes and determine the potential benefit of combination chemotherapy in patients with stage II or III CRC.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as the mean and standard deviation, and categorical variables as the number and percent of patients. Continuous variables were compared using Student's t test, and categorical variables were compared using the χ^2 test. OS and RFS were analyzed using the Kaplan–Meier method and differences were evaluated using log–rank tests. Factors associated with OS and RFS were analyzed using the Cox proportional hazards regression model. A two-sided P-value <0.05 was considered statistically significant. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated to estimate the relative risk of death or recurrence over time between groups. For the multivariable analysis, the following risk factors were considered: sex (male vs female), ASA score (≥III vs <III), BMI (≥25 vs <25 kg/m^2), rectal cancer (vs colon cancer), obstruction/perforation (vs no obstruction/perforation, T4 stage (vs T3), presence of lymph node metastasis (vs none), PNI (vs no PNI), LVI (vs no LVI), severe complications (vs no complications), and administration of chemotherapy (vs no chemotherapy), which were selected based on established clinical relevance and prior evidence identifying them as prognostic factors in CRC.

For age-stratified subgroup analysis, patients were categorized into 70–75 years and >75 years. Kaplan–Meier analyses and Cox regression models were used to compare OS and RFS, and interaction between age group and chemotherapy status was tested within the Cox model. To minimize potential selection bias, inverse probability of treatment weighting (IPTW) based on propensity scores was applied. Propensity scores were estimated using logistic regression including demographic, clinical, and pathological variables. Stabilized weights for the average treatment effect were calculated, and covariate balance was assessed using standardized mean differences (SMDs), with values <0.1 considered indicative of adequate balance. IPTW-adjusted Cox models were constructed, and a doubly robust sensitivity analysis combining IPTW and covariate adjustment was additionally performed.

Results

During the 11-year study period, a total of 1325 elderly patients aged ≥70 years underwent surgery for CRC. Of these, we excluded 27 patients with incomplete data, 22 patients with synchronous CRC, 22 patients with a history of another primary malignancy, and 71 patients who underwent neoadjuvant chemoradiotherapy before surgery. After excluding these 142 patients, 1,183 patients were included in the study, of which 628 patients did not receive chemotherapy [adCTx (−) group] and 555 patients did [adCTx (+) group]. The adCTx (+) group was subdivided into 284 patients who received monotherapy and 271 patients who received combination therapy.

Table 1 lists the patients' characteristics and pathologic outcomes according to the administration of chemotherapy. There was no difference in sex distribution between the two groups, but the mean age was greater in the adCTx (−) group (80.2 vs 75.9 years, P < 0.001), whereas BMI was greater in the adCTx (+) group (23.7 vs 22.6, P < 0.001). The proportion of patients with an ASA score of ≥III (60.0% vs 47.0%, P < 0.001), two or more comorbidities (52.9% vs 46.5%, P = 0.029), and presence of obstruction/perforation (26.6% vs 21.6%, P = 0.047) were greater in the adCTx (−) group. Regarding the pathologic results, histologic grade, number of harvested lymph nodes, and PNI were similar in both groups. However, the adCTx (+) group had a higher rate of LVI (52.9% vs 43.2%, P < 0.001), and greater proportion of stage III (58.7% vs 34.6%, P < 0.001).

Table 1 Patient Characteristics and Pathologic Outcomes by Chemotherapy Status

	adCTx (-) (n = 628)	adCTx (+) (n = 555)	P
Age	80.2 (5.5)	75.9 (4.6)	< 0.001
Sex			0.064
Male	301 (48.0)	296 (53.3)	
Female	327 (52.1)	259 (46.7)	
BMI (kg/m2)	22.6 (3.5)	23.7 (3.5)	< 0.001
ASA score			< 0.001
I/II	251 (40.0)	293 (53.0)	
III/IV/V	377 (60.0)	262 (47.0)	
Comorbidities ≥ 2	332 (52.9)	258 (46.5)	0.029
Location			0.012
Right colon	265 (42.3)	218 (39.4)	
Left colon	220 (35.1)	169 (30.5)	
Rectum	142 (22.6)	167 (30.1)	
Obst/Perfor	167 (26.6)	120 (21.6)	0.047
Complications	183 (29.1)	93 (16.8)	< 0.001
Complications ≥ 2	46 (7.3)	23 (4.1)	0.020
Clavien-Dindo Classification			< 0.001
0–II	562 (89.5)	527 (95.0)	
III–V	66 (10.5)	28 (5.0)	
Histologic grade			0.344
Well/moderately	583 (92.8)	507 (91.4)	
Poorly/undifferentiated	45 (7.2)	48 (8.6)	
n of harvested LN	23.6 (14.1)	23.0 (12.4)	0.531
LVI	270 (43.2)	293 (52.9)	< 0.001
PNI	137 (21.9)	145 (26.2)	0.085
Stage			< 0.001
II	411 (65.4)	229 (41.3)	
III	217 (34.6)	326 (58.7)	

Notes: Data are presented as the number of patients (%) or mean (standard deviation) unless otherwise stated.

Abbreviations: adCTx, adjuvant chemotherapy; n, number; BMI, body mass index; ASA, American Society of Anesthesiologists; Obstr, Obstruction; Perform, perforation; LN, lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion.

The mean duration of follow-up was 38.8. months (range, 2–110 months; adCTx (-) group: 38.3 months; adCTx (+) group: 39.2 months).In the total cohort, 5-year OS (88.6% vs 75.7%, P < 0.001) and 5-year RFS (66.5% vs 58.6%, P < 0.001) were better in the adCTx (+) group than in the adCTx (−) group (Figure 1A and B). Similarly, when analyzed by disease stage, the adCTx (+) group had better outcomes than the adCTx (−) group among patients with stage II CRC (5-year OS: 93.3% vs 82.2%, P < 0.001; 5-year RFS: 73.4% vs 65.5%, P = 0.021; Figure 1C and D) and stage III CRC (5-year OS: 84.9% vs 58.7%, P < 0.001; 5-year RFS: 61.5% vs 47.2%, P < 0.001; Figure 1E and F).

The clinicopathologic characteristics of patients who received monotherapy and those who received combination therapy in the adCTx (+) group were compared (Table 2). There were no significant differences between the two groups, except for the number of harvested lymph nodes (P = 0.019), presence of LVI (P = 0.012), and the proportion of stage III disease (P < 0.001). Among patients who underwent adjuvant chemotherapy, treatment discontinuation occurred in 57 patients (20.1%) in the monotherapy group and 67 patients (24.7%) in the combination therapy group, with no significant difference between the groups (P = 0.221).

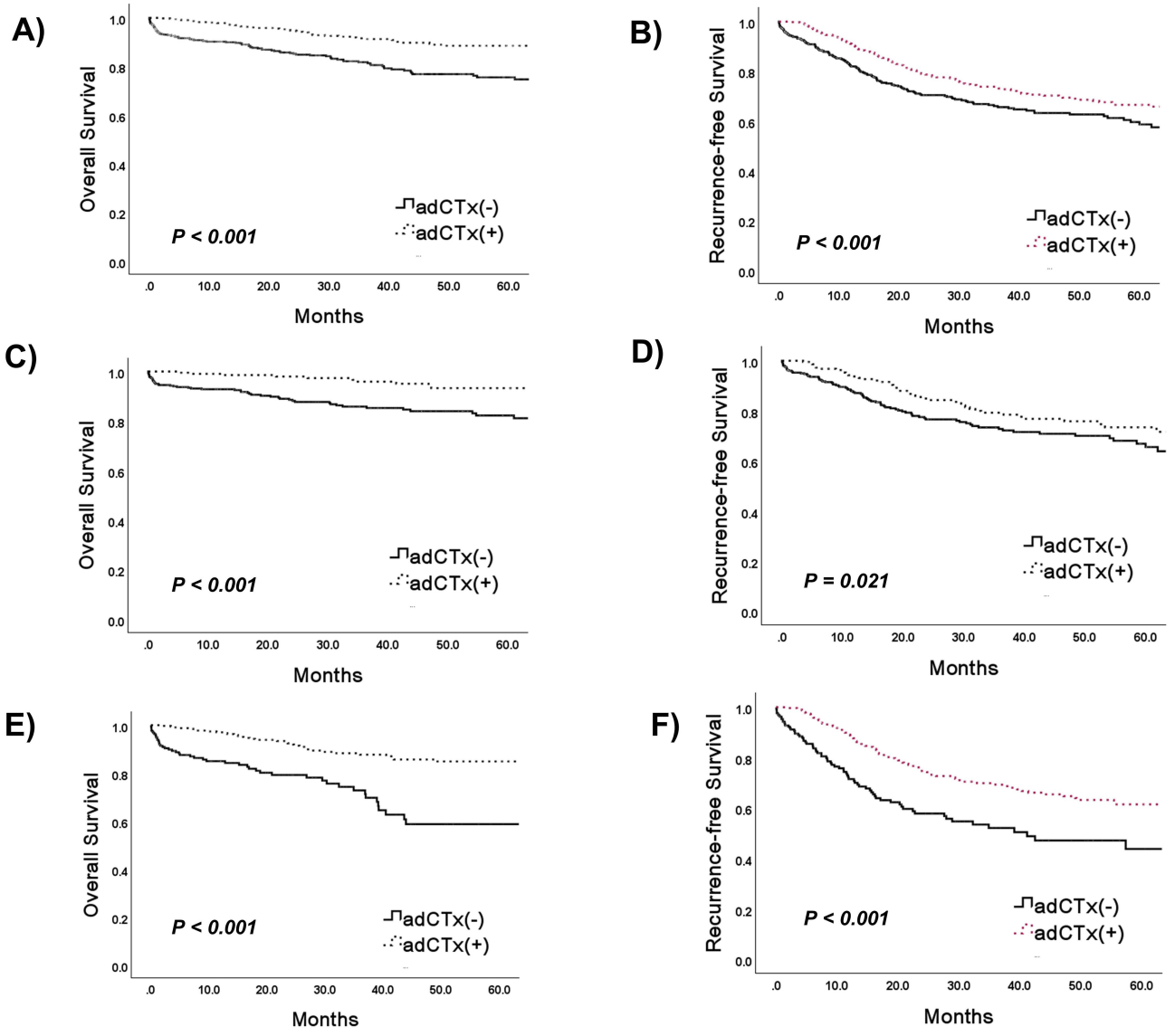

Figure 1 Comparison of oncologic outcomes according to adjuvant chemotherapy (adCTx) in elderly patients with stage II–III colorectal cancer (adCTx (+) vs (-)). Stage II–III: 5-year overall survival (OS) (88.6% vs 75.5%, P < 0.001) (**A**) and recurrence-free survival (RFS) (66.5% vs 58.6%, P < 0.001) (**B**). Stage II: 5-year OS (93.3% vs 82.2%, P < 0.001) (**C**) and RFS (73.4% vs 65.5%, P = 0.021) (**D**). Stage III: 5-year OS (84.9% vs 58.1%, P < 0.001) (**E**) and RFS (61.5% vs 47.2%, P < 0.001) (**F**).

https://doi.org/10.2147/CMAR.S589756

Table 2 A Comparison of Patient Characteristics by Monotherapy and Combination Therapy

	Monotherapy (n = 284)	Combination Therapy (n = 271)	P
Male	140 (49.3)	150 (55.3)	0.081
BMI (kg/m2)	23.5 (4.7)	23.8 (4.0)	0.981
ASA score ≥ III	121 (42.6)	139 (51.5)	0.036
Obst/Perfor	52 (18.3)	68 (25.1)	0.073
Severe complications[a]	14 (4.9)	14 (5.2)	0.899
Poorly/undifferentiated	28 (9.9)	20 (7.4)	0.299
n of harvested LN	22.4 (11.4)	23.7 (13.3)	0.019
LVI	135 (47.7)	158 (58.3)	0.012
PNI	84 (29.7)	61 (22.5)	0.066
Stage			<0.001
II	155 (54.6)	74 (27.3)	
III	129 (45.4)	197 (72.7)	
Chemotherapy regimen'			
5-FU/leucovorin	153 (53.9)		
Capecitabine	111 (39.0)		
Tegafur-uracil/leucovorin	20 (7)		
FOLFOX4		218 (80.4)	
FOLFOX 6		29 (10.7)	
XELOX		24 (8.9)	
Discontinuation	57 (20.1)	67 (24.7)	0.221

Notes: [a]Severe complication referred to the Clavien-Dindo Classification ≥ III. Data are presented as the number of patients (%) or mean (standard deviation) unless otherwise stated.
Abbreviations: adCTx, adjuvant chemotherapy; n, number; BMI, body mass index; ASA, American Society of Anesthesiologists; Obstr, Obstruction; Perfor, perforation; LN, lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion.

In terms of survival outcomes, there were no significant differences in OS or RFS between patients who received monotherapy and those who received combination therapy (OS: 90.9% vs 86.7%, P = 0.575; RFS: 68.2% vs 66.4%, P = 0.951) (Figure 2A and B). When analyzed according to disease stage, no significant differences in OS or RFS were observed between the two groups either in stage II (OS: 94.6% vs 90.4%, P = 0.661; RFS: 75.1% vs 69.1%, P = 0.822) (Figure 2C and D) or stage III disease (OS: 85.9% vs 84.9%, P = 0.705; RFS: 60.1% vs 62.9%, P = 0.424) (Figure 2E and F).

Risk factors for OS and RFS were evaluated, and the corresponding results are presented in Tables 3 and 4. Univariate analysis showed that ASA score ≥ 3 (P < 0.001), obstruction/perforation (P < 0.001), the presence of lymph-node metastasis (P = 0.003), LVI (P = 0.013), and severe complications (P < 0.001) were associated with worse OS. In the multivariable analysis, ASA score ≥ 3 (P = 0.031), obstruction/perforation (P = 0.001), presence of lymph node metastasis (P < 0.001), and severe complications (P < 0.001) were independently associated with worse OS. Adjuvant chemotherapy was associated with better OS in univariate (P < 0.001) and multivariate analysis (P < 0.001) (Table 3).

As for RFS, univariate analysis showed that ASA score ≥ 3 (P < 0.001), rectal cancer (P = 0.037) obstruction/perforation (P < 0.001), T4 (P < 0.001), presence of lymph node metastasis (P < 0.001), LVI (P < 0.001), PNI (P = 0.006), and severe complications (P < 0.001) were independently associated with worse RFS. In the multivariable analysis, ASA score ≥ 3 (P < 0.001), rectal cancer (P = 0.005), obstruction/perforation (P < 0.001), T4 (P = 0.007), presence of lymph node metastasis (P < 0.001), and severe complications (P = 0.004) were independently associated with worse RFS. Adjuvant chemotherapy was also associated with better RFS in univariate (P < 0.001) and multivariate analysis (P < 0.001) (Table 4).

To further address potential selection bias, IPTW-adjusted survival analyses were performed. After weighting, baseline covariates were well balanced between groups (all SMDs < 0.1; Supplementary Table 1). In the IPTW-adjusted Cox model, adjuvant chemotherapy remained significantly associated with improved overall survival (HR:

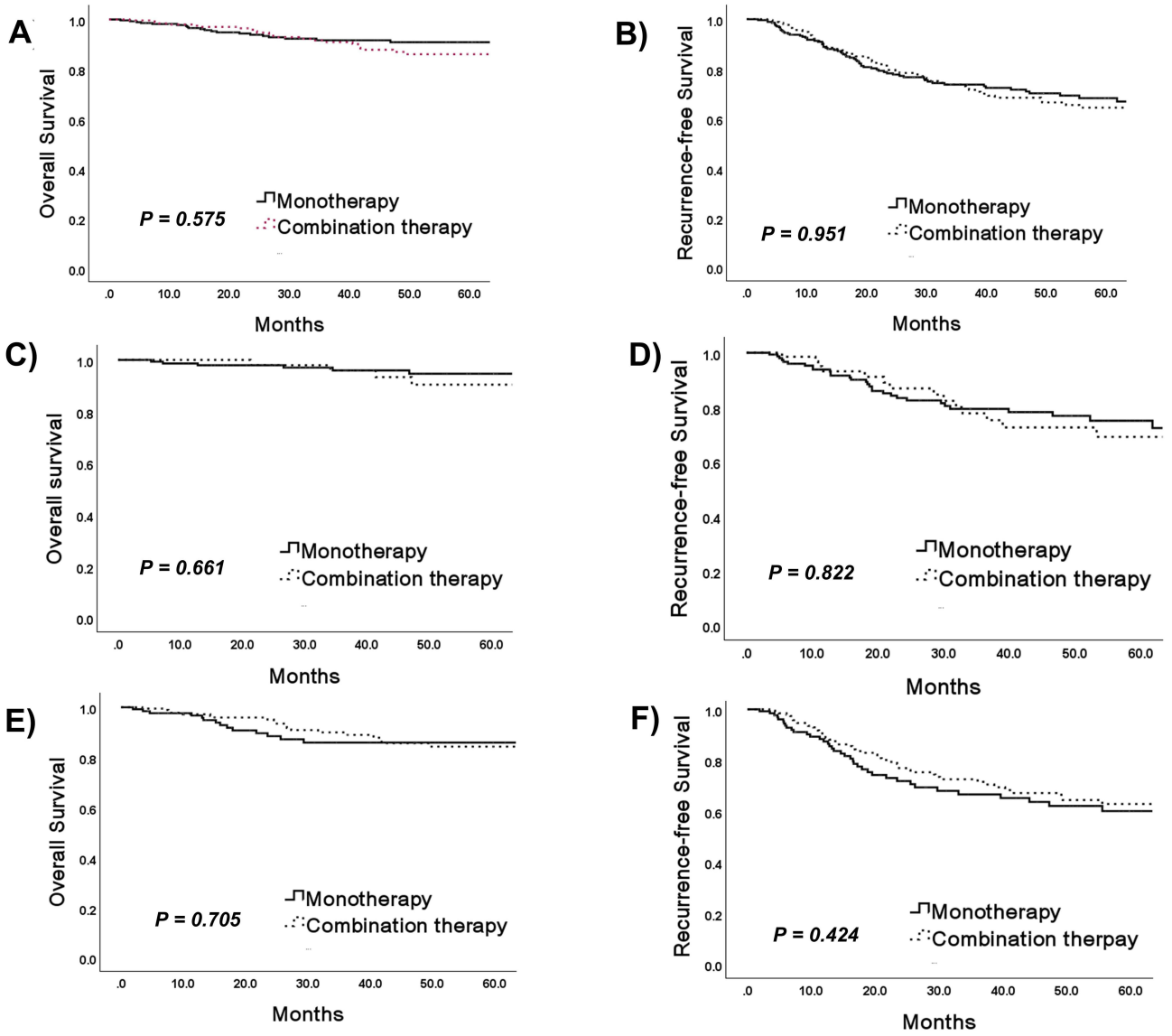

Figure 2 Comparison of oncologic outcomes of elderly patients with stage II or III colorectal cancer according to the number of chemotherapeutic agents (monotherapy vs combination therapy). Stage II–III: 5-year overall survival (OS) (90.9% vs 86.7%, P = 0.575) (**A**) and recurrence-free survival (RFS) (68.2% vs 66.4%, P = 0.951) (**B**). Stage II: 5-year OS (94.6% vs 90.4%, P = 0.661) (**C**) and RFS (75.1% vs 69.1%, P = 0.822) (**D**). Stage III: 5-year OS (85.9% vs 84.9%, P = 0.705) (**E**) and RFS (60.1% vs 62.9%, P = 0.424) (**F**).

0.467; 95% CI: 0.298–0.733; P < 0.001). Similar results were observed in the doubly robust model (HR: 0.444; 95% CI: 0.277–0.711; P < 0.001) (Supplementary Table 2 and 3).

In a subgroup analysis of patients with stage II CRC and positive risk factors, those who received chemotherapy had better 5-year OS (adCTx (-) vs adCTx (+): 81.6 vs 91.0%, P = 0.002; Figure 3A) and 5-year RFS (60.8% vs 71.0%, P = 0.006; Figure 3B). However, the number of chemotherapeutic agents did not result in significant differences in terms of either 5-year OS (monotherapy vs combination therapy: 90.5% vs 91.9%, P = 0.539) (Figure 3C) or 5-year RFS (63.3% vs 76.5% P = 0.200) (Figure 3D).

Consistent with in the overall cohort, subgroup analyses stratified by age (70–75 years vs >75 years) also demonstrated that adjuvant chemotherapy significantly improved OS, with no significant interaction between age group and treatment effect (interaction P: OS = 0.307, RFS = 0.886). Furthermore, in both age subgroups, combination therapy did not provide additional benefit over monotherapy (Supplementary Table 4).

https://doi.org/10.2147/CMAR.S589756

Table 3 Univariate and Multivariate Analysis of Overall Survival

Variable	Univariate		Multivariate	
	HR [a](95% CI)	*P*	HR (95% CI)	*P*
Male	0.842 (0.612–1.158)	0.290	0.733 (0.531–1.011)	0.059
ASA score ≧ III	1.740 (1.253–2.417)	< 0.001	1.444 (1.034–2.017)	0.031
BMI ≥ 25	0.846 (0.591–1.210)	0.359	1.001 (0.694–1.442)	0.999
Rectal cancer	0.839 (0.581–1.210)	0.347	0.944 (0.651–1.370)	0.763
Obs/perfor	2.177 (1.566–3.027)	< 0.001	1.775 (1.259–2.501)	0.001
T4	1.379 (0.896–2.121)	0.144	1.073 (0.681–1.690)	0.760
Presence of LN (+)	1.617 (1.175–2.224)	0.003	1.992 (1.395–2.845)	< 0.001
LVI	1.499 (1.090–2.061)	0.013	1.221 (0.857–1.739)	0.269
PNI	1.272 (0.886–1.826)	0.193	1.082 (0.738–1.585)	0.687
Severe complications[b]	3.708 (2.455–5.602)	< 0.001	2.757 (1.810–4.202)	< 0.001
adCTx	0.377 (0.267–0.532)	< 0.001	0.332 (0.229–0.479)	< 0.001

Notes: [a]HRs were calculated using Cox proportional hazards regression models. [b]Severe complication referred to the Clavien-Dindo Classification ≥ III.

Abbreviations: HR, Hazard Ratio; CI, Confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index; Obstr, Obstruction; Perfor, perforation; LN, lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion; adCTx, Adjuvant chemotherapy.

Table 4 Univariate and Multivariate Analysis of Recurrence-Free Survival

Variable	Univariate		Multivariate	
	HR[a] (95% CI)	*P*	HR (95% CI)	*P*
Male	0.880 (0.703–1.102)	0.264	0.828 (0.661–1.039)	0.103
ASA score ≧ III	1.756 (1.392–2.213)	< 0.001	1.505 (1.189–1.904)	< 0.001
BMI ≥ 25	0.904 (0.706–1.157)	0.422	0.979 (0.764–1.262)	0.867
Rectal cancer	1.288 (1.015–1.635)	0.037	1.412 (1.110–1.798)	0.005
Obs/perfor	1.872 (1.472–2.381)	< 0.001	1.692 (1.322–2.165)	< 0.001
T4	1.928 (1.457–2.553)	< 0.001	1.501 (1.117–2.017)	0.007
Presence of LN (+)	1.544 (1.233–1.934)	< 0.001	1.555 (1.213–1.994)	< 0.001
LVI	1.494 (1.193–1.872)	< 0.001	1.244 (0.972–1.593)	0.083
PNI	1.426 (1.108–1.834)	0.006	1.156 (0.885–1.509)	0.288
Severe complications[b]	2.144 (1.500–3.066)	< 0.001	1.708 (1.191–2.451)	0.004
adCTx	0.669 (0.534–0.839)	< 0.001	0.594 (0.467–0.755)	< 0.001

Notes: [a]HRs were calculated using Cox proportional hazards regression models. [b]Severe complication referred to the Clavien-Dindo Classification ≥ III.

Abbreviations: HR, Hazard Ratio; CI, Confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index; Obstr, Obstruction; Perfor, perforation; LN, lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion; adCTx, Adjuvant chemotherapy.

Discussion

This study demonstrated that patients who received chemotherapy had better OS and RFS than those who did not, consistent across stage II and III CRC. In multivariable analysis, adCTx was associated with improved OS and RFS. No significant differences in OS or RFS were found between monotherapy and combination therapy in either stage II or III CRC. Additionally, in stage II CRC patients with risk factors, adCTx improved survival, but no differences were observed between monotherapy and combination therapy.

Recent studies indicate that elderly patients (aged ≥70 years) are less likely to receive chemotherapy and more likely to discontinue it.[5,6,21,37] Contributing factors include age, comorbidities, economic constraints, fear of chemotherapy, and lack of family support.[21,38] In this study, the adCTx (−) group had more patients with multiple comorbidities (52.9% vs 46.5%, P = 0.029) and an ASA score ≥III (60.0% vs 47.0%, P < 0.001) than the adCTx (+) group. Jung et al reported that

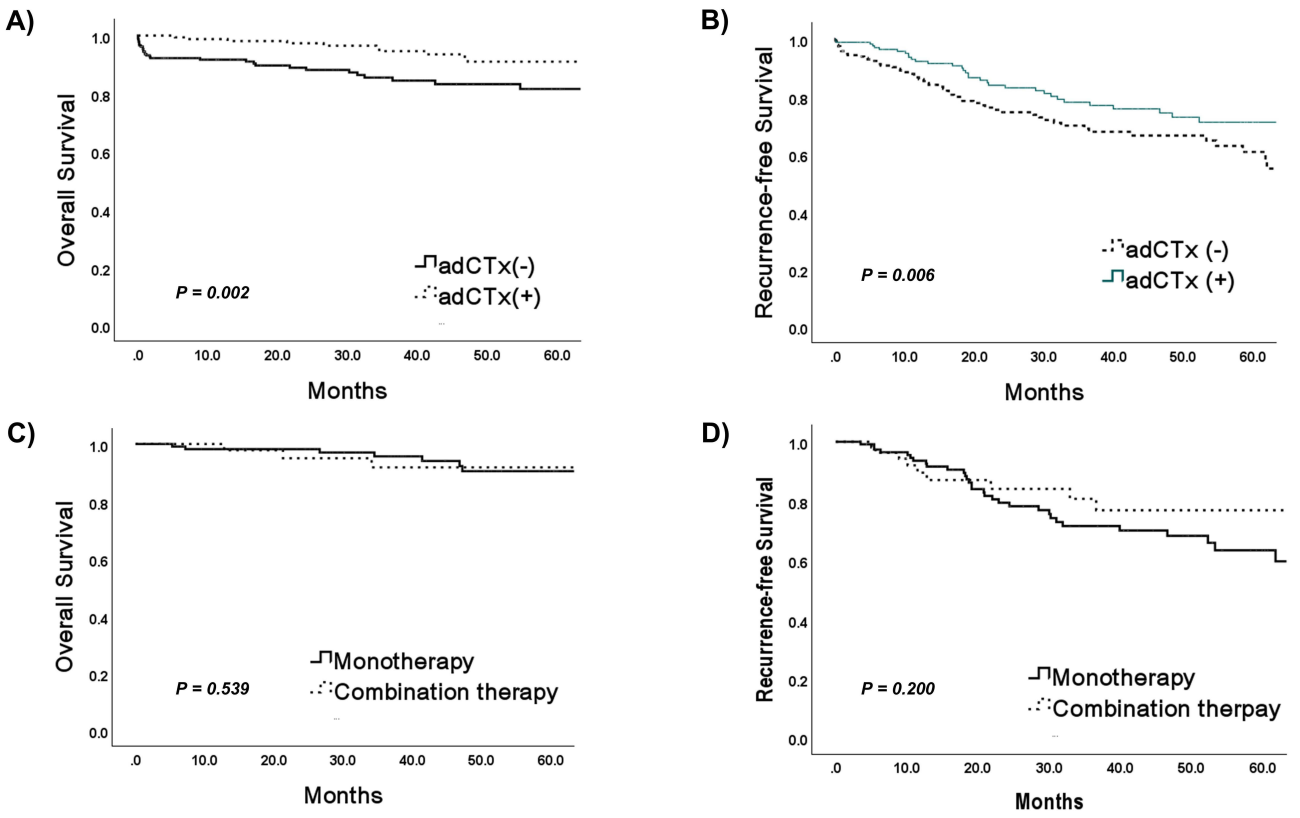

Figure 3 Comparison of oncologic outcomes of elderly patients with stage II colorectal cancer and positive risk factors; adjuvant chemotherapy (+) vs (-): (**A**) 5-year overall survival (OS) (91.0% vs 81.6%, P = 0.002), (**B**) 5-year recurrence free survival (RFS) (71.1% vs 60.8%, P = 0.006); monotherapy vs combination therapy: (**C**) 5-year OS (90.5% vs 91.9%, P = 0.539), (**D**) 5-year RFS (63.3% vs 76.5%, P = 0.200).

patients with metastatic disease were more likely to refuse treatment than those with localized disease (44% vs 16.3%).[39] These findings indicate that treatment decisions in elderly patients are influenced not only by disease stage but also by overall health status and comorbidity burden. In this population, therapeutic choices require careful balancing of potential survival benefits against the risks of toxicity.

A primary reason for discontinuing chemotherapy among elderly patients is treatment-related toxicity. Shibutani et al compared monotherapy and combination therapy safety in CRC patients aged ≥70 years, finding higher rates of grade ≥3 adverse events (46.2% vs 17.0%, P = 0.001) and overall adverse events (100% vs 62.3%, P < 0.001) in the combination therapy group, leading to a lower relative dose intensity (69.2% vs 100%, P < 0.001).[40] Haller et al reported that patients receiving XELOX had higher rates of grade ≥3 chemotherapy-related adverse events (55% vs 47%, P < 0.05), including neurosensory toxicity (11% vs 1%), hand-foot syndrome (5% vs 1%), and thrombocytopenia (5% vs 1%).[41] Even minor adverse events (grade 1 or 2) may lead to chemotherapy discontinuation in elderly patients, affecting prognosis due to insufficient treatment.

Studies on adCTx in elderly CRC patients show inconsistent results.[19–24] Lee et al conducted a 1:1 matching study of patients aged ≥70 years with stage II colon cancer, comparing surgery alone versus surgery plus adCTx. They found no differences in RFS, cancer-specific survival, or OS.[23] Conversely, a study using Korean national data showed adCTx effectiveness in both high- and low-risk groups.[19] This study found that, whether analyzed together or separately, patients in the adCTx (+) group had superior OS and RFS compared to the adCTx (−) group.

Although oxaliplatin plus 5-FU is a standard chemotherapy regimen for advanced CRC,[16] its efficacy in older patients remains controversial. Some studies support combination therapy for elderly patients,[20,25,26] while others suggest it increases toxicity and reduces efficacy, favoring monotherapy.[18,27–29] Brungs et al reported that adding oxaliplatin to 5-FU improved survival in stage III colon cancer patients aged ≥70 years (HR: 0.64; 95% CI: 0.5–0.9, P = 0.005).[26] However, in this study, OS and RFS did not significantly differ between monotherapy and combination therapy in stage II

https://doi.org/10.2147/CMAR.S589756

& III (OS: P = 0.575, RFS, P = 0.951), stage II (OS: P = 0.661; RFS: P = 0.822) and stage III (OS: P = 0.705; RFS: P = 0.424) CRC patients.

Several guidelines, including the Korean and NCCN guidelines, recommend adCTx for stage II CRC patients with high-risk factors.[35,42] Several studies examined adCTx benefits for elderly stage II CRC patients based on the presence and number of risk features. A Korean Health Insurance Review and Assessment Service analysis identified adCTx as an independent prognostic factor in high-risk elderly patients (HR: 0.48; 95% CI: 0.37–0.63, P < 0.001).[19] Conversely, Lee et al found no significant differences in RFS (adjusted HR: 2.19; 95% CI: 0.77–6.25, P = 0.143), cancer-specific survival (adjusted HR: 1.04; 95% CI: 0.18–2.44, P = 0.942), or OS (adjusted HR: 0.83; 95% CI: 0.36–1.89, P = 0.649) in the high-risk group.[23] In this study, the subgroup analysis of patients with risk factors showed that adCTx (+) patients had better OS (81.6% vs 91.0%, P = 0.002) and RFS (60.8% vs 71.1, P = 0.006) than adCTx (−) patients. Additionally, there was no significant difference in OS (P = 0.539) or RFS (P = 0.200) between monotherapy and combination therapy in this subgroup, though the sample size was small.

Moreover, while general guidelines provide standardized recommendations, they can be modified according to individual patient conditions. In particular, oxaliplatin may be considered in elderly patients aged ≥70 years if liver, kidney, and other vital organ functions are preserved. Nevertheless, our findings suggest that monotherapy remains an adequate option for most elderly patients, underscoring the importance of balancing guideline recommendations with patient-specific clinical judgment.

This study has several limitations. First, this was a retrospective, non-randomized study in which treatment allocation was not randomly assigned. Therefore, inherent selection bias cannot be completely excluded and the generalizability of the findings may be limited. Baseline differences between groups, including younger age and lower ASA score in the adCTx (+) group, further reflect the potential for treatment selection bias. To mitigate this limitation, IPTW based on propensity scores was applied, and adequate covariate balance was achieved (all SMDs < 0.1). The survival benefit of adjuvant chemotherapy remained significant in IPTW-adjusted and doubly robust analyses. Nevertheless, residual confounding from unmeasured variables cannot be entirely excluded. Second, this study included only patients aged ≥70 years with stage II or III colorectal adenocarcinoma who underwent curative resection at university-affiliated hospitals. Therefore, the findings may not be generalizable to younger patients, those with stage I or IV disease, patients with non-adenocarcinoma histology, or those treated in different clinical settings. Third, some influential factors were not analyzed, such as actual chemotherapy dosage, reasons for discontinuation, and detailed adverse effects. Although treatment discontinuation rates were reported, comprehensive toxicity data were not consistently available due to the retrospective design. Therefore, comparative tolerability between monotherapy and combination therapy could not be fully assessed. Finally, the study's sample size was smaller than big data studies, limiting definitive conclusions about chemotherapy effectiveness. Future prospective randomized studies are warranted to validate these findings and to better define optimal adjuvant treatment strategies in elderly patients. Nevertheless, these findings suggest that carefully selected patients aged ≥70 years with stage II or III colon cancer may benefit from adCTx.

Conclusion

In this retrospective multicenter study of patients aged ≥70 years with stage II or III CRC, adjuvant chemotherapy was associated with improved OS and RFS. No significant differences in oncologic outcomes were observed between monotherapy and combination therapy. These findings suggest a potential benefit of adjuvant chemotherapy in selected elderly patients. However, given the retrospective nature of this study, prospective randomized studies are needed to confirm these results.

Data Sharing Statement

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

Ethic Statement

The study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB HDT 2024-08-015) and complied with the Declaration of Helsinki. The Institutional Review Board waived the need to obtain informed consent because of the retrospective nature of the study.

Acknowledgment

The authors thank Jinseob Kim (Zarathu Co., Ltd) for his support and encouragement during this project.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors have no competing interests to declare that are relevant to the content of this article.

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