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Original Article

Survival Outcomes of Adjuvant Chemotherapy in Elderly Patients with Stage III Colon Cancer

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Abstract

Background: The survival impact of multi-agent (MAC) compared with single-agent (SAC) adjuvant chemotherapy (AC) in elderly patients with stage III colon cancer (CC) remains controversial. The aim of this study was to compare survival outcomes of MAC and SAC in this population utilizing the National Cancer Database (NCDB).

Patients and Methods: Patients aged ≥70 years with pathological stage III CC diagnosed in 2004-2015 were identified in the NCDB. Univariate and multivariable analyses were conducted, and Kaplan-Meier analysis and Cox proportional hazard models were used to identify associations between MAC vs. SAC and overall survival (OS).

Results: Among 41 707 elderly patients (≥70 years old) with stage III CC, about half (n = 20 257; 48.5%) received AC; the majority (n = 12 923, 63.8%) received MAC. The median age was 79 (range 70-90). The majority were female (n = 11 201, 55.3%), Caucasians (88%) and had moderately differentiated tumor grade (n = 12 619, 62.3%), tumor size >4 cm (11 785, 58.2%), and negative surgical margins (18 496, 91.3%). Low-risk stage III CC constituted 50.6% (n = 10 264) of the study population. High-risk stage III CC was associated with worse OS compared with low-risk disease (HR 0.35, 0.34-0.36, P < .001). Multi-agent chemotherapy was associated with a better 5-year OS compared with SAC (P < .001). High-risk stage III patients who received MAC vs. SAC had an OS of 4.2 vs. 3.4 years, respectively (P < .001). Low-risk stage III patients who received MAC vs. SAC had a median OS of 8.5 vs. 7 years (P < .001). In univariate and multivariable analyses, male sex, positive surgical margin, insurance and facility types, age, year of diagnosis, tumor size, and Charlson-Deyo score of >2 were associated with worse OS (P < .05).

Conclusions: Any adjuvant chemotherapy has a trend of survival benefits. Multi-agent chemotherapy seems to have an enhanced benefit in the 70-75 age group. Multi-agent chemotherapy seemed to have similar efficacy as SAC in those aged >76 years.

Key words: multi-agent chemotherapy; single-agent chemotherapy; above 70-survival; high risk; stage III; colon cancer.

Implications for Practice

The standard of care for patients with resected stage III colon cancer is adjuvant chemotherapy with 5-fluorouracil (5-FU) based treatment in combination with oxaliplatin. Elderly patients are under-represented in prospective adjuvant studies and the benefit of adding oxaliplatin to the 5-FU chemotherapy is not established in patients 70 years or older. This analysis is the largest retrospective data analysis showing the survival benefit of multi-agent chemotherapy when compared with single-agent chemotherapy in the adjuvant setting for stage III colon cancer in patients aged 70 years and older.

Introduction

Colorectal cancer (CC) is considered one of the most prevalent malignancies worldwide.[1] It ranks third in mortality rate after lung and prostate cancer, with approximately 861 000 deaths annually[1] and accounts for approximately 8% of all cancer deaths in the US.[2] Around 35% of patients with CC have stage III disease at presentation.[3] Age is a major risk factor for CC[4] with a median age at diagnosis of 67 years.[5] Approximately 57% of cases develop in patients over the age of 65 and 32% in those 75 years or older. The elderly population is expected to rise and thus the number of CC patients above the age of 70 will rise in parallel.[6]

Current clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend adjuvant chemotherapy (AC) as a standard treatment for patients in all age groups with stage III CC. This is based on the proven reduction in the risk of relapse and the survival benefits with overall survival (OS) benefit of 22%-32%[7,8] and a 30% relative risk reduction over surgery alone.[8] The standard of care

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now is doublet chemotherapy of fluoropyrimidine and oxaliplatin. The duration of AC depends on the risk of the stage III disease (high-risk stage, T4 or N2, low-risk stage, T3N1).[9] Analysis of 37 568 patients enrolled in 25 randomized trials of adjuvant systemic therapy derived from the ACCENT database noted that early mortality (within one to 6 months of starting adjuvant chemotherapy) was significantly more prevalent in older patients, particularly those over the age of 70.[6]

The National Comprehensive Cancer Network (NCCN) guidelines recommend multi-agent chemotherapy (MAC) in the adjuvant setting for stage III CC. However, for stage III resected CC patients above the age 70 years, NCCN commented with the statement "A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years and older has not been proven."[10,11] In fact, there is evidence that patients over 70 years who received MAC in the adjuvant setting have worse survival outcomes when compared with single-agent chemotherapy (SAC).[11] Although the median age at diagnosis of CC is 67 years, there are no prospective studies addressing the benefits of AC in the elderly population. The median ages of patients in the prospective AC studies range between 58 and 64 years.[3,12] The underrepresentation of the elderly population in prospective AC trials could be due to restrictive eligibility criteria, poor functionality, major comorbidities, or investigator bias.[13] Therefore, the generalizability of the results of these prospective studies to the elderly patient population seen in the clinics is limited and this represents an area of unmet need. Given these limitations, population-based outcome analyses are extremely important in providing evidence for clinical management. Therefore, this age group-based study was conducted to assess the impact of single-agent or multi-agent chemotherapy on the survival of patients over the age of 70 with stage III CC using the National Cancer Database (NCDB).

Patients and Methods

The NCDB includes over 1500 Commission-on-Cancer-accredited cancer programs and contains clinical and demographic data on the majority of US cancer patients. A total of 41 707 elderly patients (>70 years old) with stage III CC diagnosed between 2010 and 2015 were identified. Selection criteria included node-positive resected colon adenocarcinoma using the following ICD-O-3 morphology and topography codes: 8140, 8480, and C18.0-18.8. High-risk stage III disease is defined as pathologic stage T3N2, T4N1, and T4N2, and low-risk disease is defined as T3N1. Patients with missing follow-up data, unknown stage, prior chemotherapy, or radiation, and unknown sequence of chemotherapy to surgery were excluded. Kaplan-Meier analysis was conducted to analyze survival. Charlson-Deyo (CD) scores, which quantitated the number of comorbidities from 0 to 2, were examined. Chi-square analysis was done to determine the significance of survival differences between the treatment groups. The primary outcome was to determine the impact of single or multi-agent chemotherapy on the overall survival in patients above 70 years of age with resected stage III CC. Patient-specific covariates included age at diagnosis, gender, race, tumor size, grade, risk group, insurance status, surgical margins, year of diagnosis, and treatment received. Ethical approval was not required for the study since patient information in the database is completely de-identified and the database is legally accessible to the public.

Statistical Analysis

The clinical and demographic characteristics of the patients were summarized using descriptive statistics as appropriate for variable type and distribution. For numeric covariates, the mean, median, minimum, maximum, and standard deviation were presented. Frequency and its percentage were generated for categorical variables. For descriptive statistics, chi-square tests were presented for categorical variables and *t*-tests for continuous variables. Two-sample 2-sided *Z*-test was used to test the univariate association between patients with surgery and without surgery, as well as other treatment comparison groups. All clinically meaningful variables were included and subsequently eliminated based on the level of significance. Univariate and multivariate analyses were conducted to identify factors associated with patient outcomes. To assess the association between patient characteristics and survival, Cox proportional hazard models were fitted with a backward elimination method (removal criteria $P = .05$). The likelihood ratio test (LRT) was used to compare the model with the covariate being assessed; both added with the model and with the assessed covariate dropped. An alpha level of 0.05 was used, and any covariate with an LRT *P*-value of >.05 was removed from the final multivariate model. We used backward elimination to automate the LRTs, and determine the final model with the covariates presented. Sensitivity analysis was added to force the covariates with concerns back to the multivariate model to ascertain a significant association with overall survival (OS). Kaplan-Meier curves were generated for overall survival. All analyses were done using SAS 9.4 (SAS Institute, Inc., Cary, NC) with a significance level of .05.

Results

Patient Demographics and Tumor Characteristics

A total of 41 707 patients above 70 years of age with resected stage III CC were identified; 21 485 (51.5%) had low risk and 20 222 (48.5%) high risk disease. Baseline clinicopathological characteristics are summarized in Table 1. The median age was 79 (range, 70-90) years. There was a preponderance of females (n = 24 163, 57.9%) and Caucasians (n = 36 219, 87.4%). The most common primary tumor sites were right-sided (cecum (n = 12 307, 29.5%), and ascending colon (n = 10 545, 25.3%)), followed by sigmoid colon (n = 8242, 19.8%), and transverse colon (n = 4264, 10.2%). The majority of tumors were graded as moderately differentiated (n = 25 508, 61.2%), followed by poorly differentiated (n = 11 924, 28.6%) and well differentiated (= 2500, 6.0%). Charlson-Deyo scores of 0, 1, 2, and ≥3 were observed in 61.7%, 25.8%, 8.6%, and 3.9% of patients; respectively. Insurance coverage was mostly governmental (89.8%) in comparison to private insurance (9.7%), and no insurance (0.5%) (Table 1). The 90-day mortality reached 11% in the whole population, reaching 25% in the high risk and 16% in the low-risk stage III CC in the no chemotherapy group.

Treatment

Adjuvant Chemotherapy

Almost half of the patients (n = 20 257, 48.6%) received either SAC or MAC and met the inclusion criteria of the final analysis (Fig. 1). Adjuvant treatment was delivered to 49.3% of the patients at a community practice site, and to 23.0% at an academic or research center. Almost half of

Table 1. Descriptive statistics for all variables of interest in patients with stage III CC.

Variable label	Level	*N* (%) = 41 707
Facility type	Community cancer program	5458 (13.1)
	Comprehensive community cancer program	20 541 (49.3)
	Academic/research program	9593 (23.0)
	Integrated network cancer program	6115 (14.7)
Facility location	Northeast	9606 (23.0)
	South	13 894 (33.3)
	Midwest	11 815 (28.3)
	West	6392 (15.3)
Age at diagnosis	Mean	79.42
	Median	79.00
	Minimum	70.00
	Maximum	90.00
	SD	6.04
	Missing	0.00
Sex	Male	17 544 (42.1)
	Female	24 163 (57.9)
Median income quartiles 2000	<$30 000	5347 (13.2)
	$30 000-$34 999	7316 (18.0)
	$35 000-$45 999	11 675 (28.7)
	≥$46 000	16 305 (40.1)
	Missing	1064
Primary site	C180-cecum	12 307 (29.5)
	C182-ascending colon	10 545 (25.3)
	C183-hepatic flexure of colon	2156 (5.2)
	C184-transverse colon	4264 (10.2)
	C185-splenic flexure of the colon	1317 (3.2)
	C186-descending colon	2124 (5.1)
	C187-sigmoid colon	8242 (19.8)
	C188-overlapping lesion of colon	752 (1.8)
Grade	Well differentiated, differentiated, NOS	2500 (6.0)
	Moderately differentiated, moderately well-differentiated, and intermediate differentiation	25 508 (61.2)
	Poorly differentiated	11 924 (28.6)
	Undifferentiated, anaplastic	1775 (4.3)
Risk	Low risk	21 485 (51.5)
	High risk	20 222 (48.5)
Race	White	36 219 (87.4)
	Black	3687 (8.9)
	Other	1532 (3.7)
	Missing	269
Hispanic ethnicity	No	37 705 (95.8)
	Yes	1663 (4.2)
	Missing	2339
Insurance type	Not insured	215 (0.5)
	Private insurance	3989 (9.7)
	Government insurance	36 963 (89.8)
	Missing	540
Year of diagnosis	2004-2006	8507 (20.4)
	2007-2009	7216 (17.3)
	2010-2012	12 614 (30.2)
	2013-2015	13 370 (32.1)
Surgical margins	Negative	37 574 (90.9)
	Positive	3764 (9.1)
	Missing	369
Charlson-Deyo scores	0	25 728 (61.7)
	1	10 774 (25.8)
	≥2	5205 (12.5)
Tumor size	≤2 cm	1660 (4.1)
	2-4 cm	14 007 (34.3)
	>4 cm	25 201 (61.7)
	Missing	839
Chemotherapy type	No chemotherapy	21 450 (51.4)
	Single-agent chemotherapy (SAC)	7334 (17.6)
	Multi-agent chemotherapy (MAC)	12 923 (31.0)

the treated patients were low-risk (n = 10 264, 50.6%), the majority of these patients (n = 6236, 60.8%) received MAC. Baseline clinicopathological characteristics for patients with low-risk stage III CC who received chemotherapy are summarized in Supplementary Table S1. Low-risk stage III CC patients treated with SAC and MAC included more females (58.4% and 52.6%), government-insured patients (88.9% and 88.7%), patients with moderately differentiated tumors (68.9% and 68.2%, P = .259), patients with Charlson-Deyo score of 0 (63.3% and 66.3%, P < .001), and those treated within a comprehensive community cancer program (50.1% and 47.8%, P < .029), compared with males, private insurance/uninsured, well/poorly differentiated tumors, Charlson-Deyo score >1, and academic/research programs, respectively. The median age at diagnosis for low-risk stage III disease was higher for patients receiving SAC (78 years) compared with MAC (75 years) (in Supplementary Table S1).

Among patients with high-risk stage III CC, the majority (n = 6687, 66.9%) received MAC. Baseline clinicopathological characteristics for patients with high-risk stage III CC who received chemotherapy are summarized in Supplementary Table S2. Patients treated with SAC and MAC included more females (59.5% and 53.9%), Caucasians (88.3% and 88.17%), government-insured patients (89.27% and 89.51%), patients with moderately differentiated tumors (55.9% and 56.0%) and Charlson-Deyo score = 0 (61.3% and 67.94%), and those treated at a comprehensive community cancer program (49.6% and 48.5%) compared with males, private insurance/uninsured, well/poorly differentiated tumors, Charlson-Deyo score >1, and academic/research programs, respectively. The median age at diagnosis was slightly higher for patients receiving SAC (79 years) compared with MAC (76 years) (Supplementary Table S2).

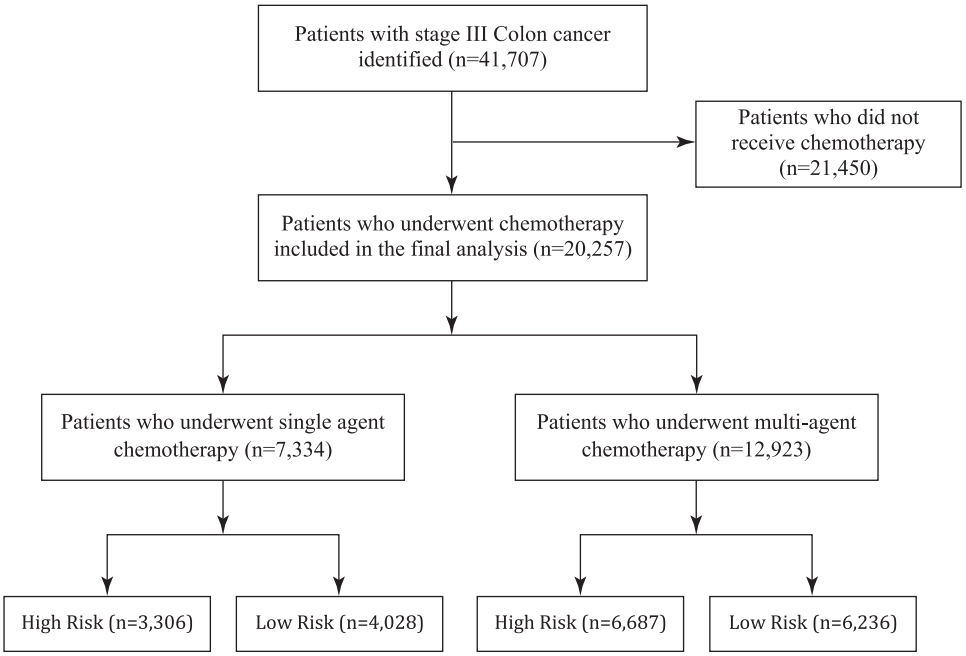
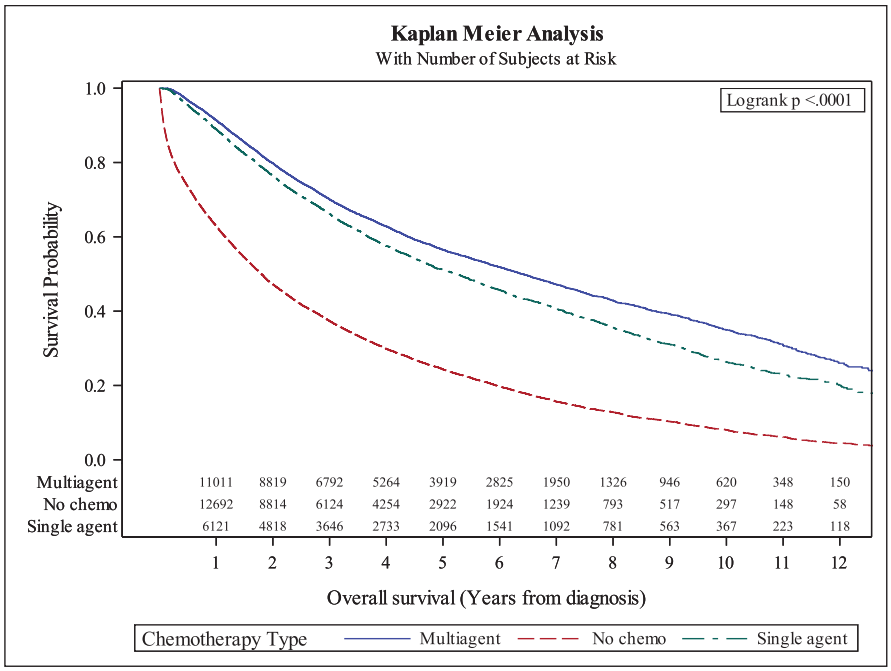


Figure 1. CONSORT diagram outlining the study selection.



Chemotherapy Type	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival	5 Yr Survival
Multi-agent	12923	5539 (43%)	7384 (57%)	6.4 (6.2, 6.6)	91.4% (90.9%, 91.9%)	79.8% (79.1%, 80.5%)	56.5% (55.5%, 57.5%)
No chemo	21450	15871 (74%)	5579 (26%)	1.8 (1.7, 1.8)	62.9% (62.2%, 63.5%)	47.2% (46.5%, 47.9%)	24.3% (23.7%, 25.0%)
Single agent	7334	3675 (50%)	3659 (50%)	5.2 (5, 5.5)	88.9% (88.2%, 89.6%)	76.5% (75.4%, 77.5%)	51.2% (49.9%, 52.5%)

Figure 2. Survival curves by chemotherapy for all patients.

Table 2. Univariate correlation with study cohort (multi-agent vs. single-agent vs. no chemotherapy for stage III low risk)

Covariate	Statistics	Level	Chemotherapy type			Parametric *P*-value[a]
			No chemo, *N* = 11 221	Single agent, *N* = 4028	Multi-agent, *N* = 6236	
Facility type	*N* (Col %)	Community cancer program	1474 (13.14)	476 (11.82)	820 (13.15)	.029
	N (Col %)	Comprehensive community cancer program	5530 (49.28)	2016 (50.05)	2982 (47.82)	
	N (Col %)	Academic/research program	2534 (22.58)	944 (23.44)	1526 (24.47)	
	N (Col %)	Integrated network cancer program	1683 (15)	592 (14.7)	908 (14.56)	
Facility location	*N* (Col %)	Northeast	2506 (22.33)	968 (24.03)	1302 (20.88)	<.001
	N (Col %)	South	3797 (33.84)	1379 (34.24)	2170 (34.8)	
	N (Col %)	Midwest	3112 (27.73)	1023 (25.4)	1958 (31.4)	
	N (Col %)	West	1806 (16.09)	658 (16.34)	806 (12.92)	
Sex	*N* (Col %)	Male	4644 (41.39)	1677 (41.63)	2958 (47.43)	<.001
	N (Col %)	Female	6577 (58.61)	2351 (58.37)	3278 (52.57)	
Median income quartiles 2000	*N* (Col %)	<$30 000	1511 (13.8)	514 (13.09)	803 (13.3)	.889
	N (Col %)	$30 000-$34 999	1990 (18.17)	711 (18.11)	1118 (18.51)	
	N (Col %)	$35 000-$45 999	3173 (28.98)	1134 (28.88)	1741 (28.83)	
	N (Col %)	≥$46 000	4276 (39.05)	1568 (39.93)	2377 (39.36)	
Median income quartiles 2008-2012	*N* (Col %)	<$38 000	2052 (18.4)	716 (17.87)	1071 (17.29)	.356
	N (Col %)	$38 000-$47 999	2645 (23.72)	935 (23.33)	1503 (24.27)	
	N (Col %)	$48 000-$62 999	3095 (27.76)	1086 (27.1)	1716 (27.71)	
	N (Col %)	≥$63 000	3359 (30.12)	1270 (31.69)	1903 (30.73)	
Median income quartiles 2012-2016	*N* (Col %)	<$40 227	2164 (19.58)	777 (19.55)	1101 (17.95)	.053
	N (Col %)	$40 227-50 353	2548 (23.06)	864 (21.74)	1442 (23.52)	
	N (Col %)	$50 354-63 332	2630 (23.8)	939 (23.63)	1502 (24.49)	
	N (Col %)	≥$63 333	3708 (33.56)	1394 (35.08)	2087 (34.03)	
Urban/rural 2003	*N* (Col %)	Metro	9176 (84.14)	3230 (82.1)	4899 (80.66)	<.001
	N (Col %)	Urban	1221 (11.2)	504 (12.81)	800 (13.17)	
	N (Col %)	Rural	508 (4.66)	200 (5.08)	375 (6.17)	
Year of diagnosis	*N* (Col %)	2004-2006	2567 (22.88)	1008 (25.02)	1120 (17.96)	<.001
	N (Col %)	2007-2009	1990 (17.73)	675 (16.76)	1155 (18.52)	
	N (Col %)	2010-2012	3368 (30.02)	1021 (25.35)	1983 (31.8)	
	N (Col %)	2013-2015	3296 (29.37)	1324 (32.87)	1978 (31.72)	
Grade	*N* (Col %)	Well differentiated, differentiated, and NOS	814 (7.25)	265 (6.58)	461 (7.39)	.259
	N (Col %)	Moderately differentiated, moderately well differentiated, and intermediate differentiation	7574 (67.5)	2775 (68.89)	4250 (68.15)	
	N (Col %)	Poorly differentiated	2502 (22.3)	856 (21.25)	1356 (21.74)	
	N (Col %)	Undifferentiated, anaplastic	331 (2.95)	132 (3.28)	169 (2.71)	
Hispanic ethnicity	*N* (Col %)	No	10163 (96.12)	3653 (95.53)	5637 (95.59)	.138
	N (Col %)	Yes	410 (3.88)	171 (4.47)	260 (4.41)	
Insurance type	*N* (Col %)	Not insured	51 (0.46)	15 (0.38)	36 (0.58)	.003
	N (Col %)	Private insurance	1018 (9.19)	430 (10.78)	658 (10.68)	
	N (Col %)	Government insurance	10003 (90.35)	3545 (88.85)	5465 (88.73)	
Surgical margins	*N* (Col %)	Negative	10696 (95.86)	3877 (96.76)	5953 (96.28)	.033
	N (Col %)	Positive	462 (4.14)	130 (3.24)	230 (3.72)	
Charlson-Deyo scores	*N* (Col %)	0	6433 (57.33)	2549 (63.28)	4137 (66.34)	<.001
	N (Col %)	1	3055 (27.23)	1008 (25.02)	1582 (25.37)	
	N (Col %)	≥2	1733 (15.44)	471 (11.69)	517 (8.29)	
Tumor size	*N* (Col %)	≤2 cm	495 (4.5)	202 (5.1)	339 (5.55)	<.001
	N (Col %)	2-4 cm	3986 (36.24)	1501 (37.88)	2449 (40.1)	
	N (Col %)	>4 cm	6517 (59.26)	2260 (57.03)	3319 (54.35)	

Table 2. Continued

Covariate	Statistics	Level	Chemotherapy type			Parametric *P*-value[a]
			No chemo, *N* = 11 221	Single agent, *N* = 4028	Multi-agent, *N* = 6236	
Age at diagnosis	*N*		11221	4028	6236	<.001
	Mean		82.01	78.17	75.17	
	Median		83	78	74	
	Min		70	70	70	
	Max		90	90	90	
	SD		5.81	4.95	4.16	

[a]The parametric *P*-value is calculated by ANOVA for numerical covariates and χ^2 test for categorical covariates.

Risk Status, Adjuvant Chemotherapy, and Overall Survival

For all patients, MAC was associated with better 1-, 2-, and 5-year OS than SAC (5-year OS [56.5% (55.5%, 57.5%); $P < .001$) compared with SAC (51.2% (49.9, 52.5%) $P < .001$] (Fig. 2). For patients with low-risk stage III CC, SAC was associated with worse OS compared with MAC in univariate (HR 0.41; 95% CI, 0.39-0.44; $P < .001$) analysis (Supplementary Table S3). Stage III low-risk patients who received MAC had better 1-, 2-, and 5-year OS (5-year OS (68.7% (67.3%, 70.0%); $P < .001$)) compared with SAC (Supplementary Fig. S1). On stratification by 5-year age intervals, benefit of MAC when compared with SAC was significant for age group 70-75 years (HR 0.81 (0.73-0.90), $P < .001$), but not to age groups 76-80 (HR (0.90 (0.80-1.00), $P = .051$), 81-85 (HR 0.97 (0.83-1.12), $P = .637$), and 86-90+ (HR 0.95 (0.72-1.25), $P = .691$). For patients with high-risk stage III CC, MAC was associated with better OS compared with SAC in univariate analysis (HR 0.35; 95% CI (0.34-0.36); $P < .001$) (Supplementary Table S4). High-risk patients who received MAC had a better 1-, 2-, and 5-year OS (5-year OS (45.4% (44.0%, 46.8%; $P < .001$) compared with SAC (Supplementary Fig. S2).

Other covariates on univariate analysis associated with worse OS in patients with low-risk stage III CC included positive surgical margin (HR 1.51; 1.38-1.64; $P < .001$), Charlson-Deyo Score > 2 (HR 1.82; 1.73-1.92; $P < .001$), undifferentiated tumors (HR 1.14; 1.00-1.30; $P = .044$), and not insured (HR 0.98; 0.72-1.32; $P < .001$) (Supplementary Table S5). For high-risk patients with stage III CC, other covariates on univariate analysis associated with worse OS included male sex, positive surgical margin (HR 1.73; 1.66-1.81; $P < .001$), and Charlson-Deyo score >2 (HR 1.53 1.45-1.61; $P < .001$) compared with female sex, negative surgical margin, and Charlson-Deyo score <1 (Tables 2 and 3).

On multivariable analysis, MAC (1.13 (1.07-1.20); $P < .001$), facility type (1.15 (1.08-1.23); $P < .001$), sex (1.26; (1.21-1.31); $P < .001$), median income (1.09 (1.02-1.17); $P < .001$), race (0.86 (0.76-0.97); $P < .001$), Hispanic ethnicity (0.83 (0.75-0.91); $P < .001$), surgical margins (1.68 (1.60-1.76); $P < .001$), Charlson-Deyo score (1.13 (1.09-1.18); $P < .001$), and age (1.02 (1.02-1.03); $P < .001$) were significantly associated with survival (Table 4). In Table 5, high-risk vs. low-risk, stratified by stage and status, showed that multi-agent chemotherapy remained positive.

Discussions

Age is an established risk factor for the development of cancer, including colon cancer. As the population ages, there will be a corresponding increase in the elderly population with cancer. Unfortunately, the elderly population is underrepresented in prospective trials. For example, in the pivotal MOSAIC trial, patients older than 65 ($n = 463$) were underrepresented when compared with younger patients aged 65 years or younger ($n = 884$).[14] Furthermore, data from prospective studies do not reflect the real-world data specific to the elderly population. The average age of participants in prospective adjuvant trials was 60 years.[15] Elderly patients were underrepresented in these studies with the highest range being 18-75 years.[15] The concern of higher rates of toxicity from AC in elderly patients is suggested by the published literature. A systematic review of 25 studies evaluating adjuvant oxaliplatin and fluoropyrimidine concluded that grade 3 or 4 adverse events were higher among older adult patients. These toxicities included cardiac disorders, neutropenia, infection, dehydration, diarrhea, and fatigue. Similarly, the ACCENT meta-analysis reported an increase in early mortality for elderly patients (>70) receiving adjuvant therapy for CC where performance status was a major determinant (ECOG PS > 2).[6] Given the ACCENT trial results, the NCCN reported a consideration of using SAC in elderly patients.[6] The added toxicity in the elderly population highlights the importance of evaluating the benefits of combination chemotherapy to confirm the role of these regimens in this population. The IDEA trial has set a new standard of care for all patients with stage III CC (in both high risk and low-risk patients) showing that XELOX for 3 months in the adjuvant therapy is non-inferior to 6 months and utilizing FOLFOX for 3 months was inferior to 6 months duration.[9] In our analysis of the largest dataset of elderly patients, we observed a significant benefit of MAC compared with SAC in low-risk and high-risk stage III CC. These results suggest that elderly patients may still benefit from combination chemotherapy mainly for the age group of 70-75 years of age. Any adjuvant chemotherapy (MAC or SAC) is better than no chemotherapy in all age groups. Patients with low and high-risk stage III CC who underwent MAC showed significantly better OS in the patient age group 70-75 when compared with SAC and no chemotherapy group. MAC compared SAC showed equal benefit for age groups of >76 years and significantly better OS when compared with no adjuvant chemotherapy. A reasonable approach is to use MAC for patients with stage III

Table 3. Univariate correlation with study cohort (multi-agent vs. single-agent vs. no chemotherapy for stage III high-risk).

Covariate	Statistics	Level	Chemotherapy type			Parametric *P*-value[a]
			No chemo *N* = 10 229	Single agent *N* = 3306	Multi-agent *N* = 6687	
Facility type	*N* (Col %)	Community cancer program	1379 (13.48)	410 (12.4)	899 (13.44)	<.001
	N (Col %)	Comprehensive Community cancer program	5134 (50.19)	1639 (49.58)	3240 (48.45)	
	N (Col %)	Academic/research program	2162 (21.14)	787 (23.81)	1640 (24.53)	
	N (Col %)	Integrated network cancer program	1554 (15.19)	470 (14.22)	908 (13.58)	
Facility location	*N* (Col %)	Northeast	2411 (23.57)	815 (24.65)	1604 (23.99)	<.001
	N (Col %)	South	3370 (32.95)	1038 (31.4)	2140 (32)	
	N (Col %)	Midwest	2815 (27.52)	906 (27.4)	2001 (29.92)	
	N (Col %)	West	1633 (15.96)	547 (16.55)	942 (14.09)	
Sex	*N* (Col %)	Male	3844 (37.58)	1338 (40.47)	3083 (46.1)	<.001
	N (Col %)	Female	6385 (62.42)	1968 (59.53)	3604 (53.9)	
Median income quartiles 2000	*N* (Col %)	<$30 000	1319 (13.2)	398 (12.36)	802 (12.3)	.392
	N (Col %)	$30 000-$34 999	1774 (17.76)	556 (17.27)	1167 (17.9)	
	N (Col %)	$35 000-$45 999	2817 (28.2)	960 (29.81)	1850 (28.38)	
	N (Col %)	≥$46 000	4079 (40.83)	1306 (40.56)	2699 (41.41)	
Median income quartiles 2008-2012	*N* (Col %)	<$38 000	1813 (17.81)	539 (16.38)	1058 (15.89)	.024
	N (Col %)	$38 000-$47 999	2388 (23.45)	776 (23.59)	1559 (23.42)	
	N (Col %)	$48 000-$62 999	2688 (26.4)	923 (28.05)	1862 (27.97)	
	N (Col %)	≥$63 000	3293 (32.34)	1052 (31.98)	2179 (32.73)	
Median income quartiles 2012-2016	*N* (Col %)	<$40,227	1938 (19.19)	584 (17.89)	1128 (17.11)	.014
	N (Col %)	$40 227-50 353	2242 (22.2)	735 (22.52)	1456 (22.08)	
	N (Col %)	$50 354-63 332	2356 (23.33)	816 (25)	1623 (24.62)	
	N (Col %)	≥$63 333	3563 (35.28)	1129 (34.59)	2386 (36.19)	
Urban/rural 2003	*N* (Col %)	Metro	8392 (84.32)	2621 (81.63)	5277 (81.04)	<.001
	N (Col %)	Urban	1075 (10.8)	413 (12.86)	840 (12.9)	
	N (Col %)	Rural	485 (4.87)	177 (5.51)	395 (6.07)	
Year of diagnosis	*N* (Col %)	2004-2006	2057 (20.11)	664 (20.08)	1091 (16.32)	<.001
	N (Col %)	2007-2009	1772 (17.32)	497 (15.03)	1127 (16.85)	
	N (Col %)	2010-2012	3137 (30.67)	931 (28.16)	2174 (32.51)	
	N (Col %)	2013-2015	3263 (31.9)	1214 (36.72)	2295 (34.32)	
Grade	*N* (Col %)	Well differentiated, differentiated, and NOS	475 (4.64)	165 (4.99)	320 (4.79)	<.001
	N (Col %)	Moderately differentiated, moderately well differentiated, and intermediate differentiation	5315 (51.96)	1849 (55.93)	3745 (56)	
	N (Col %)	Poorly differentiated	3839 (37.53)	1107 (33.48)	2264 (33.86)	
	N (Col %)	Undifferentiated, anaplastic	600 (5.87)	185 (5.6)	358 (5.35)	
Race	*N* (Col %)	White	8980 (88.37)	2903 (88.34)	5852 (88.17)	.396
	N (Col %)	Black	835 (8.22)	257 (7.82)	524 (7.9)	
	N (Col %)	Other	347 (3.41)	126 (3.83)	261 (3.93)	
Hispanic ethnicity	*N* (Col %)	No	9248 (95.88)	2970 (95.16)	6034 (95.66)	.222
	N (Col %)	Yes	397 (4.12)	151 (4.84)	274 (4.34)	
Insurance type	*N* (Col %)	Not insured	59 (0.59)	24 (0.73)	30 (0.45)	.029
	N (Col %)	Private insurance	894 (8.87)	327 (10)	662 (10.03)	
	N (Col %)	Government insurance	9124 (90.54)	2920 (89.27)	5906 (89.51)	
Surgical margins	*N* (Col %)	Negative	8382 (82.94)	2888 (88.32)	5778 (87.36)	<.001
	N (Col %)	Positive	1724 (17.06)	382 (11.68)	836 (12.64)	
Charlson-Deyo scores	*N* (Col %)	0	6040 (59.05)	2026 (61.28)	4543 (67.94)	<.001
	N (Col %)	1	2653 (25.94)	904 (27.34)	1572 (23.51)	
	N (Col %)	≥2	1536 (15.02)	376 (11.37)	572 (8.55)	
Tumor size	*N* (Col %)	≤2 cm	297 (2.96)	93 (2.87)	234 (3.58)	<.001
	N (Col %)	2-4 cm	2826 (28.2)	1020 (31.45)	2225 (34.05)	
	N (Col %)	>4 cm	6899 (68.84)	2130 (65.68)	4076 (62.37)	

Table 3. Continued

Covariate	Statistics	Level	Chemotherapy type			Parametric *P*-value[a]
			No chemo *N* = 10 229	Single agent *N* = 3306	Multi-agent *N* = 6687	
Age at diagnosis	*N*		10 229	3306	6687	<.001
	Mean		82.19	79.17	75.65	
	Median		83	79	75	
	Min		70	70	70	
	Max		90	90	90	
	SDv		5.89	5.23	4.34	

[a]The parametric *P*-value is calculated by ANOVA for numerical covariates and χ^2 test for categorical covariates.

Table 4. Multivariable survival analysis stratified by stage and status in terms of chemotherapy for stage III low risk.

Covariate	Level	*N*	Overall survival (years from diagnosis)	
			Hazard ratio (95% CI)	HR *P*-value
Chemotherapy type	No chemo	9867	2.49 (2.35-2.65)	<.001
	Single agent	3590	1.17 (1.09-1.25)	<.001
	Multiagent	5462	-	-
Facility type	Community cancer program	2464	1.10 (1.03-1.18)	.007
	Comprehensive Community cancer program	9311	1.01 (0.96-1.07)	.674
	Integrated network cancer program	2729	1.11 (1.04-1.19)	.002
	Academic/research program	4415	-	-
Facility location	Northeast	4116	0.97 (0.91-1.04)	.375
	South	6607	1.05 (0.98-1.11)	.155
	Midwest	5224	1.04 (0.97-1.11)	.265
	West	2972	NA	NA
Sex	Male	8155	1.26 (1.21-1.31)	<.001
	Female	10 764	NA	NA
Median income quartiles 2000	<$30 000	2575	1.09 (1.02-1.17)	.017
	$30 000-$34 999	3459	1.07 (1.01-1.14)	.024
	$35 000-$45 999	5486	1.03 (0.98-1.09)	.206
	≥$46 000	7399	NA	NA
Urban/rural 2003	Urban	2235	1.01 (0.94-1.08)	.843
	Rural	961	0.89 (0.81-0.98)	.020
	Metro	15 723	NA	NA
Grade	Moderately differentiated, moderately well differentiated, and intermediate differentiation	12 862	1.01 (0.94-1.10)	.751
	Poorly differentiated	4114	1.08 (0.99-1.18)	.084
	Undifferentiated, anaplastic	587	1.07 (0.93-1.23)	.355
	Well differentiated, differentiated, and NOS	1356	NA	NA
Race	Black	1871	1.04 (0.97-1.12)	.279
	Other	715	0.86 (0.76-0.97)	.014
	White	16 333	NA	NA
Hispanic ethnicity	Yes	788	0.89 (0.80-1.00)	.046
	No	18 131	NA	NA
Insurance type	Not insured	93	1.31 (0.95-1.80)	.098
	Private insurance	1852	0.96 (0.89-1.03)	.209
	Government insurance	16 974	NA	NA
Surgical margins	Positive	714	1.55 (1.41-1.70)	<.001
	Negative	18 205	NA	NA
Charlson-Deyo scores	1	5040	1.20 (1.15-1.26)	<.001
	≥2	2417	1.59 (1.51-1.69)	<.001
	0	11 462	NA	NA
Age at diagnosis		18 919	1.04 (1.03-1.04)	<.001

Table 5. Multivariable survival analysis stratified by stage and status in terms of chemotherapy for stage III high risk.

			Overall survival (years from diagnosis)	
Covariate	**Level**	***N***	**Hazard ratio (95% CI)**	**HR *P*-value**
Chemotherapy type	No chemo	9191	2.40 (2.29-2.52)	<.001
	Single agent	2995	1.13 (1.07-1.20)	<.001
	Multiagent	6014	NA	NA
Facility type	Community cancer program	2381	1.15 (1.08-1.23)	<.001
	Comprehensive community cancer program	9040	1.07 (1.02-1.12)	.004
	Integrated network cancer program	2688	1.11 (1.04-1.18)	.001
	Academic/research Program	4091	NA	NA
Facility location	Northeast	4348	0.98 (0.93-1.04)	.542
	South	6005	1.08 (1.02-1.14)	.009
	Midwest	4924	1.04 (0.99-1.11)	.141
	West	2923	NA	NA
Grade	Moderately differentiated, moderately well differentiated, and intermediate differentiation	9836	0.98 (0.90-1.07)	0.627
	Poorly differentiated	6444	1.24 (1.14-1.36)	<.001
	Undifferentiated, anaplastic	1062	1.41 (1.27-1.57)	<.001
	Well differentiated and differentiated, NOS	858	NA	NA
Race	Black	1498	1.00 (0.94-1.07)	.929
	Other	668	0.82 (0.74-0.91)	<.001
	White	16034	NA	NA
Hispanic ethnicity	Yes	776	0.83 (0.75-0.91)	<.001
	No	17424	NA	NA
Insurance type	Not insured	101	0.96 (0.74-1.26)	.791
	Private insurance	1686	0.99 (0.93-1.06)	.803
	Government insurance	16413	NA	NA
Surgical margins	Positive	2671	1.68 (1.60-1.76)	<.001
	Negative	15529	NA	NA
Charlson-Deyo scores	1	4674	1.13 (1.09-1.18)	<.001
	≥2	2243	1.39 (1.32-1.47)	<.001
	0	11283	NA	NA
Year of diagnosis	2007-2009	2920	0.98 (0.93-1.04)	.567
	2010-2012	5725	0.95 (0.90-1.00)	.059
	2013-2015	6383	0.93 (0.88-0.98)	.010
	2004-2006	3172	NA	NA
Tumor size	2-4 cm	5582	1.00 (0.90-1.12)	.937
	>4 cm	12042	1.06 (0.95-1.17)	.291
	≤2 cm	576	NA	NA
Age at diagnosis		18200	1.02 (1.02-1.03)	<.001

disease (irrespective of risk) for patients with resected CC of the age group 70-75 and SAC for patients of age group 76 and older. Treatment of cancer in the elderly is extrapolated from younger patient age groups enrolled in prospective studies. Elderly patients have specific challenges including age-related organ function decline, comorbid conditions, and decline in performance status; therefore, patient selection for AC is critical and challenging. In this analysis, a higher comorbidity Charlson-Deyo score of >2 significantly affected survival. The decision of adjuvant therapy is dependent on the bias of the treating physician in assessing the performance of the patient.

The benefits of AC have been demonstrated in stage III CC and MAC is an established standard of care, despite the evidence, only 48.5% of this study's population received any AC. One reason is likely related to the high rate of the 90-day mortality which is significantly higher in the no chemotherapy group but similar in the MAC when compared with SAC groups. The 90-day mortality reached 11% in the whole population, reaching 25% in the high risk and 16% in the low-risk stage III CC in the no chemotherapy group. This is likely related to the Charlson-Deyo high score and the age of the patient. Age and comorbidities remain to be significant factors in selecting patients who are fit for surgery. Some of the surgeries are probably done on an emergent basis which can also explain the high positive margins (9%) in this population. This analysis focuses on the differences between MAC when compared with SAC in the elderly population. In other reports, AC was less commonly delivered to patients over age 65, particularly those over 80.[9,11] Kahn et al reported that 50% of patients aged 75 years and older received AC

compared with 87% of younger patients.[14] Older patients in the community received less toxic AC regimens than younger patients.[14] These statistics highlight the missed opportunity for a large proportion of patients with CC to benefit from potentially curative adjuvant therapy. More concerning is the disproportionate disparity related to age and offering adjuvant chemotherapy in CC. Future research focused on barriers to treatment with adjuvant therapy in CC is needed.

The standard of care for resected stage III CC is doublet chemotherapy with 5FU (or equivalence) and oxaliplatin combinations.[16] In this retrospective study, there is insufficient data on the doses, toxicity, or duration (number of cycles) of AC. The study cannot account for cancer-specific survival due to a lack of data for this specific outcome. Furthermore, the average age of patients receiving SAC was 78 years compared with 75 among those receiving MAC. This reflects further the clinical bias in the selection of patients. Survival benefit by years of the diagnosis is also highlighted in this analysis. In the more recent years, a higher number of patients have received adjuvant chemotherapy compared with prior. The survival benefits of years of diagnosis could be related to the major developments in chemotherapeutic options including targeted therapies that might have affected the better survival. This is related to patients with disease recurrences. Data on disease recurrences are not available in NCDB. This study did not stratify patients based on the location of the tumor (right or left) or mutations (BRAF or MSI). This study has shown the clear benefit of MAC when compared with SAC in all risk groups of the elderly population with stage III disease. Given the projected increase in the aging population, it is important to design prospective studies addressing the question of MAC in the elderly population. This study provides real-world treatment evidence of the benefit of MAC when compared with SAC in the age group of 70-75 years. At higher age groups (>76), single-agent compared with multi-agent adjuvant chemotherapy showed no difference. A consideration in the treatment of this age group (>76) is to use a single agent for adjuvant therapy except for selected patients (poor performance, MSI high cancer, high comorbidity score). We have shown alarming evidence that more than 50% of elderly patients receive substandard treatment for stage III CC. This highlights possible bias by the providers undertreating elderly patients; in addition, to the high 90-day postsurgical mortality in this patient population, this deserves an in-depth analysis and a proposal analysis. This paper could help oncologists and patients base some of their decisions to get multiagent adjuvant chemotherapy in the age group of 70-75 years.

Conclusion

Multi-agent AC is associated with better survival than SAC in stage III CC patients aged 70-75 years and older. The enhanced benefit of MAC was shown for a patient with both low-risk and high-risk stage III CC specifically in this age group and not in the older age groups. Prospective trials focused on adjuvant therapy in elderly patients with stage III CC are needed.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: W.S., L.K. Provision of study material/patients: W.S. Collection and/or assembly of data: W.S., L.K., J.M. S. Data analysis and interpretation: X.G., J.M.S., W.S., L.K. Manuscript writing: B.F.E.-R., M.D., C.W., M.A., O.B.A., J.M.S. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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