



# Trends in Adjuvant Chemotherapy Use Among Stage III Colon Cancer in Non-Elderly and Low Comorbidity Patients

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## Abstract

**The standard of care for stage III colon cancer is adjuvant chemotherapy. Using the NCDB between 2004 and 2014, 48,336 patients between 18 and 65 years old with no or low comorbidity were selected, and factors associated with the utilization of adjuvant chemotherapy were analyzed. 10% of patients did not receive adjuvant chemotherapy. Patients from low socioeconomic backgrounds were less likely to receive adjuvant chemotherapy and had worse survival outcomes.**

**Background:** Adjuvant chemotherapy for stage III colon cancer is underutilized in the United States. The aim of this study was to assess the use of adjuvant chemotherapy in younger and medically fit patients and analyze the socioeconomic factors associated with its utilization. **Methods:** Using the National Cancer Database from 2004 to 2015, we selected stage III colon cancer patients between age 18 to 65, Charlson-Deyo Comorbidity Index (CDCI) of 0 or 1, and those that survived at least 12 months after surgery. We then compared patients that underwent surgery only with those that received adjuvant chemotherapy. Multivariable logistic regression analysis was performed to identify variables associated with adjuvant chemotherapy use in the population. Overall survival was estimated by Kaplan-Meier curves. **Results:** Of the 48,336 patients that met inclusion criteria, 43,315 (90%) received adjuvant chemotherapy. The utilization of adjuvant chemotherapy increased from 87% in 2004 to 91% in 2015. On multivariable regression analysis, the use of adjuvant chemotherapy was lower among males, Non-Hispanic Blacks and Hispanics, low-grade cancer, left-sided tumors, CDCI 1, those who travel  $\geq 50$  miles, yearly income  $< \$40,227$ , and uninsured patients. The most common reason for the omission of adjuvant chemotherapy was the patient or caregiver's choice (40% between 2013 and 2015). The 5-year and 10-year overall survival rates were 76.7% and 63.8% respectively, in those who received adjuvant chemotherapy as compared to 65.1% and 49.3% in those who underwent surgery only ( $P < .001$ ). **Conclusion:** In young and medically fit stage III colon cancer patients, most patients received guideline-compliant care in the United States. However, socioeconomic disparities adversely impacted the use of adjuvant chemotherapy. The patient or caregiver's decision was the most common reason for non-adherence to adjuvant chemotherapy and lead to poor survival outcomes. Emphasis should be placed on developing patient-centered strategies to improve adherence to chemotherapy in all patients.

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**Keywords:** Stage III colon cancer, Adjuvant chemotherapy, Age 65 or younger, NCDB, Survival Rate

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## Introduction

Approximately 106,000 new cases of colorectal cancer are estimated in the United States in 2022.<sup>1</sup> About one-third of colon cancer patients present with regional spread of cancer to the lymph nodes (stage III).<sup>2</sup> For stage III patients, surgery with lymph node dissection followed by fluoropyrimidine-based adjuvant chemotherapy is the standard treatment.<sup>3</sup> Current guidelines recommend 3 to 6 months of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) adjuvant chemotherapy for all stage III patients. The duration of chemotherapy depends upon risk-stratification based on pathological features including the depth of invasion (pathological T4 disease) and the number of involved lymph nodes.<sup>4</sup>

Despite the demonstrated benefit of adjuvant chemotherapy, various studies have shown lower utilization in stage III patients in the United States.<sup>5-7</sup> Factors associated with non-utilization of adjuvant chemotherapy include age, female gender, black race, lower-income, lack of insurance coverage<sup>6,8</sup> and the number of medical comorbidities.<sup>7-10</sup> Most studies exploring the utilization of adjuvant chemotherapy were performed in heterogeneous populations, which could lead to inaccurate assessments due to patient- and disease-related factors.<sup>7</sup> In addition, many of these studies failed to explore the reasons for the lack of use of adjuvant chemotherapy.<sup>7,11</sup> In clinical practice, the tendency is to use adjuvant chemotherapy in medically fit and younger patients unless contraindicated, but the overall rates of utilization of adjuvant chemotherapy in this population are unknown. This question is important because adjuvant chemotherapy may significantly impact outcomes in the fit and younger patient population. The main aim of this study was to assess the use of adjuvant chemotherapy among non-elderly stage III colon cancer patients with minimal comorbidities. We explored the racial and socio-demographic factors for non-use of adjuvant chemotherapy, the reasons for such decision, and the impact of non-administration of adjuvant chemotherapy on outcomes.

## Methods

### Data Source

The National Cancer Database (NCDB) is a community-oriented cancer management and outcomes database that is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Over 1500 Commission on Cancer (CoC)-accredited facilities contribute to the NCDB. The database encompasses data on patient demographics, tumor characteristics, socioeconomic factors, treatments, and survival outcomes. The NCDB dataset contains more than 34 million historical records, representing more than 70% of all newly diagnosed cancer cases nationwide.

### Cohort Definition

Colon cancer was defined based on the histopathologic confirmation (ICD-O-3/WHO 2008 site recode “C18.0, C18.2-C18.7, C19.9”). Stage III colon cancer was determined based on the pathological staging pT1-pT4, N1-2, M0 AJCC v6, and v7 in NCDB. The non-elderly (“young”) population was defined as patients  $\leq$  65 years of age, while the medically fit population was defined

by a low Charlson-Deyo Comorbidity Index score. The Charlson-Deyo Comorbidity Index is a weighted index used by the NCDB to predict the risk of death within 1-year of hospitalization.<sup>12</sup> The specific ICD-9 or ICD-10 comorbid conditions are each given a value and summed to give a total comorbidity score. For this study, we selected patients with Charlson-Deyo Comorbidity Index  $\leq$  1, which means they may have no medical comorbidity or have one of the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, and diabetes. Moreover, patients who died within the first year of surgical resection were excluded to control for survivorship bias or landmark analysis (the landmark time as determined a priori). Patients were excluded from the cohort if they suffered from more than one primary tumor, received neoadjuvant chemotherapy or if adjuvant chemotherapy status use was unknown. They were also excluded if they did not receive their first course of treatment at the reporting center, or had no documented follow-ups (Figure 1).

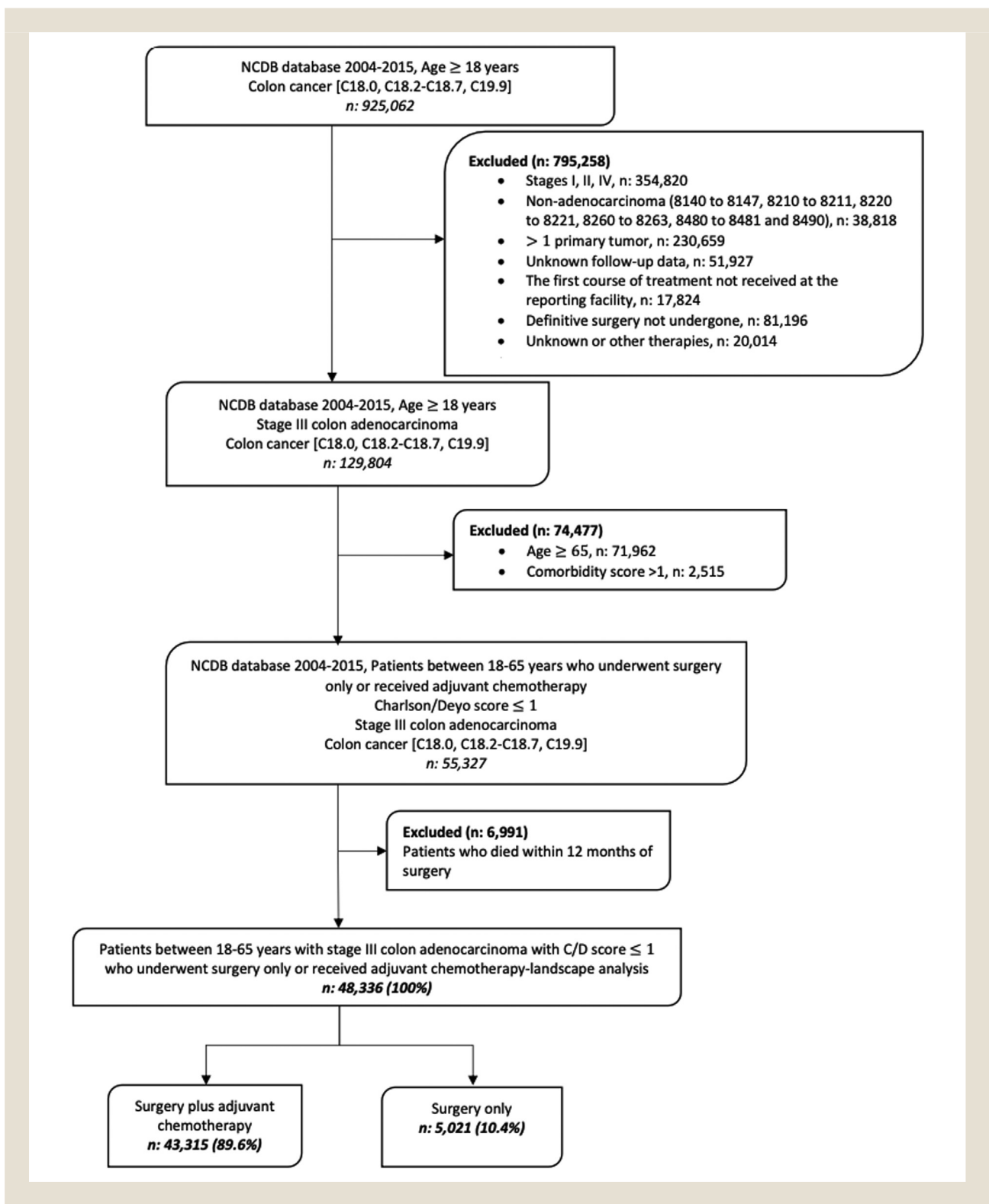
### Measured Outcomes and Variables

The primary endpoint of this study was the rate of use of adjuvant chemotherapy in the cohort. Patient-specific variables included age as a continuous variable, race/ethnicity (Hispanic, Non-Hispanic White, Black, Asian, and other), gender (male, female), year of diagnosis (2004-2006, 2007-2009, 2010-2012, 2013-2015), Charlson-Deyo Comorbidity Index (0,1), insurance status (private, Medicaid, Medicare, uninsured, other), travel distance ( $<$  12.5 miles, 12.5-49.9 miles,  $>$  50 miles), rurality (metropolitan, non-metropolitan), average neighborhood income level, tumor location (right, left), tumor grade (I, II, III, IV), and facility type (academic, comprehensive community cancer program, community cancer program, integrated network cancer program). We analyzed the reasons for non-administration of chemotherapy as listed in NCDB and the effects of non-administration on survival.

### Statistical Analysis

Patients were divided into 2 categories: those who underwent surgical resection only and those who had a resection followed by adjuvant chemotherapy (including both single and multi-agent chemotherapy). Each group's patient's demographics and tumor characteristics were reported as proportion rates and compared using the Chi-square test. A multivariable logistic regression model was used to calculate the odds ratio of adjuvant chemotherapy administration based on factors including age, gender, ethnicity, Charlson-Deyo Comorbidity Index, type of institution, travel distance, geographical location, educational background, average neighborhood income, time of diagnosis, insurance status, tumor laterality, and grade. Kaplan-Meier survival curves and Cox proportional hazards model were utilized to perform survival analysis. Overall survival curves were estimated using Kaplan-Meier method and tested with the log-rank test. A Cox proportional hazards model was performed after adjusting for age, income status, Charlson-Deyo Comorbidity Index, travel distance, gender, type of institution, insurance status, race/ethnicity, adjuvant chemotherapy receipt, geographical location, tumor laterality, and histologic grade. The

**Figure 1** Flowsheet of patients' inclusion and exclusion criteria within the NCDB dataset. NCDB = National Cancer Database.



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survival benefit was indicated with a hazards ratio (HR) < 1.0, and 95% confidence intervals were generated. Missing data was handled using multiple imputation by chained equations among these characteristics; facility location (n: 3,948 [8.2%]), facility type (n: 3,948 [8.2%]), rurality (n: 1,201 [2.5%]), tumor grade (n: 1,174 [2.4%]), insurance status (n: 913 [1.9%]), median income (n: 797 [1.6%]), education (n: 704 [1.5%]), race/ethnicity (n: 393 [0.8%]), and travel distance (n: 189 [0.4%]). 20 imputed datasets were created. SPSS software version 25 was used for all analyses. All p-values were 2-sided, and P-values < .05 was reported as statistically significant.

## Results

### Patient and Disease Characteristics

Out of 925,062 patients with colon cancer in NCDB, 48,336 patients met the criteria for our cohort (Figure 1). 43,315 young and medically fit patients in the cohort received adjuvant chemotherapy (89.6%), while 5,021 (10.4%) patients did not receive adjuvant chemotherapy (Table 1). The proportion of patients receiving adjuvant chemotherapy increased from 87.6% in 2004 to 2006 to 90.8% in 2013 to 2015. The median age at diagnosis was 54 years (interquartile range [IQR] 48-59) for the patients that received adjuvant chemotherapy and 56 years (IQR 50-60) for those who did not. Table 1 displays the patients' socio-demographics and tumor characteristics for the 2 groups based on adjuvant chemotherapy status. The median time from diagnosis to surgery was 10 days (IQR 1-22) for those who received adjuvant chemotherapy and 7 days (IQR 0-25) for the surgery-only group. The median length of stay after surgery was 5 days for both groups, and the readmission rate within 30 days for the adjuvant chemotherapy group was 9.0% and 7.9% for the surgery-only group. The median time from diagnosis to chemotherapy administration was 55 days (IQR 42-71) and the median time from surgery to the start of adjuvant chemotherapy was 41 days (IQR 33-52 days). 26,783 patients (55.4%) had low-risk stage III disease (pT1-3 and N1), while 14,232 patients (29.4%) had high-risk stage III disease (pT4 or N2). Microsatellite instability (MSI) testing data was available for 8218 patients, and 14.3% of them were MSI-high, with no difference among the groups. Similarly, 3984 patients had information about KRAS status and 39% of tumors had a mutation in the KRAS gene.

### The Trends and Factors Associated With the Use of Adjuvant Chemotherapy

Figure 2A shows the trend in the utilization of adjuvant chemotherapy in the study cohort. The use rate of adjuvant chemotherapy was 87% in 2004 and increased to 91% by 2015. On multivariable logistic regression analysis (Table 2), the factors associated with increased likelihood of receiving adjuvant chemotherapy included female gender (adjusted OR 1.14, 95% CI 1.08-1.21), patients < 50 years, high-grade tumors (adjusted OR for grade II, 1.19, 95% CI 1.06-1.33- adjusted OR for grade III, 1.21, 95% CI 1.06-1.37-adjusted OR for grade IV, 1.43, 95% CI 1.13-1.82), right-sided tumors, patients with yearly income  $\geq$  \$63,333 (adjusted OR 1.22, 95% CI 1.11-1.33) and those who live in non-metropolitan areas (adjusted OR 1.53, 95% CI 1.38-1.70). The utilization of adjuvant chemotherapy was lower among Hispan-

ics (adjusted OR 0.84, 95% CI 0.75-0.94), non-Hispanic Blacks (adjusted OR 0.77, 95% CI 0.71-0.84), patients belonging to the lowest-income groups (< \$40227), those who traveled  $\geq$  50 miles to the treatment center (adjusted OR 0.51, 95% CI 0.45-0.57) and uninsured patients or those on Medicare or Medicaid insurance (adjusted OR for uninsured patients 0.58, 95% CI 0.52-0.65).

### Reasons for Omission of Adjuvant Chemotherapy

Figure 2B displays the various reasons listed in the NCDB dataset concerning the non-use of adjuvant chemotherapy among surgery-only patients. The patient's refusal of the adjuvant chemotherapy (or legal guardian or family member) was the most common reason for the omission of treatment. This proportion increased during the years from 19.1% in 2004 to 2006 to 40% in 2013 to 2015. In parallel, the reasons were unknown among 66.8% in the 2004 to 2006 year and 42.9% in 2013 to 2015. Other reasons for omission included contraindication of chemotherapy and its recommendation without administration.

### Survival Outcomes

The overall survival in patients who received adjuvant chemotherapy compared to the surgery-alone group is displayed in Figure 3. Patients receiving adjuvant chemotherapy had significantly higher overall survival than those treated with surgery alone ( $P < .001$ ). The 5-year and 10-year overall survival rates were 76.7% and 63.8% for patients receiving adjuvant chemotherapy while the rates were 65.1% and 49.3% for patients treated with surgery alone (Table 1). After adjusting for patient factors, disease characteristics, and treatment modalities, patients who underwent surgery alone had 1.55 times higher chance of death than those who received adjuvant chemotherapy (adjusted HR 1.55, 95% CI 1.48-1.63) (Supplemental Material Table 1). Non-Hispanic Blacks versus non-Hispanic Whites (adjusted HR 1.20, 95% CI 1.14-1.26), Charlson-Deyo index of 1 versus Charlson-Deyo index of 0 (adjusted HR 1.11, 95% CI 1.06-1.16), higher tumor grades (III and IV) versus grade I (adjusted HR 1.59, 95% CI 1.46-1.72 and 1.79, 95% CI 1.58-2.04 for grades III and IV respectively) were associated with an increased risk of death. Factors associated with improved survival were female gender (adjusted HR 0.79, 95% CI 0.76-0.82), higher average yearly income (HR 0.83, 95% CI 0.78-0.88), and left-sided tumor laterality (HR 0.82, 95% CI 0.79-0.85).

## Discussion

This study aimed to determine the use of adjuvant chemotherapy among non-elderly stage III colon cancer patients with low comorbidity, a selected cohort in which most practitioners will recommend chemotherapy. Age and performance status are among the strongest predictors for the administration of adjuvant chemotherapy in colon cancer.<sup>13</sup> Our study's strength is in choosing the selection criteria for the cohort, including the requirement that patients should have survived at least 1-year post-cancer diagnosis (landmark analysis). In the selected cohort, the use of adjuvant chemotherapy was close to 90%, which is acceptable. However, we showed that the 10% younger and medically fit patients who declined chemotherapy had worse outcomes. The ethnic and socio-demographic determinants of health impacted the use of adjuvant chemotherapy in our

**Table 1** Baseline Patient Characteristics

	All Patients N = 48,336 N (100%)	Adjuvant Chemotherapy	
		Yes N = 43,315 N (89.6%)	No N = 5,021 N (10.4%)
<b>Age at diagnosis</b>			
< 50 years	14,635 (30.3)	13,434 (91.8)	1201 (8.2)
≥ 50 years	33,701 (69.7)	29,881 (88.7)	3820 (11.3)
<b>Gender</b>			
Male	24,982 (51.7)	22,241 (89.0)	2741 (11.0)
Female	23,354 (48.3)	21,074 (90.2)	2280 (9.8)
<b>Race/Ethnicity</b>			
Hispanic	3290 (10.8)	2874 (87.4)	416 (12.6)
<b>Non-Hispanic</b>			
Non-Hispanic White	34,737 (71.9)	31,464 (90.6)	3273 (9.4)
Non-Hispanic Black	7622 (15.8)	6605 (86.7)	1017 (13.3)
Asian	1756 (3.6)	1558 (88.7)	198 (11.3)
Other	538 (1.1)	481 (89.4)	57 (10.6)
<b>Education</b>			
≥ 17.6%	10,942 (22.6)	9,472(86.6)	1470 (13.4)
10.9-17.5%	12,532 (25.9)	11,202 (89.4)	1330 (10.6)
6.3-10.8%	12,963 (26.8)	11,791 (91.0)	1172 (9.0)
< 6.3%	11,195 (23.2)	10,257 (91.6)	938 (8.4)
<b>Yearly income</b>			
< \$40,227	9430 (19.5)	8241 (87.4)	1189 (12.6)
\$40,227-50,353	10,422 (21.6)	9340 (89.6)	1082 (10.4)
\$50,354-63,332	10,895 (22.5)	9767 (89.6)	1128 (10.4)
≥ \$63,333	16,792 (34.7)	15,291 (91.1)	1501 (8.9)
<b>Rurality</b>			
Metropolitan	40,075 (82.9)	35,827 (89.4)	4248 (10.6)
Non-metropolitan	7060 (14.6)	6,410 (90.8)	650 (9.2)
<b>Facility Type</b>			
Community Cancer Program	4971 (10.3)	4463 (89.8)	508 (10.2)
Comprehensive Community Cancer Program	19,544 (40.4)	17,610 (90.1)	1934 (9.9)
Academic/Research Program	13,270 (27.5)	11,704 (88.2)	1566 (11.8)
Integrated Network Cancer Program	6604 (13.7)	5883 (89.1)	721 (10.9)
<b>Facility Location</b>			
New England	2269 (4.7)	2104 (92.7)	165 (7.3)
Middle Atlantic	6184 (12.8)	5556 (89.8)	628 (10.2)
South Atlantic	10,738 (22.2)	9637 (89.7)	1101 (10.3)
East North Central	7922 (16.4)	7255 (91.6)	667 (8.4)
East South Central	3617 (7.5)	3241 (89.6)	376 (10.4)
West North Central	3223 (6.7)	2968 (92.1)	255 (7.9)
West South Central	4299 (8.9)	3641 (84.7)	658 (15.3)
Mountain	1866 (3.9)	1631 (87.4)	235 (12.6)
Pacific	4270 (8.8)	3626 (84.9)	644 (15.1)
<b>Travel Distance</b>			
<12.5 miles	29,989 (62.0)	26,899 (89.7)	3090 (10.3)
12.5-49.9 miles	14,637 (30.2)	13,270 (90.7)	1367 (9.3)
≥50 miles	3521 (7.3)	2994 (85.0)	527 (15.0)
<b>Insurance status</b>			
Uninsured	3404 (7.0)	2,986 (85.5)	508 (14.5)
Private insurance	35,587 (73.6)	32,578 (91.5)	3009 (8.5)

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**Table 1** (continued)

	All Patients N = 48,336 N (100%)	Adjuvant Chemotherapy	
		Yes N = 43,315 N (89.6%)	No N = 5,021 N (10.4%)
Medicaid	4174 (8.6)	3543 (84.9)	631 (15.1)
Medicare	3565 (7.4)	2909 (81.6)	656 (18.4)
Other public insurance	603 (1.2)	545 (90.4)	58 (9.6)
Medicaid Expansion			
Non-expansion states	18,265 (37.8)	16,218 (88.8)	2047 (11.2)
Jan 2014 expansion states	13,348 (27.6)	12,105 (90.7)	1243 (9.3)
Early expansion states (2010-2013)	6885 (14.2)	5974 (86.8)	911 (13.2)
Late expansion states (after Jan 2014)	5890 (12.2)	5362 (91.0)	528 (9.0)
Suppressed for Ages 0-39	3948 (8.2)	3656 (92.6)	292 (7.4)
Tumor Location			
Right	20,415 (42.2)	18,411 (90.2)	2004 (9.8)
Left	27,921 (57.8)	24,904 (89.2)	3017 (10.8)
Grade			
I	3253 (6.7)	2865 (88.1)	388 (11.9)
II	33,277 (68.8)	29,813 (89.6)	3464 (10.4)
III	9487 (19.6)	8553 (90.2)	934 (9.8)
IV	1145 (2.4)	1050 (91.7)	95 (8.3)
Comorbidity Score			
0	40,254 (83.3)	36,185 (89.9)	4069 (10.1)
1	8082 (16.7)	7130 (88.2)	952 (11.8)
Year of diagnosis			
2004-2006	10,724 (22.2)	9397 (87.6)	1327 (12.4)
2007-2009	11,429 (23.6)	10,166 (88.9)	1263 (11.1)
2010-2012	12,700 (26.3)	11,510 (90.6)	1190 (9.4)
2013-2015	13,483 (27.9)	12,242 (90.8)	1241 (9.2)
Diagnosis to Chemotherapy start			
Median time (days)	-	55.0 (42-71)	-
Diagnosis to Surgery start			
Median time (days)	-	10.0 (1-22)	7.0 (0-25)
Overall Survival			
5-year survival rate	-	76.7	65.1
10-year survival rate	-	63.8	49.3
Length of stay after surgery			
Median (days)	-	5.0 (4.0-7.0)	5.0 (4.0-8.0)
AJCC Pathologic Stage (TNM)			
Stage III	913 (1.9)	767 (1.8)	146 (2.9)
Stage IIIA	6408 (13.3)	5672 (13.1)	736 (14.7)
Stage IIIB	26,783 (55.4)	23,937 (55.3)	2846 (56.7)
Stage IIIC	14,232 (29.4)	12,939 (29.9)	1293 (25.8)
30-day readmission			
No readmission	42,680 (88.3)	38,144 (88)	4536 (90.3)
Readmission	4275 (8.8)	3877 (9)	398 (7.9)
Readmission unknown	1381 (2.9)	1294 (3)	87 (1.7)
Nodal Status			
Negative	1441 (2.98)	1056 (2.4)	385 (7.7)
Positive	46,833 (96.9)	42,210 (97.4)	4623 (92.07)
No nodes were examined	35 (0.07)	27 (0.06)	8 (0.2)
Unknown	27 (0.05)	22 (0.05)	5 (0.09)

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**Table 1** (continued)

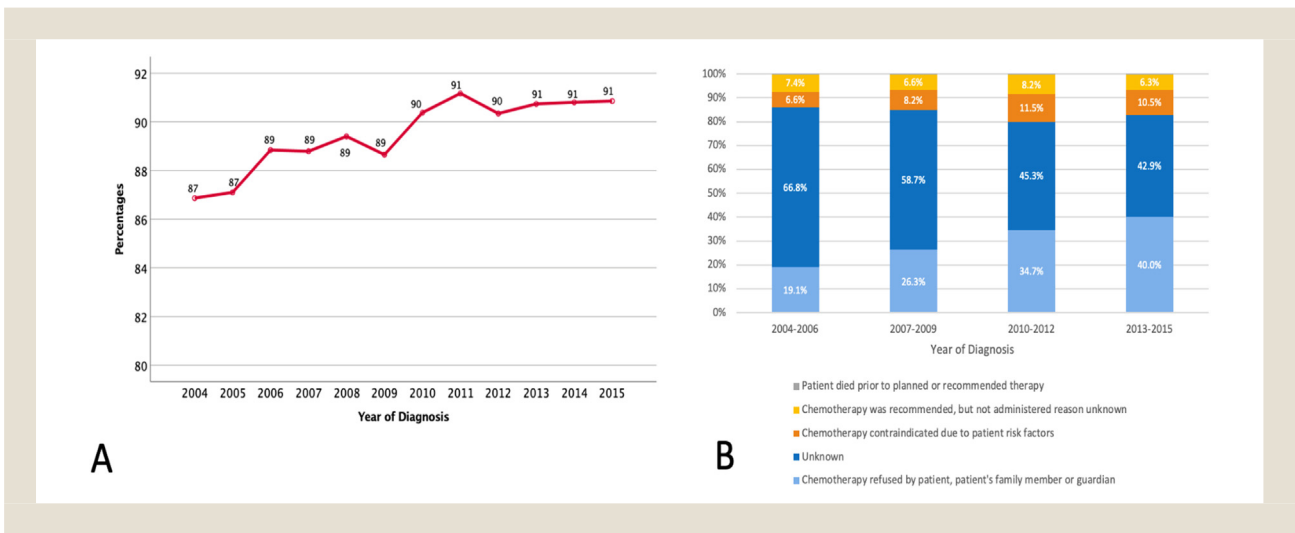
	All Patients N = 48,336 N (100%)	Adjuvant Chemotherapy	
		Yes N = 43,315 N (89.6%)	No N = 5,021 N (10.4%)
Number of Positive Regional Lymph Nodes			
Median	2.0 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-4.0)
Number of Regional Lymph Nodes Examined			
Median	19.0 (14-26)	19.0 (14-26)	18.0 (13-25)
Microsatellite Instability Status <sup>a</sup>			
No/Low MSI	7037 (85.6)	6442 (85.7)	595 (84.6)
MSI high/NOS	1181 (14.3)	1073 (14.3)	108 (15.4)
KRAS Status <sup>b</sup>			
Mutated	1553 (39)	1,439 (39)	114 (39)
Wild Type	2431 (61)	2250 (61)	181 (61)
Tumor Deposits <sup>c</sup>			
Absent	18,353 (75)	16,705 (75.3)	1648 (72.8)
Present	6106 (25)	5489 (24.7)	617 (27.2)
Time from Surgery to Chemotherapy			
Median time (days)	-	41 (33-52)	-

<sup>a</sup> MSI in total is 8218 and the percentages are from the total that we have

<sup>b</sup> KRAS wild type and mutated are calculated with a total of 3984 and the percentages are from the total that we have

<sup>c</sup> Tumor Deposits are calculated with a total of 24,459

**Figure 2** (A) Percentage in the utilization of adjuvant chemotherapy in the selected cohort between 2004 and 2015. (B). Reasons for adjuvant chemotherapy omission



cohort. Despite the relatively lower use of adjuvant chemotherapy among the uninsured, low-income, and low educational background groups, the proportion was still greater than anticipated (> 85% for these groups). This study also demonstrated a trend toward increased utilization of adjuvant chemotherapy between 2004 and 2015. Previous studies on the use of adjuvant chemotherapy were performed on unselected populations; hence, several patient-related and disease-related factors may have played a role in the reported utilization rates. In 2015, Upadhyay et al. in their analysis of NCDB patients between 2000 and 2011, showed that the overall use of

adjuvant chemotherapy in stage III patients was 65%, but 82% in sub-groups of patients < 60 years.<sup>14</sup> Kahn et al. conducted a multicenter prospective cohort study on resected stage III patients with colorectal cancer and observed that adjuvant chemotherapy was administered in 87% of those < 75 years old.<sup>10</sup> Moreover, a multicenter prospective cohort study by Sarasqueta et al. noted a utilization rate of chemotherapy of 92% in patients < 65 years, regardless of the comorbidities.<sup>15</sup> Potosky et al. found that 78% of patients < 55 years, and 24% of those > 80 years received adjuvant chemotherapy.<sup>16</sup> These studies also demonstrated that the use of adjuvant

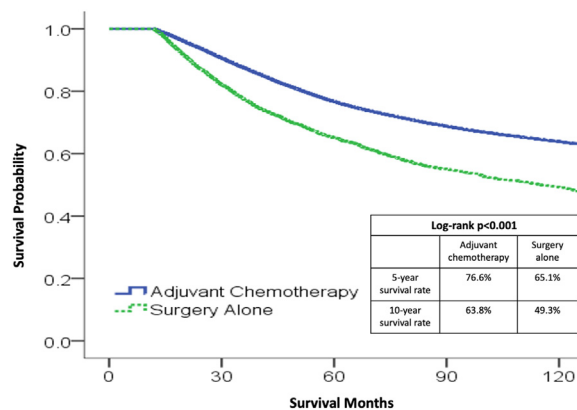
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**Table 2** Adjusted Odds Ratios of Adjuvant Chemotherapy Administration Based on Multivariable Logistic Regression

Characteristics	OR (95% CI)	P-value
<b>Age</b>		
< 50	Reference	
≥ 50	0.70 (0.66-0.75)	< .001
<b>Gender</b>		
Male	Reference	
Female	1.14 (1.08-1.21)	< .001
<b>Race/Ethnicity</b>		
Non-Hispanic White	Reference	
Non-Hispanic Black	0.77 (0.71-0.84)	< .001
Non-Hispanic Asian	0.86 (0.73-1.00)	.054
Hispanic	0.84 (0.75-0.94)	.003
Other	0.94 (0.87-1.01)	.68
<b>Comorbidity Score</b>		
0	Reference	
1	0.94 (0.87-1.01)	.098
<b>Facility Type</b>		
Academic/Research Program	Reference	
Comprehensive Community Cancer Program	1.09 (1.02-1.18)	.02
Community Cancer Program	1.06 (0.95-1.18)	.32
Integrated Network Cancer Program	0.99 (0.90-1.09)	.85
<b>Travel distance</b>		
< 12.5 miles	Reference	
12.5-49.9 miles	0.98 (0.91-1.05)	.56
≥ 50 miles	0.51 (0.45-0.57)	< .001
<b>Income</b>		
< \$40,227	Reference	
\$40,227-50,353	1.13 (1.03-1.24)	.008
\$50,354-63,332	1.09 (0.99-1.19)	.069
≥ \$63,333	1.22 (1.11-1.33)	< .001
<b>Insurance status</b>		
Private	Reference	
Uninsured	0.58 (0.52-0.65)	< .001
Medicaid	0.56 (0.51-0.62)	< .001
Medicare	0.45 (0.41-0.50)	< .001
Other Government	0.90 (0.68-1.18)	.44
<b>Rurality</b>		
Metropolitan	Reference	
Non-metropolitan	1.53 (1.38-1.70)	< .001
<b>Tumor Location</b>		
Right	Reference	
Left	0.85 (0.80-0.91)	< .001
<b>Grade</b>		
I	Reference	
II	1.19 (1.06-1.33)	.002
III	1.21 (1.06-1.37)	.003
IV	1.43 (1.13-1.82)	.003

Abbreviations: OR = Odds ratio; CI = Confidence interval



**Figure 3** Estimated overall survival between patients receiving adjuvant chemotherapy and patients undergoing surgery only (in months)

treatment led to improvement in overall survival.<sup>16</sup> Similar to our study, prior studies looking at the trend of utilization of adjuvant chemotherapy had demonstrated an overall increase in utilization among the non-selected population.<sup>6,7,14</sup>

In our cohort of young and low-comorbid patients, the patient's or caregiver's wish to decline chemotherapy was the most common reason for non-administration of adjuvant treatment. The 5-year and 10-year survival of 77% and 64% in the adjuvant treatment group compared to 65% and 49% in the surgery-only group, respectively, should inspire strong efforts to educate the patients about the benefits of adjuvant chemotherapy and the risks of refusing it in the curative setting. Among various strategies, a collaboration of a multidisciplinary disease-oriented team can offer a solution to improve adherence and outcomes.<sup>17,18</sup> Regarding the proportion of patients that did not adhere to adjuvant chemotherapy recommendations, we noticed an increasing trend over the years, but that is likely a reflection of better documentation in the database. Prior studies have also reported patient refusal<sup>19</sup> and medical advice against adjuvant treatment as common reasons.<sup>20,21</sup> The patients decline chemotherapy in adjuvant settings due to concern for toxicities.<sup>13</sup> With FOLFOX and CAPOX adjuvant chemotherapy, neuropathy and myelotoxicity are major long-term side effects. The IDEA study showed that a 3-month duration of adjuvant chemotherapy might be appropriate for most stage III colorectal cancer patients. The  $\geq$  grade 2 neuropathy rate in the IDEA trial was 14% with 3-month CAPOX therapy versus 45% with 6-month CAPOX therapy and 17% versus 48% with FOLFOX therapy for 3 and 6 months, respectively.<sup>22</sup> While all patients are at risk of side effects from adjuvant chemotherapy, not all patients benefit from it. There is emerging interest in the use of ctDNA to guide the utilization of adjuvant chemotherapy in colon cancer by targeting patients who are the most at risk of disease recurrence. CIRCULATE-US is assessing stage III colon cancer resected patients based on their molecular residual disease (MRD) on the Signatera test. In this clinical trial, patients with negative MRD are randomized into 2 groups: receiving standard of care adjuvant chemotherapy or observation.

In the future, ctDNA might be used as a predictive biomarker for the management of colon cancer; hence increasing compliance in patients who require adjuvant chemotherapy.<sup>23</sup> Patients' education and other patient-centered resources highlighting the favorable impact of adjuvant chemotherapy can empower patients and caregivers to participate in treatment decisions as well as increase their adherence to adjuvant chemotherapy. An example of such patients centered approach was a randomized controlled study that implemented a patient-navigator program for cancer patients in a resource-poor setting that demonstrated an increased acceptance and adherence to chemotherapy in lymphoma patients.<sup>24</sup> Similar programs and strategies tailored for colon cancer patients in pre-, peri- and postoperative settings can be developed to emphasize the necessity of adjuvant chemotherapy.

Among the social determinants of health, we found that age, female gender, race/ethnicity, and insurance status were also some of the factors associated with the use of adjuvant chemotherapy in our cohort. Non-Hispanic Black and Hispanic patients were less likely to receive adjuvant chemotherapy, which is consistent with the previous studies.<sup>6-8</sup> The gender difference was slight but was dissimilar to other studies where females were found less likely to receive adjuvant chemotherapy.<sup>5,6</sup> We believe this discrepancy can be due to our cohort's selection of younger patients. Shrag et al. found that females with stage III colon cancer were less likely to receive adjuvant chemotherapy, but this difference was attenuated when age was adjusted in the analysis.<sup>25</sup> Our results are concordant regarding socioeconomic barriers such as financial and insurance status and travel distance to the treatment facility that hindered access to adjuvant therapy.<sup>14</sup>

There are several limitations of our study. Although the NCDB reports few reasons why adjuvant chemotherapy was not administered, patient refusal or physicians' recommendations, might be underreported, making information bias a possibility. However, most of our covariates had a small percentage of missing data, thus minimizing the non-response bias. Even though we selected the cohort based on their Charlson-Deyo Comorbidity Index Score,

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we appreciate that this Index may not represent a patient's performance status. We balance this possibility by excluding patients who died within 12 months of surgery to limit survivorship bias. The NCDB does not collect data on the duration, the number of cycles of chemotherapy, adjustments, compliance, or quality of life during chemotherapy treatments. Moreover, the survival outcomes can be difficult to ascertain due to the variability of care provided. However, our cohort's overall size and the dataset's restriction to non-elderly patients with minimal comorbidities retain robust validity.

## Conclusion

In this cohort of non-elderly stage III colon cancer patients with low comorbidity, the majority of patients received adjuvant chemotherapy, indicating an acceptable adherence to national guidelines. Socioeconomic and demographic disparities, including race/ethnicity, lack of insurance coverage, and travel distance, negatively impacted the use of adjuvant chemotherapy in this young and medically fit population. Patients (or caregivers) who declined adjuvant chemotherapy had an undesirable impact on clinical outcomes. Therefore, strong emphasis should be placed to develop patient-centered strategies to improve compliance and adherence to guideline-concordant use of adjuvant chemotherapy in all patients.

## Clinical Practice Points

- Among non-elderly and medically fit Stage III colon cancer patients, the utilization of adjuvant chemotherapy is high.
- The most common reason for not receiving adjuvant chemotherapy is the patient's or caregiver's choice and it adversely affects their overall survival.
- Socioeconomic and demographic disparities play a role in the utilization of adjuvant chemotherapy, even among non-elderly and medically fit patients.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clcc.2022.09.001](https://doi.org/10.1016/j.clcc.2022.09.001).

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