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Adjuvant Chemotherapy is Associated with Improved Survival in Patients with Stage II Colon Cancer

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Abstract

Background—The role of adjuvant chemotherapy in patients with stage II colon cancer remains to be elucidated and its use varies between patients and institutions. Currently, clinical guidelines suggest discussing adjuvant chemotherapy for patients with high-risk stage II disease in the absence of conclusive randomized controlled trial data. In order to further investigate this relationship, the study aimed to determine whether an association exists between overall survival (OS) and adjuvant chemotherapy in patients stratified by age and pathological-risk features.

Methods—Data from the National Cancer Data Base (NCDB) was analyzed for demographics, tumor characteristics, management, and survival of patients with stage II colon cancer diagnosed from 1998-2006 with survival information through 2011. Pearson Chi-squared tests and binary logistic regression were used to analyze disease and demographic data. Survival analysis was performed with the Log-rank test and Cox proportional hazards regression modeling. Propensity score weighting was utilized to match cohorts.

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Results—In 153,110 stage II colon cancer patients, predictors of receiving chemotherapy included age <65, male gender, non-Caucasian race, community treatment facility, non-Medicare insurance, and diagnosis before 2004. Improved and clinically relevant overall survival was associated with the receipt of adjuvant chemotherapy in all patient sub-groups regardless of high-risk tumor pathologic features (poor or undifferentiated histology, <12 lymph nodes evaluated, positive margins, or T4 histology), age, or chemotherapy regimen, even after adjustment for covariates and propensity score weighting (HR 0.76, p<0.001). There was not a difference in survival between single and multi-agent adjuvant chemotherapy regimens.

Conclusion—In the largest group of stage II colon cancer patients evaluated to date, improved OS was associated with adjuvant chemotherapy regardless of treatment regimen, patient age, or high-risk pathologic risk features.

Introduction

Colorectal cancer is the third leading site of cancer in men and women and is the second leading cause of cancer related deaths in the United States[1, 2] Surgical resection with curative intent is the mainstay of treatment for locoregional disease. For patients with stage III disease, adjuvant based chemotherapy with fluoropyrimides is recommended due to demonstrated improved overall survival (OS) of 20-33% after 5-years,[3-5] however, its role in stage II disease has been debated,[6-9] and its appropriate utilization in these patients has been an ongoing challenge.[10, 11] This is in large part due to the wide range of stage II disease defined by negative lymph nodes (N0) while encompassing tumors both limited to and extending beyond the serosa (T3 and T4 tumors) and representing a spectrum of histopathological risk factors.[12] In the absence of conclusive randomized controlled trial data, clinical guidelines by the American Society of Clinical Oncology (ASCO)[13] and the National Comprehensive Cancer Network (NCCN) suggest discussing adjuvant chemotherapy in stage II disease for patients with high-risk stage II disease.[14] Recent studies have called into question the advantage of adjuvant therapy in high-risk stage II disease, however analyses have been limited by evaluation of patients with specific demographics and data collection before the widespread use of multi-agent chemotherapy.[15]

Additional large-scale and highly powered studies in patients of all ages who have been treated in the modern era with adequate long-term follow-up are needed to determine if adjuvant chemotherapy is associated with survival in stage II disease. The current study aimed to utilize a diverse database of over one million patients with colon cancer to assess associations between adjuvant chemotherapy and survival in low- and high-risk patients, and in those aged less than or over 65. Use of combination chemotherapy regimens began to increase after 2002,[16] when irinotecan, oxaliplatin, bavcizumab and cetuximab combinations were associated with improved responses in the metastatic setting, and eventually FOLFOX was FDA approved in 2004 for stage III and advanced colorectal disease in the adjuvant setting.[17] For this reason, outcomes were also evaluated by separating patients both by pre and post-2004, and by single-agent (FL) compared to multi-agent chemotherapy.

Patients and Methods

Data source

Data access was granted by the National Cancer Data Base (NCDB), a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. The ACS and CoC have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data. This study was conducted with Institutional Review Board approval.

Site and histology codes were recorded using International Classification of Diseases for Oncology, Third Edition, (ICD-O-3).[18] Disease staging was defined by the American Joint Committee on Cancer (AJCC). Site-specific information was coded according to the Collaborative Stage Data Collection System (CS), which was implemented in 2004. Chemotherapy regimen was coded according to SEER*Rx and included data on patients 1998-2011.[19] Date of last contact or death was reported as months from the date of diagnosis.

Patient selection

A total of 1,078,091 patients diagnosed with colorectal cancer between 1998-2011 were evaluated. 179,676 patients were diagnosed with stage II colon cancer between 1998-2006 for whom five-year vital status information was available. Stage II patients were excluded for appendiceal adenocarcinoma (n=5,246; 2.0%), radiation therapy (n=10,099; 3.8%), no surgery (n=3,318; 1.2%), death within 30-days of surgery (n=10,630; 4.0%), metastasis (n=1,077; 0.4%), positive nodes at diagnosis (n=2,233; 0.8%), and for initial cancer treatment other than surgery (n=1,521; 0.5%), resulting in a total of 164,668 patients eligible for these analyses (there was substantial overlap in exclusion criteria). Of these, 11,558 (7.0%) lacked information on chemotherapy and were not included in the analyses, resulting in a final cohort of 153,110 patients.

Measured outcomes and statistical analysis

The primary outcome in this study was OS measured from time of diagnosis stratified by adjuvant chemotherapy administration. All survival analysis included patients diagnosed between 1998-2006 with survival information through 2011. Patients were characterized by low- or high-risk disease, age under or over 65, single- or multi- agent chemotherapy, and diagnosis before or after 2004, the year in which the U.S. FDA approved use of oxaliplatin for adjuvant chemotherapy of colon cancer.[17]

High-risk tumor characteristics[13] captured in the NCDB database included the following: high-grade histology (poor or undifferentiated), <12 lymph nodes evaluated, positive margins, or T4 histology. Lymphovascular invasion information was available and included for patients diagnosed after 2005.

Patient demographic and disease information was compared using the Pearson Chi-squared test and binary logistic regression. Effect size was determined using Cramer's V/Phi for categorical variables, for which 0.10 corresponded to a small correlation effect, and 0.50 to a

large correlation effect.[20, 21] Survival data was analyzed using Cox proportional hazard regression. Age was used as a continuous variable in all analyses that control for age.

Survival was adjusted for potential confounding covariates: age, sex, race, risk status, facility type, facility location, average neighborhood education level, insurance type, tumor location, tumor size, and year of diagnosis. Analysis with unplanned 30-day hospital readmission after surgery, and Charlson/Deyo score were performed secondarily, as this data was available for patients diagnosed after 2003 (41% of the cohort).

Propensity score weighting was performed to account for selection bias by creating a control cohort matched to have similar representation of baseline features.[22] In brief, the probability of receiving chemotherapy based on baseline characteristics (age, sex, race, risk status, facility type, facility location, average neighborhood education level, insurance type, tumor location, tumor size, year of diagnosis, and inadequate lymph node sampling) was calculated using logistic regression, which generated a propensity score for chemotherapy receipt for each patient. The average treatment effect (ATE)[23] was assessed by weighting patients in the control arm according to the formula p/(1-p), where p denotes the propensity score, to match the baseline variables of the treatment group. Patients receiving treatment were unweighted.

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago IL) and STATA SE 12.0 (StataCorp LP, College Station, TX). P-values ≤ 0.05 were considered statistically significant.

Results

Patient characteristics

Patient and disease characteristics are shown in Table 1. Of 153,110 eligible patients with stage II colon cancer, one in 5 patients received chemotherapy, (19.3% of low-risk and 21.7% of high-risk patients, P=<0.001). Receipt of adjuvant chemotherapy was independently associated with age <65, male gender, community facility, central U.S. location, non-Medicare insurance, living in a neighborhood with higher education level, diagnosis pre-2004, and no comorbidities on the Charlson/Deyo scale. Overall, 23% of patients had one comorbidity, and 8% had two. Median age of those who received chemotherapy compared to those who did not was 64 ± 12 years and 76 ± 11 years, respectively; with high-risk versus low-risk features was 74 ± 12 years and 72 ± 12 years.

Single-agent chemotherapy was the most often used prior to 2004, which likely comprised of 5-Fluorouracil (5-FU) with or without leucovorin,[24, 25] whereas multi-agent therapy gained popularity after 2004, likely due to emergence of combinations such as FOLFOX and FLOX.[26-29] Figure 1 demonstrates the overall pattern of chemotherapy regimen use over time in patients treated from 1998-2011.

Tumor characteristics

At diagnosis, patients had predominantly stage IIA disease, higher T-stage, low-grade histology, tumors smaller than 5 cm, and disease of the right colon (Table 2). Patients more likely to receive chemotherapy had stage IIB disease, T4 stage, high-grade histology, larger

tumor size, location in the left or sigmoid colon, and unplanned readmission within 30-days of surgery. 59% were considered high-risk by meeting at least one of four criteria as defined by ASCO: high-grade (29%), positive margins (4%), T4 (14%), or <12 lymph nodes evaluated (76%). Only 20% of patients had more than one high-risk feature. Presence of any high-risk feature increased the likelihood of receiving adjuvant chemotherapy, with the exception of under-evaluated lymph nodes. When excluding inadequate lymph node sampling, the overall high-risk rate decreased to 24.4%, or 31.6% among those receiving chemotherapy and 22.6% among those without (P = <0.001).

Overall survival advantage with adjuvant chemotherapy (unadjusted)

Unadjusted OS at 3, 5, and 10-years was 88.3%, 81.2% and 71.2% for patients who received adjuvant chemotherapy, and 77.1%, 65.3% and 50.3% for those who did not. Chemotherapy was associated with an increase in median survival from 7.0-years to 13.2-years, and corresponded with improved OS regardless of high-risk features, age, or chemotherapy regimen (Table 3). In low-risk patients, 5-year OS improved from 68% to 86% with chemotherapy (P = <0.001), versus 57% to 76% (P = <0.001) in high-risk patients. Redefining high-risk without inadequate lymph node sampling did not change the association of chemotherapy with improved OS (HR 0.49, 95% CI 0.47-0.51, P=<0.001). For patients under age 65, 5-year OS improved from 82% to 86% (log-rank P = <0.001), whereas patients >65 improved with treatment from 57% to 73% (log-rank P = <0.001). The association of increased survival with chemotherapy was similar among those regardless of comorbidities (both HR 0.46, P = <0.001), or 30-day unplanned hospital readmission (HR 0.38 vs. HR 0.45, both P = <0.001). There was no evidence of a departure from the assumption of proportional hazards between treatment groups.

Overall survival advantage with adjuvant chemotherapy (adjusted)

After adjusting for covariates, all sub-groups experienced significant improvement in OS correlating with receipt of adjuvant chemotherapy (Table 3). Low-risk patients had a median OS of 13.2-years vs. 8.8-years without chemotherapy administration, while high-risk patients had median survival of 11.0-years vs. 6.9-years without chemotherapy administration (Fig 2A). Similarly, patients <65 experienced a median survival of not reached (NR) vs. 12.8 years, while those ≥65 had median survival of 10.1 vs. 6.3 years (Fig 2B). Unplanned readmission within 30-days of surgery was an independent predictor of survival (HR 1.39, P = <0.001), as was one (HR 1.55, P = <0.001) or two comorbidities (HR 2.41, P = <0.001). Regardless, chemotherapy remained an independent predictor of survival after adjustment for these covariates (HR 0.79, P = <0.001).

Figure 3 demonstrates the association between patient and tumor features and OS improvement observed with the addition of adjuvant chemotherapy. All sub-groups demonstrated trends towards improved OS with chemotherapy.

Comparison of single- to multi-agent chemotherapy

Overall survival with single-agent therapy (n=15,368) was similar to multi-agent therapy (n=12,313), both with median survival of 13.3-years (P = 0.412), (Fig 2C). After adjustment for covariates, median survival was 13.9-years vs. 13.7-years with single- vs. multi-agent

therapy. This is further reflected by similar survival associated with chemotherapy before and after 2004 (Fig 2D), suggesting a comparable effectiveness of modern era and older chemotherapy regimens on survival in stage II patients.

Overall survival advantage after propensity score weighting

Matching the patient cohorts with propensity score weighting did not affect the magnitude of improved survival associated with adjuvant chemotherapy with respect to any of the sub-groups (Table 3). One-year, 3-year, 5-year and 10-year survival was 94.7%, 83.3%, 72.9%, and 50.6% with chemotherapy, and 90.6%, 75.2%, 62.1%, and 35.4% without. Including Charlson/Deyo comorbidity score and 30-day unplanned hospital readmission as covariates in propensity score weighting did not significantly effect observed outcomes and improved OS remained associated with adjuvant chemotherapy (HR 0.76, P = <0.001).

Discussion

Though surgical resection with curative intent is the mainstay of treatment for localized colon cancer, adjuvant chemotherapy has been utilized for decades[30] despite unclear advantages in stage II disease.[9-11, 13, 14, 31] Multiple randomized controlled trials[7-9] and a recent Cochrane review[32] have demonstrated improved mortality risk ratios with adjuvant fluoropyrimidine-based chemotherapy after surgical resection in stage II disease, however, these studies have been limited by an inability to investigate the specific effect with respect to patient age, high- or low-risk disease characteristics, long-term follow-up, and modern chemotherapy regimens. A 2004 meta-analysis of seven randomized controlled trials demonstrated a trend towards an improved mortality risk ratio with adjuvant chemotherapy, but estimated that 5,000 patients would be needed to demonstrate significant differences between the groups with adequate power.[33] The largest randomized controlled trial (RCT) to evaluate this question enrolled 2,291 stage II colon cancer patients and demonstrated that chemotherapy significantly reduced all-cause mortality by 16% (relative risk (RR) = 0.84, P=0.046) and risk of recurrence by 22% (RR = 0.78, P=0.004), though the absolute improvement in five-year overall survival was of borderline statistical significance. Since only 20% of these patients had pathological data, subgroup analysis of high versus low-risk groups could not be compared.[7] Based on the currently available data, the ASCO clinical guidelines[13] and current NCCN guidelines[14] recommend consideration of chemotherapy in specific populations including in patients with high-risk tumor features despite conclusive evidence. As a result, in the practical clinical care of patients with stage II disease, the decision of whether to administer adjuvant chemotherapy is thus quite variable between individuals, institutions, and countries. Therefore, the need remains for a highly powered study of over 5,000 patients per arm and with corresponding pathologic data, use of modern-age chemotherapy, and not limited by specific patient demographics or comorbidities to address this clinical gap in knowledge without which evaluation of an association between chemotherapy and OS is not possible.

The NCDB contains 29 million patient records, and represents ~70% of all newly diagnosed cases of cancer in the US. With over one million patients with colon cancer captured and 153,110 patients meeting eligibility criteria for this study, we were able to adequately power

the analyses to evaluate this question in all subgroups evaluated, though the challenge was to determine whether the differences are clinically relevant (a two-tailed test was able to detect an effect size of 0.018, which is equivalent to a difference of 0.004 months (2.8-hours) of extended life). The current analysis included more patients than any prior study and included a minimum of 5-years and up to 14-years of actual survival data and patient follow-up. We found that chemotherapy was associated with statistically improved OS regardless of high-risk or low-risk disease features, patient age over or under 65, use of single- or multi-agent chemotherapy, and administration before or after 2004. A considerable effort was made to adjust for all available covariates, and especially age, in the database; and to create comparable cohorts using propensity score weighting and adjustment for patient comorbidities.

Few other studies have compared chemotherapy to observation alone due to overshadowing by modern-era multi-drug regimens with oxaliplatin[26] and irinotecan in advanced-stage disease.[34] The 2004 MOSAIC trial that compared fluorouracil plus leucovorin (FL) to fluorouracil- leucovorin-oxaliplatin (FOLFOX) demonstrated a trend towards improved 3-year disease free survival (DFS) in stage II disease.[26] The mature 6-year OS data did not show improved survival in stage II disease,[28] however the authors highlighted the trend towards improved DFS, bolstered by concurrent trials from the NSABP[27, 29] and the U.S. FDA approval of 3-year DFS as a primary end point for adjuvant colon cancer studies.[35] For this reason we also evaluated our data by separating patients both by pre and post-2004 (when the FDA approved adjuvant oxaliplatin for use in non-metastatic colon cancer) as a proxy for increased indications for modern-era multi-drug chemotherapy regimens, and by single-agent (FL) compared to multi-agent chemotherapy. The concept of “modern-era” chemotherapy in this case is reflective of multi-drug chemotherapy regimens compared to 5FU/leucovorin alone, rather than reflective of specific dosing regimens or patient-specific chemotherapy selection factors. In both cases, i.e. before or after 2004, or single vs. multi-agent regimens, there was no difference in the magnitude of OS increase with adjuvant treatment administration. Thus, our results also support the contention that oxaliplatin regimens may not provide additional benefit for patients with stage II disease.[36]

There are limitations to this study. First, retrospective analysis without randomization could allow for selection bias. Second, data variables were restricted by availability from the NCDB file, which did not include microsatellite instability status or disease-specific outcomes. In addition, disease-recurrence is not known, nor is the number of chemotherapy cycles administered, therefore confirmatory analyses in other large databases or, preferably, in prospective series designed to address these variables, is warranted. While the current study excluded rectal carcinoma and primary treatment other than surgery, it was not able to exclude patients based on palliative operations, enrollment in HMOs, post-mortem diagnosis of colon cancer, or presence of other malignancies. In addition, patients without knowledge of chemotherapy administration were excluded (3% or n= 42,144), which may introduce bias.

While the 5-year unadjusted OS of treated patients was similar to randomized controlled trials (81-82%),[7, 37] that of the untreated patients was lower than RCTs, but very similar to retrospective observational analyses (65% vs. 67%).[38, 39] Differentiation by risk status (5-

year OS 70.3% in low-risk vs. 60.9% in high-risk) remained consistent with prior reported unadjusted data (69% in low-risk and 57% in high-risk).[15] The reason for these variances may be a factor of non-randomization, patient population, type of chemotherapy administered, treatment location, or other inclusion/exclusion criteria (e.g. inclusion of rectal cancer in the QUASAR trial or requirement for continuous Medicare enrollment in SEER-Medicare analyses). Careful assessment of included covariates was undertaken and limited from Hierarchical Condition Categories scores, prior hospitalizations, re-hospitalizations, and complications, thus, confounding by indication such that healthier patients may have been more likely to receive chemotherapy is a possibility, and should be considered in the older patient population, though unplanned 30-day hospital readmissions after surgery and Charlson/Deyo comorbidity scores were included in the analysis and did not affect the results. Additionally, the longer follow-up available in this study with actual, and not actuarial, survival data may explain long-term differences in survival.[40]

To the authors' knowledge, this is the largest study of stage II colon cancer patients evaluating associations between adjuvant therapy and survival, including nearly 6-fold the number of patients previously analyzed in the SEER database, and 4-fold the number of Medicare patients alone.[15] Despite limitations, the results of this study add important knowledge to the clinical management of stage II colon cancer patients, including the association between clinicopathological risk factors and survival. Based on the results, adjuvant chemotherapy appears to be associated survival in patients with stage II colon cancer regardless of risk status, age, or chemotherapy regimen; and prospective validation is warranted.

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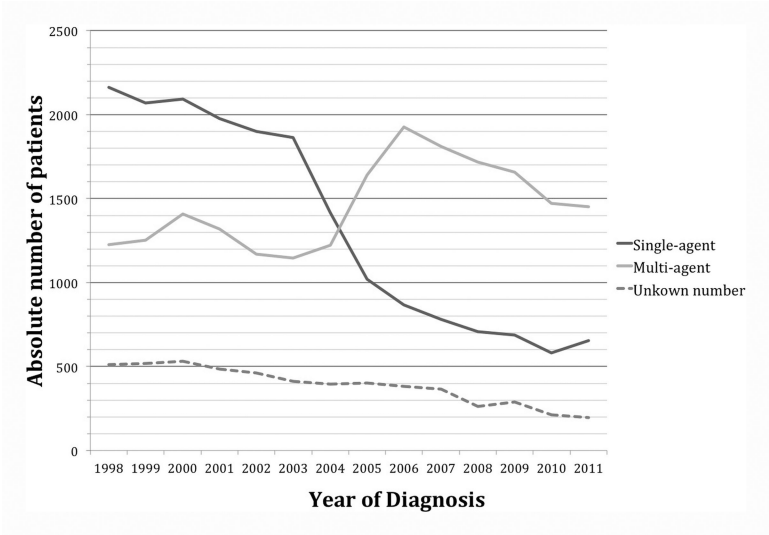
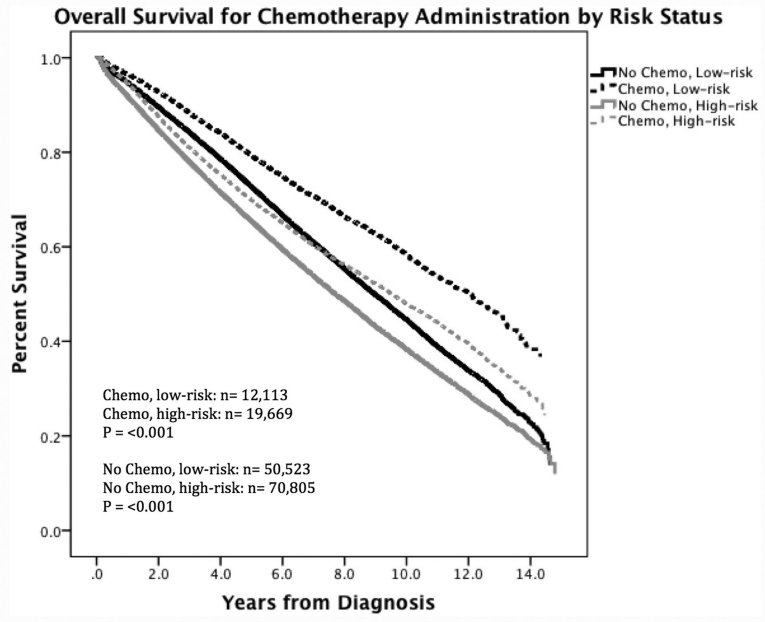
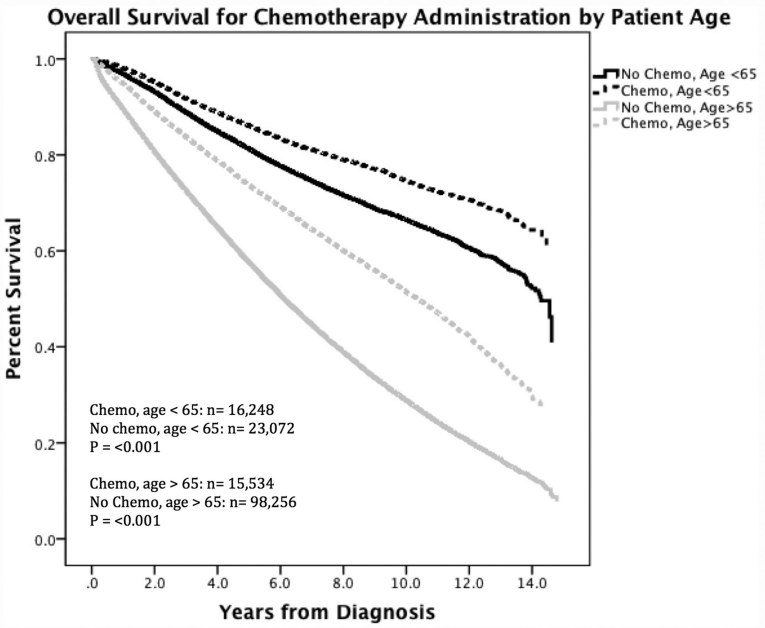


Fig 1. Chemotherapy regimens employed over time for patients with stage II disease





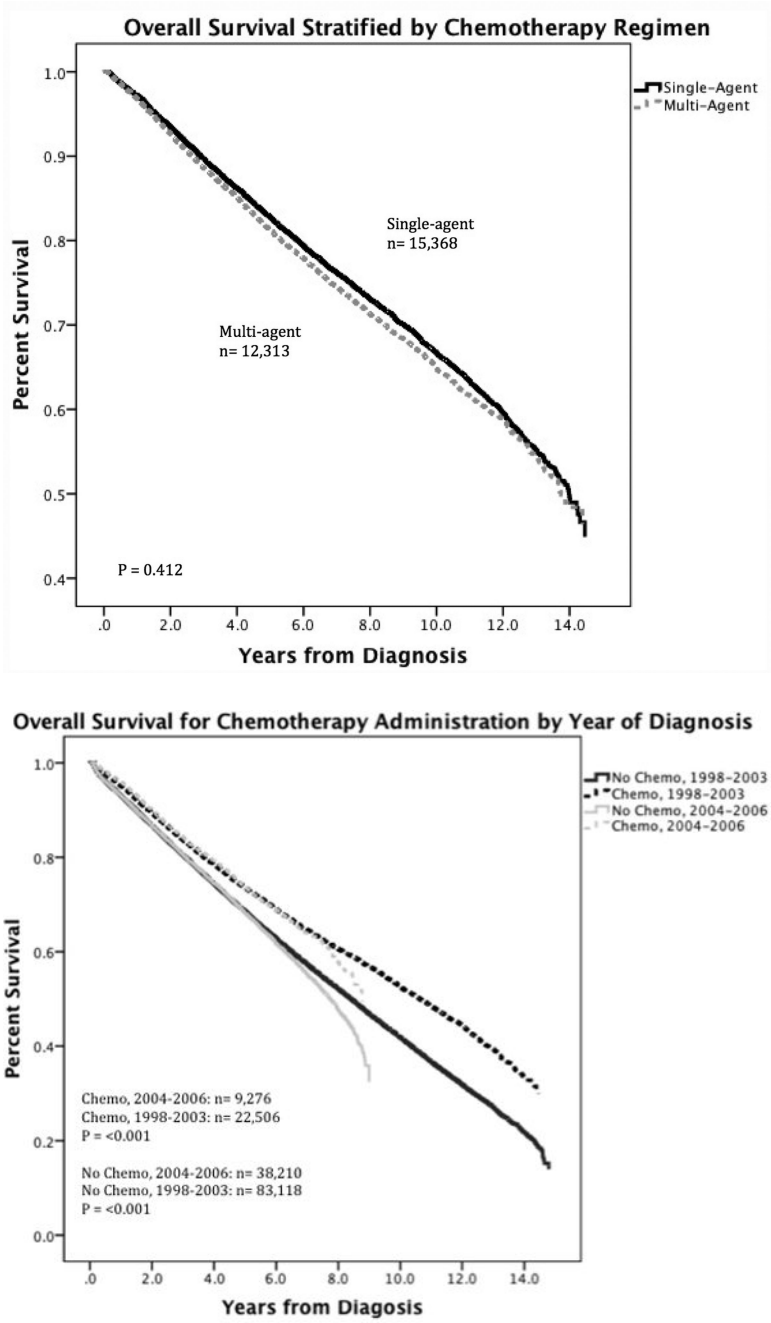


Fig 2.

Overall survival (years) with adjuvant chemotherapy adjusted for covariates. (A) Adjuvant chemotherapy administration was associated with improved survival in both low-risk patients and high-risk patients. (B) Chemotherapy was associated with improved survival of adults under age 65 and above age 65. (C) Survival was similar for single-agent vs. multi-agent chemotherapy regimen. (D) Survival associated with adjuvant chemotherapy was similar before and after 2004.

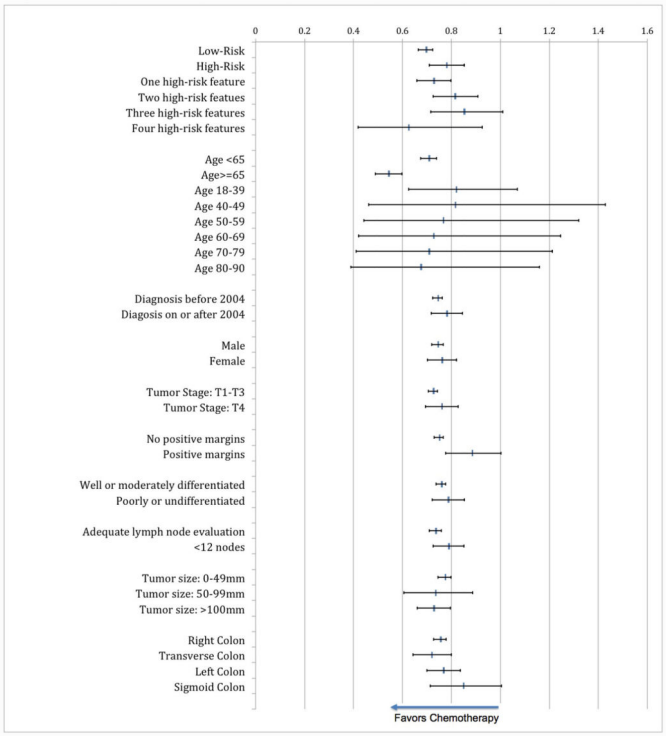


Fig 3. Impact of adjuvant chemotherapy on survival for each variable

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Table 1

NCDB Patient Characteristics for Stage II Colon Cancer Diagnosed Between 1998-2006

Measure	All Stage II					Low-Risk Stage II				High-Risk Stage II			
	Chemo (n=31,782)	No Chemo (n=121,328)	Univar	Multivar	Effect size	Chemo (n=12,113)	No Chemo (n=50,523)	Univar	Multivar	Chemo (n=19,669)	No Chemo (n=70,805)	Univar	Multivar
Age[a], %			<0.001	<0.001	-0.298			<0.001	<0.001			<0.001	<0.001
<65	51.1	19.0				57.0	22.6			47.5	16.5		
≥ 65	48.9	81.0				43.0	77.4			52.5	83.5		
Male/ Female, %	49.1/ 50.9	45.2/ 54.8	<0.001	0.028	-0.032	49.9/ 50.1	46.0/ 54.0	<0.001	0.006	48.7/ 51.3	44.6/ 55.4	<0.001	0.293
Race, %			<0.001	0.751	0.021			<0.001	0.105			<0.001	0.193
White	81.7	84.5				80.2	83.3			82.7	85.3		
Black	10.5	9.3				11.0	9.9			10.2	8.9		
Hispanic	4.4	3.2				4.9	3.4			4.1	3.1		
Asian/Pacific Islander	2.2	1.8				2.6	2.0			1.9	1.7		
Other	1.2	1.2				1.3	1.4			1.2s	1.1		
Facility Type, %			<0.001	0.037	0.024			<0.001	0.122			<0.001	0.433
Community	75.0	72.5				73.3	69.4			76.0	74.8		
Academic/Research	19.9	22.4				22.3	26.1			18.5	19.7		
Other	5.1	5.1				4.4	4.5			5.5	5.5		
Facility Location, %			<0.001	<0.001	0.027			<0.001	0.148			<0.001	<0.001
East	43.0	44.0				43.3	44.6			42.8	43.6		
Central	42.5	39.7				42.6	39.9			42.5	39.6		
Mountain/Pacific	14.4	16.3				14.1	15.5			14.7	16.8		
Insurance, %			<0.001	<0.001	0.235			<0.001	0.002			<0.001	<0.001
Not Insured	3.5	1.6				3.5	1.9			3.5	1.5		
Private Insurance	47.5	23.9				52.4	26.8			44.6	21.8		
Medicaid	3.4	2.0				3.5	2.1			3.3	1.9		
Medicare	42.6	69.5				37.6	66.4			45.7	71.6		
Other Govt	0.5	0.3				0.5	0.3			0.5	0.3		
Unknown	2.4	2.8				2.5	2.6			2.4	2.9		
Income, %			0.373	-	0.373			0.087	0.888			0.477	-

Measure	All Stage II					Low-Risk Stage II				High-Risk Stage II			
	Chemo (n=31,782)	No Chemo (n=121,328)	Univar	Multivar	Effect size	Chemo (n=12,113)	No Chemo (n=50,523)	Univar	Multivar	Chemo (n=19,669)	No Chemo (n=70,805)	Univar	Multivar
< $30,000	14.3	14.3				14.1	13.6			14.5	14.7		
$30,000-$45,999	47.5	47.9				45.7	46.8			48.5	48.7		
$46,000 +	38.2	37.8				40.2	39.6			37.0	36.6		
Education[b], %			<0.001	<0.001	0.013			0.061	0.187			<0.001	0.010
>=29%	17.0	16.3				16.6	15.8			17.3	16.6		
14-19.9%	49.0	48.3				47.6	47.5			49.8	48.8		
<14%	34.0	35.5				35.8	36.7			32.9	34.6		
Diagnosis year, %			<0.001	0.057	0.026			<0.001	0.001			0.831	-
1998-2003	70.8	68.5				68.4	63.1			72.3	72.4		
2004-2006	29.2	31.5				31.6	36.9			27.7	27.6		
Charlson/Deyo Score			<0.001	<0.001	0.094			<0.001	<0.001			<0.001	<0.001
0	77.5	67.2				79.5	68.2			76.0	66.4		
1	18.2	24.1				16.5	23.6			19.4	24.5		
2	4.3	8.6				4.0	8.2			4.6	9.1		
Mortality[c], %													
1-year	11.4	17.1				9.9	14.0			11.9	18.9		
3-year	38.0	44.3				32.4	39.4			40.3	47.1		
5-year	61.2	67.1				56.6	63.6			63.0	69.0		
10-year	93.1	95.7				92.3	95.2			93.4	95.9		
Chemotherapy, %													
Single agent	48.4	-				48.3	-			48.2	-		
Multi-agent	38.7	-				39.2	-			38.6	-		
Type not Documented	12.9	-				12.5	-			13.1	-		

[a] Median age of those who received chemotherapy versus to those who did not was 64 ± 12 years versus 76 ± 11 years

[b] Measured as percent of adults in the patient's zip code who did not graduate from high school according to 2000 US Census

[c] Represents percentage out of known deaths: n=9,751 for chemo; n=63,378 for no chemo

Table 2

Tumor characteristics and high-risk features (percent of total)

Measure	Total (n=153,110)	Chemo (n=31,782)	No Chemo (n=121,328)	P-Value	Effect Size
AJCC Stage [a], %				<0.001	0.092
Stage IIA	84.3	76.0	86.3		
Stage IIB	8.8	16.6	6.9		
T stage, %				<0.001	0.122
<T2	0.0	0.0	0.0		
T3	89.6	83.5	91.3		
T4	8.5	14.9	6.8		
Tumor grade, %				<0.001	0.036
Well differentiated	8.8	7.8	9.1		
Moderately differentiated	71.6	70.3	72.0		
Poorly differentiated	16.0	17.8	15.6		
Undifferentiated	0.8	1.0	0.6		
Tumor size, %				<0.001	0.070
0-49mm	52.3	46.0	53.9		
50-99mm	43.2	47.8	42.0		
>100mm	4.5	6.2	4.1		
Tumor Location, %				<0.001	0.058
Right Colon	51.2	46.1	52.5		
Transverse Colon	11.4	11.2	11.4		
Left Colon	10.6	12.3	10.2		
Sigmoid Colon	24.1	27.2	23.2		
High-Risk: (≥1 risk factor), %	59.1	61.9	58.4	<0.001	0.029
High-gr1ade (poorly and undifferentiated)	16.9	18.8	16.4	<0.001	
<12 nodes evaluated	45.0	42.9	45.5	<0.001	
Positive margins	2.4	3.6	2.1	<0.001	
T4 Histology	8.5	14.9	6.8	<0.001	
Number of high-risk features, %				<0.001	0.063
0	40.9	38.1	41.6		

Measure	Total (n=153,110)	Chemo (n=31,782)	No Chemo (n=121,328)	P-Value	Effect Size
1	47.1	46.2	47.3		
2	10.5	13.2	9.8		
3	1.4	2.2	1.1		
4	0.1	0.2	0.1		
30-day surgical hospital readmission, %	2.2	1.7	1.4	<0.001	0.020

[a]Percentages reported only among those scored according to AJCC Pathologic Stage Group Edition 6 (n=65,516). Edition use changed according to year of diagnosis: Edition 5 was used from 1998-2001, Edition 6 from 2002-2009, Edition 7 from 2010-2011. The other 6.9% had unknown staging.

Table 3

Overall survival with adjuvant chemotherapy versus no chemotherapy stratified by risk-stage, age over 65, and diagnosis year

Group	Chemo %Dead	No Chemo %Dead	Unadjusted HR			Adjusted HR[a]			Propensity Score Weighted[b]		
			HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
All Chemo											
Low-risk	23.4%	45.3%	0.40	0.39-0.42	<0.001	0.71	0.68-0.74	<0.001	0.59	0.56-0.61	<0.001
High-risk	35.1%	56.7%	0.48	0.47-0.50	<0.001	0.77	0.75-0.79	<0.001	0.65	0.63-0.67	<0.001
Age < 65	19.8%	24.8%	0.72	0.69-0.75	<0.001	0.71	0.68-0.74	<0.001	0.73	0.70-0.77	<0.001
Age ≥ 65	42.0%	58.4%	0.55	0.54-0.57	<0.001	0.54	0.53-0.56	<0.001	0.55	0.54-0.57	<0.001
Single-Agent Chemo											
Low-risk	24.5%	45.3%	0.40	0.38-0.42	<0.001	0.69	0.66-0.74	<0.001	0.58	0.55-062	<0.001
High-risk	35.8%	56.8%	0.47	0.45-0.48	<0.001	0.74	0.71-0.77	<0.001	0.63	0.61-0.66	<0.001
Age < 65	19.4%	24.8%	0.66	0.63-0.70	<0.001	0.66	0.62-0.70	<0.001	0.68	0.64-0.72	<0.001
Age ≥ 65	42.8%	58.5%	0.54	0.53-0.56	<0.001	0.53	0.51-0.55	<0.001	0.54	0.52-0.56	<0.001
Multi-Agent Chemo											
Low-risk	21.8%	45.3%	0.39	0.37-0.42	<0.001	0.75	0.70-0.80	<0.001	0.57	0.54-0.61	<0.001
High-risk	34.2%	56.8%	0.48	0.46-0.50	<0.001	0.80	0.77-0.84	<0.001	0.66	0.63-0.68	<0.001
Age < 65	20.3%	24.8%	0.77	0.73-0.82	<0.001	0.74	0.70-0.80	<0.001	0.79	0.74-0.84	<0.001
Age ≥ 65	40.8%	58.4%	0.56	0.53-0.58	<0.001	0.53	0.51-0.56	<0.001	0.56	0.54-0.58	<0.001

[a] Adjusted for statistically significant covariates: age, sex, race, risk status, facility type, facility location, education, insurance, tumor location, tumor size, year of diagnosis. Covariates that were also present within group selection criteria were omitted (i.e. risk status was eliminated in measures within risk groups; age was eliminated in measures within age groups, etc)

[b] Propensity score weighting performed for same covariates as above, with addition of indicator for <12 lymph nodes assessed