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ORIGINAL ARTICLE – COLORECTAL CANCER

Factors Associated with Receipt of Adjuvant Chemotherapy in Stage II Colon Cancer

Meridith C. Ginesi, MD, Jonathan T. Bliggenstorfer, MD, Daphine M. Kwesiga, MD, Samantha H. Xu, BS, MPH, Diana Jodeh, MD, J. Eva Selfridge, MD, Sharon L. Stein, MD, FACS, FASCRS, and Emily F. Steinhagen, MD, FACS, FASCRS

Department of Surgery, University Hospitals Research in Surgical Outcomes and Effectiveness Center (UH-RISES), University Hospitals Cleveland Medical Center, Cleveland, OH

ABSTRACT

Background. The benefits of chemotherapy in stage II colon cancer remain unclear, but it is recommended for high-risk stage II disease. Which patients receive chemotherapy and its impact on survival remains undetermined.

Methods. The National Cancer Database was surveyed between 2004 and 2016 for stage II colon cancer patients. Patients were categorized as high- or average-risk as defined by the National Comprehensive Cancer Network. The demographic characteristics of high- and average-risk patients who did and did not receive chemotherapy were compared using univariate and multivariable analyses. The survival of high- and average-risk patients was compared based on receipt of chemotherapy with Cox hazard ratios and Kaplan–Meier curves.

Results. Overall, 84,424 patients met the inclusion criteria. A total of 34,868 patients were high-risk and 49,556 were average-risk. In high-risk patients, the risk factors for not receiving chemotherapy included increasing age, distance from the treatment facility, Charlson–Deyo score, and lack of insurance. In average-risk patients, factors associated with receipt of chemotherapy were decreasing age, distance from the treatment facility, Charlson–Deyo score, and non-academic association of the treatment facility. In both, chemotherapy was significantly associated with increased survival on the Kaplan–Meier curve. In the Cox hazard ratio, only high-risk patients benefited from chemotherapy (hazard ratio 1.183, confidence interval 1.116–1.254).

Conclusions. Factors associated with not receiving chemotherapy in high-risk stage II colon cancers included increasing age, medical comorbidities, increasing distance from the treatment facility, and lack of insurance. Chemotherapy is associated with improved overall survival in high-risk patients.

Keywords Colon cancer · Stage II · Adjuvant chemotherapy

While adjuvant chemotherapy is generally recommended for most patients with stage III colon cancer and not recommended for stage I disease, decisions regarding adjuvant chemotherapy in stage II are less clear. Guidelines from both the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) recommend against the routine use of chemotherapy in stage II colon cancer, but recommend consideration in patients with high-risk features.[1] The National Comprehensive Cancer Network (NCCN) clinical practice guidelines also recommend adjuvant chemotherapy in patients with high-risk features, including poorly differentiated pathology, lymphovascular invasion, perineural invasion, tumor budding, inadequate surgical lymph node yield, T4 tumors, close or positive surgical margins, or those who present with perforation or obstruction.[2] There are limited data regarding the application of these recommendations in practice. In addition, previous data have demonstrated demographically

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E. F. Steinhagen, MD, FACS, FASCRS
e-mail: Emily.steinhagen@UHHospitals.org

based differences in oncologic treatment despite equivalent clinical scenarios; it is unclear whether these disparities exist for the treatment of stage II colon cancers.[3–5]

A few prior database studies have demonstrated that patients may be likely to receive adjuvant chemotherapy for stage II disease when they are younger and more medically fit, but it is unclear how oncologic factors are taken into account, or the impact on outcomes.[6,7] Large prospective clinical trials such as the Quick and Simple and Reliable (QUASAR)[8] and National Surgical Adjuvant Breast and Bowel Project (NSABP)[9] trials demonstrated a survival benefit for stage II patients who received chemotherapy compared with those who did not, while other studies such as the International Multicenter Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2)[10] showed no benefit. Similar to large trials, retrospective database studies have yielded inconsistent results. Some have concluded that patients have improved overall survival (OS) regardless of risk factors, while other studies suggest that patients only have improved survival in cases of high-risk features and others demonstrate no survival benefit.[6,7,11]

This study sought to investigate factors associated with receiving adjuvant therapy for stage II colon cancer using the National Cancer Database (NCDB) and to determine whether receipt of chemotherapy was associated with improved survival in high-risk and average-risk stage II patients. We hypothesized that while predictable factors such as increasing age would be associated with decreased use of adjuvant chemotherapy, clinical features would not account for all of the variability and that patients who received chemotherapy may have a survival benefit.

METHODS

Data Source

This study utilized the NCDB, the largest cancer database in the United States (US). The NCDB is a joint venture between the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society, which captures over 70% of all new cancer diagnoses in the US. The NCDB was chosen due to its size, to capture the largest possible sample of patients treated for colon cancer. The University Hospitals Cleveland Medical Center Institutional Review Board (IRB) designated this study as non-human subject research and was therefore exempt from IRB approval.

Inclusion and Exclusion Criteria

From 2004 to 2016, the NCDB was queried for patients with stage II colon adenocarcinoma. Patients were excluded if their pathologic staging information or any data regarding risk factors or treatments were missing, if they were noted to have declined chemotherapy, if they had a medical reason that precluded chemotherapy, or if receipt of chemotherapy was unknown. Patients were also excluded if they did not undergo surgery or if they received radiation, as this is not a standard of care, and if chemotherapy was delivered before or during surgery or if it was administered between two different surgeries. The NCDB does not provide a cancer recurrence code, therefore in order to eliminate patients who were treated for recurrent stage II cancer, records were excluded if the time from diagnosis to treatment exceeded 1 year.

Definition of High- and Average-Risk Patients

Patients were categorized as high-risk patients (HRP) based on the NCCN guidelines, and were categorized as high-risk if they were not microsatellite instability (MSI)-high and had one or more of the following risk factors: lymphovascular invasion, perineural invasion, poorly differentiated tumor, T4 tumor, inadequate lymph node yield (< 12 nodes), or close or positive margins.[2] Patients without any of these risk factors were considered as average-risk patients (ARP). The NCDB does not provide coding for obstructed or perforated tumor, therefore it was not feasible to account for this in the analysis.

Analysis of Over- and Undertreatment

Univariate and multivariate analyses were performed to compare HRPs who received chemotherapy with those who did not. Patients who were high-risk but did not receive chemotherapy, per NCCN recommendations, were considered potentially undertreated, whereas patients who received chemotherapy in the absence of risk factors were considered potentially overtreated. Similarly, univariate and multivariate analyses were performed to compare ARPs who did not receive chemotherapy with those who did (overtreated). Factors were included in the multivariate analysis if the univariate analysis was statistically significant ($p < 0.05$) or clinically relevant.

Survival Analysis

A Kaplan–Meier curve was used to estimate survival based on the presence of high-risk features and whether chemotherapy was administered. A Cox hazard ratio (HR) analysis was performed to estimate the risk of death based on receipt of chemotherapy in HRPs and ARPs, while controlling for other statistically or clinically significant factors.

Analysis by Specific Risk Factors

Cox HR analysis was performed to determine whether receipt of chemotherapy reduced the risk of death based on specific high-risk features. All statistical analyses were performed using Stata/IC 16.1 statistical software (StataCorp LLC, College Station, TX, USA).

RESULTS

Demographics

A total of 182,480 stage II colon cancer patients were identified using the NCDB, 84,424 of whom were eligible for analysis after the exclusion criteria were employed (Fig. 1). Of these, 48.1% were male and 84.6% were White. The average age was 70.2 years. The majority of patients lived in a metro area, were non-Hispanic, and had a Charlson–Deyo score of zero (Table 1). Chemotherapy was administered to 16.3% of stage II patients, and when separated by the presence of high-risk features, 25.5% of HRPs and 9.9% of ARPs received chemotherapy ($p \leq 0.001$).

Analysis of Over- and Undertreatment

Among eligible stage II patients, 34,868 (41.3%) were considered high-risk due to the presence of at least one of the following risk factors: lymphovascular invasion (11,687 patients), perineural invasion (5792 patients), T4 tumor (11,671 patients), poorly differentiated tumor (12,293 patients), positive surgical margin (2638 patients), or inadequate lymph node yield (6609 patients). Among those with high-risk features, only 8883 (25.5%) patients received chemotherapy. The remaining 25,985 (74.5%) patients did not receive chemotherapy and were considered to be

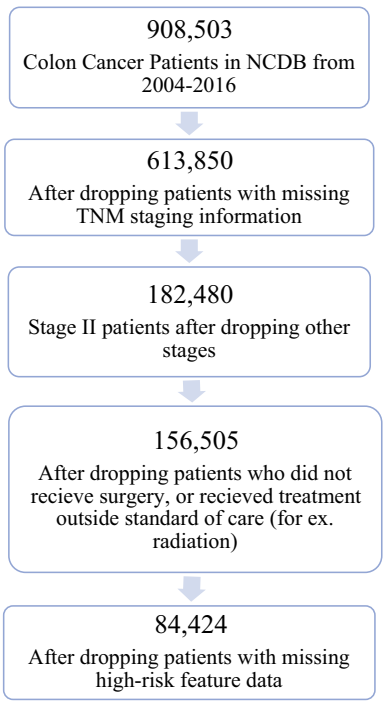

FIG. 1 Excluded patients, including each exclusion criteria. *NCDB* National Cancer Database

TABLE 1 Demographics of included stage II colon cancer patients

	n	%
Sex		
Male	40,624	48.1
Female	43,800	51.9
Race		
White	71,402	84.6
Black	9212	10.9
Other	3810	4.5
Age	70.2[a]	13.2[a]
Ethnicity		
Hispanic	4411	5.2
Non-Hispanic	77,227	91.5
Unknown	2786	3.3
Urban/rural		
Metro	69,662	84.4
Urban	11,289	13.7
Rural	1622	2.0
Insurance		
None	2649	3.2
Private	23,514	28.2
Government	57,278	68.6
Median income		
<$38,000	14,927	17.7
$38,000–$47,999	20,230	24.0
$48,000–$62,999	22,626	26.9
≥$63,000	26,469	31.4
Distance traveled	21.1[a]	85.7[a]
Charlson–Deyo		
0	55,361	65.6
1	19,615	23.2
2	6243	7.4
≥3	3205	3.8
Number of risk factors		
0	49,556	58.7
1	23,253	27.5
2	8281	9.8
3	2599	3.1
4	609	0.7
5	114	0.14
6	12	0.01

[a]Reported as mean and standard deviation as variables are continuous

potentially undertreated. Based on univariate and multivariate analyses, undertreatment was associated with increasing age, living farther from the hospital, or having more medical comorbidities based on their Charlson–Deyo score. Patients with government or private insurance were less likely to be undertreated (Table 2).

A total of 49,556 patients with stage II colon cancer were considered average-risk factors. Of these, 4885 (9.9%) received chemotherapy and were considered potentially overtreated. The remaining 44,671 (90.1%) patients did not receive chemotherapy. On multivariate analysis, overtreatment (receiving chemotherapy in the absence of high-risk features) was less likely in patients who were older, lived an increasing distance from the hospital, had a higher Charlson–Deyo score, and if they were treated at an academic/research affiliated hospital (Table 3).

Survival Analysis

A Kaplan–Meier curve (Fig. 2) was created based on the risk status and receipt of chemotherapy (high-risk, received chemotherapy; high-risk, did not receive chemotherapy; average-risk, received chemotherapy; average-risk, did not receive chemotherapy) to determine survival differences. The Kaplan–Meier curve demonstrated that while HRPs had poorer OS than ARPs, patients who received chemotherapy had higher OS regardless of the presence or absence of risk factors. This difference was statistically significant according to the log-rank test ($p < 0.001$).

A Cox HR was then calculated to analyze the risk of dying based on receipt of chemotherapy, based on this improved survival. Patients were separated into HRPs and ARPs while controlling for age, sex, insurance status, distance from a hospital, and Charlson–Deyo score. Compared with HRPs who received chemotherapy, those who did not receive chemotherapy had a 1.183 HR of death (CI 1.116–1.254). ARPs who were treated with chemotherapy had a decreased HR of death, which was not statistically significant. In addition, this analysis confirmed that women and those with private or government insurance had a lower risk of death, whereas older patients and those with multiple comorbidities had a higher risk (Table 4).

TABLE 2 Univariate and multivariate analysis comparing risks of potential undertreatment (risk of not receiving chemotherapy despite having high-risk features)

	Univariate analysis			Multivariable analysis		
	Received chemotherapy	Did not receive chemotherapy	*p*-Value	OR	95% CI	*p*-Value
Sex						
Male	4450 (50.1)	11,906 (45.8)	< 0.001	0.954	0.903–1.008	0.094
Female	4433 (49.9)	14,079 (54.2)				
Age	61.4 (12.1)	73.9 (12.2)	< 0.001	**1.084**	1.081–1.087	< 0.001
Race						
White	7259 (81.7)	22,491 (86.6)	< 0.001	0.966	0.883–1.057	0.454
Black	1172 (13.2)	2452 (9.4)				
Other	452 (5.1)	1042 (4.0)		1.050	0.919–1.201	0.472
Insurance						
None	506 (5.8)	666 (2.6)	< 0.001	**0.836**	0.729–0.959	0.010
Private	3836 (43.8)	5499 (21.4)				
Government	4427 (50.5)	19,510 (76.0)		**0.792**	0.689–0.911	0.001
Ethnicity						
Non- Hispanic	8035 (90.5)	23,886 (91.9)	< 0.001	0.960	0.847–1.089	0.526
Hispanic	589 (6.6)	1162 (4.5)				
Unknown	259 (2.9)	937 (3.6)		1.120	0.954–1.315	0.165
Distance traveled	20.9 (74.5)	22.0 (90.9)	< 0.001	**1.0006**	1.0003–1.0010	0.001
Charlson–Deyo score						
0	6580 (74.1)	16,358 (63.0)	< 0.001	**1.122**	1.049–1.199	0.001
1	1772 (20.0)	6273 (24.1)				
2	373 (4.2)	2196 (8.5)		**1.568**	1.385–1.774	< 0.001
≥3	158 (1.8)	1158 (4.5)		**2.050**	1.712–2.454	< 0.001

OR Odds ratio, *CI* Confidence interval

Significant factors on multivariable analysis ($p < 0.05$) are shown in bold

TABLE 3 Univariate and multivariate analysis comparing the risks of potential overtreatment (risk of receiving chemotherapy despite not having high-risk features)

	Univariate analysis			Multivariable analysis		
	Received chemotherapy	Did not receive chemotherapy	*p*-value	OR	95% CI	*p*-value
Sex						
Male	2531 (51.8)	21,737 (48.7)	< 0.001	0.989	0.928–1.056	0.750
Female	2354 (48.2)	22,934 (51.3)				
Age	58. 7 (12.3)	71.0 (12.6)	< 0.001	**0.929**	0.926–0.933	< 0.001
Race						
White	3737 (80.2)	37,207 (84.4)	< 0.001	0.974	0.880–1.077	0.602
Black	670 (14.4)	4864 (11.0)				
Other	254 (5.45)	2022 (4.6)		0.931	0.802–1.081	0.352
Insurance						
None	290 (6.0)	1187 (2.7)	< 0.001	1.031	0.886–1.199	0.690
Private	2448 (50.7)	11,731 (26.6)				
Government	2092 (43.3)	31,249 (70.8)		0.995	0.850–1.166	0.955
Ethnicity						
Non-Hispanic	4358 (89.2)	40,948 (91.7)	< 0.001	**1.175**	1.028–1.342	0.018
Hispanic	371 (7.6)	2289 (5.1)				
Unknown	156 (3.2)	1434 (3.2)		1.039	0.862–1.253	0.686
Distance traveled	18.2 (66.9)	21.0 (86.6)	0.141	**0.9994**	0.9988–0.9999	0.030
Charlson–Deyo score						
0	3694 (75.6)	28,729 (64.3)	< 0.001	**0.848**	0.781–0.921	< 0.001
1	903 (18.5)	10,667 (23.9)				
2	224 (4.6)	3450 (7.7)		**0.849**	0.734–0.984	0.029
≥3	64 (1.3)	1825 (4.1)		**0.456**	0.351–0.592	< 0.001
Hospital type						
Community cancer program	641 (14.0)	5344 (12.1)	< 0.001	**0.881**	0.798–0.974	0.013
Comprehensive community program	2170 (47.4)	20,633 (46.8)				
Academic/Research program	1171 (25.6)	11,105 (25.2)		**0.768**	0.687–0.857	< 0.001
Integrated Network Cancer Program	595 (13.0)	6966 (15.8)		**0.694**	0.612–0.788	< 0.001

OR Odds ratio, *CI* Confidence interval

Significant factors on multivariable analysis ($p < 0.05$) are shown in bold

Survival Based on Specific Risk Factors

The survival benefits of chemotherapy in each individual high-risk feature were evaluated while controlling for age, sex, comorbidities, distance from the hospital, type of hospital, and insurance status. When comparing Cox HRs based on individual risk factors, receiving chemotherapy reduced the risk of death in tumors that were T4 (HR 0.623), had inadequate lymph node yield (HR 0.878), lymphovascular invasion (HR 0.904), or positive margins (HR 0.760), but did not significantly alter survival in tumors with perineural invasion or those that were poorly differentiated (Table 5).

DISCUSSION

NCCN guidelines recommend the use of adjuvant chemotherapy for patients with stage II colon cancer who have high-risk features, despite conflicting evidence. This review of the NCDB demonstrates that the guidelines for receipt of chemotherapy are followed in only 25.5% of eligible patients. In addition, 9.9% of ARPs also received neoadjuvant chemotherapy, suggesting that other factors are taken into account. When investigating which factors are associated with either overtreatment or undertreatment, the results are predictable; patients who are older, sicker, live farther from a hospital, and do not have insurance are less likely to receive chemotherapy. Given the prior conflicting evidence regarding the utility of chemotherapy in stage II colon cancer, this study also sought to demonstrate whether receipt

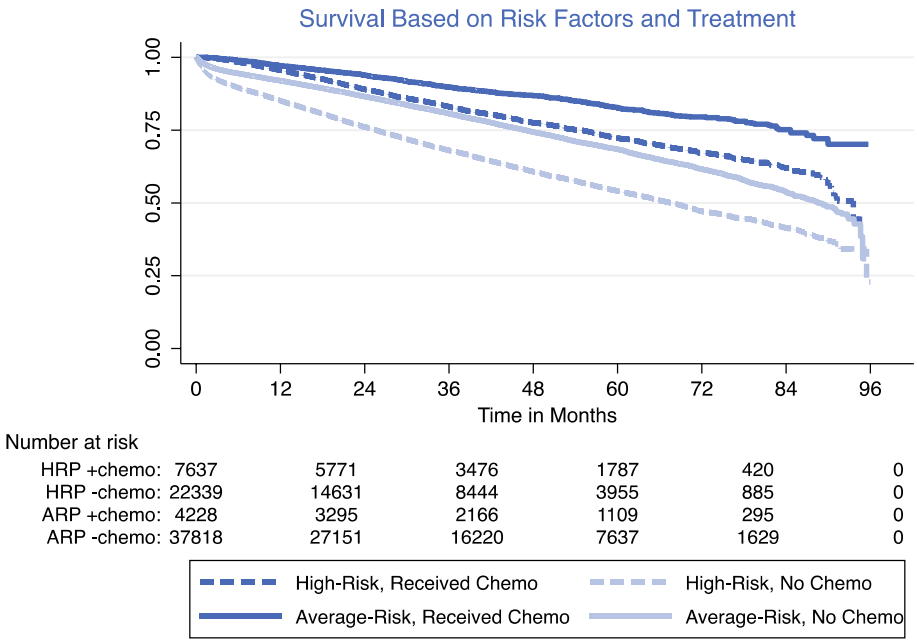

FIG. 2 Mortality based on risk factors and treatment. *HRP* high-risk patients, *ARP* average-risk patients, *chemo* chemotherapy

TABLE 4 Cox hazard ratio of dying when controlling for other factors

	HR	*p*-value	95% CI
Undertreated	**1.183**	< 0.001	1.116–1.254
Overtreated	0.977	0.622	0.894–1.069
Sex			
Female	**0.839**	< 0.001	0.806–0.873
Age	**1.045**	< 0.001	1.043–1.047
Insurance			
Private	**0.631**	< 0.001	0.549–0.724
Government	**0.783**	< 0.001	0.684–0.900
Distance traveled	0.9999	0.453	0.999–1.000
Charlson–Deyo score			
1	**1.209**	< 0.001	1.154–1.267
2	**1.529**	< 0.001	1.431–1.634
≥3	**1.882**	< 0.001	1.718–2.061

HR Hazard ratio, *CI* Confidence interval

Significant factors ($p < 0.05$) are shown in bold

TABLE 5 Cox hazard ratio of dying if chemotherapy is administered, based on risk factors

	HR	*p*-value	95% CI
T4	**0.623**	< 0.001	0.575–0.677
Inadequate LN	**0.878**	0.034	0.779–0.999
Lymphovascular invasion	**0.904**	0.042	0.821–0.996
Poorly differentiated	0.903	0.056	0.814–1.002
Perineural invasion	0.974	0.688	0.856–1.108
Positive margins	**0.760**	< 0.001	0.658–0.878

HR Hazard ratio, *CI* Confidence interval, *LN* Lymph node

Significant factors ($p < 0.05$) are shown in bold

of chemotherapy affected OS, and found that HRPs who received chemotherapy had improved survival while ARPs did not. Furthermore, chemotherapy improves survival in patients with specific high-risk features more than others.

These results indicate that the gap in survival of high-risk stage II patients can be ameliorated by chemotherapy. Previous clinical trials have also shown mixed outcomes regarding the use of chemotherapy, but failed to stratify patients according to risk factors. A pooled analysis of five studies by the NSABP demonstrated improved OS and disease-free survival (DFS) in stage II or III cancers treated with 5-fluorouracil and leucovorin, including improved OS specifically in stage II cancers (HR 0.58, 95% confidence interval [CI] 0.48–0.71).[9] Likewise, the QUASAR group showed an increased OS (relative risk [RR] of death 0.82, 95% CI 0.70–0.95) and DFS (RR of recurrence 0.78, 95% CI 0.67–0.91) in stage II cancers treated with 5-fluorouracil-based chemotherapy, resulting in an absolute improved survival of 3.6%.[8] In contrast, the IMPACT-B2 review of internationally pooled data did not show any significant difference in OS or DFS in Dukes stage B2 (node-negative disease) treated with 5-fluorouracil and leucovorin, versus those treated with surgery alone.[10] These early trials were criticized for not including modern chemotherapy regimens. The MOSAIC trial, which included oxaliplatin, showed a possible benefit for stage II patients who received FOLFOX compared with those who received 5-fluorouracil/leucovorin alone, but did not compare either group with stage II patients treated without chemotherapy.[12] Part of the ambiguity of these prior studies can be explained by the fact that all of them included all stage II patients and were not stratified by risk factors. This study adds to the current knowledge

by demonstrating that when high-risk stage II patients are separated from ARPs, treating HRPs with chemotherapy is associated with improved survival.

In situations where different treatment options exist, large clinical databases allow for the evaluation of disparities regarding the treatments administered, as well as their outcomes. Previous large database studies utilized the NCDB, Surveillance, Epidemiology, and End Results (SEER), California Cancer Registry, and other international cancer databases, and found that between 18 and 21% of stage II colon cancer patients receive chemotherapy, comparable with the 16.3% found in this study.[6,7,11,13] Factors associated with the receipt of chemotherapy were similar to those in prior studies with respect to age, Charlson–Deyo score, treatment facility type, and type of insurance associated. Our data also showed disparities based on the distance to treatment facility. Prior studies found that non-Caucasian race and male sex are associated with receipt of chemotherapy, although interestingly this study did not find any significant difference based on sex or race.[6,7] Age and comorbidities are important factors when considering the appropriateness of chemotherapy; however, the survival benefit from chemotherapy was maintained even while controlling for these risk factors. Understanding when disparities exist is an important step towards addressing them; perhaps the most striking opportunity to address disparities in this case lies in uninsured patients. Not only are uninsured patients less likely to receive chemotherapy but they also have a significantly higher risk of death when controlling for other factors. Improving access to insurance and providing data-based care universally has the potential to make a measurable improvement to outcomes for vulnerable populations.

Previous large-database studies have also reported mixed results regarding the impact of chemotherapy on survival. A 2011 analysis of the SEER database, encompassing 24,847 stage II patients, showed no survival benefit in those treated with chemotherapy, regardless of risk factors.[11] A previous NCDB study showed an OS benefit in patients treated with chemotherapy regardless of risk factors.[6] Another study utilizing the British Columbia Cancer Agency found improved OS in HRPs treated with adjuvant chemotherapy, but no difference in recurrence-free or disease-specific survival in a population with universal insurance.[14] The current study shows a survival benefit in all stage II patients treated with chemotherapy; however, when broken into high- and average-risk groups, the survival benefit reached significance in the high-risk group but not in the average-risk group. This suggests that the survival benefit of chemotherapy for stage II colon cancer in other studies may be driven by HRPs, and the data may vary based on the percentage of the population with these risk factors. This emphasizes the importance of controlling for risk factors when analyzing this heterogeneous population. Two previous studies found that only T4 patients had a survival benefit from chemotherapy.[13,14] Another study that utilized a pooled analysis of previous research suggested that a high T stage and tumor grade were the only factors whose survival was improved by chemotherapy.[15]

The NCDB is a powerful tool for analyzing a large population retrospectively, but research questions must be carefully evaluated for appropriateness owing to limitations inherent to database studies. Follow-up data may be inaccurate and recurrences in the same patient may be recorded as a new entry. An attempt was made to counteract this possibility by excluding any entries where the time from diagnosis to treatment was greater than 1 year. In addition, patients with missing or incomplete data, particularly in the case of perineural invasion or MSI, were excluded; however, this reduced the sample size, potentially skewing the results. Another limitation of using the NCDB is that while it records some high-risk factors, it does not include whether tumors are obstructing or perforated. The NCDB records the date of diagnosis and the date of surgery, which may allow extrapolation of a surgical emergency such as obstruction or perforation. However, because the NCDB does not indicate the actual urgency of the procedure, this would be an assumption that may be inaccurate. The NCDB also does not include ASA data, so no the use of ASA 'E' was also impossible. While this may account for some of the patients who apparently did not have high-risk features and still received adjuvant therapy, it does not account for all of them. In addition, obstruction and perforation have been previously shown to be associated with other high-risk features such as perineural invasion.[16] While the NCDB can answer questions about OS, it does not record information about disease recurrence or DFS, precluding those analyses. In addition, it does not provide information regarding the chemotherapy regimen that a patient receives, which may affect survival.[17]

Using the largest cancer database in the US provides an overview of patients receiving chemotherapy for stage II disease, and whether OS differs between those who received chemotherapy and those who did not. This study indicates that high-risk stage II patients have decreased survival and adjuvant chemotherapy provides a significant survival benefit, consistent with the current NCCN recommendations. However, this recommendation is followed in only one-quarter of cases.[18] The protective association of chemotherapy persists, even when age and medical comorbidities are evaluated. Many clinical trials that address the questions investigated in this study are over a decade old, over which time the treatment, risk stratification, and prognosis for colon cancer have changed considerably.[19] Therefore, it is necessary to continue to assess the outcomes for this patient group. Further research is needed to elucidate how to make practice patterns more consistent and to further elucidate the causality associated with the appropriate delivery of

chemotherapy. Further research could also focus on different chemotherapy regimens and differences based on complete or incomplete chemotherapy treatment. Further research is needed to target disparities in care, especially for those who are uninsured or underinsured.

CONCLUSION

Practice patterns vary widely when it comes to offering chemotherapy for stage II colon cancer. National and international guidelines recommend consideration of chemotherapy in high-risk stage II patients. Despite this, chemotherapy is frequently not administered, even in high-risk individuals. Factors associated with not receiving chemotherapy in both HRPs and ARPs include increasing age, increasing number of medical comorbidities, lack of insurance, and increasing distance from the treatment facility. Chemotherapy is associated with a significantly decreased risk of death in HRPs but not in ARPs.

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