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SSAT PLENARY PRESENTATION

Development of a Risk Score and Nomogram to Predict Individual Benefit Attained from the Addition of Adjuvant Chemotherapy in the Treatment of Stage II Colon Cancer

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Abstract

Background Current guidelines recommend considering adjuvant chemotherapy (AC) for stage II colon cancer (CC) with poor prognostic clinicopathologic and molecular features. However, the relative impact of individual or constellations of high-risk features remains undefined. We developed an individualized point-of-care tool to predict survival benefit attained from the addition of AC.

Methods The National Cancer Database was queried for all patients with resected stage II CC from 2004 to 2015. A prognostic risk score and nomogram were constructed using twelve clinicopathologic and molecular prognostic factors associated with outcomes for CC. Overall survival (OS) was compared between surgery alone and AC groups. The nomogram was validated for discrimination and calibration using bootstrap-adjusted Harrell's concordance index (C-index). For population-level estimation, OS was compared based on quartiles.

Results Of 132,666 patients with stage II CC, 16.8% received AC. The calibration curve of the constructed nomogram showed a good agreement between predicted and observed median and 3-, 5-, and 10-year survival (bootstrap-adjusted C-index 0.699, CI: 0.698–0.703). Population-level risk score analysis (median [Q1, Q3]; 4.9 [4.6, 5.5]) demonstrated that patients with scores > 3.34 had significantly decreased risk of death with the addition of AC (all $p < 0.001$). No survival advantage was associated with AC among patients with low risk scores (risk score < 3.34: HR: 0.94, 95% CI: 0.80–1.11, $p = 0.47$).

Discussion A composite weighted risk score is critical to individualizing AC in select high-risk patients. Our nomogram provides individualized prognostication and estimation of benefit attained from AC. This may better inform treatment decisions and aid future trial design.

Keywords Colon cancer · Stage II · High risk · Adjuvant chemotherapy

Dr. Nelson and Dr. Merritt share first authorship.

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Introduction

Colon cancer continues to be a leading cause of cancer-related mortality with an estimated 53,000 deaths projected in the USA in 2020.[1] While treatment strategies are well defined in early localized colon cancer (stage I) and for node-positive disease (stage III), uncertainty remains regarding the optimal management of patients with locally advanced, node-negative colon cancer (stage II).[2] Adjuvant chemotherapy (AC) following curative-intent resection in stage III colon cancer has been demonstrated in multiple randomized controlled trials to significantly improve both disease-free survival (DFS) and overall survival (OS) when compared with resection alone.[3–7] Conversely, similar benefits have not been consistently demonstrated in patients with stage II disease,[8] outside of the QUASAR trial, which showed a modest 29% reduction in relative risk of recurrence at 2 years among patients with stage II disease receiving adjuvant 5-FU/LV.[9]

Subsets of patients within the stage II population, however, may have particular disease characteristics associated with a high risk of recurrence and, therefore, may benefit from the addition of AC.[10–13] These high-risk features (HRF) include clinical and histopathologic factors that have been individually demonstrated to be associated with a poor prognosis. Such HRF include as follows: T4 tumors[14–16]; history of tumor perforation[16] or bowel obstruction[17]; poor or un-differentiated histology to include mucinous and signet ring histology[18–20]; < 12 lymph nodes examined[21]; perineural invasion (PNI)[22–24]; close, indeterminate or positive margins[18]; microsatellite stable (MSS)[25–27]; and the presence of lymphovascular invasion (LVI).[28] Guidelines recommend an individualized approach when considering AC for patients with stage II disease exhibiting one or more of these HRF.[29]

Currently, high-level data quantifying the relative risk of individual or multiple HRF as well as the potential benefit gained from the addition of AC in the setting of HRF is limited.[30] This makes informed decision-making challenging and introduces an inherent risk of over- or under-treatment depending on the specific clinical and histopathologic features of each individual patient. As such, we sought to first evaluate recent trends and drivers for utilization of AC in patients with stage II colon cancer as well as determine the prognostic impact of individual clinical and histopathologic HRF using a population-based dataset. This was followed by the development of an individualized point-of-care tool, based on these HRF, to predict the survival benefit attained from the addition of AC in patients with resected curative-intent stage II colon cancer.

Methods

Data Source and Cohort Selection

The National Cancer Database (NCDB) is a nationwide oncology outcomes database developed and maintained by the American College of Surgeons in collaboration with the American Cancer Society.[31] Gathering data from more than 1500 Commission on Cancer–accredited centers, this nationwide cancer registry captures more than 70% of all newly diagnosed malignancies in the USA annually.[31] The data in this study were obtained from a de-identified NCDB file. Due to the de-identified nature of the data, this study received institutional review board exemption status after an independent regulatory review. The American College of Surgeons and Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology, or the conclusions drawn from these data by the investigators.

Using the 2004–2015 NCDB participant user file, all patients with American Joint Committee on Cancer (AJCC) pathologic stage II colon cancer were identified using the International Classification of Disease for Oncology, 3rd edition (ICD-0-3), by site and histology. Only patients with available survival data and site-specified colon cancer (C18.0, C18.2–C18.7) with histologically confirmed invasive colonic adenocarcinoma, signet cell, or mucinous histology that underwent curative intent resection as the initial treatment were included for analysis. Patients with stage I disease, node-positive disease, and clinically (cM1) presumed or pathologically (pM1) confirmed metastatic disease were excluded (Fig. 1).

Statistical Analysis

Patients were divided into two cohorts according to treatment approach: surgery alone versus surgery followed by AC. Trends in utilization of AC were examined. Descriptive data including patient sociodemographic, disease, and treatment-related factors were summarized by mean (standard deviation) or median (interquartile range) for continuous and count (percentage) for categorical data. Univariate comparisons were performed using the chi-square test for categorical and Welch's t test or non-parametric Kruskal-Wallis test for continuous covariates, followed by multivariable logistic regression to determine independent factors for use of AC. OS was compared using the Kaplan-Meier method with log-rank test, followed by multivariable Cox proportional hazards modeling to examine for independent prognostic factors associated with the risk of death. All tests were two-sided and statistical significance was set at $p < 0.05$. All statistical analyses were performed using the R software, version 3.3.2.

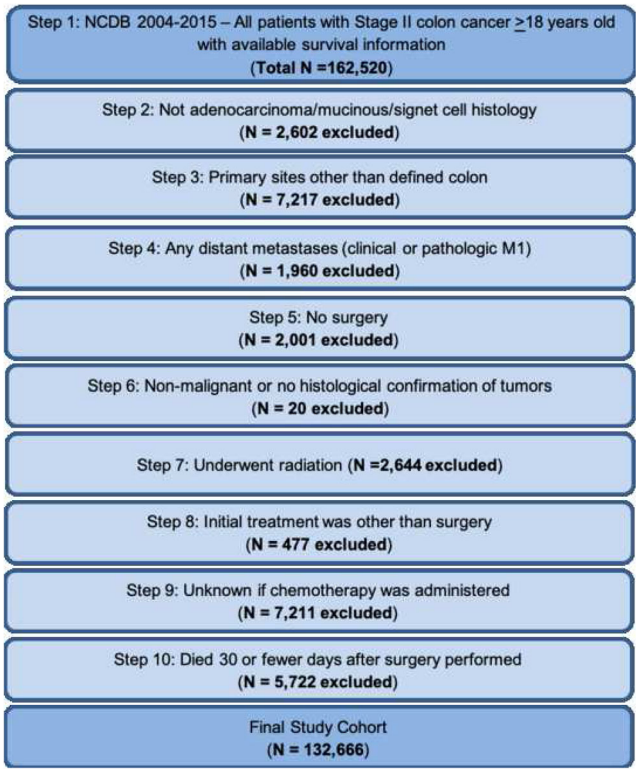

Fig. 1 Flow diagram of cohort selection

Development and Validation of the Model

Twelve clinicopathologic and molecular prognostic factors previously associated with outcomes for colon cancer were compared in patients receiving AC to those undergoing surgery alone in order to construct a nomogram for OS. These factors included as follows: age, sex, Charlson Comorbidity Index, histology, pathological tumor stage, grade, number of nodes examined, margin status, microsatellite instability (MSI), carcinoembryonic antigen (CEA) level, PNI, and LVI. A prognostic risk score was constructed and weighted with beta coefficient estimations. The prediction model with selected prognostic factors was implemented in a nomogram as a calculation tool for the median, 3-year, 5-year, and 10-year survival probabilities at an individual level. The prediction performance of the nomogram was validated for discrimination and calibration on the original cohort using bootstrapping with 1000 resamples. Discrimination was measured by bootstrap-adjusted Harrell's concordance index (C-index) with 95% confidence interval (CI). A calibration curve was used to evaluate the agreement between predicted and observed survival probabilities. Nomograms and calibration plots were generated using the rms package of R version 3.6.0. Survival was compared based on quartiles of prognostic risk groups. The discrimination abilities of risk score analysis were assessed with the C-index by considering quartile risk group classification.

Results

Population Demographics and Trends

In total, 132,666 patients with pathologically confirmed stage II colon cancer were identified. Mean age was 71.1 ± 13.0 years with the majority (71.2%) aged ≥ 65 years of age. Female gender represented a slight predominance (52.8%) and most patients were of white, non-Hispanic ethnicity (76.2%).

Patients were then stratified into groups based on treatment strategy: surgery alone (83.2%) versus surgery plus AC (16.8%) (Supplementary Table 1). Patients receiving AC tended to be younger (61.0 ± 12.3 vs 73.2 ± 12.2 years), have less comorbidities (Charlson Comorbidity Index 0: 75.6% vs 64.0%), and have private insurance (46.7% vs 23.2%) (all $p < 0.001$). Patients were more likely to receive AC if they had a grade III–IV or T4 tumors, signet cell or mucinous histology, positive margins, MSS, PNI, and LVI, or if < 12 lymph nodes were examined (all $p < 0.001$). There was an 18% decrease in the likelihood of receiving AC among all patients with stage II colon cancer (OR 0.82; CI 0.77–0.87; $p < 0.001$) (Fig. 2a) over the 10-year study period, and AC most frequently consisted of multi-agent regimens (Fig. 2b).

Predictors for Receipt of Chemotherapy

In order to determine the major drivers for administration of AC among patients with stage II colon cancer, univariate and multivariable regression analysis was performed (Table 1). Older age, increasing comorbidities, and treatment at Academic/Research or Integrated Network cancer programs were all associated with a decreased likelihood of receiving AC (all $p < 0.001$). However, patients with private or government insurance were more likely to receive AC compared with uninsured ones (both $p \leq 0.001$). T4 tumor stage was the greatest independent predictor for receipt of AC with a 4-fold increased likelihood compared with the T3 tumor stage (OR 4.0; CI 3.85–4.20; $p < 0.001$). Additional independent predictors for receipt of AC included grade III–IV and signet cell or mucinous histology, inadequate lymphadenectomy, positive margin status, preoperative CEA > 10, MSS, and presence of PNI or LVI (all $p < 0.02$). Conversely, right-sided and transverse colon tumors were associated with a decreased likelihood of receiving AC (both $p < 0.001$).

Survival Analysis

Univariate and multivariable Cox proportional hazards modeling was performed to examine independent sociodemographic and disease-related characteristics independently prognostic for survival (Table 2). After adjustment for patient-, disease-, and treatment-related variables, sociodemographic factors

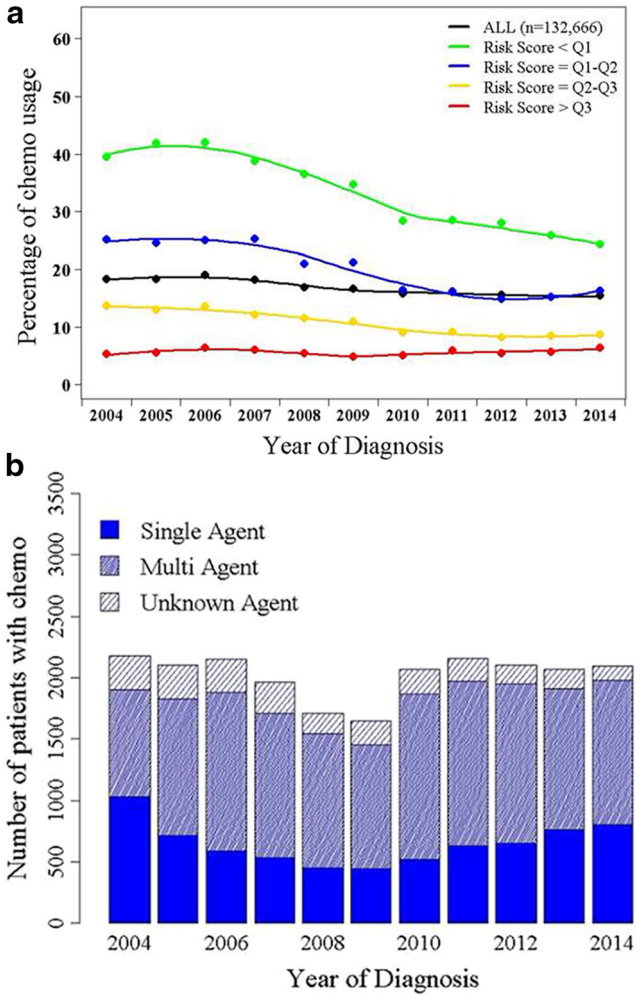

Fig. 2 **a** Rate of chemotherapy use over time for stage II colon cancer. **b** Trends in utilization of single and multi-agent chemotherapy over time

independently associated with improved survival included younger age, female gender, Asian/Pacific Islander ethnicity, private or government insurance status, higher levels of income, treatment in an academic institution, and living in a rural community (all $p < 0.001$). Conversely, an increasing number of comorbidities and black ethnicity were associated with a poor prognosis (both $p < 0.001$).

Disease-related characteristics independently associated with a poor prognosis included grade III–IV histology, inadequate lymphadenectomy, positive margin status, MSS, preoperative CEA > 10, and presence of PNI or LVI (all $p < 0.001$). T4 tumor stage was the most prognostic individual variable and was associated with a 62% increased risk of death (HR 1.62; CI 1.57–1.66; $p < 0.001$). Signet cell ($p = 0.29$) and mucinous ($p = 0.48$) histology did not independently impact survival. Conversely, right-sided tumors and receipt of AC were associated with improved survival, with receipt of AC independently associated with a 26% reduction in risk of death (HR 0.74; CI 0.72–0.76; $p < 0.001$).

Risk Score and Nomogram

A mortality risk score was constructed from a combination of prognostic factors identified from Cox proportional hazards modeling as well as previously well-described clinical prognostic factors. These variables included age, gender, Charlson Comorbidity Index, pathological T stage, grade, histology, number of lymph nodes examined, margin status, MSI status, preoperative CEA level, and presence of PNI and LVI. Two nomograms were then constructed by taking the interaction term of these 12 variables along with AC to estimate survival with and without AC on an individual basis (Fig. 3a, b, respectively, and Supplementary Table 2). Because the nomograms were developed from Cox regression analysis with addition of interaction terms for chemotherapy and other predictors, two nomograms were produced, the difference of which produces the estimated absolute survival benefit attained from the addition of adjuvant chemotherapy. The nomograms report median and 3-, 5-, and 10-year OS estimates. The C-index of the risk model was 0.70 (CI: 0.6979–0.7026) for predicting 3-, 5-, and 10-year OS, showing a good agreement between predicted and observed survival values at each time point (Fig. 4). Using the population-level risk score analysis, patients with scores > 3.34 demonstrated decreased risk of death with addition of AC (risk score 3.34–Q1: HR 0.81, 95% CI 0.76–0.87, $p < 0.001$; Q1–Q2: HR 0.78, 95% CI 0.73–0.82, $p < 0.001$; Q2–Q3: HR 0.78, 95% CI 0.74–0.82, $p < 0.001$; > Q3: HR 0.65, 95% CI 0.61–0.69, $p < 0.001$). Notably, there was no significant survival benefit from AC among patients with low risk scores (risk score < 3.34: HR 0.94, 95% CI 0.80–1.11, $p = 0.47$) (Fig. 5a, b and Table 3).

Discussion

Using population-level risk score analysis, we successfully developed an individualized point-of-care tool to predict the survival benefit attained from the addition of AC following surgery for stage II colon cancer patients (Fig. 3a, b). The mortality risk score is based on several clinical and histopathologic prognostic risk factors and provides survival estimates for treatment with or without AC. These nomograms were developed in response to a growing body of literature that supports AC use in high-risk stage II colon cancer[11–13] but is preceded by higher quality RCT data[9,32–35] that is undecided on the potential benefit of AC in this specific patient population. The nomograms can be implemented after surgery for curative intent and provide individualized survival predictions that can guide informed decision-making for further treatment.

Similar to a previous NCDB review, our analysis found that a substantial portion of stage II patients, except for the lowest risk patients, had improved survival when treated with AC.[11]

Table 1 Univariate and multivariable logistic regression analysis for predictors of receipt of adjuvant chemotherapy in patients with stage II colon cancer

	Univariate analysis				Multivariable analysis			
Characteristics	OR	Lower 95% CI	Upper 95% CI	*p* value	OR	Lower 95% CI	Upper 95% CI	*p* value
Year of diagnosis								
2004	Reference							
2005	1	0.94	1.07	0.97				
2006	1.05	0.98	1.12	0.17				
2007	1	0.93	1.06	0.89				
2008	0.91	0.85	0.98	0.01				
2009	0.89	0.83	0.96	0				
2010	0.84	0.78	0.9	< 0.001				
2011	0.86	0.81	0.92	< 0.001				
2012	0.83	0.77	0.88	< 0.001				
2013	0.8	0.75	0.85	< 0.001				
2014	0.82	0.77	0.87	< 0.001				
Age at diagnosis (years) (continuous)	0.932	0.9309	0.9331	< 0.001	0.9264	0.9249	0.928	< 0.001
Gender								
Male	Reference				Reference			
Female	0.88	0.85	0.9	< 0.001	1.03	1	1.07	0.07
Race/ethnicity								
White non-Hispanic	Reference				Reference			
Black	1.39	1.33	1.46	< 0.001	1	0.95	1.06	0.99
White Hispanic	1.64	1.54	1.75	< 0.001	1.17	1.08	1.27	< 0.001
Asian/Pacific Islander	1.34	1.23	1.46	< 0.001	0.98	0.88	1.09	0.73
Native American/other/unknown	1.19	1.12	1.25	< 0.001	1.02	0.96	1.08	0.61
Insurance status								
Uninsured	Reference				Reference			
Private	0.86	0.8	0.92	< 0.001	1.24	1.14	1.35	< 0.001
Public/government	0.27	0.25	0.29	< 0.001	1.15	1.06	1.25	0.001
Other/unknown	0.45	0.39	0.52	< 0.001	0.93	0.8	1.09	0.38
Average income								
< 38,000	Reference				Reference			
38,000–47,000	0.91	0.87	0.95	< 0.001	0.99	0.93	1.04	0.61
48,000–62,999	0.91	0.87	0.95	< 0.001	1.01	0.95	1.07	0.71
> 63,000	0.94	0.9	0.98	0	1.04	0.97	1.11	0.3
Other/unknown/missing	0.91	0.79	1.05	0.18	0.59	0.27	1.28	0.18
Average education								
> 21%	Reference				Reference			
13–20.9%	0.92	0.88	0.96	< 0.001	1	0.95	1.05	0.96
7–12.9%	0.86	0.82	0.9	< 0.001	1	0.94	1.06	0.98
< 7%	0.85	0.81	0.89	< 0.001	1	0.93	1.07	0.97
Other/unknown/missing	0.87	0.76	1	0.06	1.69	0.77	3.72	0.19
Comorbidity score								
0	Reference				Reference			
1	0.66	0.63	0.68	< 0.001	0.87	0.84	0.91	< 0.001
≥ 2	0.38	0.36	0.4	< 0.001	0.58	0.54	0.62	< 0.001
Hospital type								
Community	Reference				Reference			
Academic	1.08	1.04	1.12	< 0.001	0.89	0.86	0.93	< 0.001
Other/unknown	1.31	1.26	1.37	< 0.001	0.82	0.78	0.87	< 0.001
Hospital location								
Northeast	Reference				Reference			
South	1.02	0.98	1.06	0.36	0.88	0.84	0.92	< 0.001
Midwest	0.93	0.89	0.97	< 0.001	0.92	0.87	0.96	< 0.001
West	0.83	0.78	0.88	< 0.001	0.73	0.68	0.77	< 0.001
Other/unknown	1.74	1.64	1.85	< 0.001	0.55	0.51	0.6	< 0.001
Population density, 2013								
Metropolitan	Reference				Reference			
Urban	1.06	1.02	1.11	0.004	1.08	1.03	1.14	0.003
Rural	1.05	0.94	1.16	0.39	1.11	0.99	1.24	0.09
Other/unknown	1	0.91	1.08	0.91	0.97	0.86	1.08	0.55
Histology								
Adenocarcinoma	Reference				Reference			
Mucinous	1.03	0.99	1.07	0.19	1.07	1.01	1.12	0.01

Table 1 (continued)

Characteristics	Univariate analysis				Multivariable analysis			
	OR	Lower 95% CI	Upper 95% CI	*p* value	OR	Lower 95% CI	Upper 95% CI	*p* value
Signet cell	1.62	1.39	1.88	< 0.001	1.38	1.15	1.65	< 0.001
Pathologic T stage								
T3	Reference				Reference			
T4	3.82	3.69	3.96	< 0.001	4.02	3.85	4.2	< 0.001
Anatomic site								
Left	Reference				Reference			
Transverse	0.71	0.68	0.75	< 0.001	0.87	0.82	0.92	< 0.001
Right	0.61	0.59	0.63	< 0.001	0.82	0.79	0.85	< 0.001
Grade								
I–II	Reference				Reference			
III–IV	1.36	1.32	1.41	< 0.001	1.52	1.45	1.58	< 0.001
Other	1.35	1.23	1.48	< 0.001	1.23	1.11	1.38	< 0.001
Nodes examined								
≥ 12	Reference				Reference			
< 12	1.16	1.11	1.2	< 0.001	1.37	1.31	1.43	< 0.001
Unknown	2.17	1.79	2.64	< 0.001	1.38	1.09	1.75	0.01
Resection margin								
Negative	Reference				Reference			
Positive	2.71	2.55	2.89	< 0.001	1.61	1.49	1.73	< 0.001
Unknown	2.38	2.04	2.78	< 0.001	1.55	1.28	1.87	< 0.001
MSI status								
Positive, high	Reference				Reference			
Negative/positive, low	1.56	1.42	1.7	< 0.001	1.81	1.63	2	< 0.001
Other/unknown	1.17	1.08	1.27	< 0.001	1.44	1.31	1.59	< 0.001
Blank	1.23	1.14	1.34	< 0.001				
CEA								
≤ 10	Reference				Reference			
> 10	0.91	0.85	0.97	0.01	1.14	1.06	1.24	< 0.001
Other/unknown	1	0.93	1.07	0.89	1.06	0.98	1.15	0.18
Blank	0.97	0.91	1.04	0.35				
Surgery type								
Segmental resection	Reference				Reference			
Subtotal colectomy/hemicolectomy	0.85	0.83	0.88	< 0.001	1.05	1.01	1.09	0.02
Total colectomy	1.27	1.17	1.37	< 0.001	0.92	0.84	1	0.06
Perineural invasion								
No perineural invasion	Reference				Reference			
Perineural invasion	2.08	1.93	2.23	< 0.001	1.48	1.36	1.62	< 0.001
Other/unknown	1.63	1.56	1.71	< 0.001	1.25	1.15	1.34	< 0.001
Blank	1.18	1.14	1.22	< 0.001				
Lymphovascular invasion								
Absent	Reference				Reference			
Present	1.92	1.82	2.03	< 0.001	1.74	1.63	1.86	< 0.001
Unknown	1.48	1.37	1.6	< 0.001	1.37	1.27	1.47	< 0.001
Blank	1.35	1.3	1.39	< 0.001				
Days from diagnosis to def surgery								
≤ 30	Reference				Reference			
31–90	0.57	0.55	0.6	< 0.001	0.66	0.62	0.69	< 0.001
> 91	0.32	0.27	0.38	< 0.001	0.38	0.31	0.46	< 0.001

Despite these findings, this study demonstrates that the overall rate of AC use among stage II patients is low, and in general, not increasing (Fig. 2a). Casabadan et al. reviewed the NCDB for patients diagnosed with stage II cancer from 1998 to 2006 and found 21% of high-risk stage II patients received AC.[11] Most of the patients in our series had at least one HRF (n = 89,000; 67%), yet only 19% received AC. Patients with ≥ 2 HRF received AC 23% of the time. Other national and international studies report similar usage of AC ranging from 14 to 29% for high-risk stage II disease.[10,11,30,36,37] Although both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend considering AC in stage II patients with at least one HRF, these stable rates of AC use over time are not surprising given existence of significant equipoise regarding actual benefit attained.[29,38] Boland et al. evaluated the link between

Table 2 Univariate and multivariable Cox proportional hazards regression analysis for survival in patients with stage II colon cancer

	Univariate analysis				Multivariable analysis			
Characteristics	HR	Lower 95% CI	Upper 95% CI	*p* value	HR	Lower 95% CI	Upper 95% CI	*p* value
Age at diagnosis (years) (continuous)	1.0565	1.0556	1.0574	< 0.001	1.0509	1.0498	1.0521	< 0.001
Gender								
Male	Reference				Reference			
Female	0.95	0.94	0.97	< 0.001	0.82	0.8	0.83	< 0.001
Race/ethnicity								
White non-Hispanic	Reference				Reference			
Black	0.86	0.83	0.89	< 0.001	1.09	1.06	1.13	< 0.001
White Hispanic	0.65	0.61	0.68	< 0.001	0.83	0.79	0.88	< 0.001
Asian/Pacific Islander	0.49	0.45	0.53	< 0.001	0.7	0.64	0.75	< 0.001
Native American/other/unknown	0.96	0.93	0.99	0.02	0.98	0.95	1.01	0.27
Insurance status								
Uninsured	Reference				Reference			
Private	0.9	0.84	0.97	0.01	0.72	0.67	0.77	< 0.001
Public/government	2.35	2.19	2.52	< 0.001	0.85	0.79	0.92	< 0.001
Other/unknown	1.55	1.4	1.73	< 0.001	0.82	0.74	0.91	< 0.001
Average income								
< 38,000	Reference				Reference			
38,000–47,000	0.99	0.96	1.02	0.48	0.97	0.94	1	0.06
48,000–62,999	0.92	0.89	0.94	< 0.001	0.91	0.88	0.94	< 0.001
> 63,000	0.85	0.83	0.87	< 0.001	0.89	0.86	0.92	< 0.001
Other/unknown/missing	2.14	2	2.29	< 0.001	1.42	0.96	2.11	0.08
Average education								
> 21%	Reference				Reference			
13–20.9%	1.07	1.04	1.1	< 0.001	1.01	0.98	1.04	0.48
7–12.9%	1.04	1.01	1.06	0.01	0.98	0.95	1.01	0.19
< 7%	0.96	0.93	0.99	0	0.94	0.9	0.98	0.001
Other/unknown/missing	2.41	2.25	2.58	< 0.001	1.26	0.84	1.88	0.26
Comorbidity score								
0	Reference				Reference			
1	1.5	1.47	1.53	< 0.001	1.31	1.28	1.34	< 0.001
≥ 2	2.34	2.28	2.4	< 0.001	1.89	1.84	1.94	< 0.001
Hospital type								
Community	Reference				Reference			
Academic	0.85	0.83	0.87	< 0.001	0.94	0.92	0.96	< 0.001
Other/unknown	0.9	0.87	0.92	< 0.001	1.04	1.01	1.07	0.004
Hospital location								
Northeast	Reference				Reference			
South	1	0.97	1.02	0.71	1.04	1.02	1.07	0.001
Midwest	1.03	1	1.05	0.02	1.01	0.99	1.04	0.41
West	0.87	0.84	0.9	< 0.001	0.98	0.94	1.01	0.16
Other/unknown	0.7	0.67	0.73	< 0.001	1.06	1.01	1.11	0.02
Population density, 2013								
Metropolitan	Reference				Reference			
Urban	1.06	1.03	1.09	< 0.001	0.99	0.96	1.02	0.4
Rural	1.02	0.96	1.09	0.46	0.89	0.83	0.94	< 0.001
Other/unknown	1.31	1.25	1.37	< 0.001	0.98	0.93	1.04	0.57
Histology								
Adenocarcinoma	Reference				Reference			
Mucinous	1.06	1.04	1.09	< 0.001	1.01	0.98	1.04	0.48
Signet cell	1.22	1.11	1.35	< 0.001	1.06	0.95	1.17	0.29
Pathologic T stage								
T3	Reference				Reference			
T4	1.51	1.47	1.55	< 0.001	1.62	1.57	1.66	< 0.001
Anatomic site								
Left	Reference				Reference			
Transverse	1.14	1.1	1.17	< 0.001	0.99	0.96	1.02	0.36
Right	1.09	1.07	1.11	< 0.001	0.93	0.91	0.95	< 0.001
Grade								
I–II	Reference				Reference			
III–IV	1.19	1.16	1.21	< 0.001	1.11	1.08	1.13	< 0.001
Other	1.03	0.96	1.09	0.44	1.04	0.97	1.11	0.27

Table 2 (continued)

Characteristics	Univariate analysis				Multivariable analysis			
	HR	Lower 95% CI	Upper 95% CI	*p* value	HR	Lower 95% CI	Upper 95% CI	*p* value
Nodes examined								
≥ 12	Reference				Reference			
< 12	1.48	1.45	1.51	< 0.001	1.27	1.24	1.3	< 0.001
Unknown	1.05	0.91	1.21	0.52	1.27	1.1	1.47	0.001
Resection margin								
Negative	Reference				Reference			
Positive	1.83	1.76	1.91	< 0.001	1.55	1.48	1.62	< 0.001
Unknown	1.13	1.01	1.26	0.03	1.17	1.05	1.31	0.005
MSI status								
Positive, high	Reference							
Negative/positive, low	1.11	1.03	1.2	0.01	1.18	1.08	1.27	< 0.001
Other/unknown	1.52	1.42	1.63	< 0.001	1.28	1.19	1.37	< 0.001
Blank	1.8	1.68	1.93	< 0.001				
CEA								
≤ 10	Reference				Reference			
> 10	1.76	1.64	1.88	< 0.001	1.44	1.35	1.54	< 0.001
Other/unknown	1.96	1.83	2.09	< 0.001	1.48	1.38	1.58	< 0.001
Blank	2.23	2.09	2.38	< 0.001				
Surgery type								
Segmental resection	Reference				Reference			
Subtotal colectomy/hemicolectomy	1.03	1.01	1.05	0.01	1	0.97	1.02	0.66
Total colectomy	1.09	1.03	1.15	0.002	1.26	1.19	1.33	< 0.001
Adjuvant chemotherapy								
No	Reference				Reference			
Yes	0.48	0.46	0.49	< 0.001	0.74	0.72	0.76	< 0.001
Perineural invasion								
No perineural invasion	Reference				Reference			
Perineural invasion	1.35	1.27	1.43	< 0.001	1.29	1.21	1.38	< 0.001
Other/unknown	1.2	1.16	1.23	< 0.001	1.05	1	1.1	0.08
Blank	1.36	1.33	1.39	< 0.001				
Lymphovascular invasion								
Absent	Reference				Reference			
Present	1.27	1.22	1.33	< 0.001	1.16	1.11	1.22	< 0.001
Unknown	1.12	1.05	1.19	< 0.001	1.12	1.06	1.18	< 0.001
Blank	1.35	1.32	1.38	< 0.001				
Days from diagnosis to def surgery								
≤ 30	Reference				Reference			
31–90	0.97	0.95	1	0.04	0.93	0.91	0.96	< 0.001
> 91	1.36	1.27	1.46	< 0.001	1.13	1.05	1.21	< 0.001

compliance with NCCN guidelines and survival outcomes in colon cancer. They found that high-risk stage II patients had the worst compliance (35.7%) of all groups assessed, yet when guideline considerations were followed, 5-year survival increased from 54.5 to 67.7%.[39]

Data supporting AC use in stage II colon cancer with HRF is accumulating. A recent meta-analysis of 24 studies evaluating AC use in high-risk stage II colon cancer found AC significantly improved OS (HR 0.64, 95% CI 0.51–0.80, $p < 0.007$) and DFS (HR 0.46, 95% CI 0.28–0.76, $p = 0.002$).[13] Somewhat surprisingly, the same study showed that only patients with pT4 lesions, fewer than 12 lymph nodes sampled, intestinal perforation, and intestinal obstruction had improved OS when treated with AC. Patients with LVI, PNI, and poorly differentiated histology showed no OS advantage when treated with AC, while still other studies have found different combinations of HRF that benefit from AC.[10,15,30] In our study, patients with T4 disease were four times more likely to receive AC compared with those with T3 disease and MSI-low patients were over one and a half times as likely as MSI-high patients to receive AC. Yet other known prognostic factors, like high preoperative CEA > 10 and < 12 lymph nodes harvested, were predictive of AC use, but to a lesser degree. HRF, as defined by NCCN Colon Cancer guidelines, include MSS or low status, T4 tumor stage, poorly differentiated histology, LVI, PNI, bowel obstruction, local perforation, close/indeterminate/positive surgical margin, and < 12 sample lymph nodes.[29] No preference regarding AC use is given to any HRF in the NCCN guidelines, yet certain HRF clearly drive AC decision-making more than others. Many of the

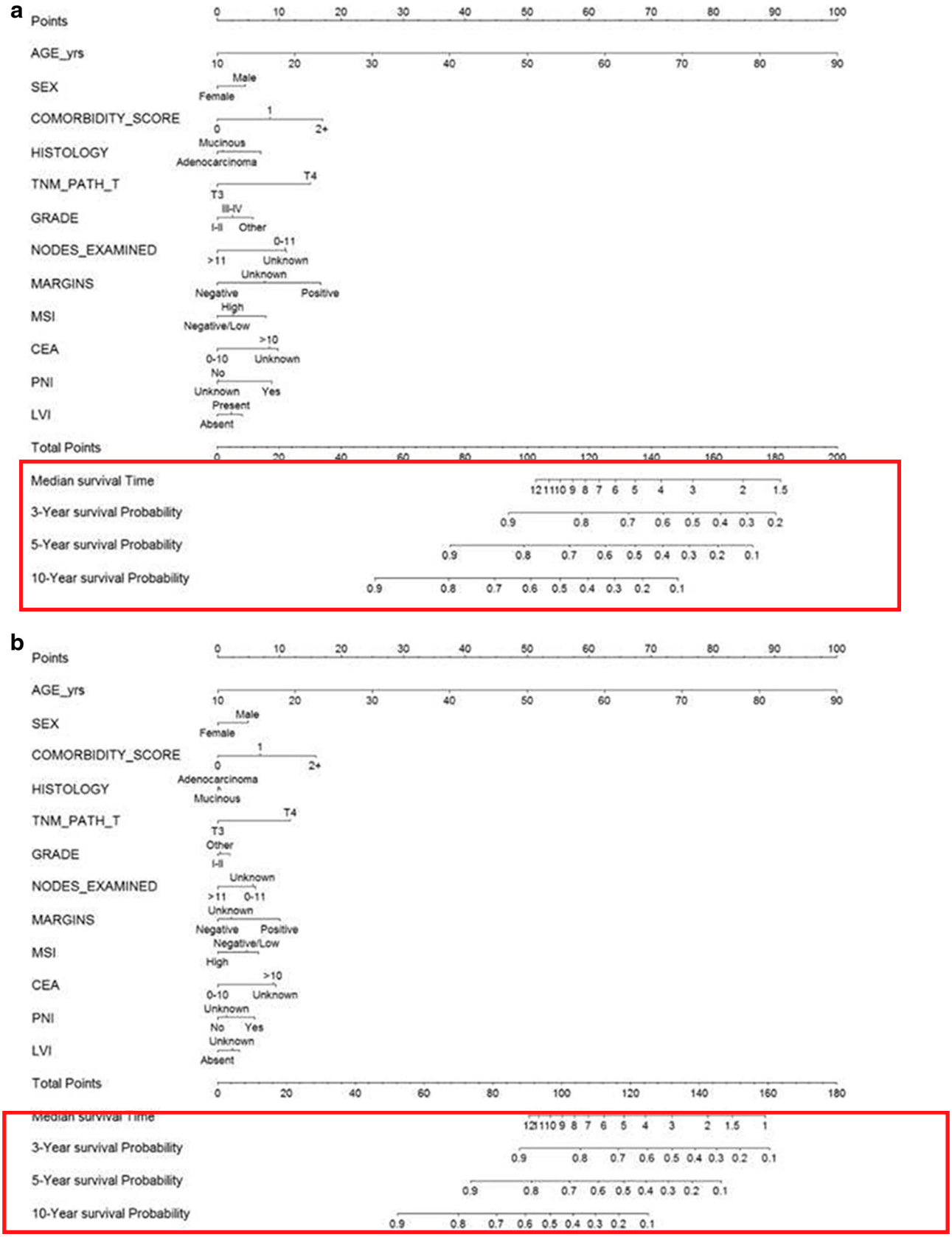

Fig. 3 **a** Nomogram predicting median and 3-, 5-, and 10-year survival probability with adjuvant chemotherapy. **b** Nomogram predicting median and 3-, 5-, and 10-year survival probability without adjuvant chemotherapy

NCCN HRF carry weight in our nomograms which helps with prediction of median and 3-, 5-, and 10-year survival for stage II cancer patients treated with and without AC.

The point-of-care instrument presented here allows individualized decision-making capacity based on the risk of mortality conferred from 12 well-known prognostic factors, many of which are not included in the standard AJCC staging system.[40] Compared with categorical staging systems like the tumor, lymph node, and metastasis (TNM) system utilized by the AJCC, nomograms can better estimate individual risk by considering continuous variables (i.e., age) and variables outside the anatomic confines of the TNM system.[41] A nomogram's performance is measured in terms of discrimination and calibration, and it is important to consider both when deciding whether to use a nomogram as an aid in clinical decision-making.[41,42] The nomograms presented have clinically useful discrimination ability with a C-index of 0.6992 (95% CI, 0.6979, 0.7026) and show good calibration with actual 3-, 5-, and 10-year survival probabilities (Fig. 4). Clinically, this means that 70% of the time the nomogram is accurately predicting who will have survival benefit from AC and that the survival predictions correlate well with true survival outcomes. To place this performance into context, the AJCC 7th staging system was found to have a C-index of 0.708 (70%) for its ability to predict death from colon cancer.[43] As far as we know, this is the first tool available to help quantify the survival benefit of AC in stage II colon cancer. We believe that the hard numbered survival predictions, rather than simply stating an advantage is present, are of paramount importance given that patient refusal of AC for colon cancer is quite high,[44,45] often for unknown reasons, and misinformation with regard to true survival benefit with AC is potentially one cause of refusal that can be attenuated by utilizing these nomograms. The nomograms presented are the pictorial form of the risk score calculated for each patient based on the cumulative risk conferred from the 12 prognostic factors discussed previously. When a patient's risk score is > 3.34, a survival benefit from AC can be expected (Fig. 5a) and as the risk score increases (i.e., multiple HRF present), survival decreases and the potential benefit from AC increases (Fig. 5b). Given the nomogram is the simpler method for the calculation of the risk score, we feel it is more likely to be remembered and therefore utilized in practice.

There are several limitations of the current study that should be considered. First, although bootstrapping is a well-established statistical technique for internal validation of the developed risk models, this method limits the overall generalizability. While the developed models are able to predict individualized survival benefit from chemotherapy,

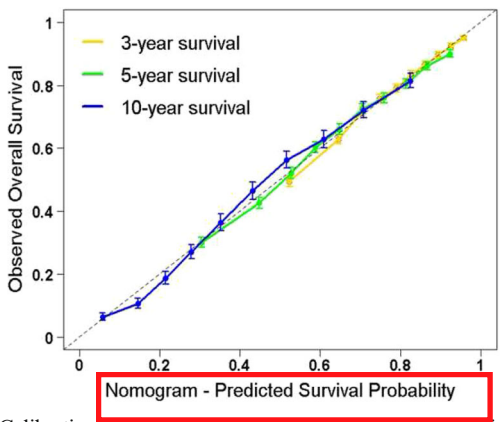

Fig. 4 Calibration curve comparing observed (actual) and predicted survival for the entire stage II colon cancer cohort. 95% CIs are measured by the Kaplan-Meier analysis. The dotted gray line indicates a perfect calibration (C-index = 1.0) model in which the predicted survival probabilities are identical to the actual survival proportions. The bootstrap-adjusted C-index of the nomogram was 0.6992 (95% CI 0.6979, 0.7026) indicating clinically useful survival prediction

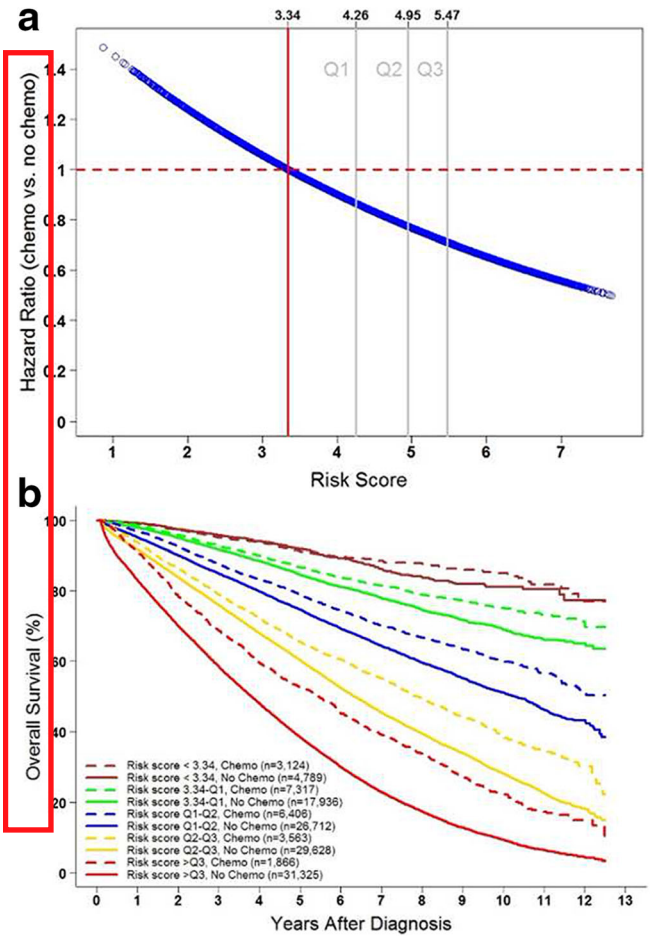

Fig. 5 **a** The scatter plot of hazard ratio of chemo (reference: no chemo) versus risk score. As risk score increases, the hazard ratio decreases indicating a survival benefit from adjuvant chemotherapy. The threshold for survival benefit is seen when the risk score is < 3.34 at which point the hazard ratio increases. **b** Kaplan-Meier curves stratified by quartiles of risk scores and the usage of chemotherapy. The risk score was estimated based on risk factors of age (years, continuous scale), sex, comorbidity score, histology, pathological T stage, grade, number of nodes examined, margin, MSI, CEA, PNI, and LVI by $\sum_{i=1}^{p} \log(HR\_i) risk\_i$, where HR_i was from the multivariable Cox's analysis model

Table 3 Corresponding survival at 3, 5, and 10 years with and without adjuvant chemotherapy stratified by risk score quartile

	Estimate OS (95% CI) (%)		
	3 years	5 years	10 years
RS < 3.34			
Chemo	95 (94–96)	91 (90–92)	85 (83–87)
No chemo	96 (95–96)	92 (91–93)	81 (79–84)
RS = 3.34–Q1			
Chemo	93 (92–93)	87 (86–88)	75 (74–77)
No chemo	92 (91–92)	85 (84–85)	69 (68–70)
RS = Q1–Q2			
Chemo	88 (87–89)	79 (78–80)	60 (58–62)
No chemo	85 (84–85)	75 (74–75)	51 (50–52)
RS = Q2–Q3			
Chemo	79 (78–80)	66 (64–67)	39 (36–41)
No chemo	76 (75–76)	60 (60–61)	28 (27–29)
RS > Q3			
Chemo	69 (67–71)	53 (50–55)	22 (19–25)
No chemo	59 (58–59)	39 (38–39)	9 (9–10)

external validation is needed. In addition, there are several limitations related to the NCDB. First, disease-free survival and disease recurrence are variables not captured in the database, although recognized as important measures when examining the role of adjuvant therapies. The NCDB does not capture several other well-known prognostic factors such as perforation or bowel obstruction at time of cancer diagnosis. Though these occurrences are rarer presentations of stage II disease, they could represent important variables that affect survival not measured by our model. The NCDB has the potential to capture several newer genetic markers (KRAS status, 18q loss of heterozygosity), but the incidence of complete data was too low to include them in our analysis. Incorporation of any or all these factors could change survival estimates and should be included in future mortality risk score construction. In addition, although we evaluated several clinicopathologic factors that have known prognostic ability in colon cancer, these same factors may not predict a good response to chemotherapy treatment. Finally, NCDB does not capture which specific chemotherapy regimen was used, beyond single, multi-agent, or unknown regimen; therefore, survival predictions cannot be attributed to any specific regimen.

Conclusion

We have developed a risk score and nomogram that provide individualized survival estimates for stage II colon cancer patients treated with or without AC. Our analysis supports AC use in stage II patients with a risk score > 3.34. These point-of-care tools should allow for more informed and individualized decision-making capacity for AC administration in this controversial subset of colon cancer patients.

Author Contributions All authors have made substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; and drafting the work or providing critical revisions; and all approved of the final version to be published. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Due to the de-identified nature of the data, this study received institutional review board exemption status after an independent regulatory review.

Conflict of Interest The authors declare that they have no conflicts of interest.

Disclaimer The results and opinions expressed in this article are those of the authors, and do not reflect the opinions or official policy of the United States Army or the Department of Defense.

Abbreviations AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; ASCO, American Society of Clinical Oncology; CEA, carcinoembryonic antigen; CI, confidence interval; C-index, concordance index; DFS, disease-free survival; HR, hazard ratio; HRF, high-risk features; LVI, lymphovascular invasion; MSI, microsatellite instability; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; OS, overall survival; PNI, perineural invasion; RCT, randomized controlled trial; TNM, tumor, lymph node, metastasis

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