Original Article

Chemotherapy exacerbates the survival paradox of colon cancer: a propensity score matching analysis

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Background: Colon cancer is one of the most common tumor diseases in the world. Currently, clinicians usually evaluate the survival and prognosis of patients according to their tumor-node-metastasis (TNM) stage. However, current studies have found that there is a certain survival paradox in TNM staging.

Methods: In the Surveillance, Epidemiology, and End Results (SEER) database, patients diagnosed with colon cancer by surgical pathology from 2004 to 2011 were selected for analysis of 5-year overall survival (OS). Propensity score matching (PSM) was performed to analyze the difference in survival between different stages and the effect of chemotherapy on prognosis.

Results: The OS of stage IIIA colon cancer sufferers was significantly superior to stage IIB/IIC and separate stage IIB or IIC colon cancer patients before and after PSM analysis ($P<0.05$ for all). Moreover, the difference in survival was more significant when stage IIB/IIC patients were compared with stage IIIA patients with chemotherapy.

Conclusions: The survival paradox existed both in all stage IIB/IIC patients, or individual stage IIB or IIC patients compared with stage IIIA sufferers, and the survival paradox between stage IIIA and stage IIC was more obvious. Moreover, chemotherapy had a positive effect on the prognosis of patients with stage IIIA, IIC and IIB in this study. Chemotherapy exacerbates the survival paradox of colon cancer, even if it is not the cause of the survival paradox.

Keywords: Survival paradox; colon cancer; chemotherapy; Surveillance, Epidemiology, and End Results (SEER); propensity score matching (PSM)

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Introduction

Colon cancer, a malignant tumor with high incidence and recurrence, has more than 1.8 million new cases worldwide every year (1). The prognosis of colon cancer has improved significantly due to the development of complete mesocolic excision (CME), neoadjuvant therapy and targeted drug precision therapy in recent decades (2-5). However, it also revealed that with the development of colon cancer research, there are still various problems to be solved.

The staging of colon cancer mainly depends on the American Joint Commission on Cancer (AJCC) tumor-node-metastasis (TNM) staging system worldwide. Clinicians can predict patient survival and prognosis and select the most appropriate treatment by accurately staging the cancer (6). The AJCC TNM system for colorectal cancer (CRC) has undergone several modifications in the past few decades. The AJCC 6th edition of the TNM stage system, in 2002, further divided stage II into stage

IIA and stage IIB (7). The staging of colon cancer was further improved by the AJCC 7th edition in 2010. Major modifications included redefining T4 as T4a and T4b, N1 as N1a and N1b, and N2 as N2a and N2b (8). Currently, stage II colon cancer has been classified as IIA, IIB and IIC. Although the AJCC TNM staging system has been updated to version 8, there are still some unresolved issues that need further study.

A major concern for colon cancer is the "survival paradox" that the outcome of colon cancer patients with stage IIIA is actually superior to those with stage IIB/IIC (9-11). Based on the AJCC TNM stage system, clinicians can predict the prognosis of lower stage cancers is significantly better than that of higher stage cancers for most solid malignancies (12). However, colon cancer, caused by the survival paradox, is one of the puzzling exceptions. The 5-year overall survival (OS) of stage IIB/IIC patients is about 46% to 60%, whereas it can reach nearly 70% for stage IIIA patients (10). The exact reason of the survival paradox in colon cancer is unclear. Many studies showed that this survival paradox may be a phenomenon caused by a variety of causes (13,14). Stage T4 colon cancer is a tumor that invasions adjacent organs and/or penetrates the visceral peritoneum, often indicating a poor prognosis (15). The 7th edition AJCC staging system divided T4 colon cancer into two groups: T4a and T4b in order to emphasize the prognostic effect of stage T4. The 5-year OS of colon cancer sufferers with stage IIB (T4aN0M0) was 60.6%, notably superior to that of sufferers with stage IIC (T4bN0M0), which was 45.7% (16). Therefore, the comparison between stage IIIA colon cancer and stage IIB or IIC respectively is crucial during the discussion of the survival paradox.

The Surveillance, Epidemiology, and End Results (SEER) database includes clinical details of a large number of cancer patients, which covers about 30 percent of clinical cancer patients in America. This research extracted data from the SEER database to analyze the survival differences between stage IIIA and stage IIB, IIC, IIB/IIC colon cancers respectively, and the effect of chemotherapy in these differences. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1630/rc).

Methods

Study population

Custom data (additional treatment areas) from 18 registries centers in the SEER database was studied in our research, which was submitted in November 2018 (from 1973 to 2016). Patients diagnosed with colon cancer by surgical pathology from 2004 to 2011 were selected for analysis of 5-year OS. The information extracted from the database also included the basic information of patients (age, race, gender, marriage, insurance status), detailed pathological data (tumor grade, pathological type, stage), follow-up information, treatment plan (surgical method, chemotherapy), tumor size, tumor location and CEA, etc. Stage T4 in the 6th edition of the AJCC TNM was subdivided into T4a (code 500, 550, 560) and T4b (code 565, 570, 600, 650, 655, 660, 675, 700, 750, 800, 850) according to the collaborative stage (CS) extension in the database. The 7th edition of the AJCC TNM stage system was adopted after 2010, while the latest 8th edition stage system was no different from the 7th edition in terms of T and N staging. This study was limited to T4a/T4bN0 and T1-2N1/T1N2a colon cancer patients with detailed pathological staging; 11,941 colon cancer patients were eventually included in this research after screening (*Figure 1*).

Statistical analysis

Survival analysis of colon cancer sufferers was performed by Kaplan-Meier (K-M) method. Univariate Cox proportional risk regression method was utilized to determine the factors remarkably related to OS. Multivariate Cox proportional risk regression analysis was undertaken to determine the independent significant elements correlated with OS and figure the hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, propensity score matching (PSM) was performed to analyze differences in survival between different stages and the effect of chemotherapy on prognosis. This study stipulated that the difference is statistically valid when the P value is ≤0.05. SPSS 26.0 (IBM, Armonk, NY, USA) was used for all statistical analyses in this study.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As this is an observation study, the Xiangya Hospital Institutional Research Ethics Committee has confirmed that no ethical approval is required and individual consent for this retrospective analysis was waived.

Table 1 The basic and clinical features of all patients (n=11,941)

Characteristics	Level	Number (%)
Marital status	Single/unknown	5,666 (47.45)
	Married	6,275 (52.55)
Age, years	<65	4,375 (36.64)
	≥65	7,566 (63.36)
Race recode	Other	2,369 (19.84)
	White	9,572 (80.16)
Sex	Female	6,215 (52.05)
	Male	5,726 (47.95)
Tumor site	The right colon	6,910 (57.87)
	The left colon	5,031 (42.13)
Grade	I	959 (8.03)
	II	8,054 (67.45)
	III/IV	2,422 (20.28)
	Unknown	506 (4.24)
Histology	Adenocarcinomas	10,368 (86.83)
	Cystic, mucinous and serous neoplasms	1,573 (13.17)
Stage	IIB	3,465 (29.02)
	IIC	3,063 (25.65)
	IIIA	5,413 (45.33)
Surgery	Partial colectomy	4,850 (40.62)
	Hemicolectomy	6,856 (57.42)
	Unknown	235 (1.96)
Chemotherapy	No/unknown	6,667 (55.83)
	Yes	5,274 (44.17)
Tumor size, cm	<5	8,705 (72.90)
	≥5	2,036 (17.05)
	Unknown	1,200 (10.05)
CEA	Negative	4,083 (34.19)
	Positive	2,587 (21.66)
	Unknown	5,271 (44.15)
Regional nodes examined	<12	3,782 (31.67)
	≥12	8,069 (67.57)
	Unknown	90 (0.76)

CEA, carcinoembryonic antigen.

Results

Patient features

The basic clinical characteristics of all subjects in this study are shown in *Table 1*. The study population was predominantly white, accounting for 80.16% (9,572 patients). Approximately 63.36% (7,566 patients) of the patients were over 65 years old, and about 52.05% (6,215 patients) were female. A total of 6,910 patients (57.87%) had lesions in the right colon. Most patients (67.45%) with colon cancer had grade II tumors, which were moderately differentiated. Adenocarcinoma accounted for about 86.83% of the pathological types of patients studied, and only patients are diagnosed with only 13.17% patients of cystic, mucinous and serous tumors. Among the 11,941 included patients, 2,321 (19.44%), 3,092 (25.89%), 3,063 (25.65%) and 3,465 (29.02%) were categorized as stage IIIA without chemotherapy, stage IIIA with chemotherapy, stage IIC and stage IIB, respectively; 57.42% of the patients underwent radical resection and 44.17% received chemotherapy in terms of treatment.

OS analysis

K-M survival curves of OS for all sufferers are shown in *Figure 2*. The marital status, age, primary tumor location, tumor grade, TNM stage, chemotherapy, number of regional nodes examined, tumor size and CEA were all correlated with the prognosis of colon cancer sufferers through univariate and multivariate analysis (*Table 2*). The 5-year OS of all stage IIB/IIC and stage IIIA sufferers were 34.83% and 56.47%, respectively (P<0.001; HRs =1.968; 95% CIs: 1.871–2.070). The 5-year OS of stage IIIA without chemotherapy and IIIA with chemotherapy patients were 40.52% and 69.85%, respectively (P<0.001; HRs =2.539; 95% CIs: 2.323–2.775). The 5-year OS of stage IIB and IIC were 36.76% and 32.80%, respectively (P<0.001; HRs =0.859; 95% CIs: 0.807–0.915). The median survival time for sufferers with stage IIB/IIC was only 70 months, compared with 148 months for stage IIIA patients. The subgroups were further refined and found that the median survival of stage IIIA without chemotherapy, IIB and IIC sufferers were 92, 78 and 61 months, respectively. The median survival of stage IIIA sufferers with chemotherapy was not calculated in this research (*Table 3*).

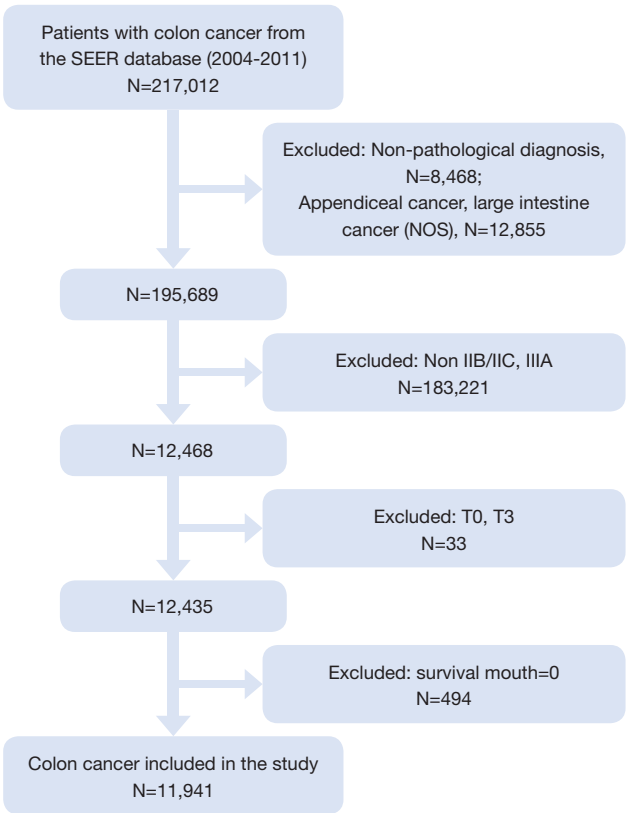
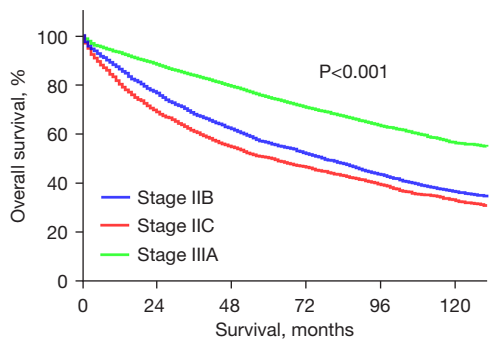


Figure 1 Inclusion and exclusion procedures for colon cancer patients from SEER database. SEER, Surveillance, Epidemiology, and End Results; NOS, not otherwise specified.



		Months					
Number at risk	Stage	0	24	48	72	96	120
	IIB	3465	2660	2122	1516	893	440
	IIC	3063	2117	1649	1189	702	353
	IIIA	5413	4773	4247	3280	2048	1053

Figure 2 K-M survival curves of OS for all colon cancer sufferers. K-M, Kaplan-Meier; OS, overall survival.

Survival differences were further analyzed with PSM. First of all, the balanced population of stage IIB/IIC and IIIA patients (n=2,365) were matched according to 1:1 propensity score. The survival analysis of the data obtained after PSM showed that 5-year OS of stage IIIA was still superior to stage IIB/IIC patients (48.95% *vs.* 35.93%; P<0.001; HRs =1.474; 95% CIs: 1.360–1.598). The balanced population of stage IIIA without chemotherapy and IIB/IIC (n=1,668), stage IIIA with chemotherapy and IIB/IIC (n=1,884), stage IIIA without chemotherapy and IIIA with chemotherapy (n=1,350) were obtained by multiple 1:1 PSMs. The OS of stage IIIA without chemotherapy sufferers was superior to stage IIB/IIC sufferers (38.59% *vs.* 32.90%; P<0.001; HRs =1.218; 95% CIs: 1.116–1.330). Moreover, the 5-year OS of stage IIIA with chemotherapy patients was remarkably superior to stage IIB/IIC patients (64.99% *vs.* 39.78%; P<0.001; HRs =2.280; 95% CIs: 2.060–2.524). The OS of stage IIIA sufferers without chemotherapy was 44.73%, compared with 63.07% for stage IIIA patients with chemotherapy (P<0.001; HRs =1.831; 95% CIs: 1.628–2.059) (*Figure 3*).

IIB and IIIA survival analysis

Stage IIIA sufferers held a better 5-year OS than stage IIB (56.47% *vs.* 36.76%; P<0.001; HRs =1.851; 95% CIs: 1.735–1.975). Furthermore, the OS of stage IIIA patients without chemotherapy was superior to that of IIB patients (40.52% *vs.* 36.76%; P<0.001; HRs =1.155; 95% CIs: 1.078–1.239). The 5-year OS of stage IIIA sufferers with chemotherapy was remarkably longer than stage IIB sufferers (69.85% *vs.* 36.76%; P<0.001; HRs =2.911; 95% CIs: 2.703–3.135). The OSs were 30.62% and 50.87% for stage IIB without and with chemotherapy, respectively (P<0.001; HRs =1.787; 95% CIs: 1.625–1.964).

Furthermore, the balanced population of stage IIB and IIIA sufferers (n=1,641) were matched by 1:1 propensity score. The 5-year OS of stage IIIA was superior to stage IIB patients (45.83% *vs.* 36.66%; P<0.001; HRs =1.345; 95% CIs: 1.222–1.480). The balanced population of stage IIIA without chemotherapy and stage IIB (n=1,341), stage IIIA with chemotherapy and stage IIB (n=1,432), stage IIB without chemotherapy and IIB with chemotherapy (n=524) were obtained by multiple 1:1 PSMs. The OS of stage IIIA sufferers without chemotherapy was better than that

Table 2 Univariate and multivariate analysis for OS of all sufferers (n=11,941)

Characteristics	Level	Univariate analysis	Multivariate analysis		
		P	HRs	95% CIs	P
Marital status		<0.001			<0.001
	Single/unknown		Reference	Reference	Reference
	Married		0.753	0.715–0.793	<0.001
Age, years		<0.001			<0.001
	<65		Reference	Reference	Reference
	≥65		2.292	2.146–2.447	<0.001
Race recode		0.162			NA
	Other				
	White				
Sex		0.571			NA
	Female				
	Male				
Tumor site		<0.001			0.002
	The right colon		Reference	Reference	Reference
	The left colon		0.908	0.854–0.965	0.002
Grade		<0.001			<0.001
	I		Reference	Reference	Reference
	II		1.123	1.015–1.243	0.025
	III/IV		1.259	1.127–1.407	<0.001
	Unknown		1.425	1.223–1.661	<0.001
Histology		<0.001			0.538
	Adenocarcinomas		Reference	Reference	Reference
	Cystic, mucinous and serous neoplasms		0.977	0.907–1.052	0.538
Stage		<0.001			<0.001
	IIB		Reference	Reference	Reference
	IIC		1.282	1.201–1.368	<0.001
	IIIA		0.676	0.632–0.723	<0.001
Surgery		<0.001			0.939
	Partial colectomy		Reference	Reference	Reference
	Hemicolectomy		0.991	0.932–1.053	0.765
	Unknown		1.012	0.846–1.211	0.896
Chemotherapy		<0.001			<0.001
	No/unknown		Reference	Reference	Reference
	Yes		0.624	0.589–0.663	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Level	Univariate analysis	Multivariate analysis		
		P	HRs	95% CIs	P
Regional nodes examined		<0.001			<0.001
	<12		Reference	Reference	Reference
	≥12		0.684	0.647–0.722	<0.001
	Unknown		1.111	0.849–1.455	0.443
Tumor size, cm		<0.001			0.005
	<5		Reference	Reference	Reference
	≥5		0.923	0.862–0.989	0.022
	Unknown		1.099	1.002–1.206	0.045
CEA		<0.001			<0.001
	Negative		Reference	Reference	Reference
	Positive		1.504	1.401–1.615	<0.001
	Unknown		1.219	1.146–1.297	<0.001

OS, overall survival; HRs, hazard ratios; CIs, confidence intervals; NA, no answer; CEA, carcinoembryonic antigen.

Table 3 Median survival and, 3-, 5-year OS of colon cancer sufferers

Stage	Median survival	3-year OS	5-year OS
IIB/C	70	48.95%	34.83%
IIIA	148	70.08%	56.47%
IIB	78	52.34%	36.76%
IIC	61	45.92%	32.80%
IIIA without chemotherapy	92	57.28%	40.52%
IIIA with chemotherapy	Not reached	80.03%	69.85%

OS, overall survival.

of stage IIB sufferers (37.86% *vs.* 34.47%; P=0.008; HRs =1.145; 95% CIs: 1.036–1.265). The 5-year OS in stage IIIA patients with chemotherapy was remarkably superior to stage IIB patients (63.07% *vs.* 40.15%; P<0.001; HRs =2.127; 95% CIs: 1.897–2.386). The OS was 37.49% for stage IIB without chemotherapy, 48.22% for stage IIB with chemotherapy (P=0.003; HRs =1.292; 95% CIs: 1.090–1.531) (*Figure 4*).

IIC and IIIA survival analysis

The 5-year OS in stage IIIA patients was superior to that in stage IIC (56.47% *vs.* 32.80%; P<0.001; HRs =1.851; 95% CIs: 1.735–1.975). The 5-year OS of stage IIIA sufferers without chemotherapy was superior to that of IIC sufferers (40.52% *vs.* 32.80%; P<0.001; HRs =1.334; 95% CIs: 1.244–1.431). The OS of stage IIIA sufferers with chemotherapy was remarkably superior to that of IIC sufferers (69.85% *vs.* 32.80%; P<0.001; HRs =3.312; 95% CIs: 3.068–3.575). The 5-year OS was 23.37% for stage IIC sufferers without chemotherapy, 46.65% for stage IIC with chemotherapy (P<0.001; HRs =1.891; 95% CIs: 1.728–2.070) (*Table 4*).

The balanced population of stage IIIA and IIC (n=1,187), stage IIIA without chemotherapy and stage IIC (n=978), stage IIIA with chemotherapy and stage IIC (n=1,022), stage

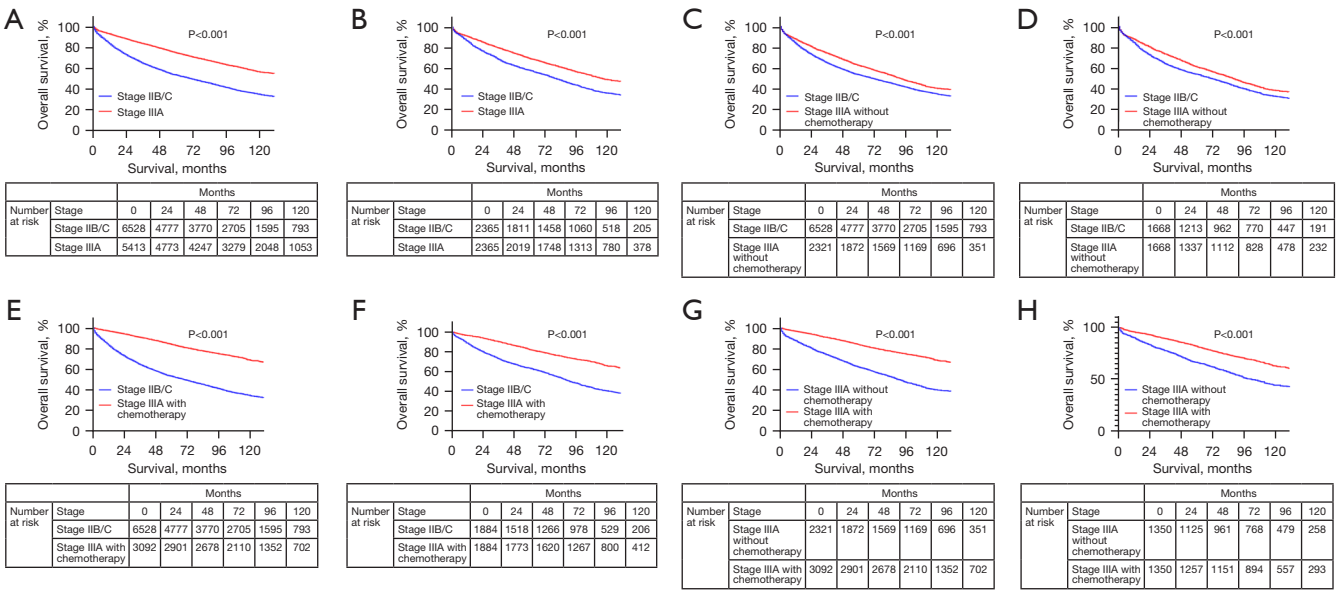


Figure 3 The K-M survival curve of OS for colon cancer patients (stage IIB/IIC *vs.* stage IIIA, IIIA without chemotherapy and IIIA with chemotherapy; stage IIIA without chemotherapy *vs.* stage IIIA with chemotherapy) before and after PSM. (A) The 5-year OS of all patients with IIB/IIC and IIIA before PSM. (B) The 5-year OS of all patients with IIB/IIC and IIIA after PSM. (C) The 5-year OS of all patients with IIB/IIC and IIIA without chemotherapy before PSM. (D) The 5-year OS of all patients with IIB/IIC and IIIA after PSM. (E) The 5-year OS of all patients with IIB/IIC and IIIA with chemotherapy before PSM. (F) The 5-year OS of all patients with IIB/IIC and IIIA with chemotherapy after PSM. (G) The 5-year OS of all patients with IIIA without chemotherapy and IIIA with chemotherapy before PSM. (H) The 5-year OS of all patients with IIIA without chemotherapy and IIIA with chemotherapy after PSM. K-M, Kaplan-Meier; OS, overall survival; PSM, propensity score matching.

IIC without chemotherapy and IIC with chemotherapy (n=484) were matched by 1:1 propensity scoring. The 5-year OS in stage IIIA was superior to that in stage IIC patients (48.58% *vs.* 29.88%; P<0.001; HRs =1.655; 95% CIs: 1.480–1.851). Similarly, the OS was better for stage IIIA sufferers without chemotherapy than stage IIC sufferers (39.05% *vs.* 27.96%; P<0.001; HRs =1.382; 95% CIs: 1.231–1.551). The 5-year OS in stage IIIA sufferers with chemotherapy was remarkably superior to that in stage IIC sufferers (62.33% *vs.* 34.01%; P<0.001; HRs =2.566; 95% CIs: 2.244–2.934). The OS was 26.40% for stage IIC without chemotherapy, 44.00% for stage IIC with chemotherapy (P<0.001; HRs =1.650; 95% CIs: 1.400–1.945) (*Figure 5*).

Survival analysis of different year groups

Based on guidelines and a review of the literature, we found that FOLFOX was established as the standard chemotherapy regimen for CRC starting in 2004 (17), and that the 2008 guidelines began recommending chemotherapy for high-risk stage IIB CRC (18). Therefore, we decided to roughly divide patients into two groups based on their year of diagnosis: 2004 to 2007 and 2008 to 2011.

In the group where patients were diagnosed between 2004 and 2007, stage IIIA sufferers held a better median survival than stage IIB/IIC (145 *vs.* 68 months; P<0.001; HRs =1.853; 95% CIs: 1.732–1.982). Furthermore, the median survival of stage IIIA patients without chemotherapy was longer than that of IIB/IIC patients (91 *vs.* 68 months; P<0.001; HRs =1.213; 95% CIs: 1.121–1.313). The median survival of stage IIIA sufferers with chemotherapy was remarkably longer than stage IIB sufferers (150 *vs.* 68 months; P<0.001; HRs =2.833; 95% CIs: 2.620–3.064). Then, the balanced population of stage IIB/IIC and IIIA sufferers (n=1,345) were matched by 1:1 propensity scoring. The median survival of stage IIIA was superior to stage IIB/IIC patients (140 *vs.* 76 months; P<0.001; HRs =1.652; 95% CIs: 1.471–1.851). The balanced population of stage IIIA without chemotherapy (n=616) and stage IIB/IIC, stage IIIA with chemotherapy (n=723) and stage IIB/IIC

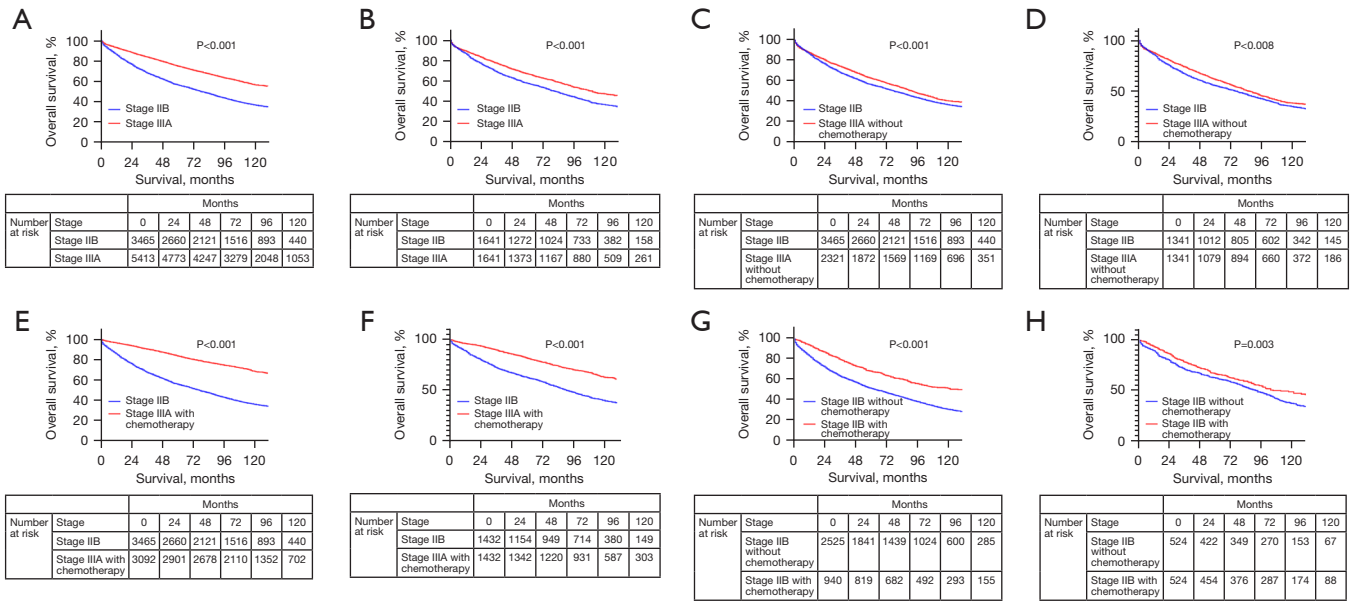


Figure 4 The K-M survival curve of OS for colon cancer sufferers (stage IIB *vs.* stage IIIA, IIIA without chemotherapy and IIIA with chemotherapy; stage IIB without chemotherapy *vs.* stage IIB with chemotherapy) before and after PSM. (A) The 5-year OS of all patients with IIB and IIIA before PSM. (B) The 5-year OS of all patients with IIB and IIIA after PSM. (C) The 5-year OS of all patients with IIB and IIIA without chemotherapy before PSM. (D) The 5-year OS of all patients with IIB and IIIA without chemotherapy after PSM. (E) The 5-year OS of all patients with IIB and IIIA with chemotherapy before PSM. (F) The 5-year OS of all patients with IIB and IIIA with chemotherapy after PSM. (G) The 5-year OS of all patients with IIB without chemotherapy and IIB with chemotherapy before PSM. (H) The 5-year OS of all patients with IIB without chemotherapy and IIB with chemotherapy after PSM. K-M, Kaplan-Meier; OS, overall survival; PSM, propensity score matching.

Table 4 Multivariate analysis of OS in colon cancer at different stages before and after PSM

Stage	Before PSM			After PSM		
	HRs	95% CIs	P	HRs	95% CIs	P
IIB/C *vs.* IIIA	1.968	1.871–2.070	<0.001	1.474	1.360–1.598	<0.001
IIB/C *vs.* IIIA without chemotherapy	1.235	1.162–1.312	<0.001	1.218	1.116–1.330	<0.001
IIB/C *vs.* IIIA with chemotherapy	3.074	2.899–3.259	<0.001	2.280	2.060–2.524	<0.001
IIIA without chemotherapy *vs.* IIIA with chemotherapy	2.539	2.323–2.775	<0.001	1.831	1.628–2.059	<0.001
IIB *vs.* IIIA	1.851	1.735–1.975	<0.001	1.345	1.222–1.480	<0.001
IIB *vs.* IIIA without chemotherapy	1.155	1.078–1.239	<0.001	1.145	1.036–1.265	0.008
IIB *vs.* IIIA with chemotherapy	2.911	2.703–3.135	<0.001	2.127	1.897–2.386	<0.001
IIB without chemotherapy *vs.* IIB with chemotherapy	1.787	1.625–1.964	<0.001	1.292	1.090–1.531	0.003
IIC *vs.* IIIA	2.129	1.990–2.279	<0.001	1.655	1.480–1.851	<0.001
IIC *vs.* IIIA without chemotherapy	1.334	1.244–1.431	<0.001	1.382	1.231–1.551	<0.001
IIC *vs.* IIIA with chemotherapy	3.312	3.068–3.575	<0.001	2.566	2.244–2.934	<0.001
IIC without chemotherapy *vs.* IIC with chemotherapy	1.891	1.728–2.070	<0.001	1.650	1.400–1.945	<0.001

OS, overall survival; PSM, propensity score matching; HRs, hazard ratios; CIs, confidence intervals.

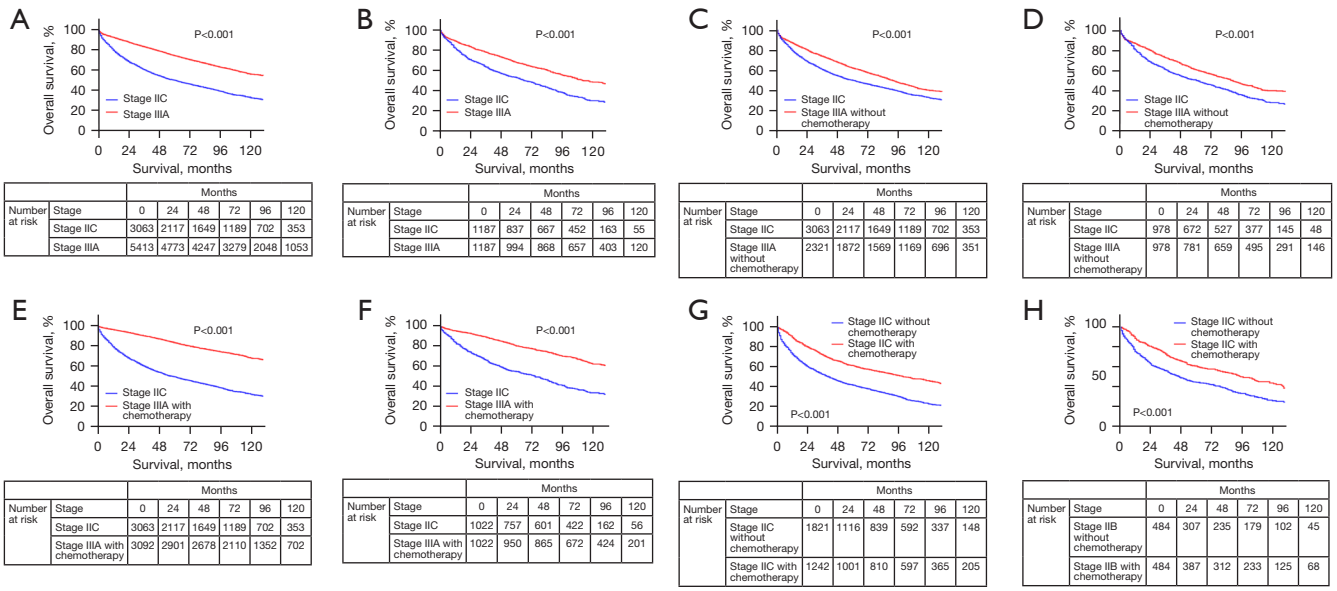


Figure 5 The K-M survival curve of OS for colon cancer sufferers (stage IIC *vs.* stage IIIA, IIIA without chemotherapy and IIIA with chemotherapy; stage IIC without chemotherapy *vs.* stage IIC with chemotherapy) before and after PSM. (A) The 5-year OS of all patients with IIC and IIIA before PSM. (B) The 5-year OS of all patients with IIC and IIIA after PSM. (C) The 5-year OS of all patients with IIC and IIIA without chemotherapy before PSM. (D) The 5-year OS of all patients with IIC and IIIA without chemotherapy after PSM. (E) The 5-year OS of all patients with IIC and IIIA with chemotherapy before PSM. (F) The 5-year OS of all patients with IIC and IIIA with chemotherapy after PSM. (G) The 5-year OS of all patients with IIC without chemotherapy and IIC with chemotherapy before PSM. (H) The 5-year OS of all patients with IIC without chemotherapy and IIC with chemotherapy after PSM. K-M, Kaplan-Meier; OS, overall survival; PSM, propensity score matching.

were obtained by multiple 1:1 PSM. The median survival of stage IIIA sufferers without chemotherapy was better than in stage IIB/IIC sufferers (88 *vs.* 75 months; P=0.027; HRs =1.108; 95% CIs: 1.006–1.263). The median survival in stage IIIA patients with chemotherapy was remarkably superior to stage IIB/IIC patients (140 *vs.* 73 months; P<0.001; HRs =2.490; 95% CIs: 2.179–2.845) (*Figure 6*).

In the group where patients were diagnosed between 2008 and 2011, stage IIIA sufferers also held a better median survival than stage IIB/IIC (95 *vs.* 73 months; P<0.001; HRs =2.138; 95% CIs: 1.979–2.309). Furthermore, the median survival of stage IIIA patients without chemotherapy was longer than that of IIB/IIC patients (92 *vs.* 73 months; P<0.001; HRs =1.270; 95% CIs: 1.156–1.394). The median survival of stage IIIA sufferers with chemotherapy was remarkably longer than stage IIB sufferers (103 *vs.* 73 months; P<0.001; HRs =3.413; 95% CIs: 3.126–3.727). Then, the balanced population of stage IIB/IIC and IIIA sufferers (n=1,253) were matched by 1:1 propensity scoring. The median survival of stage IIIA was superior to stage IIB/IIC patients (93 *vs.* 72 months; P<0.001; HRs =2.266; 95% CIs: 2.034–2.524). The balanced population of stage IIIA without chemotherapy (n=526) and stage IIB/IIC, stage IIIA with chemotherapy (n=835) and stage IIB/IIC were obtained by multiple 1:1 PSMs. The median survival of stage IIIA sufferers without chemotherapy was better than in stage IIB/IIC sufferers (92 *vs.* 70 months; P<0.001; HRs =1.344; 95% CIs: 1.179–1.532). The median survival in stage IIIA patients with chemotherapy was remarkably superior to stage IIB/IIC patients (100 *vs.* 73 months; P<0.001; HRs =3.571; 95% CIs: 3.161–4.034) (*Figure 7*).

Discussion

Our result, consistent with previous studies (19-21), showed that stage IIB sufferers held significantly more satisfactory outcomes than stage IIC. Therefore, we analyzed the survival of sufferers with stage IIB/IIC, IIB, IIC and IIIA. These results showed that the survival paradox existed both in all stage IIB/IIC patients, or individual stage IIB or IIC

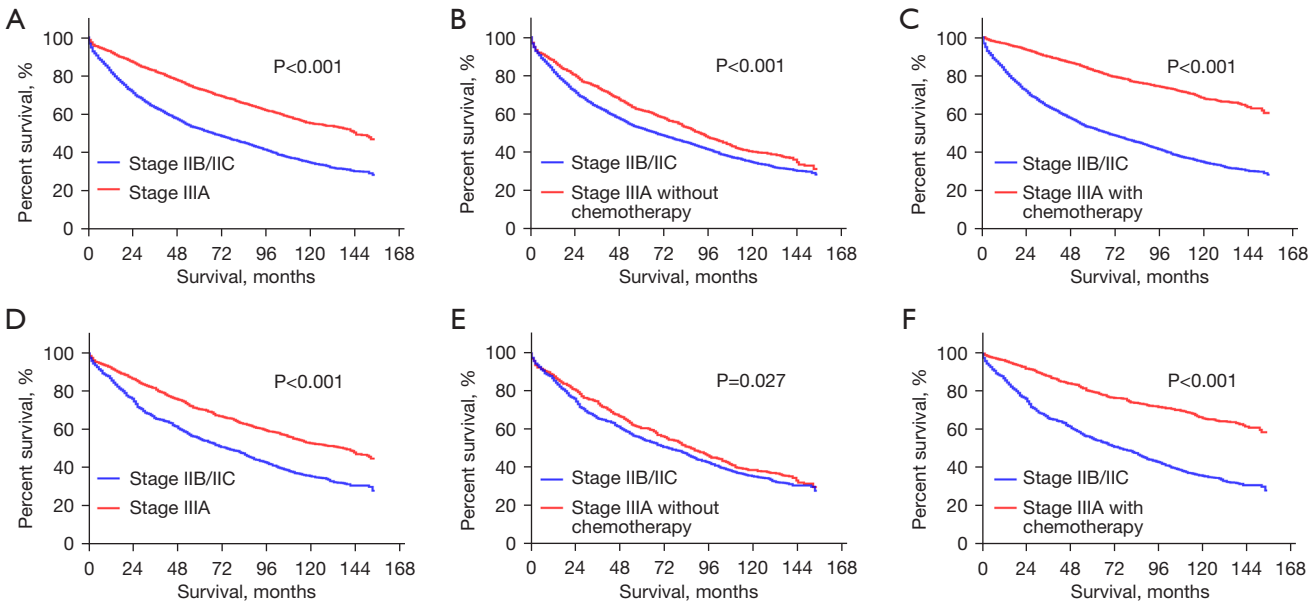


Figure 6 The K-M survival curve of OS for colon cancer sufferers (stage IIB/IIC *vs.* stage IIIA, IIIA without chemotherapy and IIIA with chemotherapy) before and after PSM (2004–2007). (A) The median survival of all patients with IIB/IIC and IIIA before PSM. (B) The median survival of all patients with IIB/IIC and IIIA without chemotherapy before PSM. (C) The median survival of all patients with IIB/IIC and IIIA with chemotherapy before PSM. (D) The median survival of all patients with IIB/IIC and IIIA after PSM. (E) The median survival of all patients with IIB/IIC and IIIA without chemotherapy after PSM. (F) The median survival of all patients with IIB/IIC and IIIA with chemotherapy after PSM. K-M, Kaplan-Meier; OS, overall survival; PSM, propensity score matching.

patients compared with stage IIIA sufferers. In other words, stage IIIA sufferers had the best prognosis among these patients. Moreover, the survival paradox between stage IIIA and stage IIC was more obvious. Some researchers attribute this to the fact that patients with stage IIB or IIC often lack systematic treatment and believe that patients with stage IIB/IIC will have better survival rates than patients with stage III if they receive adequate lymph node dissection and adjuvant chemotherapy (22,23). However, there is a lack of research to prove whether this is the case. We used the PSM system to reduce the influence of factors such as treatment style, and the results showed that the survival paradox still existed. Therefore, we believed that the survival paradox seems to be a multi-factor phenomenon rather than attributable to a single clinicopathological factor (12). Perhaps this is mainly due to the fact that the T4 colon tumor itself is biologically aggressive (14).

In addition, chemotherapy had a positive effect on the prognosis of sufferers with stage IIIA, IIC and IIB in this study. Similarly, the QUASAR (Quick and Simple and Reliable) trial which demonstrated adjuvant chemotherapy to be beneficial for prognosis in stage II colon cancer sufferers was a phase III clinical trial (24). The role of adjuvant chemotherapy in the survival paradox of colon cancer remains unclear. Some scholars deemed that stage IIIA patients priority to receive adjuvant chemotherapy may be a reason for the survival paradox (25). We divided stage IIIA into a group without chemotherapy and a group with chemotherapy, and performed survival analysis with IIB/IIC, stage IIB, and stage IIC, respectively. The results showed that stage IIIA had the best prognosis with or without chemotherapy, which suggested that chemotherapy is not the cause of the survival paradox. Meanwhile, considering that advances in chemotherapy technology may affect our results, we analyzed the survival based on the year of diagnosis according to the changes in treatment methods in the guidelines, and the results were still consistent with the results of previous studies. What's more, the value of HR was greater in the survival analysis of group IIIA patients with chemotherapy. Thus, we concluded that although adjuvant chemotherapy is not the cause of the survival paradox, it further expands the survival paradox. The reason why chemotherapy expands the survival paradox may be that chemotherapy as a systemic treatment has a positive effect on

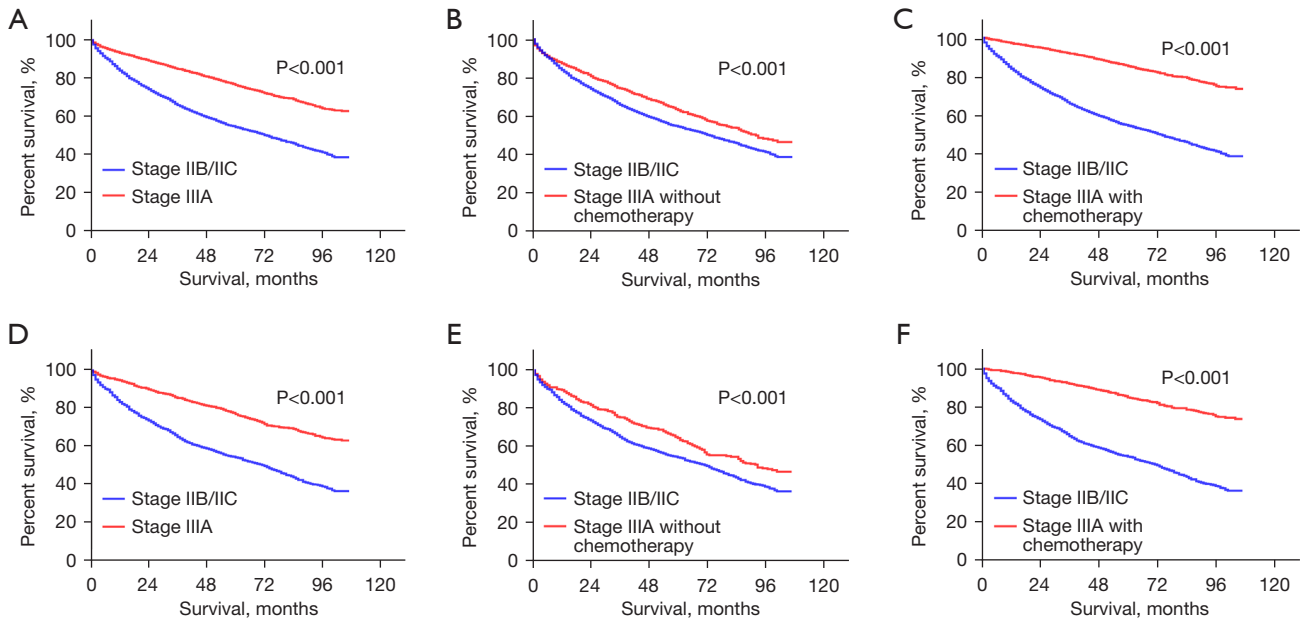


Figure 7 The K-M survival curve of OS for colon cancer sufferers (stage IIB/IIC *vs.* stage IIIA, IIIA without chemotherapy and IIIA with chemotherapy) before and after PSM (2008–2011). (A) The median survival of all patients with IIB/IIC and IIIA before PSM. (B) The median survival of all patients with IIB/IIC and IIIA without chemotherapy before PSM. (C) The median survival of all patients with IIB/IIC and IIIA with chemotherapy before PSM. (D) The median survival of all patients with IIB/IIC and IIIA after PSM. (E) The median survival of all patients with IIB/IIC and IIIA without chemotherapy after PSM. (F) The median survival of all patients with IIB/IIC and IIIA with chemotherapy after PSM. K-M, Kaplan-Meier; OS, overall survival; PSM, propensity score matching.

the prognosis of stage IIIA colon cancer sufferers (26). This positive prognostic effect further increased the difference in survival between stage IIIA with chemotherapy and stage IIB/IIC.

Our research still had certain limitations, and the results need to be interpreted carefully. Firstly, the SEER database lacks detailed chemotherapy regimens, the sequence of chemotherapy and surgery, which may have an impact on prognosis of colon patients. Additionally, the data did not include obstruction or perforation, vascular and nerve invasion, and related genetic molecular and genetic information such as microsatellite instability (MSI) and KRAS, all of which are important prognostic factors.

Conclusions

In summary, this retrospective study from the SEER database made the following recommendations: (I) whether it is the entire stage IIB/IIC, or individual stage IIB or stage IIC colon cancer, there is a survival paradox between them and stage IIIA, (II) adjuvant chemotherapy has a positive effect on the prognosis of stage IIIA and IIB/IIC colon cancers, (III) chemotherapy further exacerbates the survival paradox of colon cancer, even if it is not the cause of the survival paradox.

Summary points

- This research is the first to discuss the survival paradox of colon cancer and the role of chemotherapy in the survival paradox by using PSM analysis.
- The SEER database includes clinical details of a large number of cancer patients, which actually covers about 30 percent of clinical cancer patients in the USA.
- Among the 11,941 included patients, 2,321 (19.44%), 3,092 (25.89%), 3,063 (25.65%) and 3,465 (29.02%) were categorized as stage IIIA without chemotherapy, stage IIIA with chemotherapy, stage IIC and stage IIB, respectively. About 57.42% of the patients underwent radical resection and about 44.17% received chemotherapy in terms of treatment.
- The marital status, age, primary tumor location,

tumor grade, TNM stage, chemotherapy, number of regional nodes examined, tumor size and CEA were all correlated with the prognosis of colon cancer sufferers through univariate and multivariate analysis.

- ❖ The 5-year OS of stage IIIA colon cancer sufferers was significantly superior to stage IIB/IIC and separate stage IIB or IIC colon cancer patients before and after PSM analysis (P<0.05 for all).
- ❖ Adjuvant chemotherapy has a positive effect on the prognosis of stage IIIA and IIB/IIC colon cancers.
- ❖ Chemotherapy further exacerbates the survival paradox of colon cancer, even if it is not the cause of the survival paradox.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1630/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1630/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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