

Age and Gender Along with Adverse Histological Features Guide Adjuvant Chemotherapy for T3N0M0 Colon Cancer in a Propensity Score Matched Population Analysis

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Abstract

Purpose

To determine whether adjuvant chemotherapy (AC) improves outcomes in T3N0M0 colon cancer with adverse histology.

Methods

T3N0M0 patients aged 20–80 who underwent radical resection for colonic carcinoma diagnosed between 2004 and 2012 were analyzed from the Surveillance, Epidemiology, and End Results (SEER) 18 databases. Poorly differentiated, undifferentiated, mucinous adenocarcinoma, and signet ring cell carcinoma (SRCC) were defined as adverse histological features, while well or moderately differentiated adenocarcinoma was categorized as favorable histological features. Multivariate analysis was employed to adjust for the impact of other covariates, and the survival benefit of AC was evaluated within a propensity score-matched cohort.

Results

Adjuvant chemotherapy did not confer a survival advantage (for favorable histological features: HR, 1.076; 95% CI, 0.957–1.211; $P = 0.220$; for adverse histological features: HR, 0.995; 95% CI, 0.777–1.274; $P = 0.967$). However, for female patients at least 70 years old with adverse histological characteristics, they could derive benefit from adjuvant chemotherapy with a significant improvement in cancer-specific survival ($P = 0.019$). Neither mucinous adenocarcinoma nor SRCC significantly impacted survival when compared to adenocarcinoma (for mucinous adenocarcinoma: HR, 0.699; 95% CI, 0.488–1.002; $P = 0.051$; for SRCC: HR, 0.750; 95% CI, 0.386–1.459; $P = 0.397$). Additionally, the left-sided colon was associated with poorer survival in the group with favorable histological features (HR, 1.136; 95% CI, 1.034–1.248; $P = 0.008$).

Conclusions

Adverse histology alone should not dictate AC in T3N0M0 colon cancer; benefit is limited to women ≥ 70 year with adverse features.

Introduction

Colorectal cancer (CRC), with its rising incidence, stands as one of the most widespread malignancies worldwide, significantly contributing to cancer mortality rates[1]. A notable 24–27% of patients are diagnosed at stage II, while 27–31% are at stage III[2, 3]. The established benefits of adjuvant fluoropyrimidine therapy have been proven to enhance the prognosis for patients with stage II/III CRC who have received radical resection[4]. However, there is persistent controversy over the clinical guidelines for stage II CRC, especially regarding the value of adjuvant chemotherapy[4]. Existing clinical decision-making tools fall short in precisely identifying which CRC patients are likely to gain benefit from adjuvant chemotherapy.

Fluoropyrimidine-based adjuvant chemotherapy is nowadays standardly prescribed for stage III colonic cancer and for a select group of stage II patients with high-risk indicators such as T4 tumour status, poorly differentiated histology, tumour perforation, and inadequate lymph node assessment[4, 5]. The prevailing hope is that these high-risk individuals with stage II disease may derive survival advantages from fluorouracil-based adjuvant chemotherapy, yet such benefits remain unconfirmed[3, 4]. The controversy surrounding adjuvant chemotherapy for stage II colon cancer persists, complicated by its modest impact on survival and significant potential for toxicity, thus making it a challenging issue. It is known that the recommendation for considering adjuvant chemotherapy is founded on extrapolating the relative benefits of adjuvant therapy in stage III disease, without direct evidence from randomized controlled trials[6]. Given the toxicities, inconvenience, and cost, it is difficult to justify adjuvant chemotherapy for all stage II patients due to the limited benefit, as surgery alone offers excellent outcomes[6]. Identifying biomarkers that predict and prognosticate is essential for enhancing treatment strategies and for the judicious selection of patients. Many international clinical guidelines acknowledge poorly differentiated tumours as a high-risk clinicopathological characteristic for patients with stage II colon cancer in regard to adjuvant treatment, except for MSI-H tumours that are exempt from chemotherapy. Nevertheless, for microsatellite stable tumours, whether poorly differentiated tumours are a suitable candidate for adjuvant is still undetermined, lacking any conclusive evidence at least.

Our research endeavored to refine a more pragmatic approach, grounded in predictive and prognostic indicators, to ascertain the survival advantages of adjuvant chemotherapy, aiming to reduce its adverse effects within a substantial cohort of patients sourced from the SEER database.

Methods

Study population

Investigating the prognostic factors of a target disease is feasible through the utilization of data from the SEER database, which is sponsored by the National Cancer Institute. In this study, we meticulously identified individuals diagnosed with microscopically confirmed adenocarcinoma of the colon, excluding the rectum and rectosigmoid junction, during the period from 2004 to 2012. All data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database of the United States National Cancer Institute in strict accordance with the SEER Data-Use Agreement. Only de-identified, publicly available datasets were analyzed, and all findings are intended exclusively for academic research purposes. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments (available at <https://www.wma.net/policies-post/wma-declaration-of-helsinki/>).

The SEER database, recognized as a credible source of information in the United States, actively collects and disseminates cancer data from population-based cancer registries throughout the country, encompassing approximately 28% of the U.S. population[7, 8]. Accessible to the public (<http://seer.cancer.gov/>), the SEER Stat software version 8.3.6 was employed to access the research data, with the reference number being 12296-Nov2018. To ensure sufficient follow-up time, patients diagnosed after 2012 were excluded from the study. A comprehensive set of clinicopathological variables were extracted, including age at diagnosis, year of

diagnosis, marital status, race, sex, histologic grade, tumour type, tumour site, adjuvant chemotherapy, survival time, and cause of death.

The inclusion criteria for the study were as follows: (1) patients diagnosed between 2004 and 2012; (2) the site code (ICD-O-3) was restricted to the colon with pathologically confirmed diagnoses, excluding the rectum and rectosigmoid junction (C18., C18.2-C18.7); (3) the histology code (ICD-O-3) was limited to adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (8140/3, 8480/3, 849/3); (4) patients' TNM staging was confined to T3N0M0, based on the 6th or 7th edition of the AJCC staging system, in accordance with the prevailing version at the time; (5) patients who underwent radical resection, defined as D2 or D3 lymphadenectomy with negative resection margins (R), with a precise count of resected regional lymph nodes for evaluation; (6) the age range of patients was from 20 to 80 years old; (7) patients with a single primary tumour; and (8) availability of information on cancer-specific survival (CSS) and survival months. (See Fig. 1).

Patients were excluded for analysis as follows: (1) Patients without documentation of demographic characteristics; (2) Patients with multiple primary tumours or another malignant tumour history; (3) Patients who survived less than one month after diagnosis; (4) No adequate information about therapy; And (5) the tumour was located in the rectum (**See Fig. 1**).

Figure 1. The inclusion and exclusion criteria in seer.

Variable Declaration

Age was categorized into two groups: those under 70 years of age and those 70 years of age or older. The racial classification included Black, White, and Other ethnicities. Marital status was categorized as Married, Single, or Divorced. Histological types were divided into three groups: Adenocarcinoma, Mucinous Adenocarcinoma, and Signet Ring Cell Carcinoma (SRCC). Histological features were further classified as adverse, which included Poorly Differentiated or Undifferentiated Adenocarcinoma, Mucinous Adenocarcinoma, and Signet Ring Cell Carcinoma (SRCC), and good, which referred to Well or Moderately Differentiated Adenocarcinoma. The tumour location was divided into Right-Sided Colon and Left-Sided Colon, with the demarcation point being the splenic flexure. Adjuvant chemotherapy was recorded in a binary fashion, categorized as either Not Administered or Administered, irrespective of the treatment sequence.

Statistical Analyses

The demographic and clinical characteristics of the study cohorts are presented in Table 1. Propensity score matching (PSM) was applied to balance the baseline characteristics of the population with adverse histological features between those who received chemotherapy and those who did not. The propensity score was calculated using logistic regression, including covariates such as age (either less than 70 or 70 and above), race, sex, marital status, tumour histology, grade, tumour location, lymphovascular invasion, and perineural invasion. The PSM cohort was established to validate the impact of chemotherapy on CSS in the population with adverse histological features.

Table 1

Descriptive Characteristics of 19834 Patients of Study Population within the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked Database and 1774 Propensity Score-Matched Patients within the Adverse Histological Features Population of Colonic Carcinoma

Characteristics	Entire cohort (n = 19834)			Propensity score-matched cohort (n = 1774)		
	FH, n (%)	AH, n (%)	P Value	Chemotherapy, n (%)	Non-chemotherapy, n (%)	P Value
	n = 16626 (84.00)	N = 3208 (16.00)		887 (50.00)	887 (50.00)	
Age			< 0.001			0.951
< 70	11464(68.95)	2043(63.68)		722(81.40)	723(81.51)	
≥ 70	5162(31.05)	1165(36.32)		165(18.60)	164(18.49)	
Gender			< 0.001			0.505
Female	7801(46.92)	1724(53.74)		482(54.34)	468(52.76)	
Male	8825(53.80)	1484(46.26)		405(45.66)	419(47.24)	
Race			< 0.001			0.877
White	12796(76.96)	2679(83.51)		737(83.09)	731(82.41)	
Black	2223(13.37)	282(8.79)		73(8.23)	79(8.91)	
Other	1607(9.67)	247(7.70)		77(8.68)	77(8.68)	
Marital status			0.002			0.981
Married	10102(60.76)	1896(59.10)		571(64.37)	569(64.15)	
Single	2700(16.24)	484(15.09)		140(15.78)	143(16.12)	
Divorce	3824(23.00)	828(25.81)		176(19.84)	175(19.73)	
Histology			< 0.001			0.831
Adenocarcinoma	16626(100.00)	2760(86.03)		782(88.16)	777(87.60)	
Mucinous adenocarcinoma	0(0.00)	354(11.03)		84(9.47)	85(9.58)	
SRCC	0(0.00)	94(2.93)		21(2.37)	25(2.82)	
GH: Favorable histological features						
AH: Adverse histological features						
SRCC: signet ring cell carcinoma						

Characteristics	Entire cohort (n = 19834)		Propensity score-matched cohort (n = 1774)			
	FH, n (%)	AH, n (%)	P Value	Chemotherapy, n (%)	Non-chemotherapy, n (%)	P Value
Grade			< 0.001			0.148
Well	1330(8.00)	0(0.00)		0(0.00)	0(0.00)	
Moderate	15296(92.00)	0(0.00)		0(0.00)	0(0.00)	
Poor	0(0.00)	2912(90.77)		820(92.45)	803(90.53)	
Undifferentiated	0(0.00)	296(9.23)		67(7.55)	84(9.47)	
Tumor site			< 0.001			0.810
Right side colon	8081(48.60)	2145(66.86)		521(58.74)	516(58.17)	
Left side colon	8545(51.40)	1063(33.14)		366(41.26)	371(41.83)	
Tumor deposit						0.950
Negative	7067(42.50)	962(29.99)	< 0.001	329(37.10)	327(36.87)	
Positive	482(2.90)	129(4.02)		80(9.02)	81(9.13)	
Unknown	9077(54.60)	2117(65.99)		478(53.88)	479((54.00)	
Peritoneum invasion			< 0.001			0.894
Negative	7029(42.28)	1284(40.02)		350(39.46)	354(39.91)	
Positive	519(3.12)	141(4.40)		87(9.81)	85(9.58)	
Unknown	9078(54.60)	1783(55.58)		450(50.73)	448(50.51)	
Chemotherapy			< 0.001			-
Yes	3653(21.97)	887(27.65)		-	-	
No	12973(78.03)	2321(72.35)		-	-	
GH: Favorable histological features						
AH: Adverse histological features						
SRCC: signet ring cell carcinoma						

The Kaplan-Meier method was utilized to estimate and plot the survival curves. Survival differences were compared using the log-rank test. The primary endpoint of this study was the 5-year cancer-specific survival (CSS), which was measured from the date of diagnosis to the date of death due to cancer. Deaths from

causes other than cancer were treated as censored observations. Univariate and multivariate analyses were conducted using Cox proportional hazards regression models to identify factors that independently influenced CSS, both in the population with favorable histological features and in the population with adverse histological features. The Cox proportional hazards regression model was employed to perform multivariate analysis, utilizing a backward, stepwise variable elimination approach. Hazard ratios (HRs) were adjusted for the number of lymph nodes examined, age (either less than 70 or 70 and above), sex, race, marital status, tumour histology, grade, and tumour location. propensity score matching (PSM) analysis was performed to balance the differences for known potential baseline confounding variables in the populations with favorable or adverse histological features.

All statistical analyses were conducted using R version 3.6.2 software (<http://www.r-project.org/>) or STATA/SE 15. software (StataCorp LP, College Station, TX, USA). A two-sided P-value of less than 0.05 was considered to indicate statistical significance.

Results

Clinicopathological characteristics of the Study Population

In total, 19,834 eligible patients were enrolled in this study, with 16,626 (84.00%) exhibiting favorable histological features and 3,208 (16.00%) presenting with adverse histological features. The median duration of follow-up was 72. months, ranging from 15.0 to 168.0 months, and the median age was 65.0 years, with an age range of 20.0 to 80.0 years. Table 1 details the clinicopathological characteristics of the two groups.

Patients with adverse histological features were predominantly female, with a higher incidence in women (53.74%) compared to men (46.26%), a difference that was statistically significant ($P < 0.01$). The right side of the colon was more commonly affected in patients with adverse histological features, accounting for 66.86% of cases, compared to the left side colon, which affected 33.14% of these patients ($P < 0.01$). In fact, 22.89% of patients staged as T3N0M0 (AJCC stage II) received adjuvant chemotherapy, a treatment that was more frequently administered to patients with adverse histological features, with 27.65% of such patients receiving chemotherapy compared to 21.97% of those with good histological features ($P < 0.01$). No significant differences were observed in the characteristics of the 1,774 propensity score-matched (PSM) patients, as shown in Table 1.

Survival analysis of predictors of CSS of patients with T3N0M0 stage

Table 2 presents the findings of the univariate and multivariate analyses conducted to identify predictors of CSS among the study population with favorable histological features. In this group, the number of lymph nodes examined was significantly associated with improved survival, with each additional node examined correlating to a reduced hazard of death (hazard ratio [HR], 0.972; 95% confidence interval [CI], 0.966–0.977; $P < 0.001$). Conversely, increasing age was found to have a significant negative impact on survival (HR, 1.020; 95% CI, 1.013–1.027; $P < 0.001$). In patients with stage T3N0M0 colorectal cancer, histologic grade (favorable vs. adverse) was not independently associated with long-term oncologic outcomes (Fig. 2A). Conversely, and in contrast to the established survival advantage of left-sided primaries in metastatic disease, left-sided

tumor location was significantly associated with poorer cancer-specific survival (CSS) in this cohort (hazard ratio [HR], 1.136; 95% confidence interval [CI], 1.034–1.248; $P = 0.008$) (Fig. 2B). This adverse prognostic effect of left-sided location persisted among patients with favorable histology (Fig. 2C) but was abolished in those with adverse histology, in whom tumor location no longer influenced CSS (Fig. 2D).

Table 2
Univariate and Multivariate Analysis of Predictors of CSS of Patients in the Study Population with
Favorable Histological Features within the Surveillance, Epidemiology, and End Results (SEER)
Medicare-linked database

Risk Factors	Univariate analysis ^a			Multivariate analysis ^b		
	HR	HR (95%CI)	P Value	HR	HR (95%CI)	P Value
LN examined	0.966	0.961–0.971	< 0.001	0.972	0.966–0.977	< 0.001
Age(years)	1.026	1.022–1.031	< 0.001	1.020	1.013–1.027	< 0.001
Age70(years)						
<70	1	1		1	1	
≥ 70	1.664	1.520–1.822	< 0.001	1.221	1.061–1.405	0.005
Gender						
Female	1	1		1	1	
Male	1.154	1.055–1.262	0.002	1.261	1.149–1.383	< 0.001
Race						
White	1	1		1	1	
Black	1.339	1.189–1.509	< 0.001	1.356	1.201–1.532	< 0.001
Other	0.910	0.776–1.067	0.247	0.929	0.791–1.090	0.367
Marital status						
Married	1	1		1	1	
Single	1.488	1.322–1.674	< 0.001	1.593	1.412–1.798	< 0.001
Divorced	1.497	1.349–1.661	< 0.001	1.408	1.262–1.569	< 0.001
Grade						
Well differentiated	1	1		1	1	
Moderately differentiated	1.175	0.987–1.397	0.069	1.183	0.994–1.408	0.058
Tumor site						
Right side colon	1	1		1	1	
Left side colon	1.194	1.092–1.305	< 0.001	1.136	1.034–1.248	0.008
^a univariate and multivariate analyses were conducted using Cox regression model;						
HR, hazard ratio;						
LN examined: lymph nodes examined						
CSS: cancer-specific survival						

Risk Factors	Univariate analysis ^a			Multivariate analysis ^b		
	HR	HR (95%CI)	P Value	HR	HR (95%CI)	P Value
Chemotherapy						
NO	1	1		1	1	
YES	0.993	0.895–1.101	0.888	1.076	0.957–1.211	0.220
^a univariate and multivariate analyses were conducted using Cox regression model;						
HR, hazard ratio;						
LN examined: lymph nodes examined						
CSS: cancer-specific survival						

Figure 2. Cancer-specific survival in T3N0M0 colon cancer stratified by histological features and tumour location.

1. **(A)** CSS of patients with favourable (good differentiation, GD) versus adverse (poor differentiation, BD) histology.
2. **(B)** CSS comparison between right-sided and left-sided tumours regardless of histology.
3. **(C)** CSS in the GD subgroup further stratified by right- versus left-sided location.
4. **(D)** CSS in the BD subgroup further stratified by right- versus left-sided location.

P values were calculated using the log-rank test.

We further evaluated the therapeutic value of adjuvant chemotherapy in patients with colon cancer, stratified according to histologic grade. Eventually, adjuvant chemotherapy was not associated with a significant improvement in CSS in patients either with favourable (Fig. 3A) or adverse histology (Fig. 3B). To minimize the impact of confounding clinical factors, we further conducted propensity-score matching (PSM) analysis, which yielded consistent conclusions, as shown in **Fig. 3C,D**. To further elucidate the impact of tumor location and histologic grade on the efficacy of adjuvant chemotherapy, we conducted subgroup analyses stratified by these factors. In patients with right-sided colon cancer, adjuvant chemotherapy failed to demonstrate a significant overall survival benefit irrespective of favorable (Fig. 4A) or adverse (Fig. 4B) histologic grade. Consistently, in left-sided colon cancer, adjuvant chemotherapy was not associated with improved overall survival in either favorable or adverse histologic grade subgroups (Fig. 4C, **D**).

Figure 3. Effect of adjuvant chemotherapy on cancer-specific survival in T3N0M0 colon cancer.

1. **(A)** CSS of patients with favourable histology (GD) according to chemotherapy receipt.
2. **(B)** CSS of patients with adverse histology (BD) according to chemotherapy receipt.
3. **(C)** CSS of BD patients in the propensity-score-matched (PSM) cohort: chemotherapy versus no chemotherapy.
4. **(D)** CSS of GD patients in the PSM cohort: chemotherapy versus no chemotherapy.

P values were derived from the log-rank test.

Figure 4. Cancer-specific survival benefit of adjuvant chemotherapy in T3N0M0 colon cancer stratified by tumour location and histology.

1. **(A)** CSS of right-sided tumours with favourable histology (GD): chemotherapy versus no chemotherapy.
2. **(B)** CSS of right-sided tumours with adverse histology (BD): chemotherapy versus no chemotherapy.
3. **(C)** CSS of left-sided tumours with favourable histology (GD): chemotherapy versus no chemotherapy.
4. **(D)** CSS of left-sided tumours with adverse histology (BD): chemotherapy versus no chemotherapy.

All comparisons were evaluated with the log-rank test.

Survival analysis of predictors of CSS of patients with adverse histological features

Table 3 illustrates the results of the univariate and multivariate analyses aimed at determining predictors of CSS in patients with adverse histological features. For this cohort, the number of lymph nodes resected for examination continued to be a significant predictor of improved survival (HR, 0.958; 95% CI, 0.947–0.970; $P < 0.001$). Nevertheless, age significantly affects survival for this group in an adverse way (HR, 1.488; 95% CI, 1.087–2.036; $P = 0.013$). Neither mucinous adenocarcinoma nor signet ring cell carcinoma had a significant impact on survival when compared to adenocarcinoma, with mucinous adenocarcinoma showing a borderline non-significant trend (HR, 0.699; 95% CI, 0.488–1.002; $P = 0.051$) and signet ring cell carcinoma not reaching statistical significance (HR, 0.750; 95% CI, 0.386–1.459; $P = 0.397$). The tumour site was not found to influence survival (HR, 1.007; 95% CI, 0.806–1.257; $P = 0.953$).

Table 3

Univariate and Multivariate Analysis of Predictors of CSS In the Study Population with Adverse Histological Features within the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database

Risk Factors	Univariate analysis ^a			Multivariate analysis ^b		
	HR	HR (95%CI)	P Value	HR	HR (95%CI)	P Value
LN examined	0.951	0.940–0.963	< 0.001	0.958	0.947–0.970	< 0.001
Age(years)	1.026	1.016–1.036	< 0.001	1.012	0.997–1.028	0.117
Age70(years)					-	
<70	1	1			-	
≥ 70	1.784	1.463–2.176	< 0.001	1.488	1.087–2.036	0.013
Gender		-			-	
Female		-			-	
Male	1.458	1.195–1.779	< 0.001	1.630	1.322–2.010	< 0.001
Race		-			-	
White		-			-	
Black	1.670	1.245–2.239	0.001	1.739	1.286–2.351	< 0.001
Other	0.793	0.523–1.201	0.273	0.802	0.528–1.219	0.302
Marital status		-			-	
Married		-			-	
Single	1.321	1.000-1.744	0.050	1.410	1.058–1.878	0.019
Divorced	1.357	1.081–1.703	0.009	1.306	1.027–1.661	0.029
Histology		-			-	
Adenocarcinoma		-			-	
Mucinous adenocarcinoma	0.712	0.498–1.017	0.062	0.699	0.488–1.002	0.051
SRCC	0.749	0.386–1.451	0.392	0.750	0.386–1.459	0.397
Grade		-			-	
^a univariate and multivariate analyses were conducted using Cox regression model;						
HR, hazard ratio;						
LN examined: lymph nodes examined						
SRCC: signet ring cell carcinoma						
CSS: cancer-specific survival						

Risk Factors	Univariate analysis ^a			Multivariate analysis ^b		
	HR	HR (95%CI)	P Value	HR	HR (95%CI)	P Value
Poor		-			-	
undifferentiated	0.745	0.496–1.117	0.154	0.819	0.545–1.230	0.336
Tumor site		-			-	
Right side colon		-			-	
Left side colon	1.194	0.973–1.465	0.090	1.007	0.806–1.257	0.953
Chemotherapy		-			-	
NO		-			-	
YES	0.930	0.747–1.159	0.520	0.995	0.777–1.274	0.967
^a univariate and multivariate analyses were conducted using Cox regression model;						
HR, hazard ratio;						
LN examined: lymph nodes examined						
SRCC: signet ring cell carcinoma						
CSS: cancer-specific survival						

To identify patients with T3N0M0 tumors and adverse histology who might derive benefit from adjuvant chemotherapy, we expanded the multivariable model to include age and sex—both previously validated as independent prognostic factors in this cohort. Consequently, patients with T3N0M0 tumors exhibiting adverse histologic features were stratified into four mutually exclusive subgroups: (1) women aged ≥ 70 years, (2) men aged ≥ 70 years, (3) men < 70 years, and (4) women < 70 years. In women aged ≥ 70 years (group 1), adjuvant chemotherapy was associated with a significant improvement in **CSS** ($P = 0.019$, **Fig. 5A**). The remaining 3 groups did not obtain any benefit from adjuvant chemotherapy ($P > 0.05$), as shown in **Fig. 5B,C,D**.

Figure 5. Cancer-specific survival (CSS) benefit of adjuvant chemotherapy in T3N0M0 colon cancer patients with adverse histology, stratified by age and gender.

1. **(A)** CSS of female patients ≥ 70 years with adverse histology: chemotherapy versus no chemotherapy.
2. **(B)** CSS of male patients ≥ 70 years with adverse histology: chemotherapy versus no chemotherapy.
3. **(C)** CSS of male patients < 70 years with favourable histology: chemotherapy versus no chemotherapy.
4. **(D)** CSS of female patients < 70 years with favourable histology: chemotherapy versus no chemotherapy.

All P values were calculated using the log-rank test.

Discussion

In the current study, we conducted a propensity score matching (PSM) analysis using population-level data to investigate the survival benefits of chemotherapy for stage II colorectal cancer (CRC). Our research yielded three principal findings: Firstly, we discovered that adverse histological features of colonic cancer did not significantly impact the survival rates of patients with T3N0M0 staging. Secondly, adjuvant chemotherapy appeared to offer no survival advantage for patients with adverse histological features at T3N0M0 staging, suggesting that the considerable toxicity of chemotherapy may warrant its omission in such cases with adverse histological characteristics alone. Thirdly, female patients at least 70 years old with adverse histological characteristics could derive advantage from adjuvant chemotherapy with a significant rise in CSS, indicating that this subgroup might be the potential population that benefits from adjuvant chemotherapy, which necessitates further confirmation.

The treatment of rectal cancer is often paralleled with that of colonic cancer; however, these two conditions frequently present distinct characteristics, such as different lymphatic drainage pathways, molecular subtypes, and the use of radiotherapy. To reduce bias, only colonic cancer was included in the current study. Additionally, we employed PSM to mitigate the disparities in baseline characteristics between patients with adverse histological features who received chemotherapy and those who did not. PSM is a technique that enhances group comparability, as evidenced by the well-balanced demographics and clinicopathological features presented in Table 1. Both lymphovascular invasion and perineural invasion are recognized as adverse prognostic factors, and their distribution was effectively balanced through the PSM method, thereby minimizing confounding effects. It is important to note that specific data on these histological features were only accessible from the SEER database starting from the year 2010.

Common adenocarcinoma (AC) constitutes the majority of colonic cancer cases, with mucinous adenocarcinoma (MC) affecting 10–15% of patients and signet ring cell carcinoma (SRCC) accounting for approximately 1% of colorectal cancer (CRC) patients[9]. Although SRCC is rare, it is associated with a poorer prognosis compared to AC[10, 11]. The five-year relative survival rate for SRCC in stage II colonic cancer patients was 67.9%, compared to 77.% for AC; in stage II rectal cancer patients, the five-year relative survival rate for SRCC was 27.4%, compared to 67.1% for AC[12]. This highlights the significant impact of tumour location on survival, mirroring our findings that left-sided colonic cancer is associated with poorer survival in patients with favorable histological features, contrasting the widely accepted notion that right-sided colonic cancer has a poorer prognosis in metastatic CRC. In line with SRCC, mucinous colorectal adenocarcinomas typically exhibit poorer responses to chemotherapy[13, 14], leading to a poor prognosis in advanced stages[14, 15]. Patients with either MC or SRCC are more prone to develop metastatic disease, often manifesting as peritoneal metastases and lymphatic spread, whereas AC primarily metastasizes to the liver[13, 16], which may partially explain the poor prognosis of MC and SRCC. Standard treatments for colorectal adenocarcinoma are also recommended for MC and SRCC patients, as no specific clinical guidelines have been developed for these patient groups[17]. Due to their low incidence, SRCC and MC have not been extensively studied in stage II colonic cancer patients, and literature on these conditions is scarce. In this study, poorly differentiated histology, typically considered an adverse prognostic factor, was combined with MC and SRCC to assess the benefits of adjuvant chemotherapy in stage II colonic cancer excluding T4. In our study population, 22.89% of patients staged as T3N0M0 received adjuvant chemotherapy, which was more frequently administered to patients with adverse histological features (27.65% for adverse histological features versus 21.97% for good histological features, $P < 0.01$). This type of adverse histological feature is

therefore accepted by clinicians to evaluate the need for chemotherapy. However, in the current study, adjuvant chemotherapy was not beneficial for patients with adverse histological features alone, which are currently considered high risk, suggesting that adverse histological features alone are not sufficient for the decision to administer adjuvant chemotherapy in T3N0M0 patients.

Despite the fact that inspiring therapeutic advancements have led to a 3% annual increase in survival rates over the past decade[18, 19], colorectal cancer (CRC) remains the third leading cause of cancer-related deaths worldwide[20]. Approximately 25% of stage II patients experience recurrence even after undergoing radical surgery[21]. Surgery is the primary treatment for CRC, with adjuvant chemotherapy widely recognized as an effective treatment for stage III CRC, based on the consensus that the pathologic stage is the most significant prognostic factor for colorectal cancer[20, 22]. However, despite the recommendations of the National Comprehensive Cancer Network (NCCN) guidelines, the benefits of adjuvant chemotherapy for stage II CRC remain a contentious issue[4]. It is believed that only a subset of stage II CRC patients would benefit from adjuvant therapy[23, 24]. Several stage-specific factors in stage II CRC, such as T4 lesions, positive margins, poorly differentiated histology, and inadequate lymph node sampling[4, 5], which are indicative of high-risk stage II CRC, offer prognostic value. The 5-year disease-free survival rate is over 90% for patients without any risk factors, compared to 84.8% for those with one or more risk factors[25, 26]. Since 2004, adjuvant chemotherapy has been administered for high-risk stage II CRC or later stages[26], yet there is a lack of robust scientific data to confirm the efficacy of biomarkers in selecting appropriate patient candidates. Pathologic T4 stage has been identified as a significant predictor of poor disease-free survival (DFS)[27], and there is only a non-significant trend suggesting a benefit from chemotherapy for stage II patients without precise selection[24]. Neither the IMPACT trial nor the NSABP trial demonstrated an improvement in survival for stage II CRC patients receiving adjuvant chemotherapy[2]. Therefore, making an accurate decision about whether a stage II CRC patient should receive adjuvant chemotherapy is crucial for improving individual prognoses. We conclude that adjuvant chemotherapy may not improve survival even in patients with adverse histological features and T3N0M0 staging, with the exception for female patients at least 70 years old. It may be reasonable to consider omitting chemotherapy for these patients if the presence of adverse histological features is the sole consideration, and more precise indicators are necessary for the selection of patients who would benefit from such treatment.

One should keep in mind that in older patients, treatment decisions should factor in recurrence rates and tolerability, as well as functional prognosis, residual disease, and social factors[28]. Due to the fact that elderly patients are usually excluded from clinical trials for cancer, there is a lack of efficacy data and clear criteria to guide treatment strategy[29]. A retrospective cohort analysis which was comprised of 151 patients aged 75 years and older with stage II–III colorectal cancer revealed that adjuvant chemotherapy was not associated with 3-year RFS[29]. Its conclusion was inconsistent with ours, and the possible reason might be the short follow-up time and the lack of analysis on overall survival. Moreover, it failed to incorporate gender into the analysis, and this might be another source of disparity. It was held that over the years, the improved prognosis of patients with stage II disease stemmed from more refined staging, enhanced surgery and other mitigating factors, and the older the patients were, the less likely they were to embrace adjuvant chemotherapy[30]. Older colon cancer patients was less likely to receive adjuvant chemotherapy due to concerns that there is a paucity of data regarding the safety and efficacy for patients over 65 years old. However, pooled analysis of several major trials including NSABP C-08, XELOXA, X-ACT and AVANT did find

that DFS were improved with adjuvant chemotherapy for those that would be eligible for clinical trial due to the elder age, with a statistically significant in patients 70 or older[31]. Our data demonstrated that, for patients of T3N0M0 colonic carcinoma with adverse histological features, female patients at least 70 years old were the one who could derive benefit from adjuvant chemotherapy.

In recent times, numerous studies have been conducted to pinpoint the subset of colorectal cancer (CRC) patients with AJCC stage II who may benefit from chemotherapy. Tumour heterogeneity, encompassing mutations in KRAS[24, 32], BRAF, PTEN, or the status of microsatellite instability[33], as well as tumour metabolic markers such as NKX6.1 methylation[23], MMP77[34], and AQP1[35], have been correlated with the response to targeted therapy or chemotherapy in metastatic CRCs. However, their predictive utility for stage II CRCs remains uncertain. The HER2 status emerges as a significant predictive biomarker, particularly for patients with proficient mismatch repair (pMMR), as HER2-positive patients may derive benefit from 5-fluorouracil-based adjuvant chemotherapy[36]. Additionally, low expression of the PD-L1 gene has been linked to improved outcomes with adjuvant chemotherapy[37]. Despite these findings, there is a regrettable lack of sufficient and reliable biomarkers to identify patients with stage II colon cancer who would be appropriate candidates for adjuvant chemotherapy. The future may hold promise for personalized intertumoural and genomic biomarkers to replace traditional clinicopathological indicators.

The current study encountered several limitations: Firstly, as a retrospective analysis, it was inherently susceptible to various biases, although we have employed the Propensity Score Matching (PSM) method to minimize bias as much as possible. Secondly, the stringent selection criteria resulted in the inclusion of only 887 patients with adverse histological features at T3N0M0 stage who received adjuvant chemotherapy, potentially affecting the study's statistical power. Thirdly, the current SEER database's limitations in providing comprehensive patient data, such as genetic markers and disease-free survival (DFS), precluded a thorough investigation into the impact of adverse histological features and other genomic biomarkers on DFS or cancer-specific survival (CSS). Therefore, the development of additional chemotherapeutic regimens is imperative to enhance survival in this subset of stage II CRC patients, and the identification of more robust genomic biomarkers is essential to establish suitable selection criteria.

The strengths of our study are as follows: The use of a large-scale sample and propensity score matching (PSM) method helped to minimize potential biases and enhance the study's power. The focused analysis on the high-risk stratification of stage II CRCs and the exclusive consideration of adverse histological features represents another advantage. The SEER database's capacity to accurately identify patients with distinct histological features based on clear histological and grading criteria helps to avoid confusion in differentiation assessments. We have innovatively integrated tumour histology and grade to strengthen the persuasiveness of our findings. Furthermore, by employing a highly selective cohort with strict criteria for radical resection, we have mitigated the potential biases associated with surgical procedures.

Conclusion

Based on our analysis of the SEER database, we have discovered that adverse histological features alone do not influence survival in patients with T3N0M0 staging, and adjuvant chemotherapy merely enhance survival for these female patients at least 70 years old. This suggests that the presence of adverse histological

features alone is not sufficient to guide the decision for adjuvant chemotherapy, diverging from the current guideline recommendations.

Declarations

Authorship and Contributions:

Design and drafting the manuscript: Qinghua Wang, Xiaoxiao Chen. Acquisition of data, collection and review of the literatures: Hongjuan Zheng, Xia Zhang. Critical revision of the manuscript for important content: Jianfei Fu.

Conflicts of interest

The authors have declared that no competing interest exists.

Compliance with ethical standards

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments (available at <https://www.wma.net/policies-post/wma-declaration-of-helsinki/>). All data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database of the United States National Cancer Institute in strict accordance with the SEER Data-Use Agreement. Only de-identified, publicly available datasets were analyzed, and all findings are intended exclusively for academic research purposes.

Clinical trial number: not applicable

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Ethics approval and consent to participate

The study was approved by the institutional review board and ethics committee of Jinhua Central Hospital. All individual records were anonymous and de-identified prior to analysis.

Competing Interests

The authors have declared that no competing interest exists.

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Data Availability

The data that support the findings of this study are available from the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute (<https://seer.cancer.gov/>). Access to SEER data is subject to a signed SEER Data-Use Agreement; therefore, the authors will share any additional analyses or derived variables used in this manuscript upon reasonable request to the corresponding author, provided that the requestor complies with the SEER data-use terms.

Consent to publish

The authors confirm that all participants involved in this study have given written informed consent for the publication of the data and images contained in this manuscript.

Ethics approval and consent to participate

Not applicable

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Figures

Inclusion and exclusion criteria in SEER

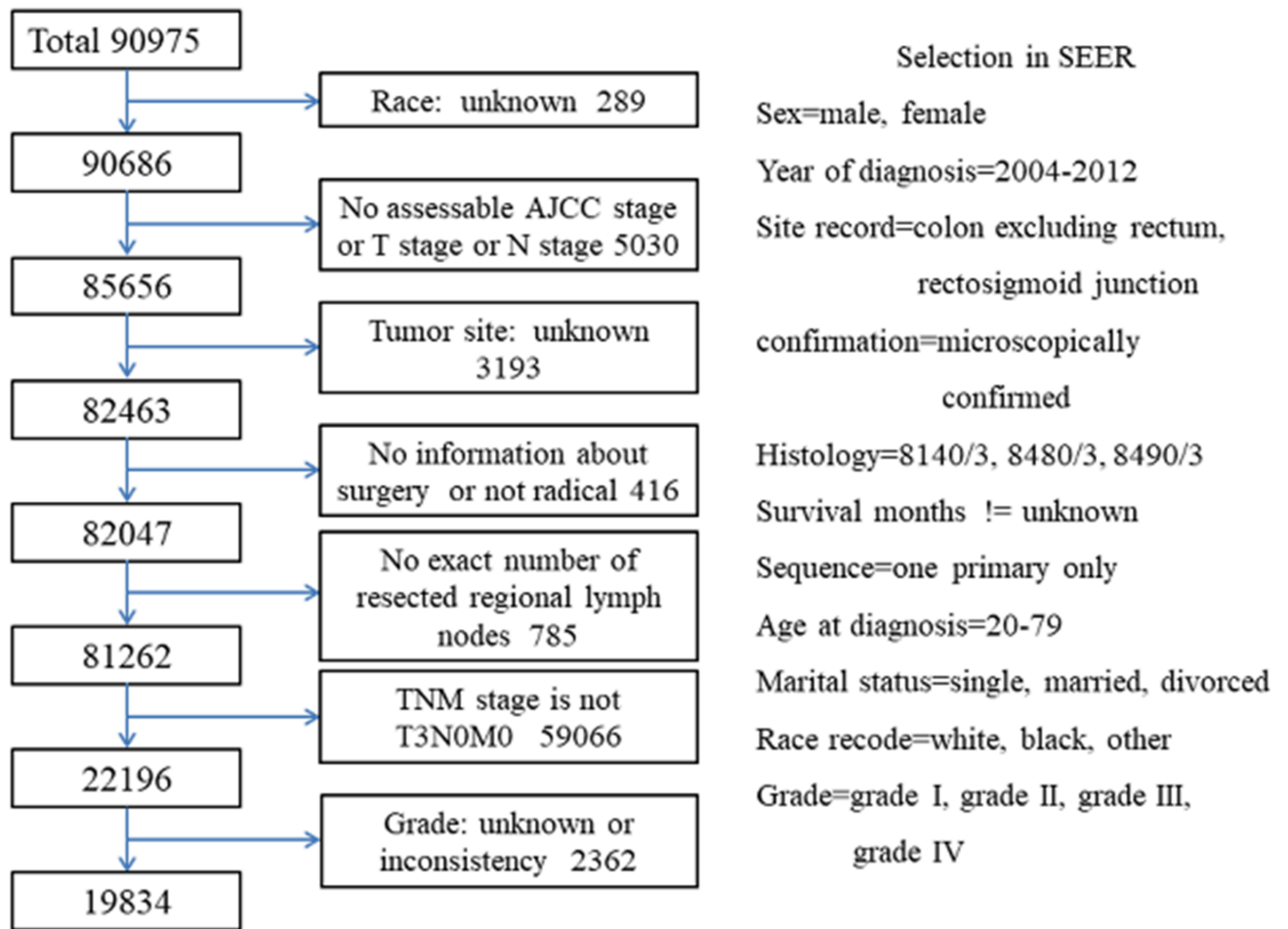


Figure 1

The inclusion and exclusion criteria in seer.

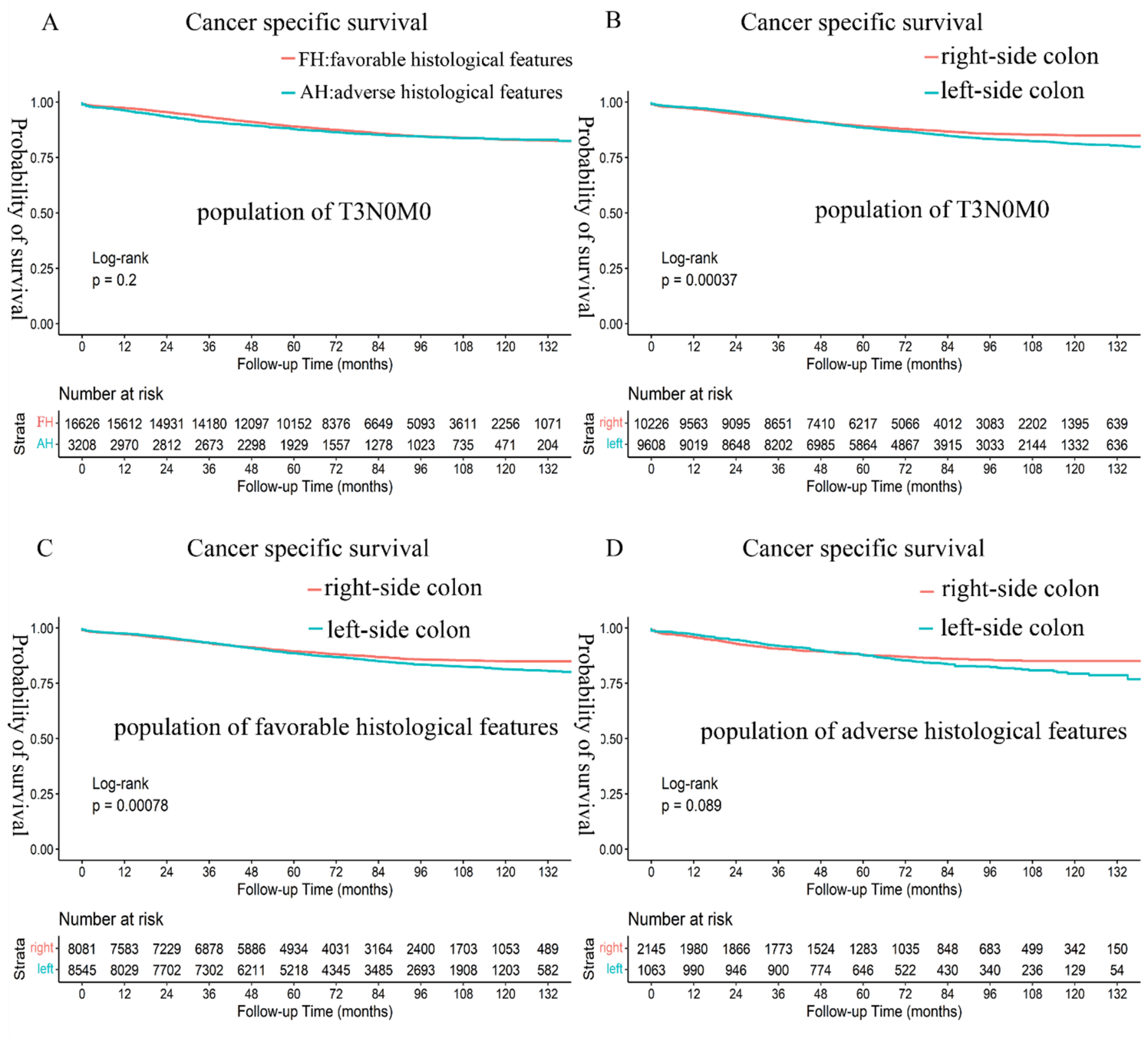


Figure 2

Cancer-specific survival in T3N0M0 colon cancer stratified by histological features and tumour location.

(A) CSS of patients with favourable (good differentiation, GD) versus adverse (poor differentiation, BD) histology.

(B) CSS comparison between right-sided and left-sided tumours regardless of histology.

(C) CSS in the GD subgroup further stratified by right- versus left-sided location.

(D) CSS in the BD subgroup further stratified by right- versus left-sided location.

P values were calculated using the log-rank test.

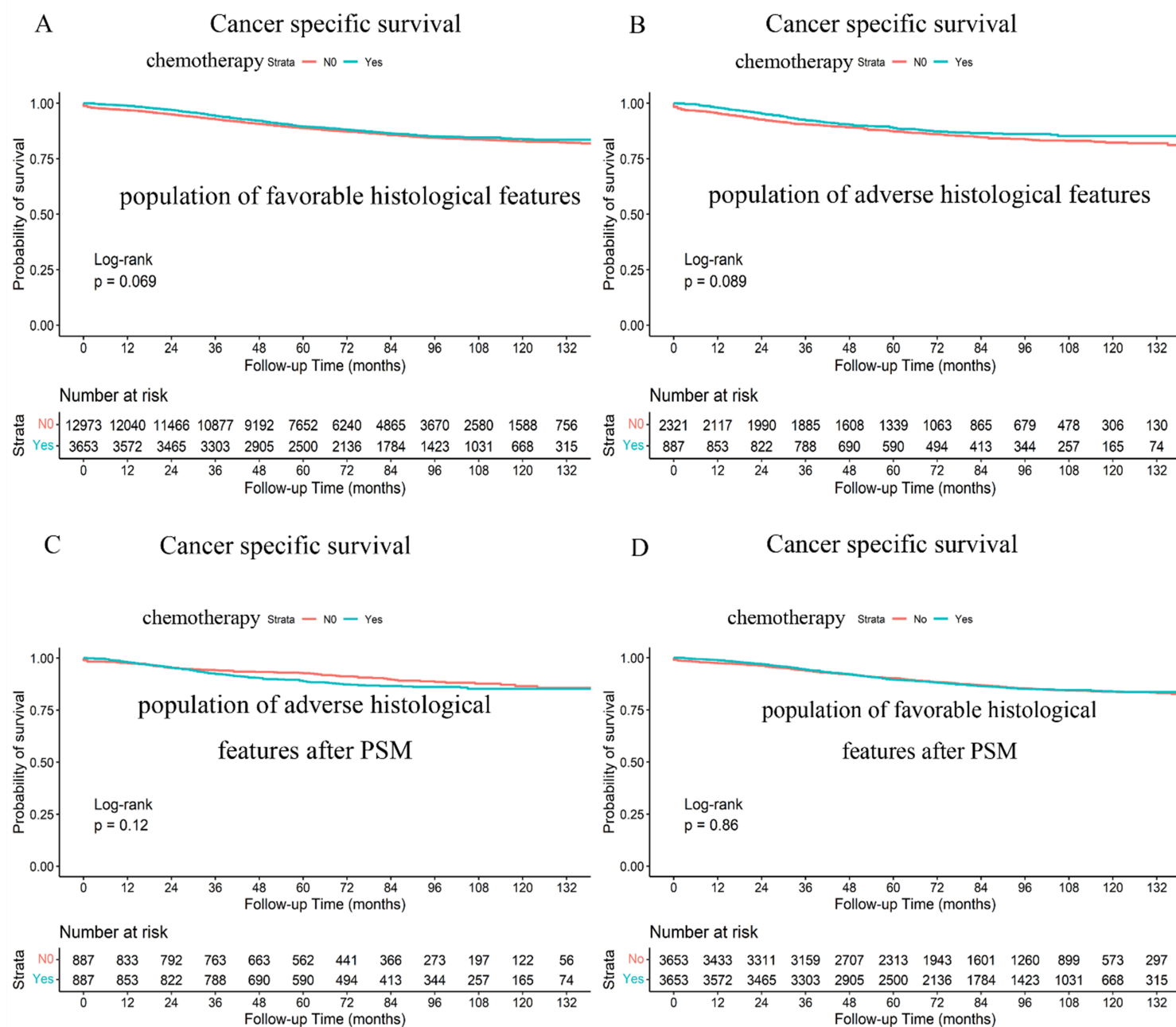


Figure 3

Effect of adjuvant chemotherapy on cancer-specific survival in T3N0M0 colon cancer.

(A) CSS of patients with favourable histology (GD) according to chemotherapy receipt.

(B) CSS of patients with adverse histology (BD) according to chemotherapy receipt.

(C) CSS of BD patients in the propensity-score-matched (PSM) cohort: chemotherapy versus no chemotherapy.

(D) CSS of GD patients in the PSM cohort: chemotherapy versus no chemotherapy.

P values were derived from the log-rank test.

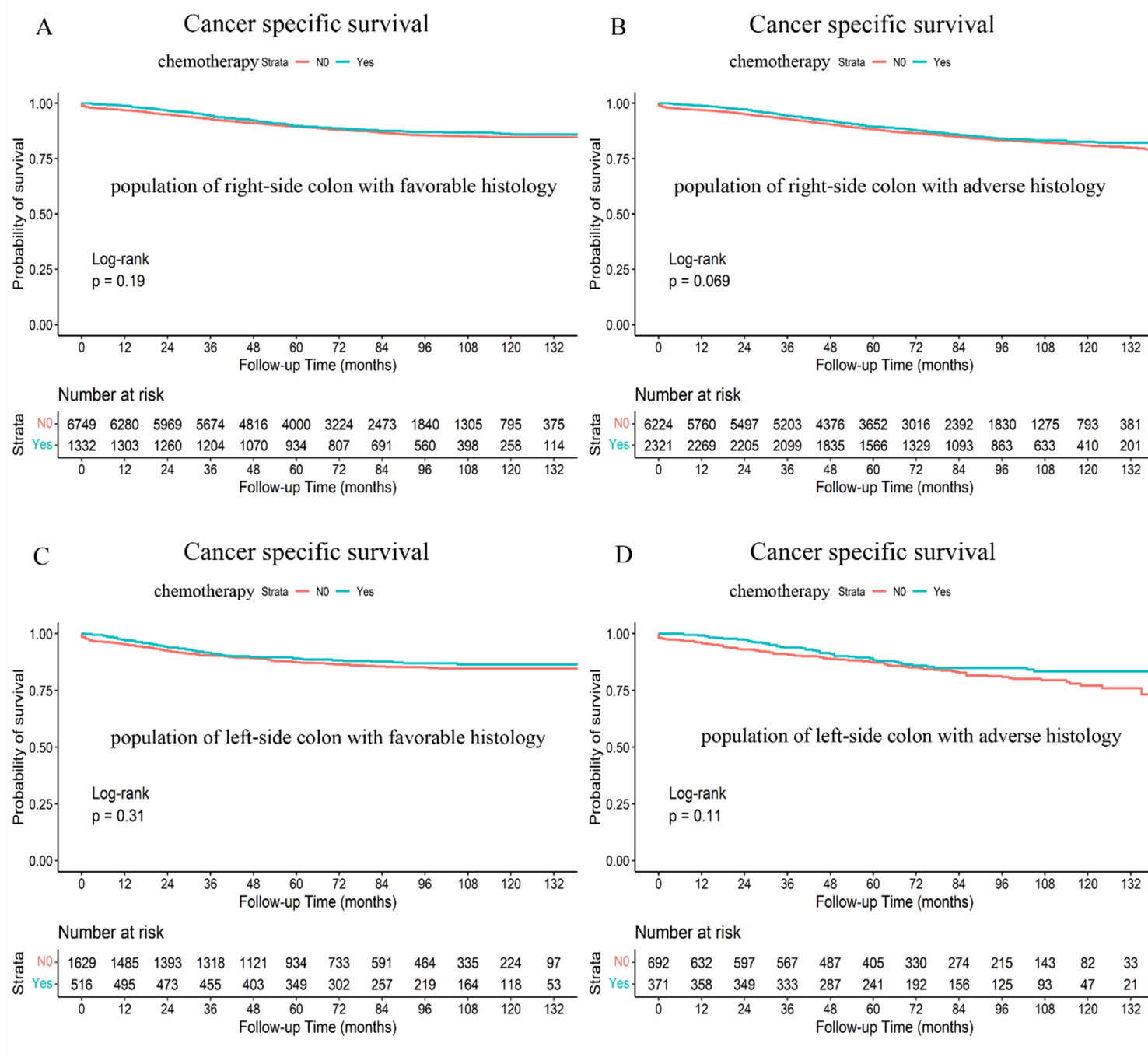


Figure 4

Cancer-specific survival benefit of adjuvant chemotherapy in T3N0M0 colon cancer stratified by tumour location and histology.

(A) CSS of right-sided tumours with favourable histology (GD): chemotherapy versus no chemotherapy.

(B) CSS of right-sided tumours with adverse histology (BD): chemotherapy versus no chemotherapy.

(C) CSS of left-sided tumours with favourable histology (GD): chemotherapy versus no chemotherapy.

(D) CSS of left-sided tumours with adverse histology (BD): chemotherapy versus no chemotherapy.

All comparisons were evaluated with the log-rank test.

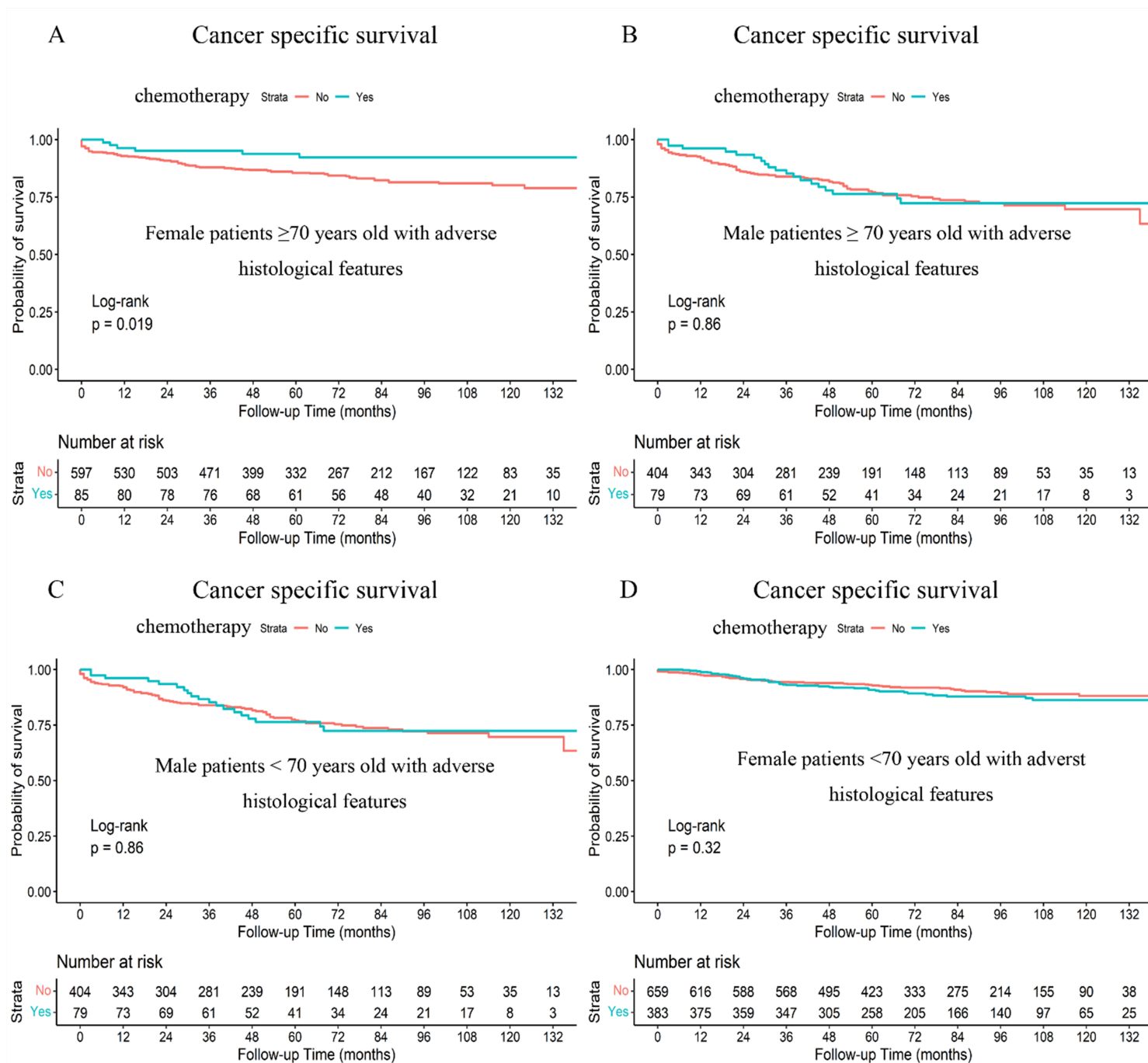


Figure 5

Cancer-specific survival (CSS) benefit of adjuvant chemotherapy in T3N0M0 colon cancer patients with adverse histology, stratified by age and gender.

(A) CSS of female patients ≥ 70 years with adverse histology: chemotherapy versus no chemotherapy.

(B) CSS of male patients ≥ 70 years with adverse histology: chemotherapy versus no chemotherapy.

(C) CSS of male patients < 70 years with favourable histology: chemotherapy versus no chemotherapy.

(D) CSS of female patients < 70 years with favourable histology: chemotherapy versus no chemotherapy.

All P values were calculated using the log-rank test.

Supplementary Files

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