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Retrospective Cohort Study

Comparison of the eighth version of the American Joint Committee on Cancer manual to the seventh version for colorectal cancer: A retrospective review of our data

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Abstract

AIM

To analyze the survival trends in colorectal cancer (CRC) based on the different classifications recommended by the seventh and eighth editions of the American Joint Committee on Cancer staging system (AJCC-7th and AJCC-8th).

METHODS

The database from our institution was queried to identify patients with pathologically confirmed stage 0-IV CRC diagnosed between 2006 and 2012. Data from 2080 cases were collected and 1090 cases were evaluated through standardized inclusion and exclusion criteria. CRC was staged by AJCC-7th and then restaged by AJCC-8th. Five-year disease-free survival (DFS) and overall survival (OS) were compared. SPSS 21.0 software was used for all data. DFS and OS were compared and analyzed by Kaplan-Meier and Log-rank test.

RESULTS

Linear regression and automatic linear regression showed lymph node positive functional equations by tumor-node-metastasis staging from AJCC-7th and tumor-node-metastasis staging from AJCC-8th. Neurological

invasion, venous infiltration, lymphatic infiltration, and tumor deposition put forward stricter requirements for pathological examination in AJCC-8th compared to AJCC-7th. After re-analyzing our cohort with AJCC-8th, the percentage of stage IVB cases decreased from 2.8% to 0.8%. As a result 2% of the cases were classified under the new IVC staging. DFS and OS was significantly shorter ($P = 0.012$) in stage IVC patients compared to stage IVB patients.

CONCLUSION

The addition of stage IVC in AJCC-8th has shown that peritoneal metastasis has a worse prognosis than distant organ metastasis in our institution's CRC cohort. Additional datasets should be analyzed to confirm these findings.

Key words: Colorectal cancer; Tumor-node-metastasis staging; Prognosis; Peritoneal metastasis; Disease-free survival

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Core tip: Since the promulgation of the eighth edition of the American Joint Committee on Cancer staging system manual (AJCC-8th), it has attracted the attention of many clinicians around the world and guided clinical work. Using our institution data we explored the prognostic differences between AJCC-8th and the seventh edition of the AJCC manual (AJCC-7th) for colorectal cancer. We found that patients with stage IV C colorectal cancer have a worse prognosis. This shows that peritoneal metastasis has a worse prognosis than organ metastasis. Considering many prognostic factors, individualized treatment is particularly important to improve the survival time of stage IV patients, especially stage IVC patients.

Tong GJ, Zhang GY, Liu J, Zheng ZZ, Chen Y, Niu PP, Xu XT. Comparison of the eighth version of the American Joint Committee on Cancer manual to the seventh version for colorectal cancer: A retrospective review of our data. *World J Clin Oncol* 2018; 9(7): 148-161 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v9/i7/148.htm> DOI: <http://dx.doi.org/10.5306/wjco.v9.i7.148>

INTRODUCTION

Colorectal cancer (CRC) is a common malignant tumor^[1-2]. In 2016, the incidence and mortality in the United States were respectively ranked fourth and second^[3-7]. In 2015, 376000 patients were newly diagnosed with CRC in China and 191000 patients died from the disease^[8]. Surgical resection remains the mainstay of treatment for local and regional disease^[9-14]. Adjuvant chemotherapy is frequently used in advanced colon cancer and CRC, but remains controversial for

stage II disease^[15-21]. Understanding the pathologic staging in conjunction with prognostic values is essential to making therapeutic decisions. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging model has provided this universal modality since its first edition in 1977^[22]. Since then, the AJCC has repeatedly revised this guideline (Figure 1) to continuously guide clinical treatment.

The eighth edition of the AJCC staging system (AJCC-8th) was released on October 6, 2016 in Chicago, IL, United States, and was implemented globally on January 1, 2018, which included significant changes for CRC patients with stage IV disease^[23]. The Cancer Council under the American College of Surgeons required the use of the AJCC-8th staging system as the "primary language" for cancer reporting. In 2013, AJCC established the "Evidence-Based Medicine and Statistics Core Group" of the 8th edition of the staging system. The organization is composed of clinical physicians, statisticians, and methodologists. It is responsible for determining the level of evidence for any updated content of the AJCC staging system.

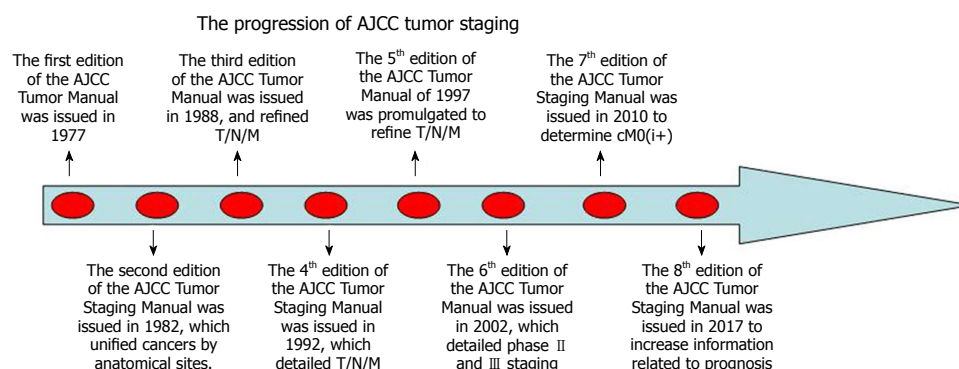
The level of evidence is divided into four levels, and the quality of evidence represented by it gradually decreases from level I to level IV. Level I requires that the evidence is from multiple large national or international studies, has consistent results, has good research requirement design and implementation, was conducted in appropriate patient populations with appropriate study endpoints and appropriate treatment options, either as prospective studies or review-based studies based on patient populations, but all studies must be methodologically assessed. Level II requires that the evidence comes from at least one large study and had good design and implementation, was conducted in a suitable patient population with a suitable study endpoint, and has external reliability (generally the representative and extrapolated capabilities of the study are better). Level III includes evidence from a study with certain flaws, defects in the number of possible subjects, size, or quality of the study, or the consistency of multiple findings, the appropriateness of the patient population, and the appropriateness of the results. Level IV includes evidence wherein no reasonable research had been done. Only evidence from levels I - III could be included in the 8th version of the staging system.

A major difference between AJCC-7th, and AJCC-8th is that the CRC staging system was revised to include a new stage involving peritoneal metastasis (named stage IVC) (see Tables 1 and 2 for details). Based on a variety of evidence-based medical evidence^[24,25], the AJCC-8th CRC staging system continues to recommend vascular lymphatic vessel infiltration and tumor deposition as prognostic level information, while microsatellite instability status and *BRAF* gene status are used as prognostic factors, and *BRAF*, *KRAS*, and degeneration of the *NRAS* gene were used as a predictor of efficacy (Table 3)^[26].

The increased complexity of the AJCC-8th staging

Table 1 Comparison of the tumor-node-metastasis stages between the 7th edition and the 8th edition

7 th edition	8 th edition
Tx: Primary tumor cannot be assessed	Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor	T0: No evidence of primary tumor
Tis: Carcinoma <i>in situ</i> , limited to intraepithelial or invasive lamina propria	Tis: Carcinoma <i>in situ</i> , limited to intraepithelial or invasive lamina propria
T1: Tumor invading submucosa	T1: Tumor invading submucosa
T2: Tumor invading the muscularis propria	T2: Tumor invading the muscularis propria
T3: Tumor penetrating the muscularis propria and arriving at colorectal fat tissue	T3: Tumor penetrating the muscularis propria and arriving at colorectal fat tissue
T4: Tumor directly invading other organs or structures	T4: Tumor directly invading other organs or structures
T4a: Tumor penetrating visceral peritoneum	T4a: Tumor penetrating visceral peritoneum
T4b: Tumor directly invading or adhering to other organs or structures	T4b: Tumor directly invading or adhering to other organs or structures
Nx: Regional lymph nodes cannot be assessed	Nx: Regional lymph nodes cannot be assessed
N0: No lymph node metastasis and no tumor deposits (TD)	N0: No lymph node metastasis and no TD
N1: 1-3 lymph nodes metastases	N1: 1-3 lymph nodes metastases
N1a: 1 lymph node metastases	N1a: 1 lymph node metastases
N1b: 2-3 lymph nodes metastases	N1b: 2-3 lymph nodes metastases
N1c: Although there was no regional lymph node metastasis, TDs were submucosal, mesangial, or peritoneum-covered para-colorectal tissue.	N1c: Although there was no regional lymph node metastasis, TDs were submucosal, mesangial or peritoneum-covered para-colorectal tissue.
N2: More than or equal to 4 lymph node metastases	N2: More than or equal to 4 lymph node metastases
N2a: 4-6 regional lymph node metastases	N2a: 4-6 regional lymph node metastases
N2b: More than or equal to 7 lymph node metastases	N2b: More than or equal to 7 lymph node metastases
M1: There is distant lymph node metastasis	M1: There is distant lymph node metastasis
M1a: Metastasis is limited to one organ or site (<i>e.g.</i> , liver, lung, ovary, and extra-regional lymph node metastases)	M1a: Metastasis is limited to one organ or site (<i>e.g.</i> , liver, lung, ovary, and extra-regional lymph node metastases)
M1b: Transfer more than one organ or site, or to the peritoneum ¹	M1b: Transfer more than one organ or site ¹
	M1c: Peritoneal metastases with or without metastasis of other organs ¹

¹Differences between the two versions.**Figure 1** The progression of American Joint Committee on Cancer tumor staging. AJCC: American Joint Committee on Cancer.

model was intended to improve the prognostic staging of CRC, but the impact of these changes remains unclear. In this study, we used data from our institutional registries to compare the prognostic accuracy of criteria from AJCC-7th and AJCC-8th in patients with stage 0-IV through survival models. We also explored the relationship between positive node and tumor size, differentiation, tumor invasion, chemotherapy, tumor-node-metastasis (TNM) staging from AJCC-7th, and TNM staging from AJCC-8th. In addition, we also discussed the pathological importance of lymph invasion, vein invasion, and nerve invasion according to AJCC-8th.

MATERIALS AND METHODS

Patients

A total of 2080 patients with pathologically confirmed

stage 0-IV CRC between 2006 and 2012 were collected from our institutional database. Then the following inclusion and exclusion criteria were applied to this cohort: (1) on the basis of a colonoscopy, computed tomography, pathological diagnosis of CRC, in or outside the hospital diagnosis in our hospital; (2) patients undergoing colorectal surgery in our hospital (including radical surgery and non-radical surgery); (3) diagnosis as a recurrence of the primary tumor or as a result of the death of the primary tumor; (4) cases with complete and detailed clinical and pathological data; and (5) cases with complete follow-up data and accurate data. Exclusion criteria were: (1) a serious heart, brain, liver, or lung disease led to intolerant surgery; (2) the non-CRC factors that led to the death of the pathological interstitial tumor, neuronal tumor, lymphoma, melanoma and other non-adenocarcinoma in addition to other malignant tumors;

Table 2 Colorectal cancer tumor-node-metastasis staging American Joint Committee on Cancer 7th and 8th editions

7 th edition				8 th edition			
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I	T1-2	N0	M0	I	T1-2	N0	M0
II A	T3	N0	M0	II A	T3	N0	M0
II B	T4a	N0	M0	II B	T4a	N0	M0
II C	T4b	N0	M0	II C	T4b	N0	M0
III A	T1-2	N1/N1c	M0	III A	T1-2	N1/N1c	M0
	T1	N2a	M0		T1	N2a	M0
III B	T3-4a	N1/N1c	M0	III B	T3-4a	N1/N1c	M0
	T2-3	N2a	M0		T2-3	N2a	M0
	T1-2	N2b	M0		T1-2	N2b	M0
III C	T4a	N2a	M0	III C	T4a	N2a	M0
	T3-4a	N2b	M0		T3-4a	N2b	M0
	T4b	N1-2	M0		T4b	N1-2	M0
IVA	Any T	Any N	M1a	IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b	IVB	Any T	Any N	M1b
				IVC	Any T	Any N	M1c

Table 3 American Joint Committee on Cancer 8th edition updates for the colorectal cancer staging system

Update points	Update details	Level of evidence
Definition of distant transfer (M)	Introduction of M1c, specifically peritoneal metastasis, is an indicator of poor prognosis	I
Definition of regional lymph nodes (N)	Further introduce the definition of tumor deposit	II
Recommended additional indicators for guiding clinical practice	Lymphatic vessel infiltration: Reintroducing the meaning of L and V ¹ positive to correctly understand lymphatic and vascular invasion	I
Recommended additional indicators for guiding clinical practice	Microsatellite instability: Further explaining its importance as a prognostic risk and efficacy predictor	I
Recommended additional indicators for guiding clinical practice	Determine the <i>KRAS</i> , <i>NRAS</i> , and <i>BRAF</i> mutations as very important prognostic risk and efficacy predictors	I, II

¹L-positive infiltrates for medics and V-positive for venous infiltration.

and (3) cases with incomplete clinical-pathologic data and cases with incomplete follow-up data. As a result, 990 cases were excluded. Therefore our analysis focused on the remaining 1090 cases.

Follow-up

Patients were routinely followed in the outpatient clinic 2 wk after surgery for 3 mo and every 3 mo for the first year, then every 6 mo for the second year and every year for the next 3 year. Follow-up data was complemented by phone contact as well as contact with written mail.

Ethics statement

This study was carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Huzhou Central Hospital.

Preliminary processing of data

Using the extent of disease codes, tumor invasion (T staging), lymph node positivity (N staging), tumor metastasis (M staging) status, CRC was staged based on the AJCC-7th and AJCC-8th (Table 4). The patients were divided into three groups (N0, N1, N2) by the number

of positive lymph nodes. Clinicopathological data were analyzed between the three groups. Patient status was designated into three outcome categories for disease-free survival (DFS): (1) death from CRC; (2) recurrence from CRC; or (3) alive at the last follow-up. Patient status was designated into two outcome categories for overall survival (OS): (1) death from CRC; or (2) alive at the last follow-up.

Statistical analysis

SPSS 21 (Chicago, IL, United States) was used for data analysis. Intergroup measurement data were analyzed using ANOVA analysis of variance and count data were analyzed using Cross-Tab χ^2 analysis.

The relationship between positive lymph node and tumor size, differentiation, tumor invasion, chemotherapy, and TNM staging from AJCC-7th, and TNM staging from AJCC-8th were analyzed by linear and automatic linear regression and the functional equations were established.

Survival curves were generated using Kaplan-Meier estimates, and 5-year DFS and OS were compared using the Log-rank test. Kaplan-Meier was also used to calculate the survival rate of DFS and OS in each group. Afterwards, Cross-table was used to compare the DFS

Table 4 Two-way classification table of staging based on tumor-node-metastasis staging from AJCC-7th vs tumor-node-metastasis staging from AJCC-8th for patients with stages 0-IV colorectal cancer from 2006-2012 (*n* = 1090)

		TNM staging from AJCC-7 th										Total
		0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	
TNM staging from AJCC-8 th	0	16	0	0	0	0	0	0	0	0	0	16
	I	0	131	0	0	0	0	0	0	0	0	131
	II A	0	0	138	0	0	0	0	0	0	0	138
	II B	0	0	0	56	0	0	0	0	0	0	56
	II C	0	0	0	0	31	0	0	0	0	0	31
	III A	0	0	0	0	0	136	0	0	0	0	136
	III B	0	0	0	0	0	0	400	0	0	0	400
	III C	0	0	0	0	0	0	0	127	0	0	127
	IV A	0	0	0	0	0	0	0	0	24	0	24
	IV B	0	0	0	0	0	0	0	0	0	9	9
	IV C	0	0	0	0	0	0	0	0	0	22	22
		16	131	138	56	31	136	400	127	24	31	1090

TNM: Tumor-node-metastasis.

and OS survival rates of sub-periods between AJCC-7th and AJCC-8th groups, and a histogram was generated. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Lymph staging (N) and clinicopathologic characteristics

During the 6-year study period, 2080 patients with stage 0-IV CRC were identified but only 1090 met our inclusion criteria. The median age at diagnosis was 66 years [interquartile range (IQR): 55-73] and median follow-up was 60 mo (IQR: 54-60). The N staging did not change between AJCC-7th and AJCC-8th, therefore we used N staging to analyze clinical pathology data. Patient demographics and pathological features were summarized in Table 5. This table also compared staging of CRC with AJCC-7th vs AJCC-8th criteria. Although there was no difference in the total number of patients with stage IV CRC, the distribution of patients in this period was different. The χ^2 test was performed for all sub-stages of CRC, and significance existed between IVA and IVB according to AJCC-7th (*P* = 0.001), and between IVA, IVB, and IVC according to AJCC-8th (*P* = 0.05).

Linear model between the number of positive lymph nodes and tumor size, differentiation, tumor invasion, chemotherapy, TNM staging from AJCC-7th, and TNM staging from AJCC-8th

The number of positive lymph nodes was related to the N anatomical stages in AJCC-7th and AJCC-8th. An automated linear model found that the number of positive lymph nodes and tumor size, tumor differentiation, depth of tumor invasion, chemotherapy, TNM staging from AJCC-7th, and TNM staging from AJCC-8th were indicators of good fit and showed significance (*P* < 0.05). The fitting degree for TNM staging from AJCC-7th was 61.3% (Figure 2A), and the index that had a significant influence on positive lymph nodes was shown in Figure 2B. However, chemotherapy was

not included in the predictive importance index (Figure 2C). The importance of TNM staging from AJCC-7th was 77%, and the importance of tumor invasion was 19%, the importance of tumor size was 3%, the degree of tumor differentiation was 1%. Figure 2D showed significant parameters of each coding amount and constant coefficient. The fitness for TNM staging from AJCC-8th was 63.3% (Figure 3A), and the indexes that had a significant influence on positive lymph nodes were shown in Figure 3B. Chemotherapy was also included in the predictive importance index (Figure 3C). The importance of TNM staging from AJCC-8th was 72%, the importance of tumor invasion was 20%, the importance of chemotherapy was 4%, the importance of tumor size was 3%, the degree of tumor differentiation was 1%. Figure 3D showed significant parameters of each coding amount and constant coefficient.

Then the linear model calculated the functional equation for these variables and positive lymph node relationships. Outcome showed that $Y_A = -0.918 + 0.409X_B + 0.18X_C - 0.583X_D - 0.460X_E + 0.669X_F$ and $Y_A = -0.821 + 0.404X_B + 0.183X_C - 0.587X_D - 0.491X_E + 0.658X_G$ (A: Positive lymph node; B: Tumor size; C: Differentiation; D: Tumor invasion; E: Chemotherapy; F: TNM staging from AJCC-7th; G: TNM staging from AJCC-8th).

DFS and OS between AJCC-7th and AJCC-8th criteria

Using Kaplan-Meier univariate analysis and Log-rank test, the 5-year survival rate of DFS and OS in 1090 patients was calculated and compared by stage and sub-stage according to AJCC-7th and AJCC-8th criteria. DFS and OS survival rate between the two editions did not change from stage 0-IV and from substage 0-IV B. However, when the 5-year DFS and OS survival rate were compared from stage IVB from AJCC-7th and from stage IVB and IVC from AJCC-8th the survival curve of DFS and OS showed a significant right shift for stage IV B and a significant left shift for stage IVC (*P* = 0.001 and *P* < 0.001, respectively). Details were shown in Table 6

Table 5 Demographic and clinical characteristics of patients with stage 0-IV colorectal cancer from 2006-2012 (*n*, mean \pm SD)

	N0	N1	N2	F or χ^2	P
Gender				2.895	0.235
Male	242	182	126		
Female	234	201	105		
Age (yr)	62.46 \pm 14.43	62.17 \pm 14.43	61.98 \pm 14.70	0.095	0.909
ASA				6.011	0.198
1	362	277	158		
2	102	94	68		
3	12	12	5		
Primary site				4.94	0.895
Ileocecum	36	26	11		
Right colon	43	30	22		
Transverse colon	70	64	40		
Left colon	88	72	46		
Sigmoid colon	53	34	21		
Rectum	186	157	91		
Tumor size (cm)	3.31 \pm 1.17	3.76 \pm 0.82	4.11 \pm 0.74	56.008	< 0.001
Operation method				8.233	0.411
RHC	97	67	43		
LHC	186	154	91		
HO	9	6	9		
AR	145	112	70		
APR	39	44	18		
Operation time (m)	151.59 \pm 36.31	156.40 \pm 34.94	153.17 \pm 31.30	2.044	0.130
Resection length (cm)	27.96 \pm 9.92	27.26 \pm 9.83	27.65 \pm 9.92	0.533	0.587
Blood loss (mL)	184.39 \pm 94.25	185.23 \pm 95.26	194.30 \pm 107.32	0.879	0.416
Tumor invasion				131.640	< 0.001
Tis	16	0	0		
T1	85	17	9		
T2	92	75	43		
T3	162	127	132		
T4a	82	108	22		
T4b	39	56	25		
Differentiation				188.64	< 0.001
Well	150	31	13		
Moderate	276	296	124		
Poor or undifferentiated	50	56	94		
Number of LNs examined	14.70 \pm 1.88	14.13 \pm 1.78	14.26 \pm 1.85	0.408	0.665
Number of positive LNs	0	1.85 \pm 0.73	5.46 \pm 1.64	3050.47	< 0.001
Complication				4.088	0.130
No	436	349	201		
Yes	40	34	30		
Chemotherapy				295.36	< 0.001
Yes	283	383	229		
No	193	0	2		
TNM staging AJCC-7 th				887.08	< 0.001
0	16	0	0		
I	131	0	0		
II A	138	0	0		
II B	56	0	0		
II C	31	0	0		
III A	45	82	9		
III B	49	234	117		
III C	9	47	71		
IV A	1	15	8		
IV B	0	5	26		
TNM staging AJCC-8 th				887.32	< 0.001
0	16	0	0		
I	131	0	0		
II A	138	0	0		
II B	56	0	0		
II C	31	0	0		
III A	45	82	9		
III B	49	234	117		
III C	9	47	71		
IV A	1	15	8		
IV B	0	1	8		
IV C	0	4	18		

TNM: Tumor-node-metastasis.

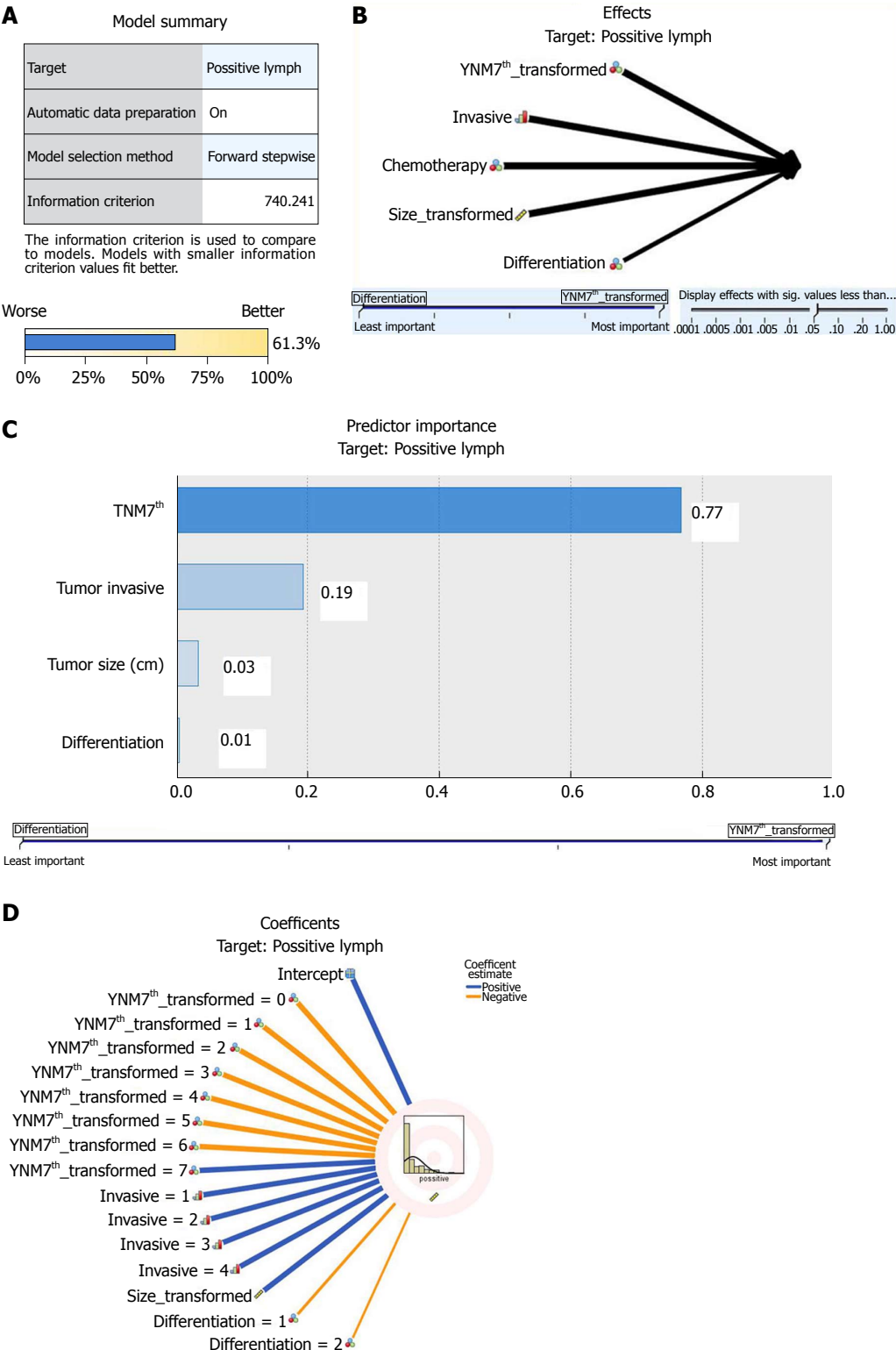


Figure 2 Automatic linear regression about positive lymph nodes and clinicopathologic parameters with tumor-node-metastasis staging from AJCC-7th. A: Clinical pathological parameters fitting degree. Fitting value is 61.3%; B: Significant effect parameters ($P < 0.05$); C: Predictor importance of positive lymph nodes and clinicopathological parameters. The values of tumor-node-metastasis staging from AJCC-7th, tumor invasion, tumor size, and differentiation are 0.77, 0.19, 0.03, and 0.01, respectively; D: Coefficients about positive nodes and clinicopathological parameters.

and Figure 4.

Nerve invasion, vein invasion, Lymphatic invasion and tumor deposit between AJCC-7th and AJCC-8th
AJCC-8th further emphasized the clinical value of tumor

lymphatic invasion, vein invasion, nerve invasion, and tumor deposit (TD) and were included in “evidence-based medicine” evidence level (Table 3). Since the release of AJCC-7th, our institution’s pathologist has attached great importance to this aspect of the test and has described

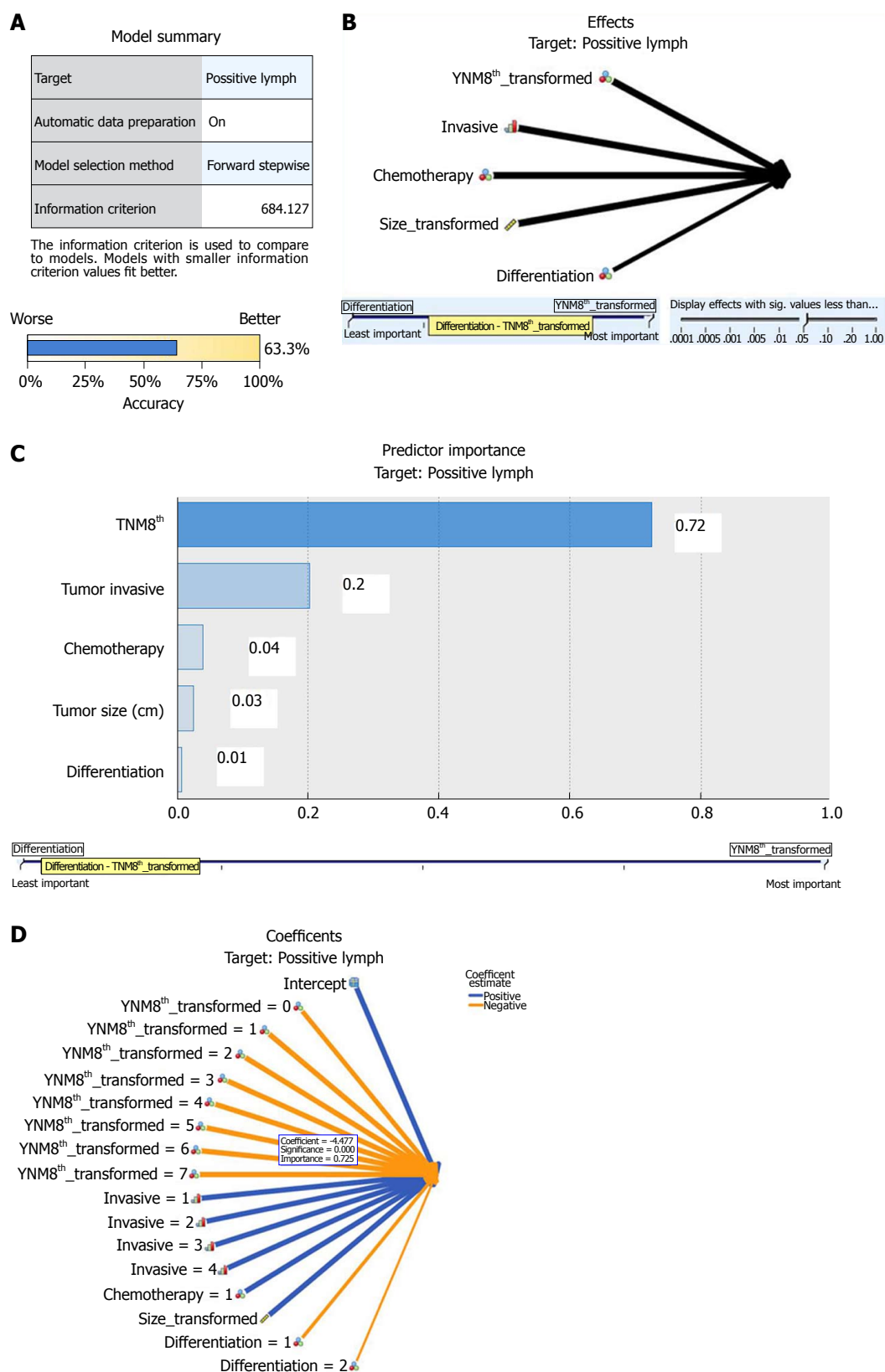


Figure 3 Automatic linear regression about positive lymph nodes and clinicopathologic parameters with tumor-node-metastasis staging from AJCC-8th. A: Clinical pathological parameters fitting degree. The fitting value is 63.3%; B: Significant effect parameters ($P < 0.05$); C: Predictor importance of positive lymph nodes and clinicopathological parameters. The values of tumor-node-metastasis staging from AJCC-8th, tumor invasion, chemotherapy, tumor size, and differentiation are 0.72, 0.2, 0.04, 0.03 and 0.01, respectively; D: Coefficients about positive nodes and clinicopathological parameters.

Table 6 Comparison of 5-year disease-free survival and overall survival rate for stage and sub-stage using American Joint Committee on Cancer-7th edition and American Joint Committee on Cancer-8th edition (%)

			0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C	Log-rank χ^2	P
OS	Sub-stage	AJCC-7	100	98.5	82.6	76.8	67.7	65.4	60	44.9	8.3	0	-	1423.53	< 0.01
		AJCC-8	100	98.5	82.6	76.8	67.7	65.4	60	44.9	8.3	0	0	1608.11	< 0.01
	Stage	AJCC-7	100	98.5		79.1			58.2			3.6		913.56	< 0.01
		AJCC-8	100	98.5		79.1			58.2			3.6		875.46	< 0.01
DFS	Sub-stage	AJCC-7	100	93.1	78.3	73.2	61.3	65.4	56.3	37	8.3	0	-	1418.9	< 0.01
		AJCC-8		93.1	78.3	73.2	61.3	65.4	56.3	37	8.3	0	0	1603.4	< 0.01
	Stage	AJCC-7	100	93.1		74.7			54.4			3.6		875.46	< 0.01
		AJCC-8		93.1		74.7			54.4			3.6		875.46	< 0.01

DFS: Disease-free survival; OS: Overall survival; AJCC: American Joint Committee on Cancer.

them in detail (Figure 5).

DISCUSSION

In 1977, AJCC established the first edition of the cancer staging system. Revision to the system have been made every 6-8 years and until recently it has been regarded as the most comprehensive tool for prognostic and predictive grouping of patients with colon cancer^[24]. However, when AJCC-6th was released in 2002^[27], it elicited criticism because survival of patients with stage IIIA colon cancer was superior to that of patients with stage IIB colon cancer^[28]. In 2010, the AJCC cancer staging system was updated to the 7th edition^[22,29]. This edition included both the refinement of the classic TNM "anatomic blood" diagnostic system, the increase in tumor regression scores, and the risk of prognoses and curative effects for circumferential resection margins.

Evaluation index

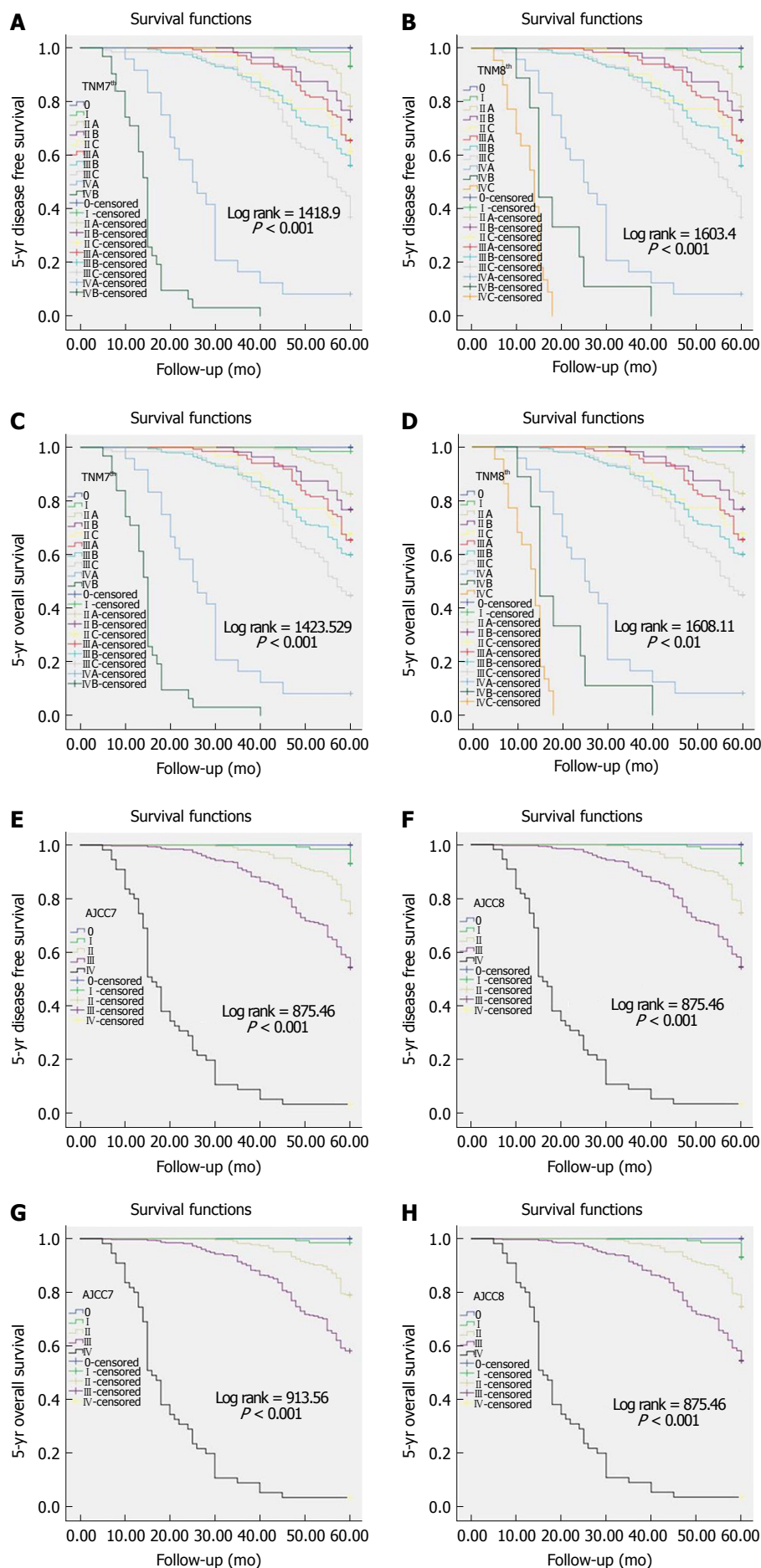
The problem with AJCC staging of CRC was initially attributed to inadequate lymph node (LN) assessment. Previous studies demonstrated that the number of examined LNs impacted survival^[30-34]. Subsequent studies showed a strong correlation between outcomes and compliance with 12-LN minimum^[35-39]. In our study, in addition to analyzing the distribution of LN numbers in different N stages, we also focused on the effect of positive LN numbers on lymphatic pathology, and established a linear function.

In recent years, researchers have recognized the importance of tumorigenesis and the role of non-anatomic markers in establishing the prognosis and anticipated response to therapy^[40-45]. Of these factors, the circumferential margin of the resected non-peritonealized surface of the specimen (CRM) is relevant for prognostic assessment of patients with tumors in the ascending and descending colon^[46,47]. Microsatellite instability, KRAS mutation and the 18q LOH have been shown to have clinical prognostic significance^[48,49]. These factors have

not been incorporated into the staging system because it is not clear how they should be used to determine prognosis or the need for adjuvant chemotherapy. In 2013, AJCC established the "Evidence-Based Medicine and Statistics Core Group" of the eighth edition system, which was responsible for determining the level of evidence for any updated content of the AJCC staging system. New evidence had to reach an evidence quality level of I - III to be factored into the staging system for the eighth edition.

AJCC-8th did not include any updates for tumor staging. The definition of TD and N1c in the N-stage was further interpreted as the presence of encouraging tumor nodules in the lymphatic drainage area of the primary tumor, and no lymph node, vessel, or nerve structure identified during the period. The presence of TD did not alter the T stage of the primary tumor, but if it was not accompanied by lymph node metastasis, the TDs would change N stage (from N0 to N1c). If there was combined lymph node metastasis, the number of TDs did not need to be counted in the number of positive lymph nodes. The latest version reaffirmed the definition of lymphatic infiltrating vessels. Any vessel lesions with or without residual vascular walls could be identified as lymphocytic infiltrates in storage vessels and become a routine item in the pathology report of the American College of Pathology. Our institutional pathologist recognized this and described them in the report (Figure 5). Vascular lymphatic infiltration could be subdivided into small vessel infiltration (lymphatic or venular infiltration, defined as "L" positive) and venous infiltration (a structure surrounded by tumor immersion and endothelial cells, which contain red blood cells coated with smooth muscle machinery was defined as "V" positive). At the same time, it was found that tumor immersion and nerve tissue were defined as infiltration around the nerve. Lymphatic infiltration and perineural invasion were both important prognostic factors^[50-56].

AJCC-7th classified the metastasis stage M1 as M1a (metastasis in one organ or site) and M1b (metastasis in



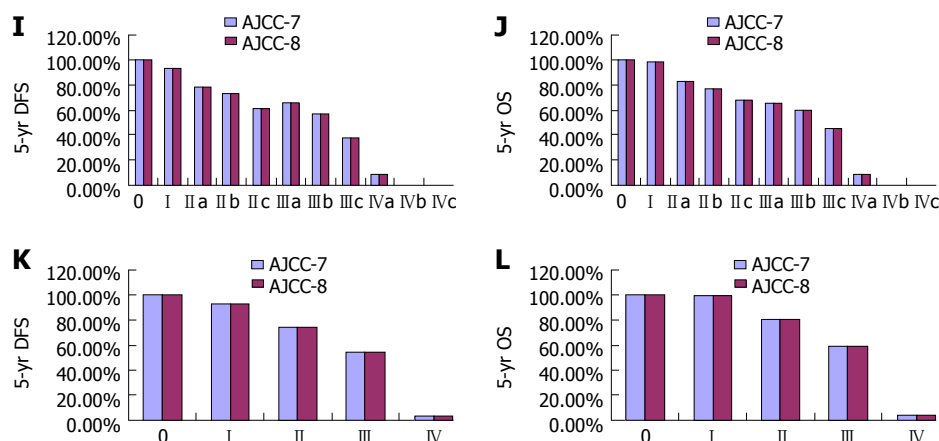


Figure 4 Disease-free survival and overall survival curves and histograms between tumor-node-metastasis staging from AJCC-7th and tumor-node-metastasis staging from AJCC-8th. A: Comparison of 5-year disease-free survival (DFS) by sub-stage from AJCC-7th ($P < 0.001$); B: Comparison of 5-year DFS by sub-stage from AJCC-8th ($P < 0.001$); C: Comparison of 5-year overall survival (OS) by sub-stage from AJCC-7th ($P < 0.001$); D: Comparison of 5-year OS by sub-stage from AJCC-8th ($P < 0.001$); E: Comparison of 5-year DFS by stage from AJCC-7th ($P < 0.001$); F: Comparison of 5-year DFS by stage from AJCC-8th ($P < 0.001$); G: Comparison of 5-year OS by stage from AJCC-7th ($P < 0.001$); H: Comparison of 5-year OS by stage from AJCC-8th ($P < 0.001$); A vs B and C vs D: Survival curves of DFS and OS in stage IVb shift right and those in stage IVc shift left; I-L: Comparison of DFS and OS by sub-stage and stage between staging from AJCC-7th and staging from AJCC-8th, all $P < 0.01$. DFS: Disease-free survival; OS: Overall survival; TNM: Tumor-node-metastasis.

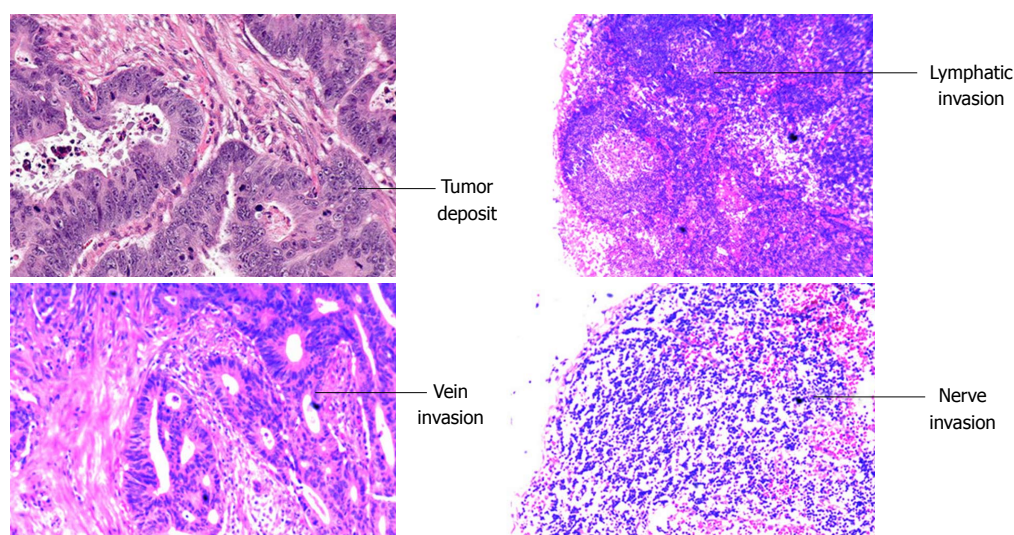


Figure 5 The focus of the eighth edition of the American Joint Committee on Cancer pathology test description. A: Tumor deposit; B: Lymphatic invasion; C: Vein invasion; D: Nerve invasion.

more than one organ or site, or in the peritoneum). In AJCC-8th, another stage was added to describe colorectal peritoneal metastases (whether or not with metastasis of other organ sites). This is called M1c, and M1a and M1b were redefined as metastasis limited to one organ or site (such as liver, lung, ovary, extra-nodal lymph nodes, etc.) and transition beyond one organ or site, but without peritoneal metastasis, respectively. The reason for the change is that although peritoneal metastasis occur in 1% to 4% of patients with CRC, the prognosis is far worse than that of M1a and M1b patients who have metastasis of substantial organs^[57-61].

We reclassified our cohort according to the AJCC-8th criteria. The results showed that the DFS and OS of the M1a stage remained unchanged, while that of the M1b stage improved, and that of the M1c stage decreased significantly. This demonstrated that the M stage

refinement was necessary. This additional classification in the eighth edition will have a positive and far-reaching effect on cancer treatment that will promote the individualized diagnosis and treatment of CRC patients. However, further analysis with additional institutional databases is needed to confirm our findings.

In conclusion, the addition of a sub-stage to classify peritoneal metastasis separately from distant organ metastasis in the AJCC-8th manual has shown that peritoneal metastasis has a worse prognosis than organ metastasis in our cohort.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a common malignant tumors. Clinicians have been using the American Joint Committee on Cancer (AJCC) system to guide clinical

diagnosis and treatment for CRC. The eighth edition of the AJCC (AJCC-8th) has received extensive attention since its promulgation in 2016. Compared to the previous version, AJCC-8th refined the stage IV classification to separate peritoneal metastasis and organ metastasis.

Research motivation

In China, there are still many hospital surgeons and physicians who still use the old version to guide clinical practice and are uneducated about the new AJCC-8th classifications.

Research objectives

We analyzed our institution's CRC cohort to determine differences in the survival trends based on the diagnostic classifications between AJCC-8th and the previous version.

Research methods

A total 1090 patients of 2080 CRC patients were included in the study. The data were classified by AJCC-7th and AJCC-8th standards. Five-year disease-free survival (DFS) and overall survival (OS) were compared.

Research results

Linear regression and automatic linear regression showed lymph node positive functional equations by TNM staging from AJCC-7 and TNM staging from AJCC-8th. Neurological invasion, venous infiltration, lymphatic infiltration, and tumor deposition put forward stricter requirements for pathological examination. AJCC-8th staging yielded a proportional decrease of IVB from 2.8% to 0.8% and a new staging of IVC to 2%. Log-rank test showed that DFS and OS survival time of patients with IVC vs IVB was significantly shorter ($P = 0.012$).

Research conclusions

The addition of a sub-stage to classify peritoneal metastasis separately from distant organ metastasis in the AJCC-8th manual has shown that peritoneal metastasis has a worse prognosis than organ metastasis in our cohort. Considering many prognostic factors, individualized treatment is particularly important to improve the survival time of stage IV patients, especially IVC patients.

Research perspective

Further studies can be done to improve outcomes for peritoneal metastasis CRC patients. Further analysis of additional institutional databases is needed to confirm our findings.

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