

Tumor size as a prognostic factor improves the accuracy of the prognostic prediction of T4 stage colon cancer: a propensity score analysis

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Abstract

The aim of this study was to evaluate the potential impact of tumor size on the long-term outcome of CC patients after curative surgery. A total of 782 curatively resected T4 stage CC patients without distant metastasis were enrolled. Patients were categorized into 2 groups according to the best threshold of tumor size: larger group (LG) and smaller group (SG). Propensity score matching was used to adjust for the differences in baseline characteristics. The ideal cutoff points for tumor size was 5 cm. In the multivariate analysis for the whole study series, tumor size was an independent prognostic factors. Patients in the LG had a significant lower 5-year OS rate, but higher distant metastatic rate than those in the SG (37.1% versus 25.2%, $P < 0.001$). After matching, patients in the LG still demonstrated a significant lower 5-year OS rate than those in the SG (63.5% versus 74.2%, $P < 0.001$). Patients in the LG benefited more from postoperative adjuvant chemotherapy than patients in the SG. The modified stage including tumor size was found to be more appropriate for predicting the OS of T4 stage CC than TNM stage. In conclusion, tumor size was an independent prognostic factor and could correlate with higher distant metastasis rate and better response of adjuvant chemotherapy. We maintain that tumor size should be incorporated into the staging system to enhance the accuracy of the prognostic prediction of T4 stage CC patients.

Introduction

Tumor size has been verified to be associated with overall survival (OS) in many types of malignancy, and it is regarded as “T” stage of many solid tumors including breast, lung and liver cancers in the tumor-node-metastasis (TNM) staging system of the Union for International Cancer Control (UICC)¹⁻⁵. Despite the value of tumor size as a prognostic indicator in those solid tumors, the prognostic significance of tumor size in gastrointestinal tumors has not been widely realized. Deng JY *et al.*⁶ demonstrated that tumor size as a T stage could accurately predict the survival of gastric cancer patients and it was an independent prognostic factor in multivariate analysis. Kunisaki C *et al.*⁷ found that tumor size was a reliable prognostic factor of gastric cancer, and thus suggested that it should be included in staging system. As for colon cancer, few studies⁸⁻¹⁶ focused on tumor size. Saha Sukamal *et al.*⁸ reported that tumor size positively correlated with grade, T stage and node stage, and it was inversely associated with survival.

As the tumor size usually correlated with tumor stage and other prognostic factors as previous studies⁸⁻¹⁶ reported, therefore, it was vital important to adjust for imbalances regarding baseline characteristics between patients with larger tumor size and those with smaller one, especially in retrospective analysis. In the present study, we used both Cox proportional hazard regression analysis and propensity score method to overcome bias due to different distribution of covariates for the groups. Our ultimate aim was to evaluate the potential impact of tumor size on the long-term outcome of CC patients after curative surgery in a single center in China.

Material And Methods

Patients

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Hainan Medical University. All the patients signed an informed consent form for the operation including surgical procedure. All processes involved in this study were in accordance with the standards of the institutional Ethics Committee. A total of 1207 patients with CC who underwent surgical resection at the First Affiliated Hospital of Hainan Medical University between January 2004 and December 2014 were eligible for this study. Eligibility criteria for this study included: (1) adenocarcinoma of the colon, (2) stage I to IV disease underwent colonectomy plus lymph node dissection with curative intent, (3) patients were completely followed-up, (4) no history of other malignancy, (5) no history of neoadjuvant chemotherapy, (6) no patients died during the initial hospital stay or for 1 month after surgery. Ultimately, 1008 patients were included in this study. The stratified survival analysis of tumor stage revealed that the prognosis of patients in IV and T1-3 stages was not affected by tumor size (Table 1). After excluding 100 patients with distant metastasis and 126 patients without serosa invasion, finally, a total of 782 T4 stage patients without distant metastasis were included in the analysis.

Table 1
Strata survival analysis of the CC patients according to tumor stages.

Tumor stage	SG		LG		χ^2	<i>P</i>
	n	5-year OS(%)	n	5-year OS(%)		
T stage						
T2	20	100.0	34	91.2	0.280	0.597
T3	23	87.0	49	71.4	0.777	0.378
T4	316	70.8	566	59.0	17.607	< 0.001
TNM stage						
I	16	100.0	30	90.0	0.256	0.613
II	214	80.6	391	72.8	7.861	0.005
III	99	68.4	158	48.7	8.429	0.004
IV	30	26.7	70	17.1	3.134	0.077
Total	359	73.5	649	61.7	17.707	< 0.001

Evaluation of clinicopathological variables and survival

Clinicopathological features studied included the following 13 factors: sex, age at surgery, tumor location, tumor size, histology, lymphovascular invasion, presence of lymph node metastasis, number of lymph nodes retrieval, surgical procedure, postoperative complications, postoperative chemotherapy, peroperative serum carbohydrate antigen 19 – 9 (CA19-9) level and carcinoembryonic antigen (CEA) level.

All the patients underwent curative colonectomy plus complete mesocolic excision and lymph node dissection. The tumors were staged according to the eighth edition of the UICC TNM classification system. Tumors were classified into two groups based on histology: differentiated type, including papillary, well or

moderately differentiated adenocarcinoma; and undifferentiated type, including poorly differentiated or undifferentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma.

Measurement of tumor size

The resected specimen was opened along the longitudinal axis of the colon wall on the opposite side of the tumor. Then, the opened colon was placed on a flat board with the mucosal side facing up. During the examination from the mucosal side, the longest tumor diameter was measured and regarded as tumor size in this study.

Follow up

The patients were followed up by his attending physician and the research nurse of our department. To increase the follow-up rate, methods such as telephone, message, correspondence and outpatient department visits were used together. The patients were followed up every 3 months up to 2 years after surgery, then every 6 months up to 5 years, and then every year or until death. Physical examination, laboratory test (including assessing CEA and CA19-9), abdominal ultrasound (US), chest and abdominal computed tomography (CT) were performed at each visit, while endoscopy was obtained every year. The OS rate was calculated from the day of surgery until time of death or final follow-up. The date of final follow-up was December 31, 2019.

Statistical analysis

For continuous variables, which were presented as mean \pm standard deviation (SD), parametric analysis was performed using Student's t test. Categorical variables were analyzed by means of the chi-square or Fisher's exact test. Overall survival curves were calculated using the Kaplan-Meier method based on the length of time between primary surgical treatment and final follow-up or death. The log-rank test was used to assess statistical differences between curves. Independent prognostic factors were identified by the Cox proportional hazard regression model. To overcome bias due to the different distribution of covariates for the two groups, the propensity score analysis was used to obtain a one-to-one match by using the nearest-neighbor matching method. And we imposed a caliper of 0.25 of the sd of the logit of the propensity score. Variables involved in the propensity model were sex, age at surgery, tumor location, tumor size, histology, lymphovascular invasion, presence of lymph node metastasis, number of lymph nodes retrieval, surgical procedure, postoperative complications, postoperative chemotherapy, preoperative serum CA19-9 level and CEA level. To compare our suggested new modified tumor-size-node-metastasis (mTSNM) stage with the eighth edition of TNM staging system, the -2 log likelihood, hazard ratio (HR) value, and 95% confidence interval (CI) related to the Cox regression model were used for measuring homogeneity and discriminatory ability. $P < 0.050$ (bilateral) was considered statistically significant. The statistical analysis was performed using the statistical analysis program package SPSS 22.0 (SPSS, Chicago, IL).

Results

Clinicopathological features and outcome of the whole study series before matching

The median follow-up for the whole study series was 67 (range: 5-105) months and the 5-year OS rate was 67.8%. Seven hundred and eighty-two patients included 439 males (56.1%) and 343 females (43.9%). The age ranges from 26 to 83 years, and median age was 61 years. Of the 782 patients who underwent curative

surgery, 597 patients underwent laparoscopic surgery, and the remaining 185 patients underwent open surgery. Of these patients, 601 received postoperative adjuvant chemotherapy with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX6); capecitabine and oxaliplatin (XELOX); or capecitabine alone.

The mean \pm SD tumor size was 6.17 ± 2.59 cm (range 0.80–17.00 cm). To identify the optimal cutoff points for tumor size, the cut-point survival analysis was adopted, and survival rates were calculated at each 1-cm interval. The tumor size with the highest χ^2 value was regarded as the optimal threshold of classification. After numerous evaluation, the optimal thresholds were determined by the best cutoff approach in terms of the log-rank test. The ideal tumor size cutoff value was 5 cm in this study. The tumor size intervals were S1, <5cm and S2, ≥ 5 cm. All the patients were categorized into two groups based on tumor size: the larger group (LG), patients with tumor size ≥ 5 cm, including 496 patients; and the smaller group (SG), patients with tumor size < 5 cm, including 286 patients. Clinicopathologic variables were compared between the two groups as shown in left columns of Table 2. There were no statistical differences in sex, age at surgery, lymph node retrieval (≥ 12 vs < 12), lymph node metastasis, preoperative serum CEA level and postoperative adjuvant chemotherapy between the two groups, whereas patients in the LG were more likely to have a larger number of lymph node retrieval (16.7 ± 7.5 vs 15.1 ± 5.6 , $P = 0.001$), and a higher ratio of tumor located at right colon (65.3% vs 54.5%, $P = 0.003$), but less likely to undergo laparoscopic surgery (71.4% vs 85.0%, $P < 0.001$) than those in the SG. Besides, undifferentiated histology (39.1% vs 29.4%, $P = 0.006$), lymphovascular invasion (18.1% vs 11.2%, $P = 0.010$), elevated CA19-9 (21.8% vs 13.3%, $P = 0.003$) and postoperative complications (10.3% vs 2.8%, $P < 0.001$) were more prevalent in larger tumors.

Table 2

Clinicopathological features of T4 CC patients grouped by tumor size: data are reported for the whole study series and for one-to-one propensity-score matched pairs

Characteristics	Whole study series			Matched pairs (Case-control Method)		
	SG(n = 286)	LG(n = 496)	P	SG(n = 286)	LG(n = 286)	P
Sex			0.118			0.397
Male/ Female	171/115	268/228		171/115	161/125	
Age at surgery (yr)			0.648			0.485
≥ 65 / <65	98/188	178/318		98/188	106/180	
Mean age at surgery			0.087			0.994
Mean ± sd	60.8 ± 11.1	59.3 ± 12.7		60.8 ± 11.1	60.8 ± 11.4	
Tumor location			0.003			0.448
Right colon/Left colon	156/130	324/172		156/130	165/121	
Histology			0.006			0.260
Differentiated/Undifferentiated	202/84	302/194		202/84	214/72	
Lymphovascular invasion			0.010			0.605
Present / Absent	32/254	90/406		32/254	36/250	
Number of lymph nodes retrieval			0.001			0.144
Mean ± sd	15.1 ± 5.6	16.7 ± 7.5		15.1 ± 5.6	15.9 ± 7.2	
lymph nodes retrieval			0.472			0.288
> 12/≤12	209/77	374/122		209/77	220/66	
Lymph node metastasis			0.167			0.520
N0/N1/N2	193/67/26	354/89/53		193/67/26	198/57/31	
CEA level			0.787			0.556
Elevated / Normal	124/162	220/276		124/162	131/155	
CA19-9 level			0.003			0.406
Elevated / Normal	38/248	108/388		38/248	45/241	
Surgical procedure			< 0.001			0.064
Open /Laparoscopic	43/243	142/354		65/221	60/226	
Postoperative chemotherapy	74.1	78.4	0.170			0.138

Characteristics	Whole study series			Matched pairs (Case-control Method)		
	SG(n = 286)	LG(n = 496)	P	SG(n = 286)	LG(n = 286)	P
Yes/No	212/74	389/107		212/74	227/59	
Postoperative complications			< 0.001			0.136
Present / Absent	8/278	51/445		8/278	15/271	

In the entire study population, patients with larger tumors had a lesser 5-year OS than those with smaller tumors (5-year OS: 63.5% vs 75.2%, $P < 0.001$, Fig. 1A). The results of the univariate and multivariate survival analyses are presented in Table 3. A total of 12 factors evaluated in the univariate analysis had a significant effect on survival: age at surgery (< 65 vs ≥ 65), tumor location, tumor size (< 5 vs ≥ 5 cm), histology, N stage, lymphovascular invasion, lymph node retrieval (> 12 vs ≤ 12), surgical procedure, CEA level, CA19-9 level, postoperative complications and postoperative chemotherapy. In the multivariate analysis, age at surgery, N stage, lymphovascular invasion, lymph node retrieval, CA19-9 level, postoperative complications, postoperative chemotherapy and tumor size (HR was 1.433 for LG, $P = 0.014$) were found to be independent prognostic factors for OS.

Table 3
Univariate and multivariate survival analysis in the whole study series.

Characteristics	n (%)	5-year OS (%)	Univariate analysis		Multivariate analysis	
			HR(95%CI)	P	HR(95%CI)	P
Sex						
Male	439(56.1)	67.9	1(ref)			
Female	343(43.9)	67.6	1.020(0.806–1.290)	0.871		
Age at surgery (yr)						
< 65	506(64.7)	71.1	1(ref)		1(ref)	
≥65	276(35.3)	61.6	1.442(1.138–1.828)	0.002	1.358(1.048–1.759)	0.021
Primary tumor location						
Right colon	480(61.4)	63.1	1(ref)		1(ref)	
Left colon	302(38.6)	75.2	0.653(0.509–0.839)	0.001	0.910(0.689–1.201)	0.504
Tumor size						
SG (< 5cm)	286(36.6)	75.2	1(ref)		1(ref)	
LG (≥ 5cm)	496(63.4)	63.5	1.710(1.318–2.217)	< 0.001	1.433(1.076–1.908)	0.014
Histology						
Differentiated	504(64.5)	72.4	1(ref)		1(ref)	
Undifferentiated	278(35.5)	59.4	1.589(1.256–2.010)	< 0.001	1.238(0.951–1.612)	0.112
N stage						
N0	547(69.9)	75.3	1(ref)		1(ref)	
N1	156(20.0)	59.0	1.835(1.386–2.429)	< 0.001	2.051(1.531–2.747)	< 0.001
N2	79(10.1)	32.9	4.033(2.976–5.465)	< 0.001	4.369(3.192–5.979)	< 0.001
Lymphovascular invasion						
Absent	660(84.4)	71.1	1(ref)		1(ref)	
Present	122(15.6)	50.0	2.209(1.542–2.670)	< 0.001	1.760(1.295–2.392)	< 0.001

Characteristics	n (%)	5-year OS (%)	Univariate analysis		Multivariate analysis	
			HR(95%CI)	P	HR(95%CI)	P
lymph nodes retrieval						
≤ 12	199(25.4)	58.8	1(ref)		1(ref)	
> 12	583(74.6)	70.8	0.674(0.524–0.866)	0.002	0.579(0.448–0.749)	< 0.001
CEA level						
Normal	438(56.0)	72.8	1(ref)		1(ref)	
Elevated	344(44.0)	61.3	1.462(1.158–2.847)	0.001	1.141(0.876–1.486)	0.329
CA19-9 level						
Normal	636(81.3)	70.8	1(ref)		1(ref)	
Elevated	136(18.7)	54.8	1.703(1.299–2.232)	< 0.001	1.514(1.130–2.027)	0.005
Surgical procedure						
laparoscopic	597(76.3)	69.3	1(ref)		1(ref)	
Open	185(23.7)	62.7	1.356(1.044–1.760)	0.022	1.223(0.934–1.602)	0.144
Postoperative complications						
No	723(92.5)	70.3	1(ref)		1(ref)	
Yes	59(7.5)	37.3	2.385(1.687–2.3.373)	< 0.001	1.815(1.247–2.642)	0.002
Postoperative chemotherapy						
Absent	181(23.1)	59.1	1(ref)		1(ref)	
Present	601(76.9)	70.4	0.639(0.494–0.826)	0.001	0.667(0.505–0.880)	0.004

Patients characteristics and survival after propensity score matching

We analyzed 286 patients in each group, who were selected by one-to-one matching using propensity scores. The median follow-up was 66 (range: 6-105) months for the matched pair. Characteristics after the propensity score analysis are shown in the right columns of Table 2. Two hundred eighty-six of the 496 patients in the LG were matched with 286 patients in the SG after covariate adjustment. The adjusted propensity score for patients in the LG was approximately identical to that for patients in the SG (0.425 ± 0.103 vs 0.425 ± 0.098 , P

= 0.927). Figure 2 displays the distribution of the propensity scores in the matched and unmatched patients in the LG and those in the SG. All covariates were equally distributed over the two matched groups. Matched patients in the LG had a similar sex ratio, mean age at surgery, tumor location, histology, lymphovascular invasion, number of lymph nodes retrieval, lymph node metastasis, CEA level, CA19-9 level, surgical procedure, postoperative complications and postoperative chemotherapy, as those of the matched patients in the SG.

In the matched study series, patients with larger tumors still had a lesser 5-year OS than those with smaller tumors (5-year OS: 58.7% vs 75.2%, $P < 0.001$, Fig. 1B).

Recurrence data of the whole study series

The patterns and incidence of recurrence are shown in Table 4. Although there were no significant differences in locoregional recurrence between the two groups, patients with larger tumors had a significantly higher overall recurrence rate than those with smaller tumors (41.1% vs 27.6%, $P < 0.001$). The incidence of distant metastasis was greater in patients with larger tumors as well (37.1% vs 25.2%, $P = 0.001$). For patients with distant metastasis, liver (19.2% vs 12.9%, $P = 0.025$), lung (9.9% vs 5.6%, $P = 0.037$) and peritoneal (6.0% vs 2.8%, $P = 0.042$) metastasis were still more common in those with larger tumors than those with smaller tumors, and the difference was statistically significant.

Table 4
Type of initial recurrence in the whole study series

Type of recurrence	SG (n = 286)	LG (n = 496)	P
Locoregional	7 (2.4)	20 (4.0)	0.242
Distant metastasis	72(25.2)	184 (37.1)	0.001
Liver	37 (12.9)	95 (19.2)	0.025
Lung	16(5.6)	49 (9.9)	0.037
Peritoneal	8 (2.8)	30 (6.0)	0.042
Others	11(3.8)	10(2.0)	0.127
Overall recurrence	79 (27.6)	204 (41.1)	< 0.001

Tumor size as an indicator for good response of postoperative chemotherapy

In the multivariate analysis, postoperative chemotherapy was an independent prognostic factor for OS. Patients receiving postoperative adjuvant chemotherapy had a significantly higher OS rate than those without chemotherapy (5-year OS: 70.4% vs 59.1%, $P = 0.001$). The proportion of receiving postoperative chemotherapy in patients with smaller tumors was almost equal to that in patients with larger tumors (74.1% vs 78.4%, $P = 0.170$). Stratified analysis of tumor size revealed that in the SG, the 5-year OS rates were 78.3% and 66.2% for patients with and without chemotherapy ($\chi^2 = 6.027$, $P = 0.014$), respectively; and in the LG, the 5-year OS rates were 66.1% and 54.2% for patients with and without chemotherapy ($\chi^2 = 8.601$, $P = 0.003$), respectively (Fig. 3). Patients with larger tumors may benefit more from postoperative chemotherapy.

Incorporation of the tumor size into the eighth edition UICC TNM staging system

The OS of N0-stage patients with larger tumors was similar to that of N1-stage patients with smaller tumors. The OS of N1-stage patients with larger tumors was equal to that of N2-stage patients with smaller tumors (Fig. 4). Based on these results, we established a newly modified tumor-size-node-metastasis (mTSNM) staging system by incorporation of the tumor size into the eighth edition of UICC TNM staging system. The new mTSNM staging system was presented in Table 5. For T4 stage CC patients without distant metastasis, the mTSNM stages were defined as follows: mIIB, N0-stage patients with smaller tumors; mIIIA, N0-stage patients with larger tumors and N1-stage patients with smaller tumors; mIIIB, N1-stage patients with larger tumors and N2-stage patients with smaller tumors; and mIIIC, N2-stage patients with larger tumors.

Table 5
T4 CC patients were divided into two groups according to the tumor size: S1 and S2 groups. S was included into staging system, then the new stages were suggested.

S	N0	N1	N2
S1	IIB	IIIA	IIIB
S2	IIIA	IIIB	IIIC
S: tumor size			

The prognostic value of the TNM stage and mTSNM stage were evaluated by univariate and multivariate analyses. In the TNM stages, the 5-year OS rates were 73.5%, 59.0% and 32.9% in the IIB, IIIB and IIIC stages, respectively ($\chi^2 = 95.542$, $P < 0.001$). In the mTSNM stages, the 5-year OS rates were 81.9%, 71.0%, 51.3% and 26.4% in the mIIB, mIIIA, mIIIB and mIIIC stages, respectively ($\chi^2 = 120.375$, $P < 0.001$; Table 6, Fig. 5A, 5B). As presented in Fig. 6, the largest subgroup in the TNM stage is IIB, whereas the largest subgroup in the mTSNM stage is IIIA. The differences in prognostic prediction between the eighth edition of the TNM stage and the mTSNM stage were compared directly. The mTSNM stage was confirmed to be a more accurate prognostic classification for predicting the OS of T4 stage CC patients after curative resection than the eighth edition of TNM stage. The $-2 \log$ likelihood of the mTSNM stage was 3469.212, which was less than the value of the TNM stage (3477.452).

Table 6
Survival analysis of the 782 CC patients according to the TNM and mTSNM stages

Characteristics	Cases	5-year OS (%)	Univariate analysis		Multivariate analysis		-2loglikelihood
			χ^2	P	HR(95% CI)	p	
TNM stage (T4M0)			95.542	< 0.001	1.512(1.374-1.663)	< 0.001	3477.452
IIB(N0)	547	75.3					
IIIB(N1)	156	59.0					
IIIC(N2)	79	32.9					
mTSNM stage (T4M0)			120.375	< 0.001	1.939(1.700-2.212)	< 0.001	3469.212
IIB(S1N0)	193	81.9					
IIIA(S1N1/S2N0)	421	71.0					
IIIB(S1N2/S2N1)	115	51.3					
IIIC(S2N2)	53	26.4					

Discussion

Tumor size, given as the maximum diameter of the tumor, was one of independent prognostic factors of many solid tumors¹⁻⁵. As for gastrointestinal carcinoma, several studies⁶⁻⁹ affirmed that tumor size positively correlated with important prognostic factors and negatively impacted survival. However, comparing with depth of invasion, tumor size is not a better predictive factor, and its prognostic value is often neglected. Some researchers believed that tumor size was easily affected by many other factors including depth of invasion and lymph node metastasis, and it could not predict prognosis independently. In addition, it was difficult to reach consensus on the best cutoff points of tumor size worldwide¹⁷⁻¹⁸. At present, the prognostic value of tumor size in CC remains controversial. In this study, we found that patients with larger tumors and patients with smaller tumors were extremely imbalanced in basic clinicopathological factors. To eliminate bias due to different distribution of covariates for the groups, propensity score matching method and multivariate Cox regression analysis were applied together. It was confirmed that tumor size was one of independent prognostic factors and larger tumor size was associated with higher frequency of distant metastasis and better response of postoperative chemotherapy. Incorporation of tumor size into the eighth edition of TNM staging system could improve the accuracy of the prognostic prediction of T4 stage CC patients.

Tumor size can be objectively and easily measured. Its prognostic value and clinical significance have been widely evaluated in gastric cancer. Several studies¹⁹⁻²¹ confirmed that larger tumor size was associated with significantly poorer OS than smaller tumor size in a given subset of gastric cancer, such as Borrmann type III, node-negative, or T4aN0M0 stage disease. As digestive tract tumors, CC and gastric cancer have some similar

clinicopathological features. Besides, tumor size is closely related to surgical methods and scope of CC. The prognostic value of tumor size in CC should be explored as well. Theoretically, tumor size increases with tumor progression, and patients with larger tumors usually have a poorer prognosis than those with smaller ones. Previous studies⁶⁻⁹ had confirmed this theory and concluded that poorer prognosis of larger tumors was associated with tumor necrosis, iron deficiency anemia, tumor grade and a more aggressive underlying biology. In contrast, some studies^{10-12,15,16} revealed that patients with smaller tumors had a worse prognosis in a given subset of CC, such as positive lymph node and IIA stage disease. In these studies^{10,13-15}, the researchers considered that the poor prognosis of CC patients with smaller tumors in the same stage was related to a more biologically aggressive phenotype. In addition, surgeons are more likely to treat larger tumors more aggressively by extending lymph node dissection or postoperative chemotherapy, which may account for the better survival of patients with larger tumors¹⁵. As tumor size is associated with lymph node metastasis, depth of invasion and other prognostic factors, it is crucial to balance the relevant factors in both groups. To the best of our knowledge, this study is the first analysis using propensity score matching methods to assess the impact of tumor size on the prognosis of CC patients. We found that the incidence of lymphovascular infiltration, undifferentiated type and postoperative complications were higher in patients with larger tumors. Besides, patients with larger tumors had a significant lower 5-year OS rate than those with smaller tumors and tumor size was an independent prognostic factor of CC patients. The results were consistent with previous studies⁸⁻⁹. After matching, patients with larger tumors still demonstrated a significant lower 5-year OS rate than those with smaller tumors (63.5% versus 74.2%, $P < 0.001$). Although previous studies have reported some possible causes of the prognostic impact of tumor size, so far, the mechanism remains unclear. Usually, the direction of primary tumor infiltration includes along the intestinal wall and perpendicular to the intestinal wall. The former forms tumor size, while the latter contributes to depth of invasion. For tumors at the same T stage, the prognosis of patients with larger tumors is worse than that of patients with smaller tumors, which may be due to the larger tumor burden and more likely to invade vascular and lymphatic channels in larger tumors. In addition, larger tumors were associated with significant reductions in serum hemoglobin and albumin, but increased chances of bowel obstruction. These factors have been affirmed to be associated with poor prognosis of CC in previous studies²²⁻²⁵. We believe that the depth of tumor invasion plays a major role in the prognosis of CC, but the effect of tumor size on survival can not be ignored.

Actually, in the present study we confirmed that tumor size was not only associated with postoperative recurrence, but also a good indication of postoperative chemotherapy. Patients with larger tumors had a significantly higher overall recurrence rate, especially distant metastasis than those with smaller tumors. Previous studies²⁶⁻²⁸ confirmed that the possibility of lymphovascular invasion increased with the increase of tumor size, which might account for higher recurrence rate of larger tumor size. We believe that tumor cells that invade lymphovascular eventually form distant metastases and larger tumor size should be regarded as a high risk factor for recurrence. CC patients with larger tumor size should be closely followed up. Besides, postoperative chemotherapy should be considered in these patients even without lymph node metastasis. In fact, these patients do benefit more from chemotherapy in the present study.

Tumor size, as a T staging of many solid tumors, has been incorporated into the TNM staging system. As for digestive tract tumors, the depth of invasion plays a greater role in prognosis than the tumor size, so it is regarded as T stage, and the role of tumor size is often ignored. However, several studies^{6,29} confirmed that

incorporation of tumor size into the staging system could improve the prognostic prediction of gastric cancer. Deng *et al.*⁶ even used tumor size as a T classification and established a new tumor size-node-metastasis classification system. They found that the new tumor size-node-metastasis classification could accurately evaluate prognosis and provide very powerful discrimination of patients' OS, as compared with TNM classification. Until now, few studies have incorporated tumor size into the staging system of colon cancer. In the present study, we found that the OS of N0-stage patients with larger tumors was similar to that of N1-stage patients with smaller tumors and the OS of N1-stage patients with larger tumors was equal to that of N2-stage patients with smaller tumors. Based on the results, we incorporated tumor size into the TNM staging system and established a new mTSNM classification. It was affirmed that the mTSNM classification was a more appropriate prognostic classification to predict the OS of CC patients than the eighth edition of the TNM staging system. We believed that the current edition of the TNM staging system had following shortcomings. Firstly, it could not reflect the continuity of tumor progression. For example, the stage of T4N0M0 patients is IIB, however, it crosses IIIA stage and jumps to IIIB and IIIC stages once lymph nodes are involved. Besides, the IIIA stage merely includes T1N1-2aM0 and T2N1M0 patients, however, lymph node metastasis is rare in T1-2 stage patients. In our suggested mTSNM staging system, patients were continuously and uniformly distributed from IIB to IIIC stage and the largest subgroup was IIIA stage.

There are several limitations to our study. First and foremost are the limitations inherent to retrospective analyses. Moreover, as the sample size was relatively small, patients was simply divided into two groups based on best cutoff value of tumor size, more elaborate division of subgroups was not performed. Optimal cut-off values vary among different parts of the large bowel, usually decreasing from the right colon to the left, while tumor location was not concerned when identifying best threshold. Nevertheless, even with these limitations our results suggested that tumor size is relevant in patients with colon cancer.

Conclusion

Tumor size is an independent prognostic factor and negatively impacts survival of CC patients. Larger tumor size could correlate with a higher distant metastasis rate and better response of adjuvant chemotherapy. Prognostic impact of tumor size should be considered when making adjuvant therapy decisions and prognosis evaluation. Besides, we maintain that tumor size should be incorporated into the staging system to enhance the accuracy of the prognostic prediction of T4 stage CC patients. Further studies are necessary to elucidate the mechanism of tumor size as a prognostic factor in CC.

Declarations

Competing interests

The authors declare no competing interests.

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Figures

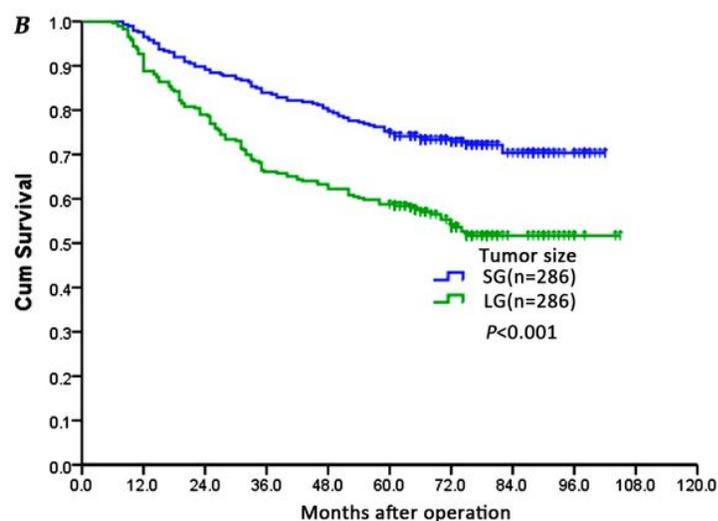
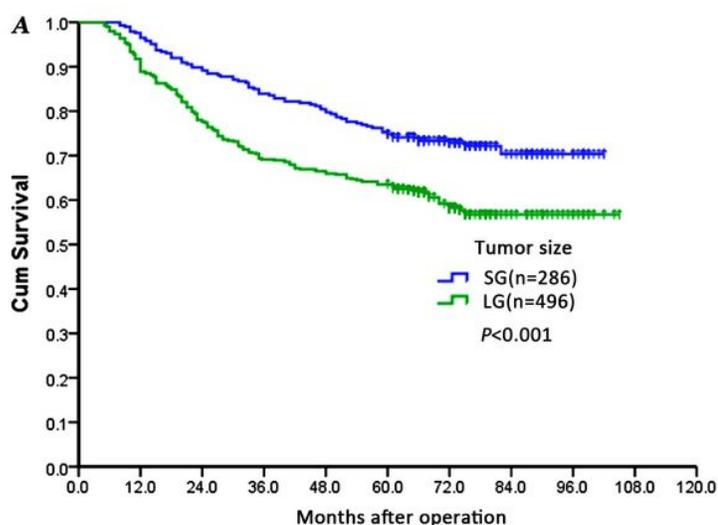


Figure 1

Prognosis of CC patients who underwent curative surgery. Patients were categorized into two groups according to the tumor size: SG and LG. (A) Survival curve for all patients: the 5-year OS rates were 75.2% and 65.3% for SG and LG, respectively ($P < 0.001$). (B) Survival curve for matched patients: the 5-year OS rates were 75.2% and 58.7% for SG and LG, respectively ($P < 0.001$).

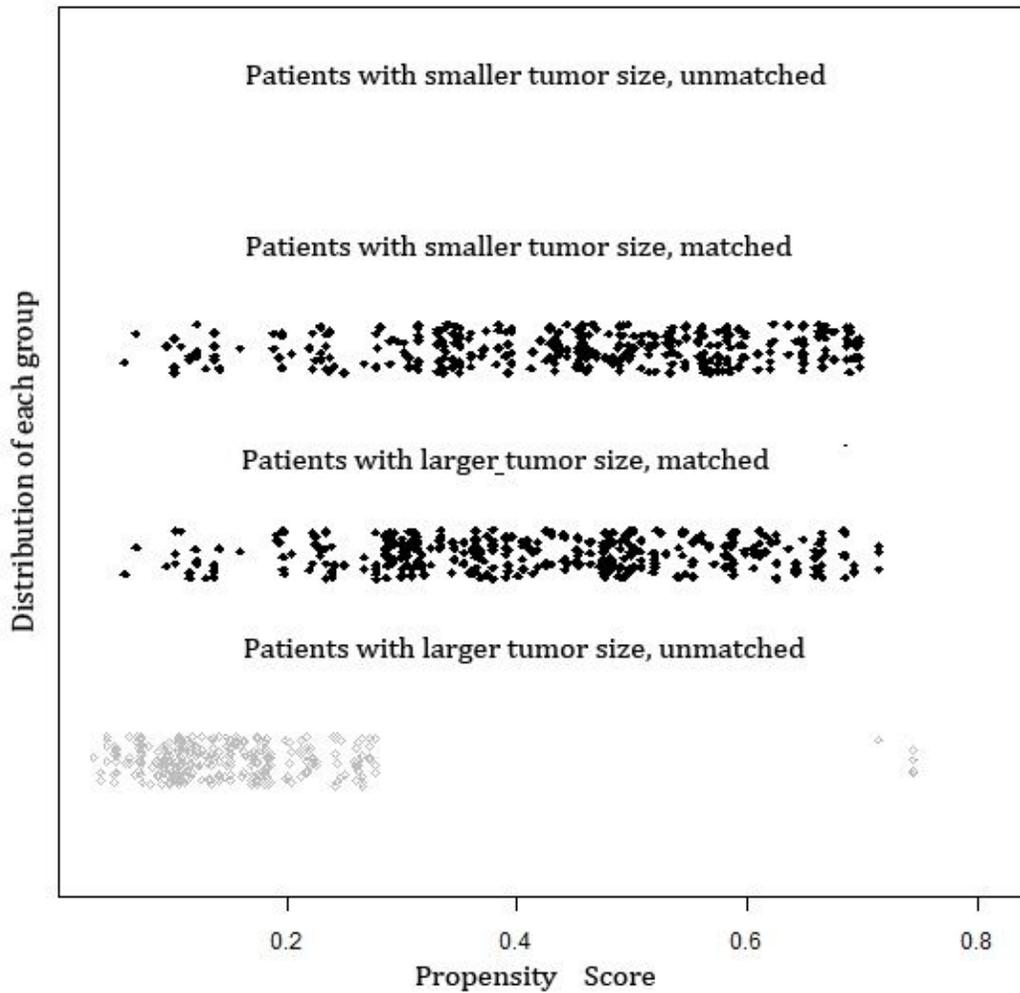


Figure 2

Distribution of the propensity scores. Each circle represents one patients.

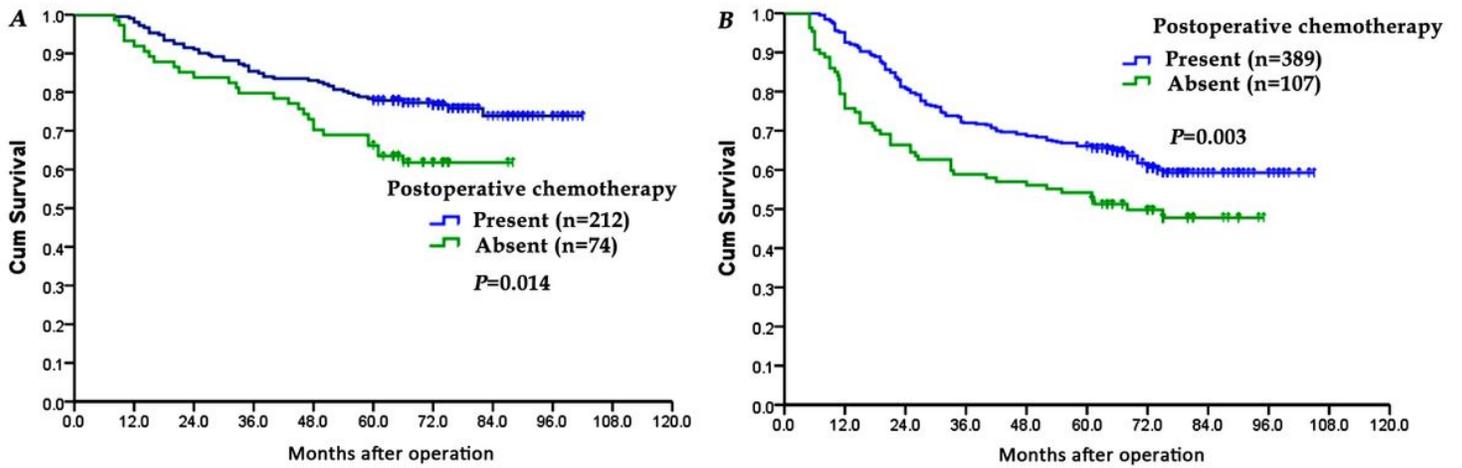


Figure 3

Survival curves of all patients categorized by postoperative chemotherapy. (A) Patients with smaller tumors: the 5-year OS rates were 78.3% and 66.2% for patients with and without chemotherapy ($\chi^2=6.027$, $P=0.014$). (B) Patients with larger tumors: the 5-year OS rates were 66.1% and 54.2% for patients with and without chemotherapy ($\chi^2=8.601$, $P=0.003$).

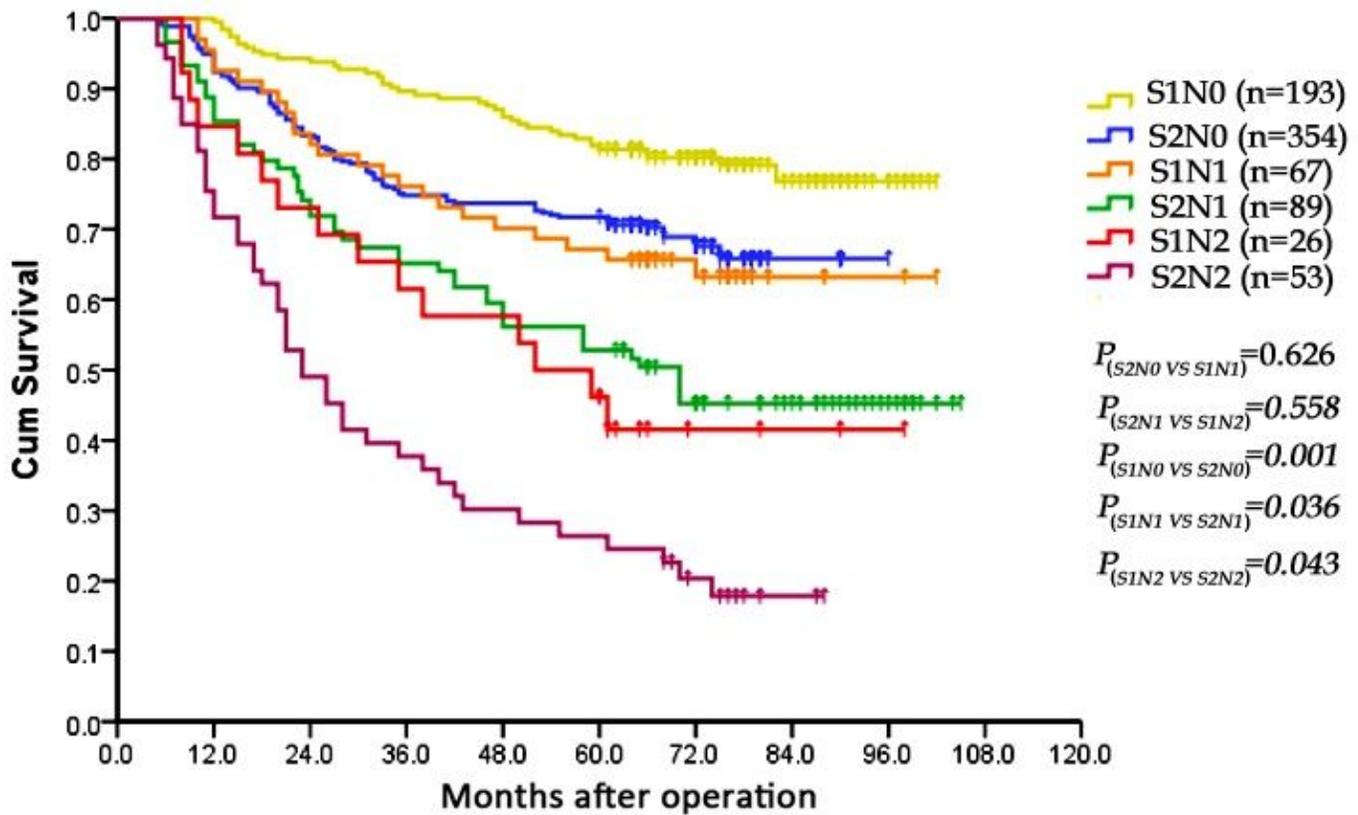


Figure 4

Comparison of survival curves of T4M0 stage patients with different N stages and tumor sizes. The OS of N0-stage patients with S2-size was similar to that of N1-stage patients with S1-size ($P=0.626$). The OS of N1-stage patients with S2-size was equal to that of N2-stage patients with S2-size ($P=0.558$).

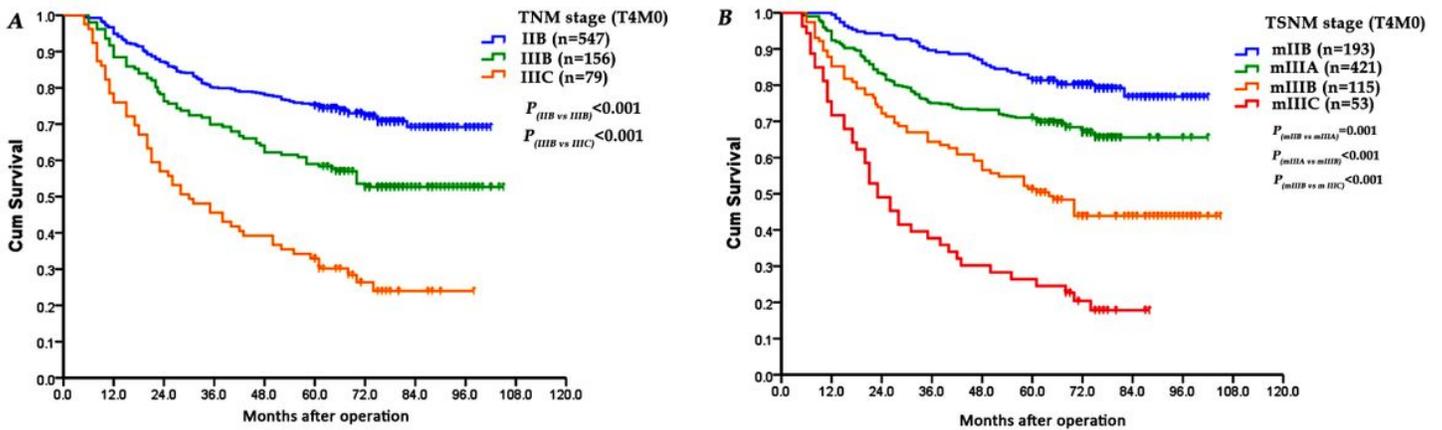


Figure 5

Survival curves of patients according to different tumor stages. (A) TNM stage ($P<0.001$). (B) mTSNM stage ($P<0.001$).

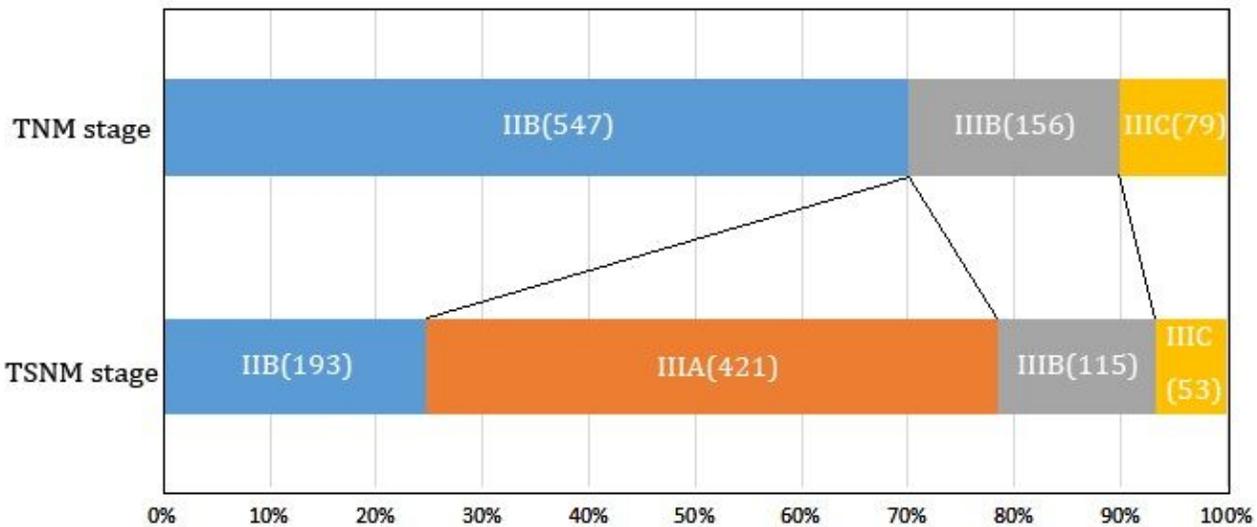


Figure 6

Patients distribution of different classification system. In the TNM staging system, patients were staged from IIB to IIIC, and the largest subgroup was IIB stage, however, there was no IIIA stage. In the mTSNM staging system, patients were continuously distributed from IIB to IIIC stage and the largest subgroup was IIIA stage.