Retrospective Cohort Study

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Identification and initial validation of maximal tumor area as a novel prognostic factor for overall and disease-free survival in patients with resectable colon cancer: a retrospective study

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Background: The tumor area may be a potential prognostic indicator. The present study aimed to determine and validate the prognostic value of tumor area in curable colon cancer.

Methods: This retrospective study included a training and validation cohorts of patients who underwent radical surgery for colon cancer. Independent prognostic factors for overall survival (OS) and disease-free survival (DFS) were identified using Cox proportional hazards regression models. The prognostic discrimination was evaluated using the integrated area under the receiver operating characteristic curves (iAUCs) for prognostic factors and models. The prognostic discrimination between tumor area and other individual factors was compared, along with the prognostic discrimination between the tumor-node-metastasis (TNM) staging system and other prognostic models. Two-sample Wilcoxon tests were carried out to identify significant differences between the two iAUCs. A two-sided $P < 0.05$ was considered statistically significant.

Results: A total of 3051 colon cancer patients were included in the training cohort and 872 patients in the validation cohort. Tumor area, age, differentiation, T stage, and N stage were independent prognostic factors for both OS and DFS in the training cohort. Tumor area had a better OS and DFS prognostic discrimination characteristics than T stage, maximal tumor diameter, differentiation, tumor location, and number of retrieved lymph nodes. The novel prognostic model of T stage + N stage + tumor area (iAUC for OS, 0.714, $P < 0.001$; iAUC for DFS, 0.694, $P < 0.001$) showed a better prognostic discrimination than the TNM staging system (T stage + N stage; iAUC for OS, 0.664; iAUC for DFS, 0.658). Similar results were observed in an independent validation cohort.

Conclusions: Tumor area was identified as an independent prognostic factor for both OS and DFS in curable colon cancer patients, and in cases with an adequate number of retrieved lymph nodes. The novel prognostic model of combining T stage, N stage, and tumor area may be an alternative to the current TNM staging system.

Keywords: colon cancer, prognostic factor, prognostic model, tumor area, tumor size

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Introduction

Colon cancer is one of the leading contributors to the global cancer burden with an increasing incidence and mortality worldwide, especially in the younger population[1,2]. Accurate prognostic stratification is important for determining therapeutic strategies, particularly in patients with advanced colon cancer[3]. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system remains the standard for stratifying the risk and progression of colon cancer[4]. Even though this staging system provides a reliable cancer assessment in order to suggest appropriate therapeutic options, its prognostic discrimination remains limited and imperfect, especially for stage II cases[5–7]. Therefore, there is still a need to develop an additional prognostic factor.

Maximal tumor diameter, that is one-dimensional tumor size, is a potential prognostic indicator for colon cancer[8–10]. Tumor area, or two-dimensional tumor size, also has the potential to be a prognostic indicator. Tumor area and maximal tumor diameter have a comparable performance in predicting lymph node metastasis for early gastric cancer, while tumor area had no advantage over maximal tumor diameter[11]. However, Kim *et al.*[12] have demonstrated that tumor area was better than maximal tumor diameter for predicting lymph node metastasis in early gastric cancer, with a greater specificity and accuracy. Furthermore, Tian *et al.*[13] have found that a larger maximal tumor area was associated with a more advanced TNM stage and disease progression and indicated worse survival outcomes in patients with thymic

HIGHLIGHTS

- Tumor area is an independent prognostic indicator of overall survival and disease-free survival in colon cancer patients.
- The American Joint Committee on Cancer 8th N stage and tumor area showed the best prognostic discrimination for overall survival and disease-free survival.
- The novel prognostic model of combining tumor area, T stage, and N stage had a better prognostic discrimination than the latest tumor-node-metastasis staging system.

Table 1

Clinicopathological characteristics of the training and validation cohorts.

	Training cohort ($n=3051$)			Validation cohort ($n=872$)		
Variables	**No./value**	**5-year OS**	**5-year DFS**	**No./value**	**5-year OS**	**5-year DFS**
Sex						
Females	1332 (43.7%)	80.0%	74.9%	396 (45.4%)	77.5%	72.1%
Males	1719 (56.3%)	77.7%	71.1%	476 (54.6%)	80.9%	73.8%
Age, years						
Median (IQR), years	59 (52–66)	—	—	59 (52–65)	—	—
Maximal tumor diameter						
Median (IQR), cm	5.0 (4.0–6.0)	—	—	5.0 (4.0–6.0)	—	—
Tumor area						
Median (IQR), cm^2	18.8 (12.4–27.5)	—	—	19.6 (12.6–28.3)	—	—
Tumor location						
Ascending colon	1269 (41.6%)	77.7%	72.4%	344 (39.4%)	74.1%	68.6%
Transverse colon	222 (7.3%)	83.0%	77.7%	76 (8.7%)	84.7%	80.8%
Descending colon	271 (8.9%)	77.9%	71.6%	66 (7.6%)	83.9%	76.4%
Sigmoid colon	1289 (42.2%)	79.0%	72.3%	386 (44.3%)	82.2%	74.9%
Differentiation						
Well differentiation	88 (2.9%)	81.3%	80.1%	12 (1.4%)	80.0%	80.0%
Moderate differentiation	2394 (78.4%)	80.1%	74.2%	635 (72.8%)	83.4%	76.2
Poor differentiation	567 (18.6%)	72.2%	65.3%	225 (25.8%)	68.1%	63.9%
Undifferentiation	2 (0.1%)	0	0	0	—	—
No. of retrieved LNs						
Median (IQR)	15 (10–21)	—	—	14 (10–20)	—	—
Inadequate ($n<12$)	956 (31.3%)	75.2%	69.9%	303 (34.7%)	78.1%	73.8%
Adequate ($n\geq12$)	2095 (68.7%)	80.5%	74.2%	569 (65.3%)	80.2%	72.8%
AJCC 8^{th} T stage						
T1 stage	19 (0.6%)	88.9%	88.9%	5 (0.6%)	80.0%	80.0%
T2 stage	62 (2.0%)	94.1%	87.1%	26 (3.0%)	95.5%	90.1%
T3 stage	1643 (53.9%)	81.1%	74.2%	471 (54.0%)	85.4%	77.3%
T4 stage	1327 (43.5%)	75.5%	70.7%	370 (42.4%)	72.0%	67.4%
AJCC 8th N stage						
N0 stage	1193 (39.1%)	82.3%	79.0%	29 (3.3%)	67.9%	65.2%
N1 stage	1305 (42.8%)	80.2%	72.8%	620 (71.1%)	84.3%	78.1%
N2 stage	553 (18.1%)	66.9%	58.9%	223 (25.6%)	66.6%	59.7%
Follow-up						
Median (IQR), months	49.4 (24.9–74.6)	—	—	60.4 (19.8–79.0)	—	—

AJCC, American Joint Committee on Cancer; DFS, disease-free survival; IQR, interquartile range; LNs, lymph nodes; No., number; OS, overall survival.

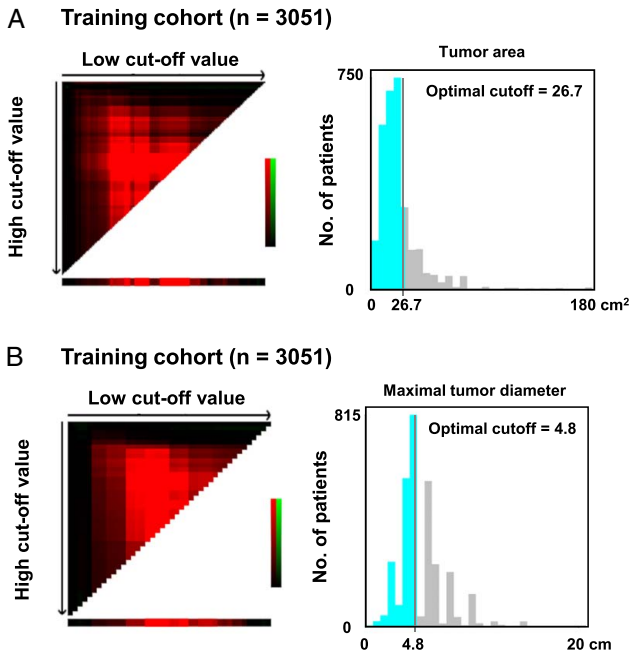

Figure 1. Identification of optimal cut-off values for tumor area and maximal tumor diameter based on the training cohort. Identification of optimal cut-off values for (A) tumor area and (B) maximal tumor diameter.

epithelial tumors. The actual prognostic value of tumor area in colon cancer remains unclear to date, and further investigations comparing the prognostic performance between tumor area and maximal tumor diameter in colon cancer are still needed.

The present study aimed to evaluate the prognostic performance of tumor area in a training cohort and to validate its prognostic discrimination in an external validation cohort of colon cancer. The prognostic discrimination between tumor area and other individual prognostic factors, such as maximal tumor diameter, were compared with an aim of improving the current AJCC 8th TNM staging system.

Patients and methods

Patient cohorts

The present study evaluated two retrospective cohorts, including a training cohort and an external validation cohort, of patients who underwent radical surgery for colon cancer. The training cohort was treated between April 2006 and December 2018 at the Department of Colorectal Surgery of A Hospital. The validation cohort was from the Department of Colorectal Surgery, B Hospital, and was treated between November 2006 and March 2018. All patients included in the study were completely anonymized. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards. The study results were reported according to the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) guidelines[14] (Supplemental Digital Content 1, http://links.lww.com/JS9/A815).

Eligibility criteria

The inclusion criteria were as follows: pathologically confirmed primary and single colon cancer; lack of metastasis (M0); informative pathology data; curable operation without residual macroscopic or microscopic tumors (R0); lack of neoadjuvant chemoradiotherapy (neo-CRT) or chemotherapy (neo-CT); age of less than 75 years; and postoperative survival of greater than 1 month.

The exclusion criteria included: additional malignant neoplasms; stage IV cases with distant metastasis (M1); residual macroscopic or microscopic tumors (R1 resection); neo-CRT or neo-CT; age of greater than or equal to 75 years; postoperative survival of less than or equal to 1 month; and previous or concomitant cancer.

Estimation of maximal tumor area

The present study defined maximal tumor diameter as one-dimensional tumor size and maximal tumor area as two-dimensional tumor size. Considering that colon cancer is generally circumferential or oval in shape, the maximal tumor area was estimated using the following formula: maximal tumor area $= \pi \times R \times r$ (Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A816). The maximal diameter (2R) was defined as the maximal longitudinal diameter of the tumor, while the minimal diameter (2r) was defined as the largest diameter perpendicular to the maximal diameter (Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A816). Accordingly, the maximal diameter and the minimal diameter were collected based on pathological reports for all participants.

Overall survival (OS) and disease-free survival (DFS)

OS represented the duration from pathological diagnosis of colon cancer to death from any cause or last follow-up. DFS represented the duration from pathological diagnosis of colon cancer to locoregional recurrence, occurrence of metachronous colon cancer, distant metastasis, death with no signs or symptoms of recurrence or metastasis, or last follow-up.

Identification of optimal cut-off values for tumor area and maximal tumor diameter

The optimal cut-off values for the tumor area and maximal tumor diameter were identified using the minimal probability by X-tile Version 3.6.1 software based on the training cohort[15]. Clinicopathological factors were compared between the tumor area and the cutoff value based on the identified optimal tumor area cut-off value.

Identification of independent prognostic factors for OS and DFS

Univariate and multivariable analyses were conducted in the training and validation cohorts to identify independent prognostic factors for OS and DFS. Factors of significance in univariate analysis ($P < 0.05$) were incorporated into multivariate analysis. Hazard ratios with 95% CIs were analyzed.

Table 2

Univariate and multivariable analyses of prognostic factors in the training cohort.

	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	1.147 (0.983–1.338)	0.081			1.168 (1.015–1.343)	0.030	1.193 (1.037–1.372)	0.013
Females								
Males								
Age	1.520 (1.306–1.769)	< 0.001	1.525 (1.310–1.774)	< 0.001	1.332 (1.161–1.527)	< 0.001	1.344 (1.171–1.541)	< 0.001
≤ 60 years								
> 60 years								
Maximal tumor diameter	1.402 (1.185–1.660)	< 0.001	1.149 (0.951–1.389)	0.151	1.374 (1.180–1.600)	< 0.001	1.129 (0.951–1.339)	0.165
≤ 4.8 cm								
> 4.8 cm								
Tumor area	1.446 (1.233–1.695)	< 0.001	1.258 (1.050–1.507)	0.013	1.445 (1.251–1.670)	< 0.001	1.291 (1.096–1.521)	0.002
≤ 26.7 cm^2								
> 26.7 cm^2								
Tumor location	0.984 (0.931–1.039)	0.560			0.997 (0.949–1.048)	0.910		
Ascending colon								
Transverse colon								
Descending colon								
Sigmoid colon								
Differentiation	1.468 (1.243–1.734)	< 0.001	1.192 (1.004–1.414)	0.045	1.528 (1.316–1.774)	< 0.001	1.246 (1.068–1.454)	0.005
Well differentiation								
Moderate differentiation								
Poor differentiation								
Undifferentiation								
No. of retrieved LNs	1.149 (0.982–1.344)	0.083			1.115 (0.967–1.287)	0.135		
Adequate ($n \geq 12$)								
Inadequate ($n < 12$)								
AJCC 8th T stage	1.309 (1.133–1.511)	< 0.001	1.419 (1.221–1.649)	< 0.001	1.188 (1.047–1.348)	0.007	1.283 (1.124–1.465)	< 0.001
T1 stage								
T2 stage								
T3 stage								
T4 stage								
AJCC 8th N stage	1.694 (1.531–1.874)	< 0.001	1.718 (1.551–1.903)	< 0.001	1.754 (1.600–1.923)	< 0.001	1.751 (1.595–1.923)	< 0.001
N0 stage								
N1 stage								
N2 stage								

AJCC, American Joint Committee on Cancer; HR, hazard ratio; LNs, lymph nodes.

Assessment of the optimal tumor area cut-off value

Five-year OS and DFS were compared based on the cutoff value of tumor area for the entire population, all subgroups, and patients with an adequate number of retrieved lymph nodes in the training and validation cohorts. Log-rank tests and Cox proportional hazards models with hazard ratios were also used.

Comparison of prognostic discrimination among prognostic factors and models

The prognostic discrimination of tumor-related prognostic factors and models was evaluated using the integrated area under the receiver operating characteristic curves with 1000 × bootstrap resampling, as described previously[3]. The iAUC was utilized to analyze the prognostic discrimination of an individual prognostic factor or a prognostic model by regarding the model as a nomogram. A higher iAUC value suggested a better prognostic discrimination ability. The prognostic discrimination was compared between tumor area and other individual factors, as well as between the AJCC 8th TNM staging system (T stage + N stage) and other prognostic models, including T stage + tumor area, N stage + tumor area, and T stage + N stage + tumor area. Two-sample Wilcoxon tests were used to identify significant differences between the two integrated area under the receiver operating characteristic curves[16].

Statistical analyses

All analyses were performed using SPSS version 22.0 (SPSS Inc.) and R version 4.2.2 (R Foundation for Statistical Computing) software with two-sided tests. A *P* value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 3051 colon cancer patients were included in the training cohort and 872 patients in the validation cohorts. The

Table 3

Univariate and multivariable analyses of prognostic factors in the validation cohort.

	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sex	0.985 (0.769–1.262)	0.904			1.046 (0.829–1.319)	0.705		
Females								
Males								
Age	1.503 (1.174–1.926)	0.001	1.499 (1.167–1.925)	0.002	1.384 (1.098–1.745)	0.006	1.400 (1.109–1.769)	0.005
≤ 60 years								
> 60 years								
Maximal tumor diameter	1.644 (1.240–2.178)	0.001	1.223 (0.885–1.690)	0.222	1.500 (1.157–1.944)	0.002	1.145 (0.851–1.541)	0.372
≤ 4.8 cm								
> 4.8 cm								
Tumor area	1.627 (1.263–2.097)	< 0.001	1.340 (1.000–1.796)	0.050	1.557 (1.227–1.977)	< 0.001	1.345 (1.023–1.768)	0.034
≤ 26.7 cm^2								
> 26.7 cm^2								
Tumor location	0.887 (0.790–0.996)	0.043	0.967 (0.854–1.094)	0.593	0.906 (0.813–1.010)	0.074		
Ascending colon								
Transverse colon								
Descending colon								
Sigmoid colon								
Differentiation	1.424 (1.102–1.841)	0.007	1.196 (0.914–1.565)	0.191	1.407 (1.107–1.788)	0.005	1.193 (0.931–1.530)	0.163
Well differentiation								
Moderate differentiation								
Poor differentiation								
Undifferentiation								
Number of retrieved LNs	1.136 (0.879–1.469)	0.329			1.185 (0.930–1.510)	0.171		
Adequate ($n \geq 12$)								
Inadequate ($n < 12$)								
AJCC 8th T stage	1.476 (1.167–1.867)	0.001	1.324 (1.041–1.685)	0.022	1.351 (1.092–1.671)	0.006	1.215 (0.997–1.511)	0.080
T1 stage								
T2 stage								
T3 stage								
T4 stage								
AJCC 8th N stage	1.735 (1.355–2.224)	< 0.001	1.631 (1.261–2.110)	< 0.001	1.741 (1.382–2.194)	< 0.001	1.645 (1.294–2.092)	< 0.001
N0 stage								
N1 stage								
N2 stage								

AJCC, American Joint Committee on Cancer; HR, hazard ratio; LNs, lymph nodes.

baseline characteristics of the training and validation cohorts are presented in Table 1. Patients had a median age of 59 years in both cohorts. The median maximal tumor diameters of both cohorts were 5.0 cm. The median tumor area was 18.8 cm^2 in the training cohort and 19.6 cm^2 in the validation cohort. The median number of retrieved lymph nodes was 15 in the training cohort and 14 in the validation cohort. A follow-up was conducted every 3–6 months until the last follow-up. The median follow-up period was 49.4 months in the training cohort and 60.4 months in the validation cohort.

Identification of optimal cut-off values for tumor area and maximal tumor diameter

The optimal cut-off value for the tumor area was 26.7 cm^2 based on the training cohort (Fig. 1A). Patients were accordingly categorized into groups with tumor areas of less than or equal to 26.7 and greater than 26.7 cm^2. Furthermore, the optimal cut-off value for the maximal tumor diameter was 4.8 cm (Fig. 1B). Patients were categorized into groups with maximal tumor diameters of less than or equal to 4.8 and greater than 4.8 cm.

Identification of independent prognostic factors for OS and DFS

In the training cohort, tumor area ($P = 0.013$), age ($P < 0.001$), differentiation ($P = 0.045$), AJCC 8th T stage ($P < 0.001$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for OS using multivariate analysis (Table 2). Tumor area ($P = 0.002$), sex ($P = 0.013$), age ($P < 0.001$), differentiation ($P = 0.005$), AJCC 8th T stage ($P < 0.001$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for DFS (Table 2).

In the validation cohort, age ($P = 0.002$), AJCC 8th T stage ($P = 0.022$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for OS (Table 3). Tumor area ($P = 0.034$), age ($P = 0.005$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for DFS (Table 3).

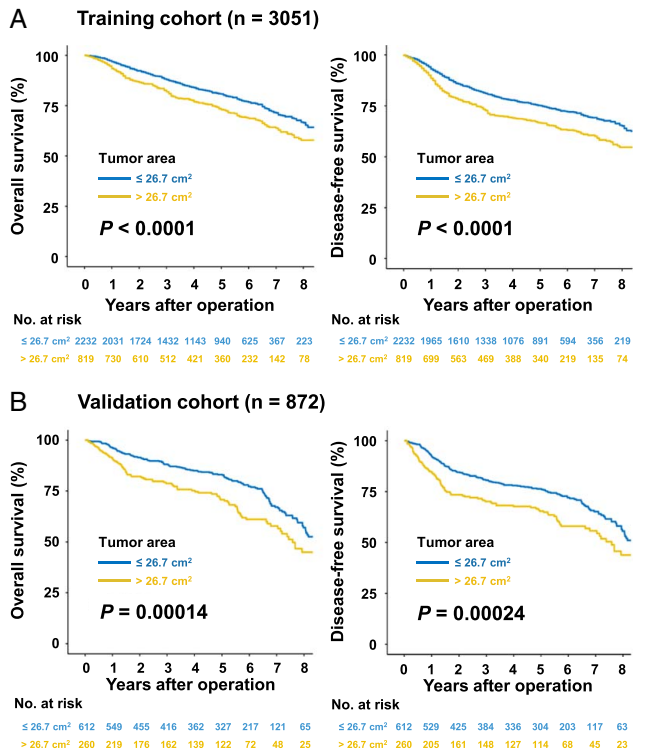

Figure 2. Kaplan–Meier estimates of overall and disease-free survival for the entire cohorts stratified by tumor area. Curves for the (A) training and (B) validation cohorts stratified by tumor area.

Univariate and multivariate analyses were also conducted in patients with adequate number (≥ 12) of retrieved lymph nodes for both OS and DFS (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A817, Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A818). In the training cohort, tumor area ($P = 0.008$), age ($P < 0.001$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for OS by multivariate analysis (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A817). Tumor area ($P = 0.001$), age ($P = 0.002$), differentiation ($P = 0.011$), and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for DFS by multivariate analysis (Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A817).

In the validation cohort, tumor area ($P = 0.007$) and AJCC 8th N stage ($P < 0.001$) were identified as independent prognostic factors for OS by multivariate analysis (Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A818). Tumor area ($P = 0.009$) and AJCC 8th N stage ($P < 0.001$) were also determined as independent prognostic factors for DFS by multivariate analysis (Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A818).

Assessment of the optimal tumor area cut-off value

In the training cohort, patients with a tumor area of less than or equal to 26.7 cm^2 had a significantly better 5-year OS and DFS rates than patients with a tumor area of greater than 26.7 cm^2 for the entire population (Fig. 2A, Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/JS9/A819). A larger tumor area was a significant risk factor for OS and DFS in the subgroups of males, females, individuals aged less than or equal to 60 years, individuals aged greater than 60 years, individuals with tumors located in ascending colon, sigmoid colon, as well as patients with moderate differentiation, greater than or equal to 12 retrieved lymph nodes, less than 12 retrieved lymph nodes, AJCC 8th T3 stage, T4 stage, N0 stage, N1 stage, and N2 stage (Fig. 3A, Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/JS9/A819).

In the validation cohort, patients with a tumor area of less than or equal to 26.7 cm^2 had a significantly better 5-year OS and DFS rates than patients with a tumor area of greater than 26.7 cm^2 for the entire population (Fig. 2B, Supplementary Table 4, Supplemental Digital Content 6, http://links.lww.com/JS9/A820). Similarly, a larger tumor area was a significant risk factor for OS and DFS in the subgroups of males, patients aged greater than 60 years, individuals with tumors located in the ascending colon, as well as individuals with moderate differentiation, greater than or equal to 12 retrieved lymph nodes, AJCC 8th T4 stage, N0 stage, N1 stage, and N2 stage (Fig. 3B, Supplementary Table 4, Supplemental Digital Content 6, http://links.lww.com/JS9/A820).

Comparison of prognostic discrimination between tumor area and other factors

Tumor area in the training cohort had a better prognostic discrimination (iAUC for OS, 0.623; iAUC for DFS, 0.596) than the AJCC 8th N stage (iAUC for OS, 0.621, $P < 0.001$), AJCC 8th T stage (iAUC for OS, 0.552, $P < 0.001$; iAUC for DFS, 0.546, $P < 0.001$), maximal tumor diameter (iAUC for OS, 0.537, $P < 0.001$; iAUC for DFS, 0.533, $P < 0.001$), differentiation (iAUC for OS, 0.533, $P < 0.001$; iAUC for DFS, 0.535, $P < 0.001$), tumor location (iAUC for OS, 0.524, $P < 0.001$; iAUC for DFS, 0.517, $P < 0.001$), and number of retrieved lymph nodes (iAUC for OS, 0.514, $P < 0.001$; iAUC for DFS, 0.512, $P < 0.001$; Table 4). Only the AJCC 8th N stage showed a better prognostic discrimination (iAUC for DFS, 0.624, $P < 0.001$) than the tumor area.

In the validation cohort, tumor area had a better prognostic discrimination (iAUC for OS, 0.551; iAUC for DFS, 0.546) than the AJCC 8th T stage (iAUC for OS, 0.543, $P < 0.001$; iAUC for DFS, 0.532, $P < 0.001$), maximal tumor diameter (iAUC for DFS, 0.541, $P < 0.001$), differentiation (iAUC for OS, 0.539, $P < 0.001$; iAUC for DFS, 0.536, $P < 0.001$), tumor location (iAUC for OS, 0.533, $P < 0.001$; iAUC for DFS, 0.527, $P < 0.001$), and number of retrieved lymph nodes (iAUC for OS, 0.516, $P < 0.001$; iAUC for DFS, 0.518, $P < 0.001$; Table 5). Only the AJCC 8th N stage showed a better prognostic discrimination (iAUC for OS, 0.583, $P < 0.001$; iAUC for DFS, 0.579, $P < 0.001$) than the tumor area.

Comparison of prognostic discrimination among prognostic models

In the training cohort, the prognostic models of T stage + N stage + tumor area (iAUC for OS, 0.714, $P < 0.001$; iAUC for DFS, 0.694, $P < 0.001$) and N stage + tumor area (iAUC for OS, 0.686, $P < 0.001$; iAUC for DFS, 0.671, $P < 0.001$) showed a better prognostic discrimination than the AJCC 8th TNM staging system (T stage + N stage) (iAUC for OS, 0.664; iAUC for DFS, 0.658; Table 4).

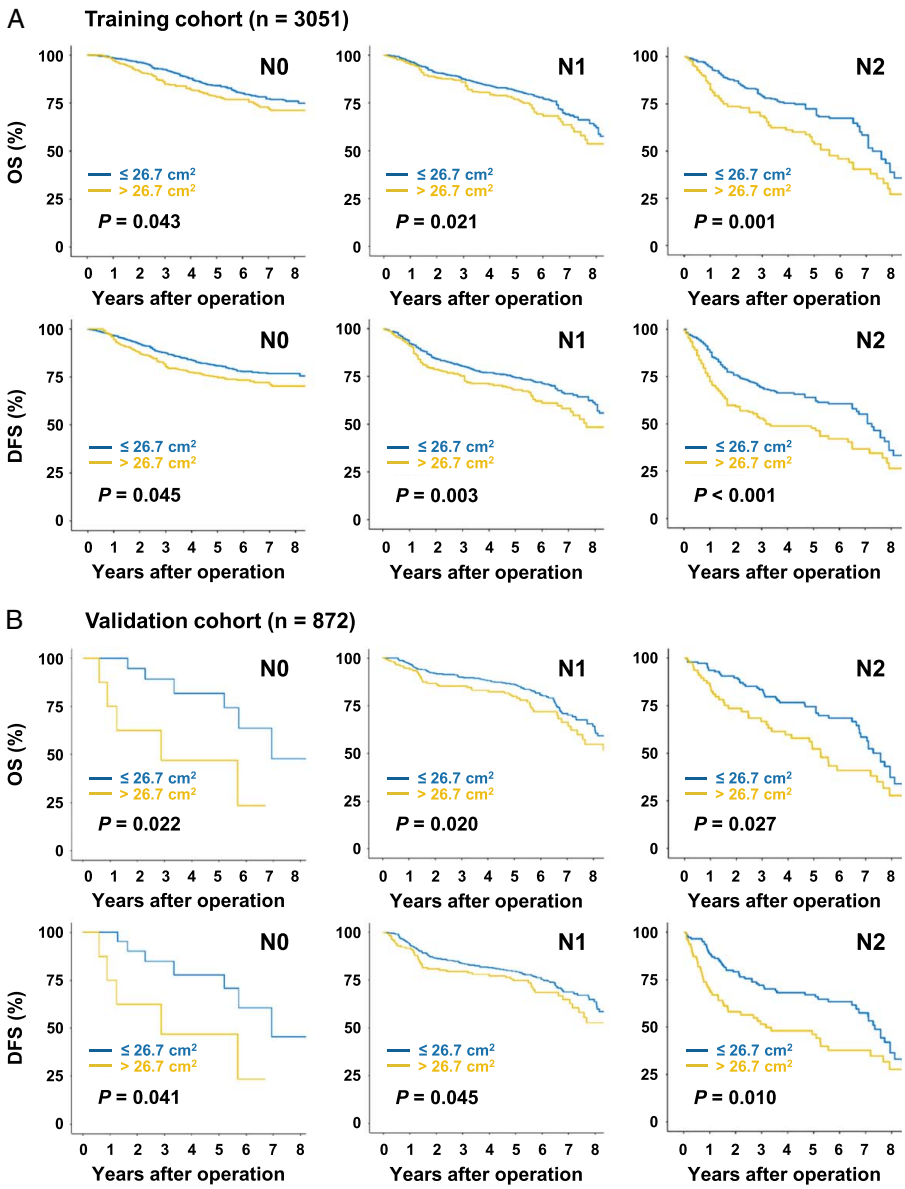

Figure 3. Kaplan–Meier estimates of overall and disease-free survival for AJCC 8th N substages (N0, N1, and N2) stratified by tumor area. Curves for the (A) training and (B) validation cohorts stratified by tumor area.

In the validation cohort, the prognostic models of T stage + N stage + tumor area (iAUC for OS, 0.624, $P < 0.001$; iAUC for DFS, 0.613, $P < 0.001$) and N stage + tumor area (iAUC for DFS, 0.603, $P < 0.001$) showed a better prognostic discrimination than the AJCC 8th TNM staging system (T stage + N stage) (iAUC for OS, 0.609; iAUC for DFS, 0.598; Table 5).

Discussion

Colon cancers have irregular contours and morphological differences[17,18], and accurately determining tumor growth is therefore clinically difficult. New measurement techniques need to balance practicality and complexity. Measuring the tumor area is potentially simple and clinically convenient. However, the prognostic value of tumor area in colon cancer is still unknown. Furthermore, it is unclear if two-dimensional tumor size, that is tumor area, has a better prognostic discrimination than one-dimensional tumor size or maximal tumor diameter in colon cancer.

The present study found that the tumor area, AJCC 8th T stage, N stage, differentiation, and age were independent prognostic factors for both OS and DFS in the training cohort. Notably, tumor area had a better OS and DFS prognostic discriminations than the AJCC 8th T stage, maximal tumor diameter, differentiation, tumor location, and number of retrieved lymph nodes. The novel prognostic model of combining the AJCC 8th T stage, N stage, and tumor area had a better prognostic discrimination than the AJCC 8th TNM staging system (AJCC 8th T stage + N stage). Consistent findings were observed in an independent validation cohort.

Table 4

Prognostic discrimination of pathological prognostic factors and prognostic models in the training cohort.

	Overall survival Wilcox test for iAUCs		Disease-free survival Wilcox test for iAUCs	
Prognostic factors or models	**iAUC* (95% CI)**	**$P^{\dagger}$**	**iAUC* (95% CI)**	**$P^{\dagger}$**
Prognostic factors				
Tumor area ($\leq 26.7/>26.7$ cm^2) (referent factor)	0.623 (0.601–0.645)	—	0.596 (0.578–0.616)	—
N stage (N0/N1/N2)	0.621 (0.598–0.643)	< 0.001	0.624 (0.603–0.643)	< 0.001
T stage (T1/T2/T3/T4)	0.552 (0.534–0.571)	< 0.001	0.546 (0.534–0.562)	< 0.001
Maximal tumor diameter ($\leq$ 4.8/> 4.8 cm)	0.537 (0.521–0.553)	< 0.001	0.533 (0.518–0.547)	< 0.001
Differentiation (well/moderate/poor-undifferentiation)	0.533 (0.516–0.550)	< 0.001	0.535 (0.519–0.551)	< 0.001
Tumor location (ascend/transverse/descend/sigmoid)	0.524 (0.510–0.542)	< 0.001	0.517 (0.507–0.531)	< 0.001
No. of retrieved LNs (inadequate/adequate)	0.514 (0.500–0.530)	< 0.001	0.512 (0.500–0.527)	< 0.001
Prognostic models				
AJCC 8th TNM staging system (T stage + N stage) (referent model)	0.664 (0.640–0.687)	—	0.658 (0.636–0.678)	—
T stage + tumor area	0.658 (0.636–0.679)	< 0.001	0.632 (0.612–0.652)	< 0.001
N stage + tumor area	0.686 (0.664–0.712)	< 0.001	0.671 (0.649–0.694)	< 0.001
T stage + N stage + tumor area	0.714 (0.691–0.739)	< 0.001	0.694 (0.672–0.717)	< 0.001

iAUC, integrated Area Under the Curve; LNs, lymph nodes; N stage, AJCC 8th N stage;
T stage, AJCC 8th T stage.
*A higher iAUC indicates a better model discrimination.
†Two-sample Wilcox test for iAUCs, comparing with tumor area, or AJCC 8th TNM staging system (T stage + N stage).

During the process of carcinogenesis, cancer cells may spread vertically and horizontally[8]. A well-established prognostic factor, such as the AJCC T category, reflects how a vertically-oriented tumor invades through the intestinal wall[4,19]. As a determinant of tumor size, maximal tumor diameter has been widely used to evaluate horizontal tumor growth, but its prognostic performance remains controversial[8–10,20]. The present study found that maximal tumor diameter was not an independent prognostic factor for either OS or DFS in the training and validation cohorts. It is possible that solid tumors grow three-dimensionally, with unequal rates of tumor spread in different dimensions[8], such that maximal tumor diameter does not accurately reflect overall tumor growth or total malignant cell burden.

The study then focused on the prognostic discrimination between tumor area and other factors. The AJCC 8th N stage showed the best prognostic discrimination among all factors, which was in line with previous studies[3,21,22]. After the AJCC 8th N stage, tumor area had a better prognostic discrimination than maximal tumor diameter, the AJCC 8th T stage, differentiation, tumor location, and the number of retrieved lymph nodes in terms of both OS and DFS. Similar findings were observed in an independent validation cohort, suggesting that tumor area is a promising prognostic factor. Furthermore, the novel prognostic model of combining the AJCC 8th T stage, N stage, and tumor area had a better prognostic discrimination than the latest AJCC 8th TNM staging system (T stage + N stage) in both the training and validation cohorts. This finding can

Table 5

Prognostic discrimination of pathological prognostic factors and prognostic models in the validation cohort.

	Overall survival Wilcox test for iAUCs		Disease-free survival Wilcox test for iAUCs	
Prognostic factors or models	**iAUC* (95% CI)**	**$P^{\dagger}$**	**iAUC* (95% CI)**	**$P^{\dagger}$**
Prognostic factors				
Tumor area ($\leq 26.7/>26.7$ cm^2) (referent factor)	0.551 (0.520–0.582)	—	0.546 (0.518–0.576)	—
N stage (N0/N1/N2)	0.583 (0.550–0.619)	< 0.001	0.579 (0.548–0.610)	< 0.001
T stage (T1/T2/T3/T4)	0.543 (0.514–0.572)	< 0.001	0.532 (0.504–0.557)	< 0.001
Maximal tumor diameter ($\leq 4.8/>4.8$ cm)	0.551 (0.526–0.576)	N.S.	0.541 (0.517–0.565)	< 0.001
Differentiation (well/moderate/poor-undifferentiation)	0.539 (0.510–0.571)	< 0.001	0.536 (0.511–0.565)	< 0.001
Tumor location (ascend/transverse/descend/sigmoid)	0.533 (0.504–0.564)	< 0.001	0.527 (0.501–0.557)	< 0.001
No. of retrieved LNs (inadequate/adequate)	0.516 (0.499–0.541)	< 0.001	0.518 (0.499–0.543)	< 0.001
Prognostic models				
AJCC 8th TNM staging system (T stage + N stage) (referent model)	0.609 (0.573–0.647)	—	0.598 (0.564–0.632)	—
T stage + tumor area	0.575 (0.539–0.611)	< 0.001	0.563 (0.532–0.595)	< 0.001
N stage + tumor area	0.610 (0.571–0.649)	N.S.	0.603 (0.568–0.641)	< 0.001
T stage + N stage + tumor area	0.624 (0.585–0.668)	< 0.001	0.613 (0.577–0.653)	< 0.001

*A higher iAUC indicates a better model discrimination.
†Two-sample Wilcox test for iAUCs, comparing with tumor area, or AJCC 8th TNM staging system (T stage + N stage).
iAUC, integrated Area Under the Curve; LNs, lymph nodes; N stage, AJCC 8th N stage; N.S., no significance; T stage, AJCC 8th T stage.

supports the idea that two-dimensional tumor size, or tumor area, reflects actual tumor growth and prognosis more accurately than one-dimensional tumor size, or maximal tumor diameter.

Furthermore, prognostic discrimination of tumor area was assessed in the entire population and in each AJCC 8th N substage (N0, N1, and N2) in the training cohort. Patients in the entire population and each AJCC 8th N substage could be divided into two groups of significantly different OS and DFS, where a larger tumor area was associated with poorer survival than a smaller tumor area. Importantly, similar findings were observed in the external validation cohort. Based on these results, tumor area can be considered a powerful prognostic indicator in patients with colon cancer.

There are several limitations in the present study. First, the relationship between tumor area and adjuvant therapy was not explored. Second, it is difficult to calculate a precise colon cancer tumor area in a clinical setting. The determination of the minimal and maximal diameters relied on pathological reports, possibly introducing potential measurement errors and subjectivity. This may affect the accuracy of the tumor area. Besides, interrater reliability for r and R measurements was not assessed, which may introduce variability in the results. The formula used assumes an oval or circumferential tumor shape, which may not always be applicable to all cases of colon cancer in a clinical setting. Future studies should consider evaluating interrater reliability to ensure consistency. The tumor area estimated in the current study was not precise, which is a limitation that must be acknowledged, and there is still a need for a more reliable method of calculating it. Third, the comparisons among one-dimensional tumor size (i.e. maximal tumor diameter), two-dimensional tumor size (i.e. tumor area), and three-dimensional tumor size (i.e. tumor volume) are still needed in future studies[23]. Therefore, more research is needed to validate the main findings of the current study.

Conclusion

In summary, tumor area was identified to be an independent prognostic factor for both OS and DFS in patients with curable colon cancer, and in cases with an adequate number of retrieved lymph nodes. The novel prognostic model of combining T stage, N stage, and tumor area may be an alternative to the current AJCC TNM staging system. However, the main findings of the present study still require a further validation.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Boards of Liaoning Cancer Hospital and Institute (20210401K) and Institutional Review Boards of Harbin Medical University Cancer Hospital (KY2022-11).

Consent

In this retrospective, observational study, all patients were completely anonymized, and informed consent was therefore not necessary.

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Author contribution

F.L.N., R.Z., L.Z.D., W.J.G., and C.D.Z.: participated in the conception and design; F.L.N., R.Z., L.Z.D., and Y.L.L.: carried out analysis and interpretation of the data; F.L.N., R.Z., L.Z.D., W.J.G., and C.D.Z.: drafted the paper, revised it critically for intellectual content; F.L.N., R.Z., L.Z.D., W.Y.D., Y.J.Z., J.K.Z., M.A., W.J.G., Y.L.L., and C.D.Z.: approved the final version to be published. All authors have read and agreed to the final version of the manuscript.

Conflicts of interest disclosure

The authors declare that there are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: research-registry9024.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/

Guarantor

Chun-Dong Zhang.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available (due to the reason that another project by our team is ongoing using the same dataset), but are available from the lead corresponding author (Chun-Dong Zhang) on reasonable request.

Provenance and peer review

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