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GASTROINTESTINAL

Extent of enhancement on multiphase contrast-enhanced CT images is a potential prognostic factor of stage I–III colon cancer

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Abstract

Objective By evaluating extent of tumour enhancement on preoperative contrast-enhanced MDCT, we aimed to establish an imaging-based model to predict cancer-specific survival in stage I–III colon cancer.

Methods A total of 548 stage I–III colon cancer patients who underwent curative resection from 2007 to 2013 were retrospectively included and divided into primary cohort and validation cohort according to admission time. The attenuation coefficient of each colon cancer was measured on the workstation by drawing the ROI in CT images. The enhancement ratio was calculated using maximum tumour attenuation value in triphasic MDCT scanning divided by the minimum. Patients were divided into low/high-enhancement groups according to the optimal cut-off value derived from time-dependent ROC curve. Kaplan–Meier method and COX regression analysis were adopted to evaluate prognostic value of variables. A nomogram for prognosis was conducted on the basis of a multivariate Cox proportional hazard model.

Results No significant differences were observed in age, sex, pTNM stage, perioperative chemoradiotherapy, serum CEA, tumour size, tumour localisation and histologic type between low- and high-enhancement groups. The high-enhancement group had a significantly shorter cancer-specific survival rate (69.5%) than the low-enhancement group (85.9%) ($p < 0.001$). Subgroup analysis indicated that high-enhancement state was closely associated with increased risk of colon cancer mortality in stage I ($p = 0.033$), stage II ($p = 0.002$) and stage III ($p = 0.014$). Cox regression analysis indicated the extent of enhancement was an independent prognostic factor (HR 2.258, 95% CI 1.476–3.455; $p < 0.001$).

Conclusions The extent of tumour enhancement on MDCT can serve as a potential risk factor for stage I–III colon cancer.

Key Points
- *Survival rates of stage I–III colon cancer vary widely even within the same stage.*
- *Prognostic value of the extent of tumour enhancement on MDCT was assessed.*
- *The high-enhancement group had a significantly shorter cancer-specific survival rate.*

Keywords Multidetector computed tomography · Colonic neoplasms · Prognosis

Zhanhuai Wang and Yao Ye contributed equally to this work.

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Abbreviations

CRC Colorectal cancer
MDCT Multidetector-row computed tomography

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignant tumours worldwide. In the USA, 134,490 new cases were diagnosed with CRC and 49,190 died from CRC in 2016 [1]. In China, 376,300 new cases were diagnosed with CRC and 191,000 died from CRC in 2015 [2]. The large numbers of CRC patients need appropriate treatments and regular follow-ups according to risk factors [2]. Postoperative adjuvant chemotherapy for colon cancer is currently required for stage III and high-risk subgroups in stage II diseases [3]. Nevertheless, chemotherapy agents may involve various toxic substances, such as oxaliplatin, that can cause long-term peripheral neuropathy [4]. It is still a controversial issue whether 6-month-long adjuvant chemotherapy for low-risk (T1–3N1) stage III disease can be shortened [5]. Meanwhile, selecting the high-risk subgroup from stage II colon cancer that will truly benefit from adjuvant chemotherapy is difficult [6, 7]. It is a great challenge to make a balance between reducing disease recurrence and limiting chemotoxicity. In fact, CRC is a heterogeneous disease and the prognoses of individual patients of each stage vary widely despite the standard treatment [8]. Highly precise tests based on patients' prognostic and predictive information are required in order to select optimal treatments for personalised management based on guidelines.

The emergence of dynamic multidetector CT (MDCT) stimulated the interest of clinicians because its high-resolution images provide a non-invasive method of differential diagnosis and preoperative tumour staging [9]. The use of intravenous contrast agents is essential to complete the staging of colorectal cancer and to evaluate recurrent or metastatic lesions [10]. As the liver is the most frequent site of metastatic colorectal cancer, preoperative abdominal triphasic MDCT scanning is routinely performed in our centre for differential diagnosis of liver lesions. Tumour density is one of the parameters measured in the form of CT attenuation coefficient (Hounsfield unit, HU). The contrast enhancement state of tumour density in the region of interest (ROI) under dynamic CT is closely related to the amount of contrast material passing through the tumour region. This process can be used to assess the functional vascularity of a region [11]. Moreover, the enhancement state of tumour density in MDCT images has been suggested as an indicator for target therapy response evaluation [12, 13].

Recently, tumour enhancement state in MDCT was indicated as a long-term prognostic factor by several studies [14–16]. However, the results need further validation because of the limited case numbers. We also would like to determine whether tumour enhancement state in MDCT is related to the clinical outcome of colon cancer. In this retrospective study, we hypothesised that the extent of tumour enhancement on preoperative multiphase contrast-enhanced CT images could serve as a prognostic factor for stage I–III colon cancer. The aim of this study was to establish an imaging-based model to predict cancer-specific survival in stage I–III colon cancer.

Materials and methods

Ethics statement

Colon cancer tissues were obtained from the Second Affiliated Hospital of Zhejiang University School of Medicine with written consent of each individual and approval by the Research Ethics Board of the Second Affiliated Hospital of Zhejiang University. Data were collected anonymously and the clinical study was carried out in accordance with the Declaration of Helsinki.

Patients

From January 2007 to December 2013, stage I–III colon cancer patients with preoperatively obtained MDCT imaging were consecutively included. Exclusion criteria were stage IV colon cancer, no contrast, poor visualisation of tumour and previous colectomy or proctectomy, and failure of follow-up. The included patients were divided into two cohort, a primary cohort and a validation cohort, according to admission time [17]. The patients admitted in 2007 to 2011 were regarded as the primary cohort and those admitted in 2012 to 2013 were included in the validation cohort. The primary outcome of this study was 5-year cancer-specific survival. Patients underwent a curative surgical procedure with en bloc regional lymph node dissection. Tumour stage was determined by the 2010 American Joint Committee on Cancer (AJCC) staging system [8]. Postoperative adjuvant chemotherapy and follow-ups were performed according to the guidelines of the National Comprehensive Cancer Network (www.nccn.org). All cases were regularly followed.

CT protocol

CT scans were conducted by a second-generation dual-source CT (Statel: SOMATOM Definition AS and Sensation 16, Siemens Medical Solutions, Forchheim, Germany). A total of 80–120 ml of iodine-containing contrast agent (Statel: Ultravist 300, Bayer AG, Berlin, Germany) was injected using an automated injector (Statel: Mallinckrodt, New Jersey, USA) at a flow rate of 3 ml/s, followed by 50 ml of 0.9% saline solution with the same flow rate. A delay of 8 s was observed before image acquisition; the delay was based on the measured transit time of each individual through the test bolus method. Images of the arterial phase were obtained using the bolus tracking method. Briefly, arterial phase scanning started when Hounsfield units approached 100 in the abdominal aorta at the level of the renal hilum. Scanning delay was conducted between the time the contrast material injection started and early arterial phase scanning started at an average time of 20 s (range of 15–28 s). Late arterial phase and portal venous phase imaging were obtained at 16 s and 50 s after the start of early arterial phase. An external workstation (Statel: Syngo Multi-Modality Workplace VE36A, Siemens Medical Solutions, Munich, Germany) was used to receive and reconstruct the images.

Analysis of CT images

Two radiologists (observer CY and observer HSG, 7 years of experience) who are majoring in gastrointestinal imaging independently analysed CT images in the digital workstation retrospectively. They were not aware of the postoperative clinicopathologic tumour data. Colon cancer lesions were located with the reference of colonoscopic findings as well as typical features in axial and coronal reformatted images under MDCT (i.e. intraluminal mass, eccentric colonic wall thickening, pericolic fat stranding and lymph node involvement) [10]. Thereafter, representative sectional images with maximal tumour diameter were chosen by consensus of the two radiologists for further evaluation (Figs. 1 and 2). The attenuation coefficient (density) of each tumour in CT images was measured in HU in the following procedure. In brief, the attenuation coefficient in CT images of each colon cancer was measured on the workstation by drawing the ROI on the images. ROI was chosen in the tumour edge without obvious necrotic areas and an air–tumour interface was kept away to avoid measurement errors. In this study, we counted attenuation values of three adjacent representative sectional images with maximal tumour diameters to reach the mean value. Attenuation values of tumour in each phase on MDCT triphasic scanning were also counted. Maximum attenuation value on triphasic MDCT scanning was chosen and minimum attenuation value of tumour was recorded in plain scanning phase without contrast. The enhancement ratio was calculated using maximum tumour attenuation value in triphasic MDCT scanning divided by the minimum.

Histopathologic analysis

Surgical specimens were cut, fixed and stained with haematoxylin and eosin. Depth of tumour size, tumour penetration, histologic type and grade, lymphovascular invasion, perineural invasion, lymph node metastasis, extranodal tumour deposits and pTNM category were evaluated by a gastrointestinal pathologist (with 10 years of experience) according to the principles of pathologic review in the NCCN guidelines and recorded in this study.

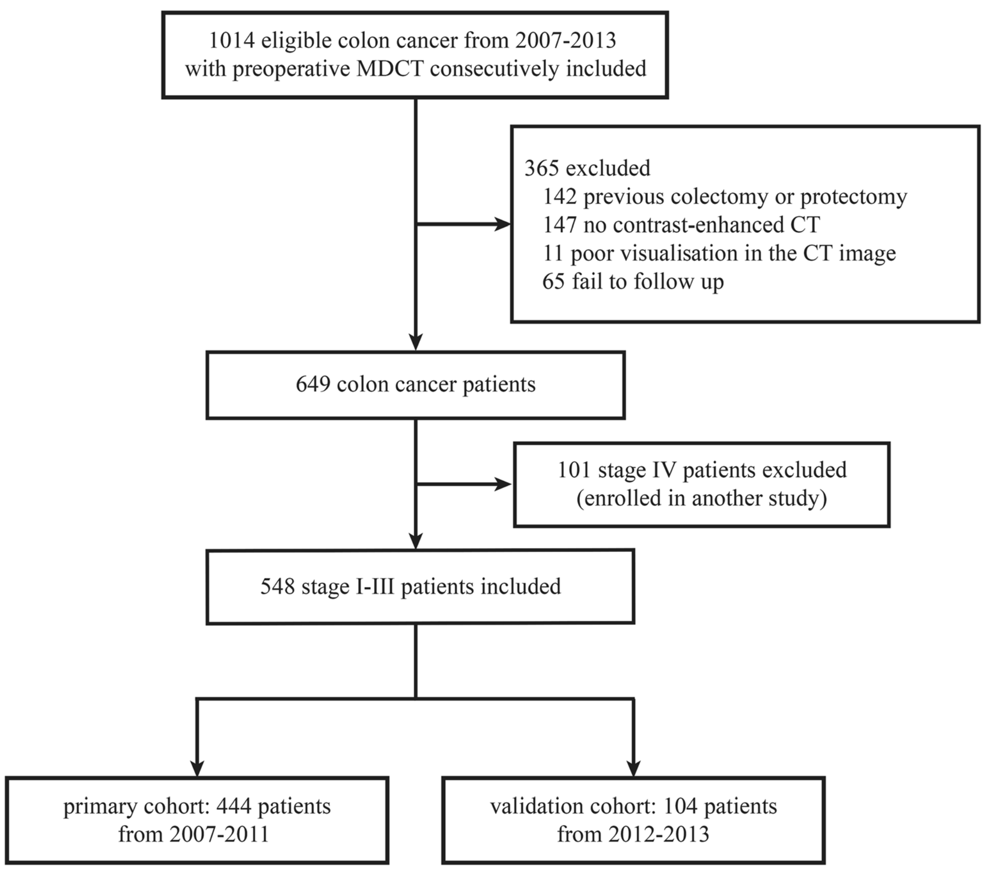

Fig. 1 Study profile. Colon cancer patients with preoperative MDCT were retrospectively included. Exclusion criteria: previous colectomy or proctectomy, no contrast enhancement, poor visualisation of the tumour and loss to follow-up. Stage IV colon cancer was excluded. Finally, 548 patients were enrolled in this study and divided into two cohorts (a primary cohort and a validation cohort) according to different admission time

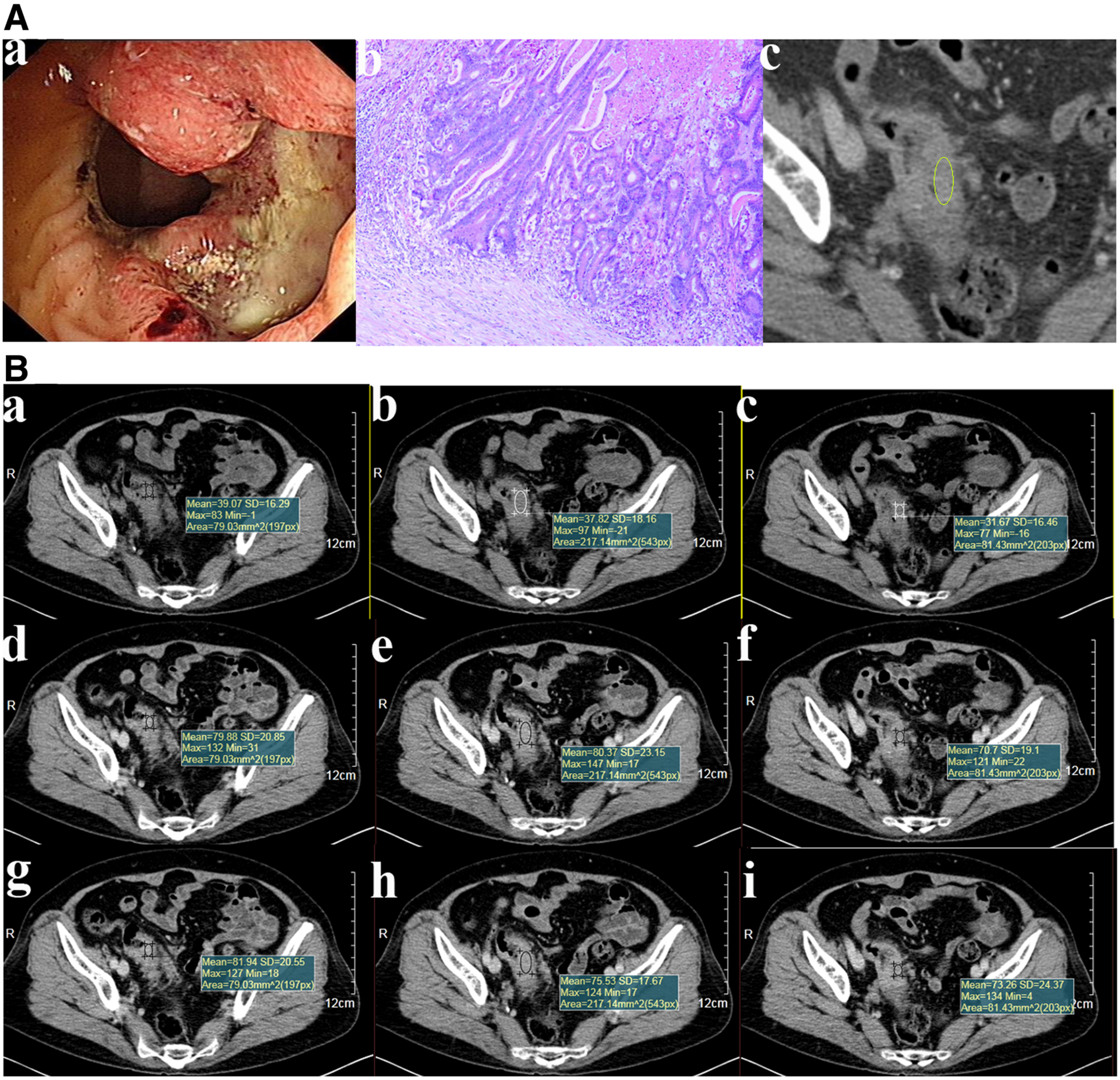

Fig. 2 Typical images of measurement procedure in CT images. Patients underwent colonoscopic biopsy for histologic confirmation of colon adenocarcinoma (Fig. 2**A** a and b). Colon cancer lesions were located by direct and indirect signs of tumour in colon under CT images and reference of colonoscopic findings. Attenuation coefficient (density) of each tumour in multiphase CT images was measured in HU through drawing of region of interest (ROI) at the images (Fig. 2**A** c and **B** a–i)

Statistical analysis

Time-dependent receiver operating characteristic (ROC) curve analysis was performed according to the Kaplan–Meier method in the primary cohort to evaluate the prognostic value of the extent of tumour enhancement during 60 months. The area under curve (AUC) was calculated and Youden index was used to determine the optimal cut-off value. Patients with colon cancer were grouped by the optimal enhancement radio into low-enhancement group (less than the cut-off value) and high-enhancement group (above the cut-off value). Differences in baseline characteristics and pathologic features between high- and low-enhancement groups were assessed by χ^2 test or Fisher exact test for categorical variables, Student's t test for continuous variables with normal distribution, and non-parametric Wilcoxon rank-sum test for ordinal variables, such as pTNM category. The Kaplan–Meier method was adopted to illustrate the timing of events during follow-up, whereas the log-rank test was used as the statistical assessment. Predictors of death were identified by simple Cox regression analysis and a stepwise multiple Cox regression analysis. A nomogram was conducted on the basis of a multivariate Cox proportional hazard model. The nomogram was internally validated using the bootstrap technique with 1000 repetitions. The concordance index (C-index), which ranged from 0.5 (denotes random splitting) to 1 (perfect prediction), was calculated to assess the discrimination ability of the model, and a calibration plot was used to evaluate the predictive ability of the model. As for the temporal validation, the total points of each patient in the validation cohort were calculated according to the established model. The total points were regarded as a factor in the Cox regression analysis to assess the C-index and calibration plot. A two-tailed *p* value less than 0.05 was deemed statistically significant. All statistical analyses were performed with SPSS version 22 (SPSS Inc, Chicago, USA).

Results

Patients' baseline characteristics

From January 2007 to December 2013, a total of 1014 consecutively registered patients with colon cancer were retrospectively included. A total of 365 patients out of the 1014 were excluded for the following reasons: no contrast enhancement (n = 147); poor visualisation of the tumour owing to enterogastric peristalsis or very early stage tumour (n = 11);

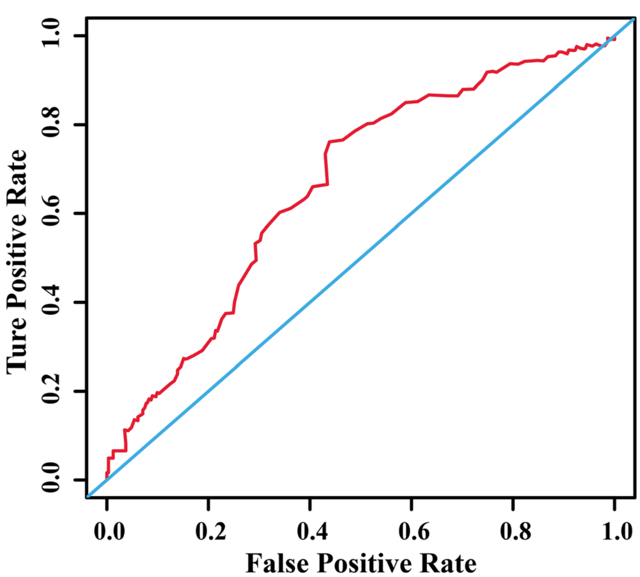

Fig. 3 Time-dependent ROC curve. The AUC of time-dependent ROC curve was 0.663 and the optimal cut-off value for extent of tumour enhancement was 1.75 according to Youden index, which was used to classify patients into binary groups

Table 1 Characteristics of two groups of patients in primary cohort

Characteristic	Low-enhancement group	High-enhancement group	*p*
No. of patients	210	234	
Age (years)	30–88 (62)	22–97 (64)	0.340
Age (class)			0.264
> 70	52	69	
≤ 70	158	165	
Sex			0.201
Men	131	132	
Women	79	102	
pTNM category			0.120
Stage I	34	27	
Stage II	90	97	
Stage III	86	110	
Postoperative chemotherapy			0.389
Yes	110	113	
No	100	121	
CEA (μg/L)			0.320
> 5	80	100	
≤ 5	130	134	
Tumour size			0.421
> 5	53	67	
≤ 5	157	167	
Tumour localisation			0.141
Proximal	65	88	
Distal	145	146	
T stage			0.588
T1	9	6	
T2	30	26	
T3	80	101	
T4	91	101	
N stage			0.181
N0	123	124	
N1	59	69	
N2	28	41	
Histologic type			0.227
Undifferentiated or poorly differentiated	37	52	
Moderately differentiated or well differentiated	173	182	
Mucinous adenocarcinoma			0.977
Yes	16	18	
No	194	216	

Categorical variables: χ^2 test or Fisher exact test; Continuous variables with normal distribution: Student's *t* test; Ordinal variables: Non-parametric Wilcoxon rank-sum test previous colectomy or proctectomy (n = 142) and lost for follow-up (n = 65); a further 101 were excluded because of stage IV colon cancer. Finally, 548 patients met the inclusion criteria and were included in this study; these patients were divided into a primary cohort (444 patients from 2007 to 2011) and a validation cohort (104 patients from 2012 to 2013) according to admission time (Fig. 1).

In the primary cohort, 444 stage I–III patients were finally included with a median follow-up of 64 months. Median age was 62.3 ± 12.3 years old (range 22–91 years old) and 59.2% (263/444) were male. According to the 8th American Joint Committee on Cancer TNM classification (AJCC), 13.7% (61/444) were stage I, 42.1% (187/444) were stage II and 44.1% (196/444) were stage III. Overall 50.2% (222/444) patients received perioperative chemotherapy; 49.7% (93/187) in stage II and 65.8% (129/196) in stage III. A time-dependent ROC curve was plotted with an AUC of 0.663 and the optimal cut-off value of the extent of tumour enhancement was 1.75 according to the Youden index, which was used to classify patients into binary groups (Fig. 3). Table 1 summarises the characteristics of patients from the primary cohort in the low- and high-enhancement groups. No significant differences were observed in age, sex, pTNM stage, perioperative chemoradiotherapy, serum CEA, tumour size, tumour localisation and histologic type between low- and high-enhancement groups.

Survival and recurrence

Out of 444 patients, 106 deaths on account of colon cancer occurred during the median follow-up of 64 months. The 5-year cancer-specific survival rate was 85.9% for the low-enhancement group and 69.5% for the high-enhancement group ($p < 0.001$, Fig. 4a). High-level enhancement was closely associated with increased risk of colon cancer mortality in both stage I (p = 0.033, Fig. 4b), stage II (p = 0.002, Fig. 4c) and stage III patients (p = 0.014, Fig. 4d). The multivariate Cox model also revealed that age (HR 1.884, 95% CI 1.273–

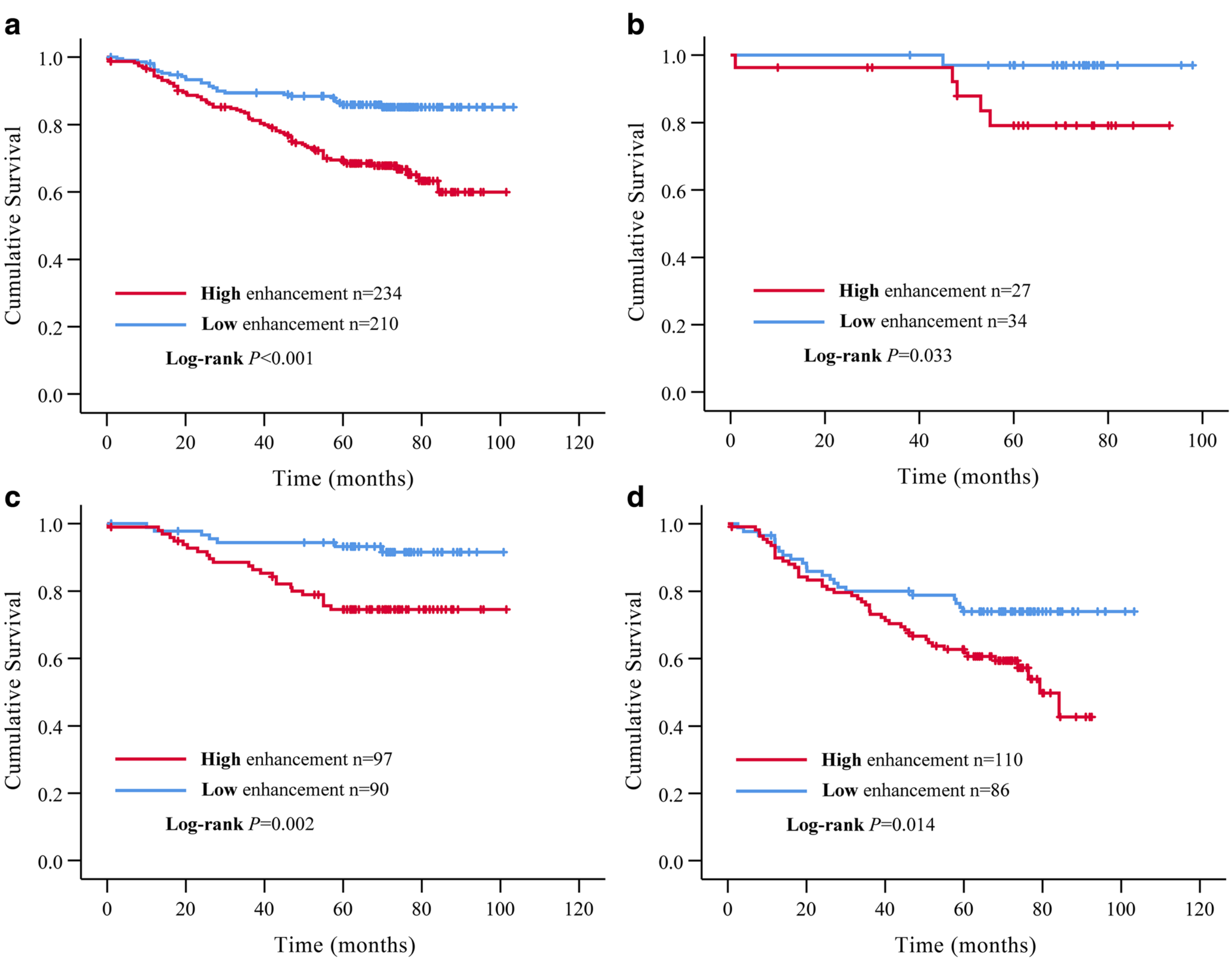

Fig. 4 Kaplan–Meier survival curves of stage I–III colon cancer patients in low- and high-enhancement groups. **a** Total patients; **b** stage I patients; **c** stage II patients; **d** stage III patients

2.786; p = 0.002), histologic type (HR 1.676, 95% CI 1.104–2.543; p = 0.015), pTNM stage (p = 0.003; stage II: HR 1.238, 95% CI 0.512–2.992, p = 0.636; stage III: HR 2.436, 95% CI 1.033–5.743, p = 0.042), CEA level (HR 1.732, 95% CI 1.160–2.585; p = 0.007) and tumour enhancement (HR 2.258, 95% CI 1.476–3.455; $p < 0.001$) are independent prognostic indicators in non-metastatic colorectal cancer.

Nomogram for survival and validation

Age, histologic type, pTNM stage and tumour enhancement were finally selected for the model as they afforded the highest predictive accuracy for 5-year cancer-specific survival rate (Fig. 5a). A nomogram with a C-index of 0.729 was well calibrated (Fig. 5b).

In the validation cohort, the C-index of the nomogram for predicting cancer-specific survival was 0.800 and a calibration curve indicated excellent goodness of fit between predicted and observed probability of 5-year cancer-specific survival (Fig. 5c).

Discussion

Tumour angiogenesis is a crucial process that is closely related to tumour progress, invasion and metastasis [18]. With the assistance of contrast agents, imaging techniques provide a distinctive

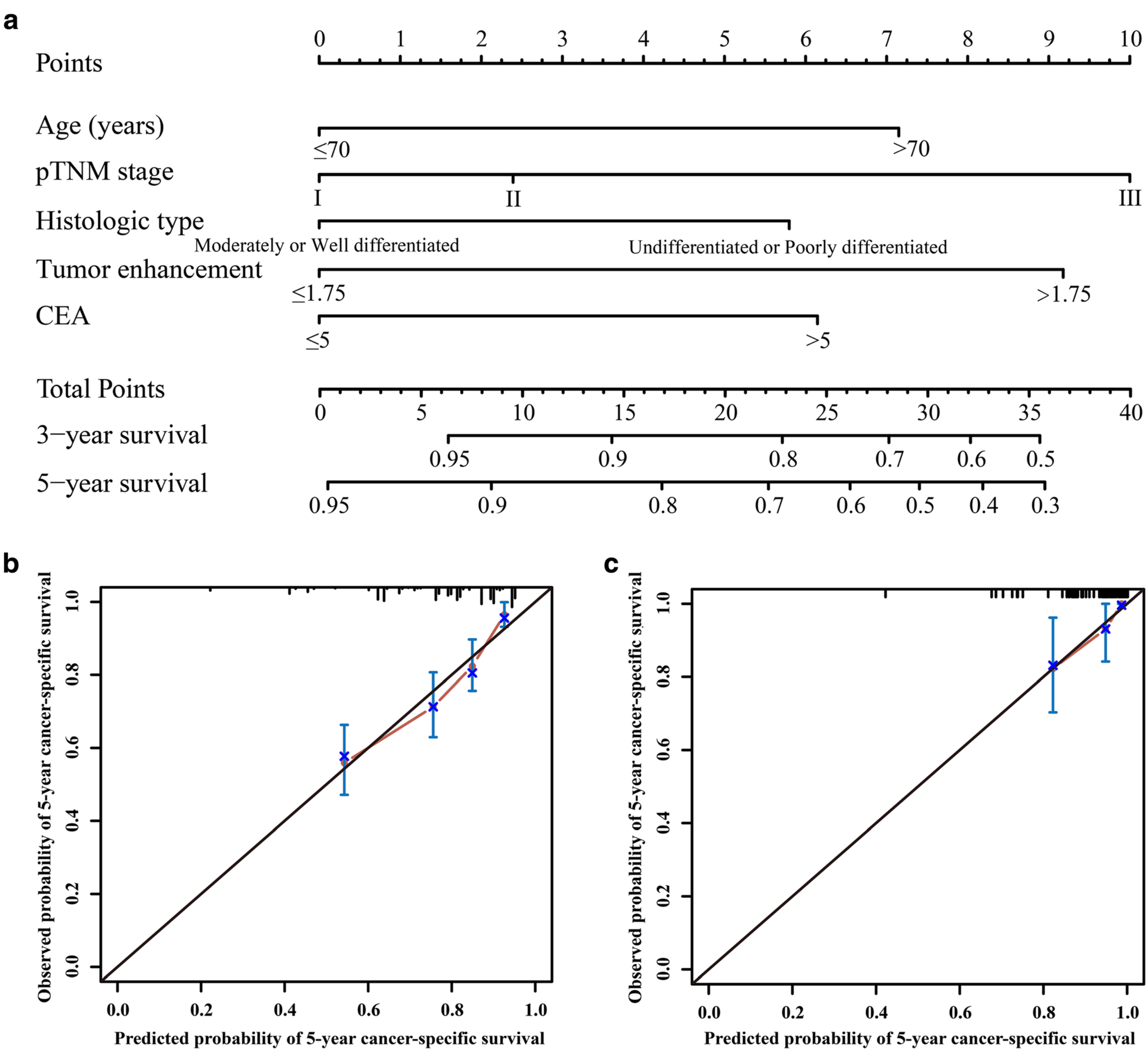

Fig. 5 **a** Nomogram for 5-year cancer-specific mortality. Calibration curve for predicting patients' 5-year cancer-specific survival in the (**b**) primary cohort or (**c**) validation cohort

way to evaluate tumour vasculature preoperatively. The state of contrast enhancement of visceral mass on MDCT images is an important parameter because it reflects tumour vascularity in vivo [9]. Goh et al reported that primary colorectal cancer blood flow measured in perfusion CT at staging could predict subsequent metastatic relapse, which shed light on future studies [19]. Currently, there is no established consensus of data acquisition and analysis methods for colorectal cancer evaluation by perfusion CT. Moreover, perfusion CT is not regularly performed for preoperative colorectal cancer evaluation in most institutions, which might limit its application in multicentre studies.

In the present study, we hypothesised that the extent of tumour enhancement on preoperative multiphase contrast-enhanced CT images could serve as a prognostic factor for stage I–III colon cancer. A total of 548 patients with stage I–III colon cancer were retrospectively included and divided into two cohorts according to admission time: a primary cohort ($n = 444$) and a validation cohort ($n = 104$). Patients were grouped by the optimal enhancement ratio into low-enhancement group and high-enhancement group. Kaplan–Meier analysis indicated that the prognosis of patients in the high-enhancement group was significantly worse than that in the low-enhancement group (Fig. 4). Cox regression analysis indicated that the enhancement state is an independent prognostic factor (Table 2). To our knowledge, this retrospective study has the largest sample size in recent years for evaluating

Table 2 Predictors of mortality in univariate and multivariate survival analysis

	Univariate analysis		Multivariate cox analysis	
	Hazard ratio (95% CIs)	*p*	Hazard ratio (95% CIs)	*p*
Age		< 0.001*		0.002*
≤ 70	Reference		Reference	
> 70	2.237 (1.522–3.290)		1.884 (1.273–2.786)	
Sex		0.420		
Male	Reference			
Female	1.171 (0.798–1.720)			
Tumour size		0.145		
≤ 5 cm	Reference			
> 5 cm	1.352 (0.902–2.026)			
Tumour localisation		0.989		
Proximal	Reference			
Distal	0.997 (0.669–1.487)			
Histologic type		< 0.001*		0.015*
Moderately or well differentiated	Reference		Reference	
Undifferentiated or poorly differentiated	2.149 (1.429–3.232)		1.676 (1.104–2.543)	
Mucinous adenocarcinoma		0.096		
No	Reference			
Yes	1.666 (0.914–3.039)			
Postoperative chemotherapy		0.231		
No	Reference			
Yes	0.792 (0.540–1.160)			
pTNM		< 0.001*		0.003*
I	Reference		Reference	
II	1.711 (0.714–4.101)	0.229	1.238 (0.512–2.992)	0.636
III	4.127 (1.792–9.506)	0.001*	2.436 (1.033–5.743)	0.042*
Extent of enhancement		< 0.001*		< 0.001*
≤ 1.75	Reference		Reference	
> 1.75	2.556 (1.674–3.901)		2.258 (1.476–3.455)	
CEA		< 0.001*		0.007*
≤ 5	Reference		Reference	
> 5	2.328 (1.581–3.427)		1.732 (1.160–2.585)	

*$p < 0.05$

the image features on MDCT and tumour prognosis. Preoperative MDCT staging for colon cancer is regularly performed in most institutions and tumour density measured by CT attenuation coefficient is an objective parameter between different institutions; the tumour enhancement state on MDCT is developed on the basis of the inherent characteristics of colon cancer. It provides a preoperative, cost-effective and objective way to evaluate the prognosis of stage I–III colon cancer in vivo.

Komori et al reported that tumour enhancement in the arterial phase on MDCT is a useful prognostic indicator for advanced gastric cancer following curative resection [15]. They calculated the gastric cancer-to-normal gastric wall enhancement ratio as an assessment indicator [15]. In light of their study, we calculated the colon cancer-to-normal colon wall enhancement ratio in the preliminary study. However, no convincing results were achieved (data not shown). This may be attributed to the thinner walls of the colon compared with the stomach because the colon is prone to air–tumour interface measurement errors in CT images. Meanwhile, biological features reflected by the image may be different between these two cancers. Afterward, we tried to calculate the enhancement state of the tumour on triphasic MDCT scanning as the assessment indicator. The enhancement phase may slightly vary in each individual; thus, the maximum attenuation value on MDCT triphasic scanning was chosen. Moreover, the minimum attenuation value of the tumour was recorded in the plain scanning phase without contrast. The enhancement ratio was calculated using the maximum tumour attenuation value divided by the minimum (Fig. 2).

Colon cancer is a group of heterogeneous diseases. For stage II disease with poor prognostic features (high-risk stage II disease) and stage III disease, the NCCN guideline recommends regular adjuvant chemotherapy [20]. Despite the universally recommended management according to TNM staging, survival rates vary largely from each individual. Microsatellite instability status can serve as a prognostic marker for stage II/III disease, but its predictive value or the detrimental impact of adjuvant therapy in stage II disease was questioned by some studies [21, 22]. Molecular classification of CRC seems to be promising, but it is not yet recommended in clinical practice [23]. Several multigene assays are now available to aid in decision-making in adjuvant therapy in stage II or III disease, but evidence of their predictive value for practical recommendation is still limited [20]. In the present study, when all the patients were divided by tumour staging, the high-enhancement group had worse prognosis than the low-enhancement group in stage I, II and III of colon cancer. Yet, as a result of the limited number of patients in stage I, research using a large sample it still needed to confirm this consequence. By combining the enhancement state with serum CEA level, age, histologic type and pTNM stage in the nomogram, we generated a model for predicting risk in patients with stage I–III colon cancer, which showed a relatively excellent prediction accuracy. The model in the primary cohort without tumour enhancement had a C-index of 0.700 and was poorly calibrated (Supplementary Fig. 1). The nomogram can be conveniently used to facilitate the accurate individualised prediction of long-term survival prognosis in patients with stage I–III colon cancer.

There were still some limitations in this study. First, this study was a single-centre retrospective study; despite its large patient numbers, multicentre prospective studies are needed to test its value in clinical practice. Second, the predictive value of enhancement state was not compared with other promising molecular biomarkers, such as microsatellite instability and *BRAF* or *RAS* mutation status. It is necessary to explore differences of high/low-enhancement groups on the basis of molecular biology. Third, the image acquisition time point of triphasic MDCT scanning may vary between different institutes. Continuous measurement techniques such as perfusion CT are required to acquire accurate tumour maximum attenuation value. Nevertheless, such an assessment method may be overcomplicated and thereby limit its wide clinical application. Therefore, further studies are needed to build a more accurate risk-predicting model by CT techniques on the basis of the present study.

Conclusion

This study generated data on the relationship between the extent of tumour enhancement on contrast-enhanced MDCT and clinical outcomes of patients with stage I–III colon cancer. The extent of enhancement of tumour on MDCT can serve as an independent risk factor, which is closely related to poor prognosis and recurrence. Moreover, it provides a non-invasive approach to assess tumour angiogenesis in vivo. The results generated new insights into the relationship between functional tumour microvessels and tumour prognosis using imaging techniques.

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results interpretation, writing the paper and the decision to submit the paper for publication.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Kefeng Ding.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry Dr. Zexing Chen kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
• retrospective
• observational
• performed at one institution

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