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# The preoperative SUVmax for $^{18}\text{F}$ -FDG uptake predicts survival in patients with colorectal cancer

Debing Shi<sup>1,2†</sup>, Guoxiang Cai<sup>1,2†</sup>, Junjie Peng<sup>1,2</sup>, Dawei Li<sup>1,2</sup>, Xinxiang Li<sup>1,2</sup>, Ye Xu<sup>1,2</sup> and Sanjun Cai<sup>1,2\*</sup>

## Abstract

**Background:** The study was to investigate whether  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake, analyzed by positron emission tomography (PET), can be used preoperatively to predict survival in Chinese patients with colorectal carcinoma.

**Methods:** A prospectively maintained colorectal cancer database was retrospectively reviewed between June 2009 and December 2011. All included patients had been newly diagnosed with colorectal cancer (of various stages) and evaluated by  $^{18}\text{F}$ -FDG-PET/computed tomography (CT) within the 2 weeks preceding surgery. Univariate and multivariate analyses were used to determine whether the maximal standardized uptake value (SUVmax) and various clinicopathological and immunohistochemical factors were correlated with survival. Receiver operating characteristics (ROC) curve and Kaplan-Meier survival curve analyses were used to explore whether SUVmax could predict survival in these patients.

**Results:** A total of 107 patients were enrolled in the study (mean age,  $59.26 \pm 12.66$  years; 66.35 % males), with 77 surviving to the end of follow-up (average 60 months). Univariate analysis indicated that tumor size, TNM stage, nodal metastasis, the ratio of metastasized nodes to retrieved nodes, cyclin D1 immunostaining and SUVmax correlated with survival ( $P < 0.05$ ). Multivariate analysis showed that only TNM stage and SUVmax were associated with survival ( $P < 0.05$ ). ROC curve analysis determined the optimal SUVmax cutoff for predicting survival to be 11.85 (sensitivity, 73.3 %; specificity, 75.3 %). Survival was significantly longer in patients with preoperative SUVmax  $\leq 11.85$  ( $P < 0.001$ , log-rank test).

**Conclusions:** SUVmax, measured by  $^{18}\text{F}$ -FDG-PET/CT, provides a useful preoperative prognostic factor for patients with colorectal cancer.

**Keywords:** Colorectal cancer,  $^{18}\text{F}$ -FDG, PET/CT, SUVmax, Histopathologic, Immunohistochemical

## Background

Colorectal cancer is a common malignancy in the Western world, and its incidence continues to increase in China [1, 2]. Generally, patients are diagnosed with colorectal cancer in the sixth and seventh decades of life, with most lesions occurring in the sigmoid (30 %), rectum (25 %) and cecum (25 %) [1]. More than 50 % of patients with colorectal cancer will have developed metastases by

the time of diagnosis [3–6], most commonly to the liver and lungs, highlighting the need for new markers that will more accurately predict prognosis.

Imaging modalities are frequently used in the screening, staging and surveillance of colorectal cancer.  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET) has proven particularly useful in the clinical staging and restaging of metastases or local recurrence of colorectal cancer [7]. However, the diagnostic accuracy of FDG/PET is limited by nonspecific colonic uptake of FDG that is unrelated to malignancy, as a result of physiologic processes, inflammation or colonic

\* Correspondence: caisanjunonco@126.com

†Equal contributors

<sup>1</sup>Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China

<sup>2</sup>Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

adenomas [8]. Accumulation of FDG in a tumor is based on enhanced glycometabolism, and there is substantial evidence that FDG uptake in tumor cells correlates with tumor growth rate, the potential for aggressive behavior, and prognosis [9]. Thus, FDG-PET may be used before surgery to assess tumor metabolism. The standardized uptake value (SUV) is the semiquantitative parameter most commonly used in current clinical practice to assess the degree of FDG accumulation.

Many clinicopathological factors have been reported to be potential prognostic markers for colorectal cancer, including lymph node status, presence of metastases and differentiation status [10]. In addition, the expressions of various endogenous proteins, detectable using immunohistochemical (IHC) techniques, have been suggested by some (but not all) studies to correlate with the proliferative capacity, invasive potential and/or prognosis of colorectal cancer. These proteins include Ki-67, proliferating cell nuclear antigen (PCNA), cyclin D1 (CCND1), and nm23 (a nucleoside diphosphate kinase) [11–13].

Unfortunately, these pathological and IHC indexes can only be assessed after surgery. Preoperative prediction of patient prognosis would have numerous benefits, allowing better selection of patients for neoadjuvant radiochemotherapy to downstage their disease, and increasing the feasibility of sphincter-sparing surgery. In addition, preoperative diagnostic markers could help to evaluate the chemosensitivity of the cancer. The present study has investigated whether  $^{18}\text{F}$ -FDG uptake, analyzed by PET, can be used preoperatively to predict survival in Chinese patients with colorectal carcinoma. Our findings could help to extend the use of FDG-PET/CT as a technique for preoperative prediction of prognosis in patients with colorectal cancer.

## Methods

### Patients

A prospectively maintained colorectal cancer database was retrospectively reviewed between June 2009 and December 2011. The patients selected for this study had been newly diagnosed with colorectal cancer (of various stages) and evaluated further by  $^{18}\text{F}$ -FDG-PET/CT within the 2 weeks preceding surgery. Patients were excluded if they were hyperglycemic ( $>9$  mmol/L) on the day of the PET/CT investigation, or had received any therapeutic or major surgical interventions before examination. All patients taking metformin stopped this drug for a week before examination. Follow-up data were collected, and each patient allocated into one of two groups (survivor or deceased) according to their clinical outcome at an average follow-up time of 60 months. This study was approved by the Ethics Committee of the Shanghai Cancer Center, Fudan University, P.R. China. Written informed consent was obtained from each patient for original data entry.

The Committee waived the need for individual consent for subsequent studies carried out using this database.

### Data collection

*Clinical data:* The following characteristics were extracted from the clinical records: patient gender, age, and tumor size (cm). Tumor size was estimated by measuring the maximal diameter of the invasive component of the tumor.

*Maximum standardized uptake value:* All patients underwent  $^{18}\text{F}$ -FDG PET/CT scans (Biograph, 16HR; Siemens, Germany) during the 2 weeks immediately preceding surgery. Patients fasted for at least 4 h before the  $^{18}\text{F}$ -FDG PET/CT study, and blood glucose analysis of capillary blood samples was undertaken 1 h before injection of FDG. Patients received 0.2 mCi/kg (74 MBq/kg) of  $^{18}\text{F}$ -FDG intravenously, via a vein in the arm, and then were allowed to rest until the start of the scan. With the patient in the supine position, three-dimensional (3D) PET acquisition was performed from the skull to the upper thighs, with 5–7 bed positions per 2 min. The images were reconstructed with a standard algorithm provided by the manufacturer. The CT component (120 kV; 300 mA, with the electric current controlled automatically by the CareDose4D software according to cine-oriented image; 5-mm slice thickness, inter-slice spacing and reconstruction) was performed without intravenous contrast or bowel preparation, for the purpose of correction of attenuation and lesion localization. PET data were acquired in the same anatomic location. The region of interest (ROI) was delineated according to the margin of the mass on the PET image. The FDG activity was measured by calculating the maximal SUV (SUV<sub>max</sub>) in the attenuation-corrected PET data. The SUV was calculated using the following formula: SUV = activity in the region of interest (MBq/mL)/injected dose (MBq)/body weight (kg).

*Pathological data:* Tissue samples were processed using a standard protocol [14]. Histological grade and type, invasion depth and lymphovascular or nerve invasion were determined for each patient by at least two observers, who were unaware of the results of the PET/CT studies. The pathological results served as the reference standard, and the tumor stage was classified according to the seventh edition of the TNM staging system for colorectal cancer. In the present study, the following pathological factors were measured: TNM stage, histological type, differentiation degree, nodal metastasis status, and the ratio of nodal metastasis to total lymph nodes retrieved. TNM stage was classified into 6 subgroups: Tis, I, IIA, IIB, III and IV; histologic type was divided into 6 subgroups: adenocarcinoma, mucinous adenocarcinoma; signet ring cell carcinoma, adenocarcinoma with a component of mucinous adenocarcinoma, adenocarcinoma with a component of signet ring cell carcinoma, and others;

**Table 1** Baseline patient data and univariate analysis of factors associated with survival at 60 months

Type	Group	Subgroup	Survivor (N = 77)	Deceased (N = 30)	P value		
Demographic data	Age (years)		59.65 ± 12.75	58.27 ± 12.58	0.614		
	Gender	Male	50 (64.9 %)	21 (70 %)	0.618*		
		Female	27 (35.1 %)	9 (30 %)			
Pathologic factors	Colorectum	Colon cancer	45 (58.4 %)	15 (50 %)	0.389*		
		Rectal cancer	31 (40.3 %)	15 (50 %)			
	Tumor size (cm)		5.0 (2.0, 10.0)	3.7 (1.0, 10.0)	0.017		
	TNM stage	Tis	2 (2.6 %)	0	<0.001*		
		I	15 (19.5 %)	0			
		IIA	21 (27.3 %)	1 (3.3 %)			
		IIB	10 (13.0 %)	2 (6.7 %)			
		III	24 (31.2 %)	14 (46.7 %)			
		IV	5 (6.5 %)	13 (43.3 %)			
		Histologic type	Adenocarcinoma	67 (87.0 %)		26 (86.7 %)	0.436*
			Mucinous adenocarcinoma	3 (3.9 %)		3 (10.0 %)	
	Signet ring cell carcinoma		1 (1.3 %)	0			
	Adenocarcinoma with component of mucinous adenocarcinoma		3 (3.9 %)	1 (3.3 %)			
	Adenocarcinoma with component of signet ring cell carcinoma		1 (1.3 %)	0			
	Other		2 (2.6 %)	0			
	Differentiation degree	Well differentiated	4 (5.2 %)	0	0.054*		
		Well or moderately differentiated	4 (5.2 %)	0			
		Moderately differentiated	54 (70.1 %)	24 (80.0 %)			
		Moderately or poorly differentiated	8 (10.4 %)	3 (10.0 %)			
		Poorly differentiated	5 (6.5 %)	1 (3.3 %)			
Undifferentiated		1 (1.3 %)	1 (3.3 %)				
Nodal metastasis		0 (0,12)	2 (0,9)	0.01			
Ratio of nodal metastasis to retrieved nodes		0 % (0 %, 100 %)	8.93 % (0, 100)	0.03			
Immunohistochemical factors	PCNA		60 % (0 %, 95 %)	52.5 % (10, 85)	0.129		
	nm23	0 = "(-)"	9 (11.7 %)	5 (16.7 %)	0.65*		
		1 = "(±)"	11 (14.3 %)	2 (6.7 %)			
		2 = "(+)"	51 (66.2 %)	22 (73.3 %)			
		3 = "(++)"	2 (2.6 %)	0			
		4 = "(+++)"	4 (5.2 %)	1 (3.3 %)			
	Cyclin D1	0 = "(-)"	14 (18.2 %)	3 (10.0 %)	0.03*		
		1 = "(±)"	28 (36.4 %)	5 (16.7 %)			
		2 = "(+)"	31 (40.3 %)	15 (50.0 %)			
		3 = "(++)"	3 (3.9 %)	6 (20.0 %)			
		4 = "(+++)"	1 (1.3 %)	1 (3.3 %)			
	Ki67		50 (0,95)	45 (5,90)	0.908		
	Maximum standardized uptake value	SUVmax		9.8 (4.4, 24.7)	13.6 (3.2, 34.2)	<0.001	

There is one missing number in "Colon or Rectal cancer" in the survivor group. And each group had a missing in "Differentiation degree"

\*Means data was shown in number (percentage) and analyzed by Chi-square test. And the other data are all shown in median (minimum, maximum) and analyzed by ANOVA

and differentiation degree was classified into 6 subgroups: well differentiated, well or moderately differentiated, moderately differentiated, moderately or poorly differentiated, poorly differentiated, and undifferentiated.

**Immunohistochemical data:** Consecutive sections with a thickness of 4  $\mu\text{m}$  were cut from representative paraffin-embedded tumor blocks. IHC staining was performed on an automated platform (BenchMark XT, Ventana Medical Systems, USA) according to the manufacturer's instructions, using the following primary antibodies: anti-PCNA (PC10, Dako, Denmark, 1:1200); anti-cyclin D1 (EP12, Dako, 1:200); anti-nm23 (4B2, Abzoom, USA, 1:200); and anti-Ki67 (MIB-1, Dako, 1:200). The IHC results were assessed by a pathologist blinded to the clinical outcome or histopathological diagnosis. PCNA, CCND1, and Ki67 immunoreactivities were restricted to the nucleus, while nm23 immunoreactivity was found in the cytoplasm. The Ki67 and PCNA indexes were obtained by counting, under a microscope, 1000 tumor cells in consecutive high-power fields in the most reactive areas, and determining (as a percentage) the number of these cells showing distinct nuclear staining. Scoring of CCND1 and nm23 expression was based on the intensity of the IHC staining and the percentage of positively stained cancerous cells, as described previously [15, 16]. Nuclear CCND1 immunostaining and cytoplasmic nm23 immunostaining was considered as positive. Scoring was as follows: 0, no staining;  $\pm$ , focal, weak staining; 1+, weak staining in < 50 % of cells; 2+, weak staining in > 50 % of cells or strong staining in < 50 % of cells; 3+, strong staining in > 50 % of cells.

### Statistical analysis

A generalized linear model (GLM) in R [17] was applied to test for effects of the clinical, pathological, and IHC factors on SUVmax. In addition, for significant factors, a multivariate regression analysis was applied in PAST [18] to test the correlations between the significant factors and SUVmax. Receiver operating characteristics (ROC) analysis with calculation of the Youden index was

used to determine the optimal SUVmax cutoff value for predicting the outcome of colorectal cancer. Kaplan–Meier survival curves were constructed to compare survival between patients with SUVmax values either side of this cutoff, with statistical comparisons made using the log-rank (Mantel-Cox) test.  $P < 0.05$  was taken to indicate a statistically significant difference.

## Results

### Baseline patient characteristics

A total of 107 patients were included in the analysis: 77 in the survivor group and 30 in the deceased group. There were no significant differences between the two groups for age or gender (Table 1).

### Univariate analysis of the factors associated with patient survival

In the univariate analysis, the pathologic factors significantly associated with survival were tumor size, TNM stage, nodal metastasis, and the ratio of metastasized nodes to retrieved nodes (all  $P < 0.05$ ; Table 1). In contrast, lesion location, histologic type, and the degree of differentiation were not significantly associated with survival. Of the IHC factors assessed, only CCND1 was significantly associated with survival ( $P < 0.05$ ); PCNA, nm23, and Ki67 showed no significant association (Table 1). SUVmax was also associated with patient survival ( $P < 0.05$ ; Table 1).

### Multivariate analysis of the factors associated with patient survival

All factors showing a significant association with survival in the univariate analyses ( $P < 0.05$ ) were entered into a multivariate analysis. The multivariate analysis revealed that only the TNM stage and SUVmax were independently associated with survival ( $P < 0.05$ ), whereas tumor size, nodal metastasis, the ratio of metastasized nodes to retrieved nodes, and CCND1 were not (Table 2).

**Table 2** Multivariate analysis of factors associated with survival at 60 months

	B	S.E.	Wald	df	Sig.	Exp(B)	95 % C.I. for Exp(B)	
							Lower	Upper
TNM stage	1.522	0.425	12.82	1	< 0.001	4.581	1.991	10.538
Tumor size	-0.006	0.180	0.001	1	0.975	0.994	0.699	1.414
SUVmax	0.261	0.091	8.268	1	0.004	1.298	1.087	1.551
Nodal metastasis	0.261	0.238	1.209	1	0.272	1.299	0.815	2.070
Ratio of nodal metastasis to retrieved nodes	-0.029	0.028	1.052	1	0.305	0.972	0.919	1.027
Cyclin D1	-0.293	0.423	0.480	1	0.488	0.746	0.325	1.710
Constant	-9.458	2.275	17.282	1	0.000	0.000		

A multivariate regression analysis was applied in PAST to test the correlations between the significant factors and SUVmax. And only TNM stage and SUVmax are independent risk factors for prognosis of colorectal cancer

**ROC analysis of the optimal SUVmax cutoff value for predicting survival in patients with colorectal cancer**

ROC analysis (Fig. 1) and calculation of the Youden index revealed that the optimal SUVmax cutoff value for predicting survival in patients with colorectal cancer was 11.85 (area under the curve, 0.763;  $P < 0.001$ ). The calculated sensitivity and specificity values for this cutoff were 73.3 and 75.3 %, respectively.

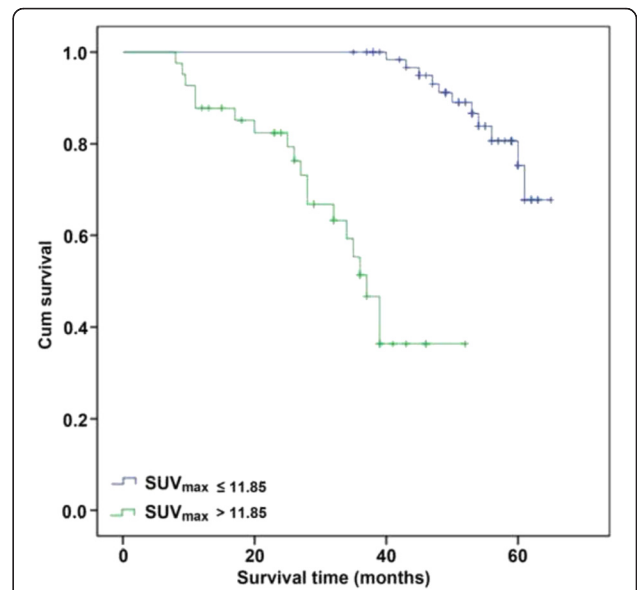
Figure 2 compares the Kaplan–Meier survival curves between patients with  $SUV_{max} \leq 11.85$  and those with  $SUV_{max} > 11.85$ . Survival was significantly longer in patients with  $SUV_{max} \leq 11.85$  ( $P < 0.001$ ). The median survival time was 37 months in patients with  $SUV_{max} > 11.85$ , whereas median survival was not reached (i.e. exceeded 60 months) in patients with  $SUV_{max} \leq 11.85$ .

**The correlation between IHC factors and SUVmax**

Regression analysis indicated that SUVmax showed a significant positive correlation with the CCND1 immunostaining score (Fig. 3;  $r = 0.63$ ;  $P < 0.001$ ). However, SUVmax showed no significant correlations with immunostaining for PCNA, Ki67, or nm23 (data not shown).

**Case study**

A 58-year-old male with ascending colon cancer is described as a case study, to explore the correlations between clinicohistopathological factors and  $^{18}F$ -FDG uptake of the primary tumor. Representative PET and CT images are shown in Fig. 4. The transaxial PET image (Fig. 4a) indicated that focal FDG uptake in the ascending colon (i.e. SUVmax) was 12.8, while the

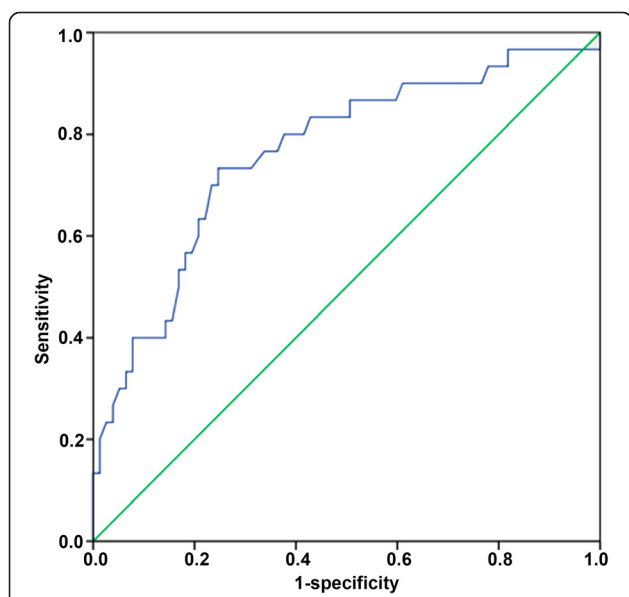


**Fig. 2** Comparison of survival curves for patients with  $SUV_{max} \leq 11.85$  and patients with  $SUV_{max} > 11.85$

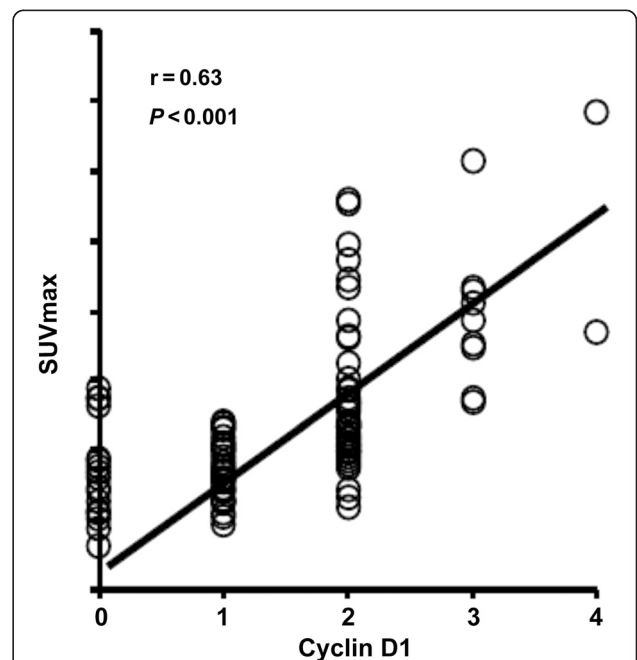
transaxial CT image of the same lesion (Fig. 4b) showed that the tumor size was 6 × 8 cm. The merged PET/CT images (Fig. 4c) showed good correspondence. A coronal PET image of the same lesion is presented in Fig. 4d.

**Discussion**

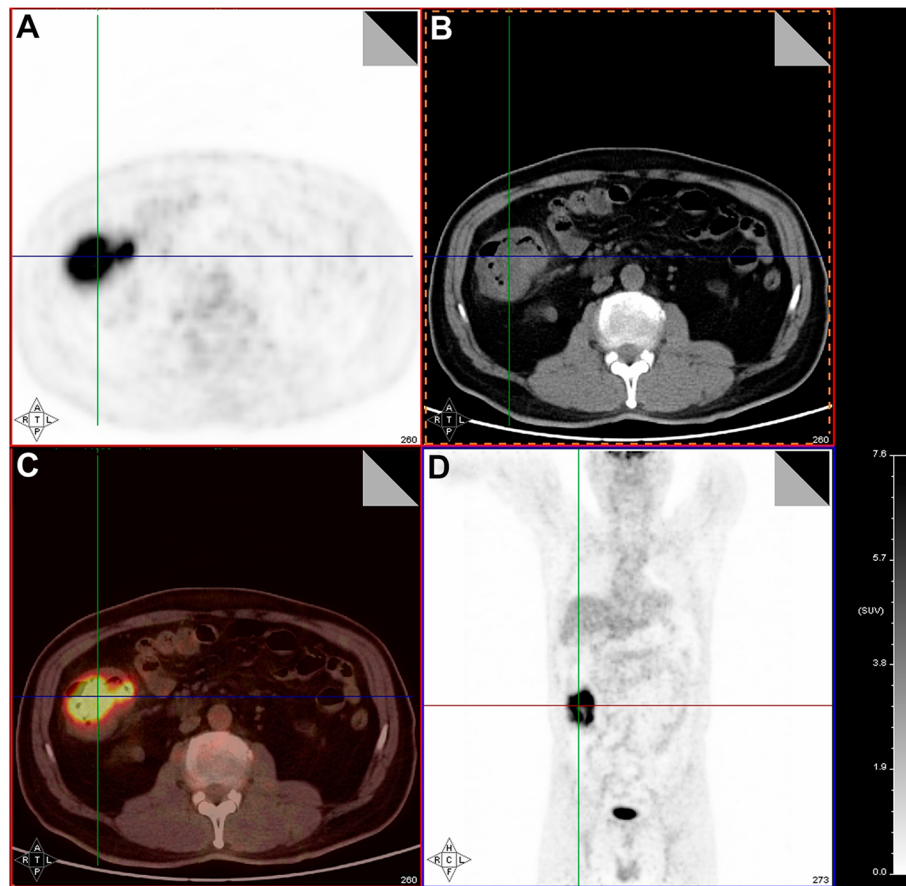
The main findings of this study are that higher TNM stage and higher SUVmax are significantly associated with shorter survival in patients with colorectal cancer,



**Fig. 1** ROC curve analysis of the optimal SUVmax cutoff for predicting survival in patients with colorectal cancer



**Fig. 3** Correlation between cyclin D1 expression and SUVmax



**Fig. 4** Case study of a patient with ascending colon cancer. **a** Transaxial PET image showing focal FDG uptake in the ascending colon, taken at the level indicated by the line. **b** Transaxial CT image of the same lesion. **c** Image obtained by merger of the PET and CT images. **d** Coronal PET image of the same lesion

and that SUVmax is a marker of prognosis in these patients. Specifically, we determined that the optimal SUVmax cutoff value for predicting survival was 11.85, with values above 11.85 being associated with significantly shorter survival. Therefore, the measurement of SUVmax with  $^{18}\text{F}$ -FDG-PET/CT scanning provides a useful preoperative prognostic factor for patients with colorectal cancer. If the cutoff value is changed to 17, then the sensitivity would be of 75 % (18/24) for predicting death, which might suggest that a small proportion (22.4 %, 24/107) of patients would receive intensive treatments and that most of them (75 %) would still benefit from the treatment.

$^{18}\text{F}$ -FDG PET/CT imaging has been employed widely to identify and stage various types of cancer, including lung cancer [19], breast cancer [20], esophageal cancer [21], sarcoma [22], and melanoma [23], and has proven particularly useful in the detection, staging, and surveillance of colorectal cancer [24–27]. Accurate preoperative visualization of cancer deposits with this technique potentially enables surgeons to perform more complete

tumor resections, improving clinical care and long-term survival. Semi-quantitative analysis with  $^{18}\text{F}$ -FDG PET/CT is gaining popularity for predicting clinical outcomes and determining the tumor response to treatment [28, 29], since changes in tumor metabolism may be observed prior to changes in tumor size. Thus, a significant change in tumor SUV potentially could be used as a measure of the metabolic response of the tumor to therapy. Our findings extend the potential clinical utility of SUVmax measurements, suggesting that in Chinese patients with colorectal cancer, preoperative values  $\leq 11.85$  can be used as a prognostic indicator of improved survival after surgery. This can provide additional guidance to clinicians treating patients with this cancer.

However,  $^{18}\text{F}$ -FDG PET/CT imaging does have some limitations including false-negative findings that can occur for several reasons (e.g., inflammation, small lesion size, and diabetes). Weston et al. found that the sensitivity, specificity, and accuracy of PET/CT at detecting colon cancer or adenomas  $>10$  mm were 72, 90 and 88 %, respectively [28]. Sarikaya et al. [30] reported that

3 of 5 patients (60 %) with false-negative PET/CT findings had mucinous adenocarcinoma diagnosed histologically. Peng et al. have shown that colonoscopy is a necessity when incidental colorectal FDG uptake is found on  $^{18}\text{F}$ -FDG PET/CT imaging [31]. These authors also reported that the SUVmax value was higher in patients with cancer, although a high value did not necessarily indicate the presence of malignancy.

Regional lymph node status is an important prognostic factor that also plays a crucial role in the selection of postoperative therapy. Preoperative nodal staging using imaging requires an assessment of the number of pericolic and mesenteric nodes that contain metastatic disease. False-negative PET findings in regional metastatic lymph nodes are not uncommon, occurring in part due to the intense FDG uptake by the primary tumor that obscures immediately adjacent structures, and in part due to the low sensitivity of PET to microscopically involved lymph nodes. As a result, FDG PET has been found to have a high specificity (>90 %) for regional lymph node metastases from colorectal cancer, but only a low sensitivity (<30 %) [32, 33]. Yu et al. have reported recently that an SUVmax cutoff of 2.0 could identify malignant juxtaintestinal lymph nodes with a sensitivity of 91.43 % and a specificity of 87.83 % [34], highlighting the benefits of using SUVmax with ROC curve analysis for optimizing the diagnostic capabilities of  $^{18}\text{F}$ -FDG PET/CT.

It was notable that our multivariate analysis highlighted SUVmax and TNM stage as the two variables significantly associated with survival. Cancer stage is well established as a prognostic factor for colorectal cancer [35]. Although univariate analysis revealed that tumor size is correlated with survival, multivariate analysis found no significant influence of this factor in Chinese patients; this is in contrast to a recent study that reported tumor size to be an independent prognostic factor in Austrian patients with colon carcinoma [36]. Whether this reflects an ethnicity-related difference remains to be determined.

There is some debate as to the utility of Ki-67, PCNA, CCND1, and nm23 expressions as prognostic factors in colorectal cancer. Several studies have suggested that the expressions of these proteins correlate with outcome [11–13], whereas others have provided contradictory data [37–40]. The reasons underlying these discrepancies remain unknown. The multivariate analysis in the present study revealed that the expressions of Ki-67, PCNA, CCND1, and nm23 did not correlate significantly with survival, suggesting that in Chinese patients, preoperative IHC assessments of these markers may not be particularly useful indicators of prognosis after surgery. Interestingly, we did find a significant correlation between SUVmax and CCND1 expression; the underlying reasons for this correlation merit further study.

The present study is not without limitations. First, this was a hospital-based study; hence, our patients may not be sufficiently representative of the general population in China. Second, a relatively small number of patients were included, raising the possibility of inherent selection bias. Third, our study did not include a healthy control group for comparison. Fourth, our study was retrospective in nature. Finally, these patients received a wide variety of adjuvant treatments that could not be taken into account in the analyses. Therefore, larger case-control and prospective randomized studies are needed to validate and extend our findings.

## Conclusions

In conclusion, TNM stage and SUVmax are independent predictors of survival in patients with colorectal cancer, and preoperative SUVmax values  $\leq 11.85$  are associated with better survival. FDG-PET/CT could be used as a method of patient stratification before surgery, helping in the selection of appropriate therapeutic strategies.

## Abbreviations

$^{18}\text{F}$ -FDG:  $^{18}\text{F}$ -fluorodeoxyglucose; CCND1: cyclin D1; CT: computed tomography; GLM: generalized linear model; IHC: immunohistochemical; NCCN: National Comprehensive Cancer Network; PCNA: proliferating cell nuclear antigen; PET: positron emission tomography; ROC: receiver operating characteristics; SUV: standardized uptake value; SUVmax: maximal standardized uptake value.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

DBS and GXC carried out the study design, data collection and analysis, wrote the manuscript. JJP, DWL, XXL and YX participated in data collection, data analysis and provided the critical revision. SJC conceived the idea and design of the study, revised the manuscript. All authors read and approved the final manuscript.

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