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ORIGINAL RESEARCH

The Preoperative Enhanced Degree of Contrast-enhanced CT Images: A Potential Independent Predictor in Gastric Adenocarcinoma Patients After Radical Gastrectomy

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Aim: To discover the value of contrast-enhanced CT parameters in predicting the prognosis of gastric adenocarcinoma (GAC) patients after radical gastrectomy.

Methods: The patients with a clinical diagnosis of GAC were retrospectively enrolled. Two radiologists drew the regions of interest (ROIs) in CT images and measured the CT attenuate value (CAV) in each phase and the corrected CAV (cCAV) in each contrast-enhanced phase. Patients were divided into two groups (high/low-enhancement) according to receiver operating characteristic (ROC) curve. Kaplan–Meier curve and Cox proportional hazards regression analysis were performed to evaluate correlation between prognosis and variables. Subgroup analysis was used to further analyze the prognostic value of variables.

Results: In total 435 patients were included. According to ROC curve, the cCAV in delayed phase (DP-cCAV) with maximum AUC and Youden index was chosen. A total of 312 patients (71.7%) entered DP-cCAV^{low} group and remaining 123 (28.3%) patients were in DP-cCAV^{high} group. According to univariate (high vs low, HR=2.120, $p<0.001$) and multivariate (high vs low, HR=1.623, $p<0.001$) Cox regression analysis, the low-enhancement state was considered as an independent protective factor. Subgroup analysis was based on age, maximum diameter of tumor, differentiation, vascular invasion status, and TNM staging. In most subgroups, the overall survival (OS) of DP-cCAV^{low} group was overwhelmingly satisfactory (all HR >1, expect TNM stage I, IV and differentiated type subgroups).

Conclusion: The prognostic effectiveness of CT parameters as biomarkers for OS in GAC patients treated with radical gastrectomy has potential value.

Keywords: gastric adenocarcinoma, radical gastrectomy, contrast-enhanced CT, overall survival, prognosis

Introduction

Gastric cancer (GC) is one of the most common cancers, with an estimated 27,600 new cases and 11,010 deaths in the US in 2020.[1] Over the recent few decades, the worldwide incidence of GC has declined rapidly owing to the discovery of some risk factors, such as *Helicobacter pylori*, dietary and environmental risks.[2–4] However, GC still is the third cause of cancerous deaths in the world, with up to 40–78% patients dying at five years.[5,6] It is obvious that the prognosis remains

poor.[7] For patients with GC, radical gastrectomy remains the best intervention for long-term survival.[8,9] Besides, many factors have been confirmed to be related to the prognosis of GC, including the extent of tumor invasion, tumor pathological classification, degree of tissue differentiation, distant metastasis, and clinical TNM staging.[10,11]

At present, gastroscopy biopsy is commonly used to acquire several pathological characteristics as described above before surgery. However, there are several factors that could affect the accuracy of gastroscopy biopsy results. For example, gastroscopy biopsy sampling is limited and the small specimens are restrictive to comprehensively cover GC lesions with high heterogeneity. And the perspective of gastroscopy biopsy is also limited, making evaluation of lesions outside the stomach wall out of the question.[12,13] Contrast-enhanced computed tomography (CE-CT), as a noninvasive imaging technique, can comprehensively and conveniently evaluate the lesion, its adjacent structures, and distant metastases at the same time,[14,15] which makes up for these shortcomings of gastroscopic biopsy to a certain extent. In recent research, CT parameter analysis shows great potential in identifying pathological characteristics and predicting clinical outcomes of tumors. Ba'Ssalamah et al indicated the radiologists could distinguish different types of common gastric tumors by CT texture analysis.[16] Liu et al held that CT parameters could noninvasively predict certain pathological features of GC, including the degree of differentiation, Lauren classification as well as vascular invasion.[14] Giganti et al critically reviewed the latest research progress of MRI and 18F-FDG PET/CT in GC. They reported that dynamic contrast-enhanced MRI reflects tumor angiogenesis, which was inversely proportional to the prognosis of GC, and the apparent diffusion coefficient of diffusion-weighted MRI could be considered as a prognostic biomarker as well.[17,18] Important results of the relationship between other biomarkers such as standardized uptake value from PET/CT and overall survival in GC were also reported.[18] To date, there have been few studies on the application of parameters analysis from CE-CT as predictive biomarkers of survival in GC.

Therefore, our research was dedicated to discover the value of CE-CT parameters in predicting the prognosis of patients with gastric adenocarcinoma (GAC) after radical gastrectomy.

Methods

Patients

From June 2013 to January 2018, all patients with a clinical diagnosis of GAC in our hospital (First Affiliated Hospital of Wenzhou Medical University) were screened. The inclusion criteria were: (1) adult patients; (2) a history of radical gastrectomy and lymphadenectomy at our hospital; (3) a diagnosis of GAC proved by postoperative pathology; (4) measurable intraoperative lesion; (5) completing CE-CT examination before radical excision. The exclusion criteria are listed as follows: (1) lost follow-up patients; (2) any treatment before surgery and CE-CT examination including chemotherapy, radiotherapy and targeted agents; (3) unavailable postprocessing due to the artifacts of the CT image; (4) limited area to outline regions of interest (ROIs) owing to small tumor size with maximum diameter <5 mm.

All data on clinical characteristics were extracted and analyzed according to the Declaration of Helsinki. This study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. Because it was a noninterventional retrospective study, the requirement for patient consent to review the medical records was waived.

Acquisition of CT Image

After signing the informed consent, all patients underwent CE-CT examinations (64-slice multidetector, Light Speed Plus 16, GE Healthcare, Waukesha, WI, USA) before radical gastrectomy. To ensure that the gastric cavity was fully dilated and expanded, they were asked to fast for at least six hours and drink 600–1000 mL of water before the examination. During a single breath-hold, the scan covered the entire and upper abdomen with the patient in the supine position. Following a noncontrast scan (0s), the examiner intravenously injected 100–120 mL iodinated contrast agent (Omnipaque 350 mgI/mL, GE Healthcare, Shanghai, China) into the patient at a flow rate of 3.0 mL/second using an automatic injector. After the infusion of contrast agent, arterial, portal, and delayed phase images were obtained at 40, 70, and 240 seconds, respectively. Picture archiving and communication system (PACS) transferred all datasets.

The following were the parameters of the abdomen CT: 64 detector rows, tube voltage 120 kVp, tube current 200 mA, rotation time 0.4 second, section thickness 0.625 mm, pitch 1.375 mm and reconstruction interval 0.625 mm.

Evaluation of CT Image

Two experienced radiologists (both with more than seven years experience in gastroenterology imaging), who only knew the clinical information of gastroendoscopic findings, checked the images and identified the gastric lesions on PACS independently.

The window level (WL) and the window width (WW) were set as 50 and 250. The gastric wall which showed focal thickening of ≥6 mm was determined to be cancerous.[19] First, the polygonal region of interest (ROI) was manually drawn along the margin of the GC on the image slice displaying the tumor in its largest cross-sectional area (Figure 1). Vessel structures, ulceration, necrosis, gastric lumen, artifacts should be avoided in the ROIs. Then, approximately the same size ROIs were outlined in the same place of the tumor on images of arterial, portal, delayed and nonenhanced phases. The two readers independently drew the ROIs which had been verified without any significant difference between them. After that, the PACS automatically read all of pixels' CT values within the ROI and calculated average CT attenuate value (CAV). Finally, a series of parameters including the CAV of ROI in arterial, portal, delayed, noncontrast phase and the cCAV of ROI in arterial, portal, delayed phase was recorded. Moreover, in order to eradicate patient-related confounding factors like the difference in contrast agent and individual's ability to absorb its, two readers also measured the CAV on the same slice of aortic canal to calculate cCAV. The algorithm was as follows: (the CAV of ROI in each contrast-enhanced phase–the CAV of ROI in noncontrast phase)/CAV in aortic canal.

Outcome

All patients were followed by means of landline telephone. The follow-up program mainly consisted of survival and the time of death, which were traced until September 1, 2019. The primary outcome was death from any reasons. And clinical information collectors were blinded to the survival data.

Statistical Analysis

Continuous variables were represented as median and range and compared by Mann–Whitney *U*-test, whereas categorical variables were expressed as frequency and percentage and compared by Fisher's exact test. As preprocessing, a receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnosis performance of seven CT parameters and develop corresponding cutoffs associated with the survival status at three years. As shown in part of Table 1, the area under the ROC curve (AUC) of PP-CAV (CAV in portal phase), PP-cCAV (cCAV in portal phase), DP-CAV (CAV in delayed

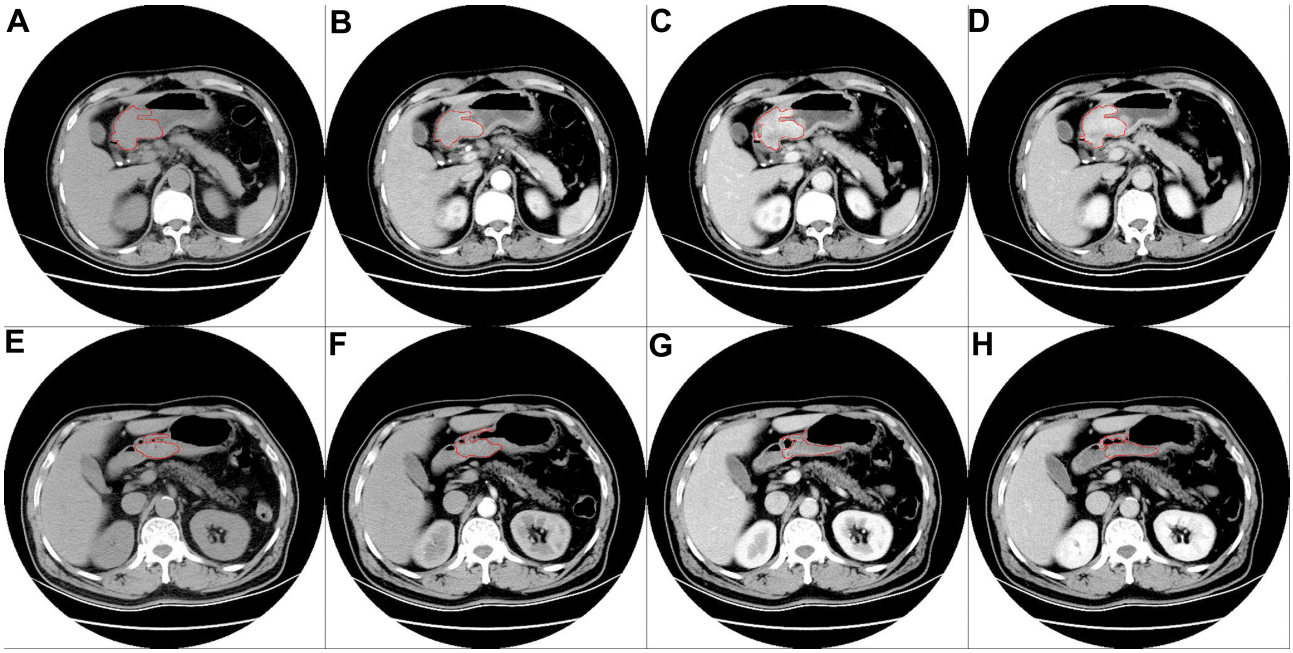

Figure 1 NC-CT and CE-CT scans of GACs with different DP-cCAV. CT images in the noncontrast phase (**A**), arterial phase (**B**), portal venous phase (**C**) and delayed phase (**D**) showed a thickened gastric wall in a patient of DP-cCAV^{high} group. CT images in the noncontrast phase (**E**), arterial phase (**F**), portal venous phase (**G**) and delayed phase (**H**) showed a thickened gastric wall in a patient of the DP-cCAV^{low} group.

Table 1 Baseline Characteristics of Patients with GAC According to CT Value Stratification

Variables	Total (n=435)	DP-cCAV^{low}(n=312)	DP-cCAV^{high}(n=123)	*p*-value
Sex				
Male	334 (76.8)	250 (80.1)	84 (68.3)	0.011
Female	101 (23.2)	62 (19.9)	39 (31.7)	
Age at diagnosis (years)				
Median (range)	65 (29–87)	66 (29–86)	65 (31–87)	0.713
Location				
Cardia and fundus	82 (18.9)	61 (19.6)	21 (17.1)	0.392
Body	111 (25.5)	78 (25.0)	33 (26.8)	
Antrum and pylorus	227 (52.2)	165 (52.9)	62 (50.4)	
Whole stomach	15 (3.4)	8 (2.6)	7 (5.7)	
Maximum diameter of tumor(cm)	4.0 (0.5–14.0)	4.0 (0.5–14.0)	5.0 (0.5–12.5)	0.001
Differentiation degree				
Differentiated type	94 (21.6)	75 (24.0)	19 (15.4)	0.003
Mixed type	104 (23.9)	83 (26.6)	21 (17.1)	
Undifferentiated type	237 (54.5)	154 (49.4)	83 (67.5)	
Vascular invasion status				
Yes/no	155/280	100/212	55/68	0.015
Neural invasion status				
Yes/no	141/294	85/227	56/67	<0.001
Pathological T stage				
T1	54 (12.4)	51 (16.3)	3 (2.4)	<0.001
T2	63 (14.5)	50 (16.0)	13 (10.6)	
T3	297 (68.3)	199 (63.8)	98 (79.7)	
T4	21 (4.8)	12 (3.8)	9 (7.3)	
Pathological N stage				
N0	138 (31.7)	117 (37.5)	21 (17.1)	<0.001
N1	82 (18.9)	63 (20.2)	19 (15.4)	
N2	109 (25.1)	73 (23.4)	36 (29.3)	
N3	106 (24.4)	59 (18.9)	47 (38.2)	
Pathological M stage				
M0	418 (96.1)	302 (96.8)	116 (94.3)	0.271
M1	17 (3.9)	10 (3.2)	7 (5.7)	
TNM stage				
I	104 (23.9)	88 (28.2)	16 (13.0)	<0.001
II	131 (30.1)	104 (33.3)	27 (22)	
III	184 (42.3)	111 (35.6)	73 (59.3)	
IV	16 (3.7)	9 (2.9)	7 (5.7)	
Chemotherapy after surgery				
Yes/no	311/124	220/92	91/32	0.556

Abbreviation: cCAV, corrected CT attenuate value.

phase), and DP-cCAV (cCAV in delayed phase) were 0.567 (p=0.038), 0.565 (p=0.042), 0.590 (p=0.005), and 0.620 (p<0.001) with statistical significance, respectively. The DP-cCAV with maximum AUC and Youden index was chosen. Thus, the patients were divided into DP-cCAV^{low} group and DP-cCAV^{high} group (cutoff value=0.425, sensitivity=0.409, specificity=0.831). The association between clinical and radiographic variables and overall survival (OS) was identified by univariable and multivariable Cox proportional hazards regression

models. Variables with the $p<0.10$ in univariate analyses were included in subsequent multivariate analyses. To see the accuracy of the multivariate Cox model by internal validation, C-index was calculated. Survival curves were estimated by using Kaplan–Meier method, and the log rank test was used for evaluating the differences.

Besides, we analyzed interobserver agreement for the measurements of CE-CT parameters of two readers with an intraclass correlation coefficient (ICC) (0.000–0.200 means poor; 0.201–0.400 means fair; 0.301–0.600 means moderate; 0.601–0.800 means good; 0.801–1.000 means excellent).

All of the tests were two-sided and the statistical significance was considered at $p<0.05$. Statistical analyses were conducted using R 3.6.0 (https://www.r-project.org/).

Results

Patients' Clinicopathological Characteristics

A total of 435 patients participated in this study. Three hundred and twelve patients (71.7%) showed low cCAV in the delayed phase, while the remaining 123 (28.3%) patients displayed high cCAV. Baseline demographic and clinical data were presented in Table 2. Compared with the DP-cCAV^{low} group, the patients with high DP-cCAV tended to show larger tumor diameters ($p=0.001$), more vascular ($p=0.015$) and neural ($p<0.001$) invasion status, more undifferentiated types and less differentiated types, higher grades of T stage ($p<0.001$), N stage ($p<0.001$) and TNM stage ($p<0.001$). In addition, males made the larger majority of patients in the DP-cCAV^{low} group ($p=0.011$).

Intra-observer Reproducibility

There were no significant differences between two independent measurements of each CT parameters measured by two readers. The ICCs of CAV were 0.686 in noncontrast phases, 0.831 in arterial phases, 0.844 in portal phases, and 0.856 in delayed phases. The ICCs of cCAV were 0.799 in arterial phases, 0.821 in portal phases, and 0.824 in delayed phases. All of them were in good or excellent agreement.

Table 2 Univariable and Multivariable Cox Proportional Hazards Regression Analyses of Clinical and Radiographic Features for Overall Survival in Patients with Gastric Adenocarcinoma

Variable	Univariate Analysis		Multivariate Analysis	
	Crude HR (95%CI)	*p*-value	Adjust HR (95% CI)	*p*-value
Gender (male vs female)	1.126 (0.787–1.612)	0.515		
Age (≥65 vs <65 years)	1.709 (1.266–2.307)	<0.001	1.805 (1.319–2.469)	<0.001
Location				
Cardia and fundus	0.540 (0.260–1.122)	0.099	1.030 (0.469–2.266)	0.941
Body	0.523 (0.256–1.069)	0.076	1.053 (0.493–2.248)	0.893
Antrum and pylorus	0.458 (0.230–0.910)	0.026	0.880 (0.423–1.833)	0.733
Whole stomach	1.0			
Maximum diameter of tumor (cm)	1.156 (1.098–1.218)	<0.001	1.082 (1.018–1.150)	0.012
Differentiation degree				
Differentiated type	0.645 (0.425–0.981)	0.040	0.886 (0.573–1.370)	0.587
Mixed type	1.153 (0.824–1.615)	0.406	1.164 (0.824–1.645)	0.388
Undifferentiated type	1.0			
TNM stage				
I	0.036 (0.017–0.077)	<0.001	0.048 (0.021–0.110)	<0.001
II	0.113 (0.062–0.205)	<0.001	0.120 (0.063–0.229)	<0.001
III	0.246 (0.142–0.427)	<0.001	0.222 (0.124–0.398)	<0.001
IV	1.0			
Vascular invasion status (yes vs no)	1.952 (1.454–2.62)	<0.001	1.323 (0.956–1.832)	0.091
Neural invasion status (yes vs no)	1.550 (1.146–2.096)	0.004	0.957 (0.681–1.345)	0.799
Chemotherapy after surgery (yes vs no)	0.815 (0.594–1.119)	0.207		
DP-cCAV (high vs low)	2.120 (1.569–2.866)	<0.001	1.623 (1.181–2.230)	<0.001

Abbreviations: CAV, CT attenuate value; DP-cCAV, corrected CT attenuate value in the delayed phase.

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	Crude HR (95%CI)	*p*-value	Adjust HR (95%CI)	*p*-value
Gender (male vs female)	1.126 (0.787–1.612)	0.515		
Age (≥65 vs <65 years)	1.709 (1.266–2.307)	<0.001*	1.805 (1.319–2.46)	<0.001*
Location				
Cardia and fundus	0.540 (0.260–1.122)	0.099	1.030 (0.469–2.26)	0.941
Body	0.523 (0.256–1.069)	0.076	1.053 (0.493–2.24)	0.893
Antrum and pylorus	0.458 (0.230–0.910)	0.026*	0.880 (0.423–1.83)	0.733
Whole stomach	1.0			
D-max of tumor (cm)	1.156 (1.098–1.218)	<0.001*	1.082 (1.018–1.15)	0.012*
Differentiation degree				
Differentiated type	0.645 (0.425–0.981)	0.040*	0.886 (0.573–1.37)	0.587
Mixed type	1.153 (0.824–1.615)	0.406	1.164 (0.824–1.64)	0.388
Undifferentiated type	1.0			
TNM stage				
I	0.036 (0.017–0.077)	<0.001*	0.048 (0.021–0.11)	<0.001*
II	0.113 (0.062–0.205)	<0.001*	0.120 (0.063–0.22)	<0.001*
III	0.246 (0.142–0.427)	<0.001*	0.222 (0.124–0.39)	<0.001*
IV	1.0			
Vascular invasion status (yes vs no)	1.952 (1.454–2.62)	<0.001*	1.323 (0.956–1.83)	0.091
Neural invasion status (yes vs no)	1.550 (1.146–2.096)	0.004*	0.957 (0.681–1.34)	0.799
Postoperative chemotherapy (yes vs no)	0.815 (0.594–1.119)	0.207		
DP-cCAV (high vs low)	2.120 (1.569–2.866)	<0.001*	1.623 (1.181–2.230)	<0.001*

Note: *$p<0.05$ statistically significant.
Abbreviations: D-max, maximum diameter; DP-cCAV, corrected CAV in the delayed phase.

Univariable and Multivariable Cox Proportional Hazards Regression Analyses

Results of univariable and multivariable Cox regression analyses for OS were presented in Table 3. According to results of univariate analysis, age (≥65 vs <65 years, HR=1.709, 95% CI=1.266–2.307, $p<0.001$), location (antrum and pylorus vs whole stomach, HR=0.458, 95%CI=0.230–0.910, $p=0.026$), tumor maximum diameter (HR=1.156, 95%CI=1.098–1.218, $p<0.001$), differentiation degree (differentiated type vs undifferentiated type, HR=0.645, 95%CI=0.425–0.981, $p=0.040$), TNM stage (I vs IV, HR= 0.036, 95%CI=0.017–0.077, $p<0.001$; II vs IV, HR=0.113, 95%CI=0.062–0.205, $p<0.001$; III vs IV, HR=0.246, 95%CI= 0.142–0.427, $p<0.001$), vascular invasion (yes vs no, HR=1.952, 95%CI=1.454–2.620, $p<0.001$), neural invasion (yes vs no, HR=1.550, 95% CI=1.146–2.096, $p=0.004$), DP-cCAV (high vs low, HR=2.120, 95%CI=1.569–2.866, p<0.001) were associated with OS, significantly.

In multivariate analysis, age (≥65 vs <65 years, HR=1.805, 95%CI=1.319–2.469, $p<0.001$), tumor maximum diameter (HR=1.082, 95%CI=1.018–1.150, $p=0.012$), TNM stage (I vs IV, HR=0.048, 95%CI=0.021–0.110, $p<0.001$; II vs IV, HR=0.120, 95%CI=0.063–0.229, $p<0.001$; III vs IV, HR=0.222, 95%CI=0.124–0.398, $p<0.001$) and DP-cCAV (HR=1.623; 95%CI=1.181–2.230, $p<0.001$) remained as the independent risk factors for OS in patients with GAC. C-index for multivariate Cox proportional hazards model was 0.736 by internal validation.

Survival Analysis and Subgroup Analysis

A total of 180 deaths (41.4% of 435 events) were observed at the end of study. As Kaplan–Meier curve (Figure 2) showed, lower mortality rate was observed in the DP-cCAV^{low} group than the high group by September 1, 2019; 109 of 312 patients (34.9%) vs 71 of 123 patients (57.7%). Median OS was not reached for the DP-cCAV^{low} group and was 28.5 months in the DP-cCAV^{high} group (Figure 3). Compared with the DP-cCAV^{low} group, there

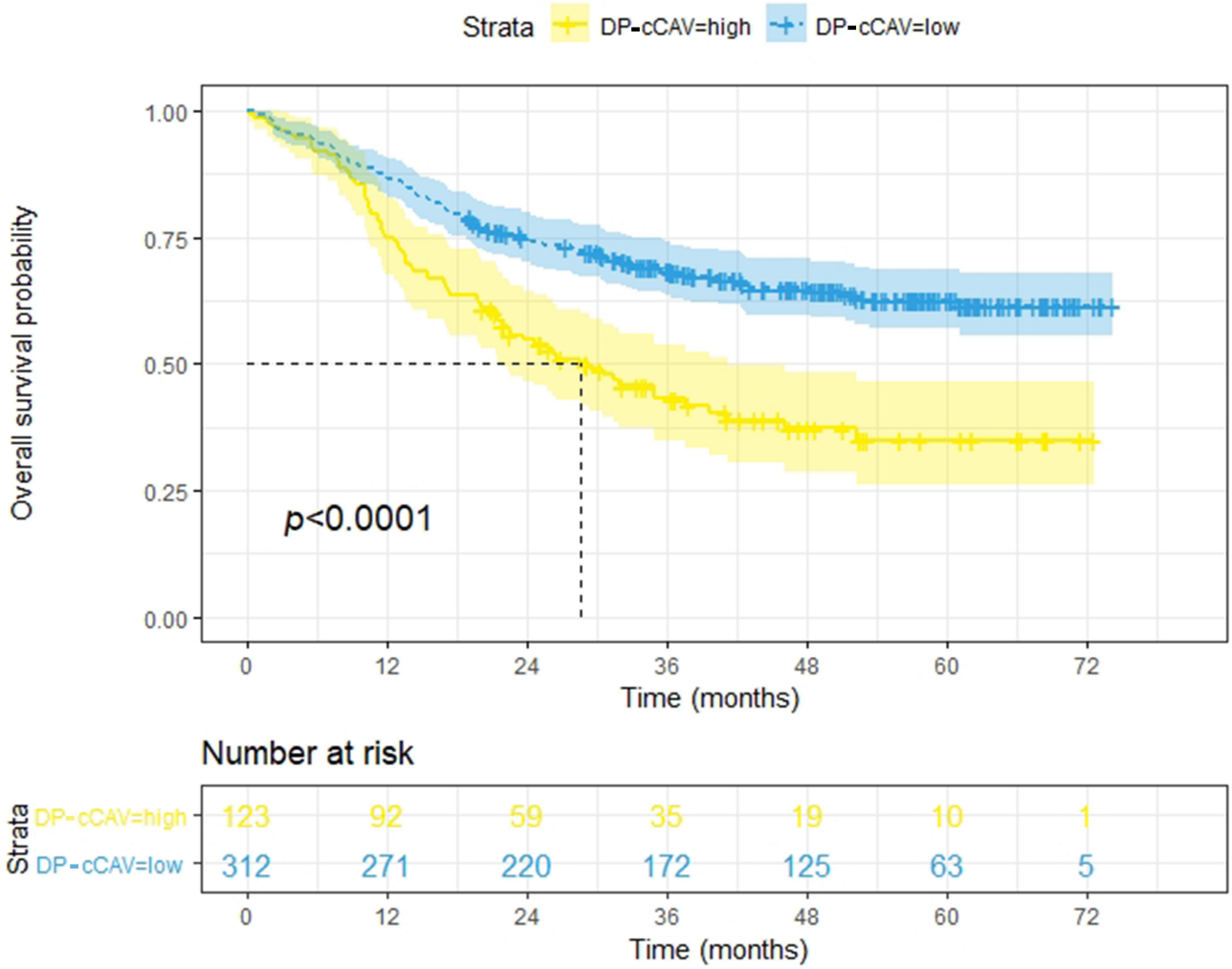

Figure 2 Overall survival for GAC patients according to CT value stratification.

was a 112% rise in the risk of death in the DP-cCAV^{high} group (HR=2.120, 95%CI=1.569–2.886, p<0.001). Moreover, accounting for the effects of confounding factors, which are reflected in Tables 2 and 3, we carried out a subgroup analysis based on age, maximum diameter of tumor, differentiation, vascular invasion status, and TNM staging (Figures 3 and 4). In most subgroups, the OS of the DP-cCAV^{low} group was overwhelmingly satisfactory (all HR >1, except TNM stages I, IV, and differentiated type subgroups).

Discussion

In our study, the preoperative CT parameters were relevant to the prognosis of patients with GAC after surgery. Both univariate and multivariate Cox regression analysis demonstrated the low-enhancement state was an independent protective factor (Table 3) and C-index revealed a good predictive ability. Survival analyses showed the prognosis of patients in the low-enhancement group was better than in the high-enhancement group, significantly (Figure 2). Besides, the ROC curve analysis suggested that other CT parameters such as PP-CAV, PP-cCAV, and DP-CAV also seemed to be related to the prognosis of GC (Table 1).

In our sample, undifferentiated GC was the majority tissue type for 54.5% of total, 49.4% of the DP-cCAV^{low} group and 67.5% of the DP-cCAV^{high} group. Varying degrees of mature and immature fibrosis were manifestations of undifferentiated-type GC, which affected the enhancement pattern of CT. Tsurumaru et al found in the delayed phase, undifferentiated-type GCs displayed the peak of enhancement, which was significantly higher CAV than other types.[20] In other words, undifferentiated GC showed a delayed enhancement pattern. It was corresponding with

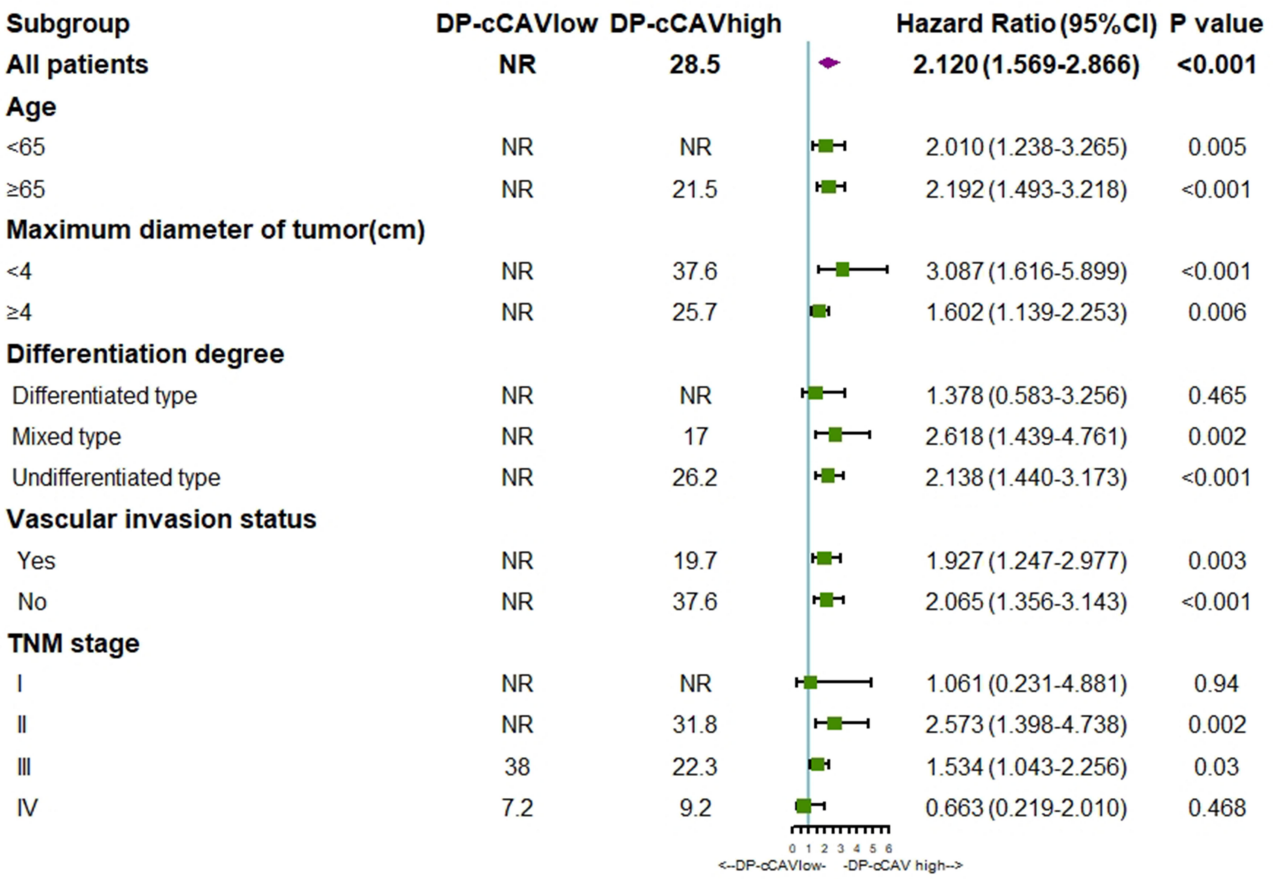

Figure 3 Subgroup analysis for GAC patients.
Abbreviation: NR, not reached.

our study: the best diagnostic performance in distinguishing the three-year survival rate was the CT parameters of the delayed phase (Table 1).

One of the parameters measured in the form of CAV is the tumor density.[21] The contrast enhancement of tumor density in the ROI under enhanced CT closely matches the physiological effect of tumor angiogenesis.[22] The state of visceral mass contrast enhancement on CT images which could reflect tumor vascularity state is an important parameter.[23] And the tumor angiogenesis, closely related to tumor development, invasion as well as metastasis, is a key course of events.[24] Several studies have been suggested that tumor enhancement status in CE-CT is a long-term prognostic factor.[25,26] The findings of our study provided strong evidence for this. Compared with the DP-cCAV^{low} group, prognoses of the high-enhancement group were almost consistently unfavorable across the great majority of subgroups, including all ages, tumor sizes, vascular invasion status, etc (Figure 3).

At present, TNM staging of GC is the most widely used clinical reference to guide patient treatment and prognosis.[27] Kunisaki et al held that tumor diameter in GC was a reliable prognostic factor which might be a candidate for use in the staging system.[28] Our research also found that the maximum diameter of tumor was inversely related to the prognosis (Table 3). It was worth noting that in Table 2, maximum diameter of tumor in the DP-cCAV^{high} group was significantly larger than in the DP-cCAV^{low} group. We speculated that it might be some underlying correlation between CT parameters and maximum diameter, which required further research.

In some previous studies, clinicians have been attracted by the high-resolution images of dynamic multi-detector CT, which contributed a noninvasive method for differential diagnosis and tumor staging.[23] However, in order to choose the best treatment method for personalized treatment according to the guidelines, we need to test the patient's prognosis and prediction information with higher accuracy. Our study quantified the functionality of CE-CT by delayed phase parameters and found it was valuable in predicting the prognosis of patients with GAC after

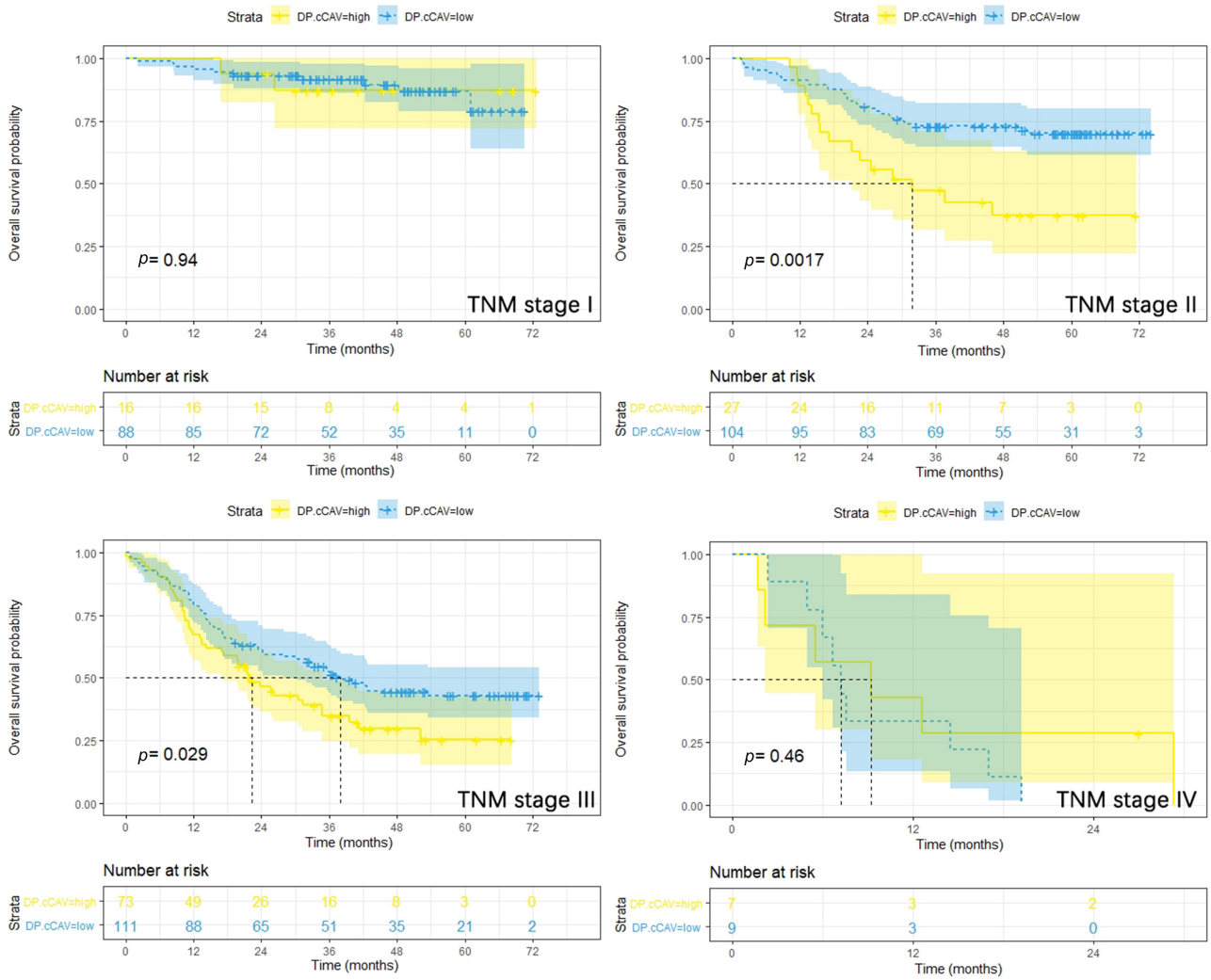

Figure 4 Subgroup analysis for GAC patients based on TNM stage. Figures display overall survival for patients with TNM stage I, II, III, IV GAC.

surgery. Moreover, although there are many studies that explore imaging parameters such as PET/CT parameter to predict tumor prognosis,[29,30] CE-CT may be more clinically valuable because it is affordable and available.

There were several limitations in this study. First, further prospective studies were needed to validate its worth because this study was retrospective. Second, it was a single institution study without a large sample size. Third, we only drew the greatest area of lesion for analysis, which may not be enough to represent the entire tumor. Although the ROIs of the largest area reflect the angiogenesis more comprehensively, minimize the effect of necrotic tissue, and analyze the heterogeneity of the entire lesion at the highest level,[31] further studies that analyze the total volume obtained by drawing the tumor contour on each slice need to be carried out.

Conclusion

In conclusion, the findings of our research indicated the prognostic effectiveness of CT parameters as biomarkers of OS in GAC patients treated with surgery may be valuable. The patients with higher DP-cCAV (high-enhancement) tended to have a higher risk of postsurgical disease progression, which could guide them to receive more aggressive treatment early to improve their prognosis as well as allow the clinician to select the most appropriate therapy and maximize the likelihood of benefit from the selected treatment.

Abbreviations

AUC, area under the curve; CAV, CT attenuate value; cCAV, corrected CAV; CE-CT, contrast-enhanced computed tomography; DP-CAV, CAV in delayed phase;

DP-cCAV, cCAV in delayed phase; GAC, gastric adenocarcinoma; GC, gastric cancer; ICC, intra-class correlation coefficient; OS, overall survival; PACS, picture archiving and communication system; PP-CAV, CAV in portal phase; PP-cCAV, cCAV in portal phase; ROC, receiver operating characteristic; ROI, region of interest; WL, window level; WW, window width.

Data Sharing Statement

Please contact the corresponding author (Mengjun Chen) for data requests.

Ethics Approval and Informed Consent

This study only investigated and analyzed the clinical data of patients treated at our institution, and we did not perform any interventional operations on the patients. These data were used daily in clinical practice. We anonymized and kept confidential the data. We conducted this retrospective study in accordance with the Declaration of Helsinki and it was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. Due to the retrospective noninterventional research design, the ethics committee did not require the patient consent to review the electronic medical record. Nevertheless, we had obtained verbal informed consent from all patients or corresponding authorized persons during the telephone follow-up process.

Consent for Publication

Not applicable.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
2. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk. *Br J Cancer*. 1990;62(1):136–137. doi:10.1038/bjc.1990.245
3. Coggon D, Barker DJ, Cole RB, Nelson M. Stomach cancer and food storage. *J Natl Cancer Inst*. 1989;81(15):1178–1182. doi:10.1093/jnci/81.15.1178
4. Nam SY, Park BJ, Nam JH, Kook MC. Effect of Helicobacter pylori eradication and high-density lipoprotein on the risk of de novo gastric cancer development. *Gastrointest Endosc*. 2019;90(3):448–456.e441. doi:10.1016/j.gie.2019.04.232
5. Fock KM. Review article: the epidemiology and prevention of gastric cancer. *Aliment Pharmacol Ther*. 2014;40(3):250–260. doi:10.1111/apt.12814
6. Kemi N, Eskuri M, Herva A, et al. Tumour-stroma ratio and prognosis in gastric adenocarcinoma. *Br J Cancer*. 2018;119(4):435–439. doi:10.1038/s41416-018-0202-y
7. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90. doi:10.3322/caac.20107
8. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11–20. doi:10.1056/NEJMoa055531
9. Ye S, Wang L, Zuo Z, Bei Y, Liu K, Gold JS. The role of surgery and radiation in advanced gastric cancer: a population-based study of surveillance, epidemiology, and end results database. *PLoS One*. 2019;14(3):e0213596. doi:10.1371/journal.pone.0213596
10. Röcken C. Molecular classification of gastric cancer. *Expert Rev Mol Diagn*. 2017;17(3):293–301. doi:10.1080/14737159.2017.1286985
11. Zu H, Wang H, Li C, Xue Y. Clinicopathologic characteristics and prognostic value of various histological types in advanced gastric cancer. *Int J Clin Exp Pathol*. 2014;7(9):5692–5700.
12. Johansen A, Sikjaer B. Gastroscopic biopsy: reliability of histological diagnosis with special reference to the single biopsy. *Scand J Gastroenterol*. 1975;10(5):453–458. doi:10.1080/00365521.1975.12096994
13. McCulloch P. The role of surgery in patients with advanced gastric cancer. *Best Pract Res Clin Gastroenterol*. 2006;20(4):767–787. doi:10.1016/j.bpg.2006.03.006
14. Liu S, Liu S, Ji C, et al. Application of CT texture analysis in predicting histopathological characteristics of gastric cancers. *Eur Radiol*. 2017;27(12):4951–4959. doi:10.1007/s00330-017-4881-1
15. Saito T, Kurokawa Y, Takiguchi S, et al. Accuracy of multidetector-row CT in diagnosing lymph node metastasis in patients with gastric cancer. *Eur Radiol*. 2015;25(2):368–374. doi:10.1007/s00330-014-3373-9
16. Ba'Ssalamah A, Muin D, Schernthaner R, et al. Texture-based classification of different gastric tumors at contrast-enhanced CT. *Eur J Radiol*. 2013;82(10):e537–543. doi:10.1016/j.ejrad.2013.06.024
17. Giganti F, Tang L, Baba H. Gastric cancer and imaging biomarkers: part 1 - a critical review of DW-MRI and CE-MDCT findings. *Eur Radiol*. 2019;29(4):1743–1753. doi:10.1007/s00330-018-5732-4
18. Tang L, Wang XJ, Baba H, Giganti F. Gastric cancer and image-derived quantitative parameters: part 2-a critical review of DCE-MRI and F-FDG PET/CT findings. *Eur Radiol*. 2020;30(1):247–260. doi:10.1007/s00330-019-06370-x
19. Kim HJ, Kim AY, Oh ST, et al. Gastric cancer staging at multi-detector row CT gastrography: comparison of transverse and volumetric CT scanning. *Radiology*. 2005;236(3):879–885. doi:10.1148/radiol.2363041101
20. Tsurumaru D, Miyasaka M, Muraki T, et al. Histopathologic diversity of gastric cancers: relationship between enhancement pattern on dynamic contrast-enhanced CT and histological type. *Eur J Radiol*. 2017;97:90–95. doi:10.1016/j.ejrad.2017.10.018

21. Wang Z, Ye Y, Hu Y, et al. Extent of enhancement on multiphase contrast-enhanced CT images is a potential prognostic factor of stage I-III colon cancer. *Eur Radiol*. 2019;29(3):1114–1123. doi:10.1007/s00330-018-5689-3
22. Miles KA. Tumour angiogenesis and its relation to contrast enhancement on computed tomography: a review. *Eur J Radiol*. 1999;30(3):198–205. doi:10.1016/S0720-048X(99)00012-1
23. Ginat DT, Gupta R. Advances in computed tomography imaging technology. *Annu Rev Biomed Eng*. 2014;16:431–453. doi:10.1146/annurev-bioeng-121813-113601
24. Folkman J, Parris EE, Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285(21):1182–1186. doi:10.1056/NEJM197111182852108
25. Komori M, Asayama Y, Fujita N, et al. Extent of arterial tumor enhancement measured with preoperative MDCT gastrography is a prognostic factor in advanced gastric cancer after curative resection. *AJR Am J Roentgenol*. 2013;201(2):W253–261. doi:10.2214/AJR.12.9206
26. Zhu YH, Wang X, Zhang J, Chen YH, Kong W, Huang YR. Low enhancement on multiphase contrast-enhanced CT images: an independent predictor of the presence of high tumor grade of clear cell renal cell carcinoma. *AJR Am J Roentgenol*. 2014;203(3):W295–300. doi:10.2214/AJR.13.12297
27. Wang FH, Shen L, Li J, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer. *Cancer Commun (Lond)*. 2019;39(1):10. doi:10.1186/s40880-019-0349-9
28. Kunisaki C, Makino H, Takagawa R, et al. Tumor diameter as a prognostic factor in patients with gastric cancer. *Ann Surg Oncol*. 2008;15(7):1959–1967. doi:10.1245/s10434-008-9884-3
29. Grut H, Dueland S, Line PD, Revheim ME. The prognostic value of F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. *Eur J Nucl Med Mol Imaging*. 2018;45(2):218–225. doi:10.1007/s00259-017-3843-9
30. Jiang H, Zhang R, Jiang H, et al. Retrospective analysis of the prognostic value of PD-L1 expression and F-FDG PET/CT metabolic parameters in colorectal cancer. *J Cancer*. 2020;11(10):2864–2873. doi:10.7150/jca.38689
31. Liu S, Shi H, Ji C, et al. Preoperative CT texture analysis of gastric cancer: correlations with postoperative TNM staging. *Clin Radiol*. 2018;73(8):756.e751–756.e759.