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Computed tomography perfusion as a predictor of gastric cancer grades

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Abstract

Background Gastric cancer stands as one of the most prevalent malignancies globally, conventional endoscopic specimens have been the primary means of diagnosing preoperative gastric histopathology, however, their limitations in capturing intra-tumor heterogeneity compromise their efficacy in evaluating angiogenesis. Perfusion Computed Tomography (P-CT) emerges as a pivotal functional imaging modality, facilitating objective assessment of tissue perfusion, serving as a marker of angiogenesis. So, our research objective was to evaluate the efficacy of CT perfusion imaging in the prediction of histological grades of gastric tumors using quantitative perfusion parameters such as permeability surface (PS), blood flow (BF), mean transient time (MTT), and blood volume (BV), in addition to the qualitative scoring system then comparing the findings with the histopathological results.

Results PS and BF were statistically significant predictors of the grade of differentiation, their odds ratio (OR) was (1.05, 95% CI 1.02–1.09, for each of them) ($P=0.004$, $P=0.009$, respectively). MTT also emerged as a significant predictor of the grade of differentiation with an OR of 0.76 (95% CI 0.57–0.93, $P=0.025$). Using multivariate logistic regression model, PS was the most potent individual P-CT predictor of differentiation of the grade and the diagnosis of poorly differentiated tumors at ≥ 39 mL/100 g/min cut off point, followed by BF at ≥ 82.2 mL/100 g/min, and MTT at < 8.4 s. Regarding the qualitative scoring system P-CT, poorly differentiated tumors generally received higher scores of PS ($P<0.001$), BF ($P<0.001$), and BV ($P=0.017$), than well and moderately differentiated tumors, however, MTT showed that poorly differentiated tumors were more frequently scored as low compared to well and moderately differentiated tumors ($P<0.001$).

Conclusions P-CT is an innovative, non-invasive biomarker for predicting gastric cancer grade by quantitative and qualitative assessment by P-CT parameters (PS, BF and MTT) with particular role of PS as the strongest individual P-CT predictor of differentiation grade followed by BF and MTT at specific cut off points.

Keywords Gastric tumor grades, Angiogenesis, Perfusion computed tomography, Permeability surface

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Background

Gastric cancer stands as one of the most prevalent malignancies globally, constituting a significant source of morbidity and mortality [1]. Identifying cases with a high risk of recurrence and poor prognosis is imperative for effective intervention through adjuvant chemotherapy [2]. The assessment of tumor perfusion and hemodynamic changes is useful in understanding the pathological background of the cancer and determining prognosis [3]. Tumor angiogenesis plays a vital role in the growth as well as metastasis of tumors due to the fluctuations in blood vessel volume and capillary permeability in new tumor vessels, and these changes lead to alterations in blood pattern [2, 4–6]).

Conventional endoscopic specimens have been the primary means of diagnosing preoperative gastric histopathology. However, their limitations in capturing intra-tumor heterogeneity compromise their efficacy in evaluating angiogenesis [7].

In this context, Perfusion Computed Tomography (P-CT) emerges as a pivotal functional imaging modality [8], and acknowledged as a potential neoangiogenesis marker, that allows precise measurement of physiological parameters associated with tumor perfusion, generating a regional map that color-codes the heterogeneous perfusion patterns across the entire tumor [7–12].

In this study, we aimed to rigorously evaluate the efficacy of P-CT imaging in the accurate prediction of histological grades of gastric tumors as it facilitates objective assessment of tissue perfusion that enables the measurement of tumor perfusion which serving as a marker of angiogenesis as evaluating angiogenesis using conventional endoscopy was difficult in certain cases due to intra-tumor heterogeneity. This was achieved by a detailed comparison of the quantitative perfusion parameters, such as PS, BF, MTT and BV and the qualitative scoring system with the findings from histopathological analysis.

Methods

Patient selection

This prospective nonrandomized study was approved by our institutional ethical committee (NO.578). Written informed consent was obtained from each patient for participation and publication after receiving information about the details of the study. This study was conducted in our radiology department at south Egypt cancer institute from February 2022 to December 2023, on 45 consecutive patients who proved pathologically to have gastric cancer through surgical or endoscopic specimens preoperatively. Stage Ia tumors, lesions undetectable on CT, history of allergy to intravenous contrast media and impaired renal function patients were excluded from our study. All the 45 patients underwent P-CT then comparing the results of perfusion parameters to the pathological grades of the tumor. Histopathological examination serves as the gold standard test and classified the tumor into, well, moderate, and poorly differentiated adenocarcinoma [13].

Table 1 Summary of the clinical and tumor characteristics of the study population

		Overall
N		45
Age (years) [median [IQR]]		46.00 [40.00, 66.00]
Location (%)	Lower	19 (42.2)
	Middle	13 (28.9)
	Upper	13 (28.9)
Size (post-operative) [%]	5 cm to below 10 cm	19 (42.2)
	Less than 5 cm	4 (8.9)
	More than 10 cm	22 (48.9)
Tumor depth (%)	T2	11 (24.4)
	T3\4	34 (75.6)
LNs (%)	Negative	16 (35.6)
	Positive	29 (64.4)
Liver mets (%)	Negative	35 (77.8)
	Positive	10 (22.2)
Peritoneal deposits (%)	Negative	23 (51.1)
	Positive	22 (48.9)
Distant mets (%)	Negative	35 (77.8)
	Positive	10 (22.2)
Pathology (%)	Well-differentiated	9 (20.0)
	Moderately differentiated	12 (26.7)
	Poorly differentiated	24 (53.3)
CT perfusion parameters:		
BV (median [IQR])		6.50 [3.50, 11.00]
BF (median [IQR])		56.90 [47.40, 82.20]
PS (median [IQR])		36.50 [22.60, 53.04]
MTT (median [IQR])		8.70 [7.20, 10.60]

Patient preparation

After fulfilling the clinical and laboratory data including, age, sex, hypersensitivity to contrast media, and serum level of creatinine; all the patients who underwent P-CT fasted six hours before the procedure, intramuscular administration of 20 mg spasmolytic hyoscine N-butylbromide (Buscopan) was given 10–15 min before scanning. To facilitate gastric distention, between 600–800 mL of water was orally administered 15–30 min before scanning, with an additional 200 mL immediately before the examination.

An 18-gauge cannula was inserted into a superficial vein within the antecubital fossa, and injection was

Table 2 CT perfusion parameters based on tumor grade

		Well-differentiated	Moderately-differentiated	Poorly differentiated	*P* value
N		9	12	24	
Age (years) [median [IQR]]		46.00 [40.00, 68.00]	46.00 [45.00, 66.00]	56.00 [38.75, 65.25]	0.839
Location (%)	Lower	6 (66.7)	4 (33.3)	9 (37.5)	0.268
	Middle	0 (0.0)	4 (33.3)	9 (37.5)	
	Upper	3 (33.3)	4 (33.3)	6 (25.0)	
Size (post-operative) [%]	5 cm to below 10 cm	9 (100.0)	4 (33.3)	6 (25.0)	< **0.001**
	less than 5 cm	0 (0.0)	4 (33.3)	0 (0.0)	
	more than 10 cm	0 (0.0)	4 (33.3)	18 (75.0)	
Tumor depth (%)	T2	3 (33.3)	8 (66.7)	0 (0.0)	< **0.001**
	T3\4	6 (66.7)	4 (33.3)	24 (100.0)	
LNs (%)	Negative	0 (0.0)	4 (33.3)	12 (50.0)	**0.028**
	Positive	9 (100.0)	8 (66.7)	12 (50.0)	
Liver mets (%)	Negative	9 (100.0)	8 (66.7)	18 (75.0)	0.171
	Positive	0 (0.0)	4 (33.3)	6 (25.0)	
Peritoneal deposits (%)	Negative	9 (100.0)	8 (66.7)	6 (25.0)	< **0.001**
	Positive	0 (0.0)	4 (33.3)	18 (75.0)	
Distant mets (%)	Negative	9 (100.0)	8 (66.7)	18 (75.0)	0.171
	Positive	0 (0.0)	4 (33.3)	6 (25.0)	**< 0.001**
-PS Quantitative (median [IQR])		22.60 [3.70, 23.60]	33.90 [4.50, 36.50]	49.97 [40.65, 91.67]	
-BF Quantitative (median [IQR])		50.07 [38.48, 51.04]	56.90 [18.00, 80.70]	81.95 [71.85, 85.78]	**0.001**
-MTT Quantitative (median [IQR])		10.80 [6.10, 18.90]	8.70 [8.40, 10.60]	7.80 [6.48, 9.20]	**0.047**
-BV Quantitative (median [IQR])		3.50 [2.60, 11.90]	5.74 [1.30, 11.58]	8.00 [6.20, 10.62]	0.619

Bold value indicates $P < 0.05$

performed using an automatic power injector with the patient's arms in the scanning position to ensure successful vein cannulation.

P-CT scanning protocol

Firstly, a routine non contrast upper abdominal plain CT scan was performed using a 16 Multidetector CT scanner (GE Bright Speed 16 row). Parameters included a 5 mm slice thickness and spacing, tube voltage of 100–120 kV, tube current of 100 mAs, matrix of 512×512 pixels, and pitch of 0.984:1.

Subsequently, P-CT scan was conducted based on the images obtained from the non-contrast scan, the slice with the largest tumor area was selected as the center and six adjacent slices including the center slice were chosen on the Z-axis. Scanning parameters for these slices included a small field of view (FOV), 4.8 mm slice thickness, tube voltage of 80–100 kV, and tube current of 80–100 mAs.

A 70 mL bolus of iodinated contrast material (iohexol) containing 350 mg of iodine per mL was injected via a power injector through an 18-gauge intravenous cannula at a rate of 5 mL/s. Scanning commenced 5 s after contrast agent injection with a scan duration of 30 s. Timing for stomach contrast material injection ensured arterial and portal phase imaging.

Image analysis

The acquired data underwent analysis using the Advantage Windows Workstation 4.7 (AWW) by GE Medical Systems, a commercial deconvolution-based P-CT software provided by GE Medical Systems was employed, and the body tumor perfusion program was utilized. Partial-volume averaging correction was implemented using the abdominal aorta. The regions of interest over the tumor section by section were drawn; these regions aimed to be as extensive as possible to minimize noise (maintaining a threshold of > 50 pixels) and cover the entire lesion, excluding peripheral fat and necrotic areas.

Automatic calculations were performed for each patient on available sections (with a reconstruction slice thickness of 5 mm) generating maps for BF, BV, MTT, and PS. Functional maps depicting BF, BV, MTT, and PS were generated displaying a color spectrum from blue to red. Blue represented the lower range of display for BF, BV, and PS while red indicated the upper range of display, but as regard the MTT, the blue color referred to the longest MTT, and the red color referred to the shortest MTT.

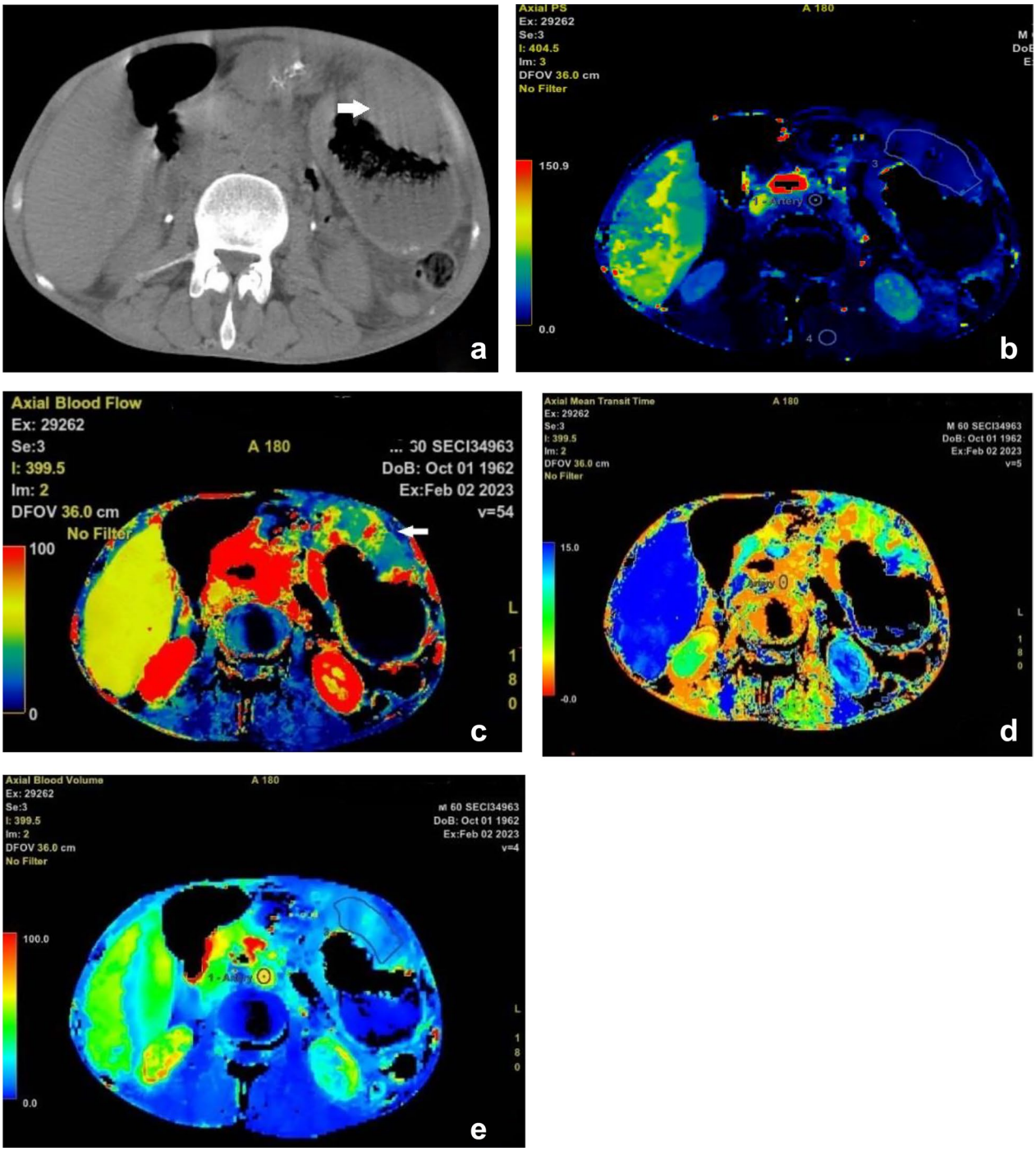

Fig. 1 A 40-year-old male patient presented by epigastric pain and vomiting. Axial CT of the upper abdomen showed focal gastric wall thickening (white arrow) (**a**). Parametric perfusion maps (qualitative assessment) showed blue colour in PS (**b**); blue and green colour in BF (**c**); predominately blue and green colour in MTT (**d**); and predominately blue colour in BV (**e**). The quantitative assessment showed that the PS value was 23.66 ml/100 g/min, BF was 35.07 ml/100 g/min, MTT was 13.7 s, and 3.5 ml/100 g for the BV. All the qualitative and quantitative perfusion parameters indicate well differentiated gastric cancer that also was proved pathologically

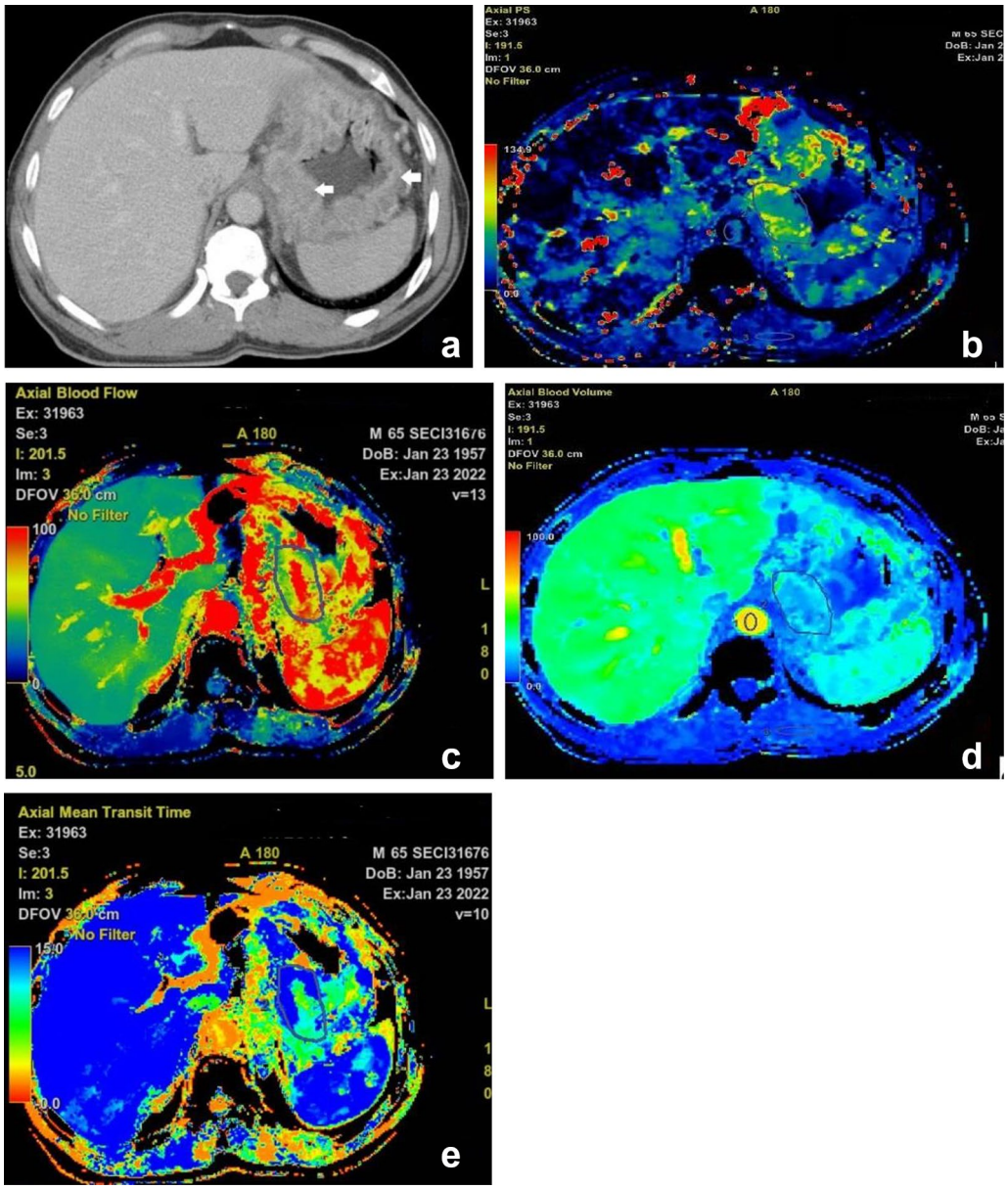

Fig. 2 A 66-year- old male patient presented by epigastric pain and weight loss. Axial CT of the upper abdomen revealed irregular enhanced gastric wall thickening (white arrow) (**a**). Parametric perfusion maps (qualitative assessment) showed mixed blue and yellow colour in PS (**b**); mixed yellow and green colour in BF(**c**); predominately blue colour in BV (**d**); and predominately blue colour in MTT (**e**) indicated long time. The quantitative assessment showed that the PS value was 36.53 ml/100 g/min s, BF was 46 ml/100 g/min, MTT was 10.56 s, and 11.5 ml/100 g for the BV. All the qualitative and quantitative perfusion parameters showed moderately differentiated gastric cancer that also was proved pathologically

Parameters are defined as follows:

(1) BF: Volume flow rate of blood through the vasculature in a tumor expressed in units of ml/min/100 g [7].
(2) BV: Volume of blood actively flowing within the vasculature in a tumor measured in units of ml/100 g [7].
(3) MTT: Average time taken by blood elements to traverse the vasculature from the arterial end to the venous end in a tumor measured in seconds [7]

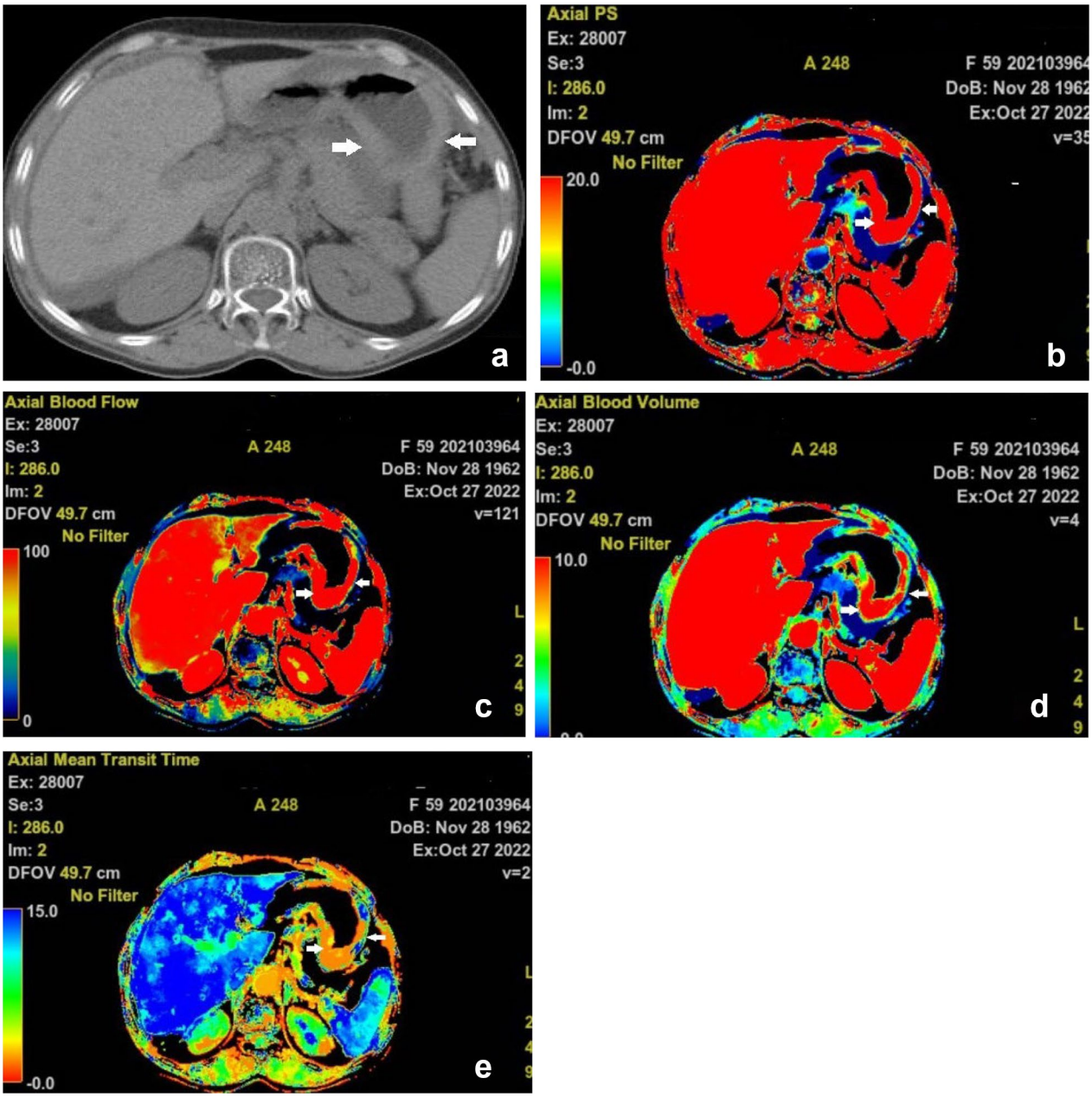

Fig. 3 A 65-year-old male patient presented by epigastric pain and melena. Non contrast axial CT of the upper abdomen (**a**) revealed circumferential gastric wall thickening (white arrow). Parametric perfusion maps (qualitative assessment) showed red colour in PS (**b**); BF (**c**); BV; (**d**) indicated high PS, BF and BV, and predominately yellow colour in MTT; (**e**) indicated short time. The quantitative assessment showed that the PS value was 46.48 ml/100 g/min, BF was 197 ml/100 g/min, BV was 11.5 ml/100 g, and MTT was 3.24 s. All the qualitative and quantitative perfusion parameters showed poorly differentiated gastric cancer that also was proved pathologically

(4) PS: Unidirectional flux of contrast from blood plasma to the interstitial space that measured in units of ml/min/100 g [7]

Statistical analysis

The statistical analyses and graph plotting were performed using R programming language version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, 2019) and R Studio version 2023.012.1–494 (R Studio, Inc., Boston, MA, USA, 2019). The Shapiro–Wilk test was utilized to verify the normal distribution of the variables BF, BV, MTT, and PS. The relationship between these variables and the reduction in tumor size was investigated using a linear regression plot and Spearman's

Table 3 Results of multivariate and univariate logistic regression models

CT parameter	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)[a]
Permeability surface (PS)	1.05 (1.02, 1.09)[a]	1.04 (1.01, 1.09)[a]
Mean transit time (MTT)	0.76 (0.57, 0.93)[a]	0.97 (0.58, 1.54)
Blood flow (BF)	1.05 (1.02, 1.09)[a]	1.04 (0.99, 1.11)
Blood volume (BV)		0.83 (0.53, 1.29)

[a] $P<0.05$

rank correlation coefficient; the interrelationships among the variables were depicted using a multiple regression model. All the differences were statistically significant at a p-value of 0.05.

Results

This study included 45 patients, their ages ranging from 40 to 66 years. On pathological assessment, about half of tumors were poorly differentiated (53%), 27% were moderately differentiated, and 20% were well-differentiated (Table 1).

As indicated in Table 2, poorly differentiated adenocarcinomas tend to exhibit more advanced invasion with all poorly differentiated tumors being classified as T3/4 ($P<0.001$). P-CT parameters were in line with the level of dedifferentiation; BF and PS progressively increase with lower differentiation, with the lowest median values in well-differentiated tumors (approximately 50 and 23 mL/100 g/minute, respectively) (Fig. 1), increasing to 57 and 34 in moderately differentiated tumors (Fig. 2), and peaking in the poorly differentiated subgroup (82 and 50 mL/100 g/minute) ($P=0.001$ and $P<0.001$, respectively) (Fig. 3). In contrast, MTT was quicker in poorly differentiated tumors (median 7.8 s) (Fig. 3) compared to moderately (Fig. 2) and well differentiated (Fig. 1) (8.7 vs. 10.8 s, respectively, $P=0.047$), indicating a more rapid vascular flow in poorly differentiated tumor. BV showed a tendency to be higher in poorly differentiated tumors although this did not reach statistical significance ($p=0.619$).

From the univariate logistic regression model (Table 3); PS and BF were statistically significant predictors of the grade of differentiation their odds ratio (OR) were (1.05, 95% CI 1.02–1.09 for each of them), that means higher PS and BF associated with slightly higher odds of poor differentiation. MTT also emerged as a significant predictor of the grade of differentiation with an OR of 0.76 (95% CI 0.57–0.93, $P=0.025$), this suggests that higher MTT values correlate with lower odds of having poorly differentiated pathology (Fig. 2).

From the multivariate logistic regression model, we noted that PS maintained its statistical significance after adjustment for other parameters. So, it was considered

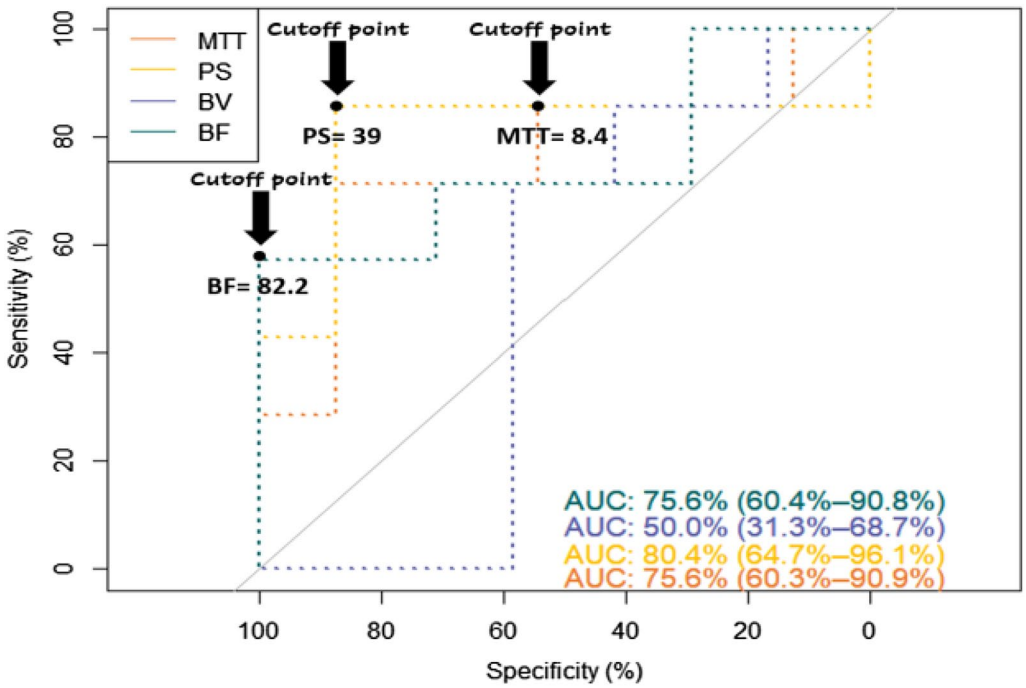

Fig. 4 Diagnostic performance of PS, BF, BV, and MTT in diagnosing poorly differentiated gastric cancer along with their different cutoff points

Table 4 A dichotomized analysis of patients into PS < 39 mL/100 g/min and PS ≥ 39 mL/100 g/min groups based on an optimal cutoff from ROC analysis

		< 39 mL/100 g/minute	> 39 mL/100 g/minute	*P* value
N		24	21	
Age (years) [median [IQR]]		46.00 [43.75, 66.00]	62.00 [40.00, 66.00]	0.513
Location (%)	Lower	13 (54.2)	6 (28.6)	0.111
	Middle	4 (16.7)	9 (42.9)	
	Upper	7 (29.2)	6 (28.6)	
Size (post operative) [%]	less than 5 cm	4 (16.7)	0 (0.0)	**< 0.001**
	5 cm to below 10 cm	16 (66.7)	3 (14.3)	
	more than 10 cm	4 (16.7)	**18 (85.7)**	
Tumor depth (%)	T_2	11 (45.8)	0 (0.0)	**0.001**
	$T_{3/4}$	13 (54.2)	21 (100.0)	
LNs (%)	Negative	4 (16.7)	12 (57.1)	**0.012**
	Positive	20 (83.3)	9 (42.9)	
Liver mets (%)	Negative	20 (83.3)	15 (71.4)	0.549
	Positive	4 (16.7)	6 (28.6)	
Peritoneal deposits (%)	Negative	20 (83.3)	3 (14.3)	**< 0.001**
	Positive	4 (16.7)	**18 (85.7)**	
Distant mets (%)	Negative	20 (83.3)	15 (71.4)	0.549
	Positive	4 (16.7)	6 (28.6)	
Pathology (%)	Well-differentiated	9 (37.5)	0 (0.0)	**< 0.001**
	Moderately-differentiated	12 (50.0)	0 (0.0)	
	Poorly differentiated	3 (12.5)	21 (100.0)	
BV (median [IQR])		5.74 [2.60, 11.58]	9.00 [5.30, 11.00]	0.305
BF (median [IQR])		51.04 [38.48, 80.70]	81.70 [47.40, 82.70]	**0.02**
MTT (median [IQR])		8.70 [8.20, 10.65]	8.00 [4.30, 9.80]	0.075

Bold value indicates $P < 0.05$

the strongest P-CT parameter to be used as predictor of grade differentiation (Table 3).

From receiver operator curve (ROC) analysis (Fig. 4), patients with PS ≥ 39 mL/100 g/min (Table 4), BF ≥ 82.2 mL/100 g/min (Table 5), and MTT < 8.4 s (Table 6), correlated strongly with aggressive features, larger size, deeper invasion, poorer differentiated tumors, greater metastatic spread, and higher perfusion. Subsequently all these values used as cutoff points to differentiate gastric cancer patients with markedly worse prognostic factors.

The qualitative analysis of P-CT parameters using a qualitative score (low, Intermediate, and high) in relation to the grade of gastric cancer revealed a notable link between gastric cancer grades and qualitative P-CT parameters (Table 7), specifically qualitative scores for PS and BF showed the highest scores observed in poorly differentiated tumors, while all well-differentiated tumors receiving low scores ($P < 0.001$). MTT qualitative scores reported that poorly differentiated tumors more frequently scored as low compared to well and moderately differentiated tumors ($P < 0.001$). Similarly, qualitative scores for BV were significantly different across tumor grades ($P = 0.017$), with a higher proportion of high scores in poorly differentiated tumors. PS was the most discerning qualitative parameter clearly separating the tumor grades with a significant p-value ($P < 0.001$).

Discussion

Gastric cancer is a leading cause of global morbidity and mortality [1, 12]. It is primarily diagnosed through preoperative gastric histopathology using conventional endoscopic specimens [10], however, these specimens often fall short in assessing angiogenesis. In cases where the tumor is unresectable, evaluating tumor perfusion with pathological specimens becomes impossible. P-CT a relatively new technology allows for the measurement of physiological parameters associated with tumor perfusion and the construction of a regional perfusion map [1, 2, 4, 5, 7]. As an imaging biomarker, it can depict alterations in angiogenesis and vascular permeability associated with aggressive tumor biology so it can differentiate

Table 5 A dichotomized analysis of patients into BF < 82.2 mL/100 g/minute and ≥ 82.2 mL/100 g/minute groups based on an optimal cutoff from ROC analysis

		< 82.2 mL/100 g/minute	> 82.2 mL/100 g/minute	*P* value	
N			33	12	
Age (years) [median [IQR]]			46.00 [40.00, 66.00]	63.50 [55.25, 65.25]	0.46
Location (%)	Lower		13 (39.4)	6 (50.0)	0.816
	Middle		10 (30.3)	3 (25.0)	
	Upper		10 (30.3)	3 (25.0)	
Size (post-operative) [%]	less than 5 cm		4 (12.1)	0 (0.0)	**0.087**
	5 cm to below 10 cm		16 (48.5)	3 (25.0)	
	more than 10 cm		13 (39.4)	9 (75.0)	
Tumor depth (%)	T_2		11 (33.3)	0 (0.0)	**0.056**
	$T_{3/4}$		22 (66.7)	12 (100.0)	
LNs (%)	Negative		10 (30.3)	6 (50.0)	0.385
	Positive		23 (69.7)	6 (50.0)	
Liver mets (%)	Negative		23 (69.7)	12 (100.0)	**0.079**
	Positive		10 (30.3)	0 (0.0)	
Peritoneal deposits (%)	Negative		17 (51.5)	6 (50.0)	1
	Positive		16 (48.5)	6 (50.0)	
Distant mets (%)	Negative		23 (69.7)	12 (100.0)	**0.079**
	Positive		10 (30.3)	0 (0.0)	
Pathology (%)	Well-differentiated		9 (27.3)	0 (0.0)	**0.001**
	Moderately-differentiated		12 (36.4)	0 (0.0)	
	Poorly differentiated		12 (36.4)	12 (100.0)	
BV (median [IQR])			5.74 [2.60, 11.07]	6.75 [6.20, 8.00]	0.758
PS (median [IQR])			33.90 [22.60, 41.20]	71.80 [35.55, 105.18]	**0.037**
MTT (median [IQR])			8.70 [8.00, 10.80]	7.40 [6.25, 7.95]	**0.004**

Bold value indicates $P < 0.05$

between aggressive and indolent tumors [1, 10, 14], and it provides complementary functional data to upgrade risk evaluation and prognosis in gastric cancer. Specifically, reducing the sampling uncertainty of preoperative biopsy grading could have a profound impact, as 24% or more of surgical resections expose higher grade disease than predicted [8, 15].

Our study provides strong evidence that P-CT imaging can differentiate gastric cancer grades beyond standard anatomical imaging; we observed a stepwise association and correlation between vital perfusion parameters (BF, PS, and MTT) and histologic grade.

When considering quantitative data taken together, higher BF and PS parameters correlated with poorer differentiation grade, and were robust indicators of the degree of differentiation, with significant differences between tumor grades. These results aligned with previous studies that were done by Sun et al. [12] and Zhang et al. [14], as their studies underscored the prognostic values of BF and PS as indicative of high blood perfusion as well as the presence of rich and newly formed vessels which are characteristic of a high malignancy degree in poorly differentiated gastric tumors. These results can be explained as the divergence in perfusion profiles is biologically based on angiogenesis and microvascular alterations that facilitate greater BF and PS in more aggressive malignancies [16].

Interestingly, our study presented a novel finding regarding the relationship between MTT and tumor differentiation. We observed that MTT was faster or shorter in poorly differentiated tumors, slower or longer MTT in well differentiated tumors, contrasting with the results reported by Dong Ho Lee and colleagues [6], who reported that longer MTT associated with poorly differentiated gastric cancer. The discrepancy in MTT values could potentially be attributed to the small size of our study population which included a high proportion of patients with poorly differentiated carcinoma, which possibly introducing a statistical bias. However Zhang et al. [14] and Sun et al. [12] demonstrated no significant relationship between MTT and histological grades in their studies. This could be attributed to variations in study design, patient demographics, or tumor biology.

Table 6 A dichotomized analysis of patients into MTT < 8.4 s and ≥ 8.4 s groups based on an optimal cutoff from ROC analysis

		< 8.4 s	**> 8.4 s**	**p-value**
N		18	27	
Age (years) [median [IQR]]		45.00 [40.00, 62.00]	46.00 [45.50, 66.00]	**0.035**
Location (%)	Lower	9 (50.0)	10 (37.0)	0.335
	Middle	3 (16.7)	10 (37.0)	
	Upper	6 (33.3)	7 (25.9)	
Size (post-operative) [%]	less than 5 cm	0 (0.0)	4 (14.8)	0.075
	5 cm to below 10 cm	6 (33.3)	13 (48.1)	
	more than 10 cm	12 (66.7)	10 (37.0)	
Tumor depth (%)	T_2	0 (0.0)	11 (40.7)	**0.006**
	$T_{3/4}$	18 (100.0)	16 (59.3)	
LNs (%)	Negative	6 (33.3)	10 (37.0)	1
	Positive	12 (66.7)	17 (63.0)	
Liver mets (%)	Negative	15 (83.3)	20 (74.1)	0.714
	Positive	3 (16.7)	7 (25.9)	
Peritoneal deposits (%)	Negative	6 (33.3)	17 (63.0)	0.1
	Positive	12 (66.7)	10 (37.0)	
Distant mets (%)	Negative	18 (100.0)	17 (63.0)	**0.01**
	Positive	0 (0.0)	10 (37.0)	
Pathology (%)	Well-differentiated	3 (16.7)	6 (22.2)	**0.001**
	Moderately-differentiated	0 (0.0)	12 (44.4)	
	Poorly differentiated	15 (83.3)	9 (33.3)	
BV (median [IQR])		5.90 [3.50, 9.00]	7.00 [4.17, 11.32]	0.143
BF (median [IQR])		81.35 [50.07, 95.00]	56.90 [42.74, 80.70]	**0.01**
PS (median [IQR])		44.05 [23.60, 90.00]	33.90 [13.55, 39.00]	0.186

Bold value indicates $P < 0.05$

Table 7 Utility of qualitative versus quantitative CT perfusion parameters for differentiating gastric grade

		Well-differentiated	**Moderately-differentiated**	**Poorly differentiated**	***P* value**
N		9	12	24	
PS Qualitative (%)	Low	9 (100.0)	4 (33.3)	0 (0.0)	**< 0.001**
	Intermediate	0 (0.0)	8 (66.7)	0 (0.0)	
	High	0 (0.0)	0 (0.0)	24 (100.0)	
PS Quantitative (median [IQR])		22.60 [3.70, 23.60]	33.90 [4.50, 36.50]	49.97 [40.65, 91.67]	**< 0.001**
BF Qualitative (%)	Low	9 (100.0)	4 (33.3)	0 (0.0)	**< 0.001**
	Intermediate	0 (0.0)	4 (33.3)	0 (0.0)	
	High	0 (0.0)	4 (33.3)	24 (100.0)	
BF Quantitative (median [IQR])		50.07 [38.48, 51.04]	56.90 [18.00, 80.70]	81.95 [71.85, 85.78]	**0.001**
MTT Qualitative (%)	Low	0 (0.0)	0 (0.0)	15 (62.5)	**< 0.001**
	Intermediate	0 (0.0)	8 (66.7)	6 (25.0)	
	High	9 (100.0)	4 (33.3)	3 (12.5)	
MTT Quantitative (median [IQR])		10.80 [6.10, 18.90]	8.70 [8.40, 10.60]	7.80 [6.48, 9.20]	**0.047**
BV Qualitative (%)	Low	6 (66.7)	5 (41.7)	3 (12.5)	**0.017**
	Intermediate	0 (0.0)	3 (25.0)	12 (50.0)	
	High	3 (33.3)	4 (33.3)	9 (37.5)	
BV Quantitative (median [IQR])		3.50 [2.60, 11.90]	5.74 [1.30, 11.58]	8.00 [6.20, 10.62]	0.619

Bold value indicates $P < 0.05$

Furthermore, from univariate model, we identified that higher PS and BF values were associated with slightly higher odds of poor differentiation, while longer MTT values correlated with lower odds of having poorly differentiated pathology. Moreover, from multivariate logistic regression model, we observed that PS might be the most potent individual P-CT predictor of differentiation grade after adjusting other parameters. Also, optimal cut-offs points obtained from ROC analysis indicated that PS ≥ 39 mL/100 g/min, BF ≥ 82.2 mL/100 g/min, and MTT < 8.4 s were strongly correlated with more aggressive disease characteristics such as deeper invasion, increased metastases, poorer differentiation, and higher perfusion. These perfusion thresholds have the potential to non-invasively differentiate tumor grades with remarkable accuracy.

Moreover, we introduced a simplified qualitative scoring system in our study for P-CT to assess gastric tumor grades based on visual features, and it was the first study to use this scoring system in gastric cancer. This system categorized tumor perfusion as low, moderate, or high and demonstrated a strong correlation with histopathologic grades offering a rapid and non-invasive method for tumor grading. Notably, poorly differentiated tumors generally received higher scores for PS (P value < 0.001), BF (P value < 0.001), and BV (P value = 0.017), than well and moderately differentiated tumors. MTT qualitative scores showed that poorly differentiated tumors more frequently scored as low compared to well and moderately differentiated tumors (P < 0.001), that highlighting the system's effectiveness in distinguishing tumor aggressiveness. This innovative approach simplifies P-CT data interpretation potentially making it more accessible for clinical use. It aligns with techniques used in other imaging modalities such as diffusion-weighted MRI, suggesting that our qualitative scoring system could help establish P-CT unique role in the clinical setting. Overall, this system presents a promising tool for the noninvasive evaluation of gastric cancer potentially enhancing patient management and treatment strategies [17, 18].

In diagnosing gastric cancers, our study identifies several limitations with P-CT, notably patient movement during scans affecting accuracy challenges in detecting small or early-stage tumors smaller than 2 cm. The small sample size in our study expanding sample size could enhance the detection of perfusion differences across tumor grades. In addition to the several challenges that face the P-CT in general such as high radiation dose than that conventional CT and allergic reactions or nephrotoxicity from administration of iodinated contrast media in some patients.

Conclusions

The study underscores P-CT as an innovative, non-invasive functional biomarker for predicting gastric cancer grade. PS stood out as the most definitive parameter, significantly distinguishing between tumor grades in both qualitative and quantitative assessments, followed by BF, and MTT that could serve as indicators of the degree of malignancy and aid in prognostic assessment of gastric cancer. Perfusion metrics, serving as physiological imaging biomarkers, provide valuable functional insights that enhance risk assessment, prognostication, and aid in selecting appropriate adjuvant therapies. The potential of P-CT to benefit patients with gastric cancer is substantial, pending further validation through larger, prospective studies.

Abbreviations

P-CT	Perfusion Computed Tomography
PS	Permeability surface
BF	Blood flow
MTT	Mean transit time
BV	Blood volume
CT	Computed Tomography
TNM	Tumor node metastasis System
UICC	The Union for International Cancer Control
AWW	Advantage Windows Workstation
ROC	Receiver operating characteristic curve
AUC	Area under curve
CI	Confidence interval

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Author contributions

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This prosepective study was approved by the Research Ethics Committee of the south Egypt cancer institute at Assiut University in Egypt. Written informed consent was obtained from each patient after receiving information about the details of the study.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors whose names are listed on the title page and shared in the Manuscript entitled: " Computed tomography perfusion as a predictor of gastric cancer grades", certified that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers, membership, employment,

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