Computed Tomography Perfusion Analysis of Pancreatic Adenocarcinoma using Deconvolution, Maximum Slope, and Patlak Methods – Evaluation of Diagnostic Accuracy and Interchangeability of Cut-Off Values

Computertomografische Perfusionsanalyse des Pankreaskarzinoms mit der Deconvolution-, Maximum-Slope- und Patlak-Methode – Evaluation der diagnostischen Güte und Austauschbarkeit von Cut-off-Werten

Authors

Marco Koell[1], Miriam Klauss[1], Stephan Skornitzke[1], Philipp Mayer[1], Franziska Fritz[2], Wolfram Stiller[1], Lars Grenacher[3]

Affiliations

1 Clinic of Diagnostic and Interventional Radiology, University of Heidelberg, Germany
2 Diagnostic Imaging Center, Radiologie Darmstadt, Germany
3 Imaging and Prevention Center, Conradia Radiology Munich, Germany

Correspondence

Prof. Lars Grenacher
Imaging and Prevention Center, Conradia Radiology Munich,
Augustenstr. 115, 80798 Munich, Germany
Tel.: +49/89/52 05 50
l.grenacher@conradia.de

ZUSAMMENFASSUNG

Ziel Ziel dieser Studie war es, die diagnostische Güte von Perfusions-Computertomografie (CT) -Parametern zu evaluieren, die mit verschiedenen mathematisch-kinetischen Methoden gemessen wurden, für die Differenzierung zwischen Pankreaskarzinom und Normalgewebe. Es sollten zudem Cut-off-Werte bestimmt und die Austauschbarkeit von Cut-off-Werten, die mit verschiedenen Methoden ermittelt wurden, evaluiert werden.

Material und Methoden Bei 23 Patienten wurde prospektiv eine Perfusions-CT-Bildgebung des Pankreas durchgeführt. 19 Patienten mit histopathologisch bestätigtem Pankreaskarzinom wurden in die Studie eingeschlossen. Der Blutfluss (BF), das Blutvolumen (BV) und das Permeabilitätsoberflächenprodukt (PS) wurden im Pankreaskarzinom und Normalgewebe mit der Deconvolution- (BF, BV, PS), Maximum-Slope- (BF) und Patlak-Methode (BV, PS) gemessen. Die Austauschbarkeit der Cut-off-Werte wurde evaluiert, indem die Übereinstimmung zwischen BF, BV und PS untersucht wurde, die mit verschiedenen mathematisch-kinetischen Methoden gemessen wurden.

Ergebnisse Die Bland-Altman-Analyse zeigte eine schlechte Übereinstimmung zwischen den Perfusionsparametern, die mit verschiedenen mathematisch-kinetischen Methoden gemessen wurden. Gemäß ROC-Analyse (Receiver Operating Characteristic) hatte das mit der Patlak-Methode gemessene PS die signifikant niedrigste diagnostische Güte (Fläche unter der ROC-Kurve = 0,748). Alle anderen Parameter hatten eine hohe diagnostische Güte (Fläche unter der ROC-Kurve = 0,940–0,997); deren diagnostische Güte unterschied sich jedoch nicht statistisch signifikant. Cut-off-Werte für BF von ≤ 91,83 ml/100 ml/min und für BV von ≤ 5,36 ml/100 ml, beide mit der Deconvolution-Methode gemessen, scheinen die geeignetsten Cut-off-Werte zu sein, mit denen das Pankreaskarzinom von Normalgewebe abgegrenzt werden kann.

Schlussfolgerung Perfusionsparameter, die mit verschiedenen Methoden gemessen wurden, sind nicht austauschbar. Daraus folgt, dass Cut-off-Werte, die mit unterschiedlichen Methoden ermittelt wurden, ebenfalls nicht austauschbar sind. Perfusionsparameter können dazu beitragen, das Pankreaskarzinom mit hoher diagnostischer Güte vom Normalgewebe abzugrenzen, mit Ausnahme von PS, das mit der Patlak-Methode gemessen wurde.

Kernaussagen:

- Perfusions-CT-Parameter zeigten eine hohe diagnostische Güte bei der Differenzierung zwischen Pankreaskarzinom und Normalgewebe.
- Nur PS, gemessen mit der Patlak-Methode, zeigte eine signifikant niedrigere diagnostische Güte.
- Perfusionsparameter, die mit unterschiedlichen mathematisch-kinetischen Methoden gemessen wurden, sind nicht austauschbar.
- Für jede Methode und jeden Perfusionsparameter muss ein spezifischer Cut-off-Wert bestimmt werden.

ABSTRACT

Purpose The goal of this study was to evaluate the diagnostic accuracy of perfusion computed tomography (CT) parameters obtained by different mathematical-kinetic methods for distinguishing pancreatic adenocarcinoma from normal tissue. To determine cut-off values and to assess the interchangeability of cut-off values, which were determined by different methods.

Materials and Methods Perfusion CT imaging of the pancreas was prospectively performed in 23 patients. 19 patients with histopathologically confirmed pancreatic adenocarcinoma were included in the study. Blood flow (BF), blood volume (BV) and permeability-surface area product (PS) were measured in pancreatic adenocarcinoma and normal tissue with the deconvolution (BF, BV, PS), maximum slope (BF), and Patlak methods (BV, PS). The interchangeability of cut-off values was examined by assessing agreement between BF, BV, and PS measured with different mathematical-kinetic methods.

Results Bland-Altman analysis demonstrated poor agreement between perfusion parameters, measured with different mathematical-kinetic methods. According to receiver operating characteristic (ROC) analysis, PS measured with

the Patlak method had the significantly lowest diagnostic accuracy (area under ROC curve = 0.748). All other parameters were of high diagnostic accuracy (area under ROC curve = 0.940–0.997), although differences in diagnostic accuracy were not statistically different. Cut-off values for BF of ≤ 91.83 ml/100 ml/min and for BV of ≤ 5.36 ml/100 ml, both measured with the deconvolution method, appear to be the most appropriate cut-off values to distinguish pancreatic adenocarcinoma from normal tissue.

Conclusion Perfusion parameters obtained by different methods are not interchangeable. Therefore, cut-off values, which were determined using different methods, are not interchangeable either. Perfusion parameters can help to distinguish pancreatic adenocarcinoma from normal tissue with high diagnostic accuracy, except for PS measured with the Patlak method.

Key Points:

- Perfusion CT parameters showed high diagnostic accuracy in differentiating between pancreatic adenocarcinoma and normal tissue.
- Only PS measured with the Patlak method showed a significantly lower diagnostic accuracy.
- Perfusion parameters measured with different mathematical-kinetic methods are not interchangeable.
- A specific cut-off value must be determined for each method and each perfusion parameter.

Citation Format

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Introduction

Pancreatic adenocarcinoma is one of the tumors with the highest mortality rate [1]. The reason is that pancreatic adenocarcinoma is discovered at an advanced, irresectable stage in more than 80 % of patients. The only chance for patients to increase the overall low five-year survival rate from about 4 % to 24 % is an R0 resection [2]. Therefore, early and accurate diagnosis is a key factor in reducing mortality. According to the current German evidence- and consensus-based (S3) guidelines, conventional contrast-enhanced computed tomography (CT) is used as the diagnostic standard for the detection of pancreatic adenocarcinoma. On contrast-enhanced CT, pancreatic adenocarcinoma mostly appears as hypodense lesion compared to the surrounding normal pancreatic tissue. However, in up to 11–20 % of cases, pancreatic adenocarcinoma appears isodense and is therefore difficult to differentiate [3–6]. Diagnosis of pancreatic adenocarcinoma is then only possible based on indirect tumor signs.

Perfusion CT appears to be a promising additional diagnostic tool for improving the diagnosis of pancreatic adenocarcinoma. Perfusion CT can be used to examine the perfusion and vascularity of pancreatic tissue. Previous studies demonstrated that differentiation between pancreatic adenocarcinoma and normal tissue based on CT perfusion parameters is feasible, since tissue blood flow (BF), tissue blood volume (BV) and permeability-surface area product (PS) are significantly lower in pancreatic adenocarcinoma than in normal tissue [5–8].

BF, BV, and PS can be calculated with different mathematical-kinetic methods. The underlying models of calculation can be found at *Miles and Griffiths* [9]. Commonly used mathematical-kinetic methods are the deconvolution method, which can be used for calculating BF, BV, and PS, the Patlak method for calculating BV and PS, and the maximum slope method for calculating BF. Studies have demonstrated that the calculation of perfusion parameters with different methods does not provide consistent results [10–16]. Mathematical-kinetic methods significantly affect the measurement results of perfusion values. This raises

▶ **Table 1** CT acquisition protocol.

▶ **Tab. 1** CT-Akquisitionsprotokoll.

phase	tube voltage [kV]	tube current [mAs]	delay [s]	rotation time [s]	acquisitions	collimation [mm]	slice thickness [mm]	reconstruction kernel
1. native[a]	120	200	–	0.5	helical	24 × 1.2	3	I30f
contrast agent: 80 ml (flow rate: 5 ml/s); bolus tracking in suprarenal aorta (threshold: 100 HU)								
2. arterial[a]	120	200	10	0.5	helical	64 × 0.6	3	I30f
3. venous[a]	120	200	50	0.5	helical	64 × 0.6	3	I30f
15-minute break for contrast agent clearance. Patient remains on CT table.								
4. native[b]	120	200	–	0.5	helical	64 × 0.6	3	I30f
contrast agent: 80 ml with a 40 ml saline solution chaser bolus (flow rate: 5 ml/s)								
5. perfusion CT imaging	80	270	5	0.5 (full rotation); 1.5 (cycle time)	34	14 × 1.2	3 × 5.0	B30f

[a] Standard 3-phase CT scan.
[b] Native scan to verify the correct position of the examination volume for perfusion CT imaging.

the question of which method is the most appropriate in terms of diagnostic accuracy and which one should be selected for clinical use.

Therefore, this study aimed to evaluate the diagnostic accuracy of three commonly used mathematical-kinetic methods, the deconvolution, maximum slope, and Patlak methods, which are implemented in dynamic CT perfusion software. Cut-off values to distinguish pancreatic adenocarcinoma from normal tissue should be determined for BF, BV, as well as PS for every mathematical-kinetic method.

This study should also answer the question of whether cut-off values, which were determined by different mathematical-kinetic methods, are interchangeable by assessing the agreement between these methods.

Materials and Methods

Study Design and Study Population

This study is a retrospective evaluation of data that were acquired in the course of a prospective study performed between August 2014 and July 2015 and was approved by the local ethics committee [17]. 23 patients underwent perfusion CT imaging. The diagnosis of pancreatic adenocarcinoma was confirmed by histopathological examination.

The inclusion criteria were clinical suspicion of pancreatic adenocarcinoma and informed consent to participate in the study. The exclusion criteria were previous treatment for pancreatic adenocarcinoma, general contraindications for the application of iodinated contrast agent, failure to follow the breathing instructions, and pancreatic adenocarcinoma not confirmed in the histological examination.

3 patients had to be excluded because pancreatic adenocarcinoma was not confirmed in the histological examination. Another patient had to be excluded because the tumor could not be seen in the perfusion CT sequence.

Finally, 19 patients were able to be included in the analysis (9 male, 10 female; mean age: 63 ± 8 years; range: 50–79 years).

CT Imaging and Data Analysis

CT examinations were performed on a 2 × 64-slice CT scanner (Somatom© Definition Flash, Siemens Medical Solutions, Forchheim, Germany) in hydro-CT technique. The acquisition protocol is summarized in ▶ **Table 1**. A non-ionic iodinated contrast agent (Ultravist 370; Schering, Berlin, Germany) was used for the standard 3-phasic CT acquisition and the perfusion CT imaging.

Perfusion CT data were analyzed by a radiologist with five years of experience, without knowing the results of the histopathological examination. Perfusion data were sent to a multimodality workplace (MMWP, Siemens Medical Solutions) and were processed with a body perfusion CT tool (Body-PCT, Siemens Medical Solutions, Erlangen, Germany) with the syngo.via imaging software version VB 30.

After motion correction, a circular region of interest (ROI) was placed in the aorta to measure the arterial input function. Then, the arterial time-attenuation curve and the mean time-attenuation curve of the tissue were calculated automatically. This data was visualized by color-coded perfusion maps. ROIs were placed in these color maps, in pancreatic adenocarcinoma, as well as in normal pancreatic tissue. Necrosis, calcifications, and large vessels were not included in the ROIs. For each ROI, the perfusion parameters BF, BV, and PS were measured, using the deconvolution, maximum slope, and Patlak methods (▶ **Table 2**).

▶ **Table 2** Overview of measured perfusion CT parameters.

▶ **Tab. 2** Übersicht der gemessenen Perfusions-CT-Parameter.

| perfusion parameter | deconvolution | compartment analysis | |
		maximum slope	patlak
BF (in ml/100 ml/min)	x	x	
BV (in ml/100 ml)	x		x
PS (in ml/100 ml/min)	x		x

Blood flow (BF), blood volume (BV) and permeability-surface area product (PS) were measured in n = 19 pancreatic adenocarcinomas and n = 19 normal tissues.

Statistical Analysis

Statistical analyses were carried out with MedCalc Statistical Software version 19.1.3 (MedCalc Software Ltd, Ostend, Belgium). Descriptive data were presented with mean ± standard deviation and box plots. For all hypothesis tests, the significance level was set at 0.05 (5 %).

Agreement Analyses

Agreement between the mathematical-kinetic methods was assessed with Bland-Altman analysis [18]. If Bland-Altman plots showed a proportional difference, a regression line of differences was drawn.

It was hypothesized that the methods yield significantly different results when calculating BF, BV, and PS. For statistical verification, the non-parametric Wilcoxon sign-rank test (Wilcoxon test) was used.

In addition, it was hypothesized that the methods yield correlating results, when calculating BF, BV, and PS. For statistical verification, the non-parametric Spearman rank correlation analysis (Spearman) was used.

According to the Shapiro-Wilk test, the test size was not normally distributed in all cases, so only non-parametric test equivalents were used for better comparability.

Determining Appropriate Cut-Off Values and Analyzing Diagnostic Accuracy

With receiver operating characteristic (ROC) analysis, diagnostic accuracy was evaluated and compared, and cut-off values with a corresponding sensitivity and specificity were determined.

Whether the areas under the receiver operating characteristic curves (AUC) and consequently the diagnostic accuracy differ significantly was assessed with the method described by DeLong et al. (null hypothesis = the compared AUCs are equal) [19]. An AUC close to 1.0 corresponds to a high diagnostic accuracy [20].

Appropriate cut-off values were determined using the Youden index (J = sensitivity + specificity − 1) [21]. In the case of identical Youden indices, the cut-off value with the higher sensitivity was

selected considering the low survival rate and poor prognosis of pancreatic adenocarcinoma.

Results

Patient Characteristics

Pancreatic adenocarcinoma was located in the head of the pancreas in 16 patients, in the pancreatic body in 1 patient and in the pancreatic body and tail in 2 patients. In the arterial and venous phases of the conventional contrast-enhanced CT examination, the tumor was hypodense in 15 patients (79 %) compared to the surrounding tissue and isodense in 4 patients (21 %).

Method Comparison for BF Values (Deconvolution Method versus Maximum Slope Method)

BF values for pancreatic adenocarcinoma and normal tissue were measured with the deconvolution and maximum slope methods. Mean values are given in ▶ **Table 3, 4**, graphical depiction in ▶ **Fig. 1**.

BF values obtained by the deconvolution method were significantly higher than those obtained by the maximum slope method for pancreatic adenocarcinoma and normal tissue, respectively (Wilcoxon test: each p < 0.001). Method comparison of BF values showed a significant correlation, both for pancreatic adenocarcinoma (Spearman: r = 0.679, p = 0.001) and normal tissue (Spearman: r = 0.526, p = 0.021).

Bland-Altman plots show poor agreement between the methods (▶ **Fig. 2a**). Mean differences indicate that the methods produce systematically different results (▶ **Table 3,4**). The bias is inconsistent but proportional, with larger differences between the methods as the average of the two methods increases (▶ **Fig. 2a**). The regression line of differences has a slope of 0.77 for pancreatic adenocarcinoma and 0.81 for normal tissue (▶ **Fig. 2a**). Furthermore, the limits of agreement are large (▶ **Table 3,4**), which indicates that the two methods provide ambiguous results.

Method Comparison for BV Values (Deconvolution Method versus Patlak Method)

BV values for pancreatic adenocarcinoma and normal tissue were measured with the deconvolution and Patlak methods. Mean values are shown in ▶ **Table 3, 4**, graphical depiction in ▶ **Fig. 1**.

BV values for pancreatic adenocarcinoma obtained by the deconvolution method were significantly higher than those obtained by the Patlak method (Wilcoxon test: p < 0.001). However, in normal tissue they did not differ significantly (Wilcoxon test: p = 0.778). Method comparison of BV values showed a significant correlation, both for pancreatic adenocarcinoma (Spearman: r = 0.684, p = 0.001) and normal tissue (Spearman: r = 0.867, p < 0.001).

Bland-Altman plots show poor agreement between the methods (▶ **Fig. 2b**). In pancreatic adenocarcinoma there is a systematic bias (▶ **Fig. 2b**, ▶ **Table 3**), whereas in normal tissue there is no significant bias (▶ **Fig. 2b**, ▶ **Table 4**). However, in pancreatic adenocarcinoma and normal tissue the differences between both

▶ **Table 3** Perfusion CT measurements in pancreatic adenocarcinoma and results of Bland-Altman analysis.

▶ **Tab. 3** Perfusions-CT-Messungen im Pankreaskarzinom und Ergebnisse der Bland-Altman-Analyse.

parameter	deconvolution	MS	patlak	mean difference	limits of agreement
BF	42.51 ± 20.33	21.02 ± 10.20		21.5 (14.1, 28.9)	−8.5; 51.5 (−21.3, 4.3); (38.6, 64.3)
BV	3.07 ± 1.58		2.48 ± 1.70	0.6 (0.2, 1.0)	−1.1; 2.3 (−1.9, −0.4); (1.6, 3.1)
PS	15.32 ± 8.14		12.33 ± 6.58	3.0 (1.6, 4.4)	−2.8; 8.8 (−5.3, −0.3); (6.3, 11.3)

Means ± standard deviation for measurements of blood flow (BF), blood volume (BV), and permeability-surface area product (PS) using the deconvolution, maximum slope (MS), and Patlak methods for n = 19 pancreatic adenocarcinomas. Bland-Altman analysis: mean differences between the methods and upper and lower limits of agreement are given with their 95 % CI in parentheses. BF in ml/100 ml/min; BV in ml/100 ml; PS in ml/100 ml/min.

▶ **Table 4** Perfusion CT measurements in normal tissue and results of Bland-Altman analysis.

▶ **Tab. 4** Perfusions-CT-Messungen im Normalgewebe und Ergebnisse der Bland-Altman-Analyse.

parameter	deconvolution	MS	patlak	mean difference	limits of agreement
BF	150.49 ± 46.55	70.06 ± 22.82		80.4 (62.9, 97.9)	9.3; 151.6 (−21.2, 39.7); (121.1, 182.0)
BV	12.04 ± 4.54		11.93 ± 5.12	0.1 (−1.4, 1.6)	−6.1; 6.3 (−8.7, −3.4); (3.7, 9.0)
PS	44.71 ± 19.58		20.23 ± 9.12	24.5 (15.1, 33.9)	−13.8; 62.8 (−30.2, 2.6); (46.4, 79.2)

Means ± standard deviation for measurements of blood flow (BF), blood volume (BV), and permeability-surface area product (PS) using the deconvolution, maximum slope (MS), and Patlak methods for n = 19 normal tissues. Bland-Altman analysis: mean differences between the methods and upper and lower limits of agreement are given with their 95 % CI in parentheses. BF in ml/100 ml/min; BV in ml/100 ml; PS in ml/100 ml/min.

methods scatter over a large agreement range, which could be even larger considering the 95 % CI of the limits of agreement (▶ Fig. 2b, ▶ Table 3, 4). This indicates that the two methods provide ambiguous results.

Method Comparison for PS Values (Deconvolution Method versus Patlak Method)

PS values for pancreatic adenocarcinoma and normal tissue were measured with the deconvolution and Patlak methods. Mean values are given in ▶ Table 3, 4, graphical depiction in ▶ Fig. 1.

PS values obtained by the deconvolution method were significantly higher than those obtained by the Patlak method for pancreatic adenocarcinoma and normal tissue, respectively (Wilcoxon test: each p < 0.001). Method comparison of PS values showed a significant correlation for pancreatic adenocarcinoma (Spearman: r = 0.938, p < 0.001). However, in normal tissue the methods did not correlate significantly (Spearman: r = 0.226, p = 0.351).

Bland-Altman plots show poor agreement between the methods (▶ Fig. 2c). There is a systematic but inconsistent bias (▶ Fig. 2c, ▶ Table 3, 4). The differences between the two methods tend to

get larger as the average of the two methods increases (▶ Fig. 2c). The regression line of differences has a slope of 0.22 for pancreatic adenocarcinoma and 1.09 for normal tissue (▶ Fig. 2c). Furthermore, the differences scatter within large limits of agreement (▶ Fig. 2c, ▶ Table 3, 4).

Comparison of Diagnostic Accuracy

The results of ROC analysis are shown in ▶ Fig. 3 and ▶ Table 5. Perfusion parameters BF, BV, and PS could distinguish pancreatic adenocarcinoma from normal tissue with moderate to high diagnostic accuracy (▶ Table 5). PS measured with the Patlak method had the significantly lowest diagnostic accuracy compared to all other perfusion parameters, as shown in ▶ Table 6. Between the other parameters, there were no significant differences in terms of diagnostic accuracy (▶ Table 6).

Determination of Appropriate Cut-Off Values

Based on ROC analysis, appropriate cut-off values were determined for BF, BV, and PS obtained by the deconvolution, maxi-
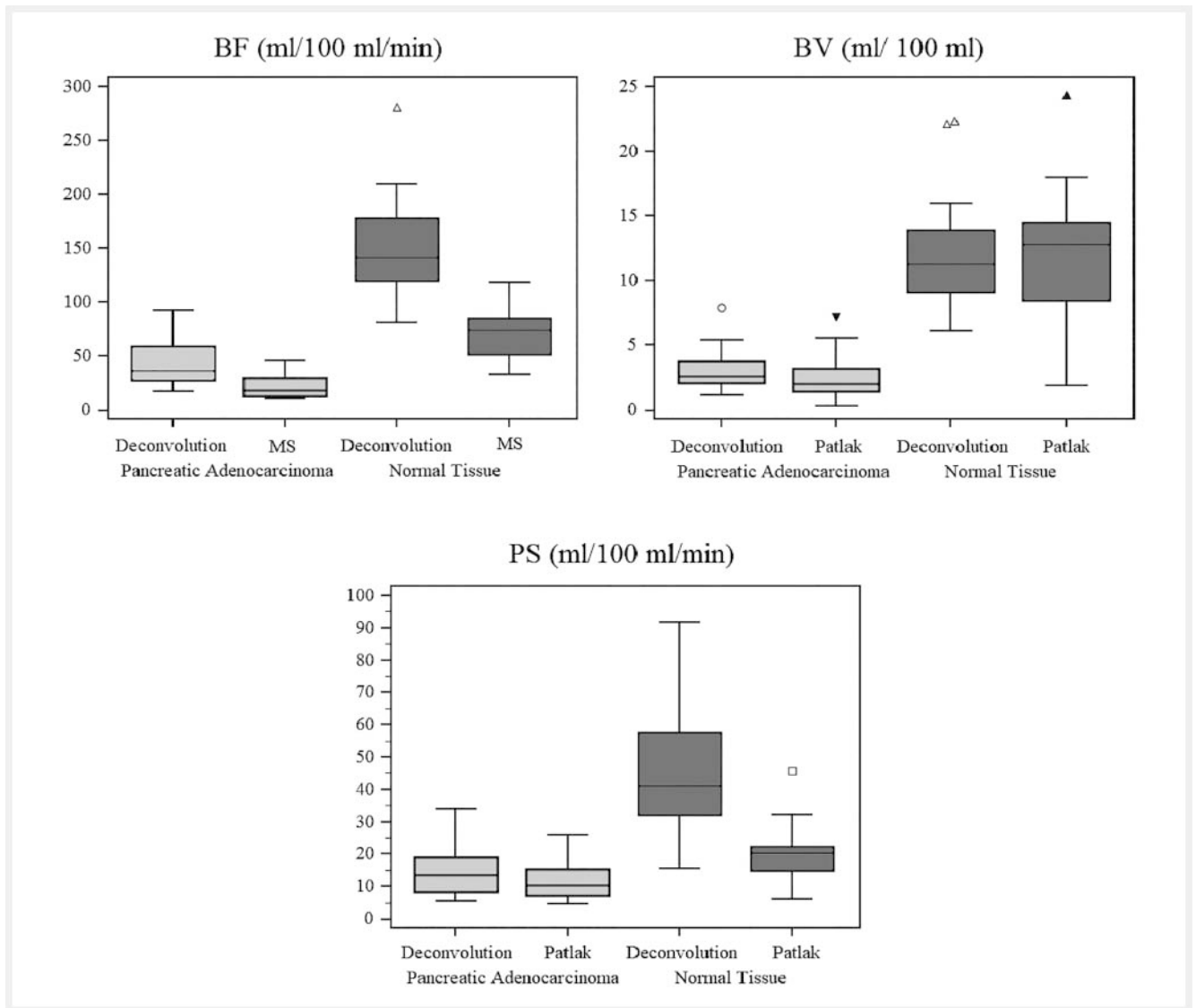
▶ **Fig. 1** Box plots show measurements of blood flow (BF), blood volume (BV), and permeability-surface area product (PS) obtained by the deconvolution, maximum slope (MS), and Patlak methods, respectively, both for n = 19 pancreatic adenocarcinomas (light grey) and n = 19 normal tissues (dark grey). Outliers are marked.
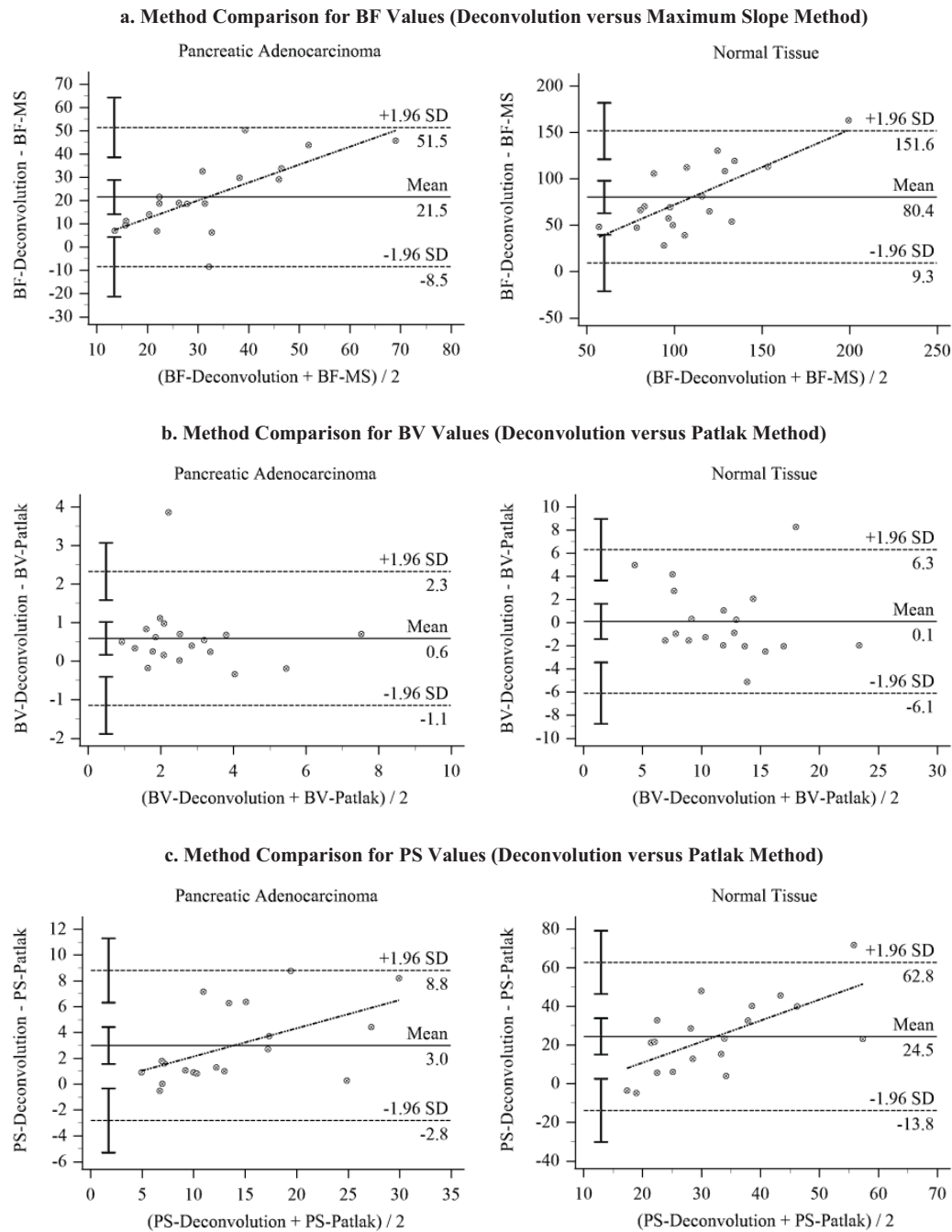
▶ **Abb. 1** Die Box-Plots zeigen die Messungen des Blutflusses (BF), des Blutvolumens (BV) und des Permeabilitätsoberflächenprodukts (PS) mit der Deconvolution-, Maximum-Slope- (MS) und Patlak-Methode, jeweils in n = 19 Pankreaskarzinomen (hellgrau) und n = 19 Normalgeweben (dunkelgrau). Ausreißer sind markiert.

mum slope, and Patlak methods for differentiating pancreatic adenocarcinoma from normal tissue. They are shown in ▶ **Table 5** with the corresponding sensitivity and specificity. Considering Youden index J, cut-off values for BF of ≤ 91.83 ml/100 ml/min (J = 0.9474) and for BV of ≤ 5.36 ml/100 ml (J = 0.9474), both measured with the deconvolution method, yielded optimal accuracy for differentiating pancreatic adenocarcinoma from normal tissue.

Discussion

This study indicates that perfusion CT has promising clinical potential in the detection of pancreatic adenocarcinoma. Perfusion parameters BF, BV and PS measured with the deconvolution, maximum slope, and Patlak methods could distinguish pancreatic adenocarcinoma from normal tissue with high diagnostic accuracy. The only exception was PS measured with the Patlak method, which showed only moderate diagnostic accuracy.

BF, BV, and PS measured with the deconvolution, maximum slope, and Patlak methods showed poor agreement, thus these methods are not interchangeable. This finding is largely consistent with previous studies [10–16]. Deficiencies in agreement

a. Method Comparison for BF Values (Deconvolution versus Maximum Slope Method)

b. Method Comparison for BV Values (Deconvolution versus Patlak Method)

c. Method Comparison for PS Values (Deconvolution versus Patlak Method)

▶ **Fig. 2** Bland-Altman plots to analyze agreement between mathematical-kinetic methods for measurements of blood flow (BF), blood volume (BV) and permeability-surface area product (PS), in n = 19 pancreatic adenocarcinomas and n = 19 normal tissues. The difference between one method and the other method (Method A – Method B) is plotted against the mean of the two measurements ((Method A + Method B)/2). The mean difference and upper and lower limits of agreement (mean difference ± 1.96 standard deviation of the difference) are given with their 95 % CI. If Bland-Altman plots showed a proportional difference, a regression line of differences was drawn. BF in ml/100 ml/min; BV in ml/100 ml; PS in ml/ 100 ml/min. MS = maximum slope method.

▶ **Abb. 2** Bland-Altman-Diagramme zur Analyse der Übereinstimmung zwischen den mathematisch-kinetischen Methoden für die Messung des Blutflusses (BF), des Blutvolumens (BV) und des Permeabilitätsoberflächenprodukts (PS) in n = 19 Pankreaskarzinomen und n = 19 Normalgeweben. Die Differenz zwischen einer Methode und der anderen Methode (Methode A – Methode B) ist gegen den Mittelwert der beiden Messungen ((Methode A + Methode B)/2) aufgetragen. Die mittlere Differenz, die oberen und unteren Übereinstimmungsgrenzen (mittlere Differenz ± 1,96 Standardabweichung der Differenz) sind mit ihrem 95 %-KI angegeben. Wenn Bland-Altman-Diagramme einen proportionalen Unterschied zeigten, wurde eine Regressionsgerade der Differenzen angegeben. BF in ml/100 ml/min; BV in ml/100ml; PS in ml/100 ml/min. MS = Maximum-Slope-Methode.
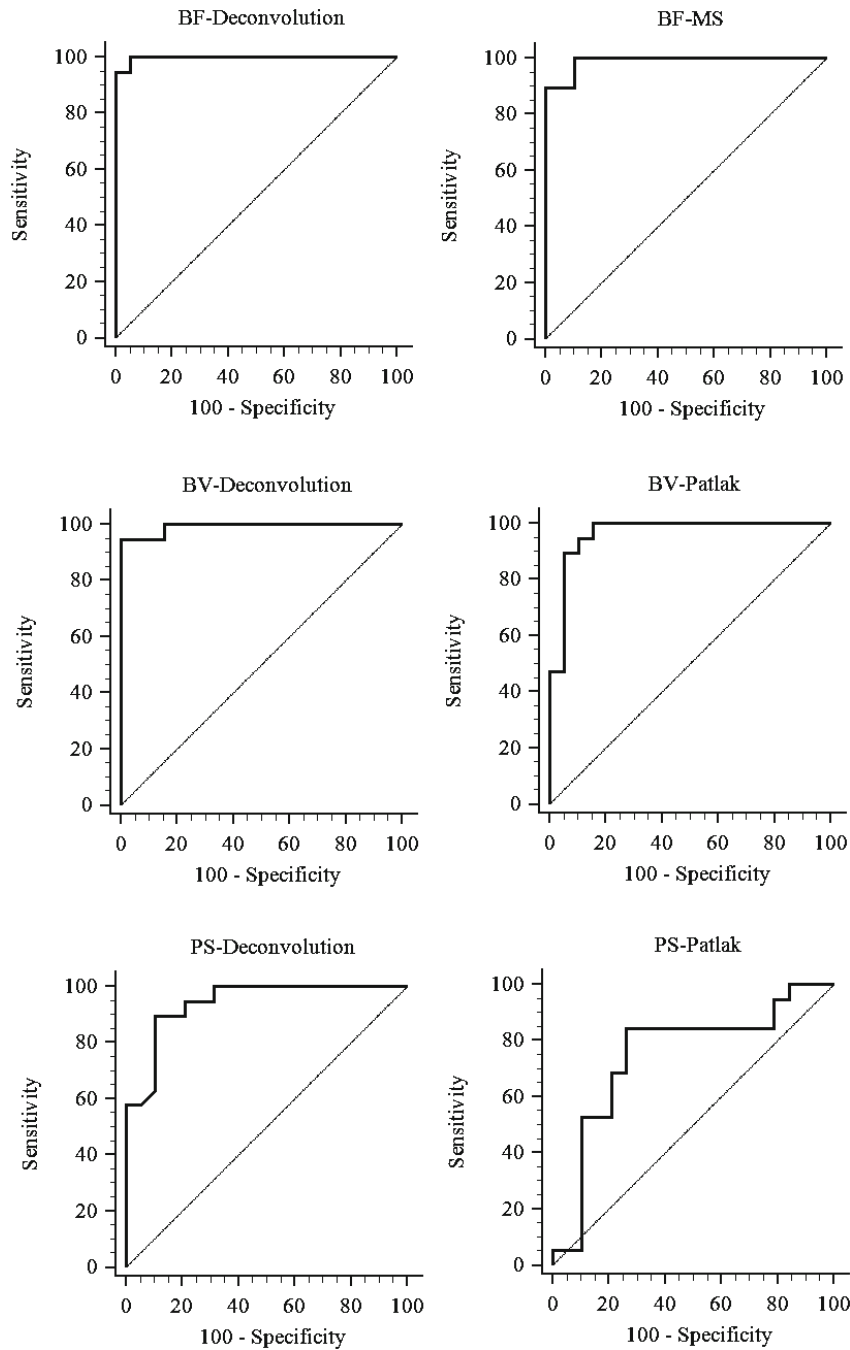
▶ **Fig. 3** ROC curves to analyze diagnostic accuracy for measurements of blood flow (BF) using the deconvolution and maximum slope (MS) methods, blood volume (BV) using the deconvolution and Patlak methods and permeability-surface area product (PS) using the deconvolution and Patlak methods for differentiating n = 19 pancreatic adenocarcinomas from n = 19 normal tissues. The true-positive rate (sensitivity, in %) is plotted against the false-positive rate (100 – specificity, in %).

▶ **Abb. 3** ROC-Kurven zur Analyse der diagnostischen Güte der Messungen des Blutflusses (BF) mit der Deconvolution- und Maximum-Slope-Methode (MS), des Blutvolumens (BV) mit der Deconvolution- und Patlak-Methode und des Permeabilitätsoberflächenprodukts (PS) mit der Deconvolution- und Patlak-Methode zur Abgrenzung von n = 19 Pankreaskarzinomen von n = 19 Normalgeweben. Die Richtig-Positiv-Rate (Sensitivität, in %) ist gegen die Falsch-Positiv-Rate (100 – Spezifität, in %) aufgetragen.

▶ **Table 5** ROC analysis and cut-off values.

▶ **Tab. 5** ROC-Analyse und Cut-off-Werte.

parameter	method	AUC	cut-off value	sensitivity	specificity
BF	deconvolution	0.997 (0.902, 1.0)	≤ 91.83	100 % (82.4, 100)	94.74 % (74.0, 99.9)
BF	maximum slope	0.989 (0.887, 1.0)	≤ 46.10	100 % (82.4, 100)	89.47 % (66.9, 98.7)
BV	deconvolution	0.992 (0.892, 1.0)	≤ 5.36	94.74 % (74.0, 99.9)	100 % (82.4, 100)
BV	patlak	0.964 (0.847, 0.998)	≤ 7.17	100 % (82.4, 100)	84.21 % (60.4, 96.6)
PS	deconvolution	0.940 (0.813, 0.991)	≤ 25	89.47 % (66.9, 98.7)	89.47 % (66.9, 98.7)
PS	patlak	0.748 (0.581, 0.874)	≤ 15.85	84.21 % (60.4, 96.6)	73.68 % (48.8, 90.9)

AUCs and cut-off values with corresponding sensitivity and specificity for n = 19 pancreatic adenocarcinomas and n = 19 normal tissues. AUC, sensitivity, and specificity are given with their 95 % CI in parentheses. Blood flow (BF) in ml/100 ml/min; blood volume (BV) in ml/100 ml; permeability-surface area product (PS) in ml/100 ml/min.

▶ **Table 6** Comparison of areas under the ROC curves.

▶ **Tab. 6** Vergleich der Flächen unter den ROC-Kurven.

	BF-MS	BV-DC	BV-Patlak	PS-DC	PS-Patlak
BF-DC	z = 0.970 p = 0.332	z = 0.824 p = 0.4098	z = 1.130 p = 0.2585	z = 1.576 p = 0.1150	**z = 2.873 p = 0.0041**
BF-MS		z = 0.346 p = 0.7290	z = 0.795 p = 0.4267	z = 1.283 p = 0.1995	**z = 2.814 p = 0.0049**
BV-DC			z = 1.029 p = 0.3035	z = 1.408 p = 0.1590	**z = 2.769 p = 0.0056**
BV-Patlak				z = 0.762 p = 0.4461	**z = 2.296 p = 0.022**
PS-DC					**z = 2.266 p = 0.023**

Comparison of ROC curves to test the statistical significance of the difference between the areas under the ROC curves which are given in ▶ **Fig. 3** and ▶ **Table 5**, for measurements of blood flow (BF) with the deconvolution (BF-DC) and maximum slope (BF-MS) methods, blood volume (BV) with the deconvolution (BV-DC) and Patlak (BV-Patlak) methods, and permeability-surface area product (PS) with the deconvolution (PS-DC) and Patlak (PS-Patlak) methods. AUCs are compared pairwise. Duplicates are not listed to avoid redundancies. Compared AUCs, which are significantly different (p < 0.05), are boldfaced.

could result from differences between the underlying calculation models [9].

Only BV values in normal tissue, which were obtained by the deconvolution method and the Patlak method, did not differ significantly. However, this does not lead to interchangeability, since differences between both methods scatter over a large agreement range that could be even larger considering the 95 % CI of the limits of agreement. In addition, in the context of

diagnosis and determination of cut-off values, the methods must come to consistent measurement results both in pancreatic adenocarcinoma and in normal tissue.

Since perfusion CT parameters obtained by different mathematical-kinetic methods are not interchangeable, cut-off values that were determined using different methods are also not interchangeable. Therefore, a specific cut-off value must be determined for each method and each perfusion parameter.

On the other hand, method comparison showed that the measured perfusion parameters correlate significantly. The only exceptions were PS values in normal tissue measured with the deconvolution method and the Patlak method. These values did not correlate significantly. This could result from the relatively short acquisition time of only 51 seconds, which limits the accuracy of any measurements of permeability [22].

However, correlation does not imply that there is good agreement between the methods, because it can be assumed that measurements using methods developed to measure the same parameter lead to related results [18].

Schneeweiß et al. described the same findings with significant correlation but poor agreement between BF, BV, and PS values obtained by the deconvolution, maximum slope, and Patlak methods in pancreatic adenocarcinoma [16]. In contrast, they reported significantly higher PS values obtained by the Patlak method compared to the deconvolution method. This may be the result of using a shorter acquisition time of only 40 seconds (versus 51 seconds in the present study). *Spira et al.* showed this effect in lung cancer with significantly increasing PS values as the acquisition time decreases when using the Patlak method [23].

Schneeweiß et al. also demonstrated the proportional bias between the deconvolution and maximum slope method for measurements of BF, with larger differences between the methods as the average of the two methods increases [16]. This may result from the proportional underestimation of BF by the maximum slope method, since the one-compartment calculation model does not consider the venous outflow [9].

Non-interchangeability leads to the question of which method and which perfusion CT parameter is the most appropriate in terms of diagnostic accuracy.

BF, BV, and PS obtained by the deconvolution, maximum slope, and Patlak methods can help to distinguish pancreatic adenocarcinoma from normal tissue with moderate to high diagnostic accuracy. Compared to other parameters, only PS measured using the Patlak method had a significantly lower diagnostic accuracy. The poor performance could result from the relatively short acquisition time of only 51 seconds, which limits the accuracy of any measurements of permeability [22].

Between the other parameters, there were no significant differences in terms of diagnostic accuracy. Consequently, the method that has the most advantages in clinical use can be selected from these methods.

The maximum slope method requires only a few image acquisitions, thus a short perfusion CT sequence is sufficient [9]. The deconvolution method is not as susceptible to image noise and motion artifacts compared to compartment methods [9]. Another advantage of the deconvolution method is that it can

measure low values of BF more accurately [22], as they usually exist in pancreatic adenocarcinoma.

Given the advantages of the deconvolution method and considering the 95 % CIs of AUCs, the deconvolution method appears to be the most appropriate mathematical-kinetic method. BF measured using the deconvolution method appears to be the parameter with the best diagnostic accuracy, since the 95 % CI of its corresponding AUC is the only one that is above 0.9, which indicates high accuracy.

It must be considered that there is currently no standardized acquisition protocol for perfusion CT, which leads to limited comparability of perfusion values. Therefore, cut-off values cannot yet be generalized. This becomes obvious when comparing the mean values of BF, BV, and PS in this study with those of previous studies. Mean values differ considerably in some cases, even if they were measured with the same mathematical-kinetic method [5–8, 16, 24, 25]. Several factors can be identified which influence perfusion CT measurements. These are bolus volume [26] and flow rate of contrast agent [9], motion [27], tube current [22], tube voltage [28], duration of perfusion CT data acquisition [23, 27], and even different versions of the same analysis software can lead to different perfusion CT values [29]. To be able to generalize cut-off values and to use perfusion CT clinically, standardized acquisition protocols for perfusion CT must be implemented.

A limitation of this study is the fact that only 19 patients were included, which should have mainly affected the determination of cut-off values. However, the evaluation of the diagnostic accuracy indicated statistical significance of the results.

Another limitation is that the same perfusion acquisition protocol was used for acquisition of input data to all mathematical-kinetic methods, since the acquisition protocol affects the results of measured perfusion parameters [22]. However, method comparison based on the same patient collective would not have been possible otherwise.

Equating healthy pancreatic tissue with tissue surrounding pancreatic adenocarcinoma for ROC analysis should not constitute a limitation since studies indicate that tissue surrounding pancreatic adenocarcinoma does not differ significantly from healthy pancreatic tissue [5, 30]. The advantage was that pancreatic adenocarcinoma and normal tissue could be examined in the same patient. Inter-individual differences were thus excluded, which would otherwise have influenced the results (for example with regard to the cardiovascular system).

Another limitation is the relatively short acquisition time of only 51 seconds, which limits the accuracy of any measurements of permeability and which could explain the poor performance of PS measured with the Patlak method [22].

In conclusion, this study indicates that Perfusion parameters measured using the deconvolution, maximum slope, and Patlak methods can help to distinguish pancreatic adenocarcinoma from normal tissue with high diagnostic accuracy, except for PS measured with the Patlak method.

This study also indicates that cut-off values that were determined using different methods are not interchangeable. Standardized acquisition protocols for perfusion CT should be implemented to be able to generalize cut-off values and to use perfusion CT clinically.

CLINICAL RELEVANCE

- The perfusion CT parameters BF, BV, and PS measured with the deconvolution, maximum slope, and Patlak methods are promising tools for diagnosing pancreatic adenocarcinoma.
- Perfusion parameters obtained by different methods are not interchangeable.
- A specific cut-off value must be determined for each method and each perfusion parameter.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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References

[1] Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009; 6: 699–708. doi:10.1038/nrgastro.2009.177

[2] Wagner M, Redaelli C, Lietz M et al. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004; 91: 586–594. doi:10.1002/bjs.4484

[3] Prokesch RW, Chow LC, Beaulieu CF et al. Isoattenuating pancreatic adenocarcinoma at multi-detector row CT: secondary signs. Radiology 2002; 224: 764–768. doi:10.1148/radiol.2243011284

[4] Ishigami K, Yoshimitsu K, Irie H et al. Diagnostic value of the delayed phase image for iso-attenuating pancreatic carcinomas in the pancreatic parenchymal phase on multidetector computed tomography. Eur J Radiol 2009; 69: 139–146. doi:10.1016/j.ejrad.2007.09.012

[5] Yadav AK, Sharma R, Kandasamy D et al. Perfusion CT – Can it resolve the pancreatic carcinoma versus mass forming chronic pancreatitis conundrum? Pancreatology 2016; 16: 979–987. doi:10.1016/j.pan.2016.08.011

[6] Klauss M, Stiller W, Fritz F et al. Computed tomography perfusion analysis of pancreatic carcinoma. J Comput Assist Tomogr 2012; 36: 237–242. doi:10.1097/RCT.0b013e31824a099e

[7] Aslan S, Nural MS, Camlidag I et al. Efficacy of perfusion CT in differentiating of pancreatic ductal adenocarcinoma from mass-forming chronic pancreatitis and characterization of isoattenuating pancreatic lesions. Abdom Radiol (NY) 2019; 44: 593–603. doi:10.1007/s00261-018-1776-9

[8] Xu J, Liang Z, Hao S et al. Pancreatic adenocarcinoma: dynamic 64-slice helical CT with perfusion imaging. Abdom Imaging 2009; 34: 759–766. doi:10.1007/s00261-009-9564-1

[9] Miles KA, Griffiths MR. Perfusion CT: a worthwhile enhancement? Br J Radiol 2003; 76: 220–231. doi:10.1259/bjr/13564625

[10] Bisdas S, Konstantinou G, Surlan-Popovic K et al. Dynamic contrast-enhanced CT of head and neck tumors: comparison of first-pass and permeability perfusion measurements using two different commercially available tracer kinetics models. Acad Radiol 2008; 15: 1580–1589. doi:10.1016/j.acra.2008.05.021

[11] Deniffel D, Boutelier T, Labani A et al. Computed Tomography Perfusion Measurements in Renal Lesions Obtained by Bayesian Estimation, Advanced Singular-Value Decomposition Deconvolution, Maximum Slope, and Patlak Models: Intermodel Agreement and Diagnostic Accuracy of Tumor Classification. Invest Radiol 2018; 53: 477–485. doi:10.1097/rli.0000000000000477

[12] Djuric-Stefanovic A, Saranovic D, Masulovic D et al. Comparison between the deconvolution and maximum slope 64-MDCT perfusion analysis of the esophageal cancer: is conversion possible? Eur J Radiol 2013; 82: 1716–1723. doi:10.1016/j.ejrad.2013.05.038

[13] Goh V, Halligan S, Bartram CI. Quantitative tumor perfusion assessment with multidetector CT: are measurements from two commercial software packages interchangeable? Radiology 2007; 242: 777–782. doi:10.1148/radiol.2423060279

[14] Kanda T, Yoshikawa T, Ohno Y et al. CT hepatic perfusion measurement: comparison of three analytic methods. Eur J Radiol 2012; 81: 2075–2079. doi:10.1016/j.ejrad.2011.07.003

[15] Kaufmann S, Schulze M, Horger T et al. Reproducibility of VPCT parameters in the normal pancreas: comparison of two different kinetic calculation models. Acad Radiol 2015; 22: 1099–1105. doi:10.1016/j.acra.2015.04.005

[16] Schneeweiss S, Horger M, Grozinger A et al. CT-perfusion measurements in pancreatic carcinoma with different kinetic models: Is there a chance for tumour grading based on functional parameters? Cancer Imaging 2016; 16: 43. doi:10.1186/s40644-016-0100-6

[17] Mayer P, Fritz F, Koell M et al. Assessment of tissue perfusion of pancreatic cancer as potential imaging biomarker by means of Intravoxel incoherent motion MRI and CT perfusion: Correlation with histological microvessel density as ground truth. Cancer Imaging 2021. doi:10.1186/s40644-021-00382-x

[18] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307–310

[19] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44: 837–845

[20] Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240: 1285–1293. doi:10.1126/science.3287615

[21] Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3: 32–35. doi:10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3

[22] Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? Br J Radiol 2003; 76: S36–S42. doi:10.1259/bjr/18486642

[23] Spira D, Gerlach JD, Spira SM et al. Effect of scan time on perfusion and flow extraction product (K-trans) measurements in lung cancer using low-dose volume perfusion CT (VPCT). Acad Radiol 2012; 19: 78–83. doi:10.1016/j.acra.2011.09.010

[24] Delrue L, Blanckaert P, Mertens D et al. Tissue perfusion in pathologies of the pancreas: assessment using 128-slice computed tomography. Abdom Imaging 2012; 37: 595–601. doi:10.1007/s00261-011-9783-0

[25] Li HO, Guo J, Sun C et al. Assessment of pancreatic adenocarcinoma: Use of low-dose whole pancreatic CT perfusion and individualized dual-energy CT scanning. J Med Imaging Radiat Oncol 2015; 59: 590–598. doi:10.1111/1754-9485.12342

[26] Bell SD, Peters AM. Measurement of blood flow from first-pass radionuclide angiography: influence of bolus volume. Eur J Nucl Med 1991; 18: 885–888. doi:10.1007/bf02258454

[27] Ng CS, Chandler AG, Wei W et al. Reproducibility of CT perfusion parameters in liver tumors and normal liver. Radiology 2011; 260: 762–770. doi:10.1148/radiol.11110331

[28] Wintermark M, Maeder P, Verdun FR et al. Using 80 kVp versus 120 kVp in perfusion CT measurement of regional cerebral blood flow. AJNR Am J Neuroradiol 2000; 21: 1881–1884

[29] Goh V, Shastry M, Engledow A et al. Commercial software upgrades may significantly alter Perfusion CT parameter values in colorectal cancer. European Radiology 2011; 21: 744–749. doi:10.1007/s00330-010-1967-4

[30] Delrue L, Blanckaert P, Mertens D et al. Assessment of tumor vascularization in pancreatic adenocarcinoma using 128-slice perfusion computed tomography imaging. J Comput Assist Tomogr 2011; 35: 434–438. doi:10.1097/RCT.0b013e318223f0c5