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Dynamic Perfusion Computed Tomography and Apparent Diffusion Coefficient as Potential Markers for Poorly Differentiated Pancreatic Adenocarcinoma

Inga Zaboriene[a] Kristina Zviniene[a] Saulius Lukosevicius[a]
Povilas Ignatavicius[b] Giedrius Barauskas[c]

[a]Department of Radiology, Lithuanian University of Health Sciences, Kaunas, Lithuania; [b]Department of Visceral and Transplant Surgery, University Hospital of Zurich, Zurich, Switzerland; [c]Department of Surgery, Lithuanian University of Health Sciences, Kaunas, Lithuania

Keywords
Adenocarcinoma · Diffusion · Pancreas · Perfusion · Tumor grade

Abstract
Introduction: Tumor grade, one of the most important risk factors for survival, is routinely determined after examining the biopsy material or a surgically removed specimen. The aim of the study was to analyze computed tomography (CT) perfusion parameters and diffusion-weighted imaging apparent diffusion coefficient (ADC) values in pancreatic ductal adenocarcinoma (PDAC) and to establish the diagnostic value of these modalities determining the tumor grade. ***Materials and Methods:*** A prospective clinical study included 56 subjects with PDAC. All the patients had a local perfusion assessment and ADC measurement of the tumor. For the prediction of poor tumor differentiation sensitivity, specificity, positive, and negative predictive values for each perfusion CT and ADC parameters based on cutoff values from ROC analysis were calculated. ***Results:*** Mean transit time (MTT) and ADC values were found to be independent prognosticators for the presence of G3 PDAC. MTT and ADC at the cutoff of 17.37 s and 1.15 × 10^{-3} mm^2/s, respectively, appeared to be significant parameters discriminating against the differentiation grade of PDAC. If both values exceeded the defined cutoff point, the estimated probability for the presence of G3 PDAC was 89.29%. ***Conclusion:*** The MTT parameter, calculated with the deconvolution method, and the ADC value may serve as effective independent prognosticators identifying poorly differentiated PDAC.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive tumor with a dismal prognosis. Long-term survival ranges from 10 to 25% even after curative surgery [1, 2]. The biological behavior of the tumor may lead to an early relapse following surgery [3]. In the preoperative period, there are only a few major determinants for the recurrence – CA19-9, pain, and hyperamylasemia. However, poorly differentiated tumors do not express CA19-9 to a relevant degree [4]. Patients with the same TNM stage may have different clinical prognosis because of the different tumor grades.

karger@karger.com
www.karger.com/dsu

Inga Zaboriene
Department of Radiology
Lithuanian University of Health Sciences, Eiveniu St., 2
LT–44307 Kaunas (Lithuania)
inga_backute@yahoo.com

Tumor grade, one of the most important risk factors for survival, is routinely determined after examining a surgically removed specimen. Tumor biopsy is not recommended in operable tumors; consequently, noninvasive identification of poorly differentiated tumors would be desirable to identify these patients prior to surgery. The aim of this study was to analyze computed tomography (CT) perfusion and diffusion-weighted imaging (DWI) apparent diffusion coefficient (ADC) parameters in PDAC, and to establish the predictive value of these diagnostic modalities determining high tumor grade.

Table 1. Patient characteristics

	(G1 + G2) group	(G3) group	Total	*p* value
Age, years	64.86 (±12.26)	66.86 (±11.86)		0.38
Female, *n* (%)	18 (32.1)	16 (28.6)	34 (60.7)	0.92
Male, *n* (%)	11 (19.6)	11 (19.6)	22 (39.3)	0.99
Total, *n* (%)	29 (51.8)	27 (48.2)	56 (100)	0.92

Values are mean ± standard deviation.

Materials and Methods

This was a prospective clinical study, in which 174 subjects with PDAC were evaluated in the period between June 2015 and September 2018. A pancreatic tumor was diagnosed by multidetector computed tomography (MDCT). A total of 56 subjects signed informed consent to be further evaluated with the perfusion CT and MRI. In 15 patients with radiological borderline or unresectable tumors, diagnosis was confirmed by core needle biopsy, and in the remaining 41 by histopathological examination of a surgical specimen.

The inclusion criteria were the presence of a pancreatic head tumor, >1.5 cm (in order to place 4 separate regions of interest [ROIs] properly), without cystic degeneration or necrosis, as based on contrast-enhanced MDCT; patients without neoadjuvant or any other treatment prior to radiological examination. The exclusion criteria for perfusion CT and MRI were impaired renal function, cystic or hypervascular pancreatic lesions, and acute pancreatitis or chronic pancreatitis with multiple parenchymal calcifications. The study was approved by the Regional Biomedical Research Ethics Committee (study protocol No. BE-2-22, as of May 2015).

CT Imaging

All the subjects underwent an MDCT scan using the GE light Speed Pro 64 CT (GE Healthcare, Milwaukee, WI, USA) scanner and a perfusion CT (p_CT) of the tumor. MDCT scanning was performed with a power injector (Ulrich Missouri, Ulrich GmbH & Co., KG, Ulm, Germany), 80–100 mL of nonionic intravenous contrast media (Ultravist 370; Bracco, Milan, Italy), at a rate of 4.5 mL/s. After the on-console CT evaluation, p_CT scanning was performed in cases of pancreatic mass detection or suspicion.

The subject was immobilized for 15 min on the table in order to cleanse the pancreatic parenchyma of the contrast media, given during MDCT, and to give instructions of slow breathing during p_CT. All the subjects had a local perfusion assessment (based on the deconvolution model of perfusion) involving an evaluation of blood flow (BF) (mL min^{-1} 100 g^{-1}), blood volume (BV) (mL 100 g^{-1} of tissue), mean transit time MTT (s), and permeability surface (PS) (mL min^{-1} 100 g^{-1}).

Pancreatic perfusion was performed within a period of 50 s after a bolus injection of 50 mL of nonionic intravenous contrast media (Ultravist 370; Bracco, Milan, Italy) at a rate of 5 mL/s, applying 120 kVp, 150 mAs, 5-mm slice thickness, and 300 mm FOV. The total number of p_CT images was 792. The lowest possible value of *z*-axis coverage was selected in order to minimize the radiation dose.

Raw data images were evaluated at a CT perfusion software-equipped workstation, using the deconvolution model (AW Workstation, GE Healthcare). The arterial input function was determined by placing a circular ROI at the abdominal aorta. The area of the ROI was standardized at 50 mm^2. Four round ROIs (50 mm^2) were placed on the different parts of the tumor for perfusion measurements. The mean value of these ROIs was calculated for each tumor. Image analysis was performed by 2 independent radiologists with 7 and 17 years of experience in abdominal radiology. The calculations were compared and, observing no major discrepancies in the obtained results, the mean values of both calculations were used for further analysis.

Magnetic Resonance Imaging

MRI examination was performed using a 1.5T MR system (Siemens Magnetom Avanto, Siemens Healthineers, Erlangen, Germany) in the supine position. The MRI protocol for pancreatic imaging included T2W turbo spin-echo (TSE), T2W half-Fourier single-shot turbo spin-echo, T1W in-phase and out-of-phase sequence, unenhanced and dynamic gadolinium-enhanced T1W fat-saturated imaging, and injection of 0.2 mL/kg of Gd-based contrast media (Gadovist®, Bayer AG, Leverkusen, Germany), at a rate of 2.0 mL/s. DW MRI was performed, and the DWI data were acquired in the transverse plane using a respiration-triggered single-shot echo-planar imaging and repetition time/echo time (TR/TE) = 5,800/66 ms; 35 slices; slice thickness 6 mm with an interslice gap 1.5 mm; flip angle 90, and the field of view 380 mm. ADC maps were automatically constructed on a voxel-by-voxel basis using 3 b values (b value = 50, 400, and 800 s/mm^2).

Four round-shaped ROIs were placed on the solid part of the tumor on the ADC map. The area of the ROI was between 0.2 and 2.4 cm^2, according to the size of the tumor. The mean ADC value was considered as the ADC value of the tumor. The results were compared with histopathological data. The median time period between the radiological imaging and biopsy or surgical procedure was 10.4 days (range 5–23 days).

Histopathological analysis was performed at the Department of Pathology, Medical Academy, Lithuanian University of Health Sciences, on a routine basis. The pathologists were blinded to the perfusion CT results and ADC values. The study patients were further grouped according to the G value: well and moderately differentiated (G1 + G2) and poorly differentiated (G3) PDAC. Images of CT, DWI ADC, and p_CT of moderately and poorly differentiated PDAC are presented in Figures 1 and 2. Unfortunately, visual differences of G1/2 and G3 PDAC images are unperceivable neither in p_CT, nor in DWI ADC; therefore, calculations are essential.

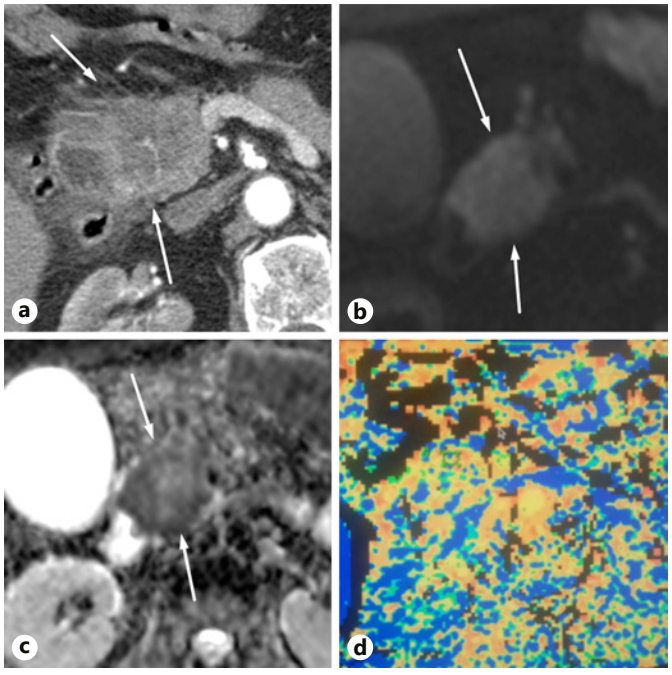

Fig. 1. a–d Images of a moderately differentiated (G2) tumor in the head of the pancreas: CT image showing a hypodense tumor in the head of the pancreas with infiltration of peripancreatic fatty tissue (white arrows) (**a**); MRI DWI – hyperintense tumor presenting with restriction of diffusion; *b* value 800 s/mm^2 (white arrows) (**b**) ADC map; the mean ADC value of the tumor is 1.16×10^{-3} mm^2/s (white arrows) (**c**); p_CT revealed moderately increased mean transit time of the tumor (MTT = 12.03 s) (**d**). CT, computed tomography; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; MTT, mean transit time.

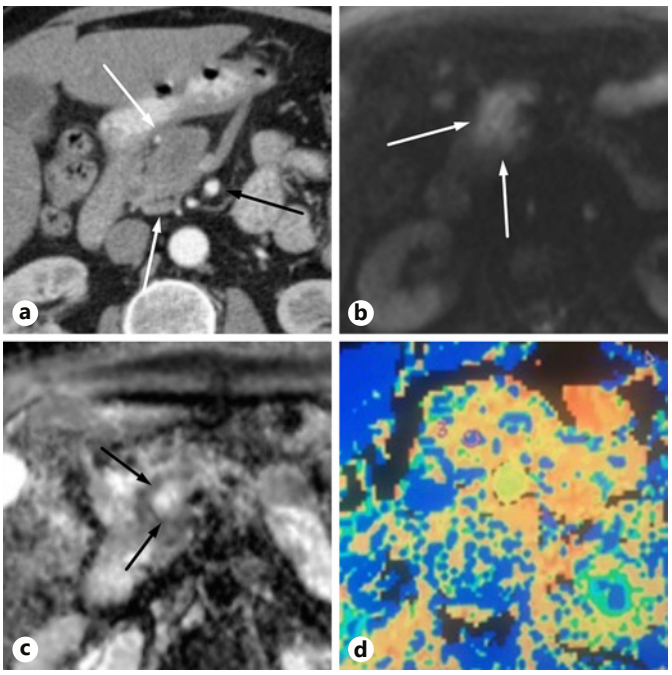

Fig. 2. a–d Images of a poorly differentiated (G3) tumor in the head of the pancreas: a hypodense mass in the head of the pancreas (white arrows) on CT image (**a**); MRI DWI – the tumor presents with restricted diffusion; *b* value 800 s/mm^2 (white arrows) (**b**); ADC map; low ADC (0.95×10^{-3} mm^2/s) value; the central part of the tumor is hyperintense due to necrosis; this area was avoided when placing ROIs for calculation of the mean ADC value (**c**); p_CT revealed highly increased mean transit time of the tumor (MTT = 18.61 s) (**d**). CT, computed tomography; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; MTT, mean transit time; ROIs, regions of interest.

Statistical Analysis

The normality and homogeneity of the study population were tested; there was no difference in the age or gender between the groups ($p = 0.38$ and $p = 0.92$, respectively) (Table 1). The sample size was calculated based on the PDAC distribution in the Lithuanian population.

The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to determine the normality of the distribution of continuous variables. Distribution of the variables was reported as mean values ± standard deviation or median (q1–q3), in cases of abnormal distribution, for BF, PS, and ADC. Variables conforming to normal distribution were compared via the Student's *t* test; otherwise, the Mann-Whitney U test was used for comparison.

Diagnostic accuracy was assessed as the area under the ROC plot. Sensitivity, specificity, positive, and negative predictive values for each perfusion CT parameter and for ADC parameter in the prediction of the PDAC grade were calculated by using cutoff values chosen on the basis of the ROC curves.

Discriminant function analysis was used to determine the differences between good/moderate and poorly differentiated PDAC. At each step, the variable that minimizes the overall Wilks' Lambda was entered. The sample size was sufficient to use the discriminant function analysis [5].

Logistic regression was performed to determine the probability of poorly differentiated (G3) PDAC; 95% confidence intervals were computed to estimate the precision of the odds ratio (OR). All calculations were performed using SPSS for Windows 23.0® software and Microsoft Excel 16®. The p value ≤0.05 was considered statistically significant.

Results

Radiological and histopathological data of 56 consecutive patients (22 men [39.3%], 34 women [60.7%]; mean age 66.86 ± 11.86 years) with PDAC in the head of the pancreas were analyzed. There were a similar number of subjects in the groups with well/moderately (G1 + G2), and poorly differentiated (G3) tumors: 29 (51.8%) and 27

Table 2. Perfusion CT and DWI-ADC parameters in different grades of PDAC

Parameters	Mean ± SD or median* (q1–q3) value (G1 + G2)	Mean ± SD or median* (q1–q3) value (G3)	*p* value
BF, mL min^{-1} 100 g^{-1}	41.74* (33.56–71.98)	34.38* (29.61–64.52)	0.11
BV, mL 100 g^{-1}	8.09±4.19	7.78±4.51	0.79
MTT, s	11.04±5.80	14.01±6.49	0.07
PS, mL min^{-1} 100 g^{-1}	31.28* (16.36–39.69)	23.48* (15.16–33.72)	0.31
ADC, ×10^{-3} mm^2/s	1.15* (1.03–1.23)	1.07* (1.01–1.12)	0.02

ADC, apparent diffusion coefficient; BF, blood flow; BV, blood volume; CT, computed tomography; MTT, mean transit time; PS, permeability surface; SD, standard deviation; PDAC, pancreatic ductal adenocarcinoma.
* Median values in abnormal distribution.

Table 3. Results of the Wilk's Lambda test

Wilks' Lambda									
Exact F									
step	entered	statistic	df1	df2	df3	statistic	df1	df2	sig
1	DWI_ADC	0.87	1	1	54.00	8.16	1	54.00	0.006
2	MTT	0.79	2	1	54.00	6.68	2	53.00	0.003

ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; MTT, mean transit time.

(48.2%), respectively. The mean size of the tumor was 34.98 ± 9.99 mm (range 15–58 mm).

Analysis of CT perfusion data revealed that BF, BV, and PS values were lower, whereas MTT values were higher in poorly differentiated as compared with well/moderately differentiated PDAC. However, the difference was not statistically significant. On the contrary, there was a significant difference in ADC values comparing G1–G2 and G3 tumors (Table 2).

Discriminant function analysis was used to determine differences between the groups. We included 4 main perfusion variables (BF, BV, MTT, and PS) and the MRI DWI ADC value in order to determine which ones contributed for the most part. At each step, the variable that minimizes the overall Wilks' Lambda was entered, thus revealing that MTT and ADC values were significantly independent discriminators (Table 3; Fig. 3). Fisher's classification coefficient was used for classification function:

$$f(g3) = -5.635 - 0.104 \times MTT + 6.203 \times ADC$$

The particular cutoff values for MTT and ADC were calculated using the ROC analysis in order to differentiate good/moderate and poorly differentiated PDAC. Based

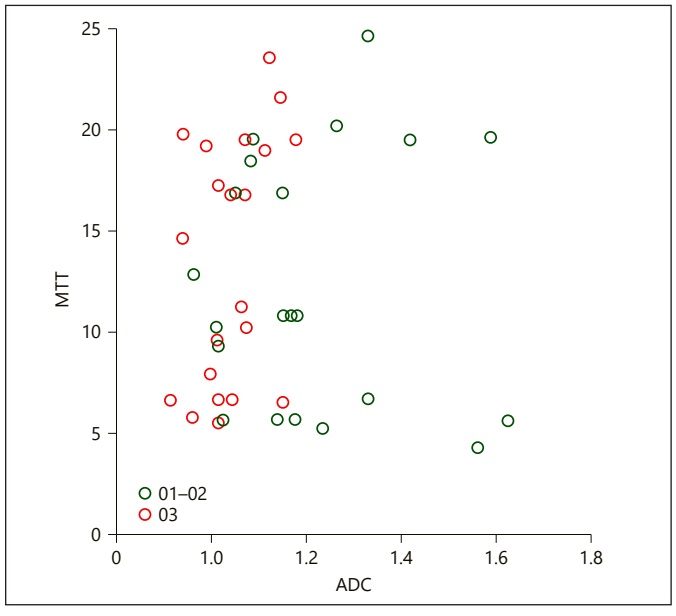

Fig. 3. Differences in MTT and ADC values between good/moderate and poorly differentiated PDAC. Discriminant function analysis shows that MTT and ADC statistically significantly discriminate between 2 groups ($p < 0.05$). MTT, mean transit time; ADC, apparent diffusion coefficient; PDAC, pancreatic ductal adenocarcinoma.

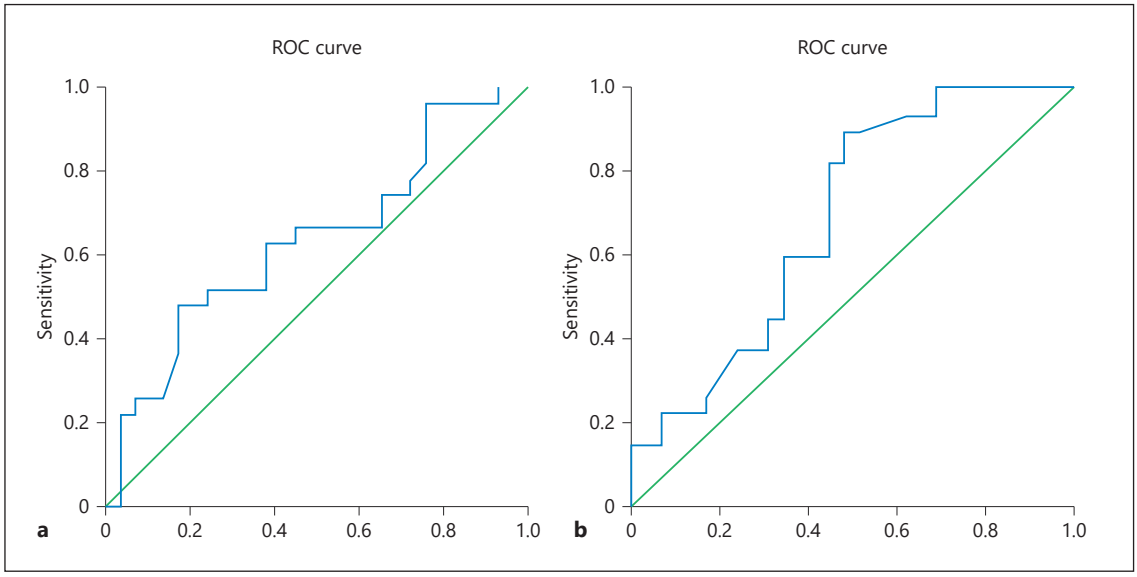

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Fig. 4. ROC curve analysis for MTT and ADC parameters. MTT value >17.37 s (AUC = 0.64) (**a**) and ADC value <1.15 × 10^{-3} mm^2/s (AUC = 0.68) (**b**) are shown to be good predictors for the presence of G3 PDAC. ROC, receiver operating characteristic; AUC, area under the curve; ADC, apparent diffusion coefficient; MTT, mean transit time; PDAC, pancreatic ductal adenocarcinoma.

Table 4. AUC, cutoff values, sensitivity, specificity, PPV, and NPV for averaged BF, BV, MTT, PS, and ADC for identification of poorly differentiated (G3) PDAC

G3 tumor	BF	BV	MTT	PS	ADC
AUC	0.62	0.51	0.64	0.58	<0.68
Cutoff point	<33.10	<6.76	>17.37	<30.99	<1.15
Sensitivity, %	48.1	59.3	48.1	74.1	<88.9
Specificity, %	86.2	58.6	82.8	51.7	<51.7
PPV, %	76.5	57.1	72.2	58.8	<63.2
NPV, %	64.1	60.7	63.2	68.2	<83.3

ADC, apparent diffusion coefficient; AUC, area under the curve; BF, blood flow; BV, blood volume; MTT, mean transit time; NPV, negative predictive value; PPV, positive predictive value; PS, permeability surface; PDAC, pancreatic ductal adenocarcinoma.

Table 5. Logistic regression for estimating the risk of poorly differentiated (G3) PDAC

	B	SE	Sig.	Exp(*B*)	95% CI for Exp(*B*) lower	95% CI for Exp(*B*) upper
MTT cutoff	2.19	0.83	0.008	9.00	1.76	46.13
ADC cutoff	2.97	0.98	0.003	19.44	2.83	133.73
Constant	−3.04	0.99	0.002	0.05		

ADC, apparent diffusion coefficient; MTT, mean transit time; PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval.

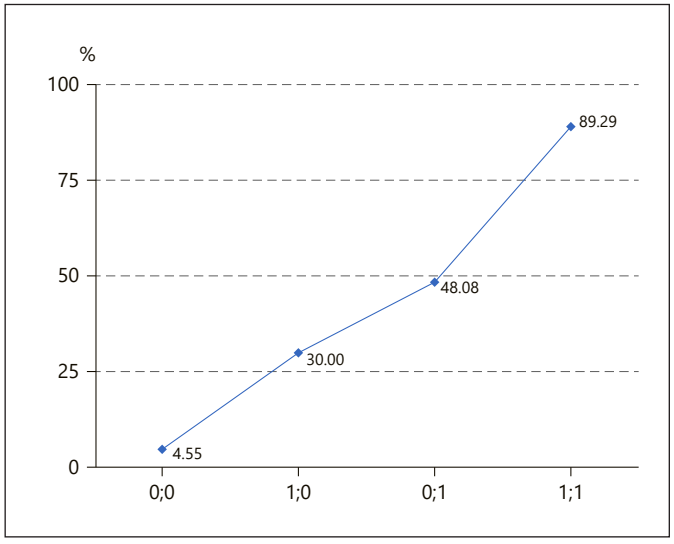

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Fig. 5. Estimated probability of the presence of poorly differentiated (G3) PDAC. The graph shows the predicted probability of poorly differentiated (G3) PDAC (%) as determined by the logistic regression analysis if MTT and ADC or both parameters exceed the defined cutoff value (MTT >17.37 s, ADC <1.15 × 10^{-3} mm^2/s). If both parameters (MTT and ADC) do not exceed the defined cutoff values, the estimated probability of the presence of poorly differentiated PDAC is 4.55%; if both variables exceed the defined cutoff value, the estimated probability reaches 89.29%. ADC, apparent diffusion coefficient; MTT, mean transit time; PDAC, pancreatic ductal adenocarcinoma.

on the ROC analysis, the area under the curve for MTT and ADC was outlined (Fig. 4). Cutoff values were determined for each perfusion parameter (BF, BV, MTT, and PS) as well as for the ADC. Sensitivity, specificity, PPV, and NPV for each parameter were calculated (Table 4). MTT at the cutoff of 17.37 s, and ADC at the cutoff of 1.15 × 10^{-3} mm^2/s appeared to be statistically significant parameters discriminating the differentiation grade of pancreatic adenocarcinoma.

Independent Prognosticators of Poorly Differentiated PDAC

The multivariate logistic regression analysis was applied to reveal the independent prognosticators of poorly differentiated PDAC. All the parameters BF, BV, MTT, PS, and ADC were included in the stepwise backward analysis. The mean transit time and ADC appeared to be significant independent prognosticators. Variables in the equation are shown in Table 5 and the estimated probability of poorly differentiated (G3) PDAC is outlined in Figure 5.

Discussion

There are several tumor-related prognostic factors for PDAC, including tumor differentiation, vascular invasion, perineural invasion, lymph node metastasis, and systemic spread. Among these, the tumor grade appears to be one of the most important predictors of survival [6, 7]. It is agreed that pathological confirmation is not required in an operable pancreatic tumor; consequently, the latter variable remains unknown prior to surgery. Functional imaging – perfusion CT and MRI with DWI – has been suggested to have a potential for improving the detection rate of pancreatic tumors as well as discriminating tumors with poor differentiation [8–13].

However, most of the studies, including the aforementioned ones, describe only one of the imaging modalities: either perfusion CT or MRI with DWI; most of them even with histologically confirmed PDAC before the radiological examination. Only in one recently published study by Kovać et al. [14], perfusion CT and MRI with DWI for evaluation of pancreatic tumor grade were described. The main limitation of this study was the retrospective design, which could have influenced or even misinterpreted the data because all the calculations were done with already known morphological characteristics of the tumor. Regarding CT imaging protocol, we performed contrast-enhanced CT and perfusion CT during examinations with 15 min break to "clean" the tumor from the contrast agent. We applied a similar protocol as recently reported by Aslan et al. [15] and Klauβ et al. [16]. The relatively short period of time to clean-up the tumor from intravenous contrast media may serve as a source of bias. There is published data reporting the delayed enhancement of the tumor, predominantly observed in lesions of 2 cm or smaller in a retrospective analysis [17]. We have conducted a prospective study including larger tumors to facilitate adequate placement of ROIs and analyzed our data before receiving pathology reports. Even if there was an influence of the not-washed-out contrast media within the tumor, it did not preclude reliably discriminating the poor and well/moderately differentiated tumors.

To our knowledge, there are only a few recent reports analyzing the ability of perfusion CT to aid in characterizing pancreatic tumors prior to pathology examination [8, 18]. Similarly, to our results, Sugimoto et al. [19] reported that prolonged MTT (calculated with a compartment model) strongly correlates with increased pancreatic fibrosis and reflects tumor progression after pancreatoduodenectomy. Poorly differentiated PDACs are characterized by intense fibrosis, possibly determining

lower BF, BV, and lower ADC parameters [20]. Moreover, fibrosis complicates the treatment contributing to a shorter survival [7, 21].

D'Onofrio et al. [8] reported a correlation between perfusion CT parameters (BV and positive enhancement integral – PEI) and tumor grade. The cutoff values for PEI (17.8 HU) and BV (14.8 mL/100 g), as based on the slope method, were able to characterize high-grade PDACs with a 60% sensitivity and a 100% specificity. Unfortunately, the cutoff values were not comparable with our data as different data acquisition protocols and different software packages were used.

We agree with Schneeweiß et al. [18], in their argument on the reliability of radiological tumor grading when solely based on a single CT perfusion parameter (e.g., BV as in D'Onofrio et al. 's [8] study or MTT as in our study). Consequently, we added MRI with DWI ADC value to improve the diagnostic accuracy.

Our results are comparable with those reported by Min et al. [22], revealing the ADC value as an independent prognostic factor for long-term and disease-free survival. In concert with the above data, Lee et al. [23] reported significantly higher ADC values in well-differentiated gallbladder adenocarcinoma. Similar results were reported by Sun et al. [24] in rectal cancer.

Up to 30% of operable patients die within a year following surgery [3]. In this subgroup, the relapse of the disease occurs very early, and survival is similar to that of patients with advanced tumors receiving systemic therapy. These "early deaths" may be attributed to inadequate preoperative staging or particularly aggressive tumor biology. Our group analyzed the data of an updated cohort of 300 PDAC subjects following pancreatoduodenectomy. Overall median survival for G1–G2 tumors reached 29.4 months, whereas it was 18.5 months in G3 group ($p = 0.03$). In addition, poor differentiation was associated with an increased risk of early death, defined as mortality within 6 months following surgery (G3 vs. G1–G2, $p = 0.03$; HR 1.94; confidence interval 1.05–3.61) [unpublished data].

A genome-wide screening was performed recently to identify 2 SNPs associated with a 2.63-fold increased risk of tumor-related death [25]. However, the identification of SNPs in everyday practice is still not available.

Noninvasive preoperative identification of poorly differentiated PDACs may have a potential for defining patients who might benefit from the preoperative biopsy followed by neoadjuvant treatment in case of morphologically confirmed poorly differentiated PDAC, or might be eligible for inclusion in further clinical trials. The greatest disadvantage of p_CT is a high radiation dose, which might be assumed as a disadvantage of the investigation. We minimized the radiation dose by selecting the lowest value allowed by the *z*-axis coverage scanner, subsequently, it was at the acceptable level of 10.4 mSv, as compared to other studies [26, 27]. On the other hand, we deal with extremely aggressive disease, and preoperative identification of G3 tumors may help to provide these patients with individualized treatment options. In this context, the increased radiation dose may be at least partially justified.

Study Limitations

This was a single-center study, performed with specific CT and MRI machines and dedicated software packages, using the deconvolution method to calculate tumor tissue perfusion parameters. To show the validity of our data, standardized perfusion CT protocols and multicenter studies are further needed.

Conclusion

The MTT parameter, calculated with the deconvolution method, and the ADC value may serve as effective independent prognosticators preoperatively identifying poorly differentiated PDAC.

Acknowledgements

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Statement of Ethics

The ethics approval was provided by the Kaunas Regional Biomedical Research Ethics Committee (study protocol No. BE-2-22, as of May 2015). All patients enrolled in this study provided written informed consent for the research study protocol. All methods were carried out in accordance with the approved guidelines.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Each named author has substantially contributed to conducting the underlying research and drafting this manuscript. Conception (constructing an idea or hypothesis for the research) – G.B., K.Z., and S.L.; design (planning the methodology to reach the conclusions) – G.B. and K.Z.; organizing and supervising the course of the study and taking the responsibility – I.Z., S.L., and P.I.; materials and referred patients – K.Z., S.L., and P.I.; data collection and processing – I.Z.; analysis and interpretation – I.Z. and G.B.; literature review – I.Z., G.B., and P.I.; reviewing the article for intellectual content, spelling, and grammar – G.B., P.I., K.Z., and S.L.

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