Doppler tissue perfusion measurement is a sensitive and specific tool for a differentiation between malignant and inflammatory pancreatic tumors

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Abstract

Differentiation between pancreatic malignant and inflammatory tumors presents an important diagnostic problem. The ability to recognize pancreatic malignant tumors using Doppler evaluation of tissue perfusion has been recently demonstrated. The aim of the study was to assess the diagnostic value of Dynamic Tissue Perfusion Measurement (DTPM) in the differentiation between malignant and inflammatory pancreatic tumors. The study included 60 patients (35M, 25F, age 60.9 ± 2.3 years) with a malignant (Group 1, n = 30) or inflammatory (Group 2, n = 30) pancreatic tumor undergoing endoscopic ultrasound with the evaluation of tissue perfusion by Color Doppler and a simultaneous biopsy of lesions for cytological evaluation. In 20 patients the diagnosis was verified in the postoperative histopathological examination. Flow velocity (FV) and percentiles of the distribution of perfusion intensity (PR) evaluated by DTPM were analyzed with regard to receiver-operator-characteristics. FV as well as PR were significantly higher in Group 2 compared to Group 1. A threshold of 2.0 cm/sec for FV identified patients with malignancies with a sensitivity of 83% and specificity of 86%. In multivariable regression analysis, the best PR parameter for differentiating between malignant and inflammatory tumors was 97.5% percentile, whose value of 0.922 allowed for the recognition of pancreatic malignant tumors with a sensitivity of 62% and specificity of 83% (p < 0.001). In conclusion, Color Doppler ultrasound tissue perfusion parameters are a sensitive and specific tool in the differentiation between malignant and inflammatory pancreatic tumors.

Introduction

Differentiation between pancreatic malignant and inflammatory tumors presents an important diagnostic problem. Adenocarcinoma is the most frequent pancreatic malignant tumor
accounting for more than 90% of all malignancies of the organ [1,2]. Each year pancreatic cancer is diagnosed in 200,000 new cases (52% men and 48% women). The highest incidence is found in developed countries such as the USA, Australia, Argentina or regions e.g., Central and Northern Europe, and comparable between sexes (8-12/10^5 male and 6-7/10^5 female). With a 5-year mortality rate of over 95%, pancreatic cancer is one of the deadliest cancers worldwide. It is the fourth leading cause of cancer-related deaths in both women and men, with an incidence rate similar to the mortality rate [3,4]. Yearly survival in Europe varies between 11.5% and 28.3%, and only 5.7% of patients survive a period of 5 years [5–7]. Therefore, a correct diagnosis of pancreatic focal lesions is a very important diagnostic issue. Endosonography is known to be the best method for diagnosing solid pancreatic lesions [8,9]. When accompanied by endoscopic ultrasound (EUS) fine needle aspiration (EUS-FNA), it is characterized by a high sensitivity and specificity in differentiating pancreatic pathologies [9,10]. Additional administration of contrast agents during that procedure allows to assess the blood flow in a tissue or to observe the changes in echogenicity of a tissue. Contrast-enhanced harmonic EUS (CH-EUS) is used to visualize parenchymal perfusion and microvasculature in the pancreas and plays an important role in the differential diagnosis of conventional EUS-detected solid pancreatic lesions and ductal carcinomas [11,12]. However, this method requires an infusion of ultrasound contrast agent, which rarely can be complicated by adverse events [13]. Contrary to contrast-enhanced ultrasound techniques, in a small group of patients we introduced recently the ability to recognize malignant pancreatic lesions using non-invasive measures of tissue perfusion obtained by Color Doppler examination [14].

The aim of this study was to provide an additional evidence for the diagnostic value of the Dynamic Tissue Perfusion Measurement (DTPM) in the differentiation between malignant and inflammatory pancreatic tumors, in a much larger group of patients.

Materials and methods

Statutory activity and the consent of the Bioethics Committee of the Military Institute of Medicine was the basis of the present work (project number 245/2014). The research tests were conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

From March 2015 to March 2017, consecutive patients presenting to the Department of Gastroenterology with a diagnosed focal pancreatic lesions in the form of carcinoma or chronic pancreatic inflammation, in whom EUS examination using Color Doppler was able to visualize the blood flow within the lesion, were included in the study.

Inclusion criteria: minimum age of 18 years; consent to participate in the study and to perform endoscopic examinations with a biopsy; no contraindications for the EUS examination of the upper digestive tract; solid focal pancreatic lesions observed in EUS examinations; vascularisation within focal pancreatic lesions visible in Color Doppler. Exclusion criteria included: lack of consent to participate in the study and to perform endoscopic examinations with a biopsy; cystic focal pancreatic lesions observed in EUS examinations; lack of possibility to visualize the flow within focal pancreatic lesions in Color Doppler.

EUS including Color Doppler assessment of the perfusion in the pancreatic lesion was performed in all study patients. Patients with malignant pancreatic lesions confirmed in histology/cytology were included into Group 1. All patients with pancreatic inflammatory tumors (Group 2) had a history of acute pancreatitis related to alcohol consumption and/or ductal biliary stones. In ultrasound and CT imaging groove pancreatitis criteria were not found [15,16]. Furthermore, based on the International Association of Pancreatology guidelines, autoimmune pancreatitis was excluded [17,18]. In histological material achieved in EUS-FNA with
the use of EchoTip ProCore needles, periductal inflammation and fibrosis with lymphocyte, plasmocyte and macrophage infiltrations, without atypical cells were confirmed.

**Histopathological examination**

The material obtained from histopathological and cytological examinations was evaluated in the local pathomorphology department. After receiving the written result, the patient was qualified to Group 1 or Group 2. Patients who were not qualified for surgical treatment were subjected to a 6-month follow-up and re-verification in order to exclude neoplastic process.

**Endoscopic ultrasound and diagnosis**

Endoscopic ultrasound (EUS) examination (Pentax EG-3870 UTK, 5–12 MHz linear transducer) was performed with 2D and Color Doppler imaging as well as EUS Fine Needle Aspiration (EUS-FNA) using EchoTip ProCore needles were performed to collect samples for histology/cytology. 20 patients with histopathologically verified lesions (17 adenocarcinomas, 3 inflammatory pancreatic tumors) were qualified for surgery. Lastly, the diagnosis was always confirmed by cytology, postsurgical histopathology, or by a follow-up of at least 6 months in order to exclude malignancy in the patients who did not undergo surgery.

**Perfusion assessment**

To assess the perfusion of solid focal pancreatic lesions, during EUS, short (3 to 6 seconds) image sequences were recorded, in which Color Doppler was able to detect the blood flow within the lesion [14]. After the examination, the recorded sequences were transferred and then evaluated by an independent operator using PixelFlux software (Chameleon Software, Leipzig, Germany) and DTPM [19]. A region of interest (ROI) was set in the focal lesion surface area within the Color Doppler frame. The frequency of Color Doppler was set consequently at 5 MHz. We analyzed the changes in the blood flow in at least one vessel within the tumor. Mean flow velocity (FV) within the tumor was evaluated by DTPM. The distribution of perfusion intensity refers, in PixelFlux, to the number of pixels within the ROI that relate to the intensity of the respective value, and is visually expressed as a Perfusion Relief (PR). The value of the perfusion intensity distribution was determined for the 2.5%, 25%, 50%, 75% and 97.5% percentiles (PR2.5, PR25, PR50, PR75, PR97.5) of perfusion intensity.

**Statistics**

Differences between perfusion parameters were assessed using U Mann-Whitney test or Student’s t-test depending on the distribution of the data. Chi-square test was used in order to test the differences between nominal variables. Receiver-operator-characteristics (ROC) analysis evaluated the predictive value of perfusion to identify a malignant lesion. Multivariable regression analysis was employed to identify the best parameter in PR differentiating between inflammatory and malignant lesions. Statistical calculations were performed using Statistica 12 software (StatSoft Inc., Cracow, Poland).

**Results**

The study included 60 consecutive patients (35 M, 25 F, age 60.9 ±2.3 years) (S1 Table) presenting to the Department of Gastroenterology with the diagnosed focal pancreatic lesion in the form of carcinoma (Group 1; n = 30) or chronic pancreatic inflammation (Group 2; n = 30). One patient with a malignant tumor and 2 patients with chronic pancreatitis were excluded from evaluation because of invisibility of the flow within the lesion (only peripheral
vessels visible). In total, perfusion was examined in 57 patients divided into the following groups: Group 1 (n = 29; 21M, 8F, age 63.1 ± 13.0) with diagnosed malignant tumors and Group 2 (n = 28; 14M, 14F, age 56.6 ± 11.3) with pancreatic focal inflammatory lesions (Table 1). Baseline characteristics of included patients are presented in Table 2. Groups did not differ in age, BMI, gender structure and presented symptoms. In Group 1, significantly lower mean flow velocity was observed, compared to the group with inflammatory lesions (Table 3, Figs 1 and 2). In the ROC analysis, FV values ≥ 2.0 cm/s identified patients with malignancies with a sensitivity of ≥ 82.8% and specificity of ≥ 85.7% (Table 4). In Group 1, the distribution of perfusion intensity was significantly lower in all but one (PR2.5) considered

### Table 1. Histopathological and cytological diagnoses in considered groups.

| Diagnosis                  | Group 1 (n = 29) | Group 2 (n = 28) |
|----------------------------|------------------|------------------|
| adenocarcinoma             | 17 (surgery)     | 3 (surgery)      |
| inflammatory tumor         | 12 (EUS-FNA)     | 25 (EUS-FNA)     |
| EUS-FNA Endoscopic Ultrasound Fine Needle Aspiration |

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### Table 2. Baseline characteristics of included patients.

|                          | All (n = 57) | Group 1 (n = 29) | Group 2 (n = 28) | p—Value |
|--------------------------|-------------|------------------|------------------|---------|
| Age (y)                  | 60.42 ±12.36| 62.69 ±13.11     | 58.07 ±11.29     | 0.160   |
| BMI (kg/m²)              | 23.40 ± 3.06| 23.49 ± 2.44     | 23.32 ± 3.64     | 0.367   |
| Male/Female              | 35/22       | 21/8             | 14/14            | 0.082   |
| Weight loss              | 13          | 6                | 7                | 0.698   |
| Abdominal pain           | 25          | 12               | 13               | 0.701   |
| Jaundice                 | 12          | 7                | 5                | 0.561   |
| Other*                   | 12          | 8                | 4                | 0.218   |

* Other symptoms: irregular bowel movements, diarrrhea, tympanites, renal/hepatic colic etc.
For nominal variables (weight loss, abdominal pain, jaundice, other) sum of positive results of the examination is presented.

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### Table 3. Results of DTPM in pancreatic tumors in considered groups.

|                        | Group 1 (n = 29) | Group 2 (n = 28) | p—Value |
|------------------------|------------------|------------------|---------|
| FV (cm/s)              | 1.584 ±0.646     | 2.653 ±0.813     | < 0.001 |
| PR2.5*                 | 0.008 (0.004; 0.028) | 0.011 (0.003; 0.035) | 0.067   |
| PR25*                  | 0.039 (0.017; 0.316) | 0.071 (0.012; 0.447) | 0.001   |
| PR50*                  | 0.118 (0.038; 0.702) | 0.252 (0.032; 1.658) | < 0.001 |
| PR75*                  | 0.255 (0.075; 1.431) | 0.656 (0.075; 3.676) | < 0.001 |
| PR97.5*                | 0.796 (0.186; 2.309) | 1.802 (0.553; 5.723) | < 0.001 |

FV—flow velocity; PR2.5, PR25, PR50, PR75, PR97.5—percentiles of the distribution of perfusion intensity, respectively 2.5%, 25%, 50%, 75%, 97.5%
*—median and range (min; max) presented.

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percentiles compared to Group 2 (Table 3). Multivariable regression analysis was performed in three models, each containing three successive PR percentiles so as to identify the best percentile interval distinguishing both groups. In each model, only the highest percentile was found to be suitable for the differentiation between the groups. Finally, in the model containing three highest percentiles (PR50, PR75, PR97.5), only the PR97.5 value was identified as an independent factor differentiating between malignant and inflammatory pancreatic tumors.

Fig 1. Example of perfusion relief and the flow intensity in a pancreatic inflammatory tumor. Upper part: Graphical presentation of the Perfusion Relief (triple arrow) in the selected ROI (double arrow). The ROI border outlines tumor area (*) within Color Doppler frame (single arrow). A diagram Pixels/Intensity is a quantitative evaluation of PR showing how many pixels within the ROI relate to the intensity of the respective value. A box-plot diagram (#) expresses the distribution of pixel intensity, in percentiles (pc) (whisker: 2.5% and 97.5%; box 25% and 75%; vertical line in the box 50%—median). In the presented case mean intensity in the ROI was 0.174 cm/s, median PR intensity (50% pc) was 0.593 cm/s, whereas 97.5% pc was 2.887 cm/s. Lower part: Graphical presentation of mean temporary values of the flow intensity (average 0.94 cm/s) within selected ROI in the same patient. The Y-axis represents intensity in cm/s. The X-axis represents consecutive images in the video file.

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\( R^2 = 0.26, p < 0.001 \). The ROC analysis performed for PR97.5 showed that a value of \( \leq 0.922 \) allowed to recognize malignant lesions with a sensitivity of \( \leq 62\% \) and specificity \( \geq 89\% \) (AUC 0.813; \( p < 0.001 \)) (Table 4). However, the PR97.5 value of \( \leq 1.198 \) suggested the potential to distinguish pancreatic adenocarcinomas with a sensitivity of \( \leq 76\% \) and specificity \( \geq 68\% \). Although the FV predictive value for the differentiation between malignant and inflammatory pancreatic lesions appears to be better than PR97.5, areas under the curve (AUC) of
the considered perfusion parameters were not significantly different (0.852 vs 0.813, $p = 0.91$) (Fig 3).

**Discussion**

In the present work, the first attempt was made to determine the usefulness of DTPM parameters in the differentiation between malignant and inflammatory pancreatic tumors. A new method based on the ultrasound Color Doppler results is DTPM which allows for quantitative and semi-automatic evaluation of perfusion in the study area. Quantification of the Color Doppler flow signal by the original software is the basis for DTPM. It was originally intended to evaluate the perfusion parameters of renal parenchyma, and then successfully employed in neurology, gynecology, oncology, gastroenterology (intestinal perfusion), and more recently in the diagnosis of cardio-renal disturbances [19–22]. Thus far, contrast-enhanced ultrasound (CEUS) has been used to assess the blood perfusion in focal pancreatic lesions and to differentiate between inflammatory lesions and pancreatic cancer [23]. The administration of intravenous contrast agent in ultrasound examination enables the calculation of the mean transit time through the tissue, using the curves of changes in echogenicity of the tissue. Two values are calculated: the time required to restore a full strengthening of the tissue and the intensity of the strengthening. The product of these two values is a measure of the flow rate. Contrast-enhanced harmonic EUS shows that the majority of pancreatic cancers exhibits hypovascular heterogeneous enhancement because of irregular network-like microvessels. The analysis of perfusion using contrast enables to differentiate poorly vascularized lesions of pancreatic cancer from focal lesions observed in autoimmune pancreatitis [24,25]. The differentiation between perfusion of pancreatic focal lesions was verified in Contrast Enhanced Computed Tomography (CE-CT). Kandel et al. found that perfusion in pancreatic cancer was significantly lower than the perfusion in normal pancreatic tissue [26]. Perfusion in 64-slice CE-CT was used by Lu et al. to distinguish between pancreatic cancers and inflammatory tumors [27]. In this study, perfusion imaging blood volume was lower by 53% in cancers compared to inflammatory tumors. Similar conclusions were obtained by Klauss et al., who applied dynamic sequences in 64-slice CE-CT in 25 patients with diagnosed pancreatic cancer [28]. Morphology of perfusion curves in CE-CT was useful in the evaluation of pathological pancreatic lesions. In the study by Zamboni et al., CE-CT allowed for the diagnosis of pancreatic cancer with a sensitivity of 74%, specificity of 94%, positive predictive value of 92%, and negative predictive value of 79% [29]. The analysis of the perfusion in focal pancreatic lesions was also performed by magnetic resonance imaging [30]. In pancreatic cancers, diffusion parameters were significantly lower which allowed for the proper diagnosis. The above-mentioned data

| Variable | OCP | Sensitivity (%) | Specificity (%) | PPV | NPV | ACC | AUC | ERR |
|----------|-----|----------------|----------------|-----|-----|-----|-----|-----|
| FV (cm/s) | 2.009 | 82.8 | 85.7 | 0.857 | 0.828 | 0.842 | 0.852 | 0.158 |
|           | 2.303* | 89.7 | 71.4 | 0.765 | 0.870 | 0.807 | 0.852 | 0.193 |
| PR25     | 0.062 | 79.3 | 71.4 | 0.742 | 0.769 | 0.754 | 0.741 | 0.264 |
|           | 0.057* | 75.9 | 71.4 | 0.733 | 0.741 | 0.737 | 0.741 | 0.263 |
| PR97.5   | 0.922 | 62.1 | 89.3 | 0.857 | 0.694 | 0.754 | 0.813 | 0.246 |
|           | 1.198 | 75.9 | 67.9 | 0.710 | 0.731 | 0.719 | 0.813 | 0.281 |

ACC—accuracy; AUC—area under curve; ERR—error rate; FV—flow velocity; NPV—negative predictive value; OCP—optimal cut-off point; PPV—positive predictive value; PR25, PR97.5—percentiles of the distribution of perfusion intensity, respectively 25%, 97.5%

*—value approximated to previous data [14].

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confirm our observation of a much reduced FV in malignant tumors compared to inflammatory ones. Moreover, percentiles of the distribution of perfusion intensity were significantly lower in malignant lesions compared to non-malignant ones. We recently demonstrated the ability to adequately differentiate malignant pancreatic lesions from inflammatory and benign cystic lesions using DTPM method on the small group of patients [14]. In this study, both reduced FV and PR25 significantly differentiated pancreatic malignant tumors from inflammatory and cystic lesions. However, cystic tumors can already be diagnosed with a high accuracy already in the EUS study, based on the identification of anechoic areas confined by smooth walls. In addition, due to the small number of patients, the PR25 parameter was
chosen arbitrarily, as a representative of the perfusion relief parameters. In the present work, we confirmed our previous observation and the value of DTPM for differentiating between malignant and inflammatory pancreatic lesions in a representative group of patients. Again, FV was significantly lower in malignant tumors compared to inflammatory ones, and a threshold of $\leq 2.0$ cm/sec allowed to recognize malignant lesions with a sensitivity and specificity of approx. 84%. In contrast to our previous study PR97.5 was the best factor differentiating between malignant and inflammatory pancreatic tumors. A PR97.5 of $\leq 0.922$ recognized malignant pancreatic lesions with a sensitivity of 62% and specificity of 89%. Our study provides evidence for the feasibility of perfusion parameters to differentiate between malignant and inflammatory pancreatic tumors. EUS using Doppler evaluation of tissue perfusion is also invasive because of combining endoscopy with FNA but does not require the administration of contrast agent. The diagnostic properties of FV and PR97.5 in recognizing pancreatic malignancies, obtained in our study, can be estimated as good [31]. Despite the promising results, our study has several limitations. Although the evaluation of perfusion in a pancreatic tumor based on the flow detected in only a single vessel can be misleading with contributory poor imaging conditions, it is only possible to record a reduced, not increased flows. Thus, overdiagnosis of malignant lesions seems to be a better option than omitting them. The literature provides sufficient evidence that endosonography is the best method for detecting solid pancreatic lesions. Nevertheless, it is still difficult to differentiate between malignant and benign lesions [6-8]. This is one of the first studies showing the features and benefits of ultrasound evaluation to differentiate solid pancreatic lesions, which can be considered as equivalent to CH-EUS or even CT [14]. This method can be successfully used in the appropriate group of pancreatic tumors and can help in the diagnosis of malignant lesions. Despite the promising results of non-invasive imaging methods the true nature of the lesion must be confirmed by histology.

**Conclusions**

Color Doppler ultrasound-derived tissue perfusion measurement is a sensitive and specific method for the differentiation between pancreatic malignant and inflammatory tumors. Measures of the flow velocity and parameters of perfusion distribution demonstrate comparable diagnostic properties. A comparative analysis of Doppler perfusion methods with other already used diagnostic tools allowing to detect pancreatic malignant tumors should be performed.

**Supporting information**

S1 Table. Results of DTPM in pancreatic tumors.
(XLSX)

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Tissue perfusion measurement pancreatic tumors

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References
1. Cascini S, Falconi M, Valentini V, Jelic S. Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21: 55–58. https://doi.org/10.1093/annonc/mdp267
2. Seufferlein T, Bachet JB, Van Cutsem E Rougier P.: Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23: 33–40. https://doi.org/10.1093/annonc/mds086
3. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Aug; 15(8):1028 –1061. https://doi.org/10.6004/jncn.2017.0131 PMID: 28784865
4. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5: v56–v68. https://doi.org/10.1093/annonc/mdv295
5. Malvezzi M, Arf e A, Bertuccio P, Levi F, La Vecchia C, Negri E, “European cancer mortality predictions for the year 2011,” Ann Oncol. 2011; 22: 947–956. https://doi.org/10.1093/annonc/mdq774 PMID: 21303801
6. Sant M, Allemani C, Sautarilani M, Knijn A, Marchesi F, Capocaccia R: EUROCASE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer. 2009; 45(6):931–91. https://doi.org/10.1016/j.ejca.2008.11.016 PMID: 19171476
7. Sharma C, Eltawil KM, Renfrew PD, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990–2010. World J Gastroenterol. 2011; 17:867–97. https://doi.org/10.3748/wjg.v17.i7.867 PMID: 21412497
8. Ignee A, Atkinson NSS, Schuessler G, Dietrich CF. Ultrasound contrast agents. Endoscopy. 2016; 5(6):355–362. https://doi.org/10.4103/2303-9027.193594 PMID: 27820424
9. Perez-Johnston R., Sainani N.I., Sahani D.V. Imaging of chronic pancreatitis (including groove and autoimmune pancreatitis). Radiol Clin North Am. 2012; 50(3):447–86. https://doi.org/10.1016/j.rcl.2012.03.005 PMID: 22560691
10. Levenick J.M., Gordon S.R., Sutton J.E. Suriawinata A, Gardner TB. A comprehensive, case-based review of groove pancreatitis. Pancreas 2009; 38:e169–175 https://doi.org/10.1097/MPA.0b013e3181ac73f1 PMID: 19629001
11. Shimosegawa T., Chari S.T., Giday S.A, Kim MH, Chung JB, Lee KT, et.al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas, 2011; 40: 809–814 https://doi.org/10.1097/MPA.0b013e3182258a15 PMID: 21747510
19. Scholbach T, Dimos I, Scholbach J. A new method of color Doppler perfusion measurement via dynamic sonographic signal quantification in renal parenchyma. Nephron Physiol. 2004; 96(4):p99–104. https://doi.org/10.1159/000077380 PMID: 15122055

20. Scholbach T.M., Hormann J., Scholbach J. Dynamic Tissue Perfusion Measurement in the Intestinal Wall—Correlation With Ulcerative Colitis. J. Med. Ultrasound 2010; 18(2):62–70.

21. Lubas A, Ryczek R, Kade G, Smoszna J, Niemczyk S. Impact of Cardiovascular Organ Damage on Cortical Renal Perfusion in Patients with Chronic Renal Failure. BioMed Research International, 2013. https://doi.org/10.1155/2013/137868. PMID: 23853766

22. Lubas A, Ryczek R, Kade G, Niemczyk S. Renal Perfusion Index Reflects Cardiac Systolic Function in Chronic Cardio-Renal Syndrome. Med Sci Monit. 2015; 21,1089–96. https://doi.org/10.12659/MSM.892630 PMID: 25881555

23. Wang Y, Yan K, Fan Z, Sun L, Wu W, Yang W. Contrast-Enhanced Ultrasonography of Pancreatic Carcinoma: Correlation with Pathologic Findings. Ultrasound Med Biol. 2016 Apr; 42(4):891–8. https://doi.org/10.1016/j.ultrasmedbio.2015.12.008 PMID: 26806440

24. Kitano M, Kudo M, Sakamoto H, Komaki T. Endoscopic ultrasonography and contrast-enhanced endoscopic ultrasonography. Pancreatology. 2011; 11 Suppl 2:28–33. https://doi.org/10.1159/000323493 PMID: 21464584

25. Vitali F, Pfeifer L, Janson C, Goertz RS, Neurath MF, Strobel D, et al. Quantitative perfusion analysis in pancreatic contrast enhanced ultrasound (DCE-US): a promising tool for the differentiation between autoimmune pancreatitis and pancreatic cancer. Z Gastroenterol. 2015 Oct; 53(10):1175–81. https://doi.org/10.1055/s-0041-103847 PMID: 26480053

26. Kandel S, Kloeters C, Meyer H, Hein P, Hilbig A, Rogalla P. Whole-organ perfusion of the pancreas using dynamic volume CT in patients with primary pancreatic carcinoma: acquisition technique, post-processing and initial results. Eur Radiol. 2009 Nov; 19(11):2641–6. https://doi.org/10.1007/s00330-009-1453-z PMID: 19471941

27. Lu N, Feng XY, Hao SJ, Liang ZH, Jin C, Qiang JW, et al. 64-slice CT perfusion imaging of pancreatic adenocarcinoma and mass-forming chronic pancreatitis. Acad Radiol. 2011 Jan, 18(1):81–8. https://doi.org/10.1016/j.acra.2010.07.012 Epub 2010 Oct 15. PMID: 20951612

28. Klaus M, Stiller W, Fritz F, Kieser M, Werner J, Kauczor HU, et al. Computed tomography perfusion analysis of pancreatic carcinoma. J Comput Assist Tomogr. 2012 Mar-Apr; 36(2):237–42. https://doi.org/10.1097/RCT.0b013e31824a099e PMID: 22446366

29. Zamboni GA, Bernardin L, Pozzi Mucelli R. Dynamic MDCT of the pancreas: is time-density curve morphology useful for the differential diagnosis of solid lesions? A preliminary report. Eur J Radiol. 2012 Mar; 81(3):e381–5. https://doi.org/10.1016/j.ejrad.2011.11.055 PMID: 22197731

30. Ma W, Li N, Zhao W, Ren J, Wei M, Yang Y, et al. Apparent Diffusion Coefficient and Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Pancreatic Cancer: Characteristics and Correlation With Histopathologic Parameters. J Comput Assist Tomogr. 2016 Sep-Oct; 40(5):709–16. https://doi.org/10.1097/RCT.0000000000000434 PMID: 27224251

31. Ray P, Le Manach Y, Riou B, Houle TT. Statistical evaluation of a biomarker. Anesthesiology. 2010 Apr; 112(4):1023–40. https://doi.org/10.1097/ALN.0b013e3181d47604 PMID: 20234303