Grading of pancreatic neuroendocrine neoplasms using pharmacokinetic parameters derived from dynamic contrast-enhanced MRI

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Abstract. The present study aimed to evaluate the diagnostic efficacy of pharmacokinetic parameters derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in prospective evaluation of pancreatic neuroendocrine neoplasms (pNENs) grading. A total of 25 histologically proven patients with pNENs (30 lesions in total) who underwent DCE-MRI were enrolled. Lesions were divided into G1, G2 neuroendocrine tumor (NET) and G3 NET/neuroendocrine carcinoma (NEC) groups based on their histological findings according to 2017 World Health Organization Neuroendocrine Tumor Classification Guideline. In addition, the same numbers of tumor-free regions were selected using as normal control group. For each group, pharmacokinetic DCE parameters: volume transfer constant (Ktrans); contrast transfer rate constant (kep); extravascular extracellular space volume fraction (ve); and plasma volume fraction (vp) were calculated with Extended Tofts Linear model. Receiver operator characteristics analysis was conducted to assess the diagnostic efficacy of these parameters in pNENs grading. There were significant differences of Ktrans, kep, ve, and vp between tumor-free areas and G1, G2 NET (P<0.001). The Ktrans and kep of G1 NET were significantly lower compared with those of G2 ones (P<0.005). The area under the curve of Ktrans and kep in differentiating G2 from G1 NET were 0.767 and 0.846, respectively. When Ktrans was >0.667 and kep >1.644, the sensitivity of diagnosing G2 NET was the lowest (53.85%), but the specificity was the highest (93.75%). When Ktrans was >0.667 or kep >1.644, the sensitivity of diagnosing G2 NET was 92.31%, but the specificity was 75.00%. Pharmacokinetic parameters of DCE-MRI, particularly the quantitative values of Ktrans and kep, are helpful for differentiating G2 NET from G1 ones.

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Abbreviations: DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; pNENs, pancreatic neuroendocrine neoplasms; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; ROC, receiver operator characteristics; NENs, neuroendocrine neoplasms; PRRT, peptide receptor radionuclide therapy; Ktrans, volume transfer constant; kep, contrast transfer rate constant; EES, extravascular extracellular space; ve, extravascular extracellular space volume fraction; vp, plasma volume fraction; TR, repetition time; TE, echo time; FOV, field of view; ROI, region of interest; MRF, Markov random fields; AIF, arterial input function; HPF, high-power field; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient

Key words: dynamic contrast-enhanced magnetic resonance imaging, pancreatic neuroendocrine neoplasms, tumor grading, pharmacokinetic parameters, quantitative evaluation

Introduction

Neuroendocrine neoplasms (NENs) are derived from neuroendocrine cells throughout the human body, and the gastroenteropancreatic tract and lung are two main sites of this disease (1). Pancreatic NENs (pNENs) are a subtype of gastroenteropancreatic NENs (2). pNENs are rare tumors accounting for only 1-2% of all pancreatic tumors. However, the morbidity has increased substantially in the last four decades (from 1.09 to 5.25 per 100,000 individuals between 1973 and 2004) (1,3). In 2017, the updated WHO classification for pNENs divided NENs into G1, G2, G3 neuroendocrine tumor (NET) and neuroendocrine carcinoma (NEC) based on the histological differentiation, including the Ki-67 proliferation index and the mitotic rate (4). One of the most important aspects to tailor the optimal treatment for the pNENs patients is tumor grading. Patients with well-differentiated pNENs are usually managed with treatment with somatostatin analogues and further treatment such as surgery or peptide receptor radio-nuclide therapy (PRRT) can be considered (5,6). Patients with poorly differentiated NEC should be referred to the oncology department with no delay (7-9). Although G1 and G2 NET are generally treated as the same entity, there are some differences...
to the treatment strategies of the two in clinical practice. So, an accurate preoperative assessment of grading is a prerequisite for individually tailored lesion therapies and prediction of patient outcomes. The current grading system is based on post-surgery or biopsy pathology, which is time-delayed and invasive. At present, sporadic reports about the preoperative grading of pNENs using CT and magnetic resonance (MR) can be found (10-12), but they were almost retrospective and based on morphology research. Meanwhile their observation points covered many aspects, including lesion morphology, border, size, bile duct dilatation, vascular invasion, signal intensity, and enhancement ratio, which was multifarious and inconvenient in application.

Dynamic contrast-enhanced MR imaging (DCE-MRI), which allows in vivo imaging of the physiology of the microcirculation, provides information related to the vascularity (13,14). By using appropriate pharmacokinetic model, DCE-MRI can generate a series of quantitative parameters, such as volume transfer constant (Ktrans), contrast transfer rate constant (Kep), extravascular extracellular space (EES) volume fraction (ve) and plasma volume fraction (vp). It has been demonstrated that these quantitative parameters can provide valuable information in clinical including characterization of cancers, guidance for treatment planning, early prediction of treatment responses and evaluation of treatment outcomes (15-22). However, to our best knowledge, no study has been done to investigate the DCE-MRI pharmacokinetic parameters and its value in grading of pNENs. Thus, the purpose of this study was to evaluate the quantitative DCE-MRI pharmacokinetic parameters in pNENs and their role in pNENs grading.

Materials and methods

Patient population. Ethical approval was obtained for this prospective research from the Ethics Committee Board and the informed consent was obtained from all participants before collecting information. From May 2014 to August 2016, 43 patients with suspected pNENs were referred from the Endocrine Department and the Department of Hepatobiliary Surgery in our hospital. For inclusion, the candidates should have documentation of eligibility criteria including: Suspected pNENs by ultrasound, CT or other imaging methods; no any disease influencing pancreas; no contraindications to raceanisodamine hydrochloride injection and MRI examination; and no treatment or intervention to pancreatic mass. Among 43 patients, 18 were excluded due to various reasons. Finally, 25 pNENs patients (30 lesions) confirmed by histopathology were included. The case accrual process was summarized in Fig. 1.

MRI protocol. Prior to scanning, patients were requested to fast at least 4 h. Then, 10 mg anisodamine (Raceanisodamine Hydrochloride Injection; Minsheng Pharmaceutical Co., Hangzhou, China) was injected intramuscularly 10 min before examination. MR images of the pancreases were acquired in our institution on a whole body 3.0 T MR scanner (Discovery MR750; GE Medical Systems, Chicago, IL, USA) with an eight-channel phased-array Torso coil positioned on the superior abdomen. Using variable flip angle T1 mapping, pre-contrast three-dimensional spoiled gradient recalled echo sequence series were performed with flip angles of 3°, 6°, 9° and 12°. The other imaging parameters of T1 mapping were set as follows: Repetition time (TR)=3.2 msec, echo time (TE)=1.5 msec, slices number=60, slice thickness=4 mm, matrix=260x160, field of view (FOV)=360x360 mm². Then, DCE-MRI scans were performed by a three-dimensional fast spoiled gradient recalled echo sequence with the following parameters: TR=3.2 msec, TE=1.5 msec, flip angle=12°, FOV=360x360 mm², matrix=260x160, slice thickness=4 mm, slice number=60, bandwidth was 83.33 Hz/pixel. It took 320 sec to complete the DCE-MRI scanning with 40 phases acquired and 8 sec for each phase. Three pre-contrast phases were obtained before bolus injection, then an administration of 0.1 mmol/kg of Gd-DTPA (Omniscan; GE Healthcare Co., Ltd., Shanghai, China) was performed with a venous cannula at a rate of 2 ml/sec followed by a 20 ml saline flush.

Data manipulation. Two abdominal radiologists, each with more than 8-year experience in clinical MRI, evaluated the acquired images and determined the placement of regions of interest (ROIs). Another experienced radiologist with more than 20 years of experience reviewed the images and made the decision in consensus when the former 2 observers had differences in reading images.

All the DCE-MRI images were transmitted to a workstation for quantitative analysis using DCE-MRI software package (Omni Kinetics, Version 2.00; GE Healthcare Co., Ltd.). First, The DCE-MRI images were post processed by Markov random fields (MRF) 3D non rigid registration algorithms to correct for patient motion that occurs between acquired phases of the dynamic data due to respiration and other involuntary movements. Second, the individual arterial input function (AIF) was obtained from a ROI in abdominal aorta. Third, identical ROIs were manually drawn on corresponding pancreatic lesions and tumor-free areas respectively. The distance of the two ROIs was at least 2 cm. ROIs were drawn manually over the entire lesion on multiple slices without reaching the perimeter to avoid partial volume effect, necrosis, cystic area and vessel. Finally, Extended Tofts Linear model (23,24) was used to calculate the quantitative parameters: Ktrans, Kep, ve and vp. The mean of each parameter in the ROIs was used for statistical analysis.

Histopathological analysis and grouping. The resected specimens were sent to the Department of Pathology in our hospital for further analysis. All lesions were divided into 3 groups based on Ki-67 proliferation index and mitotic rate according to 2017 WHO Neuroendocrine Tumor Classification Guideline (4). i) G1 NET group: Mitoses Per 10 high-power field (HPF) was <2 and Ki-67 Index was <3%; ii) G2 NET group: Mitoses Per 10 HPF was 2-20 and/or Ki-67 Index was 3-20%; and iii) G3 NET/NEC group: Mitoses Per 10 HPF was >20 and/or Ki-67 Index was >20%. Meanwhile, tumor-free areas with the same ROI size but staying away from the lesions at least 2 cm were selected as tumor-free group (normal control group).

Statistical analysis. All statistical analyses were carried out using SPSS software Version 19.0 (SPSS, Inc., Chicago, IL, USA).
Comparison of DCE-MRI parameters between pNENs grades. The mean (± SD) values of $K_{\text{trans}}$, $k_{\text{ep}}$, $v_{\text{p}}$ and $v_{\text{e}}$ for tumor-free areas, G1 and G2 NET are presented in Table II. Significant differences were found between tumor-free areas and G1, G2 NET regarding $K_{\text{trans}}$, $k_{\text{ep}}$, $v_{\text{p}}$, and $v_{\text{e}}$. $v_{\text{e}}$ of tumor-free areas were significantly lower than those of G1 and G2 NET. However, the $v_{\text{e}}$ of tumor-free areas was significantly higher than that of G1 and G2 NET. For the above comparisons, $P$-values were all less than 0.001. The $K_{\text{trans}}$ and $k_{\text{ep}}$ of G1 NET were significantly lower than those of G2 ones ($P=0.002$ and $P<0.001$, respectively; Table II and Fig. 2). No significant difference was found between G1 and G2 NET for $v_{\text{p}}$ and $v_{\text{e}}$ ($P=0.822$ and $P=0.419$, respectively). Representative images of two patients with pNENs were showed in Figs. 3 and 4.

Discussion

pNENs are divided into G1, G2, G3 NET and NEC according to the updated 2017 WHO classification of tumor. The
Table I. Clinical and pathological characteristics of patients and lesions.

| Characteristic                  | No. of patients | No. of lesions |
|--------------------------------|-----------------|----------------|
| Sex                            |                 |                |
| Male                           | 11              | 16             |
| Female                         | 14              | 13             |
| Single/multiple                |                 |                |
| Single lesion                  | 22              | 15             |
| Multiple lesion                | 3               | 4              |
| All lesions                    | 30              |                |
| Grading                        |                 |                |
| G1 NET                         | 16              |                |
| G2 NET                         | 13              |                |
| G3 NET                         | 1               |                |
| NEC                            | 0               |                |
| Site                           |                 |                |
| Head of pancreas               | 12              |                |
| Neck of pancreas               | 5               |                |
| Body of pancreas               | 7               |                |
| Tail of pancreas               | 6               |                |
| Clinical behaviour             |                 |                |
| Functional pNENs               | 19              |                |
| Non-functional pNENs           | 11              |                |
| Maximum diameter, cm           |                 |                |
| ≤1                             | 4               |                |
| >1 and ≤2                      | 15              |                |
| >2 and ≤4                      | 8               |                |
| >4                             | 3               |                |
| Heterogeneity                  |                 |                |
| Uniform                        | 12              |                |
| Non-uniform                    | 18              |                |
| Pattern of enhancement         |                 |                |
| Fast-in and fast-out           | 9               |                |
| Fast-in and slow-out           | 15              |                |
| Slow-in and slow-out           | 6               |                |

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; pNENs, pancreatic neuroendocrine neoplasms.

histological grades are related to the biological behavior and the treatment strategy. The preoperative determination of tumor grade is helpful for appropriate treatment planning. Imaging techniques have been tentatively used to grade pNENs, such as dynamic enhanced CT, MRI based on morphology and diffusion-weighted imaging (DWI) (10-12). Kim et al (11) found ill-defined borders (P=0.001) and hypo-SI on venous and delayed-phase (P=0.016) were more common in G2/3 NET than in G1 ones. The apparent diffusion coefficient (ADC) value showed a statistical difference between G1 and G2 NET (1.60±0.41×10⁻³ mm²/s vs. 1.24±0.13×10⁻³, P=0.007). Jang et al (12) classified grade 1 pNENs into benign group and grade 2 or 3 tumors into non-benign group. They found the benign pNENs were more often round or ovoid in shape than non-benign ones. Main pancreatic duct dilatation was demonstrated only in non-benign pNENs (P=0.021). In addition, non-benign pNENs had more frequent hypointensity compared with pancreatic parenchyma than benign ones in the arterial phase (P=0.029). The benign pNENs were significantly smaller than that of the non-benign group (P=0.0019). The ADC values of benign pNENs were higher than that of non-benign ones (P=0.003). Above research were almost retrospective and based on morphology except ADC value. Not surprisingly, above two researchers encountered the same problems as we were in grouping: The number of G3 was too small due to low incidence. So they all set G1 NET as a group, and G2/G3 NET as another group. However, the biological behavior and the treatment strategy are markedly different between G2 and G3 NET, such grouping may not be appropriate. Our original intention was to evaluate the diagnostic efficacy of pharmacokinetic parameters derived from DCE-MRI in prospective evaluation of pNENs grading. Finally, only one G3 NET patient was recruited in the last three years due to the low incidence. So we had to temporarily abandon G3 NET and only analyze the role of pharmacokinetic parameters in distinguishing G1 from G2 ones. As we put in the introduction, there are some differences to the treatment strategies of G1 and G2 pNENs in clinical practice. For example, for the small nonfunctional G1 NET located in pancreatic head, a follow-up can be chosen because of the significant mortality and complications of pancreaticoduodenectomy. However, for G2 NET, which has a higher Ki-67 proliferation index and mitotic rate, the treatment strategy may be aspiring and the follow-up time should be shortened. So it will tailor the optimal treatment for patients with pNENs if G1 and G2 NET could be well classified.

DCE-MRI relies on the use of fast imaging techniques with high temporal resolution and provides quantitative estimation of physiologic parameters related to the microvascular environment in vivo. Recent technical advancements, including parallel imaging and higher magnetic field unit, have enabled us to obtain continuous DCE-MRI images with high temporal resolution of a few sec, which is critical in assessing microvascular circulation. Pharmacokinetic parameters generated from DCE-MRI can help to identify different hemodynamic characteristics and characterize lesions in a quantitative manner. \(K_{trans}\) and \(k_{ep}\) have shown significant differences between G1 and G2 NET in our study. The G2 NET demonstrated a significantly higher \(K_{trans}\) and \(k_{ep}\) than G1 ones. These findings suggest that DCE-MRI has the potential in differentiating G2 NET from G1 ones. The absorption and retention of small molecular contrast agent (Gd-DTPA) on tumor mainly depends on blood flow, vascular permeability and the volume of EES (25). \(K_{trans}\) represents the transfer rate of contrast agents from vessels to EES. \(k_{ep}\) represents reflux rate from EES to vessels. Both are related to capillary permeability, meanwhile \(K_{trans}\) also depends on blood flow and capillary surface area. In this study, higher \(K_{trans}\) and \(k_{ep}\) were found in G2 lesions than in G1 ones. Similar phenomenon is also found in other kind of cancers in previous studies. Koo et al (21) found mean \(K_{trans}\) and \(k_{ep}\) were all higher in breast cancers with a higher histologic grade than lower histologic grade. Joo et al (22) found poorly differentiated gastric cancers showed a higher \(K_{trans}\) and \(k_{ep}\) than moderately
Table II. Comparison of DCE-MRI parameters between different groups.

| Parameter  | Tumor-free | G1 NET     | G2 NET     | P-value<sup>a</sup> | P-value<sup>b</sup> | P-value<sup>c</sup> |
|------------|------------|------------|------------|----------------------|----------------------|----------------------|
| $K_{\text{trans}}$ (ml/min) | 0.062±0.004 | 0.571±0.143 | 0.696±0.155 | <0.001               | <0.001               | 0.002               |
| $k_{ep}$ (ml/min)           | 0.108±0.005 | 1.464±0.193 | 1.726±0.176 | <0.001               | <0.001               | <0.001               |
| $v_e$ (ml/ml)               | 0.604±0.042 | 0.411±0.043 | 0.408±0.045 | <0.001               | <0.001               | 0.822               |
| $v_p$ (ml/ml)               | 0.247±0.041 | 0.439±0.075 | 0.456±0.087 | <0.001               | <0.001               | 0.419               |

<sup>a</sup>Tumor-free vs. G1 NET; <sup>b</sup>Tumor-free vs G2 NET; <sup>c</sup>G1 NET vs. G2 NET. NET, neuroendocrine tumor; $K_{\text{trans}}$, volume transfer constant; $k_{ep}$, contrast transfer rate constant; $v_e$, extravascular extracellular space volume fraction; $v_p$, plasma volume fraction.

Figure 2. Box plots showing significant difference using ANOVA of (A) $K_{\text{trans}}$ and (B) $k_{ep}$ among tumor-free areas, G1 and G2 NET. $K_{\text{trans}}$, volume transfer constant; $k_{ep}$, contrast transfer rate constant; NET, neuroendocrine tumor.

Figure 3. Representative imaging characteristics in a 68-year-old female patient with G1 NET in the tail of pancreas (white arrow). (A; contrast enhanced image) shows a markedly enhanced lesion in the tail of pancreas. (B) is $K_{\text{trans}}$ image ($K_{\text{trans}}=0.599$). (C) is $k_{ep}$ image ($k_{ep}=1.441$). (D) is $v_e$ image ($v_e=0.416$). (E) is $v_p$ image ($v_p=0.463$). NET, neuroendocrine tumor; $K_{\text{trans}}$, volume transfer constant; $k_{ep}$, contrast transfer rate constant; $v_e$, extravascular extracellular space volume fraction; $v_p$, plasma volume fraction.

Figure 4. 54-year-old female patient with G2 NET in the head of pancreas (white arrow). (A; contrast enhanced image) shows two significantly enhanced masses in the head of pancreas. (B) is $K_{\text{trans}}$ image ($K_{\text{trans}}=0.722$, 0.734). (C) is $k_{ep}$ image ($k_{ep}=1.783$, 1.771). (D) is $v_e$ image ($v_e=0.406$, 0.413). (E) is $v_p$ image ($v_p=0.438$, 0.453). NET, neuroendocrine tumor; $K_{\text{trans}}$, volume transfer constant; $k_{ep}$, contrast transfer rate constant; $v_e$, extravascular extracellular space volume fraction; $v_p$, plasma volume fraction.
differentiated cancers. In most cases, the DCE pharmaco-kinetic parameters yield composite information about the perfusion and capillary permeability characteristics (13). The uncontrolled angiogenic process requires that new capillaries be recruited from existing blood vessels, in order to ensure a constant supply of nutrients and oxygen, and to allow for the elimination of metabolic waste (26). The increased immaturity vasculatures contribute to higher perfusion and surface permeability, which result in higher $K_{\text{trans}}$ and $k_{\text{ep}}$.

$v_e$ represents the EES volume fraction, approximately equals to the ratio of $K_{\text{trans}}$ to $k_{\text{ep}}$. Previous studies have shown that $v_e$ increased (22) or decreased (21) with the progression of malignancy. We did not observe higher or lower $v_e$ in G2 lesions than in G1 ones. This may be due to tumor heterogeneity. $v_p$ represents the plasma volume fraction. No statistical difference was found in $v_p$ between G1 and G2 NET which may be explained by the immaturity of neovascularization and leaky tumor microcapillary.

In this study, the optimal AUC was achieved by $k_{\text{ep}}$ (AUC=0.846). A sensitivity (69.23%) and specificity (87.50%) were obtained by adopting a $k_{\text{ep}}$ cut-off value of 1.644. $K_{\text{trans}}$ value of 0.667 offered a moderate sensitivity (76.92%) and specificity (81.25%). When $K_{\text{trans}}$ was over than 0.667 or $k_{\text{ep}}$ exceeded 1.644, the sensitivity of diagnosing G2 pNENs was the lowest (53.85%), but the specificity was the highest (93.75%). When $K_{\text{trans}}$ was over than 0.667 or $k_{\text{ep}}$ exceeded 1.644, the sensitivity of diagnosing G2 pNENs was 92.31%, but the specificity is 75.00%. This result is similar, even better than that of previous studies (10-12). However, most of the previous studies are not only based on morphological indicators except for ADC value but also retrospective analysis. In addition, in order to get good differential diagnostic efficacy, previous studies need to combine multiple indicators to analyze. In our research, high sensitivity (92.31%) and high specificity (93.75%) can be obtained only with appropriate and combined cut-off values of $K_{\text{trans}}$, $k_{\text{ep}}$. Therefore, $K_{\text{trans}}$ and $k_{\text{ep}}$ may be a potential and ideal screening indicator in the preoperative grading of pNENs.

Small number of patients is a limitation of our study, especially the limited number of patients in G3 NET/NEC group deprived the statistical ability of investigating its correlations between neoplasm grading and DCE-MRI results. This study was a prospective study. Although we were eager, only 25 patients were recruited in the last three years due to the low incidence of pNENs. Fortunately, our study demonstrated the feasibility and potential value of DCE-MRI to differentiate G1 and G2 NET. Further large studies are needed to assess the correlation between DCE-MRI parameters and characteristics of lesions. Therefore, studies are worth to be conducted in larger group of patients, which would further confirm the diagnostic ability of dynamic MR and evaluate cut-off levels depending on the characteristics of patients, lesions and imaging techniques. Our study has additional limitations with regard to the methods of quantitation, including inaccuracies inherent to the manual placement of ROIs. Also, the average values in the ROIs may not reflect the heterogeneous nature of tumor tissue. In the future, larger prospective cohort studies with voxel-based analysis will be required given the relative rarity of pNENs. In addition, another potential limitation which actually not only is a problem of our study but almost of all quantitative precision medicine nowadays needs to be mentioned. DCE-MRI parameters such as $K_{\text{trans}}$ and $k_{\text{ep}}$ could have relatively high variations due to the absence of inter-institutional protocol standardization and inter-vendor differences in hardware/software and may hamper the generalizability of results. Thus, one must take care to use the proposed cut-off values directly in their research unless all procedures are the same with ours described in the paper. In the future, multi-center research and standardization of the procedures are required and would no doubt benefit the generalizability of the results.

### Table III. The diagnostic efficacy of DCE-MRI quantitative parameters in differentiating G2 from G1 NET.

| Parameter       | Sensitivity | Specificity | PPV   | NPV   | Accuracy |
|-----------------|-------------|-------------|-------|-------|----------|
| $K_{\text{trans}}$ alone | 0.7692      | 0.8125      | 0.7692 | 0.8125 | 0.7931   |
| $k_{\text{ep}}$ alone | 0.6923      | 0.8750      | 0.8182 | 0.7778 | 0.7931   |
| $K_{\text{trans}}$ or $k_{\text{ep}}$ | 0.9231      | 0.7500      | 0.7500 | 0.9231 | 0.8276   |
| $K_{\text{trans}}$ and $k_{\text{ep}}$ | 0.5385      | 0.9375      | 0.8750 | 0.7143 | 0.7586   |

NET, neuroendocrine tumor; $K_{\text{trans}}$, volume transfer constant; $k_{\text{ep}}$, contrast transfer rate constant; $K_{\text{trans}}>0.667$; $k_{\text{ep}}>1.644$; $K_{\text{trans}}$ or $k_{\text{ep}}$, $K_{\text{trans}}>0.667$ or $k_{\text{ep}}>1.644$; $K_{\text{trans}}$ and $k_{\text{ep}}$, $K_{\text{trans}}>0.667$ and $k_{\text{ep}}>1.644$; PPV, positive predictive value; NPV, negative predictive value.

Figure 5. Receiver operator characteristics (ROC) curves for $K_{\text{trans}}$ and $k_{\text{ep}}$ measurements in this study. The solid line represents the ROC curve of $K_{\text{trans}}$, and the dotted line the ROC curve for $k_{\text{ep}}$. The area under the ROC curves (AUCs) for $K_{\text{trans}}$ and $k_{\text{ep}}$ are 0.767 and 0.864 respectively. $K_{\text{trans}}$, volume transfer constant; $k_{\text{ep}}$, contrast transfer rate constant.
In conclusion, our results have shown the potential value of DCE-MRI in the assessment of pNENs grading. The pharmacokinetic parameters of DCE-MRI, including $K_{trans}$ and $k_{ep}$, could provide complementary information in differentiating G2 NET from G1 ones.

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Availability of data and materials

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

Authors' contributions

YH designed the research, applied for funding and advanced the progress of the research. WZ, ZQ and JR collected, analyzed and interpreted the patient data. WZ and ZQ were major contributors in writing the manuscript. XH, DW and GZ performed the appointments and scanning of the subjects. ZS provided technical support regarding the image post-processing. YH and HY supervised the research group. In addition, HY played a role in the design of the research and the interpretation of the results.

Ethics approval and consent to participate

Ethical approval was obtained for this prospective research and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas 39: 783-796, 2010.

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