Pancreatic neuroendocrine tumors and DWI-MRI: a better tool for detection?

Poster No.: C-1520
Congress: ECR 2013
Type: Scientific Exhibit
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Keywords: Neoplasia, Cancer, Imaging sequences, PET-CT, MR-Diffusion/Perfusion, MR, Pancreas, Abdomen
DOI: 10.1594/ecr2013/C-1520

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Purpose

Pancreatic neuroendocrine tumors (pNETs) are rare pancreatic neoplasms (accounting for 1-2% of all pancreatic tumors; 95% sporadic/5% associated with genetic or inherited disorders) originating from totipotential stem cells (nesidioblasts) or from pancreatic mature endocrine cells (islet cells of Langerhans) [1, 2, 3, 4, 5, 6]. Based on the presence of hormones' secretion, pNETs are usually subclassified into [2, 4, 5, 6]:

- Functioning tumors (those that secrete various hormones causing classical endocrine syndromes): are diagnosed in earlier stages due to the symptoms related to the secreted hormone, for this reason they are often small at diagnosis and may be difficult to detect and localize on imaging studies [2, 3, 4, 6]. However, because surgery remains the only curative treatment in localized functioning ones, accurate preoperative localization is necessary for planning the surgical approach and strategy [6];
- Non functioning tumors: may remain hidden until they reach a significant size to cause a mass effect or to metastasize; since metastatic disease is an indicator of poor prognosis, early diagnosis is essential [2, 3, 4].

Dynamic enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are common non-invasive radiologic techniques used in pNETs evaluation [4, 6] Those tumors often have characteristic imaging features, but sometimes they may be lacking, rendering the tumor invisible, or variable imaging findings may be present [1, 3, 4]. This is particularly true for small hyperfunctioning ones [1, 4, 6]. It seems that magnetic resonance diffusion weighted imaging (DWI) may better depict and characterize small pNETs, due to its greater image contrast and functional informations [1, 4, 5, 6, 7].

The over-expression of somatostatin receptors (sstr) at the cell membrane of pNETs provides the molecular basis for the use of radiolabeled somatostatin analogues, both for imaging and therapy. They are characterized by variable affinity to sstr: in particular, although all tracers bind to sstr2, $^{68}$Ga-DOTANOC also shows a good affinity for sstr3 and sstr5. However, $^{68}$Ga-DOTANOC PET/CT's false positive or false negative results, due to the tracer or to the detection system, may be taken in count [2, 8].

The aim of our study is to evaluate the added value of DWI-MRI in pNETs detection and characterization by (1) comparing MRI, with morphological and DWI sequences, and $^{68}$Ga-DOTANOC PET/CT pNETs detection rates, and by (2) estimating pNETs' apparent diffusion coefficient (ADC). To our Knowledge no previous study compared $^{68}$Ga-DOTANOC-PET/CT to MRI with DWI sequences in the assessment of pNETS.
Methods and Materials

Patients

All consecutive patients with pNET diagnosis referred to our department between January 2011 to May 2012 were considered for inclusion. Inclusion criteria for this study were: 1) MRI examinations included DWI 2) MRI studies and $^{68}$Ga-DOTANOC PET/CT examinations were performed before surgery and within 8 weeks of each other; 2) MRI and $^{68}$Ga-DOTANOC PET/CT images were of satisfactory quality and without significant artifacts.

The reference standard for the diagnosis of pNET was the pathological analysis of the pancreatic tumour (operative specimens, Endoscopic Ultra Sonography (EUS) guided ago-biopsy or fine needle aspiration) or of the liver metastases (EUS guided agobiopsy) combined with imaging (CT/MRI/PET-CT/EUS) depiction of the pancreatic tumor.

The control group for the evaluation of normal pancreas ADC values consisted of 10 patients (3 male, 7 female; mean age 60,9 years; range 46-78 years) without a known history of pancreatic disease, referred to our radiology department for upper abdominal MRI (suspected liver or kidney lesions).

Technique

MRI protocol All MRI examinations were performed on a clinical 1.5 T scanner (Signa Excite 2; GE Medical Systems, Buc, Paris, FR) in combination with an 8-channel phased-array coil (GE Medical Systems). Conventional morphological-MRI protocol consisted of unenhanced axial T1w Fast Spoiled Gradient Echo (FSPGR) sequences in- and out-of-phase, T2w single shot Fast Spin Echo (ssFSE/HASTE) and T1w 3D FSPGR multiphase (20, 50, 120 seconds) after intravenous contrast injection (Gd-BOPTA; MultiHance® 0,5 M - BRACCO; 0,1 ml/kg body weight) sequences. DWI was acquired through the pancreas at 30 slice locations utilizing axial T2*w single-shot Spin-Echo Echoplanar imaging (SE-EPI), with b-values of 100 and 600 s/mm2 and same location of ssFSE. Parallel imaging with an acceleration factor of 2 was utilized for all sequences.

The same imaging protocol was used for both healthy volunteers and the patients.

(Tab. 1)
**Table 1**: Suggested MRI protocol. Parameters were established with a 1.5-T system.

**References**: Dipartimento di Bioimmagini e Scienze Radiologiche, Catholic University of Sacred Heart in Rome, Policlinico Agostino Gemelli - Rome/IT

PET/CT protocol PET/CT was performed on a dedicated hybrid scanner (Gemini Dual or Gemini GXL; Philips Medical Systems, Cleveland, OH). PET emission images were recorded for 3 min per bed position from the skull base to the mid-thigh (eight to ten bed positions). The CT attenuation correction acquisition parameters were 120 kV voltage, 30 mA tube current and 5 mm slice thickness. Images were acquired 60 min after intravenous injection of 111-200 MBq of $^{68}$Ga-DOTANOC, according to body weight (2.5 MBq/kg). Prior to PET/CT acquisition the patients were hydrated with 500 ml of water. $^{68}$Ga-DOTANOC was prepared by our Departement of Nuclear Medicine as described previously [9].

**Image analysis**

*Qualitative analysis*
MRI data were independently reviewed by two radiologists, one senior with more than 10 years' experience of abdominal MRI (experienced radiologist) one junior with 3 years' experience in general radiology (non-experienced radiologist); PET/CT findings were evaluated by one experienced nuclear medicine physician. They were aware that all the cases had confirmed diagnosis of pNET, but they were unaware of any other information (tumors’ number, location, extension, histopathology, function ...).

Imaging data analysis was conducted into separate sessions of images:

1) Conventional morphological-MRI sequences (morphological MRI): unenhanced T1-weighted, T2-weighted and Gd-enhanced T1-weighted images (arterial, portal venous and delayed phase) (Fig. 1);

2) T2-weighted and diffusion-weighted images (DWI-MRI) (Fig. 2);

3) Combined morphological and DWI-MRI sequences;

3) PET/CT (Fig. 3).

At each review session the observers were asked to express about the presence or absence of pancreatic tumors, also describing the number and location of the lesions; in particular was considered an abnormal finding: - on MRI a definite signal anomaly, focal/nodular, well-defined lesion; - on PET/CT any focal accumulation of the tracer outside the normal distribution or higher than the surrounding physiological uptake.

After the sessions the three readers reviewed all the MRI and PET/CT images in consensus in order to record any MRI pNETS detection improvement and to achieve a consensus diagnosis, also with clinical, endoscopic and imaging follow-up informations.
**Fig. 1**: Qualitative analysis, conventional morphological-MRI. pNET in the pancreatic tail. T2-weighted image (a) shows an isointense lesion that appears hypointense on T1-weighted fat sat image (b); after contrast medium administration the lesion shows a peripheral rim enhancement in the arterial phase (c), homogeneous in the portal phase (d).

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**Fig. 2**: Qualitative analysis, DWI-MRI. pNET in the pancreatic tail. The same lesion as above appears isointense on T2-weighted (a) and hyperintense on DWI (b) images.

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Fig. 3: Qualitative analysis, 68Ga-DOTANOC PET/CT. pNET in the pancreatic tail. Nuclear medicine evaluation shows increased metabolic activity of the same lesion as above.

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Quantitative analysis

Quantitative apparent diffusion coefficient (ADC) was calculated using DWI images and fusion images between the ADC parametrics maps and T2-weighted images. A commercially available software and an imaging workstation (Functool 6.3.1e and Advantage Workstation ADW 4.04_06, GE Medical System) were employed.

In one session the radiologist reviewers calculated the ADC of the normal pancreas. Because of the ADC values of the different pancreatic regions may vary, three measurements (pancreatic head, body and tail) were performed in each patient of the control group [10]; the average of these three measurements was accepted as the final ADC value.

In another session the two radiologists in consensus measured the ADC values of both the tumors and the normal adjacent pancreatic parenchima. We considered the displayed
lesions on DWI sequences after consensus reading. A round- or oval-shaped region of interest (ROI) was placed on the solid and homogeneous portion of the proven tumor and was drawn as large as possible avoiding any cystic or necrotic portion. The same size ROI in the normal adjacent pancreas was obtained at the same pancreatic area of the tumor, for the reason described previously [10].

All the ROIs were obtained avoiding the main pancreatic duct, the boundaries of the pancreas (to avoid partial volume inaccuracies) and areas were motion artifacts were present.

(Fig. 4)

Fig. 4: Quantitative analysis. pNET in the pancreatic tail. pNETs' quantitative apparent diffusion coefficient (ADC) was calculated using DWI images (a) and fusion images between the ADC parametrics maps and T2-weighted images (b). ADC value and standard deviation was reported automatically by the software.

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**Statistical analysis**

As first outcome pNETs detection rates (per patient pDR and per lesion IDR) with the respective confidence intervals, for each review session (morphological-MRI, DWI-MRI, combined morphological and DWI-MRI, PET/CT), for each interpreter (non-experienced radiologist, experienced radiologist and nuclear physician) and combined (morphological and DWI-MRI with PET/CT), were determined. In patient-by-patient analysis, the assessment of the readers was assumed as positive when at least one lesion was detected in the pancreas.

As second endpoint pNETs, surrounding parenchyma and normal pancreas ADC mean values (expressed in square millimimeters per second, $\times 10^{-3}$ mm$^2$ /s) and standard deviations were calculated. Student's t-test was used to analyse the differences in mean ADC values between the groups (pNETs VS surrounding parenchima; pNETs VS normal pancreas); a $p$ value of < 0.05 was considered statistically significantly different.
Table 1: Suggested MRI protocol. Parameters were established with a 1.5 - T system.

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Fig. 1: Qualitative analysis, conventional morphological-MRI. pNET in the pancreatic tail. T2-weighted image (a) shows an isointense lesion that appears hypointense on T1-weighted fat sat image (b); after contrast medium administration the lesion shows a peripheral rim enhancement in the arterial phase (c), homogeneous in the portal phase (d).

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Results

Patient and tumours

The final cohort consisted of 14 patients (6 males, 8 females; median age 55.21 years, range 37-72 years). 1 patient had a MEN 1 disease. 3 patients had functioning tumors and all of them were insulinomas. At the time of the examination 5 patients were treatment-naïve, 3 patients were treated with radiometabolic therapy and 6 patients were receiving long acting somatostatine analogues therapy.

For the diagnosis of the number and site of the lesions the reference standard was the pancreatic operative specimen or the consensus diagnosis obtained by EUS, MRI and PET/CT imaging. The number of the lesions was 20 with a mean diameter of 16.5 mm (range 6-90 mm); in particular 12/20 (60 %) lesions were ≤ 1 cm. Tumors' grading obtained on histological analysis (surgical resected or agobiopsy taken specimens) was: 9/20 G1 (ki 67 < 2%) and 4/20 G2 (ki 67 3-20 %) [11]. For the unique agobiopsy specimen obtained from liver metastasis we assumed that it had the same differentiation of the primitive pNET. Tumors' differentiation resulting from cytological analysis (fine needle aspiration) in 7/20 lesions was compatible with well-differentiated pNET.

Image analysis

Qualitative analysis

MRI  In non-experienced-radiologist evaluation conventional morphological-MRI had a better DR than DWI-MRI (pDR 71% [95%CI 42-92%] VS 57% [95%CI 29-82%], IDR 70% [95%CI 46-88%] VS 60% [95%CI 36-81%]). Combining morphological and DWI-MRI, pDR and IDR were 71% [95%CI 42-92%] and 70% [95%CI46-88%] respectively.

In experienced-radiologist evaluation morphological-MRI had the same DR than DWI-MRI (pDR 86% [95%CI 57-98%], IDR 85% [95%CI 62-97%]). Combining morphological and DWI-MRI, pDR and IDR were 100% [95%CI 77-100%] and 95% [95%CI 75-100%] respectively.

False negative results in experienced radiologist evaluation were: - on both morphological and DWI sequences in one patient, because in close proximity with the stomach (air artifacts); - only on morphological but assessable on DWI sequences in one patient because of the small size (8 mm) and the atypical contrast enhancement pattern of the lesion; - only on DWI but assessable on morphological sequences in one patient because of the small size of the lesion (8 mm) and its close proximity to the duodenum (peristaltic motion artifacts) [5, 12]. However after combining the morphological and functional sequences the detection rate improved because of they detected different lesions.
PET/TC $^{68}$Ga-DOTANOC-PET/CT had a pDR of 86% [95%CI 42-92%] and an IDR of 75% [95%CI 51-91%]. False negative results were due to: - the presence of diffuse pancreatitis in the surrounding parenchima for two lesions; - the close proximity to the adrenal physiological uptake for one lesion; - the proximity of two small lesions visible as one in one case; - the long acting somatostatine analogues therapy for one lesion [2, 8].

CONSENSUS READING. After consensus reading all the 20 lesions were identified. MRI (morphological and DWI) detection rate improved, both in pDR and in IDR (14/14 patients and 20/20 lesions, pDR 100% [95%CI 77-100%] and IDR 100% [95%CI 51-91%]). However, as referred above, one tumor could not be identified on DWI sequences because of its small size (8 mm) and its close proximity to the duodenum.

(Tab. 2)

<table>
<thead>
<tr>
<th></th>
<th>pDR</th>
<th>95%CI</th>
<th>IDR per lesion</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-MRI non-experienced</td>
<td>71 % (10/14)</td>
<td>0,419-0,916</td>
<td>70 % (14/20)</td>
<td>0,457-0,881</td>
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<tr>
<td>DWI-MRI non-experienced</td>
<td>57 % (8/14)</td>
<td>0,289-0,823</td>
<td>60 % (12/20)</td>
<td>0,361-0,809</td>
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<td>M + DWI-MRI non-experienced</td>
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<td>M-MRI experienced</td>
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<td>M + DWI-MRI experienced</td>
<td>100 % (14/14)</td>
<td>0,768-1,0</td>
<td>95 % (19/20)</td>
<td>0,751-0,999</td>
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<tr>
<td>68Ga-PET/CT</td>
<td>86 % (12/14)</td>
<td>0,419-0,916</td>
<td>75 % (15/20)</td>
<td>0,509-0,913</td>
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<tr>
<td>Consensus (MRI + PET/CT)</td>
<td>100 % (14/14)</td>
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Table 2: Qualitative analysis results. Per patient and per lesion detection rates (pDR, IDR) of conventional morphological-MRI (M-MRI), DWI-MRI, combined morphological and DWI-MRI (M + DWI-MRI), and 68Ga-DOTANOC PET/CT in radiologist (non experienced and experienced) and nuclear physician evaluation. Also consensus reading results (M-MRI, DWI-MRI and PET/CT) are reported.
Quantitative analysis

Only one lesion was not detected on DWI imaging after consensus reading. One lesion had high ADC because of fibrotic structure due to multiple therapies (ADC value $3.18 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.42$), so was excluded from the calculation of pNETs' ADC mean value.

pNETs' ADC mean value was significantly lower ($p<0.005$) compared with those of surrounding and normal parenchyma. Mean and standard deviations of the ADC values $[x 10^{-3}\text{ mm}^2/\text{s}]$ were: pNETs 1, 65 ± 0, 31, surrounding parenchyma 2, 39 ± 0, 26 and normal volunteers' parenchyma 2, 16 ± 0, 37.

*(Tab. 3)*

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<th>Control group</th>
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<td>Mean ADC ($x10^{-3}\text{ mm}^2/\text{s}$) ± SD</td>
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*Student $t$-test $p < 0.05$*

**Table 3:** Quantitative analysis results. pNETs' ADC mean value and standard deviation compared to those of surrounding and control group pancreatic parenchima.

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Conclusion

In our work, a patient-by-patient and patient-by lesion analysis for detecting pNETs showed comparable diagnostic performances for conventional morphological-MRI and DWI-MRI. An improvement in the rate of lesion detection was also demonstrated when the analysis included both the two methods, because of their detection accuracy relies on different factors. This result is consistent with the literature: Bakir et al. [4] found in 18 patients similar lesions depiction for routine MRI sequences (comprised contrast enhanced T1 weighted images) and DWI sequences, Brenner et al. [1] found in 18 patients that fused high b-value diffusion-weighted and T2-weighted MR images improve detection of pNET relative to either technique alone (without the use of contrast enhanced sequences). Conventional MRI has become more widely used in the diagnosis of pancreatic neoplasm because of its exceptional soft-tissue contrast resolution, multiparametric imaging and lack of ionizing radiation [3]. In particular MRI has a high sensitivity for pNETs detection and should be recommended as the first imaging modality in patients with suspected pNET allowing the investigation of the pancreas as well as the assessment of the disease extension into the liver [1, 5]. The tumors often have characteristic imaging features (as arterial enhancement and hyperintensity on T2-weighted MR), but sometimes these classic imaging findings may be lacking or may be variable and however the use of contrast medium is crucial [1, 3, 4]. This is particularly true for small hyperfunctioning PNETs, especially small insulinomas [1, 4, 6]. DWI sequences will be particulary useful in those patients with clinical suspicion for pancreatic pNETs and with negative or suspicious conventional imaging findings or in those patient with contraindications to the use of contrast medium (allergies, renal failure ...).

Detection rate depends on reader experience too, as demonstrated by different results among our two radiology reviewers: non experienced radiologist pNETs detection rate is poor compared to that of experienced radiologist, in particular DWI resulted as more difficult to be evaluated compared to morphological imaging both in pDR and in IDR evaluation, with a small improvement after combing the two methods. This is similar to the literature [5]. Although abdominal MRI has recently become more widely used, there are still large differences in the number of abdominal MRI examinations performed between specialized hospitals, such as academic medical centers, and general hospitals and this is particulary true in the use of relatively newest sequences such as DWI.

In experienced radiologist evaluation morphological and DWI-MRI showed the same pDR of $^{68}$Ga-DOTANOC PET/CT, and a little higher IDR. Moreover, the combination of the two methods showed higher pDR and LDR in comparison to that of $^{68}$Ga-DOTANOC PET/CT. The high $^{68}$Ga-DOTANOC PET/CT sensitivity in pNETs evaluation is supported by previous studies [2, 8]. $^{68}$Ga-DOTANOC PET/CT major advantages are : - better visualization of small tumors due to the higher affinity of $^{68}$Ga-somatostatin analogues for...
sstr2, sstr3 and sstr5, as well as the higher spatial resolution; - improvement in treatment planning, because of the "panoramic" exame type; - prediction of treatment outcomes, due to the radiotracer’s high specificity for intermediate to well-differentiated pNETs which tend to express somatostatin-receptors [2, 8]. Nevertheless, possible causes of false positive and false negative results of this imaging method should be kept in mind. False negative results could be related to small lesions or pNETs with a low expression of sstr (for example undifferentiated pNETs). On the other hand, false positive results could be related to other diseases (like inflammatory diseases because activated inflammatory cells may overexpress sstr) or areas of physiological tracer uptake (like pancreatic uncinate process, adrenl gland …) [2, 8]. Another limitation is that $^{68}$Ga-DOTANOC PET/CT is limited to specialised centres as part of clinical trials [2, 8]. Morphological and DWI images will be advantageous where DOTANOC is not available and in those patients with clinical suspicion for pancreatic pNET with negative or doubtful PET/CT imaging findings.

Consensus reading between combined MRI and PET allowed a final detection rate of 100% in our series.

After consensus reading between PET/CT and MRI, quantitative assessment of ADC was performed in 19/20 lesions, because of one lesion visible at PET and morphologic MRI remained mute at DWI, probably because of artifacts derived by its localization close to the duodenum [12]. ADC measurement was aimed to lesion characterization, as an attempt to find different ADC values between lesion and normal pancreatic tissue. In 18/19 lesions, ADC was significantly lower than adjacent parenchyma and normal pancreas (p<0.05 at Student’s t-test). This result is supported by others report target pNETs qualitative and quantitative evaluation [1, 4, 5]. 1/19 case with higher ADC value consisted of a lesion previously treated by radio-metabolic therapy.

Functional DWI-MRI improves MRI pNETs detection rate, particularly for experienced radiologist evaluation. It can be an effective alternative tool to contrast enhanced MRI and $^{68}$Ga-DOTANOC-PET/CT, as it showed similar pNETs detection rate, resulting useful in doubtful imaging findings or when conventional techniques may be not performed. Moreover the combined use of radiological and nuclear imaging methods allows to reach the correct diagnosis in almost all cases.
References


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