Aus der Klinik für Nuklearmedizin
(Direktor Univ.-Prof. Dr. med. Felix M. Mottaghy)

Clinical value of ^{68}Ga -DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the
detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET)

Von der Medizinischen Fakultät
der Rheinisch-Westfälischen Technischen Hochschule Aachen
zur Erlangung des akademischen Grades eines Doktors der Medizin genehmigte Dissertation

vorgelegt von

Dirk Robert Albanus

aus Köln

Berichter: Herr Privatdozent Dr. med. Dr. phil. Alexander Heinzel
Frau Privatdozentin Dr. med. Uta Kunter

Tag der mündlichen Prüfung: 18.05.2017

Diese Dissertation ist auf den Internetseiten der Hochschulbibliothek online verfügbar.

D82 (Diss. RWTH Aachen University, 2017)
European Journal of Radiology

Clinical value of ^{68}Ga -DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET)

D.R. Albanus^{a,1}, J. Apitzsch^{a,b,1}, Z. Erdem^{a,c}, O. Erdem^{a,c}, F.A. Verburg^a, F.F. Behrendt^a, F.M. Mottaghy^a, A. Heinzel^{a,d,*}

^a Department of Nuclear Medicine, University Hospital RWTH Aachen, Pauwelsstraße 30, 52074 Aachen, Germany

^b Department of Diagnostic and Interventional Radiology, University of Gießen and Marburg, Baldingerstraße, 35043 Marburg, Germany

^c Department of Radiology, Medical Faculty of Bulent Ecevit University, Practice and Research Hospital of Bulent Ecevit University; 67600, Kozlu, Esenköy, Zonguldak, Turkey

^d Institute of Neuroscience and Medicine (INM4), Research Centre Jülich, Germany

ARTICLE INFO

Article history:

Received 3 June 2015

Accepted 22 June 2015

Keywords:

^{68}Ga -DOTA-TATE

PET/CT

Neuroendocrine tumour

Extra-hepatic metastasis

ABSTRACT

Purpose: To compare and outline the beneficial skills of combined ^{68}Ga -DOTATATE positron emission tomography (PET) with concurrent contrast enhanced X-ray computed tomography (ceCT) against stand-alone ceCT in 54 patients with neuroendocrine tumours (NET).

Methods: Patients with histologically confirmed NET and available follow-up of at least 6 months (median 12.6 months; range 6.1–23.2) were included. PET/CT and ceCT images were initially analyzed separately by two blinded nuclear medicine physicians and two radiologists, respectively. In a second step all four physicians reviewed all detected lesions together reaching a consensus-grading for PET/ceCT. The results were then compared to the reference standard consisting of clinical follow-up data.

Results: With regard to true positive lesions, PET/ceCT vs. stand alone ceCT detected 139 vs. 48 bone-lesions, 106 vs. 71 lymph node metastases and 26 vs. 26 pulmonary lesions. On a per-patient basis, PET/ceCT achieved a higher sensitivity (100% vs. 47%) and specificity (89% vs. 49%) for bone lesions than ceCT. For lymph nodes the effect was similar (sensitivity 92% vs. 64% and specificity 83% vs. 59%). For the detection of pulmonary lesions the sensitivity was identical (100%) while specificity of PET/ceCT was superior to ceCT-alone (95% vs. 82%).

Conclusion: In summary, the use of ^{68}Ga -DOTATATE PET/ceCT leads to an increase in sensitivity and specificity in the detection of extra-hepatic NET metastases compared to stand-alone ceCT. Therefore, ^{68}Ga -DOTATATE PET/ceCT should be the imaging modality of choice in patients with NET.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Accurate staging of neuroendocrine tumours (NETs) is of immense importance since the 5-year survival is directly related to

Abbreviations: NET, Neuroendocrine tumour; PET, Positron Emission Tomography; CT, Computed Tomography; CE, Contrast enhanced; Ga, Gallium; PRRT, Peptide Receptor Radionuclide Therapy; SUVmax, Maximum standardized uptake value; DOTA, 1,4,7,10-Tetraazacyclododecan-1,4,7,10-tetra acetic acid; DOTA-TATE, DOTA-Tyr3-Thre8-octreotide; DOTA-TOC, DOTA-Phe1-Tyr3-octreotide; DOTA-NOC, DOTA-Naphthyl3-octreotide; ROI, Region of interest; MBq, Megabecquerel; mCi, Millicurie.

* Corresponding author at: University Hospital Aachen, Department of Nuclear Medicine, Pauwelsstrasse 30, 52074 Aachen, Germany. Fax: +49 241 8082520.

E-mail address: ahinzel@ukaachen.de (A. Heinzel).

¹ Both authors contributed equally to the manuscript.

<http://dx.doi.org/10.1016/j.ejrad.2015.06.024>

0720-048X/© 2015 Elsevier Ireland Ltd. All rights reserved.

the appearance of metastasis. Depending on the localization, survival decreases from 96.1% in patients without metastasis to 77% in patients with nodal, 73.3% in patients with liver and 50.1% in patients with extra-hepatic distant (e.g., bone or lung) metastasis [1]. Especially bone metastasis is associated with a poorer 5-year survival rate [2]. Since up to 75% of NET-patients present with liver involvement at the time of diagnosis, the correct detection of the extra-hepatic extent of disease is of high clinical significance. Extra-hepatic distant metastatic extent excludes resection or other interventional procedures [3,4] thus resulting in significant changes of the patient's management [5,6]. ^{68}Ga -PET/CT provides both, an accurate staging and the assessment of the feasibility of peptide receptor radionuclide therapy (PRRT) in inoperable cases [7,8].

To estimate the clinical quality, studies have begun to investigate how PET/CT with ^{68}Ga -labeled somatostatin analogues, such

as DOTANOC or DOTATOC, may be helpful in the assessment of the presence of metastatic disease [9–11]. However, the additional value of especially DOTATATE-PET/CT over conventional dedicated contrast enhanced CT (ceCT) has not yet been established precisely. Although Ambrosini et al. and Putzer et al. showed an increased diagnostic accuracy with regard to the detection of bone metastases [12,13], both groups only applied PET combined with low-dose non-contrast enhanced CT or dedicated PET (without simultaneous CT). So far, only Ruf et al. performed a combined analysis however, only abdominal lesions were analyzed and lesion counts for extra-hepatic metastases were rather diminutive [14].

Thus, to date, there is no direct comparison between ceCT and PET/CT covering the whole body with regard to bone metastases, lymph node metastases and lung metastases for staging of NETs. Consequently, in many countries including Germany only ceCT but not PET/CT is reimbursed by the public health insurances for this indication.

Therefore, the aim of the present study was to compare the diagnostic value of ^{68}Ga -DOTATATE PET/ceCT to dedicated ceCT in the whole-body staging of NETs with regard to metastases to bones, lymph nodes and lungs.

2. Materials and methods

2.1. Patients

This study was approved by the local medical ethical committee. Due to the retrospective design the need for signed patient informed consent was waived. 132 patients who underwent ^{68}Ga -DOTATATE PET/ceCT scan between September, 2011 and March, 2013 were screened with regard to the following inclusion criteria:

- histologically confirmed NET
- available follow-up-period of at least 6 months
- ceCT as part of the examination.

54 patients matching these criteria (26 men, 28 women; median age 64 years, range 38–86 years) were included in our study.

Detailed information concerning the included patients is given in Table 1 and in a more detailed form in Online Resource Table 1.

2.2. Tracer production

The tracer ^{68}Ga -DOTATATE was produced in-house with an automated synthesis as described by Meyer et al. [15]. Briefly, 30 μL of 1 mg/mL DOTATATE stock solution (ABX, 01454 Radeberg, Germany) in metal free H_2O were used for standard labelling procedure. ^{68}Ga was eluted from an $\text{ItG } ^{68}\text{Ge}/^{68}\text{Ga}$ -generator (Isotope Technologies Garching, Garching, Germany).

2.3. PET/CT Protocol

Patients were given a median activity of 143 MBq, Range: 92–185 MBq (corresponds 3864 mCi, Range: 2486–5 mCi) intravenously. PET/ceCT scanning was performed starting 40 min after injection.

PET/ceCT was performed with a Philips Gemini TF 16 PET/CT scanner (Philips Medical Systems, Best, The Netherlands) with transverse and axial field of views (FOVs) of 57.6 and 18 cm, respectively.

PET/ceCT scanning was performed in cranio-caudal orientation with raised arms to decrease beam-hardening artefacts. First a low dose whole body CT from the base of the skull to the upper thigh was performed without contrast medium for attenuation correction purposes (effective tube current-time product: 30 mAs; tube

Table 1
Patients characteristics.

Sex	
Female	28/54
Male	26/54
Age	
Median	64 years
Range	38–86 years
Primary site of tumour	
Pancreas	9/54
Gastroenteric sites other than pancreas	27/54
- Duodenum	- 1/27
- Jejunum	- 2/27
- Ileum	- 14/27
- Ileocecal valve	- 2/27
- Caecum	- 3/27
- Colon	- 1/27
- Rectum	- 4/27
Lung	4/54
Neobladder	1/54
Endometrium	1/54
Paraganglioma	1/54
Cancer of unknown primacy (CUP)	11/54
- ^a Lung	- 1/11
- ^a Cervix	- 1/11
- ^a Duodenum	- 1/11
- ^a Ileum	- 1/11
- ^a Thyroid	- 1/11
- Stayed unknown	- 6/11
Indication for PET/ceCT	
Staging	27/54
- After operation	- 13/27
- Affirmation of tumour	- 7/27
- Unknown primary tumour detection	- 7/27
Re-Staging	14/54
- Increase of tumourmarker	- 6/14
- Radio-peptide-therapy	- 5/14
- Re-Operation	- 2/14
- Chemotherapy	- 1/14
Follow up	11/54
Consideration of radio-peptide-therapy	2/54

^a Later detected as primary of the respective organ.

voltage: 120 kVp). Afterwards a ceCT was acquired in the venous phase from the base of the skull to the upper thigh during deep inspiration (200 mAs; 120 kVp). For image reconstruction we used a medium-smooth soft-tissue kernel window centre 60, window width 450, at a slice thickness of 5 mm with an overlapping increment of 3.5 mm. Contrast medium (Ultravist 300, Bayer Healthcare, Berlin, Germany) was administered intravenously into an antecubital vein via a 20-gauge catheter using a power injector. Injection of contrast media was followed by a saline chaser (30 ml of 0.9% sodium chloride solution) administered at the same flow rate as the contrast medium. The venous CT was initiated 70s after the start of the contrast medium injection using a Roi in the Aorta descendens.

Following the CT, a PET was performed. Data were collected in list mode for all coincident events along with their time stamps over multiple time points with an acquisition time of 1.5 min (<100 kg body-weight) or 2 min (≥ 100 kg body-weight) per bed-position. Slices of 4 mm thickness (pixel size = $4 \times 4 \text{ mm}^2$) were reconstructed using the iterative proprietary BLOB-OS-TF algorithm (number of iterations = 3, number of subsets = 33) provided by the manufacturer. Datasets were fully corrected for random coincidences, scatter radiation and attenuation.

2.4. Image analysis

A PET-positive lesion was defined as any area with an intensity higher than background intensity that could not be identified as physiological uptake (liver, spleen, pituitary gland, adrenal glands,

Table 2

Five-point-grading system: bones, lymph nodes and lungs were judged by principles of rating adapted according to Nakamoto et al. [6].

Grading	Meaning	Definition
Lesions in bones and lymph nodes		
4	Definitely malignant	Intense focal uptake that was obviously in the defined structure and considered to definitely represent a metastasis to this structure, with or without a morphological change seen in CT
3	Probably malignant	Intermediate focal uptake seen in PET without a morphological change or distinct morphological changes in CT
2	Equivocal	No focal uptake seen in PET, but morphological changes seen in CT which were indeterminate for metastasis
1	Probably benign	No focal uptake seen in PET, but morphological changes seen in CT, being of benign origin in all likelihood
0	Definitely benign	no abnormal findings indicating metastasis
Lesions in lungs		
4	Definitely malignant	intense focal uptake that corresponds to morphological change in CT
3	Probably malignant	Multiple (minimum 3) morphological lesions seen in CT, without focal uptake in PET
2	Equivocal	Single morphological lesions seen in CT, without focal uptake in PET
1	Probably benign	unspecific morphological changes in CT
0	Definitely benign	no abnormal findings indicating metastasis

pancreatic head, thyroid, urinary tract) and that had a SUVmax >2.7 for bones, >2.2 for lymph nodes and >2.3 for pulmonary lesions. These values represent the upper limit of the physiological uptake in these regions (Bone marrow 0.4–2.7; Lymph nodes: 0.5–2.2; Lungs 0.6–2.3) and were therefore adopted as cut-off values [16].

The review process consisted of two steps. In the first step, PET and ceCT images were analyzed separately by two nuclear medicine specialists and two radiologists, respectively, in consensus reading.

In the second step all four reviewers performed a consensus reading of images in order to achieve consensus on each detected lesion, using a five-point-grading system as adapted from Nakamoto et al. (Table 2). The results of this grading were then transferred into positive lesions (grade 3 or 4) and negative lesions (grade 2 or less) [6]. This was considered to represent the result of

Table 3

Five-point-grading results of consensus-decision at PET/ceCT.

Bones				
Grade	No. of lesions	Percentage	Positive vs. Negative	Percentage
0	1	0.5	54	27.1
1	35	17.6		
2	18	9.0		
3	66	33.2		
4	79	39.7		
Lymph nodes				
0	1	0.5	71	38.2
1	19	10.2		
2	51	27.5		
3	37	19.9		
4	78	41.9		
Lung				
0	1	2.4	11	26.2
1	1	2.4		
2	9	21.4		
3	29	69.0		
4	2	4.8		

combined PET/ceCT. All reviewers were blinded to patients' identities and histories.

The results from the ceCT and the PET/ceCT were then compared to the reference standard which consisted of clinical and follow-up data (median 12.6 month, range 6.1–23.2 months), in order to classify a lesion as true-positive, false-positive, true-negative or false-negative. Follow-up consisted among others of the repeat PET/CT imaging, magnetic resonance imaging (MRI), repeat CT as well as measurement of the tumour marker Chromogranin A together with clinical follow-up.

2.5. Change in clinical management

To evaluate the change in clinical management, patients' medical history was analysed according to the guidelines of Ramage et al. [5]. We then analyzed how the additional information provided by PET/ceCT had influenced the patients' management.

2.6. Statistics

Statistical analyses were performed using Medcalc version 12.7.5.0 (MedCalc Software bvba, Ostend, Belgium). Sensitivity and specificity values were calculated and compared on a per-patient-basis using decision matrices and matched sample tables [17]. For aligned measurements the McNemar test and for non-aligned measurements Fisher's exact test was employed.

Table 4

Sites of verified lesions detected by PET/ceCT and stand-alone ceCT.

	PET/ceCT		ceCT	
	Amount of true positive lesions	True-positive on a per-patient basis	Amount of true positive lesions	True-positive on a per-patient basis
Bones total	139	17/17	48	8/17
- Trunk	56 ^a	14/14	20	5/14
- Vertebrae	54 ^a	15/15	23	6/15
- Long bones	29 ^a	8/8	5	4/8
Lymph nodes total	106	23/25	71	16/25
- Head/Neck	6	3/3	2	2/3
- Mediastinal	13	6/6	9	4/6
- Abdominal	87	22/24	60	13/24
Lung total	26	10/10	26	10/10

^a Multiple or uncountable lesions were classified as 10 lesions (in 2 patients).

Fig. 1. ^{68}Ga -DOTA-TATE PET/CT shows the presence of three true-positive bone lesions not visible in CT (patient 27 – part A1-3 and B1-3) and a true-positive lymph node (para-aortal) appearing not suspicious in CT (patient 49 – part C1-3).

3. Results

Patient characteristics are summarized in Table 1. The 5-point-grading results of consensus-decision at PET/ceCT are given in Table 3. Overall 145 bone-lesions, 115 nodal lesions and 31 pulmonary lesions were graded 3 or 4 and therefore were deemed to be probably or definitely malignant.

3.1. Image analysis

3.1.1. Bones

Detailed results for bone-subregions are given in Table 4. In summary, PET/ceCT detected 139 true positive bone-lesions in contrast to 48 true positive bone-lesions by ceCT (Table 3). On a per-patient basis these lesions are distributed among 17 patients, who were identified as positive in follow-up, leaving no false-negative patients in PET/ceCT. Among these, stand-alone ceCT deemed 8 patients to be true-positive and left 9 patients falsely negative; an example of which is presented in Fig. 1 (A1-3, B1-3). Considering the 37 patients who were deemed negative for bone metastases based on follow up, PET/ceCT was false positive in 4 cases, while ceCT was false positive in 19 cases.

3.1.2. Lymph nodes

Detailed results for lymph-node-subregions are given in Table 4. PET/ceCT detected 106 true-positive lymph node metastasis whereas ceCT detected 71. These metastases were found by PET/ceCT in 23 patients, who all were identified positive in follow-up, leaving 2 patients false negative. ceCT found at least one true positive lesion in 16 patients while 9 patients were left false negative (Fig. 1, C1-3). Out of 29 true lymph node negative patients, PET/ceCT showed at least one positive lymph node in 5 patients, whereas ceCT was positive in 12 cases.

3.1.3. Lungs

PET/ceCT and ceCT both detected at least one metastasis in 10 patients that were proven positive during follow-up. Both techniques missed no lesions. PET/ceCT and ceCT-alone each detected all of the 26 lung metastases.

Out of 44 patients who were negative for lung metastases during follow-up, PET/ceCT was falsely positive in 2 whereas CT showed false positive lesions in 8 patients.

3.2. Second look

22 lymph node metastases in three patients could be verified through a positive second look on the PET-images, after these lesions were identified in the ceCT scan. Furthermore, 30 lesions (7 bone-lesions in 7 patients; 22 lymph node lesions in 14 patients, 1 lung-lesion in 1 patient) were only identified in a second-look on the ceCT scans following identification in the corresponding PET/CT images (Example in Fig. 2, second look on CT: A1-3; second look on PET: B1-3).

3.3. Sensitivity, specificity, PPV and NPV

These results show a higher sensitivity (100% vs. 47%; $p=0.0039$) and specificity (89% vs. 49%; $p=0.0004$) for ^{68}Ga -DOTATATE PET/ceCT than for ceCT-alone in the detection of bone lesions. For lymph nodes the effect was comparable (sensitivity 92% vs. 64%; $p=0.0156$ and specificity 83% vs. 59%; $p=0.0386$). In the detection of pulmonary lesions, sensitivity was 100% for both methods while specificity of PET/ceCT was superior to ceCT-alone (95% vs. 82%; $p=0.0313$).

The positive predictive value (PPV) and negative predictive value (NPV) of PET/ceCT concerning the different body-regions were higher than for dedicated ceCT as well, with the exception

Fig. 2. Part A – A bone-lesion can be recognized on CT image via a second look (A3) after ^{68}Ga -DOTA-TATE PET (A2) showed an intense focal uptake to that structure (A2) (patient 1).

Part B – CT revealed suspicious lymph nodes in the abdomen (B1), which can be judged positive via a second-look to PET image (B2), SUVmax 4.31 (patient 5)

of the NPV for pulmonary metastases: PPV PET/cCT 81% vs. 30% ceCT (bones), 82% vs. 57% (lymph nodes), 83% vs. 56% (lung); NPV PET/cCT 100% vs. 67% ceCT (bones), 92% vs. 65% (lymph nodes), 100% each (lung).

3.4. Changes in clinical management

The detection of at least one lesion in one of the investigated regions resulted in a change of clinical management. In 7/9 patients who suffered from additional bone metastases, PRRT was deemed feasible. In one case the patient was deemed amenable to chemotherapy and in one further patient treatment with a non-radioactive somatostatin analogue was initiated.

Of the seven patients who showed at least one lymph node metastasis in PET/cCT, but were deemed negative in dedicated ceCT, two patients underwent PRRT. Two patients underwent reoperation with resection of lymph node metastases in an attempt at achieving a cure. In three patients the disease was upstaged by the PET/cCT without further direct clinical consequences.

4. Discussion

The present study shows that the use of ^{68}Ga -DOTATATE PET/cCT significantly improves the whole-body staging of patients suffering from NETs. We demonstrated that it leads to an increase in sensitivity and specificity in the detection of bone metastases, lymph nodes metastases and with reservations lung metastases. Moreover, compared to stand-alone ceCT it allows very reliable exclusion of suspected metastases.

With regard to bone metastases Putzer et al. found similar values with a sensitivity of 97% and a specificity of 92% for ^{68}Ga -DOTA-TOC PET/CT in comparison to CT and bone scintigraphy [13]. Ambrosini compared ^{68}Ga -DOTA-NOC PET/CT to CT alone and achieved a sensitivity and specificity of 100% for PET/CT [12].

Our results with regard to lymph node metastases are also in line with previous studies. Haug et al. could confirm all lymph node lesions found by ^{68}Ga -DOTA-TATE PET/CT [18]. Wild et al. detected 39 of 43 lymph node lesions by ^{68}Ga -DOTA-TATE PET/CT [19] and Srirajaskanthan et al. found 63 of 99 lymph node lesions detected by MRI and CT [20]. In the study of Ruf et al., being the only one applying three-phase contrast-agent CT, a sensitivity of 67.2% and

Fig. 3. False-positive tracer-uptake of ^{68}Ga -DOTA-TATE in PET (A2) (SUVmax: 23.85, SUVmean: 9.85) correlating to a mass seen in CT (A1) due to an inflammatory process build around fibers placed in the abdomen (Patient 20).

specificity of 100% was achieved for ^{68}Ga -DOTA-TOC PET/CT compared to a sensitivity of 55.2% and specificity of 85.7% for venous CT detecting lymph node metastases [14]. Using all three contrast-agent phases together, the sensitivity of CT could be raised to 56.9% while specificity stayed the same at 85.7% for lymph nodes.

Compared to the data of the lungs by Srirajaskanthan et al., who found 9 lung lesions out of 16 by ^{68}Ga -DOTA-TATE PET/CT, our results show a higher sensitivity for PET/ceCT (sensitivity 100%). This may be attributable to the preselected group of patients in their survey, which only included patients with negative or only weakly positive findings on DTPA-octreotide-scintigraphy. Beyond that the CT-part was enhanced in the arterial phase, resulting in a potentially altered tumouruptake and detectability [20].

Our data demonstrate a high negative predictive value for ^{68}Ga -DOTA-TATE PET/CT for all evaluated body-regions (100% bones, 92% lymph nodes and 100% lung), thus allowing to exclude the suspicion of metastasis very reliably. However, false-positive results may occur since tracer accumulation represents expression of somatostatin receptors rather than malignancies per se [21]. Among our patients, we would like to present case number 20, who was false-positive for lymph node metastasis. As you can see in Fig. 3, in PET/ceCT an intensive tracer accumulation (SUVmax: 23.85, SUVmean: 9.85) was detectable in the lower abdomen, which was in accordance with a mass seen in ceCT. Histopathology after surgical resection revealed an inflammatory process due to fibers placed in the abdomen during a former operation of the bowel. Since SST-receptors are expressed on macrophages and lymphocytes, false-positive tracer-uptake is at least not excludable [22,23].

A major difficulty of CT is the differentiation between benign and malignant lesions once abnormal structures are identified. It was one aim of our study to outline the clinical benefit of PET in addition to stand-alone ceCT. One of the approaches we employed to achieve this was to investigate the information given by the consensus-discussion. The “second look” to the other imaging modality revealed important additional information in 25 patients (3 times second look on PET; 22 times second look on ceCT). In most cases ceCT was important to provide detailed anatomic information, assisting in delineation of abnormal PET-findings, thus illustrating the complementary nature of the two imaging modalities.

Some limitations have to be noted: The study design was retrospective and for ethical and practical reasons, it was not possible to obtain histological confirmation for every detected lesion. Hence, for most of the lesions the reference standard consists of follow-up information. Therefore false-positive results may have been left unnoticed, since tracer accumulation represents expression of somatostatin receptors rather than malignancies per se [21]. Moreover, our ceCT results may be considered at the lower edge of the range compared with the literature [5]. A possible reason may be a selection bias, since patients receiving a successful stand-alone CT for their detection or staging of NET may not have been referred to our department to receive an additional PET/CT. In addition, we did not include the arterial phase for the CTs in our analysis as in most patients this phase was not acquired. Therefore the sensitivity especially with regard to detection of lymph node metastases may be negatively affected.

5. Conclusion

In summary, the use of ^{68}Ga -DOTATATE PET/ceCT is associated with an increased diagnostic accuracy in the detection of extra-hepatic NET metastases compared to stand-alone ceCT. Especially for bone and lymph nodes sensitivity and specificity could be increased significantly, resulting in an upstaging of disease and/or change in clinical management in >25% of patients.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejrad.2015.06.024>

References

- [1] F. Panzuto, S. Nasoni, M. Falconi, Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization, *Endocr. Relat. Cancer* 12 (2005) 1083–1092, <http://dx.doi.org/10.1677/erc.1.01017>
- [2] S. Gupta, M.M. Johnson, R. Murthy, K. Ahrar, M.J. Wallace, D.C. Madoff, et al., Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors, *Cancer* 104 (2005) 1590–1602, <http://dx.doi.org/10.1002/cncr.21389>
- [3] T. Steinmüller, R. Kianmanesh, M. Falconi, A. Scarpa, B. Taal, D.J. Kwekkeboom, et al., Consensus Guidelines for the Management of Patients with Liver Metastases from Digestive (Neuro) endocrine Tumors: Foregut, Midgut, Hindgut, and Unknown Primary, *Neuroendocrinology* 87 (2008) 47–62, <http://dx.doi.org/10.1159/000111037>
- [4] C.J. Auernhammer, K.W. Jauch, J.N. Hoffmann, Lebermetastasierung bei neuroendokrinen Karzinomen des gastro-entéro-pankreatischen systems – Therapiestrategien, *Zentralbl Chir* 134 (2009) 410–417, <http://dx.doi.org/10.1055/s-0029-1224607>
- [5] J.K. Ramage, A. Ahmed, J. Ardill, N. Bax, D.J. Breen, M.E. Caplin, et al., Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs), *Gut* 61 (2011) 6–32, <http://dx.doi.org/10.1136/gutjnl-2011-300831>
- [6] Y. Nakamoto, C. Cohade, M. Tatsumi, D. Hammoud, R.L. Wahl, Appearance of Bone Metastases Detected with FDG PET as Part of the Same PET/CT Examination, *Radiology* 237 (2005) 627–634, <http://dx.doi.org/10.1148/radiol.2372031994>
- [7] V. Cuccurullo, A. Faggiano, M. Scialpi, G.L. Cascini, A. Piunno, O. Catalano, et al., Questions and answers: what can be said by diagnostic imaging in neuroendocrine tumors? *Minerva Endocrinol.* 37 (2012) 367–377.
- [8] D. Kwekkeboom, J. Mueller-Brand, G. Paganelli, L. Anthony, S. Pauwels, L. Kvols, et al., Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs, *J. Nucl. Med.* 46 (2005) 62S–66S.
- [9] V. Ambrosini, D. Campana, L. Bodei, C. Nanni, P. Castellucci, V. Allegri, et al., 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors, *J. Nucl. Med.* 51 (2010) 669–673, <http://dx.doi.org/10.2967/jnumed.109.071712>
- [10] M. Gabriel, C. Decristoforo, D. Kendler, G. Dobrozemsky, D. Heute, C. Uprimny, et al., 68Ga-DOTA-Tyr3-Octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT, *J. Nucl. Med.* 48 (2007) 508–518, <http://dx.doi.org/10.2967/jnumed.106.035667>
- [11] T.D. Poeppel, I. Binse, S. Petersenn, H. Lahner, M. Schott, G. Antoch, et al., 68Ga-DOTATOC Versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors, *J. Nucl. Med.* 52 (2011) 1864–1870, <http://dx.doi.org/10.2967/jnumed.111.091165>
- [12] V. Ambrosini, C. Nanni, M. Zompatori, D. Campana, P. Tomassetti, P. Castellucci, et al., 68Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours, *Eur. J. Nucl. Med. Mol. Imaging* 37 (2010) 722–727, <http://dx.doi.org/10.1007/s00259-009-1349-9>
- [13] D. Putzer, M. Gabriel, B. Henninger, D. Kendler, C. Uprimny, G. Dobrozemsky, et al., Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-Octreotide PET in comparison to CT and bone scintigraphy, *J. Nucl. Med.* 50 (2009) 1214–1221, <http://dx.doi.org/10.2967/jnumed.108.060236>
- [14] J. Ruf, J. Schiefer, C. Furth, O. Kosiek, S. Kropf, F. Heuck, et al., 68Ga-DOTATOC PET/CT of neuroendocrine tumors: spotlight on the CT phases of a triple-phase protocol, *J. Nucl. Med.* 52 (2011) 697–704, <http://dx.doi.org/10.2967/jnumed.110.083741>
- [15] G. Meyer, H. Maecke, J. Schuhmacher, W. Knapp, M. Hofmann, 68Ga-labelled DOTA-derivatised peptide ligands, *Eur. J. Nucl. Med. Mol. Imaging* 31 (2004) 1097–1104, <http://dx.doi.org/10.1007/s00259-004-1486-0>
- [16] M. Shastri, I. Kayani, D. Wild, M. Caplin, D. Visvikis, S. Gacinovic, et al., Distribution pattern of 68Ga-DOTATATE in disease-free patients, *Nucl. Med. Commun.* 31 (2010) 1025–1032, <http://dx.doi.org/10.1097/MNM.0b013e32833f635e>
- [17] N. Hawass, Comparing the sensitivities and specificities of two diagnostic procedures performed on the same group of patients, *Br. J. Radiol.* (1997) 360–366.
- [18] A. Haug, C.J. Auernhammer, B. Wängler, R. Tiling, G. Schmidt, B. Göke, et al., Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours, *Eur. J. Nucl. Med. Mol. Imaging* 36 (2009) 765–770, <http://dx.doi.org/10.1007/s00259-008-1030-8>
- [19] D. Wild, J.B. Bomanji, P. Benkert, H. Maecke, P.J. Ell, J.C. Reubi, M.E. Caplin, Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors, *J. Nucl. Med.* 54 (2013) 364–372.
- [20] R. Srirajaskanthan, I. Kayani, A.M. Quigley, J. Soh, M.E. Caplin, J. Bomanji, The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy, *J. Nucl. Med.* 51 (2010) 875–882, <http://dx.doi.org/10.2967/jnumed.109.066134>
- [21] I. Virgolini, V. Ambrosini, J.B. Bomanji, R.P. Baum, S. Fanti, M. Gabriel, et al., Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE, *Eur. J. Nucl. Med. Mol. Imaging* 37 (2010) 2004–2010, <http://dx.doi.org/10.1007/s00259-010-1512-3>
- [22] D. Pasquali, A. Notaro, G. Bonavolonta, P. Vassallo, A. Bellastella, A. Sinisi, Somatostatin receptor genes are expressed in lymphocytes from retroorbital tissues in Graves' disease, *J. Clin. Endocrinol. Metab.* 87 (2002) 5125–5129, <http://dx.doi.org/10.1210/jc.2002-020790>
- [23] C. Armani, E. Catalani, A. Balbarini, P. Bagnoli, D. Cervia, Expression, pharmacology, and functional role of somatostatin receptor subtypes 1 and 2 in human macrophages, *J. Leukocyte Biol.* 81 (2006) 845–855, <http://dx.doi.org/10.1189/jlb.0606417>

Danksagungen

Meinem Doktorvater PD Dr. med. Dr. phil Alexander Heinzl für die sehr gute Betreuung.

Dem Institut für medizinische Statistik für die Beratung.

Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

in der **Klinik für Nuklearmedizin** des Universitätsklinikums Aachen

hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Dirk Robert Albanus**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation:

Albanus DR, Apitzsch J, Erdem Z, Erdem O, Verburg FA, Behrendt FF, Mottaghy FM, Heinzel A: Clinical value of ⁶⁸Ga-DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET); European Journal of Radiology; geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

D.R. Albanus:	Datenerhebung und Auswertung (60%), statistische Auswertung (80%), Studiendesign (30%), Erstellung des Manuskriptes
J. Apitzsch:	Datenerhebung und Auswertung (20%), Studiendesign (25%), kritische Begutachtung des Manuskriptes (35%) 1. Ansprechpartner bei allen Fragen zusammen mit A. Heinzel
Z. Erdem:	Datenerhebung und Auswertung (5%), kritische Begutachtung des Manuskriptes (5%)
O. Erdem:	Datenerhebung und Auswertung (5%), kritische Begutachtung des Manuskriptes (5%)
F.A. Verburg:	Statistische Auswertung (10%), kritische Begutachtung des Manuskriptes (5%)
F.F. Behrendt:	Statistische Auswertung (10%), kritische Begutachtung des Manuskriptes (5%)
F.M. Mottaghy:	Studiendesign 5%, kritische Begutachtung des Manuskriptes (5%)
A. Heinzel:	Studiendesign (40%), Datenerhebung und Auswertung (10%), kritische Begutachtung des Manuskriptes (40%)

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautor.

Unterschrift des Doktoranden

Als Doktorvater und korrespondierender Autor bestätige ich die Angaben von Dirk Robert Albanus und in Vertretung für die Kooperationspartner [Z. Erdem und O. Erdem]

Unterschrift des Doktorvaters

Ich schließe mich der Erklärung von PD Dr. med. Dr. phil A. Heinzel als Koautor an

Namen und Unterschriften aller deutschsprachigen Koautoren