First Experience on Chemokine Receptor CXCR4 Targeted Positron Emission Tomography (PET) Imaging in Patients with Solid Cancers

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ABSTRACT

Objective: CXCR4 is a chemokine receptor that is overexpressed in various human cancers and is involved in tumor metastasis. The aim of this proof of concept study was to evaluate a novel CXCR4 targeted Positron Emission Tomography (PET) probe in patients suffering from solid cancers with reported in vitro evidence of CXCR4 overexpression and to estimate its potential diagnostic value.

Material and Methods: 21 patients with histologically proven pancreatic cancer, laryngeal cancer, non-small cell lung cancer (NSCLC), prostate cancer, melanoma, breast cancer, hepatocellular carcinoma (HCC), glioblastoma, sarcoma or cancer of unknown primary (CUP) underwent PET imaging using the novel CXCR4 nuclear probe $^{68}$Ga-Pentixafor. Maximum standardized uptake values (SUVmax) of the liver, spleen and bone marrow were measured for determination of physiological tracer distribution. For evaluation of tracer accumulation in solid cancers, SUVmax and tumor-to-background ratios (T/B ratio) were determined in a total of 43 malignant lesions including 8 primary tumors, 3 local recurrent tumors and 32 metastases. When available, SUVmax of malignant lesions was compared to corresponding SUVmax measured in standard routine $^{18}$F-FDG PET.

Results: Moderate tracer accumulation was detectable in the liver, bone marrow and spleen with a mean SUVmax of 3.1, 3.7 and 5.6, respectively. By visual interpretation criteria, 9 of 11 primary and local recurrent tumors were detectable, exhibiting a mean SUVmax of 4.7 (range 2.1 to 10.9) and a mean T/B ratio of 2.9. 20 of 32 evaluated metastases were visually detectable (mean SUVmax of 4.5, range 3.2 to 13.8; mean T/B ratio of 2.8). Highest signal was detected in a patient suffering from NSCLC (SUVmax 10.9; T/B ratio 8.4) and a patient with CUP syndrome (SUmax 13.8; T/B ratio 8.1) respectively. Compared to $^{18}$F-FDG PET additionally obtained in 10 patients, tracer accumulation in $^{68}$Ga-Pentixafor PET revealed a lower SUVmax in all measured malignant lesions.
Conclusion: Based on these first observations in a small and heterogeneous patient cohort, the *in vitro* CXCR4 expression profile of solid cancers and metastases described in previous literature does not seem to sufficiently depict the *in vivo* distribution revealed by CXCR4-tageted PET. Moreover, the detectability of solid cancers investigated by means of $^{68}$Ga-Pentixafor seem to be in general lower compared with $^{18}$F-FDG PET.
INTRODUCTION

CXCR4 is a 7-transmembrane G-coupled receptor belonging to the chemokine receptor family and is expressed by a variety of cells during development and thereafter (1). With its cognate ligand stromal cell-derived factor 1α (SDF-1α) (2,3) its main role in the hematopoetic system is to control stem cell retention and the homing of hematopoetic cells to the bone marrow (4). In addition to these physiological roles, CXCR4 has been found to be overexpressed by various human cancers including breast, lung, colon, and pancreatic cancer, melanoma and hematopoietic malignancies including multiple myeloma (1,5–10). Furthermore, a growing body of evidence shows that the CXCR4-SDF-1α axis plays a crucial role in the mechanism of cancer and metastasis. High levels of SDF-1α in organs and tissues, such as lymph nodes, lung, liver and bone/bone marrow (BM) are thought to direct the metastasis of CXCR4-expressing tumor cells (11,12). Concordantly, the level of CXCR4 expression was shown to be higher in metastatic sites as compared to the primary tumors (13), and changes in CXCR4 signaling have been shown to significantly alter metastatic burden in animal models (14). Accordingly, CXCR4 overexpression has been identified as an adverse prognostic factor in malignancies including non-small cell lung cancer (NSCLC) and breast cancer (6,15). Due to its critical role in cancer, CXCR4 has been designated as a potential therapeutic target and a number of CXCR4 inhibitors have been developed with some of them reaching clinical trials (2,16).

These observations highlight and support, that non-invasive imaging of CXCR4 could become a highly interesting new diagnostic or prognostic imaging biomarker through the in vivo quantification of CXCR4 expression levels in tumors and the identification of aggressive subpopulations, e.g. after chemotherapy. In addition, CXCR4 imaging may serve as a tool for monitoring novel CXCR4-targeted treatment options, e.g. pharmacological or endoradiotherapeutic interventions.
However, despite the fundamental role of CXCR4 in cancer pathogenesis and metastasis, no clinically suitable method for CXCR4 assessment and in vivo quantification has been approved so far. To meet the clinical need for a highly specific and sensitive tool for CXCR4 assessment and quantification in vivo, $^{68}$Ga-Pentixafor (formerly known as $^{68}$Ga-CPCR4.2), a CXCR4 targeted high affinity nuclear probe has recently been developed and evaluated in small cell lung cancer (SCLC) models for Positron Emission Tomography (PET) by Wester et al. (17,18). Proof-of-concept investigations in lymphoma xenografted animal models and in first patients with hematological malignancies confirmed high tracer accumulation in tumors with low background uptake and concomitant fast tracer clearance from non-target tissues (18,19). In addition, whole body dosimetry studies in man revealed excellent pharmacokinetics and thus very low radiation burden to patients (20). Subsequent investigations in mice xenografted with human CXCR4-positive multiple myeloma (MM) cell lines and patients with advanced MM by means of PET provided high contrast images with higher detection rates of MM manifestations compared to standard $^{18}$F FDG PET/CT scans (21).

Based on these highly encouraging data we present our first results on $^{68}$Ga-Pentixafor PET in patients suffering from solid cancers. We selected malignancies with previously reported in vitro evidence of CXCR4 overexpression in order to evaluate if this imaging modality might be of diagnostic value in CXCR4 expressing cancers. Specifically we intended to correlate tracer accumulation with reported in vitro expression pattern.

Signal intensities in physiological and tumor tissue were assessed by means of SUVmax measurements. When available, signal intensities were compared with $^{18}$F-FDG PET.

MATERIAL AND METHODS
Patients

Between 2013 and 2014, 21 patients (mean age 63, range 55-85) with histologically proven solid cancers underwent either \( ^{68}\text{Ga-Pentixafor PET/CT} \) or \( ^{68}\text{Ga-Pentixafor PET/MR} \). Detailed patient characteristics including cancer type and therapeutic status are given in Table 1. 10 patients additionally received a diagnostic \( ^{18}\text{F-FDG PET/CT} \) for staging purposes within 2 weeks after \( ^{68}\text{Ga-Pentixafor imaging} \). No therapy was performed between the two imaging modalities.

The synthesis and administration of \( ^{68}\text{Ga-Pentixafor} \) was performed under the condition of the pharmaceutical law (The German Medicinal Products Act, AMG §13 2b) according to the German law and have been approved by the local responsible regulatory authority (Regierung von Oberbayern). Prior to the investigation written informed consent was obtained from all patients. The data analysis was approved by the local responsible ethics committees.

Synthesis of \( ^{68}\text{Ga-Pentixafor} \)

Synthesis of \( ^{68}\text{Ga-Pentixafor} \) was performed on a fully automated, GMP-compliant procedure using GRP module (Scintomics GmbH, Germany) equipped with disposable single use cassette kits following the previously described method (17,19). Prior to injection, tracer quality was assessed according to the standards of the European Pharmacopoeia available at www.edqm.eu. The radiochemical purity of the ready-to-inject formulation was always >99% as confirmed by radio-HPLC and TLC, the specific activity was in the range of 30-65 GBq/µmol.

PET Imaging Protocol
15 of 21 $^{68}$Ga-Pentixafor and all $^{18}$F-FDG PET scans were performed on a Sensation 64 Biograph PET/CT scanner (Siemens, Erlangen, Germany), whereas 6 of 21 $^{68}$Ga-Pentixafor scans were performed on a PET/MRI device (Siemens Biograph mMR, Siemens Medical Solutions, Germany). The CT-scan protocol included a low-dose CT (26mAS, 120kV, 5mm slice thickness) from the base of the skull to the mid thigh for attenuation correction followed by the PET-scan and a diagnostic CT (240mAS, 120kV, 5mm slice thickness) in the portal venous phase in case of $^{18}$F-FDG PET/CT scans. Injected activities for $^{68}$Ga-Pentixafor ranged from 147 to 275 Mbq and for $^{18}$F-FDG from 198 to 359 MBq. PET acquisition was performed after a mean of 62 minutes post injection for $^{68}$Ga-Pentixafor and 75 minutes post injection for $^{18}$F-FDG PET/CT respectively. All PET/CT scans were acquired in 3D mode with an acquisition time of 3min per bed position. Images were reconstructed by an attenuation-weighted ordered-subsets expectation maximisation algorithm (four iterations, eight subsets) followed by a post-reconstruction smoothing Gaussian filter (5 mm full-width at half-maximum). In PET/MR, acquisition was performed after a mean of 72 minutes post injection for $^{68}$Ga-Pentixafor. A coronal 2-point Dixon 3D volumetric interpolated examination (VIBE) T1w sequence was performed for generation of attenuation maps as recently published (22). In addition, diagnostic dedicated sequences dependent on the examined malignancy were performed. PET data was acquired simultaneously in three dimensional mode with 3min emission time per bed position.

**Image Analysis**

All $^{68}$Ga-Pentixafor PET/CT or PET/MR images were reviewed and interpreted by board certified Nuclear Medicine physicians and by radiologists in a binary fashion. Lesions were defined as visually detectable, if both reviewers were able to visually identify the lesions on the PET-images. Semiquantitative SUV analysis with determination of SUVmax involved drawing region of interests (ROI) around the primary tumor in case of preoperative Imaging and around
the metastases, when detectable. If patients presented with more than five metastases, up to
five of those lesions with the highest visual uptake were chosen for analysis. Lesions that were
either histological verified or were unambiguously malignant due to their morphological
characteristics and dynamic behavior in follow-ups were considered. Lesions below 10mm in
diameter were omitted in order to reduce partial volume effects. Analysis of $^{18}$F-FDG PET/CT in
patients, who underwent both imaging modalities, was performed analogous to $^{68}$Ga-Pentixafor
PET/CT. SUVmax of $^{18}$F-FDG and to $^{68}$Ga-Pentixafor PET images were compared and
correlated with each other. Referring to Drzezga et al. we did not differ between PET/MR and
PET/CT follow ups assuming comparable semiquantitative values (22).

Statistics

Statistical analysis was performed using MedCalc Version 10.2 (Mariakerke, Belgium).
To test for significance between variables in the patients subgroups, we used Mann-Whitney U
test. Spearman rank test was performed for correlation between SUVmax of $^{68}$Ga-Pentixafor
PET and SUVmax of $^{18}$F-FDG PET and $^{68}$Ga-Pentixafor PET.

RESULTS

Patient characteristics

21 patients with histological proven solid malignancies including pancreatic cancer,
laryngeal cancer, NSCLC, prostate cancer, melanoma, breast cancer, HCC, glioblastoma, CUP
syndrome (Table 1) were examined. 9 patients did not receive any therapy prior to imaging and
a primary tumor was present in 8 cases. One patient suffered CUP syndrome and imaging was
unable to identify the primary tumor. 12 patients already received therapy (chemotherapy,
radiotherapy or surgery) with a local recurrence of the primary tumor observed in three cases. 13 of 21 patients had evidence of metastases with three of them demonstrating more than five metastases.

**Physiological tracer accumulation**

A moderate accumulation of $^{68}$Ga-Pentixafor occurred in the liver and in BM with a mean SUVmax of 3.1 (range 1.5 - 4.1) and 3.7 (range 1.52 - 6.2) respectively. The spleen demonstrated highest mean $^{68}$Ga-Pentixafor positivity with a SUVmax of 5.6 (Fig. 1) and ranging from SUVmax 2.5 to 10.5. None of the organ SUVmax showed any significant correlation between treated and non-treated patients.

**$^{68}$Ga-Pentixafor accumulation in solid tumors**

43 malignant lesions were evaluated in 21 patients (8 primary tumors, 3 local recurrent tumors and 32 metastases; Table 1). By visual interpretative criteria, 9 of 11 primary and local recurrent tumors were detectable, exhibiting a mean SUVmax of 4.7 (range 2.1 to 10.9) and a mean T/B ratio of 2.9 (range 0.2 to 8.4). Highest SUVmax of 10.9 was measured in a patient with NSCLC. 20 of 32 evaluated metastases were visually detectable (mean SUVmax of 4.5; range 3.2 to 13.8; mean T/B ratio of 2.8, range 1.3 to 8.1). Highest SUVmax of 13.8 was measured in cervical metastases of a patient suffering from CUP syndrome. Spearman’s correlation revealed a low correlation between SUVmax and number of lesions per patient ($r=0.3$).

**Comparison of $^{68}$Ga-Pentixafor PET with $^{18}$F-FDG PET**
\(^{18}\)F-FDG PET performed within two weeks after \(^{68}\)Ga-Pentixafor PET was available in 10 patients with a total of 27 lesions evaluated (2 primary tumors and 25 metastases) (Table 2). All 27 lesions were visually detectable on \(^{18}\)F-FDG PET, whereas only 19 of 27 lesions were detectable using \(^{68}\)Ga-Pentixafor PET imaging. Semiquantitative analysis of tracer uptake in \(^{18}\)F-FDG PET revealed significantly higher SUVmax and T/B ratios in all measured lesions compared to \(^{68}\)Ga-Pentixafor PET (Fig.2 and 3). Accordingly mean SUVmax of all lesions measured on \(^{18}\)F-FDG PET images was significantly higher compared to \(^{68}\)Ga-Pentixafor PET (SUVmax of 13.8 vs. 5.0, P>0.001). Details of per patient analysis are given in Table 2. Spearman´s correlation test revealed low correlation between SUVmax of \(^{18}\)F-FDG PET and \(^{68}\)Ga-Pentixafor PET (r=0.3; P=0.99).

**DISCUSSION**

CXCR4 is a key chemokine receptor involved in many processes during tumorigenesis and critical for cancer dissemination (1,5-10). In this study we performed CXCR4-targeted PET imaging of cancers with reported *in vitro* evidence of CXCR4 overexpression for estimating it`s diagnostic potential in solid CXCR4-expressing cancers (Table 1). Wang et al. for example demonstrated significant CXCR4 overexpression in pancreatic cancer cells compared to normal tissue (23). In chondrosacromas (24), high staining intensities for CXCR4 were observed by immunohistochemistry with most pronounced expression profile in high grade sarcomas. Similarly, aggressiveness of glioblastoma seems to correlate with CXCR4 expression pattern (25). High accumulation of CXCR4 was also reported in breast carcinomas especially in tumors with high metastatic potential (5,6). In melanoma and NSCLC, the detection of high CXCR4 expression even has led to the preclinical development of antagonists with promising results (26,27).
Interestingly, despite reported *in vitro* evidence of CXCR4 overexpression in aforementioned solid cancers, $^{68}$Ga-Pentixafor positivity varied significantly between different tumor entities with a high signal exceeding SUVmax of 10 observed only in two cases (one patient suffering from NSCLC with a T/B ratio of 8.4 and a patient with cervical metastases suffering from CUP syndrome with a T/B ratio of 8.1). All other solid malignancies including pancreatic carcinoma, laryngeal carcinoma, HCC, melanoma, breast cancer, glioblastoma and sarcoma demonstrated low to moderate $^{68}$Ga-Pentixafor positivity. A visually detectable $^{68}$Ga-Pentixafor accumulation was found only in 29 of 43 cancer lesions including primary tumors and metastases.

Different reasons might account for the discordance between reported high CXCR4 expression profile described in previous literature and our current findings. For example, the level of CXCR4 expression assessed by either transcript or whole cell protein level analysis is not necessarily representative for the CXCR4 expression level on the cell surface (10,28). Shim et al for example demonstrated that CXCR4 expression in lymph node metastases of breast cancer patients predominantly occurs in the cytoplasm (28). Since $^{68}$Ga-Pentixafor PET binds to membrane associated chemokine receptors, a significant discordance between CXCR4 expression profiles determined by aforementioned methods and *in vivo* CXCR4 quantification using PET probes might occur. Further relevant factors in this setting might involve the overexpression of CXCR4 on cancer stem cells (CSC), which are believed to represent a drug-resistant cell population even surviving chemotherapy (29–32). Interestingly, the amount of CSC seems to be different depending on the molecular subtype of the tumor (33) and is believed to correlate with tumor aggressiveness and metastatic potential.

In order to estimate the diagnostic potential of $^{68}$Ga-Pentixafor PET imaging compared to $^{18}$F-FDG PET, 10 of 21 patients suffering from solid malignancies underwent both modalities. We found that all 27 evaluated malignant lesions within this subpopulation were visually
detectable on $^{18}$F-FDG PET compared to 19 of 27 detectable lesions on $^{68}$Ga-Pentixafor PET. Moreover, SUVmax measured on $^{18}$F-FDG PET was higher in all lesions compared to $^{68}$Ga-Pentixafor PET (SUVmax of 13.8 vs. 5.0, $P<0.001$). Our results indicate that the detectability of solid cancers investigated by means of $^{68}$Ga-Pentixafor might be in general lower when compared with $^{18}$F-FDG PET. According to these preliminary findings, CXCR4 targeted PET imaging consequently doesn’t seem to be suitable as a standard oncological tool as is $^{18}$F-FDG PET. However, it’s potential might be found in certain specialized applications that have to be elucidated in further studies. Several other receptor binding PET imaging probes are already being used in clinical routine that are tailored to certain specific tumor types and characteristics. Apart from the often used somatostatine receptor ligands DOTATATE, DOTATOC, DOTANOC, or HA-DOTATATE for imaging on neuroendocrine tumors with low proliferation rates, Prostate Specific Membrane Antigene (PSMA)-ligands that bind with high affinity to PSMA have proved to significantly enhance the specificity of prostate cancer imaging (34). Similarly, imaging of CXCR4 might be valuable only in certain subtypes of solid tumors. The benefit of CXCR4 PET imaging was recently demonstrated by Philipp-Abbrederis et al. in a subset of multiple myeloma patients, yielding superior specificity and contrast compared to $^{18}$F-FDG PET (21).

Future efforts should focus on characterization of further cancer types, where CXCR4 imaging might demonstrate a diagnostic benefit. Besides the potential to perform high specificity imaging in certain cancer types, CXCR4 expression profile would be highly interesting, when considering $^{68}$Ga-Pentixafor as a selection marker for CXCR4 directed treatment. $^{177}$Lu or $^{90}$Y-coupled Pentixafor analogues could become attractive radiopharmaceuticals for a theranostic approach with $^{68}$Ga-Pentixafor PET as a marker for patient selection.

The only moderate $^{68}$Ga-Pentixafor positivity of the liver and the bone marrow demonstrated in this study might indicate a favorable side effect profile. The significance of the high variance in splenal tracer uptake however has to be further elucidated.
One of the major limitations of this current ‘design’ is the heterogeneity of the patient cohort investigated and the low number of patients per tumor entity. We included patients with different types of malignancies in various stages of disease. Further limitation includes the lack of immunohistochemical crossvalidation. However, we intended to provide a cross section of different cancer entities that have been described in literature as cancer types with considerable CXCR4 expression. General imaging characteristics of $^{68}$Ga-Pentixafor, such as specificity of binding, low unspecific binding and low background has already been demonstrated in first patient studies with this tracer (21). Consequently, this study can only serve as a first impression on the suitability of $^{68}$Ga-Pentixafor PET-imaging for patients suffering from solid tumor listed in Table 1. Such an approach is plausible, considering that experience with this new target and tracer is extremely limited and the area of application still needs to be found. Based on the observed findings, patients with NSCLC for example might be worthy of being further examined using CXCR4 targeted tracers. Moreover, CUP metastases exhibited highest tracer uptake of all examined lesions, also suggesting a potential diagnostic benefit in this syndrome, i.e. in the detection of the primary cancer. Prospective clinical studies on dedicated tumor entities will include the correlation with biopsied tumor samples and are currently initiated.

In summary, our data demonstrates the feasibility of $^{68}$Ga-Pentixafor for PET imaging of solid malignancies. The cancers examined seem to exhibit a heterogeneous $^{68}$Ga-Pentixafor accumulation and demonstrate lower tracer uptake compared to $^{18}$F-FDG PET.

Moreover, the in vitro CXCR4 expression profile of solid cancers and metastases described in previous literature does not seem to sufficiently depict the in vivo distribution revealed by CXCR4-tageted PET due to factors discussed above, making it necessary to put further efforts into this area of research. However, once the areas of Pentixafor imaging are more clearly defined, PET imaging of CXCR4 might prove as a valuable modality, either as a
stand alone diagnostic tool, or in combination with $^{18}$F-FDG PET and i.e. when considering $^{68}$Ga-Pentixafor for monitoring CXCR4 directed pharmacological or endoradiotherapeutic treatment.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

Hans-Jürgen Wester is CEO of Scintomics, Distributor of Pentixafor. The remaining authors declare, that they have no conflict of interest.
REFERENCES


Figure 1:

Maximum intensity projection (MIP) of a patient following tumor excision demonstrating physiological distribution of $^{68}$Ga-Pentixafor PET tracer. Highest physiological uptake is observed in the urinary tract due to renal excretion and in the spleen. The tracer accumulation at the right elbow reflects injection site.
Figure 2:

50y old patient with histologically proven invasive ductal carcinoma of the right breast. The tumor demonstrates intensive tracer-uptake on $^{18}$F-FDG PET/CT (upper row, A: transversal PET image; B: coronal PET image; C: fusion image). In comparison, tracer uptake on $^{68}$Ga-Pentixafor is significantly lower (lower row D: transversal PET image; E: coronal PET image; F: fusion image)
Figure 3:

50y old patient with Invasive ductal carcinoma of the right breast and diagnosis of a bone metastasis (white arrows). The metastasis demonstrates intensive focal tracer uptake on $^{18}$F-FDG PET (upper row, A: transversal PET image; B: coronal PET image; C: fusion image). In comparison, tracer uptake on $^{68}$Ga-Pentixafor PET is visually not detectable (lower row D: transversal PET image; E: coronal PET image; F: fusion image).
Table 1:

Analyzed patients with solid malignancies showing type of malignancy, therapeutic status (pre-therapeutic: no previous therapy of any kind), SUVmax, tumor to background (T/B) ratio and visual detectability of primary tumors (PT) when present. Further information provided is the quantity, mean SUVmax, T/B ratio and visual detectability of metastases (MTS) per patient. Of note, a maximum of 5 metastases was recorded, if patients presented with more than 5 metastases. * indicates local recurrence of primary tumors after therapy.

<table>
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<th>Modality</th>
<th>SUVmax PT</th>
<th>T/B ratio PT</th>
<th>VD PT</th>
<th>No. MTS</th>
<th>SUVmax MTS</th>
<th>T/B ratio MTS</th>
<th>VD MTS</th>
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<td>PET/CT</td>
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Mean or quantity: 9/21 15/21 4.7 2.9 9/11 32 4.5 2.8 20/32

Abbreviations: pre-ther.: pre-therapeutic; SUVmax: max. standardized uptake value; PT: primary tumor; T/B ratio: tumor-background ratio; VD: visual detectability; MTS: metastases; HCC: hepatocellular carcinoma, NSCLC: non small cell lung cancer;
Table 2:

Mean SUVmax of solid malignant lesions quantified on $^{68}$Ga-Pentixafor PET images compared to $^{18}$F-FDG PET available in 10 patients. An overall of 27 lesions was evaluated (2 primary tumors and 25 metastases). Of these, all were visually detectable (VD) on $^{18}$F-FDG PET, whereas only 19 of 27 lesions were detectable on $^{68}$Ga-Pentixafor PET Imaging. Moreover mean SUVmax and mean tumor-to-background ratio (T/B ratio) measured on $^{18}$F-FDG PET were higher in all cases compared to $^{68}$Ga-Pentixafor PET. (*) indicates lesions, were a primary tumor was present.

<table>
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<tr>
<th>Type of Malignancy</th>
<th>No. of MTS</th>
<th>$^{68}$Ga-Pentixafor PET</th>
<th>$^{18}$F-FDG PET</th>
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</tbody>
</table>

Abbreviations: SUVmax: max. standardized uptake value; T/B ratio: tumor-background ratio; VD: visual detectability; MTS: metastases; NSCLC: non small cell lung cancer; CUP: cancer of unknown primary