Investigating the Chemokine Receptor 4 as Potential Theranostic Target in Adrenocortical Cancer Patients

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Purpose: Adrenocortical carcinoma (ACC) is a rare but aggressive endocrine tumor with limited treatment options. Preclinical studies confirmed overexpression of the chemokine receptor 4 (CXCR4) in this cancer type. This study aimed to analyze the role of CXCR4 imaging using ^{68}Ga-pentixafor for ACC staging and selection of patients for CXCR4-directed endoradiotherapy.

Methods: Thirty patients with histologically proven advanced, metastasized ACC underwent ^{18}F-FDG PET/CT and ^{68}Ga-pentixafor PET/CT within a time interval of 3 ± 4 days to evaluate suitability for CXCR4-directed endoradiotherapy. Scans were analyzed retrospectively for visual extent of ACC and $SUV_{max/mean}$ of the tumor lesions. ^{68}Ga-pentixafor PET was compared with ^{18}F-FDG PET, the reference imaging standard. All patients were rated for suitability of CXCR4-directed endoradiotherapy considering patient's history, previous treatment, and CXCR4 expression of FDG-positive lesions compared with background activity within the same organ.

Results: All patients had lesions that were positive for both ^{18}F-FDG and ^{68}Ga-pentixafor PET and were rated as positive for disease. In 2 patients (7%), ^{68}Ga-pentixafor PET identified more lesions compared with ^{18}F-FDG PET. In 5 patients (17%) and 10 patients (33%), complementary and comparable information, respectively, was provided by dual-tracer imaging. In 13 patients (43%), more tumor lesions were identified by ^{18}F-FDG PET compared with ^{68}Ga-pentixafor PET. The ^{18}F-FDG uptake of the malignant lesions was significantly higher ($P < 0.01$) than the $SUV_{max/mean}$ for ^{68}Ga-pentixafor. Overall, 70% of the patients were rated as suitable or potentially suitable for CXCR4-directed treatment.

Conclusions: ^{68}Ga-pentixafor allows in vivo imaging of CXCR4 expression in patients with advanced ACC and may serve as companion diagnostic tool in selecting patients for potential CXCR4-directed endoradiotherapy. Seventy percent of the patients with advanced, metastasized ACC may be suitable for a CXCR4-directed treatment after failure of standard treatment options.

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Author's contributions: Conception and design: K.H., S.H., C.B., B.H.; development of methodology: K.H., C.B., M.F., S.H.; acquisition of data: K.H., C.B., T.A.B., A.K.B., M.K., S.H., B.H.; analysis and interpretation of data: K.H., C.B., C.L., T.A.B.; writing, review and/or revision of the manuscript: all authors; administrative, technical, or material support: A.K. B., A.S., S.K., H.-J.W.; supervision: K.H., A.K.B., H.-J.W., S.H., M.F.

Preliminary results were presented at the SNM (Society of Nuclear Medicine) and EANM (European Association of Nuclear Medicine) Meeting 2015. Four patients are included in a submission about preclinical data on CXCR4 expression in adrenocortical cancer (unpublished).

Conflicts of interest and sources of funding: S.K. is CEO of Scintomics; H.-J.W. is founder of Scintomics.

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Adrenocortical carcinoma (ACC) is a rare (incidence of 0.7–2.0 cases per million people per year)[1,2] and aggressive endocrine tumor with an unfavorable prognosis (5-year survival rate ≤17% for stage IV).[3,4] Relapse rates after radical surgery have been reported in single series as high as 85%.[5,6] Besides local therapy (surgery, radiation therapy, radiofrequency ablation), systemic treatment with mitotane or cisplatin-based chemotherapy is available for adjuvant, recurrent, or metastatic disease.[7–9] However, all available systemic therapies are only palliative and associated with disease response in only a minority of patients. Thus, there is an urgent need for new therapeutic targets. More recently, targeted endoradiotherapy has been explored, and preliminary clinical data reported a sufficient retention of iodometomidate and therapeutic efficacy with long-term disease stabilization in several patients.[10–12] However, only a third of patients show sufficient uptake of iodometomidate, which is a prerequisite for treatment.[10,12,13]

A promising potential target is the chemokine receptor 4 (CXCR4), which has been shown to be overexpressed in many types of hematopoietic and solid malignancies. This G protein–coupled receptor plays a central role in proliferation of cancer cells, tumor growth, vascularization, and metastasis development.[14–17] Recently a CXCR4-directed PET ligand, ^{68}Ga-pentixafor, was introduced, and promising results have been shown for imaging but also CXCR4-directed endoradiotherapy of patients with multiple myeloma.[18–21] Moreover, preclinical studies confirmed an overexpression of CXCR4 in ACC cell lines.[22] Accordingly, we hypothesized that CXCR4-directed PET imaging may help identify patients potentially qualifying for CXCR4-directed treatment strategies such as targeted endoradiotherapy with ^{177}Lu-/^{90}Y-pentixather.

Therefore, the aim of this study was (i) to evaluate the feasibility of the CXCR4-directed PET ligand ^{68}Ga-pentixafor for in vivo visualization of CXCR4-expression in ACC patients and (ii) to determine the percentage of patients potentially suitable for future CXCR4-directed treatment concepts.

MATERIALS AND METHODS

Patients

From May 2014 to July 2015, 30 patients with histologically proven, metastasized ACC underwent ^{18}F-FDG PET/CT and ^{68}Ga-pentixafor PET/CT. ^{18}F-FDG PET/CT was performed for standard follow-up restaging, whereas ^{68}Ga-pentixafor PET/CT was performed to evaluate a potential therapeutic option. As previously reported for other ^{68}Ga-labeled peptides,[23] ^{68}Ga-pentixafor was administered under the conditions of pharmaceutical law (The German

Medicinal Products Act, AMG §13 2b) according to the German law and in accordance with the responsible regulatory body (Regierung von Oberfranken). All patients gave written informed consent prior to the investigations for receiving the ^{68}Ga-pentixafor PET (on a compassionate use basis), as well as undergoing a standard ^{18}F-FDG PET. Imaging data were retrospectively analyzed. A formal review for this retrospective analysis was waived by the ethics committee of the Universitätsklinikum Würzburg, Germany.

Synthesis of ^{68}Ga-Pentixafor

Synthesis of ^{68}Ga-pentixafor was performed in a fully automated, GMP-compliant procedure using a GRP module (SCINTOMICS GmbH, Fürstenfeldbruck, Germany) equipped with disposable single-use cassette kits (ABX, Radeberg, Germany). Method[24,25] and standardized labeling sequence have been previously described.[26] Prior to injection, the quality of ^{68}Ga-pentixafor was assessed according to the standards described in the European Pharmacopoeia for ^{68}Ga-edotreotide (European Pharmacopoeia; Monograph 01/2013:2482; available at www.edqm.eu).

PET/CT Imaging Studies

All ^{18}F-FDG PET/CT and ^{68}Ga-pentixafor PET/CT scans were obtained on a dedicated PET/CT scanner (Siemens Biograph mCT 64; Siemens Medical Solutions, Erlangen, Germany) within a mean time interval of 3 ± 4 days (range, 1–22 days). Patients with a time interval of more than 28 days between ^{18}F-FDG PET/CT and ^{68}Ga-pentixafor PET/CT were excluded from the retrospective analysis.

Before the acquisition of ^{18}F-FDG PET/CT, patients fasted for at least 6 hours prior to injection of a dose of 302 ± 23 MBq (range, 256–354 MBq). Patients' blood glucose levels had to be less than 180 mg/dL. The image acquisition from head to midthigh started 60 minutes after tracer injection. Corresponding diagnostic-dose CT scans with (23 patients [77%]) or without contrast enhancement (4 patients [13%]) for diagnostic issue and attenuation correction were obtained (210 mAs, 120 keV, 512 × 512 matrix,5-mm slice thickness, increment of 5 mm/s, rotation time of 0.5 second, and pitch index of 1.4; CAREDOSE 4D; Siemens Medical Solutions, Erlangen, Germany). In 3 patients (10%), CT was performed as a low-dose CT without contrast enhancement.

Prior to obtaining ^{68}Ga-pentixafor scans, patients fasted at least 4 hours. Injected activity was in mean 127 ± 23 MBq (range, 87–156 MBq), and image acquisition started 60 minutes post injection in accordance with the recently published dosimetry study.[20] Corresponding CT scans for attenuation correction were acquired using a low-dose protocol (35 mAs, 120 keV, a 512 × 512 matrix, 5-mm slice thickness, increment of 5 mm/s, rotation time of 0.5 second, and pitch index of 0.8).

PET emission data both for ^{18}F-FDG PET and ^{68}Ga-pentixafor PET were acquired in 3D mode with a 200 × 200 matrix with 2- to 3-minute emission time per bed position. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction using a dedicated software (Siemens E-soft).

PET and CT Analysis

All PET scans were analyzed separately by 2 nuclear medicine physicians (C.B., K.H.) with at least 5 years' experience. All PET scans were analyzed qualitatively and interpreted in a binary visual fashion as positive or negative for disease. CT information was added after identification of tumor lesions to determine the location (local recurrence, lymph node metastases, lung or liver metastases, etc). CT scans were analyzed separately by an experienced radiologist.

The primary readout was the detection rate of ^{18}F-FDG PET. Diagnostic information provided by CT was separately assessed. ^{68}Ga-pentixafor PET/CT was compared with the reference imaging standard ^{18}F-FDG PET/CT to assess if all lesions highly suggestive of disease showed a CXCR4 expression. Lesions with uptake highly suspected to be false positive (eg, due to inflammation) were not compared with ^{68}Ga-pentixafor PET/CT. In the present study, ^{18}F-FDG PET/CT was used as standard of reference based on previous publications for staging and restaging of ACC patients.[27–29] A lesion on PET was rated as positive if the uptake was higher compared with the background activity within the same organ or tissue. Secondary readout for ^{18}F-FDG PET and ^{68}Ga-pentixafor PET was the semiquantitative tracer uptake as expressed by SUV_{max} and SUV_{mean} for the tumor lesion with the highest uptake per organ. The SUV_{max} was assessed by a 3D volume of interest and the SUV_{mean} by a 2D ROI with a diameter of 1.5 cm around the hottest pixel. If the hottest lesions were not the same one in the ^{68}Ga-pentixafor PET and ^{18}F-FDG PET, 2 lesions in 1 organ were reported.

Finally, all patients were rated as suitable, potentially suitable, or not suitable for CXCR4-directed therapy with ^{177}Lu/^{90}Y-pentixather based on patient's history, previous treatment, and CXCR4 expression of FDG-positive lesions. Patients were rated as suitable if all lesions suggestive of a potential site of disease showed a CXCR4 expression higher than surrounding healthy tissue and liver. Patients were rated as potentially suitable if the majority of lesions showed a high CXCR4 expression.

Statistical Analysis

Qualitative parameters of CT, ^{18}F-FDG PET, and ^{68}Ga-pentixafor PET were descriptively compared. Quantitative values were expressed as mean ± SD or median and range as appropriate. Comparisons of related metric measurements were performed using Wilcoxon signed ranks test. All statistical tests were performed using SPSS Statistics version 22 (IBM). The bars shown represent the SEM. $P < 0.05$ was considered statistically significant.

RESULTS

Patients

The mean patient age was 51.9 ± 12.2 years (range, 26.3–77.2 years). Mean duration of disease at time of PET imaging was 2.6 ± 2.9 years (range, 0.3–13.0 years). Patients were previously treated with surgery (29 patients [97%]), mitotane (29 patients [97%]), radiotherapy (7 patients [23%]), systemic chemotherapy (23 patients [77%]), and/or tyrosine kinase inhibitors (2 patients [7%]). The detailed patient characteristics are shown in Table 1. At time of ^{18}F-FDG PET/CT, 22 patients (73%) had progressive and 4 patients (13%) had stable disease. One patient showed mixed response, and another one responded to therapy (7%), whereas 2 patients (7%) had no previous imaging for comparison available.

Diagnostic Information Provided by ^{18}F-FDG and ^{68}Ga-Pentixafor PET and CT

In summary, all ^{18}F-FDG and ^{68}Ga-pentixafor PET (100%) scans were rated visually positive for potential site of disease. In the reference standard ^{18}F-FDG PET/CT, 12 patients (40%) had local recurrence, 13 patients (43%) had peritoneal or mesenterial tumor lesions, 12 patients (40%) had a retroperitoneal tumor manifestation, 9 patients (30%) had lymph node metastases, and 28 patients (93%) had distant metastases. The most common distant metastases were lung metastases (23 patients [77%]), liver

TABLE 1. Patient Characteristics

	No. of Patients	% of All Patients	Mean ± SD (Range)
Age, y			51.9 ± 12.2 (26.3–77.2)
Sex			
Female	17	57%	
Male	13	43%	
Survival time, y			2.6 ± 2.9 (0.3–13)
Therapy			
Tumor resection	29	97%	
Mitotane	29	97%	
Chemotherapy	23	77%	
Radiotherapy	7	23%	
Tyrosine kinase inhibitor	2	7%	
Cortisol and/or aldosterone secretion at time of diagnosis			
Yes	11	37%	
No	6	20%	
Unknown	13	43%	

metastases (20 patients [67%]), and bone metastases (7 patients [23%]). Two patients had a metastasis affecting the contralateral adrenal gland (7%), and 2patients had multiple pleural metastases (7%).

Visual comparison of both tracers resulted in comparable findings in 10 patients (33%). In 13 patients (43%), ^{18}F-FDG PET identified more lesions with high uptake compared with ^{68}Ga-pentixafor PET. In 2 patients (7%), ^{68}Ga-pentixafor PET (Fig. 1) identified more metastatic lesions. In 5 patients (17%), ^{68}Ga-pentixafor PET and ^{18}F-FDG PET provided complementary information regarding the number and intensity of lesions. An example is given in Figure 2. In 2 patients (7%), distant metastases (lung) were detected only by CT and not by PET. In 2 patients (7%), metastases in an additional location (liver, tumor lesion in the inferior vena cava, lung) were detected only by CT. In 15 patients (59%), CT detected additional (small) FDG-negative lesions in locations with also FDG-positive metastases (11 patients, lung; 2 patients, liver; 2 patients [retro], peritoneal).

Lesion-Based and Semiquantitative Comparison of ^{18}F-FDG and ^{68}Ga-Pentixafor

The hottest lesion per metastatic location or organ was analyzed semiquantitatively. In 7 patients (23%), the lesion with the highest uptake in ^{18}F-FDG PET did not correspond with ^{68}Ga-pentixafor PET, and therefore 2 lesions per organ were analyzed. The evaluated target lesions per patient ranged from 1 to 9 lesions (mean, 4 ± 2) accounting for a total of 112 lesions. In 12 patients (40%), 15 ^{18}F-FDG–avid metastatic lesions (13%) did not show an increased uptake in the ^{68}Ga-pentixafor PET. In 4 patients (13%), 4 ^{68}Ga-pentixafor–avid lesions (4%) did not show an increased ^{18}F-FDG uptake (eg, brain metastasis).The corresponding mean SUV_{max} value for ^{18}F-FDG was 12.5 ± 7.8 (range, 2.2–47.0) and thus higher ($P < 0.01$) than the SUV_{max} for ^{68}Ga-pentixafor (mean, 8.4 ± 5.5; range, 1.7–34.2). Detailed results are summarized in Table 2.

Patients Suitable for ^{177}Lu/^{90}Y-Pentixather Therapy

Including patients' history and the results of the ^{68}Ga-pentixafor scan, 17 (57%) of 30 patients were rated as suitable, and 4 patients (13%) as potentially suitable for a CXCR4-directed treatment. In these patients, the uptake of ^{68}Ga-pentixafor in the tumor lesions was comparable to or significantly higher than in the ^{18}F-FDG scan. In 9 patients (30%), the FDG-avid tumor lesions demonstrated no or only a faint uptake in

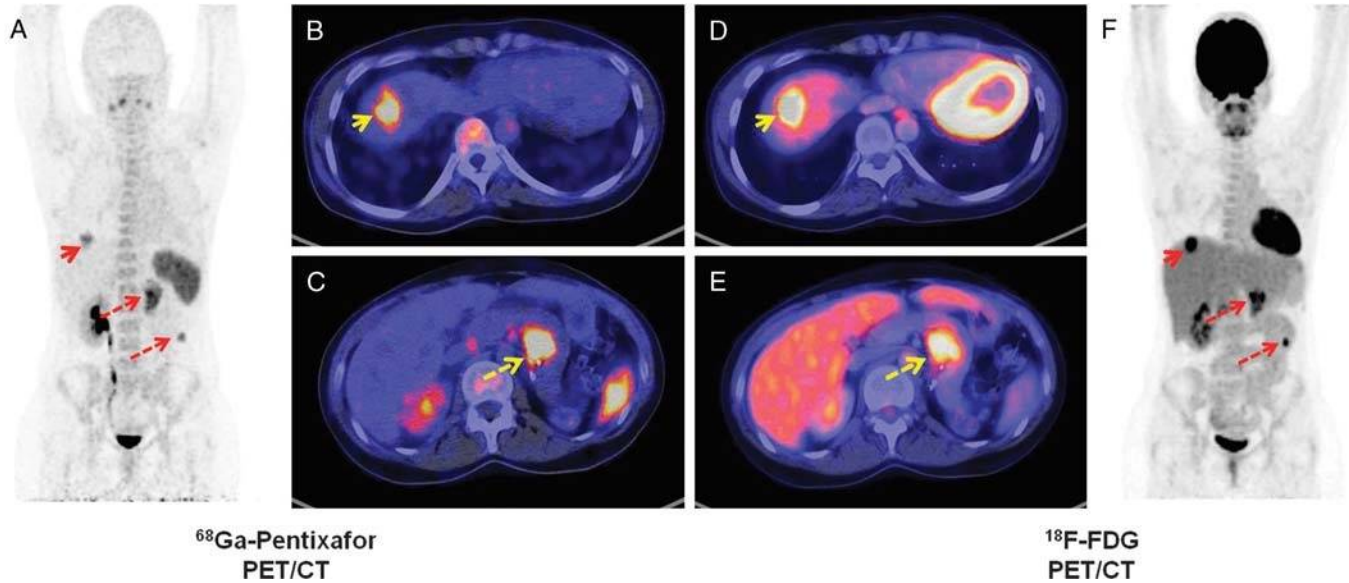

FIGURE 1. Comparable results of ^{68}Ga-pentixafor PET/CT and ^{18}F-FDG PET/CT. MIPs of ^{68}Ga-pentixafor (**A**) and ^{18}F-FDG PET/CT (**F**) of a 26-year-old woman with histologically proven metastasized adrenocortical cancer. Transaxial views of the abdomen (**B**–**E**) demonstrate the comparable findings of ^{68}Ga-pentixafor PET/CT and ^{18}F-FDG PET/CT in detecting liver metastases (**A**, **B**, **D**, and **F**, arrows) and (retro)peritoneal tumor lesions (**A**, **C**, **E**, and **F**, dotted arrows).

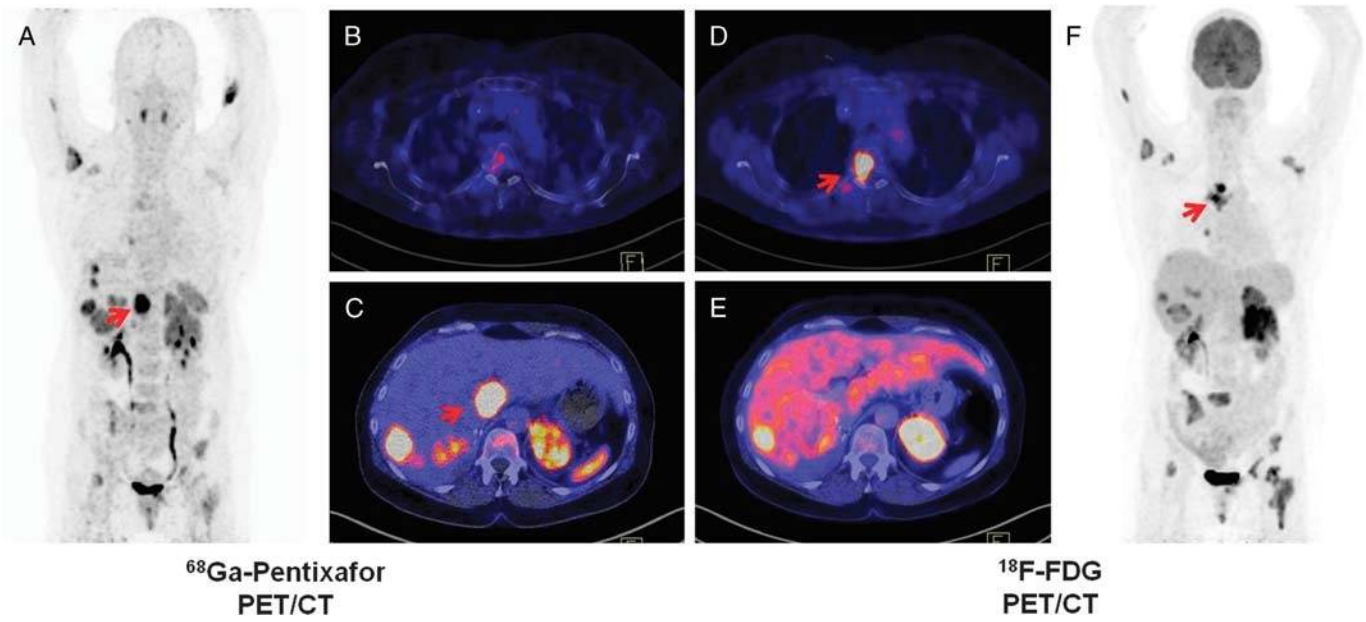

FIGURE 2. Complementary results of ^{68}Ga-pentixafor and ^{18}F-FDG PET/CT. MIPs of ^{68}Ga-pentixafor (**A**) and ^{18}F-FDG PET/CT (**F**) of a 53-year-old woman with metastasized adrenocortical cancer. Transaxial views of the thorax (**B** and **D**) and abdomen (**C** and **E**) demonstrate the higher sensitivity of ^{68}Ga-pentixafor (**C**, red arrow) compared with ^{18}F-FDG (**E**) for detection of liver metastases. Complementary results are shown for a bone metastasis in the thoracic spine (**B** and **C**, red arrow).

the ^{68}Ga-pentixafor scan. These patients were rated as not suitable for CXCR4-directed treatment.

DISCUSSION

^{68}Ga-pentixafor PET/CT is feasible for the in vivo detection of metastatic ACC. However, ^{18}F-FDG PET/CT provided a superior detection rate than ^{68}Ga-pentixafor PET/CT with visually higher uptake in 43% of patients. This finding is in agreement with a previous study in a mixed population of 10 patients with solid tumors reporting a superior visual detectability for ^{18}F-FDG compared with ^{68}Ga-pentixafor.[27] Interestingly, in multiple myeloma (n = 14 patients) ^{68}Ga-pentixafor PET/CT identified more lesions than ^{18}F-FDG PET/CT in 50% of patients, and also a significantly higher uptake of ^{68}Ga-pentixafor was documented.[19]

Only in 7% of the ACC patients ^{68}Ga-pentixafor PET/CT identified more lesions, whereas both imaging methods provided complementary information in 15%, respectively. ^{68}Ga-pentixafor uptake often differed between lesions of the same individual, indicating some heterogeneous CXCR4 expression of the tumor. Comparison of tracer uptake in different tumor lesions did not reveal significant differences between local recurrence in the tumor bed and distant metastases, suggesting that the level of CXCR4 membrane expression is not per se higher in distant metastases.

As already known,[28] sensitivity of PET for detection of small lesions was lower compared with CT for both PET imaging modalities. In 7% of the patients, distant metastases (particularly lung metastases) were identified only by CT because of their small size. In 59% of the patients, additional PET-negative lesions were found by CT in PET-positive locations. The combination of both full-dose CT and ^{18}F-FDG PET was superior to either method alone. This fits well to the results of previously published studies reporting a significant impact on patient management.[28,29] In regard to our findings, ^{18}F-FDG PET/CT, preferably combined with a contrast-enhanced CT, should remain the criterion standard for staging and restaging of ACC and cannot be replaced by ^{68}Ga-pentixafor PET/CT. ^{68}Ga-pentixafor PET/CT is also not suitable for discrimination between ACC and adrenal incidentaloma, because CXCR4 overexpression has also been seen in aldosterone-producing adenoma.[30]

The results of our in vivo analysis demonstrate that CXCR4 overexpression is present in a significant subgroup of metastatic ACC, and therefore CXCR4-directed treatment concepts might be a future option in patients with advanced ACC and tumor progress under standard treatment. Overall 57% of the ACC patients were rated as suitable or 13% as potentially suitable for CXCR4-diretected endoradiotherapy using ^{177}Lu/^{90}Y-pentixather. Recently, a proof of concept has been published for CXCR4-targeted endoradiotherapy in 3 patients with multiple myeloma.[19,20,31] In these patients, a remarkable therapeutic effect was shown by pretreatment and posttreatment ^{18}F-FDG PET/CT.[31] Endoradiotherapy was well tolerated and safe, but in ACC or other solid cancers, this treatment may have limitations because of its adverse effects. CXCR4/CXCL12 is involved not only in hematopoietic malignancies but also in physiological processes including hematopoiesis, organogenesis, and immunity. The stem cell compartment of normal tissue especially the bone marrow might be affected, resulting in the need of posttherapeutic stem cell transplantation for rescue of bone marrow. Therefore, this treatment option may currently be regarded as a potential last-line therapy. Unless proven as unnecessary, a prerequisite for treatment should be the availability of hematopoietic stem cells. So far, none of the patients in this study received a ^{177}Lu/^{90}Y-pentixather therapy.

A limitation of the study is that because of the retrospective design no biopsies of the lesions were performed for histopathologic correlation of the imaging results. So far, no follow-up of the patients is available. Further evaluation has to be performed to assess if CXCR4 overexpression also in ACC is a poor prognostic factor as shown for other cancer types.[32]

In conclusion, ^{68}Ga-pentixafor is suitable for in vivo imaging of CXCR4 expression in metastatic ACC and therefore a useful

TABLE 2. SUVs of ^{18}F-FDG PET/CT and ^{68}Ga-Pentixafor PET/CT

	^{18}F-FDG SUV_{max}	^{68}Ga-Pentixafor SUV_{max}	*P*	^{18}F-FDG SUV_{mean}	^{68}Ga-Pentixafor SUV_{mean}	*P*
Local recurrence						
n = 13			0.152			0.087
Mean ± SD	11.6 ± 7.4	8.3 ± 3.4		8.6 ± 5.5	5.9 ± 2.7	
Min	5.5	4.5		3.8	3.0	
Max	32.9	18.0		25.1	13.9	
Peritoneal/mesenterial						
n = 14			0.016			0.013
Mean ± SD	9.9 ± 6.6	6.3 ± 3.7		7.5 ± 4.9	4.3 ± 2.6	
Min	3.3	2.3		2.7	1.2	
Max	23.6	14.6		17.5	9.5	
Retroperitoneal						
n = 15			0.233			0.125
Mean ± SD	13.7 ± 6.6	11.5 ± 8.7		10.5 ± 6.6	7.2 ± 4.6	
Min	4.3	2.7		3.3	2.1	
Max	25.5	34.2		29.8	19.0	
Lymph nodes						
n = 10			0.074			0.028
Mean ± SD	11.1 ± 4.6	6.8 ± 6.0		7.2 ± 2.0	4.4 ± 3.3	
Min	5.5	2.3		4.6	1.8	
Max	19.3	22.9		10.3	12.8	
Distant						
n = 60			<0.01			<0.01
Mean ± SD	13. ± 8.8	8.4 ± 4.8		9.1 ± 6.8	5.5 ± 3.7	
Min	2.2	1.7		0.9	0.5	
Max	47.0	27.4		40.8	20.9	
All lesions						
n = 112			<0.01			<0.01
Mean ± SD	12.5 ± 7.8	8.4 ± 5.5		8.8 ± 6.1	5.5 ± 3.6	
Min	2.2	1.7		0.9	0.5	
Max	47.0	34.2		40.8	20.9	

tool for identification of patients potentially benefiting from CXCR4-directed endoradiotherapy. More than 50% of the patients qualified for a CXCR4-directed treatment.

ACKNOWLEDGMENTS

The authors thank Simone Seifert, Simone Groß, Michael Schulze-Glück (members of the nuclear medicine PET team) for their support and assistance.

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