

# Uptake of Cis-4-[<sup>18</sup>F]Fluoro-L-Proline in Urologic Tumors

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Tumor uptake of the amino acid cis-4-[<sup>18</sup>F]fluoro-L-proline (cis-FPro) was studied with PET in eight patients with urologic tumors. **Methods:** Three patients had primary renal cell carcinomas (RCCs), one had a local recurrence of RCC, one had squamous RCC, one had an adrenal hemangioma, one had inguinal metastases of penile squamous carcinoma, and one had suspected metastatic disease from prostate cancer. PET scans of the trunk were acquired at 1 and 3–5 h after intravenous injection of 400 MBq cis-FPro and compared with <sup>18</sup>F-FDG PET scans and CT. **Results:** None of the tumors or metastases showed significant uptake of cis-FPro. FDG uptake was seen in one of the three primary RCCs, in the local recurrence of RCC, in the squamous RCC, and in the metastases of penile cancer. **Conclusion:** Cis-FPro appears not to be a promising PET tracer in oncology.

**Key Words:** cis-4-[<sup>18</sup>F]fluoro-L-proline; radiolabeled amino acids; renal tumors; PET

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**T**he diagnostic value of <sup>18</sup>F-FDG PET for the evaluation of renal malignancies is limited (1). Radiolabeled amino acids may help to overcome some of the diagnostic limitations of FDG. Most of the interesting amino acids proposed for PET, however, can be labeled with only the short-lived positron emitter <sup>11</sup>C (20-min half-life), whose use is restricted to a few PET centers with a cyclotron and a radiochemistry laboratory on site. Recently, the diastereoisomers cis-4-[<sup>18</sup>F]fluoro-L-proline (cis-FPro) and trans-4-[<sup>18</sup>F]fluoro-L-proline (trans-FPro) labeled with the longer lived <sup>18</sup>F (110-min half-life) have been presented. These can be synthesized with high radiochemical yields, allowing large-scale production for clinical purposes (2). Animal experiments have shown that more cis-FPro than trans-FPro accumulates in osteosarcomas, and tissue homogenates revealed protein incorporation of only cis-FPro (3). In this

pilot study, we investigated the potential of cis-FPro for tumor imaging in humans.

## MATERIALS AND METHODS

### Patients

Eight patients (two women, six men; age range, 37–81 y) were included in this pilot study. Table 1 gives further information on the patients. Histopathologic data were obtained by surgical resection of the primary tumors after the PET studies or were already known from previous resection of the primary tumors in patients with recurrences or metastatic disease. Patient 3 had advanced metastatic disease and did not undergo surgery, so no information on the histopathology of the tumor is available. Three patients had primary renal cell carcinomas (RCCs) (one with distant metastases), one patient had recurrent RCC, one patient had squamous RCC with regional lymph node metastases, one patient had a hemangioma of the left adrenal gland, one patient had inguinal lymph node metastases of penile squamous carcinoma, and one patient had suspected metastatic disease from prostate cancer. The study was approved by the local ethical committee and federal authorities. All patients gave written informed consent to participate in the study. Laboratory values of kidney and liver function were normal in all patients.

### Radiopharmaceuticals

Cis-FPro was prepared with a radiochemical yield of 36% ± 7%, a radiochemical purity > 98%, and a specific radioactivity of >18.5 GBq/μmol as previously described (2). The tracer was administered to the patients intravenously as a phosphate buffer solution with a pH of 6.5–8.

FDG was synthesized according to a drug master file created at the Institute of Nuclear Chemistry in Jülich, Germany. The average specific activity was >370 GBq/μmol.

### PET

All patients fasted for at least 12 h before the PET studies. After intravenous injection of 400 MBq cis-FPro early (1 h after injection) and late (between 3 and 5 h after injection), PET scans of the trunk (three to five bed positions) were obtained for each patient.

All patients except patient 3 underwent comparative investigations after intravenous injection of 400 MBq FDG within 1 wk before or after cis-FPro PET using the same scanning protocol. The studies were done using either an ECAT EXACT HR+ scanner (Siemens Medical Systems, Inc., Hoffman Estates, IL/CTI, Knoxville, TN) (full width at half maximum, 4.5 mm; 15-cm

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**TABLE 1**  
Data on Patients and on Cis-FPro and FDG Uptake in Urologic Tumors

Patient no.	Age (y)	Sex	Clinical diagnosis	Maximum tumor size (cm)	Histologic type	Pretreatment	Cis-FPro uptake	FDG uptake
1	68	M	Right renal mass	9	Clear cell carcinoma	None	–	+
2	72	M	Left renal mass	11.5	Clear cell carcinoma	None	–	–
3	53	M	Right renal mass, pulmonary metastases	7	Unknown	None	–	–
4	59	M	Tumor recurrence, left para-aortic	4	Clear cell carcinoma	Nephrectomy Left	–	+
5	81	F	Left renal mass, lymph node metastases	6	Squamous carcinoma	None	–	++
6	37	F	Left adrenal mass	10	Hemangioma	None	–	–
7	66	M	Penile cancer, metastases	ND	Squamous carcinoma	Penectomy	–	++
8	63	M	Prostate cancer, metastases	ND	Prostate carcinoma	Prostatectomy	–	–

ND = not detectable with CT.

transaxial field of view) or a PC4096+ scanner (General Electric Medical Systems, Milwaukee, WI) (full width at half maximum, 5.4 mm; 10-cm transaxial field of view). Transmission scanning was performed with  $^{68}\text{Ge}/^{68}\text{Ga}$  rotating line sources and used for measured attenuation correction. After correction for random and scattered coincidences, dead time, and decay, data were reconstructed with an iterative algorithm. Using transaxial slices and whole-body reprojected images, two independent observers visually evaluated the data and compared them with the corresponding transaxial CT scans. Tumor uptake was rated as – (uptake at or below background level), + (discrete tracer uptake above background level), or ++ (intensive tracer uptake, or hot spot).

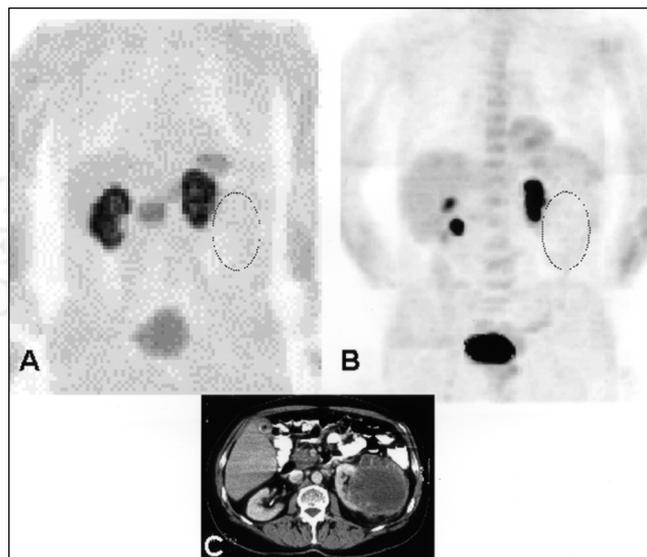
## RESULTS

Table 1 gives the data on cis-FPro and FDG uptake. None of the tumors or metastatic lesions in this series of patients showed relevant uptake of cis-FPro. Cis-FPro distribution did not significantly differ between the early and the late scans. Of the three patients with primary RCC, only one showed discrete uptake (+) of FDG. The reprojected PET scans of cis-FPro and FDG uptake, as well as the CT scan of an RCC that was negative for uptake of either tracer, are shown in Figure 1 (patient 2). The squamous carcinoma of the kidney showed intensive FDG uptake in the primary tumor (++) and in the regional lymph node metastases (Fig. 2), whereas cis-FPro was negative for FDG uptake. The hemangioma was negative for uptake of either tracer. The inguinal lymph node metastases of a penile squamous carcinoma could be detected by FDG scanning (++) but were negative for cis-FPro uptake.

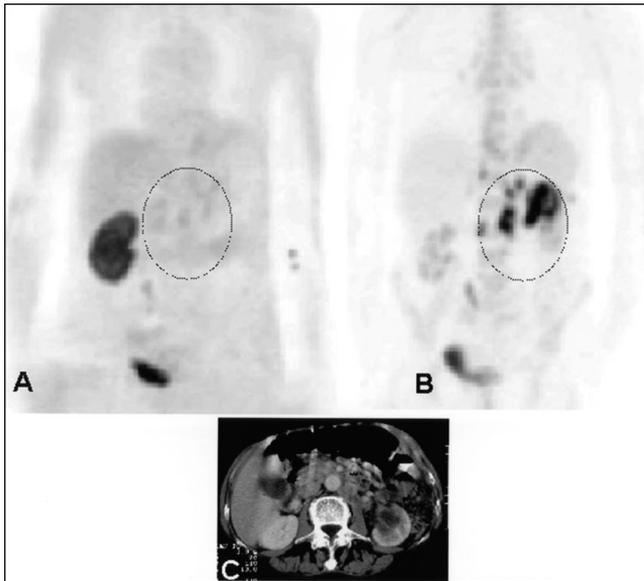
The PET scan of the patient with suspected metastatic disease from prostate cancer was negative for uptake of either tracer. The suspicion of metastatic disease in this patient was based on an elevated prostate-specific antigen level of 39.7 ng/mL. The CT scan and the whole-body bone scan were negative for uptake at the time of the PET studies, but bone metastases developed 12 mo later.

## DISCUSSION

Several pathologic processes, such as tumor growth, lung fibrosis, and hepatocirrhosis, are related to increased regional collagen synthesis. Because proline and hydroxyproline represent major constituents of mammalian structural proteins, especially of collagen, the  $^{18}\text{F}$ -labeled proline analogs cis-FPro and trans-FPro have been proposed as potential tracers for PET imaging of tumors and abnormal collagen synthesis rates (2). Experiments on the biodistribution of cis-FPro and trans-FPro in tumor-bearing mice have shown that more cis-FPro than trans-FPro accumulates in osteosarcomas, and tissue homogenates revealed protein incorporation of only cis-FPro (3).



**FIGURE 1.** PET and CT scans of 72-y-old man (patient 2) with left-sided renal clear cell carcinoma. (A) Reprojected whole-body scan using cis-FPro shows negative findings (dotted oval). Note uptake in renal cortex and pancreas. (B) Reprojected whole-body scan using FDG shows negative findings (dotted oval). (C) Transaxial CT scan at tumor level shows large, hypodense mass in left kidney.



**FIGURE 2.** PET and CT scans of 81-y-old woman (patient 5) with left-sided renal squamous carcinoma. (A) Reprojected whole-body scan using cis-FPro shows relevant uptake neither in primary tumor nor in metastases (dotted oval). (B) Reprojected whole-body scan using FDG shows intensive uptake in primary tumor and regional lymph node metastases (dotted oval). (C) Transaxial CT scan at tumor level shows hypodense renal mass and enlarged para-aortic lymph nodes.

In this pilot study, we examined cis-FPro for the imaging of renal tumors and one case of penile cancer with metastatic disease. However, this tracer significantly accumulated neither in renal clear cell carcinomas nor in squamous carcinomas. Also, no uptake was apparent in prostate cancer metastases. These data indicate that the tumor affinity of cis-FPro is limited, and the promise of cis-FPro as a tracer for human tumors appears questionable. Nevertheless, other histologic entities, such as osteosarcomas, breast carcinomas, and colon carcinomas, may be evaluated because experimental studies have shown tumor uptake of cis-FPro (3). Why cis-FPro fails to image the tumor entities investigated in this study remains unclear. Animal experiments have

shown that cis-FPro incorporates some protein, although slowly. The processes involved in the transport mechanisms of this nonphysiologic amino acid need further study.

After a preliminary evaluation, we reported an increased uptake of cis-FPro in some RCCs (4). This increase, however, proved to be a misinterpretation because of cis-FPro uptake in the adjacent pancreas. A more sophisticated evaluation of the data in comparison with transaxial CT scans revealed that the tumor area itself showed no uptake of cis-FPro.

The diagnostic value of FDG imaging in renal tumors is also questionable because only a fraction of these tumors exhibit FDG uptake (1). The results of our study confirm the limited potential of FDG for the diagnosis of renal tumors.

## CONCLUSION

In this series of urologic tumors, no relevant cis-FPro uptake could be detected. The promise of cis-FPro as a PET tracer in oncology appears questionable. Other malignancies, however, have to be studied before final conclusions can be drawn.

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