Study protocol

Study ID: RCCSCAN

"An exploratory study regarding the use of the biomarker DAT for image diagnosis of clear cell renal cell carcinoma"

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Synopsis

Titel	"An exploratory study regarding the use of the biomarker DAT for image diagnosis of clear cell renal cell carcinoma"
Developmental Phase	Phase 2
Background	The background to why the study should be done Kidney cancer affects approximately 1000 people a year in Sweden and globally, approximately 340,000 people are diagnosed with this disease. The most common form of kidney cancer is clear cell renal cell carcinoma (ccRCC), which accounts for about 80% of all cases. Despite some treatment progress, over 40% of patients who suffer from kidney cancer die. The presence of this tumor form is increasing globally and the annual growth rate is estimated at 6.25% in the period 2013-2023. Localized kidney cancer has good prognosis; The tumor, or tumor-bearing kidney is usually surgically removed. However, the symptoms of renal cancer are diffuse and in about 25% of cases, the disease has already spread beyond the kidney at the time of diagnosis. An additional 25% of patients with localized disease later display metastases, although the first analysis showed that the disease was limited to the kidney. For patients with metastatic disease, the prognosis is very poor, as kidney cancer does not respond to common cancer treatments such as cytostatics and radiation and less than 10% of these patients are expected to survive for five years. It is therefore crucial to be able to clarify the spread of the disease. Today there are no diagnostic methods that can specifically detect kidney cancer and distinguish between subtype of renal cancer. Small metastases are likely

	to be missed by today's methods. The need for new diagnostic methods is therefore eminent. We have identified the molecule Dopamine Transporter (DAT) as a new, highly specific, biomarker for clear cell kidney cancer. This molecule is usually only expressed in the brain of dopaminergic neurons, but we have now shown that it is found to be very high in clear cell kidney cancer, but not in other cancers. DAT is used today in the diagnosis of Parkinson's disease. DaTSCAN is a radioactively labeled substance that binds to DAT and thus to dopaminergic neurons. The signal from the binding can be detected using SPECT camera and a decreased signal is evidence of loss of dopaminergic neurons and thus Parkinson's disease, which then can be distinguished from other neurodegenerative diseases. This study aims at investigating whether clear cell kidney cancer can be detected by a DaTSCAN analysis, where in this case an increased signal is expected, unlike Parkinson's diagnostics
Study design	Open single arm trial with a small number of patients (10) for proof of concept of the use of DaTSCAN for the detection of clear cell RCC. Recruited patients with suspected dissiminated kidney cancer will, after informed consent to participate in the study, be investigated using CT and DaTSCAN followed by SPECT. DaTSCAN is injected intravenously and followed by SPECT examination 5h later. The images from the DaTSCAN investigation will be analyzed and anatomically compared to CT examination of the patient. Any side effects of the study will be reported.
Objectives	**The main objective** is to investigate whether DaTSCAN with subsequent SPECT can detect elevated DAT levels in at least one lesion identified with CT in patients with clear cell renal cell carcinoma, as assessed by pathologist? DaTSCAN signal will be seen as positive, when displaying intensity ≥3ggr higher than the background and correlating anatomically with at least one lesion found with CT. DaTSCAN is used routinely to detect the loss of dopaminergic neurons in the striatum of patients with clinically uncertain Parkinsonian Syndromes. The active substance in DaTSCAN, Ioflupane specifically binds to DAT. By analyzing the focal uptake of Ioflupane (123I) with SPECT / CT the progression of the disease may be clarified. In light of our findings that clear cell renal cancer express significantly elevated levels of DAT, we postulate that DaTSCAN can be used for detection of clear cell renal cell carcinoma. **The exploratory objective** is to investigate whether:

	• DaTSCAN with subsequent SPECT, by detecting elevated levels of DAT in clear cell renal cancer, can be used to distinguish clear cell renal cancer from other subtypes of renal cancer such as papillary renal cell cancer, chromofob kidney cancer and benign tumors such as oncocytoma? • Surgically removed DaTSCAN positive lymph nodes exhibit infiltration of clear cell renal cell carcinoma cells, regardless of the CT status? • DAT-mRNA expression in primary tumor correlate with DaTSCAN signal where the surgically removed tumor material with high DaTSCAN intensity also exhibit high mRNA levels of DAT?
Study population	This study is an exploratory single-arm study at Skåne University Hospital. The study intends to include 10 patients, if one of the research subjects withdraws from the study, this subject will be replaced so that the number of persons is 10 in total. After 10 analyzed patients, an evaluation is made. If less than 8 patients out of the 10 analyzed have been diagnosed as ccRCC by pathologist, an additional 3 patients will be included. Each patient will be evaluated continuously after completion of the study. For ethical reasons, the study will be terminated if 4 patients diagnosed with clear cell kidney cancer by pathologist, all display negative DaTSCAN signal in primary tumor. The patients / research subjects will be recruited through the Urological Clinic in Malmö. The DaTSCAN study will be conducted at the department of Clinical Physiology / Nuclear Medicine VO Image and Function in Malmö Pathologic assessment of surgically removed material from each study subject will be obtained from the Pathological Clinic in Malmö
Inclusion and exclusion criteria	This study plans to include subjects that comply to the following inclusion and exclusion criteria: **Inclusion criteria** -suspected kidney cancer diagnosis -suspected spread of the cancer -the patient is scheduled for surgery alternatively biopsy of kidney tumor -the patient is 18 years or older -the patient has given their consent to participate in the study **Exclusion criteria** -known or suspected allergy to the active substance in DaTSCAN,

	ioflupane or any of the following ingredients: • Sodium acetate • Acetic acid • Ethanol -the patient suffers from moderate to severe liver disease with liver enzymes (transaminases)> 2 times the upper limit -the patient suffers from moderate to severe renal impairment and exhibits GFR <40 -the patient is medicated for Parkinson's disease -the patient is medicated with any of the following medications: • Amphetamine • benzatropine • Buproprion • Cocaine • mazindol • Methylphenidate • Phentermine • Sertraline • levodopa (Sinemet, Pharma Copa, Atamet, Stalevo, Madopar, Prolopa) -the patient is /or plans to become pregnant -breastfeeding -the patient suffers from mental inability, unwillingness or language difficulties resulting difficulty in understanding the meaning of taking part in the study
Methodology	Patients with suspected renal cancer are screened for the suitability to participate in the study. After informed consent, a 3-phase CT examination of abdominal and thoracic baseline for tumor burden is performed. If an equivalent CT scan was performed in Region Skåne <28 days before the inclusion date, this study will be the basis of the baseline for tumor burden. Thereafter, the patient is scheduled for DaTSCAN examination, which is performed before any surgery. Prior to DaTSCAN injection the patient takes potassium iodide tablets, according to local clinical practice for DaTSCAN studies, to protect the thyroid gland. At the time of investigation of DaTSCAN, the patient is slow-paced injected with the DaTSCAN solution in the arm, not faster than 15 seconds. The patient then waits for 5h before image diagnosis with abdomen / thoracic SPECT / CT is performed. Possible side effects are documented. The collected image material is analyzed and compared for anatomical localization with previously performed CT examination.

	Two days after the DaTSCAN study, the patient is contacted for follow-up of possible side effects following the study. Pathological assessment statement collected from pathologist after surgery / biopsy. If the patient has consented to biobanking tissue samples from removed tumor according to ethical approval: LU680-08 and LU289-07, mRNA levels of DAT are also analyzed for these samples. The study closes after 10 patients are subjected to DaTSCAN-examination, the results have been analyzed and pathological responses are obtained. The study is expected to end after 1 year. For ethical reasons, an early stopping rule is applied if four patients with pathologically verified ccRCC display negative signal from the DaTSCAN examination, the study is in that case ended.
Test product	**Test product, dose and mode of administration, batch number:** <u>Test product</u> Substance Generic Name: Ioflupan (I-123), Product Name: DaTSCAN, ATC Code: V09AB03 Pharmaceutical form and strength: Solution for injection 74MBq/ml, Manufacturer: GE Healthcare DaTSCAN was ordered from GE Healthcare, and provided with patient-specific labeling by the clinician responsible for administering DaTSCAN to patient. <u>Mode of administration:</u> The patient takes potassium tablets prior to the examination, to protect the thyroid gland. At the time of the DaTSCAN examination, the patient is injected intravenously at slow rate with 185MBq DaTSCAN solution. Using a dose calibrator, 185MBq of DaTSCAN is drawn into the syringe to be given to the research person. A label is printed and put on the syringe with the following information: patient name, drug, batch, dose and draw time. Thereafter, the drug is administered directly to the patient. Afterwards, the remaining activity in the syringe is measured and the exact dose is recorded in the patient's journal. The patient then waits for 5h before performing diagnostic examination with SPECT.
Evaluations	**Criteria for evaluation:** Each patient is continuously evaluated after completion of the DaTSCAN-examination and analysis. **Efficacy** <u>Analysis of the image material from the SPECT study</u> Signal from DaTSCAN is quantified and compared with an internal control in the form of the previous CT imaging. DaTSCAN signal is considered positive when ≥3 times higher than background and correlating anatomically with at least one lesion found with CT. <u>Pathological assessment</u>

	The patient's surgically removed tumor/metastasis will be examined by a pathologist for kidney cancer subtype determination. This assessment will be compared to the DaTSCAN expression. If patients with pathologically verified ccRCC tumor also have positive DaTSCAN signal, the DaTSCAN study will be considered to detect clear cell kidney cancer. <u>mRNA levels of DAT in tumor tissue from biobank</u> In the cases where the recruited research persons have given consent to that material from surgery/biopsy is save for research (biobank) in accordance with licence number LU680-08 and LU289-07, these samples will be requested from the biobank. These samples will be examined for mRNA levels of DAT and then compared to DaTSCAN signal in the same tissue to investigate any correlation. **Safety** Potential Adverse Events is registered at each study visit. • When injecting DaTSCAN (Ioflupan I123) • Immediately after the SPECT investigation • 2 days after the DaTSCAN survey (through telephone interview from research nurse) The incidents may be observed by a doctor / nurse or reported by the subjects themselves. At each study visit (above), an open question is asked to the subjects: "Have you had any health problems since taking potassium iodide?"
End of Study	The patient / research subject can end their participation in the study at any time without any consequences for his/hers further treatment. The doctor / sponsor may suspend the patient's participation in the study at any time e.g. because of adverse effect or that the subjects does not comply the study protocol. If the research subject exhibits hypersensitivity reaction of the DaTSCAN injection, the patient does not need to proceed to SPECT examination.
Statistical plan	As this is an exploratory study with a low number of patients, thus there is no basis for a power calculation. However, assuming that the proportion of clear cell kidney cancer (ccRCC) is 80% of all kidney cancer cases, we plan to include 10 patients with the probability that at least 6 patients had ccRCC of 96,7% and with a probability of 8 ccRCC patients of 67,8%. The results will be presented with descriptive statistics. An exploratory objective is whether DaTSCAN can be used for differential diagnosis of renal cancer. With a recruitment of 10 renal cancer patients, there is 62.4% probability that we include 2 patients of non-clear cell subtype.

Adverse Events	Incidents will be registered at each study visit. That is on the following occasions: When injecting DaTSCAN (Ioflupan I123) Immediately after the SPECT investigation 2 days after the DaTSCAN investigation On these occasions, open questions will be asked to the subjects: "Have you had any health problems since taking potassium iodide?" The incidents may be observed by a doctor / nurse or reported by the subjects themselves. Incidents are entered into patient records and subsequently recorded in CRF. Assessment of relationship, severity and seriousness is done by the investigator in CRF. As a minimum, registered for each incident: description of the incident, start and stop, relationship, severity, and if considered serious, actions and outcomes. All serious side effects will be followed until they are restored or until confirmed by the examiner as no longer necessary to follow these incidents.
Potential benefit:	In a longer perspective, a new method of renal cancer imaging would be of great importance Today, many cases of small metastases that require systemic treatment missed. Through a more accurate picture of the spread of the disease, treatment could be adapted.