PROTOCOL

Title

Perfusion scanning's for kidney tumors

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Background.

The number of diagnoses of renal cell carcinoma has increased over the past two decades because of the incidental detection of small renal tumours resulting from increased use of computed tomography [1,2]. There are distinct subtypes of renal cell carcinoma (RCC), and the biological aggressiveness and prognoses for these subtypes have been documented. Clear-cell RCC is the most common RCC subtype, followed by papillary RCC, chromophobe RCC and unclassified RCC. Collecting duct carcinoma is a rare and highly malignant type of RCC. Although most enhancing renal masses in adults are RCC, a significant percentage are benign (commonly oncocytoma), and these benign tumours cannot be distinguished from malignant tumours based on our standard imaging technology alone.

Benign primary renal masses include simple renal cysts, psuedotumours, angiomyolipomas, oncocytomas, juxtaglomerular tumours, multilocular cystic nephromas, mesoblastic nephromas and papillary adenomas. In a recent surgical series of 228 patients who underwent partial or radical nephrectomy with lesions ≤4 cm, 26.3% were benign [3]. The relatively high percentage of patients with benign renal cortical neoplasms who undergo surgery highlights the importance of new diagnostic technology in avoiding over-treatment.

Ultrasound (US) and CT scanning guided biopsy is the most commonly used method to diagnosis RCC. The sensitivity of biopsy for small masses (≤3 cm) is lower than for large masses [4]. Sensitivity is limited by false-negative results, which are due to a failure to properly target a small mass or the presence of impossible-to-differentiate benign from malignant cells due to insufficient cells, morphological overlap or cellular heterogeneity. Non-diagnostic biopsy is not necessary benign, as repeated biopsy reveals malignancy diagnosis in
the majority[5]. There is no radiologic criteria consistent with oncocytoma because of a lack of sensitivity and specificity [6]. MR-scanning and CT-scanning are not feasible diagnostic methodologies for oncocytoma because of the possibility of overlapping results from oncocytoma and RCC [7].

**Hypotheses:** To investigate the ability of perfusion CT/US-scanning to facilitate recognition of different tumour sub-types in small renal masses less than 7 cm by non-invasive imagining technology.

**Purpose:** To recognize different subtype’s renal tumor by non invasive scanning.

**Design:** A descriptive study

**Inclusion criteria:**

1. Patients suspecting to have renal tumors by CT/UL-scanning.

2. Patients age between 35 and 75 years

3. Normal renal function

4. Can read and understand Danish

5. Non – metastasis disease detected by scanning

**Exclusion criteria:**

1. Patients have a nephropathy (defined as e-GFR less than 50 ml/min/1.73cm³).

2. Previous allergic reaction to intravenous contrast material.

3. Untreated hyperthyroidism.

**Recruitment:**

Patients referred to our department by family doctors or the primary sector with a suspicion of renal tumour by Ultrasound or CT-scanning, from November 2014 will be invited to the project, if they suit to the inclusion criteria. We are expecting that 100 patients will be included in the study.

**Procedure:**

Patients will be invited to the Department of Radiology / Roskilde Hospital to perform the perfusion scanning. Patients will get a cannula in dorsal metacarpal vein to get an access to give the contrast material, both CT scanning and UL scanning will be performed at the same day, patients not need to be fasting. Before the perfusion scan, patients will be instructed to hold their breath during the entire scan or to minimize respiratory excursions, if breath holding is no longer possible.

CT-scanning will take about 30 minutes and UL-scanning will take about 15 minutes.

**Methods:**

**CT-scanning technique.**

All patients will receive a three-phase MDCT scan consisting of pre-contrast, corticomedullary and nephrographic phases. The pre-contrast scan is performed prior to the administration of contrast material. The scan delay times were 30–40 s for the corticomedullary phase and 150–180 s for the nephrographic phase. CT scans begin by using the bolus-tracking technique.

All patients will be examined using a Philips-I-CT brilliance 256 slice CT machine. An unenhanced CT scan of the upper abdomen covering the kidneys will be performed initially to locate the renal mass. On the unenhanced images, a supervising radiologist will identify the...
tumour and then place the predefined scan volume of 8 cm in only one axis to cover the lesion for the perfusion study. For perfusion imaging, 60 mL of iomeron (350 mg iodine/mL) will be administered intravenously at a flow rate of 5 mL/s followed by 20 mL of saline solution at the same flow rate. Scanning commences 6 seconds after beginning the contrast material injection. This is followed by a scan time of 2 seconds for each direction (total examination time, 40.17 seconds) and a final scan of 15 minutes. Further scanning parameters include the following: tube potential, 100 kV; tube current-time product, 100 mAs; slice collimation, 256 x 0.6 mm; and gantry rotation time, 0.28 seconds. Prior to the perfusion scan, patients will be instructed to hold their breath during the entire scan or to minimize respiratory excursions, if breath-holding is no longer possible.

The volume computed tomography dose index of the CT perfusion scan according to the patient protocol is 92 mGy and the dose-length product is 1084 mGy x cm, leading to an estimated effective radiation dose of 10-15 mSv for a total of 31 scanning images. The time required to perform perfusion scanning is approximately 30 minutes. Blood flow, blood volume, flow extraction, and perfusion curve will be recorded, as well as the Hounsfield unit of the tumour and normal parenchyma at different phases of scanning.

For standardization, the plain, arterial (cortical phase), venous (nephrographic phase) and delayed (excretory phase) phases of the CT for the tumour and the renal cortices will be abbreviated as P1, P2, P3, P4 and C1, C2, C3, C4, respectively. The readings will be analyzed as three independent groups and the results collated: mean enhancement values for the individual phases in the tumour and renal cortex and mean difference in enhancement between the arterial, venous and delayed phases will be compared to the plain phase for the tumour and the renal cortex (P2-P1) (P3-P1) (P4-P1) (C2-C1) (C3-C1) (C4-C1);
The enhancement pattern of the tumour in relation to the cortex will be calculated according to the Bird Index \((P2-P1/C2-C1)\) \((P3-P1/C3-C1)\) \((P4-P1/C4-C1)\) \cite{8} and according to the following index:

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\text{Washout study of the tumour mass will be calculated from plan scanning, 6-10 seconds, 60 seconds and 15 minutes after contrast injection according to the formula:}
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\textbf{UL-scanning technique}
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A baseline ultrasound will be performed to visualize the kidney and enable targeting of the tumour area. The localization, size, and echogenicity of the tumour will be registered. Then, a dynamic contrast enhanced ultrasound examination (CEUS) will be performed. A bolus of 1.2 ml of US-contrast (SonoVue, Bracco) will be injected through a cannula. Following the bolus injection of contrast, the cannula will be flushed with approximately 5 ml of saline.

After injection of US-contrast, a 3-minute video recording will be started. The entire examination will be stored in the PACS system and in the GE workstation \cite{9}.

For standardization, a wash-in/wash-out analysis (TIC-curves) for each tumour will be performed. The contrast enhancement of tumours will be registered with regards to the amount of vascularity of the tumour according to the following: 25\%, 50\%, 75\% and 100\% enhancement.
Experimental conditions: There is no need for special preparation before scanning.

Laboratory tests: Standard blood test (15 ml) will be taken at the outpatient visit according to instruction of the Department of Urology/Roskilde Hospital according to appendix 1. Blood sample will be analyzed at the same time at Roskilde Hospital laboratory and will be destroyed immediately after analyses.

Statistic power: This study is a descriptive study and need no statistic power

Results: The reading of scanning's will be collected and analyzed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Pearson correlation will be used to distinguish the differences between different tumor subtypes. Multiple regressions analyses will be used to describe the relation of results of scanning to pathologic outcome.

Projects schedule: The study will start at November 2013, about 100 patients will be included in the project.

Place to perform the project: Department of Radiology/Urology, Roskilde Hospital.

Publication: Nessim H. Azawi is responsible for conception and design, acquisition, analysis and interpretation of data. Hanne Standstrum is responsible for perfusion CT-scanning. Steen Kastrup responsible for perfusion UL- scanning. Nessim H. Azawi, Hanne Standstrum, Steen Kastrup, Claus Dahl, Tom Christensen, Thomas Norous and Hans-Erik Widendorff are responsible for drafting the article or revising it critically for important intellectual content. Negative as well positive results will be published in international journals where Nessim H. Azawi will be the first author and Hanne Sandstrum will be the last author, other authors will be arranged according to vancouver rules.

Ethics: The study will be reported to the Regional Ethical Committee of Region Sjaelland.

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Data are reported to Region Sjaelland data control agency “Region Sjælland paraplygodkendelse fra Datatilsynet”, as well as clinical trials database.

Act on processing of personal data will be observed.

**Data:** Data will be collected with share point data program. Data will be stored secure in Region Sjaelland server and in anonymous form in PC with access only to the project’s involved persons and backup disk placed in a looked cabinet. Data will be stored for 10 years after which the data will be deleted. Danish low on personal data observation will be met.

**Economy:** We will apply funds to support project charges. We will apply to research account at Department of Urology/Roskilde hospital/ region Sjaelland.

There are no economic interests in the results of the study. There will be no connection between the investigators and the donors.

**Budget:**

- Etabloring of database 10.000 kr.
- Statistic helps 20.000 kr.
- Statistic courses 20.000 kr.
- Transport 10.000 kr.
Appendix 1

Hæmatologi, Hæmoglobin, Leukocytter, Trombocytter.

Leukocyttype:liste: Basofilocytter, Eosinofilocytter, Lymfocytter, Metamyelo+Myelo+Promyelocytter, Monocytter, Neutrofilocytter.

Væske og elektrolytbalance: Kalium, Natrium, Kreatinin, eGFR (1,73 m²), Calcium-ion frit, Fosfat.

Hæmostase: Koagulationsfaktor II+VII+X.

Organmarkører: Laktatdehydrogenase.

Immunologi og inflammation: BAC-test, Blodtype(ABO; Rh D), C-reaktivt protein [CRP], Sedimentationsreaktion.
References


