SYNOPSIS

Title:	Tumor heterogeneity of renal tumors assessed by multiparametric MRI with direct radiological-histopathological correlation: an explorative study
Short title / Investigation ID:	mpMRI and Heterogeneity in Renal Tumors, registry number will be added after ethics approval
Clinical Investigation Plan, version and date:	Version 1.1 of 01.08.2022
Category and its rationale:	Study category A1. The MR scanner used is clinically approved with a CE label. MRI exams are performed according to clinical standard (i.e., in terms of specific absorption rate etc.).
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	All MRIs will be performed on a clinically used 3.0 Tesla MR scanner (Siemens Medical Solutions, CE label). The MRI performed is an extension of a clinical kidney MRI by addition of MRI sequences to quantify tumor biology. Study sequences run under the CE label of the MRI scanner (the company does not provide CE labels for single MR sequences, but for the whole MR scanner system including the sequences running on this scanner). All MRI sequences are product sequences used in clinical routine. No pre-clinical sequences are used. All examinations will be performed on Siemens Vida Fit scanners at the University Hospital Zurich (SN: 10432915 and 10849580).
Stage of development:	Post-market stage
Background and rationale:	Renal cell carcinomas (RCC) are known to display heterogeneity on both imaging and histopathological analysis. This has particular impact on possible sampling errors in renal biopsy, which is routinely performed for therapy stratification in metastatic patients or patients with serious medical co-morbidities/frailness, in which surgical resection of the tumor is not possible. Therefore, being able to identify areas in the tumor prior to the intervention that may harbor a different tumor grading/genomic make-up as the rest of the tumor could be extremely helpful: This would allow for a more complete assessment of a tumor's aggressive potential and histopathological variations with as few biopsies as possible, thus decreasing the chance to falsely underestimated a tumor's aggressiveness or the presence of a mutation that may potentially offer predictive information on patient outcome or change systemic treatment. Multiparametric MRI is known to be able to offer insights into a tumor's microenvironment by non-invasive quantification of tissue parameters. Several techniques, assessing, for example, tumor microperfusion, diffusivity or fat content, have been developed over the last few years and investigated in renal tumors e.g., to differentiate between tumor subtypes or grades. However, these analyses have focused on MRI parameters generated from the whole tumor volume or a single region-of-interest placed somewhere in the tumor and did not feature a direct correlation between distinct tumor regions with differing histopathological characteristics and the corresponding region on imaging. The purpose of this study is to directly explore the correlation between parameters of mpMRI and histopathology from matching regions on pathological examination and imaging. This information could potentially be used to guide upfront biopsy in patients with metastasized or locally advanced disease in the near future.

Objective(s):	• To investigate renal cell carcinoma heterogeneity by exploring direct radiological-pathological correlations between parameters of preoperative multiparametric MRI and histopathological parameters (tumor subtype, grading, necrosis, presence of mutations, etc.) using matching tumor region analysis on imaging and pathology. •
Outcome(s):	The primary outcome will be the tumor entity, grade and the presence of distinctive mutations in the histopathological specimen.
Design:	Open label, non-randomised study
Inclusion / exclusion criteria:	Inclusion criteria: • Patients with confirmed or suspected renal tumor with an approx. size of ≥ 2 cm who are scheduled for clinical MRI examination and surgical resection of the tumor • Informed consent as documented by signature (Informed Consent Form) • Patients ≥18 years of age Exclusion criteria: • Women who are pregnant or breast feeding • Intention to become pregnant during the course of the study and lack of safe contraception • Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders, dementia, etc. of the participant • Previous enrolment into the current study • Enrolment of the investigator, his/her family members, employees and other dependent persons • Patients with non-MRI compatible metallic or electronic implants, devices or metallic foreign bodies (cardiac pacemaker, shrapnel, cochlea implants, neurostimulator, or other non-MRI compatible implants). • Patients with known hypersensitivity reactions to MRI contrast agents will undergo the examination without application of a contrast agent
Measurements and procedures:	The patients will undergo a multiparametric MRI examination prior to surgical resection of the renal tumor. After surgical resection, the resected specimen will be transferred to the Department of Pathology, cut, and divided into several tumor areas. These tumor areas will then undergo individual histopathological analysis and their results will be compared to the MRI parameters in the matching tumor area to assess tumor heterogeneity.
Intervention:	Patients will undergo pre-surgical MRI to non-invasively assess tumor heterogeneity on imaging. The resected specimen will then be divided into tumor areas and the histopathological results of this area will be matched and compared to the MRI parameters from the corresponding area on imaging.
Duration of the investigation:	The estimated duration for the main investigational plan is 3 years (i.e., from start of screening of first participant to last participant processed and finishing the study).
Investigation schedule:	10/2022 First-Participant-In (planned) 10/2025 Last-Participant-Out (planned)

Statistical considerations:	This is an explorative study to assess intra-tumor heterogeneity on MR imaging and histopathology and possible correlations between imaging and histopathological parameters. We plan to recruit 30 patients, with each tumor being divided into 4 – 8 tumor areas to allow for sufficient cohort size for statistical analysis. For the continuous parameters, mean and standard deviation, or if more appropriate (due to skewed distributions), median and inter-quartile range will be reported. Correlations will be assessed using the Pearson correlation coefficient. Statistical comparisons may be performed using t-tests or non-parametric Wilcoxon rank sum tests (also referred to as Mann-Whitney U tests), respectively.
Compliance statement:	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.