Pilot study to correlate contrast-enhanced ultrasound of renal masses with pathologic grade: a prospective comparison of quantitative and qualitative findings

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Aim

In patients with suspected renal cell carcinoma, to evaluate radiologic features using contrast-enhanced ultrasound (CEUS), and compare them with pathologic grading at surgery.

Rationale

Renal malignancies are relatively common, with lifetime risk ranging from 1 in 48 in men to 1 in 83 in women, of which renal cell carcinoma (RCC) is the most common. RCC comes in a variety of subtypes, and pathologic grade has been shown to be one factor that correlates with patient prognosis. Commonly used pathologic grading scales are the WHO / Fuhrman scales, which rely on the histologic features of the tumor, such as nuclear size, irregularity, and nucleolar prominence.

Patients with renal lesions suspicious for RCC have a variety of different treatment pathways available to them. These pathways are dependent on a number of factors, in particular size and pathologic grade. As such, radiologic surveillance with CT and MRI is common, particularly with smaller lesions. Moreover, our radiologists are being asked by urologists to biopsy more and more renal lesions to better guide their decision making. While percutaneous biopsy of renal masses is the least invasive way to obtain tissue, it still entails nontrivial cost and risk, especially that of hemorrhage given the highly vascular nature of the kidneys and renal tumors.

Contrast-enhanced ultrasound (CEUS) with Lumason contrast (Bracco) was approved for use in the USA two years ago, after many years of experience in Europe. CEUS has been shown to have the ability to differentiate renal masses from normal background renal parenchyma , with sensitivity and specificity of over 95 percent regardless of lesion size in one large study (Barr et al) It has the unique ability to be used in patients with renal dysfunction, as it is excreted by the liver and lungs. As such, it is well suited for use in patients with underlying renal pathology. It is relatively inexpensive, and the injection and use of ultrasound contrast (microbubbles) is low-risk compared with percutaneous biopsy.

Scarce literature is available regarding the utility of CEUS to help differentiate imaging findings of more aggressive RCCs versus less aggressive ones. This study will aim to use CEUS to evaluate the quantitative and qualitative imaging features of RCC prior to surgical removal, and to correlate these features with pathologic grade following surgery. We hypothesize that tumors with different pathologic grades will show different patterns of qualitative enhancement, as well as different perfusion kinetics. If findings on CEUS do correlate with pathologic grade, CEUS could possibly add additional information to the clinical decision making process, separately or in addition to biopsy at the discretion of the clinical team.

Performance site

University Hospital

Patient selection

Inclusion criteria

1. Males and females
2. Age 18 years or greater
3. RCC suspected by referring urologist, based on clinical presentation and radiologic appearance
4. Partial or total nephrectomy planned at the performance site

Exclusion criteria

1. History of acute cardiac ischemia
2. History of hypersensitivity reaction to Lumason
3. Pregnancy
4. Pathologic diagnosis at surgery is not RCC, or pathologic grading not applied to RCC
5. Renal mass unable to be visualized by grayscale ultrasound
6. Known renal vein thrombosis

Methods

From the urologic clinic at the performance site, a urology co-investigator will identify all patients who meet inclusion criteria. The urology co-investigator will inform the patient about the study, and ascertain whether the patient is interested in participating. If so, the urology co-investigator will contact radiology research scheduling and have the patient scheduled for CEUS at the performance site, later the same day if possible. The urology co-investigator will also contact a radiology co-investigator, so that this person can consult the medical record and ensure that exclusion criteria 1-3 are not met. The patient will be given a copy of the informed consent to read prior to return for imaging.

On arrival at the ultrasound suite, a radiology co-investigator, in a room away from other patients or staff, will again describe the study, answer any questions, and seek written informed consent.

If consent is granted, the patient will undergo CEUS.

In the procedure, the patient will be imaged in the US suite at University Hospital by technicians trained in use of CEUS, under supervision of one of the study's radiologist personnel. 2.5 mL Lumason (lipid type A lyophilized powder + sulfur hexafluoride, in saline) will be injected intravenously into the antecubital fossa immediately prior to US imaging. US imaging of the kidney will then be performed, and the parameters below measured. A second injection of the same amount of contrast material may be used at the discretion of the study radiologist dependent on the quality of tumor visualization (ie. suboptimal lesion enhancement, contrast

injection malfunction, excess patient motion) with the initial dose.

Following CEUS, the lesions will be evaluated by radiology study personnel. Evaluation will consist of subjective, qualitative review of the images for pattern of enhancement, especially in relation to the normal renal cortex, which has been described as the preferred way to identify malignant renal lesions. Additional evaluation will include quantitative analysis of lesion and normal renal parenchyma perfusion dynamics using available software.

Items to be documented from the medical record, radiologic studies (CEUS and prior imaging), and surgical and pathologic records include age, sex, indication for each radiologic study, pertinent results of prior radiologic studies, time interval from RCC clinical diagnosis to surgery, CEUS quantitative findings (peak signal intensity, time to peak, area under the curve, mean transit time, of both the mass and normal renal tissue), CEUS qualitative findings (description of enhancement pattern), pertinent surgical findings, and pathologic findings including grade.

This study will monitor for adverse events (as defined below) related only to the injection of and/or physiologic reaction to Lumason. Available data shows that reactions to Lumason are rare, with the most common reactions being headache, nausea, and dizziness. True allergic reactions (ranging from hives and urticaria to anaphylactoid reactions) are even less common. Patients will be monitored by study personnel during and for at least 30 minutes after intravenous injection of contrast for immediate reactions. The patients will also be given instructions to call with any concerns in the 48 hours following contrast injection.

Adverse Event (AE)

Any untoward medical occurrence in a patient, not necessarily having a causal relationship with the study. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the study, whether or not related to the study.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

1) Results in death or ANY death occurring within 28 days of date of study intervention (even if it is not felt to be study related)
2) Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3) Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
    - **NOTE**: Hospitalizations that are not considered SAEs are:
        - Hospitalization planned prior to first study intervention

- Hospitalization less than 24 hours
- Hospitalization for elective treatment of a pre-existing condition unrelated to the study intervention

4) Results in persistent or significant disability/incapacity
5) Is a congenital anomaly or birth defect
6) Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Unexpected Adverse Event

An adverse event not associated as a known risk or adverse event.

Determining Attribution to the Investigational Procedure

Attribution: An assessment of the relationship between the AE and the study intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	**Attribution**	**Description**
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

Descriptive statistics will be performed, documenting total number of patients with each item above, and comparing numbers for different pathologic grades, where pathologic grades 1 and 2

and pathologic grades 3 and 4 will be combined for inferential analysis. We will analyze how each item varies with pathologic grade using students t-test (continuous variables) and Fisher's test (categorical variables). With 40 subjects enrolled, we expect to see approximately 20 grade 1/2's and 20 grade 3/4's. At least 12 subjects per group is considered sufficient for a pilot study (ref: Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics. 2005;4(4):287–91.).

Data monitoring

CEUS is an inherently low-risk procedure when performed in centers with expertise. IU has been one of the leaders in the USA in studying the use of CEUS since it was approved by the FDA. We will have a data safety committee composed at minimum of the PI, a listed investigator urologist and radiologist, and another radiologist not involved in the study. The committee will meet after the first five patients have completed the renal CEUS to monitor accrual, workflow, any issues affecting recruitment and patient safety, data acquired thus far, and any new research impacting the study. The study will also collect adverse event details, including defined adverse events of interest, timeframe for collection, etc.

Primary data will be collected via direct data capture from measurement instrument and stored electronically in REDCap. The storage location will be backed up automatically. Quality assurance steps will include testing of database by study team prior to moving to production mode. The following quality control methods will be used: single entry with random checks of accuracy and extraction and cleaning of data that will be used for analysis quarterly.

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **Low Risk Trials.**

Investigators will conduct continuous review of data and subject safety. **Quarterly review meetings** for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Quarterly** meeting summaries should include review of data, the number of subjects, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee
The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer

must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/ Oncore Reporting Requirements
The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting
In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Protocol Deviation Reporting
Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

Enrollment

This is a pilot study to determine whether there is evidence that CEUS findings have correlation with pathologic staging. There has been almost no prior work done in this area and we do not have data to support sample size and power calculations. We propose imaging 40 patients because the cost of 40 Lumason doses is what we can reasonably expect to be reimbursed by our department. If we have promising results, we expect to apply for an industry or federal grant to study CEUS in a much larger population of patients with renal tumors, either at IU alone or together with other centers.

Resources/Budget

We have applied to our departmental project development team for funding for Lumason doses. A budget is under development. All other costs associated with CEUS, including imaging time

and the time of the investigators, will be the responsibility of the departments of Urology and Radiology and Imaging Sciences.

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