

## **Evaluation of the accuracy of ultrasound in monitoring the size and growth of small renal masses**

IRB Protocol

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August 30, 2010

### **A. Study Purpose and Rationale**

Over the past 20 years, the incidence of SRM has increased secondary to increased rates of abdominal imaging. During the time period from 1997 to 2006, an almost 26% increase in renal cancer incidence has coincided with a 12% increase in the number of deaths from the same disease.<sup>12</sup> The discrepancy between incidence and mortality reflects the increasing number of benign and indolent cancers – cancers that previously would not have been detected nor would have become clinically relevant. A rise in the detection of solely benign and/or indolent cancer should manifest as decrease in the overall mortality from renal cancer. However, the rise in mortality and discrepancy between the expected and observed mortality rates must reflect either an environmental change, an evolution in the character of renal cancer or a failure in the general methods used to treat the disease. In 2009, the American Urological Association (AUA) released its “Guideline for the management of the clinical T1 renal mass.” In these guidelines, the AUA lists AS as a viable option for masses up to 7cm (pT1b) given certain patient criteria regarding suitability for surgery. However, for small renal masses less than 4cm (pT1a), the AUA recommends AS for high-surgical-risk patients and lists AS as an option for healthy patients willing to avoid treatment and willing to assume increased oncological risk of delaying intervention.<sup>3</sup>

However, despite these new AUA guidelines, it is unknown how to best survey these patients. Abdominal imaging techniques, usually MRI (magnetic resonance imaging) or CT (computed tomography) scan, are the modality by which most of these RCTs are incidentally found. These scans are often able to discern malignant and dangerous cancers from more benign-behaving growths. However, it must be recognized that repeat exposure to radiation may place patients at increased risk of malignancy. While no study has definitively linked CT scans to increased cancer risk (NEJM),<sup>4</sup> a number of publications insinuate that even single exposure to CT may increase the risk of malignancy,<sup>5</sup> even as high as 1 in 80.<sup>6</sup> Therefore patients must be informed of the risks of serial CT imaging and alternatives (MRI and ultrasound, US) must be offered. As MRI is currently far less available in many parts of the United States in comparison to CT/US, the most feasible alternative to CT in patients enrolled in AS may be ultrasound.

Although various imaging modalities have not been compared for patients undergoing AS, ultrasound has been shown to be an adequate alternative to CT in diagnosing small renal masses <3cm. Among lesions 10-35 mm, 80% and 82% were correctly characterized with CT and US, respectively.<sup>7</sup> Additionally, intravenous contrast enhancing agents are increasingly being utilized to increase sensitivity of ultrasound. Preliminary studies show that contrast-enhanced US provides more information than color Doppler imaging alone.<sup>8</sup> Although CT has been the gold standard for the diagnosis and surveillance of SRMs, given increasing concerns about

radiation exposure due to CT, it is important to evaluate whether ultrasound may have adequate accuracy in monitoring SRMs for change in size.

In Summary, with the increasing incidence of SRMs found incidentally during abdominal imaging, more patients are opting for non-surgical management of these localized tumors. These patients are surveyed every 4-6 months, and if the mass is found to increase in size or shape, they are referred for surgery to remove the lesion. For patients who desire active surveillance, the benefits of CT, the gold standard image for renal tumor evaluation, must be balanced with the potential radiation exposure of this modality. Ultrasound may prove to be a viable alternative in monitoring these SRMs for growth.

I propose to examine the correlation in tumor diameter using ultrasound vs CT in patients with incidentally found renal masses <4cm enrolled in active surveillance protocols.

## **B. Study Design**

The study design is a prospective examination of the correlation between renal mass diameter on ultrasound and measurement of renal mass diameter on CT at every 4-6 month time interval during a patient's active surveillance protocol. Subjects will be drawn from the current Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) protocol. Each subject will undergo an ultrasound in addition to their current CT regimen at each surveillance interval. The primary outcome will be accuracy of ultrasound in predicting whether a CT will show change in tumor size.

## **C. Study Procedures:**

### **Review: general DISSRM procedures**

Patients with SRM (greatest dimension equal to or less than 4cm) incidentally diagnosed by CT imaging or MRI, will be offered entrance into the trial. As described in the Introduction, intervention and surveillance are reasonable options for patients with renal masses of this size. Patients will be counseled by their primary urologist outside the study regarding the appropriateness of intervention and surveillance, and in the case of intervention, the most appropriate modality. In addition, patients will be offered percutaneous renal biopsy prior to choosing a management option. After a decision has been made by the patient and their physician, they will be offered entry into the DISSRM protocol, designed to capture, in a prospective manner, the clinical and pathological data of patients undergoing standard-of-care AS for SRM. The standard-of-care involves serial imaging every three to six months annually. We therefore created a standard protocol to follow patients with serial imaging every four to six months for two years and then every six months to a year thereafter. Consultation and management of patients will occur prior to and outside of the study. After a decision has been made by patient and treating physician regarding AS or intervention they will be offered entrance into this prospective study. ***This additional arm of the protocol will ask the additional question if the study subject would agree to having both a CT and ultrasound. If the subject responds affirmatively that individual will enter this additional study arm. If the study subject does not wish to receive both images, they will remain apart of the general DISSRM registry as such.*** Note, consultation occurs prior to and outside of the study. The study is designed to capture practice patterns (i.e. how many patients select AS versus intervention) and prospective outcomes after a clinical decision has been reached. The decision-making process is *not* part of the study *nor* will patients will be assigned to a treatment arm.

The following is an example of the expected data that would come out of this analysis:

		CT change in size		
		yes	no	
Ultrasound Change in size	yes	30	15	45
	no	10	145	155
		40	160	

Accuracy =  $(175/200)0.875$

In this pilot study, using the expected accuracy of 95%, a sample of 44 ultrasound measurements is required to detect an accuracy of 80% with 95% confidence and 80% power ( $\alpha=0.05$ ).

**D. Study Drugs**

Not applicable.

**E. Medical Device**

Not applicable

**F. Study Questionnaires**

Not applicable.

**G. Study Subjects**

INCLUSION:

1. Must have a solid, enhancing renal mass  $\leq 4$ cm at its greatest dimension found on incidental scanning in the last 6 months.
2. Age  $\geq 18$  and able to read, understand and sign informed consent.
3. Must have an ECOG status of 0, 1 or 2. (See Appendix IV)
4. Must be willing to adhere to the treatment algorithm and time constraints therein.
5. Must have agreed to participate in DISSRM registry before agreeing to ultrasound arm of study

EXCLUSION:

1. Cannot have suspicion of metastases to the kidney if any other malignancy diagnosed within two years of study entry.

### ***Criteria for removal***

- Patients who are non-adherent to the protocol will be removed from the study. Non-adherence is defined as the failure to keep an appointment, specifically a follow-up CT scan within two months of their scheduled appointment.
- Withdrawal of informed consent.

### **H. Recruitment of Subjects**

All eligible subjects referred to or being treated at the Department of Urology at Columbia University Medical Center (CUMC) or the Johns Hopkins Brady Urological Institute who meet the inclusion criteria will be offered study participation.

### **I. Confidentiality of Study Data**

Any information obtained during this study will remain confidential. A record of study data will be kept at the CUMC Department of Urology and the JHH Brady Urological Institute for each institute's respective patients. Personal identifiers will not be listed on study data collected, patient numbers will be used instead. Information obtained from this study and from subjects' medical records may be used for research purposes and published. No patient identification information will be released without separate consent, except as specifically required by law.

### **J. Potential Conflict of Interest**

There are no potential conflicts of interest.

### **K. Location of the Study**

The study will be conducted in Department of Urology at CUMC.

### **L. Potential Risks**

Ultrasound measurement of renal mass diameter carries minimal risks, including discomfort from pressure applied to obtain ultrasound images and potential allergy to the gel used to lubricate the ultrasound probe.

### **M. Potential Benefits**

It is not possible to predict whether patients will benefit from this study. Patients will be followed closely for progression of disease and may avoid unnecessary surgery.

### **N. Alternatives**

There are no experimental alternatives for the management of small renal cortical tumors. Alternatives to this study include follow-up and treatment not based on the treatment protocol outlined in this study.

### **O. Compensation of Subjects**

Subjects will not be compensated for participating in this study.

### **P. Costs to Subjects**

There will be no cost to the subjects.

### **Q. Minors as Research Subjects**

Patients under the age of 18 will not be eligible for this study.

### **R. Radiation and Radioactive Substances**

Not applicable.

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## S. References

- <sup>1</sup>Cancer Facts and Figures: The American Cancer Society, 1997
- <sup>2</sup> Cancer Facts and Figures: The American Cancer Society, 2006
- <sup>3</sup> Campbell, S. C., Novick, A. C., Belldegrun, A. et al.: Guideline for management of the clinical T1 renal mass. *J Urol*, **182**: 1271, 2009
- <sup>4</sup> Smith-Bindman, R.: Is computed tomography safe? *N Engl J Med*, **363**: 1
- <sup>5</sup> National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation.: Health risks from exposure to low levels of ionizing radiation : BEIR VII Phase 2. Washington, D.C.: National Academies Press, pp. xvi, 406 p., 2006
- <sup>6</sup> Smith-Bindman, R., Lipson, J., Marcus, R. et al.: Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med*, **169**: 2078, 2009
- <sup>7</sup> Jamis-Dow CA, Choyke PL, Jennings SB, et al: Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. *Radiology* 198: 785-788, 1996.
- <sup>8</sup> Ascenti G, Zimbaro G, Mazziotti S, Gaeta M, Settineri N, Scribano E. Usefulness of power Doppler and contrast-enhanced sonography in the differentiation of hyperechoic renal masses. *Abdom Imaging* 2001; 26: 654–60