Format for ANSWERING REVIEWERS

August 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16859-review.doc).

Title: Advances of multidetector computed tomography in the characterization and staging of renal cell carcinoma

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Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 16859

The manuscript has been improved according to the suggestions of reviewers:

Comment No 1: This is a comprehensive review paper of MDCT in characterization and staging of renal cell carcinoma. This is a well written article and the authors must be congratulated for their efforts. CT is also useful in differential diagnosis. So please add a part of differential diagnosis of RCC and other lesions, such as lipid-poor AML.

-**Response to reviewer Comment No 1:**

DIFFERENTIATION OF RCC FROM BENIGN RENAL TUMORS

The wide use of cross-sectional imaging studies has also led to an increase of incidentally discovered benign renal masses, including angiomyolipoma (AML) and renal oncocytoma. Because radical nephrectomy is not desirable for a benign tumor, the accurate characterization of renal masses is required to avoid unwanted surgery. CT findings may prove helpful in characterizing the nature of renal tumors[53-62].

AML can be accurately diagnosed on CT, by detecting the intratumoral fat component with negative density on unenhanced scanning. However, in approximately 4.5% of all AMLs intratumoral fat cannot be visualized at CT. Kim et al in a retrospective study of 19 AMLs with minimal fat and 62 RCCs on two-phase helical CT, reported that homogeneous tumor enhancement and prolonged enhancement pattern were the

most valuable CT findings in differentiating these tumors, more often detected in the first group[53]. Hyperdensity of a renal mass on plain CT images is another CT finding reported for AML with minimal fat[54]. Zhang et al in a retrospective study of 44 AMLs with minimal fat and papillary RCCs reported that the unenhanced CT density, the presence of intratumoural vessels, and the CT density of early excretory phase images may be used to differentiate these tumors[55]. Woo et al reported unenhanced tumor-kidney CT density difference and long-to-short axis ratio as the simplest and more accurate features in differentiating AMLs with minimal fat from non-clear cell RCCs on three-phase MDCT[56].

Several studies have described CT imaging features of renal oncocytoma, including well-defined margins, homogeneous contrast enhancement, presence of a central stellate scar, spoke-wheel pattern of arterial enhancement and absence of hemorrhage, calcifications and necrosis[58,59]. More specifically, renal oncocytoma has been described as a sharply-demarcated solid homogeneous mass, with homogeneous contrast enhancement, except for a hypodense stellate, central area. However, these classic findings do not always allow a confident characterization of this tumor, because they are often seen in patients with RCC[58,59]. MDCT improved the diagnostic performance of CT in differentiating these tumors[60-62]. The enhancement and washout values in MDCT may aid in distinguishing small oncocytomas from RCCs of similar size[60,61]. Bird et al reported that early phase enhancement greater than 500% and washout values of greater than 50% were mostly seen in renal oncocytomas[60]. Cho et al reported characteristic contrast enhancement patterns for renal oncocytomas smaller than 4 cm in diameter on MDCT[62]. The authors assessed segmental enhancement inversion during the corticomedullary phase and early excretory phase, defined as follows: in a renal mass showing two parts with different degrees of enhancement during corticomedullary phase, the relatively more enhanced part became less enhanced during early excretory phase, whereas the less-enhanced part during corticomedullary phase became highly enhanced during early excretory phase. Segmental enhancement inversion was found to be characteristic of small renal

oncocytomas in this study[62].

-**Comment No 2:** This is a review paper about the application of MDCT in pre-operation evaluating or staging renal cell carcinoma. 1. the data is updated. 2. The detail of the review is adequate. 3. No particular bias noted. suggestion: all the quantitative data should be shown in the abstract.

-Response to reviewer Comment No 2:

Abstract

Renal cell carcinoma (RCC) accounts for approximately 90-95% of kidney tumors. With the widespread use of cross-sectional imaging modalities, more than half of RCCs are detected incidentally, often diagnosed at an early stage. This may allow the planning of more conservative treatment strategies. CT is considered the examination of choice for the detection and staging of RCC. Multidetector CT (MDCT) with the improvement of spatial resolution and the ability to obtain multiphase imaging, multiplanar and three-dimensional reconstructions in any desired plane brought about further improvement in the evaluation of RCC. Differentiation of RCC from benign renal tumors based on MDCT features is improved. Tumor enhancement characteristics on MDCT have been found closely to correlate with the histologic subtype of RCC, the nuclear grade and the cytogenetic characteristics of clear cell RCC. Important information, including tumor size, localization, and organ involvement, presence and extent of venous thrombus, possible invasion of adjacent organs or lymph nodes, and presence of distant metastases are provided by MDCT examination. The preoperative evaluation of patients with RCC was improved by depicting the presence or absence of renal pseudocapsule and by assessing the possible neoplastic infiltration of the perirenal fat tissue and/or renal sinus fat compartment.

-**Comment No 3:** -Well written manuscript. Comprehensive review of MDCT in RCC. Very narrow focus, which is both a strength and a weakness: there is only one sentence in the text that "CT is widely accepted as the examination of choice...". Suggestion: expand with a short paragraph regarding other imaging procedures, e.g. ultrasound, MRI, FDG-PET, refer for example to ACR appropriateness criteria, in order to

substantiate that CT is the preferred imaging as compared to other modalities.

-Response to reviewer Comment No 3:

According to the recommendations by the American College of Radiology, multidetector, multiphasic CT of the abdomen is considered appropriate for staging of small or incidentally detected renal tumors (equal or smaller than 3 cm in diameter)[52]. For renal tumors larger than 3 cm in diameter, MDCT is the diagnostic modality of choice. MRI of the abdomen is a suitable substitute, when patient cannot undergo contrast-enhanced CT. Ultrasonography may be considered more appropriate for staging small renal tumors, when the intravenous administration of contrast medium is contraindicated. Positron emission tomography (PET) does not yet have an established role in staging RCC. PET with the tracer fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG-PET) may find difficulties even in the detection of primary carcinoma against the normal background of hyperactivity in the kidneys. PET may be used as a complementary examination for confirming metastatic disease in lesions detected by CT, MRI, or bone scan, and it may be used to detect unsuspected metastases in high-risk patients[52].