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Name of Journal: *World Journal of Radiology*

ESPS Manuscript No: 22192

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ANSWERING REVIEWERS

Reviewer's code: 01560036

COMMENTS TO AUTHORS

Very nice and very useful review

Thank you for the highly positive comments !

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Reviewer's code: 00227565

COMMENTS TO AUTHORS

Dear I interestingly enjoyed this neat manuscript. It is an organized nearly comprehensive review about one of the common urologic neoplasms, renal cell carcinoma (RCC). The authors described the pathologic typographies and background. Then they rapidly passed across the different imaging features of renal cell carcinoma as well as their similar. I feel they go deep for pathology more than imaging, however. It will be good to raise a concise discussion on applying advanced imaging technique in differential diagnosis of RCC. I have the following comments that aim to improve the work. 1) Please compare these percentages with the article of Sun et al and correct them. 2) May you provide some images on the differential diagnostic entities of RCC. 3) Lymphomatous infiltration of the kidney is a commonly met entity and finding during staging of lymphoma. An example will be an addition to the work. 4) The 149 references are too much for such review…May you reduce it to 100 and less. Multiple references discuss the same point could solve this problem. 5) As regard Figure-5; kindly a hint about the Dixon reconstruction and its applications in renal masses; within the text; will be a plus for this manuscript. 6) As regard Figure-7; the mass looks like to be completely within the confinement of the renal parenchyma even invading the renal medulla!! This is not an exophytic mass if it is that in the subfigure 7-a; is not? Good Luck

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Thank you for the highly positive comments !

1. We have reviewed the Sun et al [ref 26] paper in detail, and the percentages quoted in our manuscript correspond accurately to that reported by Sun et al's publication.

Sun MR, Ngo L, Genega EM, Atkins MB, Finn ME, Rofsky NM, Pedrosa I. Renal cell carcinoma: dynamic contrast-enhanced MR imaging for differentiation of tumor subtypes--correlation with pathologic findings. Radiology 2009; 250(3): 793-802 [PMID: 19244046 DOI: 10.1148/radiol.2503080995]

2. We have now included images of renal angiomyolipoma [FIGURE 9A, B, C], oncocytoma [FIGURE 10] and secondary renal lymphoma [FIGURE 11]

3. We have now included an image of secondary renal lymphoma [FIGURE 11]

4. We respectfully cannot agree with the reviewer. The large number of references used is a by-product of the very extensive review carried out in the manuscript. In keeping with ethics in publishing, we strongly believe that every source that we obtain information from needs to be included in the references. Some statements include more than one source/reference, but this is valuable as it serves to highlight to the

reader that the statement in question has strong agreement from multiple publications.

5. The following are included:

'The presence of intralesional fat (either macroscopic or microscopic), is a recognized feature of some clear cell RCCs [11, 15, 53, 59]. However, this finding is not subtype specific as rarely papillary RCC and chromophobe RCC may contain fat [1, 11, 55, 60, 61]. Karlo et al. found that while all 3 subtypes may contain microscopic fat as visualized by signal intensity loss on opposed-phase compared to in-phase T1-weighted MR images [FIGURE 5], a > 25% signal loss was predictive for clear cell RCC [61]. *The use of a simple two-point Dixon fat-water separation technique derived from a dual-echo chemical shift T1 sequence is often helpful in aiding the radiologist in identifying small quantities of microscopic fat in a renal mass.* '

6. The term 'exophytic' has been removed from the Figure legend for 7a and 7b

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Reviewer's code: 00214317

COMMENTS TO AUTHORS

The manuscript is well writtern but need minor Title change into Review imaging of renal cell carcinoma as you discuss other issues than subtypes more data about subtypes of RCC

Thank you for the highly positive comments !

We have changed the title to the following: "Review of Renal Cell Carcinoma and its Common Subtypes in Radiology" as this is suggested verbatim by the next reviewer and seems a nice compromise with the suggestions of this reviewer.

The data that we have provided on the RCC subtypes is as detailed as you will find in almost any journal publication in the literature, outside that of a book chapter. The large number of references used is testament to this.

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Reviewer's code: 00225366

COMMENTS TO AUTHORS

This paper reviewed the renal cell carcinoma and its common subtypes. A lot of examples as CT and MRI images were given. This is a serious work including over 140 references. Readers of WJR should be benefited from that. My only comment is that the title should be changed to "Review of Renal Cell Carcinoma and its Common Subtypes in Radiology", because it is focused on the radiology study on the cancer cell.

Thank you for the highly positive comments !

We have changed the title to the following: "Review of Renal Cell Carcinoma and its Common Subtypes in Radiology" as suggested.

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Reviewer's code: 00058381

COMMENTS TO AUTHORS

Major Comment: This manuscript provides an interesting review on an important topic. As it is a bit lengthy and as it is written for a radiological journal, I would recommend shortening the parts not dealing with imaging in order to make them more concise. Minor Comments: Page 11: "Kim et al. showed that the presence of calcifications were significantly more frequent in papillary RCC…" Suggestion: "Kim et al. showed that calcifications were significantly more frequent in papillary RCC…". The format of the references is not consistent with the journal style described in the "Instructions to Authors".

We respectfully cannot agree on shortening the non-imaging parts of the manuscript as these sections are essential material for understanding RCC which is a multifaceted complex entity. The current information provides the readership of WJR with a very comprehensive review of the topic and the non-imaging sections are beneficial to radiologists (some of whom may not be completely abreast with the non-imaging aspect of RCC as an entity) and physicians of other medical and surgical specialties that read the article. With PubMed being the most common means for searching the medical literature, the readership of WJR includes physicians of many different disciplines not just radiologists. Having non-imaging sections in the review only serves to increase the articles applicability and potential usefulness and citability amongst physicians and researchers.

Suggestion: "Kim et al. showed that calcifications were significantly more frequent in papillary RCC…". [The manuscript is edited to incorporate the reviewer's suggestion]

The format of the references is now changed to reflect the Instructions for Authors of WJR. Please note that there are inherent limitations with this as some references do not possess either PMID or a DOI.

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Reviewer's code: 02348457

COMMENTS TO AUTHORS

Please add some figures of the differential diagnosis, such as AML, oncocytoma, lymphoma

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Thank you for the highly positive comments !

We now include figures for AML [FIGURES 9A, B, C], oncocytoma [FIGURE 10] and lymphoma [FIGURE 11].

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Reviewer's code: 02887637

COMMENTS TO AUTHORS

1)This is a nice review on appearance of the different subtypes of RCC and mimics. Tumour characteristic on morphologic sequences and perfusional features are reported which help differentiating different histotypes. Appearance of the different tumors on diffusion weighted imaging is lacking, however. I suggest to enclose this information. 2) Page 17, fat-poor angiomyolipoma. Lipid poor AML much be differentiating from AML lacking completely fat. The former display signal loss on opposed-phase compared with in-phase T1-weighted MR images, at least in some areas, while the latter do not. 3) The Authors provide a nice review of the huge literature in which attempt was made to characterize oncocytoma from malignant neoplasms. Some papers report very high sensitivity and specificity, but other deny these findings. As a matter of fact, evidence is now lacking that oncocytoma can reliably be differentiated from malignant neoplasms, in the clinical practice, based on imaging features. This final comment should be enclosed. 4) Appearance of renal lymphoma on diffusion weighted MR imaging should be reported. 5) Information is lacking on use of CEUS in evaluation of solid renal masses. Please, refer to the EFSUMB guidelines (Ultraschall in Med 2011) for current indications. See also: Ultrasound Clin 8:581-592, 2013 AJR 2015; 205:W557-W565

Thank you for the highly positive comments !

1. The appearances of RCC including its subtypes on diffusion weighted imaging is now provided. The following is included:

''Several preliminary studies have shown encouraging results in utilizing diffusion-weighted imaging (DWI) for characterizing RCCs into its main subtypes as well as into high grade and low grade tumors [67-70]. In a study of 33 patients with 36 RCCs (clear cell 32 and 4 non-clear cell) of which 23 were grade I or II and 13 were grade III or IV at 1.5-T, Goyal et al. found that clear cell RCCs (1.6 x 10^{-3} mm^2/s) had significantly higher mean apparent diffusion coefficient (ADC) values than non-clear RCCs (1.0 x 10^{-3} mm^2/s) ($p = 0.005$) while lower grade tumors (1.7 x 10^{-3} mm^2/s) had higher mean ADC values than higher grade tumors (1.3 x 10^{-3} mm^2/s) ($p = 0.005$) [67]. In a study of 77 patients with 78 RCCs (59 clear cell tumors, 12 papillary tumors and 7 chromophobe tumors) at 3-T, Choi et al. found that papillary RCCs (1.3 x 10^{-3} mm^2/s) and chromophobe RCCs (1.6 x 10^{-3} mm^2/s) had significantly lower mean ADC values than clear cell RCCs (1.8 x 10^{-3} mm^2/s) ($p < 0.01$) [68]. No significant differences were found between papillary and chromophobe tumors ($p = 0.26$). In addition, high grade clear cell RCCs (1.7 x 10^{-3} mm^2/s) were noted to have significantly lower mean ADC values than low grade clear cell RCCs (2.0 x 10^{-3} mm^2/s) ($p = 0.021$) [68]. In a study of 83 patients with 85 RCCs (49 clear cell tumors, 22 papillary tumors and 14 chromophobe

tumors) at 3-T, Wang et al. found that papillary RCCs (1.1 x 10^{-3} mm^2/s) and chromophobe RCCs (1.3 x 10^{-3} mm^2/s) had significantly lower mean ADC values than clear cell RCCs (1.8 x 10^{-3} mm^2/s). No significant differences were found between papillary and chromophobe tumors ($p = 0.068$) [69]. Furthermore, a meta-analysis by Lassel et al. of 17 studies with 764 patients found that ADC values on DWI could differentiate RCC (1.6 ± 0.08 x 10^{-3} mm^2/s) from benign renal lesions such as oncocytoma (2.0 ± 0.08 x 10^{-3} mm^2/s) ($p < 0.0001$) [70].''

2. The following is now included about lipid poor AML vs. AML completely lacking fat:
''Furthermore, lipid poor AMLs should be differentiating from AMLs that completely lacks fat. The former displays signal loss on opposed-phase compared with in-phase T1-weighted MR images, at least in some areas, while the latter does not.''

3. The following is now included about oncocytoma:
''Despite these promising preliminary reports, there remains a strong clinical body of opinion that oncocytoma cannot be reliably differentiated from RCC based on imaging features alone.''

4. The following is now included about renal lymphoma and diffusion weighted imaging:
'' Due to high cellularity, renal lymphoma generally show restricted diffusion and low DWI values although further analysis is required to determine if DWI can be used to differentiate renal lymphoma from other renal tumors [124].''

5. The following is now included about contrast enhanced US and renal masses.
''In patients with moderate or severe renal impairment, where CT or MR contrast agents may be contraindicated, contrast-enhanced ultrasound (US) may be used as a viable alternative for evaluating renal masses [71]. It can discriminate if a focal lesion is solid or cystic and can differentiate a solid neoplasm from a pseudotumor such as a column of Bertin [71]. In 103 patients with complex cystic renal masses, Xue et al. found that contrast-enhanced US was superior to both contrast-enhanced CT and conventional US in evaluating cystic masses including determining the cyst wall thickness, the number of internal septa and the presence of solid components [72].''

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Reviewer's code: 00227564

COMMENTS TO AUTHORS

(1) There are lack of new visions in imaging and characterization of renal mass. Authors just reviewed the established data and there is lack of new data. (2) Authors mentioned only CT & MRI findings, US and role of contrast enhanced US not mentioned also the role of diffusion weighted MRI, CT perfusion, PET CT not mentioned.

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1. We respectfully disagree with the reviewer.

Many of the other reviewers have found this to be a strong review.

A reviewers from Canada wrote ''A lot of examples as CT and MRI images were given. This is a serious work including over 140 references. Readers of WJR should be benefited from that.''

A reviewer from Russia wrote '' Very nice and very useful review''

A reviewer from Austria wrote '' This manuscript provides an interesting review on an important topic''

A reviewer from Egypt wrote ''Dear I interestingly enjoyed this neat manuscript. It is an organized nearly comprehensive review about one of the common urologic neoplasms, renal cell carcinoma (RCC)'' and another reviewer wrote '' This is a nice review on appearance of the different subtypes of RCC and mimics.''

2. We have focused the article predominately on CT and MRI as these are the workhorse modalities for detecting and characterizing renal masses. Furthermore, the majority of publications on the subject discuss the use of these two modalities while the majority of the readership of WJR will be familiar with these modalities and so find such information of personal relevance. The use of contrast enhanced US, CT perfusion, PET-CT and DWI are also now included in the manuscript.

For contrast enhanced US, the following is included:

''In patients with moderate or severe renal impairment, where CT or MR contrast agents may be contraindicated, contrast-enhanced ultrasound (US) may be used as a viable alternative for evaluating renal masses [71]. It can discriminate if a focal lesion is solid or cystic and can differentiate a solid neoplasm from a pseudotumor such as a column of Bertin [71]. In 103 patients with complex cystic renal masses, Xue et al. found that contrast-enhanced US was superior to both contrast-enhanced CT and conventional US in evaluating cystic masses including determining the cyst wall thickness, the number of internal septa and the presence of solid components [72].''

For DWI, the following is included:

''Several preliminary studies have shown encouraging results in utilizing diffusion-weighted imaging (DWI) for characterizing RCCs into its main subtypes as well as into high grade and low grade tumors [67-70]. In a study of 33 patients with 36 RCCs (clear cell 32 and 4 non-clear cell) of which 23 were grade I or II and 13 were grade III or IV at 1.5-T, Goyal et al. found that clear cell RCCs (1.6 x 10^{-3} mm^2/s) had significantly higher mean apparent diffusion coefficient (ADC) values than non-clear RCCs (1.0 x 10^{-3} mm^2/s) ($p = 0.005$) while lower grade tumors (1.7 x 10^{-3} mm^2/s) had higher mean ADC values than higher grade tumors (1.3 x 10^{-3} mm^2/s) ($p = 0.005$) [67]. In a study of 77 patients with 78 RCCs (59 clear cell tumors, 12 papillary tumors and 7 chromophobe tumors) at 3-T, Choi et al. found that papillary RCCs (1.3 x 10^{-3} mm^2/s) and chromophobe RCCs (1.6 x 10^{-3} mm^2/s) had significantly lower mean ADC values than clear cell RCCs (1.8 x 10^{-3} mm^2/s) ($p < 0.01$) [68]. No significant differences were found between papillary and chromophobe tumors ($p = 0.26$). In addition, high grade clear cell RCCs (1.7 x 10^{-3} mm^2/s) were noted to have significantly lower mean ADC values than low grade clear cell RCCs (2.0 x 10^{-3} mm^2/s) ($p = 0.021$) [68]. In a study of 83 patients with 85 RCCs (49 clear cell tumors, 22 papillary tumors and 14 chromophobe tumors) at 3-T, Wang et al. found that papillary RCCs (1.1 x 10^{-3} mm^2/s) and chromophobe RCCs (1.3 x 10^{-3} mm^2/s) had significantly lower mean ADC values than clear cell RCCs (1.8 x 10^{-3} mm^2/s). No significant differences were found between papillary and chromophobe tumors ($p = 0.068$) [69]. Furthermore, a meta-analysis by Lassel et al. of 17 studies with 764 patients found that ADC values on DWI could differentiate RCC (1.6 ± 0.08 x 10^{-3} mm^2/s) from benign renal lesions such as oncocytoma (2.0 ± 0.08 x 10^{-3} mm^2/s) ($p < 0.0001$) [70].''

For CT perfusion, the following is included:

''CT perfusion is an advanced technique that calculates quantitative parameters that reflect the tumor's intrinsic microvascular environment such as blood flow, blood volume, capillary permeability and mean transit time [73]. In a study of 85 patients that included a subset of 66 clear cell RCCs, 7 papillary RCCs and 5 chromophobe RCCs, Chen et al. found that mean equivalent blood flow and blood volume were significantly higher in clear cell RCCs vs. papillary RCCs ($p < 0.001$), while mean equivalent blood volume was significantly higher in clear cell RCCs vs. chromophobe RCCs ($p < 0.001$) [74]. In a CT perfusion study of 15 patients with 15 RCCs, Reiner et al. found that parameters such as blood flow and blood volume had a strong correlation with tumor microvascular density on histology with lower blood flow and blood volume noted in poor prognosis RCCs that had lower microvascular density [75]. This suggests that CT perfusion may have a potential role as a prognostic marker as a greater microvascular density is associated with improved prognosis and longer survival for RCC [75, 76]. In patients with metastatic RCC, CT

perfusion could be used to select patients that would benefit from targeted anti-angiogenic therapy as well to evaluate the post-treatment response [73].''

For PET CT, the following is included:

'' Finally, 18F-fluorodeoxyglucose (FDG) PET-CT is another modality that has been used to evaluate RCC. In a study of 100 patients with 107 RCCs, Nakajima et al. found that clear cell RCCs had significantly higher maximum standardized uptake and tumor-to-normal tissue ratio than non-clear cell RCCs ($p < 0.001$) when evaluated during the early dynamic phase [77]. During the whole body phase, the authors found that RCCs that were of higher stage, higher grade, and associated with vascular or lymphatic invasion showed higher maximum standardized uptake than less aggressive RCCs [77]. However, PET-CT is limited in primary tumor assessment as physiologic tracer excretion by the kidneys can mask an RCC leading to false negative results. PET-CT has more of a defined role for disease re-staging in advanced RCC and in recurrent RCC [78, 79]. Alongi et al. suggested that PET-CT was able to predict disease progression and survival in patients with recurrent RCC after surgery and so influence clinical decision making [80]. The study found that patients with a PET positive scan had a worse 5-year survival (19% vs. 69%, $p < 0.05$) and a lower 3-year progression free survival (20% vs. 67%, $p < 0.05$) compared to patients with a PET negative scan [80]. A PET positive scan was also associated with a higher risk of disease progression than a PET negative scan with a hazard ratio of 3.8 ($p < 0.05$) [80].''