# Format for ANSWERING REVIEWERS

Jun 8, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3365-review.doc).

**Title: Positron emission tomography/computerized tomography in the evaluation of primary non-Hodgkin's lymphoma of prostate**

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**Name of Journal:** World Journal of Clinical Oncology

**ESPS Manuscript NO:** 3365

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

2 Revision has been made according to the suggestions of the reviewer
We would like to express our sincere thanks to the reviewers for the constructive and positive comments.
(1) **Replies to Reviewer 1**
Specific Comments
1.Why was rituxan not used?
We neglected rituximab drugs when we prepared for this article and have added it to the chemotherapy regimen.

2.PET is routine part of workup for NHL, regardless of location and not a novel concept.
Since the primary prostatic lymphoma is rare, in my opinion,$^{18}$F-FDG PET/CT in the evaluation of the treatmemt on PPL is interesting from the view of nuclear medicine.

3. A thorough review paper of the entire literature and pt by pt analysis would be more helpful and advance field as opposed to case report.

Morphology of lymphoma in this case is typical, diffuse infiltrate lymphoid cells in prostate tissue. Immunohistochemical examination showed diffuse expression of CD79a and CD20 in tumor cell,which are the typical characteristics of diffuse large B cell lymphoma; CD3 being negative and diffuse expression of Mum-1 suggested that tumor cell originated from B cells; CD30 being negative tips for non-Hodgkin lymphoma; negative CK suggesting non epithelial maligancies, combined with negative PSA, exclude the possibility of prostate cancer; Positive bcl-6 indicates that the biological activity; the proliferation fraction was 60% with Ki67 antibody. combine these conditions together, a diagnosis of non germinal center origin of diffuse large B cell lymphoma was made.Compute Tomography(CT)and Trans-Rectal UltraSound（TRUS） prostate plays an important role in the

location and staging of the primary prostatic lymphoma, it usually manifests as the enlargement of the prostate with low density or hypoechoic lesions with or without abdominal and pelvic enlargement of lymph nodes on CT or US, in addition, CT and TRUS are also of great significance to treatment response to PPL[7,8], Gallium scan is optional when distant lymph node involvement was suspected[9]. There were no specific markers for Lymphoma at present, Prostatic Acid Phosphatase(PAP) May be a sensitive tumor marker protein indicating development and progression of intravascular LBCL, which was a Subtype of diffuse LBCL[10]

[7] Jhavar S, AgarwalJP, Naresh KN, Shrivastavaa, SK, Borges AM, Dinshaw KA. Primary Extranodal Mucosa Associated Lymphoid Tissue (MALT) Lymphoma of the Prostate. Leukemia and lymphoma 2001;41(3-4):445-449.

[8] Lee WC,Chiang PH. Primary Prostate Lymphoma Presented as Urinary Retention in a Young Male Patient: A Case Report. JTUA 2009;20(2):86-88.

[9] Mermershtain M, Benharroch D, Lavrenkov k, Geffen DB, German I, Cohen Y. Primary Malignant Lymphoma of the Prostate - A Report of Three Cases. Leukemia and Lymphoma 2001;42:(4) 809-811.

[10] Seki K, Miyakoshi S, Lee GH, Matsushita H, Mutoh Y, Nakase k,Ida M, Taniguchi H. Prostatic Acid Phosphatase Is a Possible Tumor Marker for Intravascular Large B-Cell Lymphoma. Am J Surg Pathol 2004;28:1384–1388.

(2) **Replies to Reviewer 2**

The authors report an interesting and well documented case of DLBCL primary of the prostate and discuss the value of the PET scan in the diagnosis and follow-up of this uncommon type of lymphoma. Some minor points should be pointed out 1. With regards to the literature review (“about 200 cases reported”), it should be mentioned in the text of the article the method of the literature search, the descriptors used and the period of the literature search. 2. The DLBC lymphoma of the patient expressed CD20. The authors should explain the reason of not combining rituximab with the CHOP schedule. In addition, it would be desirable to know from the literature review if the R-CHOP schedule provides better results than the classic CHOP schedule in patients with primary DLBCL of the prostate 3. The quality of the figure of immunohistochemistry (figure 3B) should be improved.

Minor considerations:

1.With regards to the literature review (“about 200 cases reported”), it should be mentioned in the text of the article the method of the literature search, the descriptors used and the period of the literature search.

We use PubMed search method, with key words of primary prostatic lymphoma , 87 Articles were retrieved by the end of Jan 2013.

2.The DLBC lymphoma of the patient expressed CD20. The authors should explain the reason of not combining rituximab with the CHOP schedule. In addition, it would be desirable to know from the literature review if the R-CHOP schedule provides better results than the classic CHOP schedule in patients with primary DLBCL of the

prostate.

We neglected rituximab(mabthera) drugs when we prepared for this article and have added it to the regime. A recent study showed that R-CHOP chemotherapy is superior to CHOP and is the first choice for curative intent, this combination should become the standard for treating DLBCL[11,12,13].

[11] Anca L, Paul R, Bogdan P, Cristina K. R-CHOP VS. CHOP: A COST-EFFECTIVENESS ANALYSIS on Aggressive Non-Hodgkin's Lymphoma (NHL). Management in health 2009;2:18-21.

[12] Feugier P, Hoof AV, Sebban C, Solal-Celigny P, Bouabdallah B, Fermé C, Christian B, Lepage E, Tilly H, Morschhauser F, Gaulard P, Salles G, Bosly A, Gisselbrecht C, Reyes F, Coiffier B.Long-Term Results of the R-CHOP Study in the Treatment of Elderly Patients With Diffuse Large B-Cell Lymphoma: A Study by the Groupe d'Etude des Lymphomes del'Adulte. J Clin Oncol 23:4117-4126.

[13] Csomor J, Kaszás H, Kollár B, Pajor L, Egyházi Z, Fekete S, Egyed M, Timár B. Prolonged Survival Using Anti-CD20 Combined Chemotherapy in Primary Prostatic Intravascular Large B-cell Lymphoma. Pathol. Oncol. Res 2008;14:281-284.

3.The quality of the figure of immunohistochemistry (figure 3B) should be improved.

The quality of the figure including clarity, resolution, contrast and saturation, have been modified, and a pair of CD20 image also been added to the article(figure 3C).

(3) **Replies to Reviewer 3**

This manuscript is a case report showing that 18F-fluoro-deoxy glucose (FDG) PET/CT contributed to diagnosis of DLBCL of the prostate as well as response to treatment. Because primary malignant lymphoma of the prostate is very rare and symptoms present as misdiagnosed as benign prostatic hyperplasia or prostatitis, and there is no consensus on management of the disease, new methods contributing to better diagnosis and measuring response to treatment are needed. Data shown include the before and after treatment PE and PET/CT scans of the patient. Of concern is the high level of FDG uptake in the kidneys and heart that is about equal in intensity to the signal shown for the prostate before treatment. In the scans of after treatment, the intensity of the FDG uptake in the whole body PET image in theses organs appears similarly decreased making this reviewer wonder how the authors can conclude that this method indicates specificity of prostate disease. Discussion of the similar decrease in metabolic activity in all these organs and why the authors consider the differential decrease prognostic of primary malignant lymphoma of the prostate is justified. In contrast, the PET/CT fusion image shows significant differences in intensity of the signal before and after treatment, suggesting the utility of the fusion method. Also, they should include the combined morphological and immunophenotyping (CD79a) of the prostate tissue after treatment as well to show reduction in the proliferating cells of DLBCL.

Of concern is the high level of FDG uptake in the kidneys and heart that is about equal in intensity to the signal shown for the prostate before treatment.

Because the $^{18}$F-FDG is excretion through urinary system, so the kidney, ureter and bladder, can be abnormal uptake under normal circumstances, the extent of uptake is associated with the body state, water diversion and micturition . As for the uptake of the heart, belongs to the physiologic uptake, which was related to the blood glucose level.

the scans of after treatment, the intensity of the FDG uptake in the whole body PET image in theses organs appears similarly decreased making this reviewer wonder how the authors can conclude that this method indicates specificity of prostate disease.

In addition to the uptake of prostate, the rest are physiological uptake, it is influenced by many factors, including blood glucose, the mount of drinking water, and so on. The decreases of( kidney, heart )metabolism for second time, is caused by physiological uptake, unrelated to the treatment. To distinguish between physiological uptake and tumor tissue uptake, the examination method is specially high.

Discussion of the similar decrease in metabolic activity in all these organs and why the authors consider the differential decrease prognostic of primary malignant lymphoma of the prostate is justified.

The physiological uptake of kidney and heart is associated with the state of body, such as blood glucose level, the mount of drinking water and so on, it is unrelated with treatment. And the second time in heart and kidney of low metabolism, perhaps attributed to these fators, on the contray, the uptake of prostatic lesion was not affected by above factors, and related to treatment.

In contrast, the PET/CT fusion image shows significant differences in intensity of the signal before and after treatment, suggesting the utility of the fusion method.

The fusion images of PET/CT have been added to the paper.

Also, they should include the combined morphological and immunophenotyping (CD79a) of the prostate tissue after treatment as well to show reduction in the proliferating cells of DLBCL.

In this paper, prostate biopsy was done before treatment, complete remission was not confirmed by another prostate biopsy after treatment. It was diagnosed as complete remission based on the lesion decreased or disappeared on ultrasound or compute tomograpy, and the reduced the activity or near to background on PET/CT, laboratory examinations were within normal range. so the morphological and immunophenotyping (CD79a) after treatment was not acquired.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Clinical Oncology.

Sincerely yours,

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