Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1001.

Reviewer A

Many thanks for allowing me to review this manuscript. This is a well-written study on the important topic of MRI-USS fusion prostate biopsy and the need for systematic biopsy. I have raised the following points for this study.

Comment: The authors have stated that unique selling point of this study is that this has been performed in a developing country. There have been recent economic reports that Romania is now on the verge now being classed as a developed country. I also understand that according to the WorldBank Romania is now classed as a high-income country. The authors would need to provide up-to-date evidence stating that Romania is still considered as a developing country. Nevertheless, my issue is that the protocols, hardware and facilities used in this study does not reflect urological practice of a low-income country and is more in-keeping with one I am accustomed to in my practice (Western Europe). If I am correct regarding the economic description of Romania the I would struggle to find what is the unique selling point of this study as it is a single centre one with the numbers being significantly lower than modern comparator studies.

Reply: We thank the reviewer for this important correction. Indeed, according to the World Bank, Romania is classified a High Income country. The classification of countries depending on the economy is performed by several organizations: 1. United Nations (by Human Developing Indices - HDI), 2. Organization for Economic Cooperation and Development (OECD), 3. International Monetary Fund (IMF, by World Economic Outlook Database), 4. World Bank (Gross National Income, GNI). For a country to be considered developed it has to meet the criteria for each of the previously mentioned organizations. At the current moment Romania meets the criteria only for United Nations HDI and World Bank GNI. It is not part of the OECD and according to the International Monetary Fund WEO database it is not a developed country. Taking all these into consideration, we consider that the more suitable term would be emerging country.

Last, but not least, what matters more than the global economy is the budget allocated to the Health System. According to the World Bank statistics of 2017, the mean percentage gross domestic product employed by European countries for the Health System was 9.8%, going as high as 11% in France, Germany or Sweden, whereas in Romania it was 5.1% (https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?end=2017&locations=RO-EU&start=2000&view=chart).

The lower numbers reported in our series could be a result of the fact that the patients included in the study were referred from other centers with significant heterogeneity in the image quality and reporting. Furthermore, as we highlighted in the limitations section, the data regarding radiologists experience was lacking.
We performed the recommended modifications accordingly – page 5, line 117; page 6, line 136; page 6, line 138; page 12, line 331; page 15, line 432.

Comment: The authors state the 77% harboured aggressive disease. Can the authors expand on their definition of this aggressive disease? For instance, they said 77 (54.6%) PCa patients with ISUP 2 had aggressive disease – does this mean they had high PSA or T3 disease because ISUP 2 itself does not fall into the category of high-risk disease.
Reply: We thank the reviewer for this comment. The term aggressive disease refers to any PCa with ISUP grading >=2. We corrected the phrase accordingly – page 9, line 218.

Comment: Can the authors provide a more detailed explanation of the limitation they have mentioned regarding how the mpMRIs were scored? They have stated 99 (one-third) of them were performed in their centre using PiRADs v1-2.1 in the methodology section. They then state that one-third of the mpMRIs were not evaluate using the PiRADs system in their limitation section. This does not match. Furthermore, if they did not score with PiRADs which system did they use to report these mpMRIs.-
Reply: We thank the reviewer for this important clarification. As indicated in the methodology section, a number of 99 patients performed MRI in our centre and 201 were referred. The 99 patients assessed in our centre had the MRI reported according to PIRADS criteria. Also, from the 201 patients referred to our centre, a number of 109 patients had received a PIRADS score. The rest of 92 patients had an MRI result without PIRADS scoring, only with the description of a ROI considered suspicious by the radiologist (corresponding to a ROI with Likert score >=3).
Thus, one third of the patients were scanned in our centre. Also, one third of the whole group did not receive a PIRADS score.
We added the supplementary data in the Methodology section, page 7, lines 170-171.

Comment: The authors have quoted 3 studies which they state that demonstrates the necessity of performing systematic biopsies. These studies have used low numbers and more contemporary large multi-centre studies have shown the contrary PMID: 31411968
Can the authors please make a reference/comment to such studies to balance the article discussion?
Reply: We thank the reviewer for the recommendation. Indeed, the necessity of

systematic biopsy is a matter of high interest and debate. The available literature so far, as also presented in the EAU guidelines 2020 show a strong degree of evidence to perform target and systematic biopsy in patients with a PIRADS 3 lesion or more on mpMRI, potentially due to increased worldwide heterogeneity in MpMRI quality.
Indeed, Miah et al. published a study on 640 patients who underwent prostate biopsy, of which 357 patients underwent systematic and targeted biopsies. They found that 0,8% of the patients presented csPCa on systematic biopsy with negative targeted biopsies. Still, there are some important differences that may explain these differences: the authors report twice as many cores per target as compared to our study: 4-6 cores/target vs a median of 3 cores/ target. Also, no details are provided by the authors on how many cores where taken for the systematic biopsies. Secondly Miah et al. performed the biopsy via a transperineal approach compared to our transrectal approach.
We included these details as advised, in the Discussion section – pages 13-14, lines 375-386.

Comment: Ideally the authors should state important secondary outcomes of this cohort namely the incidence of sepsis +/- readmission rates post TRUS-biopsy
Reply: We thank the reviewer for this comment. The current analysis did not aim to assess these secondary outcomes, as such we do not have the complete data regarding all complications. We added the available information regarding the readmission for sepsis in our cohort, which was 2% – page 11, lines 280-282. We also detailed the information regarding the antibiotic prophylaxis – page 7, lines 159-161.

Comment: Finally, the trans-rectal route of biopsy in this study needs to be stated as a limitation. In Europe and beyond there is movement towards adoption of the trans-perineal method. The trans-perineal method has been shown with level 1 evidence (PROMIS & PRECISION) to have superiority of the diagnosis of csPCa compared to the trans-rectal route. The discovery of a number of exclusive prostate cancers on systematic biopsies could be explained by this?
Reply: We thank the reviewer for this comment. Indeed, there is a movement towards changing the standard transrectal route for prostate biopsy to the transperineal one, mainly with the aim of reducing post-biopsy sepsis. With regards to PCa detection rate, current evidence to support significant difference between transrectal and transperineal approach is scarce. PROMIS Study provided evidence regarding template transperineal prostate biopsy in order to evaluate the performance of multiparametric MRI. In this case, for sure, a 12 core transperineal biopsy cannot provide the same diagnosis accuracy as the template transperineal biopsy. PRECISION Study included both approaches to perform targeted biopsy, but did not aim to compare the two techniques nor provided any comparison between the two approaches.

Furthermore, in our cohort, the 67.85% of csPCa cases lost by MRI-TRUS fusion biopsy were located in the peripheral area, which is accessibile to the transrectal route. None of the patients missed by MRI-TRUS biopsy had a lesion located in the anterior area. Thus, we do not consider that the transperineal route would have significantly improved PCa detection rate in our cohort. The complications rate was not an outcome provided by our study.
We added the recommended information in the discussion section – page 15, lines 425-428.

Reviewer B

Congratulations on this work. It remains very important to prospectively determine the effect of MRI targeted and systematic biopsies. Although you papers is promising, I suggest some alterations in the results section and discussion. I think this will significantly improve your manuscript. Please consider the following suggestions.

Comment: Were no systematic biopsies performed in patients with a negative MRI? If SBx were performed in patients with a negative MRI this data should be provided.
Reply: We thank the reviewer for the comment. Indeed, the negative predictive value of mpMRI is of great importance to assess the quality of the interpretation. In our current study we included only patients who had a mpMRI with suspicious ROI, were scheduled and underwent MRI-TRUS fusion biopsy in our department. Also, patients were referred from multiple centers, thus the decision to perform systematic biopsy in case of negative MRI remained at the discretion of every urologist. We added the supplementary information in the methodology section – page 7, line 172.

Comment: Why is this definition of csPCa taken? No gleason score 3+3 should be considered as significant prostate cancer, no matter how many biopsies are positive. Moreover, gleason score 3+4 should be splitted into two groups, one with cribriform or intraductal carcinoma, one without. csPCa should be defined as Gleason 3+4 with CR/IDC or higher (see also recommendations for Active Surveillance in EAU guidelines).
Reply: We thank the reviewer for this important comment. The definition of true csPCa has been a matter of debate in the last years. The Epstein criteria state as clinically significant PCa any Gleason pattern 4 or greater, or Gleason 3 + 3 disease with core length 50% or greater and/or more than 2 cores positive on standard 12-core TRUS guided biopsy. Also, according to the EAU Guidelines 2020, apart from ISUP grading, the number of positive biopsy cores and the extent of tumor involvement per biopsy core can be used to predict BCR and post-prostatectomy progression. In 2015, Nguyen

et al published in J Urol an analysis of 10000 patients with low risk cancer (cT1c-cT2a, PSA<10 ng/ml, Gleason 6=3+3) who underwent radical prostatectomy. The upgrading rate to Gleason 7-10 was 44%, with the number of positive biopsy cores being an independent predictor factor for upgrade (p<0.001). Therefore, we considered that Gleason score 3+3 with high number of positive cores /high ROI volume as csPCa. Also, in almost 50% of cases biopsy-proven low risk PCa can be false due to the limitations of the prostate biopsy technique. Furthermore, there are multiple studies that evaluated different prostate biopsy techniques and defined csPCa as a Gleason 3+3 along with other characteristics such as: maximum cancer length (MCL) of 4 or 5 or 6 mm, or number of positive cores (>2 or 3): Rastinehad et al (https://doi.org/10.1016/j.juro.2013.12.007), Tontilla et al (http://dx.doi.org/10.1016/j.eururo.2015.05.024), Boesen et al (DOI: 10.1177/0284185117718400), Porpiglia et al http://dx.doi.org/10.1016/j.eururo.2016.08.041); Rouviere et al/MRI-First Trial (http://dx.doi.org/10.1016/j.eururo.2016.08.041).
Only one case was reported as harboring intraductal carcinoma at biopsy, as such we considered that including this result will not have significant impact
We added the supplementary information in the methodology section – page 8, lines 185-187.

Comment: Result section should be rewritten. Start with overall detection of clinical significant prostate cancer found. Then what would have been missed if TBx were performed without SBx and then vice versa. Next point should be reduction of significant prostate cancer by performing TBx solely or SBx solely.
Then detection of PCa stratified by PIRADS score. Location of csPCa can be described.
Lastly the location of csPCa detected by SBx missed by TBx, elaborate more on this.
Reply: We thank the reviewer for these recommendations. We modified the results section as advised – pages 9-11.

Comment: Diameter of lesion on MRI is incorporated in the PIRADS score. This should not be separately evaluated, therefore, line 216 to 223 should be removed.
Reply: We thank the reviewer for the comment. Indeed, lesion diameter is incorporated in PIRADS v2 guidelines and the detailed information might not be of use in this case. Still, since some of the patients included in our study were assessed using PIRADS v1 criteria, which do not include lesion dimension, or had no PIRADS score reported, we considered that lesion dimension could be of interest. We added this information in the methodology section – page 7, line 169.

Comment: Start discussion with main outcome, how good are TBx and SBx. What is

your recommendation based on your data? Perform TBx solely? SBx solely? Both? Both only in PIRADS 4 or higher?

Reply: Thank you for these recommendation. We modified the discussion section as advised – page 12.

Comment: The fact that the operator was not blinded for MRI result limits the strength of you results. Actually you can not really compare TBx with SBx. I agree that this often is current practice, therefore provides interesting data. Please insert in the discussion the possibility of MRI guided saturation biopsies instead of systematic biopsies.

Reply: We thank the reviewer for this comment and the suggestions. We agree that a clear comparison between targeted and systematic biopsy is biased in our cohort, taking into consideration that the operator was aware of the MRI result. We included this information in the limitations section.

Furthermore, the saturation biopsy of the targeted lesion has gained much interest in the last years, potentially excluding systematic biopsy. We added this information in the Discussion section – page 14, lines 386-390.

Comment: Was there a second reading of MRI? Most interesting of this study would be if quality of MRI influenced TBx outcome. Was there is difference between the MRIs from the different centers? Did this influence your results?

Reply: We thank the reviewer for this comment. Indeed, the quality of MRI is a main factor to influence the targeted biopsy results. There was no second reading of the MRI, due to difficulty of access to this imaging investigation and specialized radiologists in our country. We did not assess these outcomes of external patients, as they were referred to our department from more than 10 centers with significant heterogeneity in the quality of the images and reporting result. Some external MRI were of high quality, and the radiologist provided also the drawing of the lesion, that could be comparable to our centre. On the contrary, others provided minimal information regarding the suspected lesion. Only 109 of these patients received a PIRADS score, while the rest were classified suspicious or not for PCa. Nonetheless, we performed an analysis to see whether external MRI had any influence upon the results of the biopsies as compared to the ones performed in our centre – there was no statistical significance.