Peer Review File

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Review Comments (Round 1)

Reviewer A

Comment 1: The authors report on biopsy outcomes of men that underwent a biopsy. We know nothing about men that were referred to their clinic but did not undergo a biopsy.

REPLY 1: Thanks for the valuable comments. In this work we have analyzed the patients who have received a prostate biopsy (see page 4, line 82-86). According to the reviewer, it would have been very interesting to have analyzed all those patients who were not indicated for biopsy due to low clinical suspicion of prostate cancer, however these data are not collected in our database since they have not been the objective of our study.
Changes in the text: NO changes.

Comment 2: I suspect most of these findings and the increase in grade and stage are more likely due to proper triaging and selection of patients most likely to benefit from evaluation of suspected prostate cancer and not due to any small delay that may have been due to the strain of COVID 19 on the healthcare system.

REPLY 2: Thank you for the professional advice. We agree with the reviewer as described in the lines 202-205 page 9. We think that undergrading at biopsy appears to be the most reasonable cause of these findings. It has been published that the risk of transmission of COVId-19 may increase during biopsy (19). While we lack data regarding factors that might have influenced the quality of biopsy such as number of cores or total core length affected, we cannot exclude that this quality has been affected possibly due to social distance measures.
We have eliminated the sentence that affirmed that the upgrading was due to a delay in the diagnosis
Changes in the text: we have modified the text as advised (see page 9, line 210-215).

Comment 3: Therefore, the clinical impact and how these data may influence practice patterns is questionable. Ultimately, I am not certain that this paper adds significantly to the literature in this disease space as there are multiple reports which demonstrate that time from diagnosis to biopsy and biopsy to treatment has no to minimal effect on prostate cancer outcomes. I would suggest the authors try to reframe this report to better emphasize what they believe are the novel aspects of these data

REPLY 3: Thank you for the professional suggestion. As reflected on the page 10 lines 229-230, a delay in the diagnosis does not imply worse oncological outcomes in our study. The main differences found in the literature is in patients with high-risk PC (see page 10, line 226-228). However, it is clinically significant that in the year of the pandemic, adverse pathology findings were found in patients undergoing radical prostatectomy being a priori patients with similar PSA and Gleason scores. In line with what is published by Nyk el at, a possible cause of these findings could be the undergrading at biopsy. For this reason we think that this study serves to raise awareness of the risk of deterioration of PC care due to possible underdiagnosis of our patients, since the magnitude of the COVID-19 pandemic on prostate cancer care is still unknown.
Changes in the text: we have modified the text as advised (page 9 lines 210-211),(page 10 line 212-215)

Comment 4: I apologize for such a comment, but the grammar, sentence structure, phrasing, and word choices impair the readability of the manuscript making it difficult to understand the message the authors are trying to relay in this report.

REPLY 4: we attached the certificate of language editing
Changes in the text: we have modified the text as advised according to language editing.

Comment 5: The manuscript seems to lack structure. After my first pass through, I'm not certain I had a good grasp of what the primary and secondary outcomes of the study was or what the major take away was. I would ask the authors to consider restructuring the manuscript to make the objectives clear in the M/M section and then mirror reporting and displaying the results in the same fashion.

REPLY 5: Thank you for the valuable comment. We have structured the objectives in primary and secondary following the suggestions of the reviewer. We have concisely described the secondary objectives and more clearly worded the primary objective

Changes in the text: we have modified the text as advised see page3 line 69-70 and page 4 lines 71-78.

Comment 6: Methods: The authors start the COVID period of their study in Jan 2021. Was COVID a significant factor in Spain at this time? I believe the first COVID shut down/shelter in place started in mid-march in the US. Can the authors comment as to this time frame and when clinical operations became disrupted due to COVID at their center?

REPLY 6: The lockdown in our country was decreed on 14 March , 2020. The clinical operations became disrupted on 16 March 2020. Those periods were stipulated because they facilitated data collection and analysis.

Changes in the text: we have modified the text as advised (see page 4 line 86-87).

Comment 7: "globally, in 2020 there were fewer urology consultations." Can the authors comment as to what they mean by globally? Is this within their institution? How was this number calculated? Additionally, we don't know how many consultation were for suspect cancer, only the number that underwent biopsy.

REPLY 7: Thank you for the professional suggestion. We have withdrawn the word globally because it is imprecise. Consultations for suspected prostate cancer are those consultations in which a biopsy is indicated. It has been rewritten again for lack of clarity following the instructions of the reviewer.

Changes in the text: we have modified the text as advised (see page 6 line 120-121).

Comment 8: Conclusions: The authors seem to merely restate the results in a qualitative fashion in the conclusions. I would ask the authors to draw conclusions from these data. Personally, I would look at these data and say that the healthcare system did a good job of

evolving to the stresses of COVID and appropriately triaging patients that needed to be seen in a timely fashion.

REPLY 8: Thank you for the valuable comment. As the reviewer can see in the conclusions section of the page, they have been rewritten trying to interpret the data obtained.
Changes in the text: we have modified the text as advised (see page 11 line 243-251)

Comment 9: Title. Consider single center instead of "unicenter." Additionally, I would favor "association" rather than "influence"

REPLY 9: we have modified our text as advised removing "unicenter". However we have kept the word influence as we think it better describes the impact of the pandemic on prostate cancer.
Changes in the text: we have modified the text as advised (see title page)

Comment 10: Abstract/introduction: the first sentence of the background stating the arm is awkwardly worded. As a result, it makes it difficult for the reader to understand and what they should expect to see in the following sections.

REPLY 10: Thank you for the professional advice. We have changed it in order not to make it difficult for the reader to understand. Finally it will be: "The aim was to evaluate the impact of COVID-19 on waiting times for diagnosis and treatment of prostate cancer (PC), as well as the possible effect on the treatment results in PC patients undergoing radical prostatectomy".
Changes in the text: we have modified the text as advised (see page 1 line 2-4)

Comment 11: Abstract M/M: I would suggest the authors list specific outcomes and what hypothesis test they are using to compare groups. I'm not sure I could state what results the authors are going to present from the M/M section.

REPLY 11: Thank you for the valuable comment. We have added some data regarding the hypothesis test: Mann-Whitney and Chi-square test were used to compare continuous variables and percentages, respectively. The specific outcomes have been described in detail previously

(see page 1 line 2-4). In the M/M section, the patients under study, the variables analyzed, as well as the periods that are the objective of our study have been described in detail.
Changes in the text: we have modified the text as advised (see page 1 line 7-13)

Comment 12: Abstract/results: The authors report the PSA as higher in 2020 compared with 2019, but they do not give us the median PSA in 2019.

REPLY 12: Thank you for the professional advice. We added the median PSA in 2019
Changes in the text: we have modified the text as advised (see page 1 line 16)

Comment 13: Abstract/results: the authors note that the wait time from consultation to biopsy was 35 days in 2019 and 42 days in 2020 and not this difference was statistically significant. Can the authors comment as to if they believe this difference that is statistically significant if it is clinically significant, and if its not clinically significant, why should we care.

REPLY 13: Thank you for the valuable comment. It is statistically significant but not clinically relevant since there is no difference in the results of prostate biopsies between groups. However, we think it is important to highlight it since it is a direct impact of Covid-19 on the care of the CP.
Changes in the text: no changes

Comment 14: Abstract/results: The authors report on multiple operative pathologic outcomes include GG2 and pT stage. From what we know about the slow and prolonged history of prostate cancer, I am uncertain that a delay in 6 months would lead to higher GG, pT3, or metastatic disease. Can the authors comment as to this. I believe this is more likely due to national changes and trends in prostate cancer screening and care than a small delay due to COVID.

REPLY 14: Thank you for the valuable comment. This aspect is possibly the most debatable of all the results. For that reason, we have developed it extensively in the discussion section. As we have shown previously, we think that undergrading at biopsy appears to be the most

reasonable cause of these findings. we cannot exclude that the quality of the biopsy has been affected possibly due to social distance measures.
Changes in the text: we have modified the text as advised (see page 9 line 207-212 and page 10 line 213-220)

Comment 15: Abstract/Conclusion: The first sentence of the conclusions is regarding data on presented in the results (fewer prostate biopsies).

REPLY 15: this statement has been removed
Changes in the text: we have modified the text as advised see page 2 line 32-37.

Comment 16: Abstract/Conclusion: The conclusions are merely restarting the results but not drawing conclusions or interpreting these results.

REPLY 16: Thank you for the professional advice. we have modified the conclusions interpreting our results.
Changes in the text: we have modified the text as advised see page 2 line 32-37.

Reviewer B

Comment 1: While the time from biopsy to surgery is similar in both periods, would the authors please suggest a possible postulation why the upstaging of tumors in the final pathology happened more often in 2020?

REPLY 1: Thank you for the valuable comment. As the reviewer can read on the page 9 and 10 line 207-220, a possible cause of these findings could be the undergrading at biopsy. It has been published in the literature that the risk of covid-19 transmission can increase during the biopsy. it cannot be excluded that the quality of the technique has been compromised due to social distance measures.

Changes in the text: we have modified the text as advised (see page 9 line 207-212 and page 10 line 213-220)

Comment 2: Would the authors please comment that during COVID time, was there a limitation in access to pre-operative assessment e.g. MRI, PSMA scan? If so, would this lead to less accurate staging before intervention?

REPLY 2: Thank you for the professional suggestion. In our center we do not routinely use the PSMA scan as a staging test before surgery. It is only approved for recurrence after primary treatment of the disease from PSA >0.5. With regard to MRI, in 2019 and 2020 it was not done routinely prior to performing the biopsy, only in second or successive biopsies, or in patients who were candidates for Active Surveillance after the first biopsy. As of the year 2021, it is already done in all those patients with PSA <20 and normal DRE, but these years have not been the objective of our study.
Changes in the text: no changes.

Reviewer C

Comment 1: The text is well written and well composed, however, it needs significant editorial and language improvement due to numerous stylistic and linguistic issues.

REPLY 1: we attached the certificate of language editing
Changes in the text: we have modified the text as advised according to language editing.

Comment 2: In the Abstract, in the Results section, please provide the median value of PSA in the 2019 cohort. Also, please review this whole section, so that you make it clear which numbers represent 2019 or 2020.

REPLY 2: Thank you for the valuable comment. We added the median PSA in 2019, ad we have reviewed the whole section rewriting what was not clearly understood

Changes in the text: we have modified the text as advised page 1 line 16-19 and line 29-30.

Comment 3: You should also present a definition of "oncological evolution"

REPLY 3: Thank you for the professional suggestion. We have presented a definition of oncological outcomes as you can read: "Oncological outcomes were recorded in terms of PSA after treatment. Biochemical recurrence was defined as a confirmed serum PSA level of >0.2 ng/dl after surgery or a PSA level 2 ng/dl higher than the nadir value after EBRT. Persistent PSA was defined as PSA >0.1 ng/dl."

Changes in the text: we have modified the text as advised see page 5 line 106-109.

Comment 4: the Conclusions section should provide most important considerations in regard to the results and emphasize their potential clinical impact. Please rewrite this.

REPLY 4: following the instructions of the reviewer we have rewritten this section in order to emphasize their potential clinical impact.

Changes in the text: we have modified the text as advised see page 11 line 244-252.

Comment 5: please note that you observed a difference between the rates of patients presenting with metastatic disease, not between number of metastases at diagnosis (lines 28-29).

REPLY 5: Thank you for the valuable comment. We have modified the wording of that sentence so that it is better understood.

Changes in the text: we have modified the text as advised see page 1 line 18-19.

Comment 6: Please specify (in the abstract and in the main text) what was the point at the timeline at which PSA levels were recorded (at presentation, at biopsy, or before treatment?).

REPLY 6: Thank you for the professional suggestion. PSA levels were recorded at consultation previous to biopsy and after treatment.
Changes in the text: we have modified the text as advised see page 1 line 11.

Comment 7: Please discuss why the 31st of December 2019 was taken as the phase threshold. It may seem obvious, but needs explanation (for example, you aimed at examining equal periods of time and those time brackets made data collection and analysis most feasible). You might have obtained different results, if you chose, for example, 1st of March 2020 for the threshold.

REPLY 7: Thank you for the valuable comment. The lockdown in our country was decreed on 14 March, 2020. The clinical operations became disrupted on 16 March 2020. As the reviewer has said, those periods were established because those time brackets made data collection and analysis most feasible
Changes in the text: we have modified the text as advised see page 4 line 87-88.

Comment 8: Mean waiting times until (between?) diagnosis and treatment were compared". Please specify the exact moments that comprised for the time brackets. I guess that the start point was prostate biopsy. What was the end point? A study must be reproducible. Please define the time points for each treatment strategy. You list these time points in lines 91-95, however, you should make it clear how the waiting times were calculated. E.g., you considered date of MRI or date of confirmatory biopsy as the start of treatment? The date of RT consultation, or the start of RT?

REPLY 8: With the intention of making the study more reproducible and establishing waiting times more clearly, we have rewritten these data in the methods section: we have collected the baseline variables in order to calculate waiting times: time to biopsy, time between biopsy and results and time between results and applied treatment.
Changes in the text: we have modified the text as advised see page 5 line 94-105.

Comment 9: Please provide which statistical tests were used for data analysis. Please provide the version and manufacturer of the software used.

REPLY 9: we have provided the statistical tests and the version and manufacturer of the software used
Changes in the text: we have modified the text as advised see page 5 line 110-112.

Comment 10: In Table 1, there is no p value provided for the number of consultations for PC.

REPLY 10: Thank you for the professional suggestion. We have added the number of consultations for PC in the results section. This data has been removed from table 1.
Changes in the text: we have modified the text as advised see page 6 line 121-122.

Comment 11: You may choose to write "biopsy waiting time" instead of this long phrase. Important: you did not include in the Methods how was that waiting time calculated. "Time from Biopsy to Results in consultation" - I do not understand what do you mean.

REPLY 11: following the instructions of the reviewer, they have been modified in the tables and text for better understanding. In the methods we have explained in detail how were all the waiting times calculated taking into account the variables collected.
Changes in the text: we have modified the text as advised see page 5 line 94-105 and all tables 1, 3 and supplementary table 1.

Comment 12: Also, I can see that one p-value is provided for all three types of biopsy results. Did you use a 6x2 contingency table? Please, specify. In my opinion, it would be better to calculate a 2x2 table for every variable.

REPLY 12: Thank you very much for your appreciation. In Table 1 we have reordered the biopsy result data to show a single variable with several categories, to which a single “p” corresponds. For example, with 4 categories we would have 6 possible comparisons and this would increase the probability of type I error.

Changes in the text: we have modified the text as advised see table 1.

Comment 13: Applies to all Tables: I have similar comments in regard to the p value, as discussed above. It would be best to recalculate the p-values for 2x2 contingency tables (separately for each ratio).

REPLY 13: If we recalculate the p-values for 2x2 contingency tables (separately for each ratio), in the case of a variable with 4 categories we would have 6 possible comparisons and this would increase the probability of type I error.
Changes in the text: NO changes

Comment 14: In the Results section, I think that rewriting the Tables into the main text is not necessary. Either provide Tables or put the data into the main text. Only most important results should be included in the main text. You may move some comments to the Discussion section.

REPLY 14: following the reviewer's suggestions, we have rewritten the results section, omitting data that was already reflected in the tables and leaving only the most relevant, avoiding duplicating information.
Changes in the text: we have modified the text as advised see page 6 line 128-131, page 7 142-149 mainly.

Comment 15: Line 168: Do you mean EAU? Please explain the abbreviation.

REPLY 15: EAU: European association of urology.
Changes in the text: we have modified the text as advised see page 8 line 175.

Comment 16: Lines 173-175: Either provide a reference, or do not say "in all departments". Again, 175-176: note that you are providing a statement that is not supported by any reference. You should use less judgmental language instead.

REPLY 16: we have used less judgmental language following the suggestions of the review, removig “all”.
Changes in the text: we have modified the text as advised see page 8 line 181.

Comment 17: Lines 189-190: Do you have data to support this theory? Please state whether this was the institutional policy or is this a hypothesis. If so, please use less judgmental language.

REPLY 17: as the reviewer shows, it is a hypothesis rather than a institutional policy. We have reviewed the discussion section using less judgmental language.
Changes in the text: we have modified the text as advised see page 8 line 183-184

Comment 18: Lines 194-195: You should be more cautious when providing such explanations. There is plenty of data to support the opposite, e.g., Diamand et al. (DOI: 10.1007/s00345-020-03402-w) or the study by Ginsburg et al (included in your manuscript).

REPLY 18: following the reviewer's recommendations, we have been more cautious when providing explanations, discussing the most recent data ,Diamand el al, (DOI: 10.1007/s00345-020-03402-w) .
Changes in the text: we have modified the text as advised see page 10 line 223-229

Comment 19: Lines 206-207: In the Results, I cannot find data that addresses safety or feasibility issues. You may delete the phrase "our data suggests".

REPLY 19: Thank you very much for your appreciation. We have deleted some phrases of which we had no data.
Changes in the text: we have modified the text as advised see page 10 line 230-231.

Comment 20: In the Conclusions section, please emphasize the potential impact of your results on the clinical practice - is this article a lesson that may make us be more aware of possible PC care deterioration?

REPLY 20: we have rewritten the conclusions in order to emphasize the potential impact of our results on the clinical practice

Changes in the text: we have modified the text as advised see page 11 line 244-252.

Comment 21: Final comment: Please discuss the most recent data in regard to the association between COVID-19 pandemic and prostate cancer management or outcomes, as there are studies that have already addressed the same or very similar topic. Examples: Nossiter et al. (DOI: 10.1111/bju.15699), Nyk et al. (DOI: 10.3390/curroncol29040225), van Deukeren et al. (DOI: 10.1016/j.ctarc.2022.100553).

REPLY 21: Thank you for the professional suggestion. We have discussed the most recent data in regard to the association between COVID-19 pandemic and prostate cancer management or outcomes at the discussion section, including reviewer suggestions.

Changes in the text: we have modified the text as advised see page 8 line 187-188, page 9 line 189-195 and page 10 line 216-220.

Reviewer D

Comment 1: As the time to the patient's first visit cannot be collected, it is represented by the patient background at the time of the first visit and the prostate biopsy. It would be interesting to know more about the differences in the patient background at this point (e.g., clinical T stage, metastases sites, etc.).

REPLY 1: Thank you very much for your appreciation. We have included in Table 2 the PSA and the type of metastases in each year. We have not included clinical T stage because it is not collected homogeneously: in some cases it was collected taking into account the MRI, in others without MRI.

Changes in the text: we have modified the text as advised see table 2.

Comment 2: L13: It isn't easy to understand what 53.1% (N=401) refers to. The table shows what it means, but the notation should be changed to be easier to understand.

REPLY 2: It has been rewritten according to the suggestion of the reviewer. We have also corrected a data transcription error:53,1% (N=264 patients, not 401).
Changes in the text: we have modified the text as advised see page 1 line 16-19.

Comment 3: L14, 15, 22, etc.: Significant figures for p-values should be aligned.

REPLY 3: Thank you for the professional suggestion. p-values have been aligned.
Changes in the text: we have modified the text as advised see page 1 line 18-20, page 23-30.

Comment 4: L25: "oncological evolution" is an infrequently used term.

REPLY 4: Thank you very much for your appreciation. We have removed this term, and we have explained in detail.
Changes in the text: we have modified the text as advised see page 2 line 29-30.

Comment 5: L29: "Long waiting times are...". Please specify the period from when to when.

REPLY 5: Thank you for the valuable comment. Conclusion section has been rewritten in order to interpret the results described.
Changes in the text: we have modified the text as advised see page 2 line 32-37.

Comment 6: L32: The phrase "oncological results" is ambiguous and adds to confusion.

REPLY 6: Thank you for the professional suggestion. We have removed this term, and we have explained in detail in methods section: Oncological outcomes were recorded in terms of PSA after treatment. Biochemical recurrence was defined as a confirmed serum PSA level

of >0.2 ng/dl after surgery or a PSA level 2 ng/dl higher than the nadir value after EBRT. Persistent PSA was defined as PSA >0.1 ng/dl.
Changes in the text: we have modified the text as advised see page 5 line 106-109.

Comment 7: Table 1: Is the font of the word 'value' intended? Table 1: 53.11 should be 53.1, and the significant figures for p-values should also be aligned.

REPLY 7: We have put in all tables only p. We have removed the word "value". The significant figures for p-values have been aligned with 3 decimals.
Changes in the text: we have modified the text as advised see tables 1,2,3 and supplementary tables 1 and 2.

Comment 8: Table 2: The total of the ISUP results for 2020 is not 137. Why is this? Table 2: p = 0.00 in the method section is incorrect. Please specify the period from when to when.

REPLY 8: Thank you for the valuable comment. We have stated p <0.01 instead of p=0.00 in tables and text. The total of the ISUP results for 2020 is 137. However, there was an error in the data. The correct data was: ISUP 4 in 2020: 35 patients (24.8%)
Changes in the text: we have modified the text as advised see table 2, ISUP grade 4.

Comment 9: L32: The phrase "oncological results" is ambiguous and adds to confusion.

REPLY 9: Thank you for the professional suggestion. Conclusion section has been rewritten in order to interpret the results described. We have removed the phrase "oncological results"
Changes in the text: we have modified the text as advised see page 2 line 32-37.

Comment 10: Table 1: Is the font of the word 'value' intended? Table 1: 53.11 should be 53.1, and the significant figures for p-values should also be aligned.

REPLY 10: Thank you for the valuable comment. We have put in all tables only p. We have removed the word “value”. The significant figures for p-values have been aligned with 3 decimals. When the third decimal is a 0, it has not been included (example: 0.710→0.71).
Changes in the text: we have modified the text as advised see table 1.

Comment 11: Table 2: The total of the ISUP results for 2020 is not 137. Why is this? Table 2: p = 0.00 in the processing method section is incorrect. It should be stated, for example, "<0.01".

REPLY 11: Thank you very much for your appreciation. We have stated p <0.01 instead of p=0.00 in tables and text. The total of the ISUP results for 2020 is 137. However, there was an **error in the data The correct data was: ISUP 4 in 2020: 35 patients (24.8%)**
Changes in the text: we have modified the text as advised see table 2, ISUP grade 4.

Comment 12: Table 3: The total number of ISUPs in 2019 is not 92. What do you think?

REPLY 12: The total number of ISUPs in 2019 is 92. However, there was an error in the data. The correct data was: ISUP 2 in 2019: 32 patients (33.7%)
Changes in the text: we have modified the text as advised see table 3, ISUP grade 2 at biopsy.

Comment 13: Supplementary Table 1: Please unify the notation of n

REPLY 13: Thank you very much for your appreciation. We have unified the notation of n putting only one decimal in all percentages
Changes in the text: we have modified the text as advised, see Supplementary Table 1.

Comment 14: Supplementary Table 2: Please state the p-value as “<0.01” instead of “0.00”, e.g.

REPLY 14: Thank you for the professional advice. We have stated the p-value as "<0.01" instead of "0.00".

Changes in the text: we have modified the text as advised, see Supplementary Table 2.

Review Comments (Round 2)

Comment 1:

#12, #13

This is not what I meant. My idea was to compare prostate cancer 2019 (yes/no) to 2020 (yes/no). Then, to compare ASAP, and so on. That would be three 2x2 contingency tables, i.e. three comparisons and three p values, one value for each row. The way you computed it is not wrong, but doing it the other way could have led to different results. However, as far as I can calculate the data in Table 1 myself, the p-value for a Chi-square for prostate cancer yes/no only would be 0.11, so still this is not a significant result (the small difference between 0.104 and 0.11 may be explained by the relatively small input from these few ASAP cases).

Response 1:

Thank you very much for this comment. I will take your assessment into account for subsequent data analysis.

Changes in the text: No

Comment 2:

Besides, I do recommend some language editing.

Response 2:

Thank you very much for this comment. Attached certificate of linguistic edition.