Comment 1: "The manuscript has to state if an institutional review board approval was obtained prior to conducting the study."

Reply 1: Thank you for your reminder. Our research has obtained ethical approval from Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. We have added corresponding explanations in the methods section.

Changes in the text: We have added the following sentence to the first paragraph of the Methods section (**Page 6-7, line 130-131**): "This study was approved by the ethics committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences."

Comment 2 : "The authors used a new method of dividing the prostate specimens into horizontal and vertical sections/ quadrants. This approach does not include the well-established histo-anatomical outlining of the prostate into specific anatomical zones, mainly the transition zone (TZ) and peripheral zone (PZ). As well demonstrated in recent studies, prostate size and TZ volume have a significant impact on the growth pattern and mechanics of PCa expansion within the PZ (where the majority of PCa originates, as correctly cited by the authors). Therefore, the authors should try in a revised manuscript to correlate their data with the total prostate volumes of the cases (the data should be available), and then discuss the possible impact on growth mechanics."

Reply 2: We wholeheartedly agree with and appreciate the feedback from the reviewer, as it holds significant guidance for broadening the scope of our research results. We categorized prostate volume into three levels and examined the impact of varying prostate volumes on both the horizontal and vertical origins of prostate cancer. Building upon these newly incorporated findings, we have made adjustments to Table 2 and the section titled "The origin of prostate cancer lesions". Furthermore, we have delved into the potential reasons behind the conclusions drawn from these novel insights in the discussion section.

Changes in the text: In light of the additional content, we have revised **Table 2** and

made adjustments to the initial paragraph of the "The origin of prostate cancer lesions" section (**Page 9, lines 195-202**). Furthermore, we introduced a new paragraph at the end of this section (**Page 10, lines 212-217**). Additionally, pertinent information has been incorporated into the discussion section (**Pages 15-16, lines 326-335**).

Comment 3 : "Under Methods, the authors specify that 124 autopsy specimens were collected and that 111 met the inclusion criteria, but only 39 harbored PCa. It should be stated whether these cases were consecutive or selected cases, if selected – the criteria have to be explained."

Reply 3: Thank you for the thoughtful reminder from the reviewer. In fact, the autopsy specimens in our study were collected consecutively over a specific period. We have now added the word "consecutive" in the relevant sentence.

Changes in the text: We have added the word "consecutive" in **Pages 7, lines 134**.

Comment 4 : "Under Methods it is stated that patients with neoadjuvant therapy were excluded. However, does this include BPH treatment with 5-alpha reductase inhibitors such as Finasteride as these drugs selectively shrink the TZ and may give more space for tumors in the PZ. This phenomenon may have influenced the PCPT study results with finasteride which was prematurely closed due to higher incidence of clinically significant PCa (Gleason grade 7 and higher), unexpected results at the beginning of the study."

Reply 4: Thank you sincerely for the reviewer's comments. This suggestion has deepened our comprehension of the growth patterns of prostate cancer. Regrettably, our statistical data does not encompass details about prostate hyperplasia and medication, thereby limiting the scope of further analysis. We have elucidated this constraint in the research limitations section of our discussion.

Changes in the text: We have incorporated clarifications in the discussion section, addressing the constraints inherent in our research on this particular subject (**Pages 17, lines 354-359**).

Comment:

1) There are no a-c groups in Figure 2. Please check and revise.

2) It is suggested to remove "n, (%)" in the table head of Table 2.

3) Please indicate the meaning of "n" and "N" in Table 3.

4) There has different "N" in "Positive rates of lesions of all lesions" in Table 3, please double-check if it is correct."

Reply:

1) We have added annotations for groups a, b, and c in Figure 2 and re uploaded Figure 2.

2) We agree with the editor's suggestion and have removed "n, (%)" in the table head of Table 2.

3-4) "n" represents the number of positive lesions in the corresponding slide; "N" represents the number of specimens having the corresponding slide. As the volume of the prostate organ varies, the number of vertical slices would be different. In fact, we have already provided an explanation in the manuscript (**Page 8, line 151-156**). We have provided an explanation in Table 3, and the new content in Table 3 has been highlighted in red font.