Dear Editor,

We would like to express our deepest gratitude to your reviewers for their insightful and valuable comments to improve the scientific value of our manuscript. They really emphasized important issues related with our study. Our point-by-point responses to our reviewers were provided.

Sincerely,

Gokhan Ozyigit, M.D.

Point by Point Response to Reviewers' Comments on 'The prognostic significance of castrate testosterone levels for patients with intermediate and high risk prostate cancer'

Reviewer #1 (03733131):

1. Lymphovascular invasion is an important prognostic factor in patients with malignant tumor (e. g. PMID: 29145818 and PMID: 30101131). Authors should evaluate the lymphovascular invasion of cases (exist or not exist is OK).

Response-1: All pathology reports are centrally reviewed, but LVI are not routinely reported in their biopsies. Therefore, there is inadequate information about the lymphovascular invasion.

2. The manuscript would be better if authors refer to the presence or absence of background adenocarcinoma component in this study cases.

Response-2: According to the comment of the reviewer the pathology information is added to the 'Patient characteristics' section of the manuscript.

*'We have a prospective treatment protocol for the definitive treatment of prostate **adenocarcinoma** patients which was approved by the institutional ethical review board.'*

Reviewer #2 (03677735):

1. The unit of testosterone level is inconsistent: ng/dL, ng/mL. They should check the correct unit.

Response-1: We agree with the reviewer. Units are revised and corrected according to the comment of the reviewer.

2. I would suggest to add "numbers at risks" into the figures.

Response-2: The figures are Kaplan-Meier graphs that represents the survival plots adequately. We could not completely be sure about what the reviewer meant by "numbers at risks", since this is methodologically unrequited for such a graph. Nevertheless, we have revised the figures according to what we inferred from the comment of the reviewer.

3. In the paragraph 4 of DISCUSSION, I would suggest to add the P value of 10-year biochemical recurrence rates comparison.

Response-3: 'p vales' are added to the 'DISCUSSION' section of the manuscript according to the comment of the reviewer.

'With a median follow up of 5 years the results showed that compared to the <20 ng/dL group, the 20-49 ng/dL group showed higher 10-year biochemical recurrence rates (28.1% vs. 18.3%, **p=0.016***) and metastasis rates (12.9% vs. 7.8%,* **p=0.01***).'*

Reviewer #3 (00069601):

1. As the authors suggest, this manuscript was conducted in a single institution with relatively formal treatment protocol, but multivariate analysis involving other variables that might affect BFFS was not performed. If you have performed a multivariate cox regression analysis as described in materials and methods, it is essential to specify the parameters involved in the analysis and to mention the hazard ratio, confidential interval with the p value.

Response-1: According to the comments of the reviewer we added the results of this analysis to the 'biochemical relapse free survival' section of the results part of the text and the values are shown as a separate table (Table-2)

*'Multivariate analysis for independent predictors of BRFS was presented in **Table-2**. Accordingly, BFFS was found to be independent from the baseline patient characteristics including D'Amico risk group, AJCC 2010 tumor stage, and Gleason Score and LHRH type.'*

Table 2: Multivariate analysis for independent predictors of BRFS

	p	HR	95% CI for HR	
			Lower	Upper
LHRHa Type	0,757	0,0	0,0	1,24E+19
D'Amico Risk Group (ref: intermediate)	0,397	1,5	0,6	3,89E+00
AJCC 2010 T Stage (ref: T1)	0,953			
T2a	0,909	2869,3	0,0	2,85E+62
T2b	0,915	1646,5	0,0	1,64E+62
T2c	0,912	2150,3	0,0	2,14E+62
T3a	0,91	2583,9	0,0	2,57E+62
T3b	0,908	3108,0	0,0	3,10E+62
Gleason Score (ref: <= 6)	0,799			
7	0,932	1,0	0,5	1,99E+00
>= 8	0,564	1,3	0,6	2,71E+00

Abbreviations: LHRHa= Luteinizing Hormone-Releasing Hormone analog; AJCC= American Joint Committee on Cancer; T=tumor; HR= Hazard Radio; CI=Confidence interval

2. It is also necessary to mention the p value, sensitivity and specificity as well as AUC for each cutoff value in ROC analysis.

Response-2: According to the comment of the reviewer Table-3 is added to the manuscript to show sensitivity and specificity as well as AUC for each cutoff value in ROC analysis

Table-3: Receiver operating characteristic curve analysis for two cut-off values of castrate testosterone levels

	AUC	SE	p	Sensitivity	Specificity
Castrate level testosteron (<=20)	0,628	0,049	0,011	63,6%	62,0%
Castrate level testosteron (<50)	0,582	0,052	0,107	31,8%	84,5%

Abbreviations: AUC= Area under curve, SE= Standard error of mean