

Peer Review File

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Reviewer A

Comment 1

- Authors mentioned “A Gleason pattern 5 is pathologically different from Gleason pattern 4. Gleason pattern 5 is characterized by the complete loss of glandular lumina, whereas Gleason pattern 4 is characterized by fused glands or cribriform patterns. Because the microscopic characteristics of Gleason patterns 4 and 5 are different, the aggressiveness and responsiveness to therapeutic agents for a GS of 9, which includes Gleason pattern 5, could be different from those for a GS of 8.” GS8 is a heterogeneous group which might be composed of GP 3+5 or 4+4 or 5+3. Therefore, Gleason component 4 vs. Gleason component 5 comparison is not a relevant for GS8 group. The authors should specify their concerns.

Reply 1:

Thank you for your comment and raising an important issue. We agree with your thoughts. However, in our study GS8 cases were comprised of only 4+4 so we were able to avoid the issues you raised. Nevertheless, these are important issues that need to be discussed. Indeed, it has been reported that GS8 containing GP5 has a worse prognosis than GS8 containing only GP4 (4+4). We have added the following comment to the Discussion section.

Changes in the text:

Line194-196

Stenmark MH et.al reported that GP5 has a worse prognosis than GP4 in patients with high-risk prostate cancer treated with dose-escalated external-beam radiation therapy and androgen deprivation (13).

Comment 2

METHODS:

- Could the authors please indicate which guidelines were used for the GS calculation and assignment.

Reply 2

Thank you for your comment. We used the Gleason classification, revised at the consensus meeting of the International Society of Urologic Pathology (ISUP) 2005.

Changes in the text:

Line117-119

The Gleason classification, revised at the consensus meeting of the International Society of Urologic Pathology (ISUP) 2005 was used to calculate and assign GS.

Comment 3

- Was the presence of cribriform architecture assessed during the pathological assessment?

Reply 3

Thank you for your comment.

The presence of cribriform architecture is classified as Gleason pattern 4 based on the Gleason pattern definition. However, we did not study the association of the presence or absence of cribriform architecture with prognosis.

We have added the following to “Discussion”.

Changes in the text:

Line229-231

For example, Choy B et al reported the presence of cribriform architecture may affect prognosis (19). However, we did not assess the presence of cribriform architecture in biopsy specimens.

Comment 4

- Did the authors determined any threshold to define that first line treatment was not successful?

Reply4

Thank you for your comment.

We defined the treatment resistance as 25% and +2 increase of PSA levels from the nadir point.

We added the following.

Changes in the text:

Line 130-131

Treatment resistance is defined as 25% and +2 increase of PSA levels from the nadir point.

Comment 5

DISCUSSION:

- The authors reported that all the GS8 patients in their cohort were GS4+4. Since the authors indicate that the growth patterns 4 and 5 have different responses to therapeutic agents, how would they discuss the use of first and second-line treatment in patients with GS4+4=8 and GS9-10 within their cohort?

Reply 5

Thank you for your comment.

As a result of this study, in the case of GS 8, we consider using ARSI for the 1st line treatment for patients with mCRPC.

If the patient is refractory to treatment with 1st line ARSI, other ARSI or Taxane should be considered for the 2nd line. On the other hand, taxane in the 1st -2nd line was not effective with GS 9-10. Specific gene mutation, such as *RB*, is reported to be predictive for the effect of taxane.

We changed it as following.

Changes in the text:

Line217-224

Based on this study, in the case of GS 8, we consider using ARSI as 1st line treatment for patients with mCRPC. If the patient is refractory to treatment with 1st line ARSI, other ARSI or Taxane should be considered for the 2nd line. On the other hand, taxane as 1st -2nd line was not effective in patients with GS 9-10. However, de Leeuw R et al. reported that loss of RB function induces sensitization to taxanes. Thus, patients with mutated *RB* could benefit from taxane treatment. Therefore, we believe that genetic testing early in treatment may be useful to better strategize treatment regimens.

Comment 6

- How would the authors discuss the impact of uneven distribution of the comparison groups eg. 30 pts GS8 vs 75 pts GS9-10.

Reply 6

Thank you for your comment. As the reviewer's comments, the uneven distribution of the 2 cohorts might have affected the results of analysis.

We added the limitation as following.

Line225-227

First, it was a **very** small-scale study. **The cohort was inhomogeneous, and each physician independently decided the course of treatment.**

Reviewer B

The authors report the prognostic importance of having Gleason score 5 or not in 105 patients with mCRPC included retrospective from 2011 -> 2019.

General comment:

Is there a trend over time? We generally consider an improvement in the OS about +2 years achieved within the last 5-7 years (hence the time where enzalutamid, abiraterone, cabazitaxel, and later radium-233 and even later apa/daro was made available)

Reply to general comment

Thank you for your advice.

We divided the cases into those collected between 2011-2015 and 2016-2019. Although no significant differences were observed, there was a trend toward a poorer prognosis in the group with GS 9-10. In patients during 2011-2015, only 2 patients received only docetaxel and others received the ARSI or cabazitaxel. This could be the reason why there was no significant difference between patients during 2011-2015 and 2016-2019. We added the following sentence in the Results.

Changes in the text:

Line167-169

When patients were divided into 2 cohorts, patients treated during 2011-2015 and those during 2016-2019, no significant differences regarding OS were observed (P = 0.37).

Related to specific sections:

Comment 1

L97

Consider used phrases like antiandrogens and CYP17 inhibitors rather than mentioning some

Reply 1 :

Thank you for your comment.

We have made the following changes.

Change in the text:

Line92-94

First-line treatments for CRPC are docetaxel or next-generation antiandrogens and CYP17 inhibitors.

Comment 2

L98

How well is patient preference examined? We know from STAMPEDE that QoL is better in abi than docetaxel.

Reply 2 :

Thank you for your comment. As the reviewer's comment, patients prefer ARSI to taxane due to maintaining QOL.

We have made the following changes.

Change in the next:

Line94-95

Patients with metastatic CRPC prefer ARSIs to docetaxel because of their severe side effects and worse quality of life.

Comment 3

L122

Not the classic PCWG2 interpretation. The 25% increase is treatment response. Typically it is interpreted as +50% above nadir and >2. Please include PCWG2 reference.

Reply 3:

Thank you for your comment. I'm sorry. We were wrong. We have made the following changes.

Change in the next:

Line125-128

CRPC was diagnosed based on the definition of the Prostate Cancer Working Group 2 as a confirmed relative increase in the PSA level from the nadir value by $\geq 50\%$ and by ≥ 2 ng per milliliter under the serum testosterone levels less than 50 ng/dL.

Comment 4:

L125

Extend of disease is used as a parameter without reference. I am not familiar with this parameter. Please state reference.

Reply 4:

Thank you for your comment. Extend of disease based on the number of bone metastasis.

We have added to the reference of the report of Soloway MS et al in line 126-7.

Change in the next:

Line129

The extent of disease (EOD) score was used to classify bone metastases (7).

Line286-288

Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer 1988;61(1)195-202.

Comment 5:

Line 139

With regards to patient characteritis, did all patients have 10 or 12 biopsies performed at diagnosis?

Reply 5:

Thank you for your comment.

All patients underwent 12 or 16 echo-guided transperineal needle biopsies at diagnosis. We have added following sentences to Methods.

Change in the text

Line146-147

All patients underwent 12 or 16 echo-guided transperineal needle biopsies at diagnosis.

Comment 6:

Line 148

It is stated that the use of first line taxane is 26,7% in the GS 8 gorup. In table 2 it is stated that 0 recieves taxanes. Please explain.

Reply 6:

Thank you for your comment.

No patients with GS8 received taxane use in 1st line. The text has been corrected as follows.

Chang in the next

Line154-158

Fifteen patients (50.0%) with GS 8 received abiraterone acetate, 14 (46.7%) received enzalutamide and none (0%) received docetaxel as the first-line therapy for CRPC, while 27 (36.0%) with GS 9–10 received abiraterone acetate, 21 (28.0%) received enzalutamide, and 26 (34.7%) received docetaxel.

Comment 7:

L150

Did a patient die within the first month of follow-up? You have included patients from 2019 and has a range of 0 months follow-up.

Are some of the patiens trail patients? COU-AA-302 waw pushlished in 2013 and PREVAIL was in 2014. Patients in your paper was included from 2011 and all recieved an ARSI as first line treatment. How can that be so?

Reply 7:

Thank you for your comment.

I apologize for the error. Follow up period is 1-86 months. The 1-month case was terminated due to a hospital change. Also, as you noted, our study included cases who received ARSI as clinical trials.

Changes in the text

Line160

The median follow-up duration was 22 months (range, 1–86 months).

Comment 8:

L 167

Please be consistent. Now it is called GS=> 9.

Reply 8:

Thank you for your comment.

We have made the following changes.

Changes in the next

Line182-184

In this study, we found that patients with metastatic CRPC with GS 9-10 had a poor prognosis compared to patients with GS 8 (Gleason Pattern 5 was not included); and early (primary and secondary) taxane treatments did not contribute to improved OS.

Comment 9:

L170

Is there some considerations about the latest ISUP grading system?

Reply 9:

Thank you for your comment.

The Gleason Grade classification is used in ISUP 2005. On the other hand, the Gleason score classification is still used in many clinical trials. Thus, we used the Gleason score classification in this study.

Changes in the text

Line185-187

In recent years, the Gleason Grade classification is often used in ISUP 2005. On the other hand, it is also true that the Gleason score classification is still often used in many clinical trials. Thus, we used the Gleason score classification in this study.

Comment 10:

L 186

You state that time to CRPC is important. In you data it is not significant between groups although medians are 30 and 17 months respectively. Is that just due to the relative small datasize or why do you think that is so?

Reply 10:

Thank you for your comment.

We believe this is due to the small data size. This study does not include time to CRPC as a consideration. We believe that it would be desirable to increase the data and include Time to CRPC in the study.

Changes in the text

Line207-214

Two prognostic factors were noted in the multivariate analysis: length of first-line ADT for less than or more than 12 months and PSA level at the time of CRPC diagnosis (17). Our univariate analysis showed that PSA level at the time of CRPC diagnosis was a prognostic factor for OS using PSA levels of 10 ng/mL at the time of CRPC diagnosis as a cutoff value, but the multivariate analysis did not show any significance. **When PSA values were analyzed in continuous form, univariate analysis showed a significant difference, but not in multivariate analysis. This discrepancy might be due to the small sample size.**

Comment 11:

L189

Did you use the PSA value as a dichotomized value on continuous value in both univariate and multivariate your tests?

Reply 11:

Thank you for your comment.

Yes, we used the PSA value as a dichotomized value. We also performed the statistical analysis with PSA value in continuous form and the results in univariate and multivariate analysis was the same, Gleason score 9-10 was a poor prognostic factor in both models.

We added the following in the Discussion.

Changes in the text.

Line212-214

When PSA values are analyzed in continuous form, univariate analysis showed a significant difference, but not in multivariate analysis. This discrepancy might be due to the small sample size.

Comment 12:

L191

Be consistent. You have chosen ARSI (not ARTA).

Reply 12:

Thank you for your comment.

We have unified on “androgen receptor signaling inhibitor”.

Changes in the text

Line215-216

Our results suggest that patients with Gleason 9–10 metastatic CRPC have a poor prognosis compared to patients with Gleason 8, even with the ARSI or taxane.

Comment 13:

L192 / 193

Wouldn't it be more fair to say that more research in predictive markers are needed in this group of patients?

Reply 13:

Thank you for your comment.

We changed the following.

Changes in the text:

Line216-217

More research in predictive markers is needed in patients with GS 9-10.

Comment 14:

Table 2

Is it correct that more than half of the patients failing first line ARSI is switch to another ARSI in the GS8 group?

Reply 14:

Thank you for your comment. In our cohort, more than half of the patients failing first line ARSI were switched to other ARSI in the GS8 group. In Japan, many patients prefer switching to taxane.

Comment 15:

Table 3

M1c is subdivided into positive or negative. Consider "bone only" or "soft tissue metastasis"

Reply 15:

Thank you for your comment.

We changed “bone only” or “visceral metastasis”.

Changes in the text:

Site of metastasis

Bone only

Visceral metastasis

Reviewer C

Prognostic factors in mCRPC are an important topic. The authors concluded that GS 9-10 is a significant predictor for OS. However, the paper has several limitations who could bias the conclusions.

retrospective analysis

very small, inhomogeneous cohort

several known factors for prognosis where not investigated (e.g. tumor volume, PSA, localization of metastasis ...)

This study had several limitations. First, it was a very small-scale retrospective study. Each physician independently decided the course of treatment. Although we performed multivariate analysis, other confounding factors affecting survival might have existed. Further large-scale studies are required

Thank you for your comment.

We all agree with your comments.

We evaluated tumor volume by EOD score, PSA values at initial diagnosis and at the time of CRPC diagnosis, and metastatic localization by the presence of visceral metastases. However, a further confounding factor might have affected the results. We added the following limitation in the Discussion.

Change in the text:

L225-231

This study had several limitations. First, it was a **very** small-scale retrospective study. **The cohort was inhomogeneous, and each** physician independently decided the course of treatment. Although we performed multivariate analysis, other confounding factors affecting survival, **such as tumor volume, PSA, localization of metastasis,** might have existed. For example, **Choy B et al reported the presence of cribriform architecture may affect prognosis (19).** However, we did not assess the presence of **cribriform architecture in biopsy specimens. Therefore,** further large-scale studies are required.