Reviewer’s report

Title: Impact of clinical trial participation on survival in patients with castration-resistant prostate cancer: A multi-center analysis

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Reviewer: Alexander Glaser

Reviewer’s report:

The authors submit a manuscript detailing a retrospective review of 299 patients with CRPC. The authors split the population into patients who were eligible and participated in a clinical trial, and patients who were either ineligible or declined participation in a clinical trial. The hypothesis is that patients who are ineligible or decline participation have worse cancer-specific survival.

Overall the scientific validity of this approach as well as the authors' conclusion that "Participation in CTs… confers as inherent survival advantage" is flawed.

Patients who are ineligible for clinical trials are by definition sicker or have other disease or comorbidities that exclude them from trial eligibility. It is therefore not surprising that CSS is better in patients who enroll in trials. The patients who were ineligible for clinical trials had worse PSA, albumin, and performance status. Furthermore, Age, PSA, Alk Phos, Gleason Score, performance status, and clinical trial participation were all significant in multivariate logistic regression analysis (Table 5). There are also undoubtably unmeasured variables in patients who are ineligible or decline a clinical trial. It is unlikely that the authors can adequately control for all of these variables to conclude that clinical trial participation alone is associated with survival.

A better way to answer this question would be to match a group of trial participants with a set of patients who declined (but were not ineligible) for trial, as well as performing propensity-score matching.

Other notes:

In the discussion, the authors state that PSA levels "were comparable between the groups indicating that CT participants were not simply a more prognostically favorable group". However, this is not true. See table 2, PSA 22.5 vs 88.4, p=0.005. Albumin and PS were also different between groups. There are also very likely unmeasured variables that make the patients who are trial-ineligible more sick / prognostically unfavorable.

Figure 1: recommend including p-value in any future submission

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No

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