Peer Review File

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Reviewer A

Comment 1: The authors queried for male patients diagnosed with a pancreatic mass who obtained a testosterone level over a 14-year period. These were infrequent, occurring in about 2%. Separately they measured testosterone levels in a cohort of 89 patients and found that nearly half were testosterone deficient, and 70% had symptoms c/w testosterone deficiency—though by this they include fatigue, which is likely multifactorial in PDAC patients.

They state that pts with testosterone deficiency were not more likely to have fatigue than those without—so the contribution of testosterone deficiency here is unclear.

Reply 1: Thanks to our reviewers for their thoughtful consideration of our manuscript.

Comment 2: Testosterone level did not correlate with PFS or OS—although it did in one prior study they referenced from 2011 in patients who had more advanced stage. Did testosterone deficiency correlate with stage in the patients in the Iowa study?

Reply 2: In our analysis of Cohort B comparing normal and low testosterone groups, we did not find an association between cancer stage and testosterone level. This information was previously located in Table 2 but has now been highlighted in the text (page 6, lines 153-154).

Comment 3: They conclude that testosterone supplementation should be explored in PDAC patients. They nicely review the limitations of their study, but do not mention that just b/c a patient has a pancreatic mass does not mean that they have pancreatic adenocarcinoma (they could have pancreatitis, neuroendocrine ca, etc)—so cohort A likely overestimates the # of pts with PDAC.

Reply 3: We completely agree with this comment and regret that we did not address this in our initial draft. We have revised our text to include this limitation point (page 8, lines 214-217).

Comment 4: As a physician who routinely treats pancreas cancer, I have never ordered a testosterone level. This provocative paper may lead me to consider doing so.

Reply 4: Thank you for this very kind comment. Our team works very hard to ask questions that are going to lead to meaningful benefits for cancer patients, and it's very gratifying to hear that we're starting to succeed in this. Thanks again for your very thoughtful review.

Reviewer B

Comment 1: For an Original Article, the Methods section should contain a subsection of '**Statistical Analysis**' in the main text. Please provide, or clarify the reasons if it is not applicable.

Reply: We have now labeled our statistical section "**Statistical Analysis**".

Comment 2: Figures and tables

- Please defined all the abbreviated terms in each Figure and Table. For example, please provide the full names of PFS in the legend of Figure 1.
- Please indicate how data are presented in Tables 1-2. N (%) for example.
- Please supplement the units in Tables. kg/m^2 for BMI for example.

Reply: We believe we have updated our tables to define all abbreviations, more clearly show that data are mostly presented as N (%), and have added units where needed. A new table file is attached.

- Please check whether the below term should be "prior testosterone level" in Table 1.

Previous Testosterone Level	Yes	-	2 (2.2)
	No	-	87 (87.8)
Symptoms of Low Testosterone	Yes	-	62 (69.7)
	No	-	27 (30.3)

Reply: We agree that prior is a better term – we have updated table to state "prior testosterone assessment"

Low Testosterone (<300 ng/dL)	No	15 (42.9)	45 (50.6)
Prior Testosterone Assessment	Yes	-	2 (2.2)
	No	-	87 (87.8)
	Yes	-	62 (69.7)

- The data below in your main text don't match with Figures 1-2 legends.

189 testosterone level was not evidenced on univariate analysis (Figures 1 and 2). Only the presence of
190 metastatic disease and receiving surgery remained associated with both PFS and OS on multivariable
191 analysis. After adjusting for metastatic disease at the time of diagnosis and treatment, testosterone
192 level had no statistically significant association with PFS (p=0.66) or OS (p=0.95).

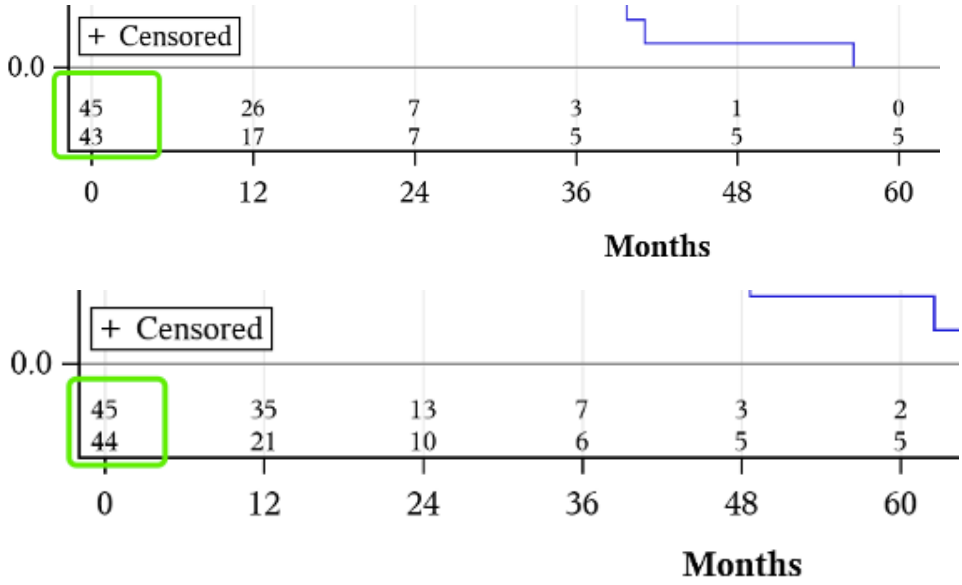
395 **Figure Legends**
396 **Figure 1:** Progression free survival by low testosterone status for the serum sample cohort. PFS was
397 not different between patients with low or normal testosterone levels (p=0.56).
398
399 **Figure 2:** Overall survival by low testosterone status for the serum sample cohort. OS was not different
400 between patients with low or normal testosterone levels (p=0.81).

Reply: Figure 1 and Figure 2 are for univariate analysis of testosterone, and the p values in the text are from multivariable analysis. We have added this information to the figure title so that it is clearer, but they are correct.

371 **Figure Legends**

372 **Figure 1:** Univariate analysis of progression free survival (PFS) by low testosterone status for the
373 serum sample cohort. PFS was not significantly different between patients with low or normal
374 testosterone levels (p=0.56).
375
376 **Figure 2:** Univariate analysis of overall survival (OS) by low testosterone status for the serum sample
377 cohort. OS was not significantly different between patients with low or normal testosterone levels
378 (p=0.81).

- Why the total numbers are not equal in your Figures 1-2? Please make sure the data are correct.



Reply: For one patient, the date of progression is unknown, and therefore they cannot be included in the progression-free survival analysis. We have added this information to the methods.