Peer Review File

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Reviewer A

Williams and team investigate the outcomes in patients with advanced pancreatic cancer, stratified by race, at a single institution. This work supplements the growing body of literature exploring the potential disparities of care in our health system. This important work, though without particular novelty and with acknowledgements of the major limitations posed by the methods, merits publication following several minor revisions.

Comment 1: Title: would recommend revision of the title to, at least, remove the name of the reporting institution (replace with description of institution type) and remove abbreviations. Would also either expand the reporting of clinicopathology (with emphasis here on pathology) in the manuscript or remove this term from the title.

Reply 1: Thank you for this suggestion, the title has been revised with these changes.

Changes in the text: See new title, "Racial disparities in advanced stage pancreatic cancer characteristics, treatment, and outcomes at an urban institution"

Comment 2: Adjust running head/title to eliminate reference to authors' institution.

Reply 2: Thank you for this suggestion, the running title has been revised with these changes.

Changes in the text: See new running title, "Race Disparities in Pancreas Cancer Patients at an Urban Center"

Comment 3: Methods: please expand description of methodology used to assess survival analysis (starting point at time of diagnosis for all? or at time of disease recurrence for those resected prior?). Also please describe methods used for multivariable analysis. Please clarify the methods used to accurately capture mortality (EMR? SSI database? online obit searching?, etc.)

Reply 3:

Thank you for the comment. We apologize for the missing information and less than ideal methods section. We have added the expanded the description of methodology used to assess survival outcomes to Methods on page 7.

Changes in the text: See Methods, page 7: "Inverse Kaplan-Meier method was used to estimate the median follow-up time. OS was calculated from the start date of the first line chemotherapy to the date of death or last follow-up date. Time to progression was defined as time from the date of the first line therapy to the date of first progression after the first line therapy. Electronic medical record data was utilized to accurately capture mortality. Survival after progression was calculated from the date of first progression after the first line chemotherapy to the date of death or last follow-up date. Univariable and multivariable Cox proportional-hazard models were fitted to assess the associations between the survival outcomes and the covariates including gender, race, ECOG performance status, insurance, best CA19-9 response and tumor differentiation. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Variables which were significant in the univariable models were added to the multivariable model. All statistical analyses were performed using R statistical package version 3.6.3 (R Core Team, Vienna, Austria)."

(4) Results:
Comment 4a: surely there is a difference in biology between the cohort presenting with metastatic disease at diagnosis versus those recurring after resection? I would hesitate to include the latter in this report.

Reply 4a: Thank you for this comment. While it is possible that there are biological differences between the cohort presenting with metastatic disease at diagnosis VS those recurring after resection, there were no differences in the proportion of patients presenting with metastatic disease VS recurrence between racial groups (p=0.192). Many landmark clinical trials of advanced disease in the literature include patients who presented with recurrence after initially having resectable disease. Our discussion compares the proportion of such patients included in this study to the NEJM FOLFIRINOX and gem/abraxane trials, and we do state that our sample includes a higher proportion of those patients. Additionally, approximately one third of the total patients in this study recurred after resection; to eliminate these patients would significantly limit the statistical power to draw any meaningful conclusions. The aim of this study was the investigate the response to treatment for all patients with advanced PDA treated at our institution, but this limitation will be included in the discussion section.

Changes in the text: See Discussion, third paragraph third to last sentence, "It is possible that there is a difference in tumor biology between patients presenting with metastatic disease at diagnosis versus those recurring after resection, and the inclusion of a larger proportion from the latter cohort in our study likely contributed to the observed difference in OS. In our cohort, median survival for patients presenting with metastatic disease was inferior to patients presenting with recurrent disease (HR 2.63, P=0.009, data not presented)."

Comment 4b: following along with thoughts about disease biology, was the median time to progression different for patients with advanced/metastatic disease present at different sites?

Reply 4b: Thanks for the comment. The median time to progression was different for patients with different metastatic sites. We have added the median time to progression of patients with different metastatic sites to Results.

Changes in the text: See Results, page 10, "However, there was a difference in median time to progression among patients with different metastatic sites (bone: 2.0 months, pancreas: 5.2 months, liver: 6.1 months, lung: 6.3 months, other: 10.0 months)."

Comment 4c: greater exploration into an expanded set of relevant clinicopathologic factors is warranted for publication. Considerations include a measure of disease burden at presentation (site, multifocality, number, size of mets for example), differentiation status of histopathologic biopsy specimen, CA19-9 longitudinal response, etc. Surely the work is limited by both the relatively low number of patients and the statistical methodology used, this relative limitation could be mitigated by a more detailed analysis of clinicopathologic factors that should be available retrospectively.

Reply 4c: Thanks for this comment. Quantifying the multifocality and size of metastases was not feasible and was limited by the level of detail provided in our institution's radiology reports. Differentiation status and CA19-9 longitudinal response were investigated and incorporated into our univariable model.

Changes in the text: See Results, last paragraph second to last sentence, "There was also no significant association between OS and number of metastatic sites (HR: 0.91, p=0.696), best CA19-9 response (<50% vs. ≥50% decrease, HR: 1.28, p=0.473), and tumor differentiation (Poor vs. well/moderate HR: 1.07, p=0.871)."

Comment 4d: was the survival driven by inclusion of the surgical cohort?

Reply 4d: Thanks for this comment, this discussion point was included in the Discussion section.

Changes in the text: See Discussion, third paragraph third to last sentence, "It is possible that there is a difference in tumor biology between patients presenting with metastatic disease at diagnosis versus those recurring after resection, and the inclusion of a larger proportion from the latter cohort in our study likely contributed to the observed difference in OS. In our cohort, median survival for patients presenting with

metastatic disease was inferior to patients presenting with recurrent disease (HR 2.63, P=0.009, data not presented)."

(5) Discussion/Conclusions:

Comment 5a: very much appreciate and support the look into the US census data ... well done! Related, I'm a bit surprised that the EMR doesn't have zip code for each patient to draw more information from the dataset on socioeconomic determinants of health.

Reply 5a: Thanks for this comment. While zip data was available in the EMR, we decided that this level of analysis was beyond the scope of this paper but should be included in future studies. See the Discussion section second to last paragraph, fourth sentence "Some specific additional factors that would be useful for future studies include the investigation of the impact of ZIP code, income level, and education level, among others on PDA OS."

Changes in the text: N/A

Comment 5b: I would argue that the rationale used to caution looking into molecular or genetic determinates of outcome, and associating with race, is a fair point, that once acknowledged should be explored and would greatly add value to this work.

Reply 5b: Thanks for this comment. We agree with this point and did in fact retrospectively retrieve the molecular data that was available for these patients. 30 patients (~20%) of patients had next generation sequencing data available that could characterize somatic mutational burden, and 6 patients (~4%) had germline data available. Therefore, the limitations associated with the retrospective nature of this report preclude our ability to perform statistical comparisons with molecular data between groups. However, we do mention that future investigation of tumor biology is needed. See the final sentence of the manuscript, "Further study of socioeconomic contributors to this health disparity along with possible disparities in tumor biology is warranted."

Changes in the text: See Discussion, second to last paragraph, third and fourth sentences, "Next generation sequencing data was available for 30 patients (~20%), and 6 patients (~4%) had germline molecular data available. The limitations associated with the retrospective nature of this report precluded our ability to perform statistical comparisons with molecular data between groups."

Comment 5c: Just how many patients were lost to follow up? At what length? This is a

major limitation of the work here that calls much of the conclusion (or absence of finding a difference) into a bit of question when the primary outcome looks at long-term outcomes/survival.

Reply 5c: Thanks for this comment. We agree that the number of patients lost to follow up is a significant limitation of this study. Text addressing the number of patients lost to follow up and the median follow up time was added to the manuscript. Figure 2 contains the "patients at risk" for each time point, providing a detailed visual representation of this exact point.

Changes in the text: See Results, Survival outcomes, first sentences "There were 50 deaths (38%), and 82 patients were lost to follow-up (62%) with complete survival data. Follow-up time ranged from 0.2 to 64.0 months, and the median follow-up time was 11.6 months." Additionally see Discussion, paragraph 4, second to last sentence, "To demonstrate this limitation, figure 2 incorporates the "patients at risk," providing an accurate visual representation of the number of patients lost to follow up at each timepoint for each group."

Reviewer B

I would like to congratulate the authors for the work of putting together data on racial determinants of survival in pancreatic cancer, a subject that is very controversial and important. However, there are some issues that should be addressed before the manuscript publication process can move forward.

Abstract:

1. Chi-square statistics are only used for comparing the distributions of categorical variables. They are not meant for descriptive statistics and they do not deal with numerical variables. Moreover, no mention was given to the proportional hazard model in the abstract.

Reply 1: Thank you for this comment. We apologize for the text, which was less than ideal. We have revised the abstract and added the text below.

Changes in the text: See Abstract, "Continuous and categorical variables were tested using t-test, Mann-Whitney U, chi-squared or Fisher's exact test as appropriate. Kaplan-Meier curves were generated and Cox proportional hazards models were used to analyze survival outcomes."

Introduction.

2. Well-written and addresses the relevant issues.

Methods.

Comment 3: Perhaps it would be interesting to known how race was documented. It is said in the text that it was self-reported, but given the importance of this variable to the paper, it would be advisable to have as many data as possible on how this was extracted (e.g.: under which circumstances it was self-reported - face-to-face interview, phone call). Also, when a patient had more than one ethnical background, in which group was she or he allocated?

Reply 3: Thanks for this comment. We agree that there are challenges associated with the operationalization of race as a variable in retrospective clinical projects. It is institutional policy that patients designate race on their initial intake forms when they arrive for their first visit with a provider within our health system. There were no patients in this study who had documented multiple racial backgrounds within our electronic medical record system, although it is possible that such patients could have checked "Other" on their initial intake forms.

Changes in the text: See Methods section, Clinical Data section, fourth sentence, "It is institutional policy that patients designate race on their initial intake forms when they arrive for their first visit with a provider within our health system."

Comment 4: Still regarding ethnicity, I would recommend creating a group of Hispanic/Latinos in an attempt to separate them from the rest. It is an important ethnic group in your population and I think it should be separated from other rare races.

Reply 4: Thank you for this comment, and we agree with this assessment. See Table 4 and Results section Survival outcomes.

Changes in the text: See Table 4 and Results section, Survival outcomes, last paragraph, "Additionally there were no differences in OS between Hispanic or Latino and non-Hispanic or Latino White patients nor between non-Hispanic or Latino "Other" and non-Hispanic or Latino White patients (HR 1.69, p =0.192, HR 0.82, p=0.816, respectively) (Table 4)."

Comment 5: The objectives and outcomes of the study should be described in the methods section (not in results).

Reply 5: Thanks for this comment. We have added a "Study Objectives" section to the Methods section.

Changes in the text: See Methods, Study Objectives section, "Our study aims to systematically evaluate clinical outcomes for all advanced stage PDA patients treated

with modern chemotherapy regimens at a single urban specialty care medical center. Our primary endpoint was OS between AA VS White PDA patients. Secondary endpoints include OS differences between White patients and other racial groups and racial differences in cancer risk factors, clinicopathologic characteristics, receipt of systemic therapy, and systemic therapy related toxicity."

6. Univariate analyses and multivariate analyses of time-to-event outcomes are generally performed using the Cox proportional hazard method. Please describe which method was used to generate the models. Also, describe which statistical software was used to analyze the data and also provide boundaries for statistical significancy.

Reply 6: Thank you for this comment. We have added further information regarding the analysis and the software to Methods.

Changes in the text: See Methods, page 7, "Univariable and multivariable Cox proportional-hazard models were fitted to assess the associations between the survival outcomes and the covariates including gender, race, ECOG performance status, insurance, best CA 19-9 response and tumor differentiation. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Variables which were significant in the univariable models were added to the multivariable model. All statistical analyses were performed using R statistical package version 3.6.3 (R Core Team, Vienna, Austria).".

Results.
Comment 7: There is a very low number of patients who underwent metastasectomies. For that, I would recommend using only descriptive statistics while analyzing this variable.

Reply 7: Thanks for this comment, and we agree with this statement. Comparative statistical test is no longer mentioned in the results.

Changes in the text: See Results, Therapy for advanced PDA, paragraph four, "There were 5 patients who underwent metastasectomies for ovarian, lung, liver, and splenic disease."

8. Primary endpoint should be stated on the methods section.

Reply 8: Thank you for your suggestion. We have added a statement regarding the primary and secondary endpoints to Methods.

Changes in the text: See Methods, Study Objectives, pages 7-8, "Our primary endpoint was OS between AA VS White PDA patients. Secondary endpoints include OS differences between White patients and other racial groups and racial differences in cancer risk factors, clinicopathologic characteristics, receipt of systemic therapy, and systemic therapy related toxicity."

Comment 9: In the discussion, the authors state that a significant number of patients were lost to follow-up. Please provide metrics of follow-up time (perhaps using the inverse KM methods) and the frequency in which patients were lost to follow-up.

Reply 9: Thanks for this comment. We agree that the number of patients lost to follow up is a significant limitation of this study. Text addressing the number of patients lost to follow up and the median follow up time was added to the manuscript. Figure 2 contains the "patients at risk" for each time point, providing a detailed visual representation of this exact point.

Changes in the text: See Results, Survival outcomes, "There were 50 deaths (38%), and 82 patients were lost to follow-up (62%) with complete survival data. Follow-up time ranged from 0.2 to 64.0 months, and the median follow-up time was 11.6 months." Additionally see Discussion, paragraph 4, second to last sentence, "To demonstrate this limitation, figure 2 incorporates the "patients at risk," providing an accurate visual representation of the number of patients lost to follow up at each timepoint for each group."

10. Figure 2: please replace black by african american.

Reply 10: Thank you for this comment. We have replaced "Black" by "African American."

Changes in the text: Figure 2 "Black" by "African American".

11. Figure 2: check the need to describe the sampling distribution of patients (total number of patients per group would be clearer).

Reply 11: Thank you for your suggestion. We have updated the figure and added the numbers per group.

Changes in the text: The numbers per group has been added to Figure 2.

Comment 12: Table 2: the table is too long and difficult to read. I would recommend

splitting the table into two or three different ones, approaching different aspects of the population (e.g.: first/second-line treatment; toxicity)

Reply 12: Thanks for this comment. We agree with this suggestion. Table 2 was split into two different tables, now Tables 2 and 3.

Changes in the text: See updated tables created incorporating this suggestion and appropriately referenced throughout the text.

Comment 13: Why was the Hispanic group evaluated separately from the other ethnic groups in univariate analysis? This does not seem very sound.

Reply 13: Thanks for this comment. We agree with this notion and have created a separate Hispanic or Latino group. Please see Table 4 and Results section, Survival outcomes. However it is worth noting that race and ethnicity are different variables that can be considered to be mutually exclusive. As stated by the US Census, "People may choose to report more than one race group. People of any race may be of any ethnic origin." http://www.census.gov/topics/population/race.html

Changes in the text: See Results section, Survival outcomes, last paragraph, "Additionally there were no differences in OS between Hispanic or Latino and non-Hispanic or Latino White patients nor between non-Hispanic or Latino "Other" and non-Hispanic or Latino White patients (HR 1.69, p =0.192, HR 0.82, p=0.816, respectively) (Table 4)."

Comment 14: In the univariate model, surgery in the metastatic setting was used as a potential prognostic factor. However, given the immortality bias associated with this, I would recommend dropping this variable (also very few patients underwent metastasectomy).

Reply 14: Thanks for this comment. We agree with this assessment, and we have dropped this variable from our univariable analysis.

Changes in the text: See new Table 4 incorporating this suggestion in our univariable model.

Comment 15: Although I mathematically agree the log transformation of CA 19-9 is often needed, many people are not familiar to the logarithmic scale and this could lead to difficulties in data interpretation (optional).

Reply 15: Thanks for this comment. We have added further clarification regarding the interpretation of CA 19-9.

Changes in the text: See Table 4, "Every 10-fold increase in CA 19-9".

Comment 16: Other important variables were not considered in the univariate/multivariate analyses, such as marital status, age, and comorbidities. This should be addressed.

Reply 16: Thanks for this comment. We agree that it would have been ideal to investigate the effect of these variables on OS, however given the limitations associated with statistical power due to the retrospective nature of this study it was not possible to include all variables of interest into the univariate and multivariate analysis.

Changes in the text: See Discussion section, paragraph 4, final sentence, "Finally, the retrospective nature of this study also created limitations in statistical power, which precluded our ability to include all variables of interest into univariate and multivariate analyses."

Comment 17: Please describe in the methods section how variables were taken from the univariate to the multivariate model. The multivariate model ignores many well-established prognostic variables, such as ECOG performance status. Even though they might not have been important ones in your univariate models, they are widely accepted as important. Including more variables brings the issue of increased degrees of freedom of the statistical test. However, I really believe you should consider reviewing the way in which your prognostic model was built.

Reply 17: We have added further explanation regarding variable selection. Given the limitations of the dataset, we selected the variables based on statistical significance. However, we added ECOG PS and observed that the model's performance was worse. Therefore, we only included the variables which showed significant association in the univariable analyses.

Changes in the text: See Methods, page 7, "Variables which were significant in the univariable models were added to the multivariable model".

Discussion.
Comment 18: The conclusion part should be replaced discussion

Reply 18: Thanks for this comment. The *Annals of Pancreatic Cancer* website formatting instructions for authors states that the paper should be formatted with the

following sections: Introduction, Methods, Results, and Conclusions. If this is not the case, then we can change the "Conclusions" heading to "Discussion."

Changes in the text: See that the "Conclusions" heading has been changed to "Discussion."

Comment 19: The data on different mutational background among diverse ethnic groups is interesting. I would suggest exploring this a little bit more.

Reply 19: We agree with this point and did in fact retrospectively retrieve the molecular data that was available for these patients. 30 patients (~20%) of patients had next generation sequencing data available that could characterize somatic mutational burden, and 6 patients (~4%) had germline data available. Therefore, the limitations associated with the retrospective nature of this report preclude our ability to perform statistical comparisons with molecular data between groups. However, we do mention that future investigation of tumor biology is needed. See the final sentence of the manuscript, "Further study of socioeconomic contributors to this health disparity along with possible disparities in tumor biology is warranted."

Changes in the text: See Discussion, second to last paragraph, third and fourth sentences, "Next generation sequencing data was available for 30 patients (~20%), and 6 patients (~4%) had germline molecular data available. The limitations associated with the retrospective nature of this report precluded our ability to perform statistical comparisons with molecular data between groups."