Dear Editor-in-chief, Science-editor and Peer-Reviewers,

Thank you for assessing our manuscript, for the constructive comments made in your review notes and for the opportunity to revise and resubmit our paper "Clinical Characteristics and Outcomes in CA 19-9 Negative Pancreatic Cancer – a single center experience". Your suggestions have been addressed on a point-by-point basis and changes have been made accordingly, which are highlighted throughout the manuscript.

Point 1

However, I have some comments: the study title should indicate the retrospective single center nature of the study according to strobe statements (the study setting is arguable, but not described, in the abstract).

Author's reply

Thank you for this suggestion, we've updated the title and abstract accordingly.

Point 2

In the methods, paragraph "study design and patients population, the acronim IAP should be replaced by the non abbreviated version of the term".

Author's reply

Thank you for your comment, we've replaced the acronym IAP with the full version of the term.

Point 3

The sentence about grouping of tumors according to the location should be rewritten because is not clear.

Author's reply

Thank you for pointing out this issue, we've revised the sentence about tumor location in order to make it clearer.

Point 4

Major comments regard the discussion: except for the first paragraph, in which the authors resume the study results, the remaining discussion uniquely contains results from studies previously published on this issue. In the discussion, the authors should also comment their results and interpret such results taking into account available literature and creating

comparison with it. Given that the manuscript focus has already been analyzed by many studies, the authors should try to identify and discuss peculiarities of their study, in order to make their study results more interesting.

Author's reply

Thank you for this comment, we've revised the discussion section and critically analyzed findings from our study compared to literature data. Also, we've added several paragraphs according to reviewers' suggestions.

Point 5

In particular, the paragraph reporting on the prognostic role of additional biomarkers among patients with no elevation of CA19.9 seems inappropriate, given that the authors did not perform a subanalysis focused on patients with CEA-Ca125 + patients: Could such subanalysis be performed? Maybe it may add to the study

Author's reply

Thank you for this observation. We performed a sub-analysis on CEA and CA 125 positive cases with regard to prevalence, but an in-depth analysis of these cases could not be carried out due to small sample of such patients. A descriptive characterization of these patients was added in the corresponding paragraph.

Point 6

Similar, speaking extensively about the prognostic role of Lewis antigen status, without having such status assessed in this manuscript, is confusing.

Author's reply

Thank you for your comment. Although genotyping Lewis status is not common practice, we consider important to point out its role for PDAC management from evidence-based information, in order to raise awareness for clinicians about the peculiarities of CA 19-9 testing. Considering the impact of Lewis antigen testing, some authors have even proposed incorporating its use along with CA 19-9 in PDAC management.

Point 7

Also, would suggest adding another table to discuss outcomes, complications and histopathological characteristics between the two groups.

Author's reply

We are grateful for this suggestion, but unfortunately, we don't have data on complications. Regarding outcome, we could only assess survival in this research.

Point 8

The main limitation of the study is the sample size and the lack of Lewis antigen genotyping that would have improved the power of the study.

Author's reply

We agree that sample size and lack of Lewis antigen genotyping are limitations of our research and we acknowledged them in a paragraph in the discussion section. However, we consider that focusing on CA 19-9 is more clinically relevant, as Lewis antigen genotyping is not routinely done in clinical practice.

Point 9

I note the references lack DOI.

Author's reply

Thank you for pointing out the lack of DOI, we've added the code in the revised version of the manuscript.

Point 10

My question to authors: despite the cancer being resectable in nearly 14% in group A compared to 7% in group B the 6 months survival was not significantly higher in group A?

Author's reply

Thank you for this question. We believe the lack of statistical significance is because of small number of lesions in each stage (particularly resectable and borderline tumors), across the two groups.

Point 11

(1) In Abstract (Results part), you can try to present percentage differences always in the same way. That is, sometimes you compare positive vs negative (e.g. abdominal pain) while on other cases negative vs positive (e.g. smoking). While this is not very problematic, it may lead to misunderstanding of results. Example is "Abdominal pain was more frequently reported in positive vs negative CA 19-9 PDAC cases (76.83% vs 55.17%), while smoking was slightly more prevalent in the latter group (31.03 vs 28.04%)". Here, at first glance I

thought that the latter group is indeed negative group, but the percentages in brackets were switched. In my opinion, all comparisons should be referred in the same way, for example positive vs negative, so in the case of smoking the brackets should be 28.04% vs 31.03%. Hopefully, you understand my intention. Moreover, add missing "%" next to 31.03. By the way, the sentences such as "6-months survival was higher for the negative CA19-9 group (58.62% vs 47.56%)" are not vague, the problem is when you use "former" or "latter" while mixing the order of groups in comparison.

Author's reply

Thank you for this suggestion, we agree our initial representation of results might have been confusing. We've reported comparisons uniformly along the abstract and manuscript.

Point 12

(2) Throughout the manuscript, there are decimal separators but not equivalent for thousands. Please correct.

Author's reply

Thank you for pointing out this issue, we've added the decimal separators accordingly.

Point 13

(3) Not sure if Figure 1 or 3 could be created using separate objects - I think the merged graph must be provided at later stages. Also, please delete excessive space in Figure 1 on the right (next to heterophilic antibodies). Moreover, the title of Figure 3 should be put below figure, not above it. GM

Author's reply

Thank you for pointing out this issue, we've deleted the excessive space and provided the Figures as separate objects in PPT.

Point 14

(4) Explain "IAP" abbreviation, that is first mentioned in Methods.

Author's reply

This was addressed in point 2.

Point 15

(5) Consider highlighting the statistically significant results in tables (e.g. abdominal pain in Table 1) using e.g. bold.

Author's reply

Thank you for your suggestion, we highlighted the significant p-value in bold.

Point 16

(6) Use "tumor" or "tumour" consistently. Example of first option is in Abstract while the second one in Table 1.

Author's reply

Thank you for pointing out this issue, we've replaced "tumour" with "tumor" across the revised manuscript.

Point 17

(7) The sentence "However, CA 19-9 remains a valuable biomarker for PDAC management, in several aspects" could be "However, in several aspects the CA 19-9 remains a valuable biomarker for PDAC management".

Author's reply

Thank you for your suggestion, we've modified the sentence accordingly.

Point 18

(8) What is the purpose of "lot" inclusion in this sentence: "In our study lot, 34.47% of CA 19-9 negative PDAC cases had elevated levels of CA 125, 37.92% for CEA and 20.68% for both"

Author's reply

Thank you for pointing out this issue, we have removed the word "lot" in the mentioned sentence.

Point 19

(9) In Conclusions section, you should add information that is provided in equivalent from Abstract, and vice versa. For example, in section "5" there is no mention about symptomatology or tumor burden while in conclusion of Abstract there is no data regarding CEA or CA 125.

Author's reply

Thank you for these suggestions, we have added information in the conclusion section and in the abstract conclusion such that the information to be equivalent.

Thank you again for all your comments, which were highly appreciated and taken into account for this revised, improved version of our manuscript. We hope that all changes made are satisfactory resolutions for your inquiries. We remain open to any further corrections.

Best regards,

The authors