

Reply to the reviewer's comments

DETAILED CRITIQUE:

1. Page 3- introduction: " PC is the fifth leading cause of death worldwide". However, more recent papers (Siegel RL et al, Cancer Statistics 2015) describes PC as the 4th cause of cancer death and is expected to be the second cause of cancer death by 2030 in Western countries

Thank you for the comments. This data for PC as the 4th cause of death is the estimated statistics in USA 2016. Therefore we only added future information in 2030 because fifth cause of death as referred to the reference is correct.

2. Page 4- overview of standard chemotherapy for PC: what was the survival benefit of other chemotherapeutic regimens compared to gemcitabine alone? (for example: MPACT trial, consisting of Gem+Nab-paclitaxel had OS (overall survival) of 8.5 months compared to 6.7 months in patients treated with gemcitabine alone). Mentioning this data allows to better understand the minimal improvement of survival by current chemotherapy regimens

Thank you for the comments. Accordingly we added this information in detail.

3. Authors should describe treatment regimens for patients with PC based on stage (Locally advanced vs metastatic) and patient performance status. Also, what is the benefit of radiation in combination with chemotherapy before surgery ?

Accordingly, we described the patient characteristics in the clinical trial.

3. It should be mentioned that the low 5 years survival rate is due also to chemoresistance ,relapse and metastasis even after surgical resection

We fully agreed with this suggestion and put additional description in the manuscript.

4. Page 6- infiltrating T lymphocytes- it is worth mentioning that there is a study by Tewari N et al, BMC Cancer 2013) that demonstrated a positive correlation between prognosis and the presence of tumor infiltrating T cells

We added this reference.

6. Page 6- regulatory T cells- a study by Yamamoto et al, Pancreas 2012) shows that low Treg percentage in circulation at 1 year after PC resection correlates with improved survival. Another paper by Keinan BP et al, Gastroenterology 2014) showed that immunization of mice with Listeria Monocytogenes engineered to express k-ras along with depletion of Treg cells reduces progression of early stages PAN INs. This could describe the role of Treg in cancer development.

We added these references.

7. Page 9- Myeloid derived suppressor cells (MDSCs). A paper worth mentioned in the review is by Markowitz et al, 2014, Cancer Immunology that describes MDSC in peripheral blood as a possible predictive biomarker of chemotherapy failure in PC patients

8. A few data regarding dendritic cells, another component of tumor microenvironment should be added- it has been showed that in PC, dendritic cells display maturation defects (Tjomsland V et al, PLoS One, 2010). Therapy aimed at improving DC function could be beneficial in PC treatment.

Accordingly, we added the new section for dendritic cells and put the suggested reference.

9. A subchapter regarding vaccine therapy against PC should be added

We appreciate this advice. However the main focus of this manuscript is the change of the tumor microenvironment after chemotherapy. Therefore it seems like that the inclusion of the topic about cancer vaccine therapy might be getting out of this focus.

10. Throughout the paper, there are multiple words that are misspelled. For example: page 8- title "Myeloid derived suppressor cells" or page 11: " Conclusions"

We apologize for the misspellings. According to the reviewer's comments we correct those words.