Dear Editor,

We would like to resubmit the revised manuscript entitled "Neoadjuvant Therapy in Resectable Pancreatic Cancer: A Promising Curative Method to Improve the Prognosis". We would like to thank the reviewers for thoroughly reviewing our manuscript and making many thoughtful comments. We were very pleased to see that all two reviewers recognized the novelty and potential significance of our work. We have added significant new data, described in detail below, and revised the manuscript to address reviewers' comments. Here are our point-by-point responses:

Reviewer #1:

Comment 1: Background: Consider “which would preclude surgical resection” instead of “which leads to the loss of the chance of surgery”
Response: Thanks for your suggestion, we have accepted this comment and revised it in manuscript.

Comment 2: Factors about local recurrence: Tumoral diameter Consider “Four of 19 (21%) patients in arm B were pT1-2 while only 2 of 23 (9%) of patients in arm A were this stage” instead of “Four of 19 (21%) patients in arm B were in the pT1-2 stage, while only 2 of 23 (9%) patients in arm A were in this stage.”
Response: Thanks for your suggestion, we have accepted this comment and revised it in manuscript.

Comment 3: Resection margins Consider “(17/33)” instead of “(17-33)”
Response: Thanks for your suggestion, we have accepted this comment and revised it in manuscript.

Comment 4: Table 2 comments: This table is unclear and could use a little more explanation as to what these trials are investigating. Place trial name above NCT number. For example, trial 1 is ICI20-00047 and trial 2 is CISPD-1, while trial 3 is A021806 and trial 4 is the most recognizable name: PREOPANC-3. Describe the phase of each trial. Be a little more specific on treatment arms. For example, trial 1 is investigating Surgery with or without neoadjuvant FOLFIRINOX and SBRT, trial 2 is investigating surgery with or without either neoadjuvant nPt/GEM or mFOLFIRINOX before surgery, and trial 3 is investigating Perioperative vs. adjuvant mFOLFIRINOX, and trial 4 (PREOPANC-3) is investigating perioperative vs. adjuvant mFOLFIRINOX.
Response: Thanks for your recommendation, we have accepted this comment and revised it in manuscript. We have revised the title to “Ongoing randomized controlled trials comparing surgery alone with neoadjuvant therapy following by surgery for resectable pancreatic cancer” in order to explain what these trials are investigating. Trial names have been placed above NCT number. The treatment arms have been described more specific.

Comment 5: Are NCT01521702 and NCT01314027 the same trial? Both are called NEOPAC

and are investigating the same regimen.
Response: Thanks for your suggestion, these two trials are not the same trial.

Reviewer #2:

Comment 1: The aim of this manuscript is not clearly declared. In the abstract the authors define it a meta-analysis, but the paper could only meet the criteria for a narrative review. The type of article must be specified.
Response: Thanks for your suggestion, we have revised the abstract to specify the type of this manuscript.

Comment 2: Background - I think that a precise definition of resectability according to the main guidelines could be useful and could be added.
Response: Thanks for your suggestion, definition of resectability according to the latest NCCN guideline have been added.

Comment 3: Studies about NAT in R-PA - The title should be changed in a plural form
Response: Thanks for your suggestion, we have accepted this comment and revised it in manuscript.

Comment 4: Long term results of the PREOPANC trial have been recently published and must be updated.
Response: Thanks for your suggestion, we have updated data from the long-term results of the PREOPANC trial in page 4 before the **1.Safety and feasibility** (The latest results of the PREOPANC trial showed that the HR of OS was 0.79 for patients with R-PA (P=0.23).[12]) and **3.2 Invasion of vessels and perineural spread** (Based on the latest results from the Dutch trial, vascular invasion was less frequently observed in the NAT group (36% vs. 65%; P<.001).[12])

Comment 5: Page 3. It is stated that the median OS appeared to be better in the NAT group. This could not be stated since this is not a meta-analysis. The subsequent results that are reported for the single studies should include the p value.
Response: Thanks for your suggestion, we have modified the inaccurate discussion. P value was not provided from the single arm study. All available P value were reported in the manuscript.

Comment 6: Page 3. The final sentence section is not clear and must be reformulated.
Response: Thanks for your suggestion, we have reformulated the final sentence section: “NAT might actually benefit patients with low-risk factors for long-term survival. According to the OS of the Dutch trial (Figure 1), the 1-, 2-, 3-, and 4-year OS rates were comparable between the NAT group and the upfront surgery group.[8] The latest results of the PREOPANC trial showed that the HR of OS was 0.79 for patients with R-PA (P=0.23).[12] The reason for this outcome might be that this trial excluded T1 tumors (2 cm, without vascular

involvement). Because patients with high-risk factors always die due to recurrence within 2 years, almost the only patients who were in the long-term follow-up were those with low-risk factors. Thus, when patients with low-risk factors were excluded, the benefit of NAT on long-term OS disappeared.
In the PACT-15 trial,[10] the 1- and 2-year OS rates were similar between the NAT group and the upfront surgery group. However, the NAT group showed better 3-year OS (55%) and 5-year OS (49%) than the surgery alone group (3-year OS 35% and 43%; 5-year OS 13% and 24%). The reason for this difference could be that T1 tumors were included. Tumors with low-risk factors could benefit from NAT and obtain better 3- and 5-year OS.
According to a recent meta-analysis, the NAT groups showed superior 1-, 2-, 3-, 4-, and 5-year survival rates compared to the upfront surgery group.[13]".

Comment 7: 2.1 - It is not reported the edition number of the AJCC TNM
Response: Thanks for your suggestion, we have reported the edition number of the AJCC TNM.

Comment 8: Conclusion - In the final discussion it should be highlighted the importance of selecting patients that could mostly benefit from neoadjuvant therapy.
Response: Thanks for your suggestion, we have highlighted the importance of selecting patients that could mostly benefit from neoadjuvant therapy in the final discussion.

Comment 9: A recent review examining putative predictive factors for neoadjuvant therapy in resectable pancreatic cancer has been published (10.3389/fsurg.2022.866173).
Response: Thanks for your suggestion, we have added this review to our manuscript in the last paragraph: "Some novel predictive factors in R-PA were addressed recently, such as molecular profiles, tumor microenvironments, immune cell infiltration, microRNAs, circulating tumor DNA, organoids and the gut microbiome.[48]".