**Peer Review File**

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**Reviewer A**

Comment 1. I find the analysis of ICER and WTP a bit complex to comprehend. I am unclear if the WTP threshold of 150000 USD if supported by literature or it is a result of this study? Also 1 month OS and 150000 USD public money will have different value compared to own money.

**Reply 1**: Thank you for your insightful comments regarding the complexity of the incremental cost-effectiveness ratio (ICER) and willingness-to-pay (WTP) analysis. We appreciate the opportunity to clarify these aspects of our study.

The WTP threshold of $150,000 was not derived from this study but was adopted from published literature on cost-effectiveness analyses in pancreatic cancer (References 23-25). This threshold represents the total treatment cost threshold for managing locally advanced pancreatic cancer (LAPC) rather than a per-month overall survival (OS) cost. Considering the poor prognosis and limited therapeutic options for LAPC, it reflects the societal willingness to invest in treating LAPC. Similar WTP thresholds have been used in previous cost-effectiveness evaluations of pancreatic cancer therapies.

We acknowledge that the perceived value of OS gains and the public acceptance of spending $150,000 for treatment may vary across different healthcare systems and economic contexts. We conducted a probabilistic sensitivity analysis (PSA) to address this uncertainty, varying the WTP threshold from $20,000 to $300,000. This approach provides a broader perspective on the cost-effectiveness of FOLFIRINOX versus gemcitabine/nab-paclitaxel under different economic conditions. The acceptability curves generated from this analysis illustrate the probability of each neoadjuvant treatment (NAT) regimen being cost-effective across a range of WTP values.

We agree that public healthcare funding decisions may differ from individual spending priorities. Our analysis adopts a societal perspective, which is the standard approach in cost-effectiveness analyses. This perspective considers collective resource allocation decisions, reflecting the broader societal burden of disease rather than individual out-of-pocket expenses. Our approach aims to provide insights relevant to healthcare policymakers who must make funding decisions based on population-level benefits and resource constraints.

To enhance clarity, we have revised the Methods section to explicitly state that the WTP threshold was based on previous literature and expert consensus. Additionally, we have emphasized the variation of WTP in the PSA to acknowledge differences in economic perspectives across various healthcare settings. We hope these revisions address your concerns.

**Changes in the text**: Manuscript page 7, line 225-240 (marked in blue):

Cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB), compared against a willingness-to-pay (WTP) threshold of $150,000, which represents the total treatment cost for managing LAPC rather than a per-month cost of OS. This threshold was derived from published literature on LAPC-related expenditures, expert consensus, and societal values reflecting the high disease burden and limited treatment options for LAPC (23-25). The societal perspective was adopted to emphasize the efficient allocation of healthcare resources for severe conditions where survival gains are highly valued. A NAT regimen was deemed cost-effective if its ICER was negative (indicating lower costs and higher effectiveness) or fell below the $150,000 WTP threshold. The regimen with the highest NMB was considered the most cost-effective. A positive incremental NMB (FOLFIRINOX NMB – gemcitabine/nab-paclitaxel NMB) favored FOLFIRINOX, while a negative value favored gemcitabine/nab-paclitaxel. A probabilistic sensitivity analysis (PSA) was conducted to capture variations in healthcare systems and economic perspectives, varying the WTP threshold from $20,000 to $300,000. This approach provided a more comprehensive evaluation of cost-effectiveness across different economic contexts. The PSA was carried out using a Markov Monte Carlo simulation with 1000 hypothetical patient cohorts per strategy, incorporating real-world variability in model parameters. Results were visualized through a cost-effectiveness plane and acceptability curves, illustrating the probability of each NAT regimen being cost-effective at different WTP thresholds.

Comment 2. I find generally the article to be well written with good introduction and method sections. The result and discussion section are also ok and I don't have any comments or criticism for further improvement.

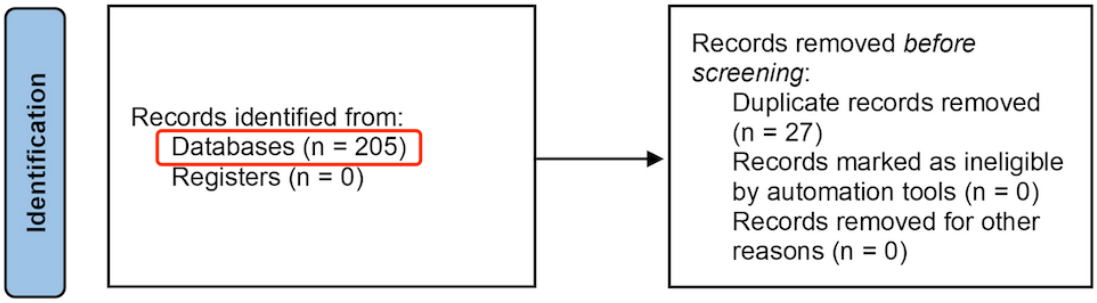
**Reply 2**: Thank you very much for your positive feedback on our manuscript. We appreciate your kind words regarding the clarity of our introduction and methods sections, as well as your acknowledgment that the results and discussion sections are satisfactory.

**Changes in the text**: not applicable

**Reviewer B**

**1. Figure 1**

Please list out all the databases in the box, and also the number of studies in each database.




Reply: We have listed all the databases along with the corresponding number of studies retrieved from each.

Changes in the text: Revised Figure 1 attached

**2. Figure 2**

Please check if the main text matches with the figure

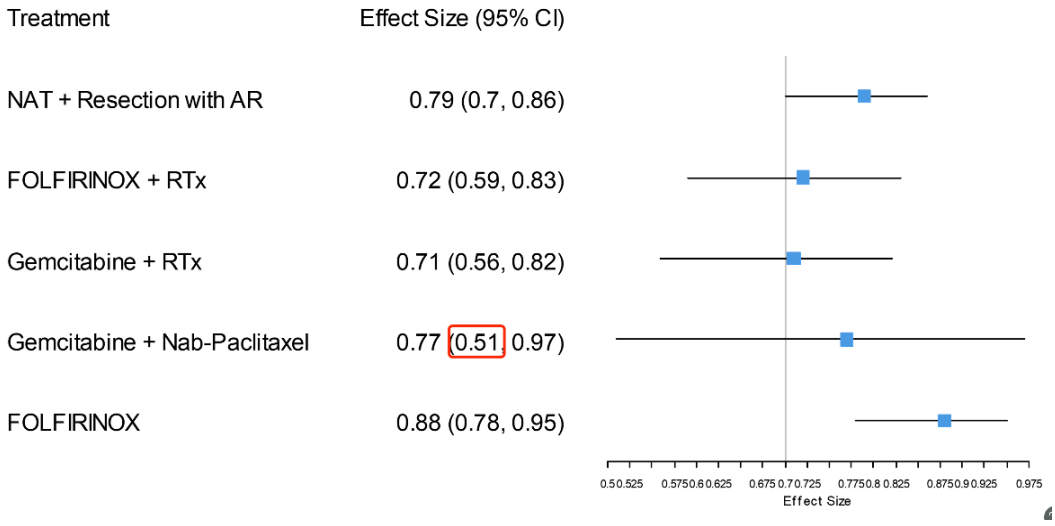
294 Six meta-analyses reported R0 resection rates after NAT. A comparative meta-analysis involving 977 LAPC

295 patients from six primary studies demonstrated a significantly higher R0 rate for FOLFIRINOX compared to

296 gemcitabine/nab-paclitaxel (RR: 0.77, 95% CI: 0.60-0.97, $P < 0.05$). The remaining five meta-analyses were

297 single-arm studies, with pooled R0 rates and 95% confidence intervals presented in **Figure 2B**. One meta-analysis

**B**




Reply: The lower bound 0.60 in the text is correct.

As stated on page 10, line 284-287:

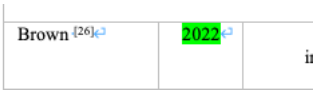
"A comparative meta-analysis (27) involving 977 LAPC patients from six primary studies demonstrated a significantly higher R0 rate for FOLFIRINOX compared to gemcitabine/nab-paclitaxel (RR: 0.77, 95% CI: 0.60-0.97, $P < 0.05$). The remaining five meta-analyses were single-arm studies, with pooled R0 rates and 95% confidence intervals presented in Figure 2B."

The 0.60 value comes from the comparative meta-analysis (Reference 27), whereas Figure 2B presents the pooled R0 rates and 95% confidence intervals for the remaining five single-arm meta-analyses.

Changes in text: We have added the corresponding reference numbers to the meta-analyses mentioned in the results section.

**3. Table 1**

Please check if the year matches with the citation.




Reply: Thank you for bringing this to our attention. We have revised Table 1 and Supplementary Table 1 to reflect the correct year, Brown 2023.

Changes in text: Revised Table 1 and Supplementary Table 1