Author's response to reviews

Title: A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma

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The Editor
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RE: Manuscript 6933647606346461

Dear Editor,

Thank you for the comprehensive and insightful review of our manuscript "A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma". We extensively revised the manuscript to take into account all the suggestions of the expert reviewers. We believe that this definitely enhances the quality of the manuscript.

A point-by-point response to each of the reviewer's comments is given below. We look forward to your favorable consideration of this revision.

Yours sincerely,

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Point-by-point responses to reviewers’ comments

Reviewer #1: Thierry T Conroy

1. Major compulsory revisions:
   
a. Toxicities in the biliary stent group should be reported separately and discussed.
   
   • Table 4 has been revised to separate the toxicities for patients who had stents versus those who did not. Also, the last paragraph on page 10 has been updated to include the following sentence: “There were no significant differences in the toxicity profile for patients who had biliary stents versus those who did not.”

b. Bilirubin levels (with the range) before the first course of chemotherapy should be reported because irinotecan has a biliary elimination and high levels of bilirubin may explain observed toxicities.
   
   • All the patients who were included in this study had normal bilirubin levels prior to starting FOLFIRINOX. A new row has been included in Table 2 to report the median and range of serum bilirubin levels prior to chemotherapy. The following sentence has also been added to the second paragraph on page 6: “For patients who presented with biliary obstruction, adequate biliary drainage was required prior to initiation of any chemotherapy.”

c. Results in unresectable group and borderline resectable group should be reported separately.
   
   • The results for these two groups are now represented separately in Figure 1. This is described in greater detail in #13 below.

2. Minor Essential Revisions:
   
a. The median number of cycles to achieve a response should be reported.
   
   • This information is reported in the first line of page 10 as follows “the median number of FOLFIRINOX cycles delivered was 6 (range 5-17).” This statement is referring to the subset of patients who achieved R0 resections, i.e. those who achieved a response.

b. In the abstract, Folfiriniox was demonstrated superior to gemcitabine in patients with metastatic pancreatic cancer (not "advanced pancreatic cancer”).
   
   • The word “advanced” has been replaced by the word “metastatic” in line 2 of the abstract.
c. What kind of stent was used: metallic? plastic? Was the drainage sufficient?
   • On page 9, paragraph 1, the word “metallic” has been inserted for clarification. Also the following sentence has been added to the end of the same paragraph: “All patients who had stents or bypass procedures achieved normalization of their serum bilirubin levels prior to the start of chemotherapy.”

3. Discretionary revisions:
   a. It could be interesting to know if any case with an abutment of the SMA or celiac trunk encased was resectable after neoadjuvant treatment.
      • There was one patient with encasement of the SMA who achieved a successful R0 resection after neoadjuvant treatment. This is described in the first paragraph on page 10.
   b. References 5, 6, 8 should be precised.
      • References 5 and 6 have been updated to reflect the full citation. Reference 8 was presented in abstract form only and the full citation of the abstract is given.

Reviewer #2: Paula Ghaneh

1. In the introduction the authors state ‘Radiation therapy has also been shown to be beneficial in patients with LAPC and combined chemoradiotherapy (CCRT)’. There is no level one evidence for this – could the authors qualify this statement and say that prospective randomised trials are ongoing to evaluate whether there is a survival benefit of CRT versus systemic chemotherapy.
   • The third paragraph of the introduction has been revised as follows: “Radiation therapy may be beneficial in patients with LAPC and combined chemoradiotherapy (CCRT) has been tested in this population. Although 5-FU-based CCRT is commonly used in this setting, gemcitabine-based CCRT is safe and effective [5, 6]. The best sequence of treatment administration has not been established. Prospective randomized trials are ongoing to evaluate whether there is a survival benefit of CCRT versus chemotherapy alone.”

2. In the ACCORD trial there were a high proportion of patients with body tumours, not jaundiced and with good performance status. An important outcome for this study would be to look at the complications and toxicity for patients with head tumours and jaundice. The authors could highlight that in the introduction/discussion.
   • As suggested, the following sentence has been added to the end of the introduction: “The aim of this retrospective study was to
define the efficacy and toxicities of this regimen in LAPC, especially in patients with pancreatic head tumors and biliary obstruction – a group that was relatively underrepresented in the ACCORD-11 trial.”

3. The authors need to describe their aims and outcome measures more clearly at the end of the introduction (these are listed in the methods but a small sentence here would be useful).
   - The aims are now mentioned in the sentence that has been added to the end of the introduction as described in #2 above.

4. As there is no internationally agreed definition of locally advanced/unresectable and borderline resectable pancreatic cancer – it is really important that this group is very clear on their definitions and although they are treating them in the same way – for the outcomes such as resection rate etc the two groups need to be described separately.
   - We used the AHBPA/SSO/SSAT criteria to define resectability (reference 2). We understand that there is no internationally agreed definition and now acknowledge this in paragraph 2 of the methods section on page 6. The results for the UR versus BR groups are now reported separately as described in more detail in #13 below.

5. Tumors were defined as UR if there was extensive peripancreatic lymph node involvement – we would not define this as unresectable. Could the authors perhaps include a table of the exact criteria of unresectability and borderline unresectability?
   - We have now included a new table (Table 1) to describe the criteria used for determining resectability. Although the AHBPA/SSO/SSAT criteria defines tumors as UR if there is extensive peripancreatic lymph node involvement, we did not have any patients in our series who fell into this category.

6. In the methods section, I am not clear what criteria was used for response - RECIST1.1? Could the authors clarify maximum response and tolerability?
   - A new paragraph has been added on page 7 to clarify this as follows: “After every CECT scan during treatment, each patient’s case was reviewed at a multidisciplinary conference to determine whether the reason for defining the patient as UR or BR had improved. Since size was not the only criteria used in this evaluation, traditional response criteria (such as RECIST) were not employed. For example, if a tumor was categorized as BR due to abutment of the SMA up to 180°, the extent of abutment was re-evaluated after every scan to determine if this was improving and if the patient would not be a surgical candidate. If two consecutive
scans during treatment showed similar findings with no improvement, this was considered to be the maximum response. Maximum tolerability was defined as the point when excessive toxicities warranted stopping FOLFIRINOX, even if a patient had not achieved their maximum response. Because we used an algorithm of real-time monitoring of response and toxicity, there was no predefined minimum or maximum number of cycles.”

7. Did the authors have a prescribed number of cycles for their therapy – it is not clear?
   - There was no predefined number of cycles. This information is now explained in paragraph 2 of page 7.

8. How soon after completion of therapy did the patients undergo resection?
   - Patients were taken to surgery within 6-8 weeks after chemotherapy. A statement specifying this has been added to paragraph 3 on page 7.

9. The primary endpoint was R0 resection rate – how is this defined? Tumour at or less than 1mm from the resection margin R1?
   - Our definition of R0 resection was at least 1 mm free margins. R1 resection was defined as tumor within 1mm from the closest margin. A sentence specifying this has now been included in paragraph 2 on page 8.

10. Statistical analysis includes Kaplan Meier survival curves – was there an event rate to be reached before analysis? The numbers are very small so univariate analyses of any prognostic factors will be fraught with problems and may not be difficult to interpret. Also the authors should state that descriptive statistics were used for data.
   - Since this was not a prospective study, we did not have a predefined event rate to trigger the survival analysis. We analyzed all events at the time of this report. We have added a statement acknowledging that the small sample size as well as the low event rate makes the results difficult to interpret (on paragraph 2 of page 13). A statement has also been added to the last paragraph of the methods section on page 8 stating that descriptive statistics were used.

11. In the results section - in Table1 – basis for unresectability should be divided into what the authors thought was unresectable and borderline resectable.
   - Within this table, the basis for resectability has now been divided into borderline and unresectable categories.
12. Were the stents covered metal or plastic – any complications associated with the stents – eg. cholangitis – could the authors comment?
   - The stents used were all metallic. This is clarified on page 9, paragraph 1. We did not observe any episodes of cholangitis – this is stated on page 11, paragraph 1.

13. The flow chart groups the patients together (UR and BR) it would be informative to have the flow for UR and BR patients separate so we can see the outcomes.
   - Figure 1 has now been altered to show the flow of patients with borderline resectable disease separately from those with unresectable disease.

14. The survival curves should be altered – to one overall survival curve and another demonstrating the survival of those patients who had a resection and those who did not. The numbers at risk should be along the x axis.
   - The reviewer did not specify if the second suggested curve should represent OS stratified by resection status or PFS stratified by resection status. We have now altered Figure 2 to include 4 panels – the two on the left showing PFS and the two on the right showing OS. The curve showing OS stratified by resection status (now panel 2D) was initially omitted because there are only 2 deaths in this series thus far and the curves overlap for most of the way. The number at risk was not included because the overall numbers are small and events can be extrapolated from the steep dips in the curves. Also, in the present format, if we insert the number at risk on the x-axis, this is likely to significantly clutter the figure and may make it difficult to follow.

15. The main interest at this stage for specialists is the feasibility and toxicity of this regimen in this group of patients. Therefore it cannot be stressed too much that the discussion needs to highlight the toxicity and complications of this approach as this information is very important and vital for future studies.
   - The second paragraph of the discussion has been significantly revised to address the toxicity profile and the importance of patient selection for this regimen.

16. The authors also need to highlight the very short follow up which makes interpretation of the data difficult. Such as analysing R1 and R0 survival differences.
   - The limitations of short follow-up and small sample size have been highlighted in the discussion, page 13, paragraph 2, which states inter-alia: “…the follow-up is relatively short…” and “Since
our series is small and the event rate is low, it is difficult to draw definite conclusions.”