Author's response to reviews

Title: Evaluation of Survival in Patients after Pancreatic Head Resection for Ductal Adenocarcinoma

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Author's response to reviews: see over
Dear Dr. Rowles,
Dear editors,

Please find attached the revised version of our manuscript, “Evaluation of Survival in Patients after Pancreatic Head Resection for Ductal Adenocarcinoma” (AW: 4610513318048008)

Thank you very much for the excellent review and the helpful corrections. We appreciate the opportunity to re-submit our manuscript. In the following, we provide an answer to every item raised by the reviewers (corrections in the manuscript are highlighted in yellow):

Response to reviewer 1

1. Several spelling and grammatical errors, please correct

A: We thoroughly read the MS and corrected spelling and grammatical errors. Revisions are indicated in yellow. Furthermore, we acknowledge the service of “American Journal Experts” (Durham, NC, US) for English language editing of the paper.

2. Discrepancy in the reporting of mortality as perioperative mortality was defined as "in-hospital mortality" yet Table 4 indicates "30 day or in-hospital mortality". Please report 30-day mortality for the cohort and clarify in the manuscript as this is more useful.

A: Please excuse this fault on p. 19. We revised the manuscript accordingly. Due to the retrospective character, we can only report in-hospital mortality.
3. Post-operative pancreatic fistula was defined according to ISGPF criteria, which was defined in 2005. The cohort includes 12 years of patients prior to the introduction of the ISGPF criteria. Given that the prospective database utilized in this study may not have defined or detected leaks based on traditional ISGPF criteria, please clarify how pancreatic leaks were defined in these patients from years 1993-2005. Were charts retrospectively reviewed to ensure patients met ISGPF criteria?

**A:** Our comprehensive database encompasses amylase and lipase values in the drains and the serum for the first 10 postoperative days, further days of removal of the drain and comprehensive documentation of complications. Therefore, we were able to retrospectively determine the grading of POPF.

4. In Table 5, how were the categories for continuous variables defined (Age, CEA, CA19-9, Lymph node ratio, BMI)? These seem arbitrarily chosen and the mean, median, and range values are not provided for these continuous variables. Please address as this may affect the final analysis.

**A:** The categories for age and BMI were determined in accordance to previous publications of other groups. CEA and CA19-9 were grouped according to the cut-off values used in our hospital. The lymph node ratio was grouped according to a study by Riediger et al. The mean and range for the continuous variables are given in Table 1. We added this information to the Patients and Methods chapter on p. 5.

5. Bilirubin levels are known to affect CA19-9 and CEA levels and was mentioned in the discussion section but not specifically addressed. Given that 81.5% of patients presented with obstructive jaundice and 71.3% received a biliary stent, please clarify if bilirubin levels were recorded/reported after normalization of bilirubin levels to prevent data from being skewed.

**A:** Although we waited several days after stenting, we cannot exclude that obstructive jaundice might affect the CA19-9 levels. We added a discussion of jaundice in the “discussion” section on p. 10. Revisions are indicated in yellow.

6. It is interesting that R status had no impact on survival, despite data that suggests otherwise. This would imply that adjuvant therapy may be able to make up for a positive margin yet only 40.5% of patients in the cohort received adjuvant therapy and a large portion of the study was in the era prior to gemcitabine based chemotherapy. What was the recurrence rate in the cohort and who recurred locally versus distant, specifically for patients who had a local recurrence yet had an R0 resection as this may imply they actually had a positive margin.

**A:** A study by Esposito in 2008 showed that most resections in patients with pancreatic cancer are R1-resections due to the aggressive infiltrative character, especially at the retroperitoneal margin. Some researchers have stated that pancreatic cancer is a “systemic disease”. Unfortunately, although our database encompasses survival, it does not comprise data on the
location of the recurrence. It would be interesting to analyze the location of the recurrence; however, because our center is responsible for treating pancreatic cancer patients in a large region, many patients received follow-up examinations in their hometowns. When recurrence occurred, most of the patients underwent palliative systemic treatment and only presented for palliative surgery in rare cases. Moreover, it was difficult to determine whether recurrence was local or distant in medical imaging because of the fast growth of the tumor. We added a discussion of this important topic on p. 10 of the manuscript.

7. Was adjuvant chemotherapy regimen controlled for in the survival analysis? From the manuscript it appears that various regimens were utilized with criteria that were not necessarily standardized until 2003 when your institution more routinely used gemcitabine.

A: Even after 2003, the cohort was very inconsistent because adjuvant treatment was performed primarily by ambulant oncologists. Although we controlled adjuvant treatment in our survival analysis, it did not show an improved outcome, which may have been due to the heterogeneity of the protocols. A discussion of this point was added in the discussion section of the manuscript on p. 11.

8. Please clarify the definition of hard versus soft pancreatic texture, there is significant subjectivity when the experience of 8 surgeons over 18 years is taken into account.

A: Thank you very much for this important suggestion. We agree that there is significant subjectivity concerning the evaluation of pancreatic texture. We added a discussion of this problem on p. 10 of the manuscript.

9. Suggest deleting figure 2 as it does not add to the manuscript.

A: Thank you for this comment. Because adjuvant treatment did not show a significant influence, we omitted Figure 2.

10. The discussion is somewhat cursory and merely reiterates the results. Please expand.

A: Thank you for this comment. We accordingly revised the discussion chapter of the manuscript. Revisions are indicated in yellow.

11. Table 6 reports the multivariate analysis of factors that influence patient survival. Is this 3-year survival or overall survival? Please clarify. Also, the multivariate analysis may be overfit given that 5 variables are being analyzed for approximately 40 patients. Suggest analyzing univariate factors with $p<0.05$ (which would eliminate age, this directly relates to #4 above).

A: We used 3-year survival for our analysis because this patient group consisted of more patients, which allowed a multivariate analysis to be performed. For multivariate analyses, it is generally recommended that the patient cohort should at least consist of seven patients per
parameter. Although a larger cohort gives more confidence in the tested parameters, we performed our analysis to actual recommendations.

Response to reviewer 2

1. A little over two-thirds of patients underwent a PPPD, while the remaining patients were treated by a conventional Whipple. Please specify what the indications for choosing either of these approaches were. Was this decision made in the preoperative phase or during the operation? Was this associated with the era during which the patient was operated on.

A: Indication for the procedure was performed during the operation. Whenever possible, a PPPD was performed. According to the tumor growth, in some cases, a Whipple operation was necessary to achieve an en bloc tumor resection. In all the operations, the aim was to achieve an R0 resection. We added a clarification of this important issue in the method section of the manuscript on p. 4.

2. On that same page, the length of stay is presented in mean and standard deviation. However, there seems to be a non-normal distribution, therefore this parameter should be expressed in median and range. Moreover, a longer length of stay could be a surrogate for the lack of homecare of other reasons for patients not being able to leave the hospital. Conversely to length of stay, it would be more insightful to express the time to functional recovery. This variable is more insightful as it is less influenced by non-patient related factors. Please provide some information on the time to functional recovery. Does this differ significantly from the length of stay? Was the length of stay comparable throughout the inclusion period?

A: Kurtosis is 18, so we included the median and range. We corrected this on p. 6 of the manuscript and in table 2. Although the time to functional recovery is a very helpful parameter, it was not included in our database. Due to the retrospective character of our study, we did not provide this parameter.

3. In the discussion is it mentioned that patients with a higher CEA have an adverse outcome. At which point was this CEA measured? Moreover, which CEA is considered most specific; at time of diagnosis, at time of operation or at time of follow up? Moreover, did patients with higher CEA have certain adverse characteristics? In other words, is this simply a surrogate for tumor biology?

A: CEA was measured at the time point of presentation (preoperatively). In most cases, this was performed in our outpatient clinic. We did not consider CEA levels during or after operation because we wanted to determine the prognostic value of this parameter. Because CEA was also significant in the multivariate analysis, we were not able to use this value as a surrogate. However, because biological analyses can never consider all the potential variables
(and in this regard, retrospective analyses have the lowest level of significance), there is always a risk that this type of coherence can be overlooked.

4. In the discussion, there is a paragraph on the role of the texture of the pancreas on survival. However, this influence is only seen on univariate analysis and not on multivariable analysis. Therefore it must be a surrogate for another variable influencing outcome. Please revise this paragraph accordingly.

A: Thank you very much for this suggestion. For surgeons, this is an interesting aspect; therefore, we added a discussion of the texture. The revisions are indicated in yellow on p. 11 of the manuscript.

5. Table 5: What are the cut off values of CEA and CA 19-9 based on? More importantly, in addressing the influence of variables on survival, one must take the time aspect into account. Therefore, a Cox proportional hazards model would be more appropriate in my opinion. Please provide the hazard ratios for the variables mentioned instead of only providing the p values.

A: CEA and CA19-9 were grouped according to the cutoff values used in our hospital. Our database encompasses 273 variables. We first performed univariate analysis to identify parameters with possible influence on survival. To obtain more evidence, we performed a multivariate analysis. Although there are several ways to perform multivariate analyses, we chose the log rank test. The Cox proportional hazard model might also be an effective method to identify factors predicting survival. However, as shown in the following table, the Cox proportional hazard model gives the same outcome as the log rank test. Therefore, we prefer to show data obtained with the log rank test.

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
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</thead>
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<tr>
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<td>1</td>
<td>.087</td>
<td>1.245</td>
<td>.969</td>
</tr>
<tr>
<td>Konsistenz_Pa_Gewe_test</td>
<td>.081</td>
<td>.256</td>
<td>.101</td>
<td>1</td>
<td>.750</td>
<td>1.085</td>
<td>.657</td>
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<tr>
<td>G</td>
<td>.295</td>
<td>.122</td>
<td>5.883</td>
<td>1</td>
<td>.015</td>
<td>1.344</td>
<td>1.058</td>
</tr>
<tr>
<td>pT</td>
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<td>.183</td>
<td>.866</td>
<td>1</td>
<td>.352</td>
<td>.844</td>
<td>.589</td>
</tr>
<tr>
<td>LN_Ratio_zwei</td>
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<td>.006</td>
<td>1</td>
<td>.937</td>
<td>1.015</td>
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<td>.326</td>
<td>1.226</td>
<td>.816</td>
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<td>.000</td>
<td>2.651</td>
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<td>.761</td>
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<td>.383</td>
<td>1.101</td>
<td>.887</td>
</tr>
</tbody>
</table>
6. Table 6: This table is inconveniently arranged. Please, instead of the OR provides the HR, as this takes the survival time into account. Tumor grading is a categorical variable; please provide the hazard ratio per category.

A: As stated above, we would like to show data obtained with the log rank test because this test is also accepted for this purpose.

Minor Essential Revisions
7. The article contains 195 patients during a 10-year period; question rose whether the authors consider their center specialized?

A: The time frame was 15 years. The number of 195 occurred as a result of data selection: we only considered pancreatic head resection in patients with pancreatic ductal adenocarcinoma. The number of pancreatic head resections in the given time frame was 672, which included left resections, central resections, duodenum-preserving operations and total pancreatectomies. In the given time frame, we performed more than 1,200 pancreatic resections. We therefore performed approximately 80 major pancreatic resections each year. The number required to carry the title “pancreatic center” in Germany is 15.

8. Patients who had portal vein involvement, venous resection was performed. Was the number of patients who underwent this aggressive form of treatment the same throughout the inclusion period? Was there ever reconstruction with a patch of bypass performed?

A: We do not consider portal venous resection to be an aggressive form of treatment. It could be considered a standard procedure because infiltration or contact of the portal vein is common in pancreatic head cancers. Furthermore, venous infiltration is not one of the criteria for irresectability of the tumor. In most cases, only a partial (tangential) resection of the portal vein was necessary. In some cases, segmental resection of the portal vein needed to be performed with an end-to-end vascular anastomosis. Reconstruction with a patch or bypass was not necessary in any of the presented cases.

9. On page 4 it is stated that drains were removed after exclusion of a POPF – Please clarify this abbreviation. Also, were drains always left? Or only on indication? If so, please specify the indications.

A: Thank you very much. The drains were routinely placed intraoperatively (minimum of one drain). During the postoperative course, we routinely monitored the amylase and lipase levels in the drain fluid to detect a postoperative pancreatic fistula (POPF). The definition for pancreatic fistula was according to the ISGPF criteria bei Bassi et al (Surgery 2005). See p. 5

10. On page 5, factors that were significant a p<0.10 were included in the multivariable model. Why was this cut off chosen, as the more broadly used cut off is <0.20.
A: The p-value can be defined prior to analysis and there is to our knowledge no stringent
definition for that. According to our biomathematics, we performed the analysis with a p-
value <0.1

11. On page 6 it reads that 139 of the patients were preoperatively stented.
Please clarify the criteria which were used for stenting? Were these criteria the
same throughout the inclusion period?

A: Thank you very much for this important suggestion. In most of the cases, the patients with
obstructive jaundice were stented by the gastroenterologists and were presented in our
department. Formerly, every patient with obstructive jaundice was preoperatively stented.
Today, the indication for preoperative stenting is degraded on the background of the latest
publications on this topic. Uniform criteria for preoperative biliary stenting could not be given
in our analyses due to the retrospective character.

12. In discussing the morbidity and mortality on page 7; please refer to the
Clavien and Dindo grades of complications. During which period did
perioperative mortality occur?

A: We did not use this score because it involves 5 classifications and 7 subclassifications,
which was not convenient for clinical use. For specific complications after pancreatic surgery,
we routinely use the definitions of the International Study Group of Pancreatic Surgery
(ISGPS). See p. 5 and p. 9. Mortality is defined as in-house mortality.

Definitions
Perioperative mortality was defined as in-hospital mortality. Postoperative pancreatic
hemorrhage (PPH) was categorized according to the ISGPS consensus definition. [15].
Delayed gastric emptying (DGE) was classified according to the suggested definition by the
ISGPS [16]. Postoperative pancreatic fistula (POPF) was defined analogous to the ISGPF
criteria [17].

13. The sentences on resection margin are mentioned twice; please delete one
of the segments.

A: Thank you very much, and please excuse this mistake. We corrected this mistake in the
manuscript. We also added the section titled Histological analysis of the specimen on p.7 of
the manuscript.

14. In the discussion, complications are described as severe; please correlate to
the grades according to Clavien/Dindo

A: When referring to severe complications, we used the ISGPS definition. Additionally, our
database encompasses different common complications such as pneumonia, urinary tract
infection, wound infection, etc. We did not classify common complications according to
Clavien/Dindo. Due to the retrospective character of our study, we were not able to evaluate
this issue. However, our analysis showed that mortality was highly correlated with bleeding or postoperative pancreatic fistula.

15. Table 1: Please add the year or era in which patient were operated on. This might have influenced the outcome of patients undergoing surgery for their pancreatic head carcinoma.

A: Univariate analysis showed that the age of the patient had a significant impact on survival. However, this was not significant in the multivariate analysis. Grouping patients by years would render the groups too small for statistical analysis. Therefore, we did not perform this analysis.

16. Figure 1: For Table 4: Please mention the readmission rate as well

A: Due to the architecture of our database, this could not be evaluated.

17. Kaplan Meier curves, when the proportion of the population alive is too small, it is better the cut off the graph. Therefore, in this case, it might be better to stop after 5 years (ie 60 months).

A: Although the number was small, it shows the fate of an interesting subgroup of our patients, the long-time survivors. Because this might be interesting to clinicians, we would prefer to show the data.

We thank the reviewers for their helpful comments and hope the manuscript is now suitable for publication in “BMC Surgery”.

Thank you very much for your kind consideration,

Yours sincerely,

Marius Distler