Author's response to reviews

Title: Resectable adenocarcinomas in the pancreatic head: The retroperitoneal resection margin is an independent prognostic factor

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

Thank you for your constructive response to our submitted manuscript regarding the retroperitoneal resection margin in periampullary adenocarcinomas. We hereby submit a revised and improved manuscript in accordance with the points raised by the reviewers.

In brief, we have followed the recommendations by both reviewers in adding more descriptive data on our standardized pathological approach, describing how best to evaluate the retroperitoneal margin and the tumour origin. Moreover, we have carefully reconsidered to what extent data on prognostic markers should be presented in order to provide sufficient proof for our main findings, and thus omitted one whole table and reduced the length of two tables as well as the text referring to these tables (results section).

However, we note that the two reviewers seemingly did not entirely agree on how much data on prognostic markers to include. Reviewer 2 wanted more descriptive data on prognostic markers for the individual subgroups of periampullary adenocarcinoma (provided in revised table 1), while reviewer 1 recommends us to focus more on pathological approach (new figures 2 and 3) and less on description of histopathologic factors (omitted one whole table and reduced length of two tables). We have thus tried to balance the presentation of histopathologic data in accordance with both the reviewers’ comments, and we now hope that the manuscript will be suitable for publication in your journal.

Please see the below point-by-point response to the reviewers’ comments.

Yours sincerely,

Arne Westgaard, M.D.
Response to reviewers’ comments

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Reviewer 1

GENERAL

Comment 1: “The numbers included in this study are reasonable but certainly not larger than previous reports concentrating on the same area.”

Response: We agree that the numbers included in this study are not larger than previous reports, although sufficient to test our hypothesis and provide proof for our findings. We believe that our study adds important knowledge to what may be derived from previous reports, in particular with respect to the retroperitoneal resection margin, which is the margin most often involved in non-curative pancreaticoduodenectomy.

MAJOR COMPULSORY REVISIONS

Comment 2: “The authors seem a little confused between making this a paper looking at prognostic markers or a paper suggesting that a specific evaluation of the retroperitoneal resection margin is important. They might be better concentrating on a more pathological approach and describing how best to evaluate this margin and leaving the more descriptive work on prognostic markers to other studies.”

Response: Previous investigators have emphasized both the need to perform meticulous surgical dissection at the retroperitoneal resection margin in order to obtain an R0 resection, and the need to evaluate the retroperitoneal margin by a standardized, systematic approach in order to obtain reliable histopathologic data. However, it has not been shown previously that involvement of this margin independently predicts the prognosis after resections of periampullary adenocarcinomas. In order to determine whether, upon standardized histopathologic evaluation, involvement of this margin independently predicts the prognosis, it was necessary to examine the associations between resection margin involvement and other histopathologic factors, and to adjust for these other prognostic markers in the multivariate survival analysis.

We agree that it is important to describe the pathological approach used for evaluation of this margin and have therefore included two new figures describing the pathological approach (figures 2 and 3). Furthermore, we have reduced the amount of presented data on prognostic markers to what we believe is necessary to provide evidence for our main findings. Specifically, we have omitted one whole table (previous table 2), reduced the amount of data presented in two of the other tables (previous tables 3 and 4), and shortened the text in the RESULTS-section concerning the latter two tables. The most important information from previous table 2 (the particular associations between resection margin involvement and the other histopathologic factors), has been included in
revised table 1, which now also includes some additional descriptive data asked for by reviewer 2 (see reviewer 2’s comment 4 below).

Comment 3: “In addition I believe that the discussion is too long and that there are too many tables for the message that they are trying to deliver.”

Response: As mentioned above, we have omitted one whole table and reduced the length of two other tables in order to deliver our message most effectively. However, in accordance with the opinion expressed by reviewer 2, we found it necessary in the discussion to briefly address the problems with standardization of histopathologic examination, and to compare our main findings with relevant data from the literature, without excessive deliberation or duplication of content from other sections.

Review 2

DISCRETIONARY REVISIONS

Comment 1: Why was the anterior surface and surface along the SMV groove not included in the analysis of this study?

Response: From the perspective of the surgeon, the margins at which sharp dissection has been performed are the margins most likely to be affected by tumour spread. The retroperitoneal margin is the margin most probably affected by poor surgery. The SMV groove, which is normally only sharply dissected by the surgeon in the presence of tumour involvement (or inflammation) was indeed examined in the present study, although not separately from the retroperitoneal margin, since our definition of the retroperitoneal margin included the SMV groove in cases where the tumour extended into this area (see legend of figure 1). However, examination of the anterior surface of the pancreatic head was not included due to an understanding of this not being a true surgical margin, and this was thus only examined in cases when the pathologist had reason to suspect involvement of this particular area.

Comment 2: The authors may wish to explain why they restricted the examination of the “retroperitoneal” margin to the area of sharp dissection.

Response: Previous reports have often limited the definition of the retroperitoneal resection margin to the area directly adjacent to the superior mesenteric artery (for example the AJCC definition, ref 16). However, others (for example the Royal College of Pathologists, ref 15) include a larger area in their definition of this margin. The surgical procedure for dissecting the posterior aspect of the pancreatic head free from the retroperitoneum (Kocher’s manoeuvre) starts from underneath the duodenum and extends medially towards the superior mesenteric artery. The first part of this dissection procedure is the easiest, and may often be performed bluntly in cases without tumour growth or inflammation. This area is included in the Royal College of Pathologists’ definition of the retroperitoneal resection margin, but not in the AJCC definition, where the same area is denoted the “posterior” margin. However, the most crucial part of the dissection is when it comes to free the specimen from the superior mesenteric artery, this
margin of resection being the area defined by the AJCC definition as the retroperitoneal resection margin (ref. 16 & 19). Dissection at this margin should always be performed sharply, skeletonizing the superior mesenteric artery. Recognizing that the surface towards the mesenteric artery is the surface most often involved in a non-curative resection, but also realizing that sharp dissection of a larger area of the posterior margin and the SMV groove could indicate tumour growth into these areas in the retroperitoneum, we thus decided to widen the strictest definition of the retroperitoneal margin to also include the posterior margin and the SMV groove in cases with sharp dissection of these areas. Thus, we defined the retroperitoneal resection margin pragmatically as the margin subject to sharp dissection at the posterior aspect of the pancreatic head, including the surface towards the superior mesenteric artery, and in some cases, also the surface towards the SMV groove.

Comment 3: More detail about the technique used in this study, in particular,

- the plane of sectioning and how many slices were obtained per specimen:

Response:
Information about the plane of sectioning has now been added to the text in the methods section. A new figure 3 has been added in order to provide visual information about how tumour origin was determined. The average number of slices obtained per specimen was 20.

- the thickness of the tissue slice from the retroperitoneal margin before subsequent perpendicular slicing

Response:
Information about this (thickness: 5–10 mm) has been added to the text in the methods section.

- whether tumour extension to the specimen surface away from the retroperitoneal margin was included in the analysis

Response:
Since our understanding of “resection margin” relates to areas subject to surgical dissection, the anterior surface was not included as a resection margin. This is in accordance with the AJCC cancer staging manual (ref 16), in which the anterior surface is not listed as one of the resection margins. In cases with local spread from the anterior surface into adjacent organs (for example the colon), pancreaticoduodenectomy was combined with hemicolecction performed en bloc. Considering this a more extensive and separate procedure compared to an ordinary pancreaticoduodenectomy, these patients (two patients) were excluded from the present series of adenocarcinoma in the pancreatic head. Thus, although we agree that R-status is independent of the surgical dissection technique (according to the UICC classification), we still do not believe that the anterior surface of the pancreatic head should be regarded as a resection margin in cases where there has been no resection at this surface. However, since none of the 114 pancreaticoduodenectomies included in the present study had tumour spread directly from the anterior surface to an adjacent organ, and no surgical resection was thus
performed at this surface, tumour involvement of the anterior surface did not affect R-classification in our study.

Comment 4: It would be of interest to see absolute data regarding tumour size, lymph node status etc for the pancreatic subgroup and ideally for the other subgroups.

Response: We agree. Data for the individual subgroups has been added in table 1.

Comment 5: May the better survival for cancer of the distal common bile duct be explained by a lower incidence of other adverse prognostic factors?

Response: Yes, indeed, as indicated by the data added to table 1. Distal bile duct tumours were significantly smaller (p=0.013) and had less nodal involvement (p=0.015) compared to pancreatic tumours (pancreatic vs distal bile duct tumours, chi square test).