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Editor-in-Chief
World Journal of Gastroenterology

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Anstalt des öffentlichen Rechts**

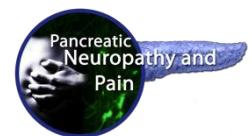
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Munich, 10.01.2014

Researchgroup Ceyhan:
Pancreatic Neuropathy & Pain

**Revised manuscript submission (ESPS Manuscript NO: 7284):
Pain sensation in pancreatic diseases is not uniform - the
different facets of pancreatic pain**



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Dear Editor-in-Chief

We thank you for your response and for the possibility to submit a revised version of our above-mentioned manuscript for publication in the *World Journal of Gastroenterology* as an original article.

We have taken into consideration all comments of the reviewers and incorporated their suggestions into the revised manuscript. The attached list contains a point-by-point response in the order of the reviewers' comments. All changes made in the manuscript were highlighted in red.

The authors again confirm that neither the submitted paper nor any similar paper, in whole or in part, other than an abstract has been submitted to or published in any other scientific journal.

The authors again confirm that all authors have contributed to and agreed on the revised content of the manuscript, and the respective roles of each author. There are no relationships with commercial companies involved in a product under study. The authors are willing to meet the cost for publication.

This study did not involve any interventions on human subjects and therefore did not require any ethical approval.

Vorstand:
Univ.-Prof. Dr. Reiner Gradinger
(Ärztlicher Direktor, Vorsitzender)
Dr. Philipp Ostwald
(Kaufmännischer Direktor)
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(Pflegedirektorin)
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We again confirm that the revised manuscript has been checked by a native English speaker.

We thank you for your attention to this matter.

Sincerely,
Güralp Ceyhan, M.D.

Reply to Reviewer 1:

- 1) *An excellent discussion of pain associated with pancreatic pathology. Some comments: Although there was no obvious difference between t stage and pain, was there any correlation between the size of the tumor and pain between head and body/tail.*

We thank the reviewer for this comment and we agree that tumor size would have been an interesting clinicopathological parameter to investigate. Unfortunately, this information was not part of our database and has therefore not been generated for these patients. Therefore, tumor size can only be taken from the t stage and not correlated directly. For this reason, we unfortunately cannot include this valuable information in the revised form of our manuscript.

- 2) *Similarly was there any difference between lymphovascular or neural invasion microscopically between head and body/tail cancers? Similarly if this is the case, then you have confirmed the long standing clinical truism of pain being a surrogate marker of more advanced disease. This should be commented on with some possible comment on whether the presence of pain could be used as an indication for more aggressive regional therapies such as radiotherapy or prolonged adjuvant therapies.*

We thank reviewer 1 for this remark. Lymphovascular and especially neural invasion are without any doubt key parameters in pancreatic cancer. The patients included in this study were recruited from resected cases of the years 2002-2006. At this time the UICC classification did not imply regular recording of perineural invasion in pancreatic cancer, so that in these patients and also in the other pancreatic malignancies we do not have these data to compare.

However, concerning your statement of pain as a surrogate marker of more advanced disease, we did not find any correlation of tumor stage and grade with pain as we have stated in the respective results section. Nevertheless, we saw an impressively worse survival outcome in those pancreatic cancer patients that had pain and with this have underlined our previous observation (Ceyhan GO et al. *Gastroenterology* 2009) now in a much bigger cohort, that not only the presence but even more the severity of pain is directly associated with dismal prognosis in pancreatic cancer. Therefore, the sole presence of pain and especially severe pain could indeed be used as an indication for more aggressive regional therapies such as radiotherapy or prolonged adjuvant therapies in pancreatic cancer. We did not observe any difference in survival for the other pancreatic diseases. We have included this aspect in our revised manuscript which can be found on page 9 :

“It has been shown that pain in **pancreatic cancer** is probably not as frequent as commonly stated [6]. In our study population, only 51% of patients with **pancreatic cancer** suffered from pain, which is even somewhat lower than the majority of previously published frequencies. But once pain is detected in **pancreatic adenocarcinoma**, it serves as a predictor of poor outcome, which was also the case in the presented study [4, 19, 20]. **In all other pancreatic malignancies, where neural invasion of cancer cells is not a key pathomorphological phenomenon, no association of pain and survival was registered. We can only speculate why pancreatic cancer patients with pain do have a dismal prognosis. Besides increased neural cancer cell invasion, patients with severe pain may develop more comorbidities. They will most likely be on analgesics and narcotics and probably be not as mobile and physically fit as patients without any pain. They may therefore easier develop thrombosis and pneumonia which may further immobilize and worsen prognosis. However, since pain is a predictor of poor outcome, the sole presence of pain and especially severe pain may be used as an indication for more aggressive regional therapies such as radiotherapy or prolonged adjuvant therapies especially in pancreatic adenocarcinoma but not in the other pancreatic malignancies.**”

Reply to Reviewer 2:

- 1) *This is the largest study to date with the aim to characterize pain in patients with pancreatic tumors, and provides important information on this common and difficult to treat condition. As such, it is of great interest. It is clearly written. I have some minor comments. There is minor English language editing needed.*

We thank the reviewer for these positive comments and we are pleased to hear that the reviewer believes that our study is of great interest. The entire manuscript has been rechecked and revised by an English native speaker.

- 2) *Why did the authors use that specific pain scale? Where other pain scales (such as the visual analogue scale) performed? Where there differences when considering pain as a continuous variable, instead of a categorical variable?*

We thank the reviewer for these remarks. This specific pain scale was used since it is very easy to apply and especially since it does not only reflect on the intensity of pain (like the visual analogue scale does) but also on the pain frequency and therefore on the patients pain history. In our experience, this specific pain scale is easy to apply and reflects patient's pain status very well as already published earlier (Ceyhan GO et al. *Ann Surg* 2007; Ceyhan GO et al. *Gut* 2007; Ceyhan GO et al. *American J Gastroenterology* 2009; Ceyhan GO et al. *Gastroenterology* 2009; Demir IE et al. *PLoS One* 2013; Wang K et al. *Carcinogenesis* 2013). Concerning the question of using a continuous instead of a categorical variable for pain we agree that the VAS scale has more subscales than the scale we have been using (0-10 instead of 0-3). Nevertheless, the VAS scale is in our opinion also not truly continuous since patients will usually not state their pain intensity to the decimal place but use the predefined scale from 0-10. We would therefore expect no relevant differences when pain would have been considered as a continuous variable.

- 3) *The references on the pathophysiology of "pancreatic pain" are somewhat dated (references 8 and 9). Excellent recent reviews deal exclusively with this subject (Pancreatology. 2012 Mar-Apr;12(2):104-12, Langenbecks Arch Surg. 2011 Feb;396(2):151-60; Gut. 2008 Nov;57(11):1616-27), including some by the authors own research group.*

We thank the reviewer for this remark and we agree that the cited references are somewhat outdated. We have therefore updated the references and revised the manuscript according to the reviewer's suggestions. These changes can be seen on page 4 (and after this reviewer's comment 4) of the revised manuscript.

- 4) *The discussion on the mechanisms in the introduction section and the discussion section could be expanded.*

We thank the reviewer for this suggestion and we have expanded the discussion on pain mechanisms in both the introduction and the discussion section. These changes to the manuscript can be found on pages 4 and 10 in the revised manuscript and have as all changes been highlighted in red:

Introduction part page 4 following:

“Mechanisms of pain generation in **pancreatic cancer** and **chronic pancreatitis** have not been completely understood. At first glance, pain was reported to occur by completely different mechanisms in **pancreatic cancer** and **chronic pancreatitis**. In **chronic pancreatitis**, pain generation was attributed to ductal strictures, increased intraductal pressure, interstitial hypertension, and pancreatic pseudocysts [7, 8]. The initial hypothesis on the generation of abdominal pain in **pancreatic cancer** was based on the mechanical pressure and/or invasion of neighboring organs, and especially by cancer cell invasion of the neural plexus. Nowadays a variety of ligands and their respective receptors have been identified to play roles in the initiation of pancreatic pain [9]. It is now widely accepted that pain sensation in both pancreatic cancer and chronic pancreatitis has been identified as *neuropathic* due to the prominent neuroplastic alterations which cannot be seen to that extent in any other GI disorders [10, 11]. This **specific** pancreatic neuropathy is characterized by enlarged intrapancreatic nerves which are increased in number and frequently infiltrated by inflammatory and/or cancer cells, leading to *pancreatic neuritis* and *perineural cancer cell invasion* [12-15]. Furthermore, **pancreatic neuropathy is characterized by numerous molecular and morphological alterations at both the peripheral and the central nervous system level** [10]. Increased peripheral nociceptive signals mediated by neurotransmitters and

neurotrophic factors together with neural damage and neuroplastic alterations are paralleled by hypersensitive dorsal root ganglia and spinal cord neurons [10]. At last, the cerebral cortex adapts to these changes by increasing its basal activity [16]. These phenomena are closely associated with increased abdominal pain sensation in the respective patients [4]. Such neuropathic changes or neuropathic pain sensation were not registered in other pancreatic tumors like, cystadenomas, IPMN, neuroendocrine neoplasia and ampullary cancer."

Discussion part page 10 following:

"Abdominal pain in pancreatic cancer has a strong neuropathic component due to the characteristic intrapancreatic neuropathic alterations like neural hypertrophy, increased neural density and especially due to the prominent perineural cancer cell invasion [4, 14, 15, 17, 22, 23]. The increase in neurite formation suggests that neurotrophic factors, growth factors, and axonal guidance molecules can be key molecules in the development and maintenance of these phenomena. A few mediators of these neuroplastic changes have been identified, like artemin and neurturin as the members of the glial cell-derived neurotrophic factor (GDNF) family of ligands [17, 23, 24]."

- 5) Besides pain quantification, do the authors have data on pain characteristics? Where all events of "pancreatic pain" of the same quality? (i.e. "standard" burning pain vs transflitive pain vs dull pain etc.). If so, does pain characteristics other than intensity predict mortality, outcome or anatomical location of tumor?

We agree that an evaluation of pain characteristics would have been very interesting, especially regarding the idea of a neuropathic pain component, but unfortunately, pain characteristics besides severity and frequency were not recorded in our study. We are currently investigating these characteristics in a prospective study and hope to have final results by the end of this year.

- 6) There is some evidence that diabetes reduces pain in pancreatic cancer, possibly due to nerve damage (Cancer Med. 2012 Dec;1(3):357-62). The

authors data suggests otherwise, this point could be more fully developed as it seems relevant for their ideas.

We thank the reviewer for this interesting suggestion. We are aware that some evidence suggests that diabetes may reduce pain in pancreatic diseases and we realize that we have not discussed this issue thoroughly enough in our discussion section. We have therefore revised this section and included the suggested reference which can be found on page 11:

“Although diabetes and consequent peripheral neural damage is known to largely influence general pain sensation, this does not seem to be the case for pancreatic pain **in our study**. There was no difference in pain sensation between diabetic and non-diabetic **chronic pancreatitis patients** in our study population. **A recently published study investigated the association of diabetes in pancreatic pain in the case of pancreatic cancer. Here, the authors report that patients with diabetes had a significantly lower frequency of abdominal pain [29] with at the same time significantly higher prevalence of perineural invasion. Further studies will be needed to investigate whether diabetes as such can induce neural plasticity in pancreatic diseases.** “

7) *Do the authors speculate regarding the reason for increased mortality in patients with pain other than increased neural invasion? Are there other causes (more hospitalizations, opiate use, comorbidities etc.)?.*

We thank the reviewer for this comment and we realize that we did not discuss the observed increased mortality in cancer patients with pain in detail. We can only speculate why pancreatic cancer patients with pain do have a dismal prognosis. Besides increased neural cancer cell invasion, patients with severe pain may develop more comorbidities. They will most likely be on analgesics and narcotics and probably be not as mobile and physically fit as patients without any pain. They may therefore easier develop thrombosis and pneumonia which may further immobilize and worsen prognosis. As suggested by the reviewer, we have extended our

discussion on this issue in the revised manuscript which can be found on page 9:

“It has been shown that pain in **pancreatic cancer** is probably not as frequent as commonly stated [6]. In our study population, only 51% of patients with **pancreatic cancer** suffered from pain, which is even somewhat lower than the majority of previously published frequencies. But once pain is detected, it serves as a predictor of poor outcome, which was also the case in the presented study [4, 19, 20]. **We can only speculate why pancreatic cancer patients with pain do have a dismal prognosis. Besides increased neural cancer cell invasion, patients with severe pain may develop more comorbidities. They will most likely be on analgesics and narcotics and probably be not as mobile and physically fit as patients without any pain. They may therefore easier develop thrombosis and pneumonia which may further immobilize and worsen prognosis. However, since pain is a predictor of poor outcome, the sole presence of pain and especially severe pain may be used as an indication for more aggressive regional therapies such as radiotherapy or prolonged adjuvant therapies in pancreatic cancer but not in other pancreatic malignancies.** When interpreting these results, however, one has to bear in mind that in the present study we only analyzed patients that were resected, meaning that there may be a bias towards less advanced, resectable tumors in our study cohort.

- 8) *In tables, p values could be specified by letters (say, for pain II, $p=0.2$ in PCa vs CP....) to indicate specific differences. Tables 3 and 4 could be collapsed into a single figure table. Table 5 could be eliminated, and the result only mentioned in the text.*

We thank the reviewer for these suggestions. We have further specified the p-values and have now stated the exact p-values in the remaining tables as suggested by the reviewer. We agree that tables 3 and 4 could be collapsed into one figure but taking also the comment 7 from reviewer 4 into account we have decided to eliminate all three tables (tables 3, 4, and 5) and included the data in the text as the reviewers have suggested. These changes in the text can be found on page 7 + 8 of the revised manuscript:

“Pancreatic tumor localization tends to influence pain sensation independent of tumor histology. The percentage of patients with no pain (Pain 0) was considerably lower in patients with tumors in the pancreatic body (39.0%) or tail (42.0%) compared to those in the pancreatic head (51.0%). In the entire pancreatic tumor population the most severe pain was detected in patients with a tumor located in the pancreatic body (16.9% **vs. 13.5% in the pancreatic head and 14.8% in the pancreatic tail**), but this difference showed no statistical significance. **35.9% of patients with a tumor in the pancreatic head showed mild pain (Pain I) sensations (vs. 44.2% of patients with a tumor in the pancreatic body and 43.2% of patients with a tumor in the pancreatic tail)**. But regarding the largest subgroup **of patients with pancreatic cancer**, it was evident ($p < 0.02$) that 29.8% of **these pancreatic cancer** patients with a tumor at the pancreatic body were pain free (Pain 0), 46.8% revealed mild (Pain I) and 23.4% moderate/severe (Pain II) pain. In contrast, the majority of patients with **pancreatic cancer** in the pancreatic head had no pain (53.0% **vs. 33.0% Pain I and 14% Pain II**). Accordingly, the rate of patients with moderate to severe pain (Pain II) was considerably higher for **pancreatic cancer** patients with a pancreatic body tumor when compared to **pancreatic cancer** patients with a pancreatic head or tail cancer (23.4% vs. 14.0% and 17.5% respectively).”

Reply to Reviewer 3:

- 1) *Abdominal pain is a major clinical feature in chronic pancreatitis and pancreatic cancer. It is the first study about the pain patterns in all pancreatic tumors and correlate pain with the respective clinicopathological data. This study is well designed and properly performed. The statistical analysis is reasonable. The result is credible. The conclusion is helpful in clinical practice.*

We thank the reviewer for this purely positive response and we are glad that the reviewer thinks that our study is well designed and finds our conclusions to be helpful in clinical practice.

Reply to Reviewer 4:

- 1) *D'Haese and colleagues have submitted a retrospective analysis of patients treated with pancreatic resection in order to evaluate 'pain patterns' in patients with various pancreatic pathologies. The authors present their manuscript as an evaluation of pain in patients with pancreatic diseases other than pancreatic cancer and pancreatitis since little is known about 'pain sensation and their mechanisms' in these patients and that it requires more characterization. The aim of the study was therefore to evaluate pain in patients with less common pancreatic neoplasms and how it compared to patients with pancreatic cancer and pancreatitis. There are some interesting findings in this paper from a large series of patients. Although the authors note that pain sensation and pain patterns in patients with rare neoplasms is not well known, it is unclear what these data would add to the literature. This reviewer has a few comments. General – there are too many abbreviations and it is confusing (e.g., Ptm, Pca, NEN, AmpC, IPMNI, NENh). None of these are used in the pancreas surgical or medical literature.*

We thank the reviewer for this general remark. We agree that we have used many abbreviations and we have therefore now reduced these considerably and changed all of them (except IMPN which is a common term in medical literature) to the full names throughout the manuscript in order to make the revised manuscript more understandable.

- 2) *Introduction – paragraph 2 – the authors discuss retrospective studies and different hypotheses for the etiology of pain in patients with chronic pancreatitis – the studies cited were not designed to evaluate the pathophysiology of pain. Furthermore, this paper is not designed to evaluate the pathophysiology of pain or develop an hypothesis about pain. Furthermore it is well known that these rare neoplasms are most often found incidentally. When they are symptomatic, they are more often malignant and therefore would be potentially in the cancer group. The authors should focus the discussion on what is known about pain in the rare neoplasms rather than the review of pancreatitis and cancer related pain. This can include pain as presenting symptoms, what it may or may not indicate, etc. This will help set the paper up much better since pain may be an indication to operate on patients with serous cysts but a marker of malignancy in a patient with a*

mucinous cyst. Also, a patient with a mucinous cyst with pain may need resection vs one that does not have pain. A better foundation for the study should be provided

We thank the reviewer for this detailed comment. We agree that the studies in paragraph 2 of the introduction were not designed to explicitly investigate the etiology or the mechanisms of pain and of course our study was not either. Nevertheless, we still believe that both the hypotheses of the mentioned papers and our own hypotheses on the possible pain mechanisms are worth discussing in the current manuscript. We believe that understanding the underlying neuropathic changes may help us to better understand and treat these painful conditions. We fully agree that when these rare neoplasms are symptomatic, that they are potentially on the malignant side. But, to the best of our knowledge, this is the first study that can actually support this hypothesis and therefore has a solid foundation (page 8). We furthermore agree that the presence of pain should be used in the diagnostic workup and can assist us in our decision making for or against surgery. We realized that we may not have expressed this thoroughly enough and have therefore added a passage on this issue which can be found on page 10 of the revised manuscript:

“Keeping these data in mind, it is not over speculated when regarding abdominal pain sensation as a reliable parameter that mirrors neuro-cancer interactions in **pancreatic cancer** patients. Interestingly, the other investigated pancreatic tumors showed a similar correlation between the localization in the pancreatic body and pain sensation even though these tumors are known to show significantly less neural invasion and neuroplastic changes when compared to **pancreatic cancer** ^[4]. Even though these neuropathic alterations were detected significantly less often, they were still all present in these pancreatic neoplasms ^[4]. Therefore, it is possible that the observed pain pattern in other pancreatic tumors may be explained by similar mechanism as in **pancreatic cancer**. This is moreover underlined by our finding that pain was more frequently present and more severe in patients with malignant pancreatic neoplasms as compared to their benign counterparts. **Therefore, pain history should be carefully investigated since malignancy could be suspected in patients with especially severe pain states and apparently benign pancreatic neoplasms.**

Pain should therefore be integrated in the diagnostic workup and may help us in our indications for surgery."

- 3) *Methods – the authors cite previous reports on how the pain was assessed – this is not adequate for a study focused on pain as this was the primary methodology. Please provide more details in the Methods.*

We thank the reviewer for this remark and we understand that citing a previous report on how pain was assessed may not be sufficient for the present manuscript. We have therefore provided more details which can be found on page 6 of the revised manuscript:

"In all patients, the individual pain score was prospectively recorded prior to the operation **in hospital one day before surgery**, including pain intensity and frequency. The intensity of pain was graded by using the following scale: 0 = none, 1 = mild, 2 = moderate (**abdominal discomfort or pain which is non-disabling but requires analgesics**) and 3 = severe pain (**pain which is disabling and controlled only by narcotic analgesics**) **In addition**, the frequency of pain was graded as 3 = daily, 2 = weekly, and 1 = monthly. To calculate the severity of pain, pain intensity and pain frequency of each individual were multiplied. According to the final pain score, the patients were categorized into 3 groups: Pain 0 (0) representing the group of patients who did not have any pain; Pain I (1-3) representing the group of patients with mild pain; and Pain II (4-9), the group that suffered from moderate to severe pain, as demonstrated previously [13, 17, 18]"

- 4) *Methods – the authors state that pain analysis was performed prior to the operation. When was it analyzed? In clinic, the day of surgery?*

Pain analysis in our study was performed in the clinic one day before surgery. This information has been added in the methods section of the revised manuscript as can be found on page 6 (please also see our comment and revised paragraph above).

- 5) *Methods – was it determined whether patients were taking narcotics during the time of the pain assessment? This would impact pain scores.*

We thank the reviewer for this very important comment. In our study, pain intensity was partly defined by the use of analgesics/narcotics which is of course quite common in patients with pancreatic pain. Patients with non-disabling pain that requires analgesics received the pain intensity score 2, while patients with disabling pain that could only be controlled by the addition of narcotics received the pain intensity score 3, as primarily described in 2001 (Shrikhande et al. *Pain* 2001). In accordance with comments 3 + 4, we have added this additional information to the method section as can be found on page 6 (please also see our comment and revised paragraph above).

- 6) *Results – the Tables are very difficult to interpret with all of the abbreviations. Furthermore, numbers should be provided in addition to percentages.*

We thank the reviewer for this suggestion. In accordance to comment 1 of the same reviewer we have largely reduced the abbreviations to make both the manuscript and the tables easier to read. Furthermore, we have also provided all numbers with the percentages in the remaining tables (tables 3-5 have been eliminated from the manuscript upon reviewer's suggestion).

- 7) *Results – the data in Tables 3 and 4 could be provided in the text and are not informative and simply demonstrate the selection of patients who need or who are candidates for resection.*

We thank the reviewer for this comment. We have decided to eliminate tables 3 and 4 from the revised manuscript and have provided the information in the text. These changes to the manuscript can be found on pages 7 + 8.

"In the entire pancreatic tumor population the most severe pain was detected in patients with a tumor located in the pancreatic body (16.9% vs. 13.5% in the pancreatic head and 14.8% in the pancreatic tail), but this difference showed no statistical significance. 35.9% of patients with a tumor in the pancreatic head showed mild pain (Pain I) sensations (vs.

44.2% of patients with a tumor in the pancreatic body and 43.2% of patients with a tumor in the pancreatic tail). But regarding the largest subgroup of patients with pancreatic cancer, it was evident ($p < 0.02$) that 29.8% of these pancreatic cancer patients with a tumor at the pancreatic body were pain free (Pain 0), 46.8% revealed mild (Pain I) and 23.4% moderate/severe (Pain II) pain. In contrast, the majority of patients with pancreatic cancer in the pancreatic head had no pain (53.0% vs. 33.0% Pain I and 14% Pain II)."

"Tumor grading and staging did not show any significant correlation to pain sensation in all of the analyzed pancreatic cancer cases. Patients with more advanced disease showed a tendency to suffer from more severe pain than those with earlier tumor stages (moderate/severe pain in 5.9% of pT2 tumors vs. 16.0% of pT3 and 36.4% of pT4 tumors). On the other hand, most patients with pT2 tumors were pain free (61.8%) while only 47.9% of patients with pT3 and 36.4% of patients with pT4 tumors did not have any pain."

8) Table 5 – please clarify – T4 pancreatic tumors (adenocarcinoma and neuroendocrine) are unresectable.

We understand the reviewers concern about resected T4 tumors. We have had some rare cases (altogether 11 cases) where postoperative histology revealed a pT4 stage pancreatic cancer. Most of these were R1 resections in relatively young and physically fit patients where a probable benefit of an R1 resection in these specific patients was assumed. A few highly select T4 cases in our study also included arterial resections where it has been shown that these highly select patients may benefit (Mollberg et al, Ann Surg 2011). Nevertheless, we have removed table 5 from the manuscript as reviewer 2 has suggested in his comment nr. 8.

9) The information on pain and outcomes for adenocarcinoma are very interesting and in itself are important and should be more carefully analyzed. Including these data with the other rare tumor types makes the manuscript unclear and disorganized without a clear message.

We thank the reviewer for this comment and we tried to further clarify our statements and make our conclusion more clear to the reader. In our recent publication (Ceyhan GO et al., *Gastroenterology* 2009) we have for the first time described that pain and especially pain severity is an independent prognostic marker in pancreatic adenocarcinoma. In that study no in-depth analysis of pain impact on other pancreatic malignancies was performed. In the submitted study, we demonstrate for the first time in a comprehensive analysis that the sole presence of pain and its severity do not have an impact on survival in invasive IPMN, in high stage neuroendocrine neoplasms and in ampullary cancer patients. But again, in a much bigger cohort we could underline and confirm our previous data, that pain in pancreatic adenocarcinoma has this striking impact on survival. Due to that novel and structured analysis, we hope that our message is clear, that the parameter of pain is only a prognostic feature for pancreatic adenocarcinoma patients and not for the other pancreatic malignancies. We have modified our discussion part concerning this point, which can be found on page 9:

“ It has been shown that pain in **pancreatic cancer** is probably not as frequent as commonly stated [6]. In our study population, only 51% of patients with **pancreatic cancer** suffered from pain, which is even somewhat lower than the majority of previously published frequencies. But once pain is detected **in pancreatic adenocarcinoma**, it serves as a predictor of poor outcome, which was also the case in the presented study [4, 19, 20]. **In all other pancreatic malignancies, where neural invasion of cancer cells is not a key pathomorphological phenomenon, no association of pain and survival was registered. We can only speculate why pancreatic cancer patients with pain do have a dismal prognosis. Besides increased neural cancer cell invasion, patients with severe pain may develop more comorbidities. They will most likely be on analgesics and narcotics and probably be not as mobile and physically fit as patients without any pain. They may therefore easier develop thrombosis and pneumonia which may further immobilize and worsen prognosis. However, since pain is a predictor of poor outcome, the sole presence of pain and especially severe pain may be used as an indication for more aggressive regional therapies such as radiotherapy or**

prolonged adjuvant therapies in pancreatic cancer but not in other pancreatic malignancies.”

Reply to Editorial Comments:

- The font has been changed to Book Antigua size 10 with 1.5 line spacing.
- DOI and PMID numbers have been included in the references where available
- An additional section with “highlighted content” has been added according to the journals requirements as requested