Author’s response to reviews

Title: Indwelling pleural catheters for malignancy-associated pleural effusion: report on a single centre’s ten years of experience

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Author’s response to reviews:

Point-by-point reply to the reviewer’s comments

We would like to thank the reviewers again for the time and effort invested in reviewing our work. The constructive comments have helped us to further strengthen key aspects of the study and to underscore the validity of our findings. We are solidly confident that our revised manuscript will meet the high standards of the reviewers and readers of BMC Pulmonary Medicine.

Saadia A Faiz (Reviewer 1):

Comments and revisions noted. The response to reviewers have not all been integrated into the manuscript. The major flaw remains overstating that this is the largest study without adding what is unique in their cohort to the medical literature. There are aspects of their study which are definitely unique and these should be integrated better in the discussion and the abstract as well.
Reply: We thank the reviewer for her detailed commentaries and discussion on our study. We emphasized what is unique in our cohort and integrated it in the discussion and the abstract (see detailed discussion below).

Major:

1. They author are still stating they have the largest single center investigation. I do think this needs to de-emphasized, as they are not proving anything new about the IPC
   a. In abstract last line is "Largest single-centre investigation". In their response to reviewers, they report that gynecologic and gender predominance but this is still in the abstract or in the discussion.
   b. Remove "largest single centre report to date" in introduction line 49. Could consider over a decade in european center. But typically this should not be in the introduction statement anyhow

   Reply: We have removed the notion of “the largest single centre investigation to date” in the entire manuscript. As suggested, we added our study’s key issue of reporting on a large cohort of gynaecologic cancer (with consequent predominance of female patients) to the abstract as well as the discussion.

2. With regard to statistics on pleurodesis, was drainage schedule specified in the methods or results?

   Reply: As mentioned in the methods part, patients were educated to perform a daily drainage regimen until decrease of fluid amount to less than 200 ml/day and then continue with a two-day regimen. As drainage was performed in an outpatient setting, our database lacks detailed information of when drainage intervals were changed. Thus, this information could not be integrated in the statistics on pleurodesis.

3. The discussion still reads as review of the literature on IPCs to date, and it is really lacking integration of the study data.
   a. The first paragraph of the discussion typically sums up the major points. Again the authors mention being the "largest single center experience to date" and "first published results on IPC in paramalignant and disease-associated cytology negative pleural effusions
   i. IPC is the standard of care. Collecting data on them longer does not add to the medical literature
   ii. Numerous other studies have included paramalignant effusions as well, so this is not unique
iii. What is unique is that your data

1. has the largest number of patients with gynecologic tumors

2. Your data showed improved survival in those with gynecology tumors and bilateral effusions

3. First study with gender predominance with women (will have to review and check but suspect this is the case)

Reply: We thank the reviewer for pointing out to give priority to the unique findings of our study. As mentioned (see #1), these aspects have been strengthened and the statement on the study being the largest (single centre) investigation has been removed.

b. The first paragraph of the discussion specifically discusses previous trials re IPC. Could consider incorporating into the introduction, but not sure what it adds to the discussion

i. Consider using this population to highlight their unique population of women and gyn tumors

ii. Again response to the reviewers re ovarian cancer and ascites could fit nicely here especially since they did not have catheters in the abdomen. This is a question clinically faced often as to should a catheter be placed in the belly for ascites or in the thorax for pleural effusion?

Reply: As proposed by the reviewer, we moved the part concerning (prospective) trials on life quality into the introduction to underline the advantages of IPC in this setting. Ovarian cancer, especially in advanced stages, regularly goes along with (large amounts of) ascites. Nonetheless, no patient received an abdominal indwelling catheter, emphasizing the importance to control pleural effusion for patient’s comfort. As a major contribution to pleural effusion in ovarian cancer is mediated via transdiaphragmatic pleuroperitoneal communications, the clinician, faced to address the site of concern, might give the patient a durable relief using an IPC only.

c. In the second paragraph about AP, this has better incorporation of the data

i. The statement that young patients might experience AP more often based on their study result is a little suspect since their data has a very wide range of age from 15 to 92 with a median of 65. Could add potentially and further study is warranted to support this claim

Reply: We appreciate the reviewer’s recognition of our revised work. We fully agree with the appraisal of age (just) being potentially predictive for AP and therefore have moderated our statement.

ii. How many of the patient had pleurodesis via the IPC? Would specify in that statement
Reply: 14 Patients received an additional talc pleurodesis via the IPC, the number has been added to the paragraph.

d. The survival paragraph is the best formulated in the discussion

i. OSI and OS2 are mentioned, but not really emphasized in the result of discussion?

ii. Where are the Kaplan-Mier curves?

Reply: We thank the reviewer for this positive assessment. As requested, we emphasized the different implications of OS1 and OS2 in the discussion. Survival after primary diagnosis (OS1) strongly depends on the cancer entity reflecting tumour biology as well as effective treatments available. Not surprisingly, we observed wide differences with lung and breast cancer patients on the extremities. The rather short survival after IPC placement (OS2) may be strongly influenced by a large proportion of patients having received the IPC as a palliative measure for symptom control with limited systemic treatment options available for cancer control (thus reflecting a negative selection). Kaplan-Meier curves for OS1 and OS2 have been added as figure 1.

e. The complications paragraph again has a lot of medical literature, but could consider more integration of their data.

i. In the response to reviewers they mentions complications worse in men with regard to mechanical. This reflect the gender predominance and would be rather interesting to emphasize in this chapter. Also noteworthy is that it is not present in infections. Could this also be related to type of malignancy the men have? The drainage schedule could be impactful here as well? Those that don't drain daily tend to loculate.

Reply: These are very interesting remarks. As the majority of mechanical catheter problems were due to occlusions one might imply a certain carelessness in male patients. On the other hand, the predominance of thoracic malignancies in men (46.2 vs. 7.9%, p<0.001) implicating certain anatomic particularities favouring obstructions could also have contributed to the gender-specific differences. E. g., the rate of postobstructive effusions was higher in men (10.0 vs. 4.5%, p=0.04). In contrast, the rate of infections did not differ with regard to gender. This is all the more astonishing, as the mentioned anatomic alterations associated to lung cancer should predispose to infectious complications. Whether the drainage interval might play a role in our study cannot be answered as our dataset unfortunately lacks the information on the used schedules (see #2).

ii. Their complications are in the range suspected. This likely has to do with enhanced patient and provider education based on the all the experience to date. Could consider emphasizing whatever patient education they have set up which may contribute or the fact the IPCs are drained by nurses in their country here which could explain the low rate as well. Again they have a nice response to the reviewers but it is not integrated here.
Reply: We agree with the reviewer, that our complication rates have a wider range than other series published before. We ascribed this to the learning curve over the reported decade (during which a certain standardization of the procedure took place) as well as to the ambulatory care provided by specialized nursing teams (the modalities have been described in the patients and methods section). As suggested, we emphasized the fact, that ambulatory care was provided by specialized nursing teams in the discussion.

f. The conclusion is similar to the introduction in again repeating the "largest single-center case series", IPC as a first line option, IPC in symptom relief". This study supports this, but their original research is only supportive of this and not proof of this. The way the conclusion is written it really does not prove or add to the IPC literature to date. The conclusion should highlight the unique conclusions that this study adds to what we already know.

Reply: We integrated our unique findings to the conclusion. Especially, the current investigation provides a large single-centre case series with IPC in malignant diseases with a strong focus on underrepresented gynaecologic cancer in this setting until now. The higher rates of mechanical complications in men are hypothesis generating warranting further study. With an appropriate patient education and the help of specialized nursing teams, rates of infectious complications are low, even in a long-term setting. Furthermore, in our opinion, mentioning, that our study strengthens previous results of IPC (being highly efficacious in symptom relief and displaying a favourable safety profile in daily routine) is justified due to the large dataset presented.

4. In table 2 there is ovarian cancer vs other and gynecologic cancer vs other, was ovarian cancer not grouped with gynecologic cancer?

Reply: Due to the large number of patients with ovarian (n=121) and breast cancer (n=45), these entities were investigated separately. The remaining gynaecologic malignancies were grouped together (n=15; endometrial cancer: n=6, cervical cancer: n=6, vulvar cancer: n=3).

Minor:

1. Introduction, line 3, first sentence: Consider removing "chronic" and just start with Recurrent

Reply: The first sentence of the introduction has been changed as suggested

2. In introduction, would recommend a line also mentioning the IPC have also been used to instill talcs, so combination of modalities are used to treat malignant effusions

Reply: Thank you for the remark, the IPC-PLUS trial has been mentioned.

3. Under patient and methods, line 14, what does quality of effusion mean? Do you mean etiology? This was reportedly addressed in their response to reviewer 3 but not changed in the manuscript
Reply: The term “quality” has been substituted by “aetiology” (indeed, this referred to malignant vs. paramalignant and cytology-negative pleural effusions).

4. Under patient and methods, line 4, after overall survival need (OS)

5. In statistical analysis, overall survival was added so consider OS (OS1, OS2) since likely KM was used for both

Reply: The definition of overall survival was moved to statistical analysis: “Overall survival was assessed with the Kaplan-Meier method in two different ways: OS1 was defined as the interval in months between diagnosis of the malignancy and death, OS2 as the interval in months between IPC insertion and death.”

6. In results, line 4 "reflecting a certain referral bias with .." should be removed. Results should just report your results. This can be added in the limitations paragraph

Reply: This part has been moved to the limitations paragraph.

7. For table 4, in headings for table would specify OS2 not just OS

Reply: This change has been made to clarify the used survival interval.

Robert John Hallifax (Reviewer 3): The changes made to the manuscript have significantly improved it.

Reply: We thank the reviewer for acknowledging our efforts made during the first revision.

I have a few minor comments:

1. Page 20 line 41: Be careful using “autopleurodesis” when referring to talc - clearly this is no longer "auto". I should suggest that in the few patients who had talc - it was effective in causing pleurodesis in line with other published studies (AMPLE, ASAP, TIME1, IPC-PLUS).

Reply: We fully agree with the reviewer, that the use of talc excludes autopleurodesis. The inaccuracy of our manuscript has been corrected and “AP” has been replaced by “pleurodesis”.

2. Page 21, line 54: I disagree with the statement that intrapleural fibrinolytics are an efficacious option [41]. This study was a retrospective study of pleural fluid output and sonographic appearance, which has fundamental selection bias. Please see this recent RCT of fibrinolytics vs placebo;Mishra EK et al. Randomized Controlled Trial of Urokinase versus Placebo for Nondraining Malignant Pleural Effusion. Am J Respir Crit Care Med. 2018 Feb 15;197(4):502-508.It showed no difference between the two arms
Reply: We thank the reviewer for this important remark and added this absolutely relevant clinical trial to our discussion addressing the repeatedly raised question on how to manage these complications.

3. In the concluding paragraph, rewrite "IPC are highly efficacious in symptom relief" - your study has not looked at symptom control. The only head-to-head studies have shown IPC to be as efficacious as chest drain and talc for symptoms. Also what does "infectious mechanical" mean? I suggest removing this and just stating "complications (including infection)".

Reply: Following the reviewer’s suggestion, the mentioned part of the concluding paragraph has been stated more precisely: “Our study strengthens the estimation (of IPC) as a feasible first-line option in the management of recurrent pleural effusion, efficient in symptom relief and with a favourable safety profile in daily routine. … With an appropriate patient education and the help of specialized nursing teams, rates of infectious complications are low, even in a long-term setting.”