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 for the time and effort invested in reviewing our work. We appreciate the insightful comments and advice, which we have taken very seriously. Following the suggestions, we added further data. 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):

The authors describe a 10 year experience of IPC use in a population with primarily women. Their purpose was to evaluate clinical outcomes of IPC in a variety of cancers, and to determine predictors of clinical outcomes and survival. They conclude IPCs are safe and effective. Although well written for the most part, there are some major flaws. Please see my point by point commentary below
Reply: We thank the reviewer for the positive assessment of our study. We have carefully re-analyzed our data and performed additional analyses to verify our findings as described in greater detail below.

1. IPC was introduced in 1997. It has become the standard of care. The results of the study are not novel except that this study is in Europe and has primarily women due to ovarian cancer.

Reply: It is absolutely correct that since the introduction of IPC over 20 years ago several studies have been published concerning clinical experiences and outcomes with IPC. But, as the reviewer also mentioned, our intention was to add to the existing literature by reporting on a very large cohort of patients with the particularity of a large proportion of gynaecologic cancer entities, especially ovarian cancer.

2. The discussion reveals a review of the literature to date and there is very little integration of their data.

Reply: We thank the reviewer for her statement and tried put the major results of our study, namely efficacy data, autopleurodesis, survival and complications more into context.

3. Given that they have a large number of ovarian and gynaecologic cancers, could consider looking at the data.

   a. In terms of gynaecologic specific malignancies with presence of ascites, modality of spread of the cancer, and survival of ovarian cancer based on presence of pleural effusion or not.

Reply: These are very interesting aspects warranting a further and closer insight. Unfortunately, our database lacks the information concerning ascites and the modality of cancer spread. Porcel et al. discussed the prognostic effect of pleural effusion in ovarian cancer in a review (Porcel JM et al., Respirology 2012, cited as reference #35 in our manuscript). Hence, one third of the patients present with pleural effusion at the time of primary diagnosis. Given that the IPC was not the first treatment for pleural effusion, the proportion of patients with MPE was comparable in our study with 25% of patients having received an IPC within 2.2 months after primary diagnosis (median 19.4 months). Patients with a cytology-negative effusion received an IPC at a median interval between primary diagnosis and catheter placement of 26.5 months (p n.s.). From our point of view, this delay reflects an advanced therapeutic situation with (in part heavily) pretreated patients, presenting with cachexia and hypoalbuminemia as surrogate of the advanced cancer. In several studies, survival was substantially shorter in patients with MPE at primary diagnosis. The impact of MPE was comparable to that of a larger residual tumour volume after major surgery, a well-established prognostic factor (see Wimberger P et al., Ann. Surg. Oncol. 2010, cited as reference #4 in our manuscript; Eitan R et al., Cancer 2005; Mironov O et al., Radiology 2011)

   b. Another interesting aspect would be IPC in women compared to men. Perception would be less infection etc but not sure if this is the case.
Reply: We thank the reviewer for this interesting question. Indeed, we were able to observe gender-specific differences. Complication rates were higher in men than women (18.6 vs. 12.4% of all procedures, p=0.023). The likelihood for mechanical catheter problems was higher in men (8.6 vs. 3.9 of all procedures, p=0.038). If this may be attributable to a less careful handling of the catheter in male patients remains speculative. We did not see any differences concerning infections, especially empyema.

c. This is likely the largest series in Europe. Could there be differences in the care following placement that could be highlighted?

Reply: From a local point of view, institutional handling of patients with IPC has been standardized within the reported decade. After placement every patient is seen at least once in our department. Afterwards, patients are regularly seen by specialized nursing teams from the local provider of PleurX in Germany. Therefore, (long term) complication rates should have decreased over time. Comparing the period from 2006-2012 to 2013-2016, especially infectious complications substantially decreased (8.6 vs. 3.9%, p=0.032). A difference in every-day care compared to the US could be the use of gravity bags instead of vacuum bottles (see comment #7).

Major issues

1. Abstract. The term auto-pleurodesis was used in the ASAP trial. Others refer to this as "spontaneous pleurodesis" Regardless the objective of the IPC is really more for symptom management rather than for pleurodesis. The rate of spontaneous pleurodesis varies in trials anywhere from 16 to 66%. So using the term "regularly" is not valid.

Reply: We thank the reviewer for this suggestion and have replaced the term “regularly” with “potentially”.

2. Abstract. In the results section, there was no subsequent intervention required over what time? After 6 months? Within 30 days?

Reply: This refers to the entire observation period until the last visit or death. The manuscript has been updated correspondingly.

3. The purpose of the study is to: evaluate clinical outcomes with IPC in the largest single centre report to date in the general setting of malignancy. Unfortunately, this is not novel or unique in its purpose or results. IPC are now standard of care and have been described in numerous series for both solid and hematologic malignancies. Their outcomes also are no different than what has been described in the medical literature

4. The secondary goal was to assess survival outcomes depending on patient and clinical variable to determine predictors of clinical outcome and survival to guided clinical care. Again there is no unique recommendations from this data described to support this.
5. Would refrain from using PE as the abbreviation for pleural effusion. It is inconsistently abbreviated in the text.

Reply: This is a helpful suggestion; the abbreviation has been replaced.

6. Patient and Methods. Line 23. Did patients undergo pleural biopsy or pleuroscopy?

Reply: A pre-interventional pleuroscopy or pleural biopsies were not routinely performed.

7. Patient and Methods. Line 35. The Pleurx system has vacuum bottles. Why was gravity drainage used?

Reply: According to the local standard of care, gravity bags were used instead of vacuum bottles as they assure a slow and comfortable drainage. Gravity bags, provided by the German vendor of PleurX, are widely used in Germany instead of vacuum bottles.

8. Results. Line 10. Did any of the ovarian cancer patient have ascites? If so did any have interperitoneal catheters?

Reply: Patients with locally advanced (FIGO stage III) or metastatic ovarian cancer at primary diagnosis (FIGO stage IV) represented 92.6% of all patients. Only 1.6% had stage IA or B. Hence, >95% also had ascites at the time of primary diagnosis, the number increased to 100% at the time of IPC implantation. But no patient received an additional intraperitoneal indwelling catheter.

9. Efficacy and AP. Line 47 Repeat intervention in what time frame?

Reply: This refers to the entire observation period until the last visit or death. The manuscript has been updated correspondingly.

10. Survival with IPC line 1. Survival really should be based on the disease or when the pleural effusion arised. See Faiz SA, Annals of ATS, 2017 14(6) in which authors assess survival in terms of diagnosis of disease and point at which pleural effusion arises. Survival after IPC just reflects advanced disease with pleural effusion.

Reply: We thank the reviewer for this insightful comment. Therefore, and analogously to the mentioned study from Faiz et al., we have changed our survival reporting. In order to being able to put the results into a better context, overall survival was assessed 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. Whereas OS1 shows the entire course of
disease (with the respective histology-dependent prognosis), OS2 represents the final common pathway for the patient cohort investigated in the present study.

11. Survival with IPC. Lines 13 and 17. These are conflicting statements: bilateral effusions carry a better prognosis, but catheter laterality prognostic. Is the bilateral effusions in ovarian only? Needs clarification

Reply: As mentioned in our study, the high percentage of patients with ovarian cancer in our cohort is likely to have influenced our results. Regarding the literature, bilateral effusions are common in ovarian cancer (Wimberger P et al., Ann Surg Oncol 2010). In our study, bilateral effusions were not exclusively correlated to ovarian cancer but the proportion of patients with bilateral IPC was substantially higher and represented 19.8% of all patients with ovarian cancer. In comparison, the number of patients was lower in lung (6.6%) or breast cancer (13.3%).

12. Page 14, line 2. What is the rationale for bilateral effusions prognostic effect in ovarian cancer? Meigs? diaphragmatic defects? not the primary source of malignancy?

Reply: Reasons for the observed differences remain speculative. E. g., a more aggressive abdominal cytoreductive surgery, conferring a prognostic effect in ovarian cancer, might have contributed to bilateral effusions (Porcel JM et al., Respirology 2012). Meigs syndrome causing bilateral effusions can be ruled out, as all patients had histologically confirmed ovarian cancer (and not a benign diagnosis), so effusions did not disappear after surgery in any patient.

13. Page 14, line 14. Need to breakdown pleural infections. Really the one most significant is empyema. Also in results need to describe definitions of tunnel and empyema. Was as separate thoracentesis performed to diagnose empyema or just cultures from IPC?

15. What is the percentage of empyema? How many site infections and how many tunnel infections:

Reply to 13 and 15: These are important remarks. Localization of the infection has been clarified in the results section. Superficial infections were defined as infections at the exit site (cellulitis) or the tunnel, whereas empyema was a deep infection. The diagnosis of empyema was made using cultures drawn from the IPC, additional thoracenteses were not routinely performed. Empyema concerned 2.5% of all interventions, infections at the exit site and tunnel infections made up 2.2% and 0.9%, respectively. Simultaneous superficial and deep infections never occurred.

14. Page 14, line 18. Infectious complications tend to occur in the first 6 weeks but up to 14 weeks after placement.


c. Faiz SA et. al. Annals of ATS 2017

Reply: Dividing infections as described, we observed a time-dependent pattern of occurrence: Local infections at the exit site occurred rather early within the first 5 weeks (median 38 days (range, 1-186, IQR, 10.8-61)), while empyema and tunnel infections were seen significantly later (median 116 days (range 35-552 days, IQR 44-191) and 103 days (range, 8-552, IQR, 8.3-463.3); p=0.003). In the study from Fysh et al. (Chest 2013), pleural infections occurred earlier at a median of 62 days, but the IQR was very broad (IQR, 39-177). Similar to our results, Chalhoub M et al. also reported late occurrences for empyema in their review on IPC (J Thorac Dis. 2018 Jul; 10(7): 4659–4666).

16. Page 14, line 41. Loculations are not significant unless the patient is symptomatic, and then if they require intervention (tpa, repeat procedure)

Reply: We thank the reviewer for this remark. Indeed, only symptomatic loculations were regarded as significant and therefore classified as a complication. The section has been stated more precisely in the manuscript. All of the 5 loculations received intrapleural fibrinolysis. This was successful in two cases, two IPC were removed after failure of (repeated) fibrinolysis, one catheter was left in place (after failure of fibrinolysis) due to the patient’s reduced performance status.

17. Did any patients get talc pleurodesis via surgery or the IPC?

Reply: An additional talc slurry pleurodesis via the IPC was performed in 14 procedures. The success rate was 71.4%.

18. The concluding paragraph lists the limitations of the paper. There needs to be concluding paragraph summarizing the main conclusions of the paper.

Reply: This is a helpful remark. The study’s main results have been added to the concluding paragraph: “To conclude, the current investigation provides the largest single-center case series with IPC in malignant diseases and strongly supports them as a safe and feasible first-line option in the management of malignant or paramalignant pleural effusion. IPC are highly efficacious in symptom relief and display a favourable safety profile in the daily routine. With an appropriate patient education, rates of infectious mechanical complications are low, even in a long-term setting.”

Minor

1. "Chronic" pleural effusion is somewhat ambiguous. Consider malignant or malignancy-associated
Reply: We changed the title of the study to “Indwelling pleural catheters for malignancy-associated pleural effusion: report on a single centre’s ten years of experience”

2. Key words. If pleurodesis is a main outcome, then add to key words

3. Line 38, add common after percutaneously

4. Discussion. Line 3, change PE to pleural effusion

Reply: Thank you for the remarks, all changes have been made.

5. There were 22 hematologic malignancies noted in table 1. What type were these?

Reply: We updated table 1 and added footnotes. Hematologic malignancies consisted of lymphoma (n=13; 7x B-NHL, 4x CLL, 2x T-NHL), multiple myeloma (n=7) and leukaemia (n=2; 1x ALL, 1x AML).

6. Why not group all the gynaecologic neoplasms together?

Reply: For logistic regression (for AP) and survival analysis we now have grouped all gynaecologic malignancies together. Nevertheless, as we have observed some interesting differences (e.g. concerning the percentage of MPE, survival advantage for bilateral effusions) and to emphasize the large cohort of patients with ovarian cancer, at least the large entities (ovarian and breast cancer) were analysed separately concerning baseline characteristics and the course of disease.

Nikhil K. Meena (Reviewer 2):

A well done retrospective study to evaluate the performance of TPC for chronic pleural effusion.

It is one of the better retrospective study, with underscores the benefit of TPC.

I would probably not read more than the abstract as the findings have been described with varied methodologies, as both retrospective cohort studies, RCTs.

I'm not surprised by the findings, except for the complication rate which is higher than expected based on available literature.

Reply: We thank the reviewer for the positive assessment and for acknowledging the importance of our study. Concerning complications, we have re-assessed rates over time and were able to demonstrate a clear drop over the decade described in our study. Comparing the period from 2006-2012 to 2013-2016, especially infectious complications substantially decreased (8.6 vs. 3.9%, p=0.032). So, breaking down complications in 2 periods, the on a whole higher complication rate expresses the institution’s learning curve with handling IPC over (a long period of) time.
Robert John Hallifax (Reviewer 3):

This is a single centre retrospective review of IPC usage. As such, it is not practise changing, but the large number cases make it an interesting study.

Overall it is well presented with good discussion of key points.

Reply: We thank the reviewer for this positive assessment.

Major comments:

1. Although paramalignant pleural effusions are described in the ATS guidelines, PPE is NOT a commonly used acronym so would avoid using it: instead just say "paramalignant effusion".

Paramalignant effusions are uncommon and are a specific clinical entity. It is well known that pleural fluid cytology sensitivity is poor (50-60%), and CT radiology also has a poor negative predictive value (Hallifax et al, Thorax. 2015 Feb;70(2):192-3). Therefore, there is a danger a significant number of patients will have 2x negative cytology and "bland" radiology will actually have pleural malignancy. Furthermore, a "cytology negative" free flowing effusion would behave very differently to an effusion resulting from central obstruction.

I therefore suggest that the authors restrict their definition of paramalignant effusion to those with central obstruction or lymphatic involvement. An additional category of "cytology negative" effusions in the context of known malignancy would be reasonable. Likewise, cachexia and hypoalbuminemia should not be lumped together with obstructive effusions.

Reply: These are helpful suggestions. We now have re-grouped the non-malignant effusions in 3 categories: Paramalignant postobstructive effusions, cytology-negative disease-associated effusions and treatment-related effusions. In the second group, we integrated effusions due to hypoalbuminemia and cachexia as well as those effusions with unknown provenience. Most likely due to the relative small number of non-malignant effusions, no significant survival differences were seen in this group. Survival in paramalignant and cytology-negative effusions was nearly equal and very short (1.4 vs. 1.7 months), only the 5 patients with treatment-related effusions had a numerically longer survival of 4.2 months. But as the variable “treatment” must be regarded as a time-dependent covariate, no substantial survival differences are given with regard to the first two groups.

2. Table 3 is confusing. There needs to be headings about columns 1-2 and 3-4 specifically stating that they refer to AP and survival, respectively (not just stated in the legend. I have concerns about the use of regression. Please list all of factors assessed in the cox analysis. The authors have already stated that those surviving longer were more likely to achieve AP. Will this not confound the analysis? Was talc included in the analysis.
Reply: We have separated logistic regression for AP and Cox regression for survival in two different tables to improve the readability. As the probability for AP is time-dependent and normally needs at least 3-4 weeks to occur, we performed an additional logistic regression for AP in all patients (448 procedures) to investigate whether a restriction to those surviving ≥30 days would confound our analysis. Furthermore, as suggested by the reviewer, we added the use of talc in our analysis. Results were comparable for both groups with the exception of complications and bilateral effusions: For all procedures, age <60 years (HR 1.62, p=0.024), and the use of talc slurry via the IPC (HR 6.70, p=0.002) increased the likelihood of AP. The predictive effect of complications (HR 2.1, p=0.002) and bilateral effusions (HR 2.52, p=0.001) was no longer significant in patients surviving ≥30 days, whereas age <60 (HR 1.71, p=0.030) and talc (HR 6.68, p=0.015) remained predictive for AP. The significant influence of the variable “complications” in the entire cohort is attributable to its property as being time-dependent. Thus, it was no longer significant in the second analysis in patients surviving ≥30 days.

Additionally, using multiple logistic regression, talc and age <60 years predicted AP independently.

3. "Quality of effusion" should be renamed "Cause of effusion". What is the difference between MPE vs PPE/Unknown and MPE vs PPE/Unknown*?

Reply: We have replaced the term as proposed. “MPE vs PPE/Unknown*” referred to the subgroup of patients with ovarian, breast or lung cancer only. Having regrouped the non-malignant effusions, this subgroup analysis has been removed.

Minor comments:

1. Table 2. I think it would be useful to present the % of complications out of the total number (rather than just the total complications). This would allow readers to better assess the overall rate of empyema (2.3%) which is not explicitly listed in the table.

Reply: We thank the reviewer for this suggestion and have added an additional column to table 2 relating complications to all procedures.

2. the word "albeit" is used incorrectly in the manuscript and should be replaced with "Although". "vice versa" should be replaced with "conversely".

Reply: Thank you for the remarks, all changes have been made.