PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC).
AUTHORS	Rovers, Koen; Lurvink, Robin; Wassenaar, Emma; Kootstra, Thomas; Scholten, Harm; Tajzai, Rudaba; Deenen, Maarten; Nederend, Joost; Lahaye, Max; Huysentruyt, Clément; van 't Erve, Iris; Fijneman, Remond; Constantinides, Alexander; Kranenburg, Onno; Los, Maartje; Thijs, Annemarie; Creemers, Geert-Jan; Burger, Jacobus; Wiezer, René; Boerma, Djamila; Nienhuijs, Simon W.; de Hingh, Ignace

VERSION 1 – REVIEW

REVIEWER	Günther Rezniczek, PhD Ruhr-Universität Bochum Germany
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	This is a carefully considered and well written study protocol. I have nothing to add and would like to offer the authors my best wishes for a successful completion of the study.

REVIEWER	Aditi BHATT Zydus Hospital, India
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	It was my pleasure to review this interesting protocol for evaluating the feasibility of e-PIPAC as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases (PM). Thank you for the invitation. From the manuscript, it may be inferred that any patient with unresectable colorectal PM irrespective of previous systemic and surgical therapies will be included in the study provided they fulfil the inclusion criteria. The authors must clarify the following 1. Will any patient with newly diagnosed synchronous isolated unresectable PM be included in the study ? And what is the rationale for recommending e-PIPAC alone in this setting as opposed to systemic chemotherapy or a combination of the two? The explanation provided by the authors in 'rationale for intervention' is a 'hypothesis' and this should be mentioned.

	Though the authors state in the introduction that systemic chemotherapy produces poorer results in isolated PM as compared to other metastatic sites, systemic chemotherapy does produce good results in selected patients and even a complete response in nearly 10%- there are no established criteria for identifying the responders and non-responders though. In the experimental study (ref 20) quoted by the authors, it has been shown that systemic chemotherapy produced a similar reduction in PCI compared to PIPAC. Systemic chemotherapy would have the additional benefit of acting on micrometastatic disease and thus delaying or preventing other distant metastases. How do the authors justify using e-PIPAC monotherapy? It would be useful if the authors could state the harms/disadvantages they anticipate with PIPAC monotherapy (apart from the side effects of PIPAC itself) 2. The authors should specify if the following patients will be included or excluded - H/O prior CRS for colorectal PM -h/o prior oxaliplatin HIPEC -synchronous large ovarian metastases -signet ring cell carcinomas 3. What is the rationale for performing a laparoscopy/laparotomy in all patients? It is possible to diagnose unresectable disease on imaging for many patients. 4. What do the authors consider unresectable disease- is it a high PCI (if so, what value?). 'Unresectable' should be clearly defined. 5. It may be presumed that atleast some patients would have received prior FOLFOX chemotherapy. What is the therapeutic rationale for treating such patients with oxaliplatin PIPAC alone? 6. The therapeutic rationale for PIPAC comes from experimental studies which have not considered the morphology of PM. Diffuse carcinomatosis with gross ascites is different from one or more unresectable implants in the pelvis both morphologically and biologically. It will be useful if such information is recorded and reported. It is known that other forms of intraperitoneal chemotherapy do not benefit most patients with tumor nodules measuring >2.5mm but such information is not availble regarding PIPAC. 7. The criteria for discontinuation need to be specified in more detail. If there is progression after the first or second e-PIPAC, will all three still be administered? The radiological criteria for progression should be specified. 8. The limitations of the study should be mentioned

REVIEWER	Martin Graversen Odense PIPAC Center Upper GI and HPB Surgery Department of Surgery Odense University Hospital Odense Denamrk
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	Thank you for giving me the opportunity to review this highly relevant protocol article on ePIPAC-OX for peritoneal metastasis of colorectal or appendiceal origin. This reviewer agrees on the assumption, that ePIPAC is used throughout many PIPAC centres, despite the fact that little is known on the superiority or toxicity compared to standard PIPAC directed treatment. The protocol article is well-written and well-structured with a clear definition of study rationale and outcome. According to the article, the study has enrolled patients since 2017 with an estimated accrual period of three years (20 patients/60 ePIPAC-OX procedures). As such, no big changes can be applied to the methods, but please accept the following questions that aim to clarify certain details. Page refers to the number at the top of each page in the pdf version, line refers to the actual line (right column) Major - P9, L30: “incisions may be additionally sutures”. This is a pivotal safety issue in PIPAC, so please rephrase to e.g. “the external fascia may be additionally sutures”. The problem is the risk of subcutaneous necrosis due to chemotherapy, if only the skin is closed around the trocar. - P10, L32-34: You don’t include histological progression (according to PRGS) as reason for discontinuation? - P11, L1: This reviewer finds it rather unethical to continue a local treatment of the peritoneum if the patient has systemic disease progression, even if there is no systemic alternative. - P12, L12-13: How do you plan to quantify “amount of adhesions and technical difficulties”? - P12, L17-18: How do you separate the reporting of organ-specific toxicity from the four weeks CTCAE reporting (which should also include blood-samples)? - P13, L11-19: A sample-size of 20 is a bit low if you want to perform 60 procedures in this highly-palliative setting. As you have been recruiting patients since 2017 you probably know if it is enough. - P13, L32-34: Does this sentence imply that you don’t evaluate histopathological (PRGS) or radiological response before study completion? Please clarify. Minor - P5, L33: Past tense? Then received - P6, L7-8: ePIPAC-OX or (e)PIPAC-OX. Please decide and uniform throughout the manuscript. - P7, L12-13: Upper Normal Limit abbreviated as UNL not ULN. - P8, L8-9: These are cancer patients with a high risk of thromboembolic events. Why don’t you use thromboembolism prophylaxis?

VERSION 1 – AUTHOR RESPONSE

POINT-BY-POINT RESPONSE TO COMMENTS OF REVIEWER 1
Comment
Response

1. This is a carefully considered and well written study protocol. I have nothing to add and would like to offer the authors my best wishes for a successful completion of the study.
Dear reviewer, thank you very much for your positive remark.

POINT-BY-POINT RESPONSE TO COMMENTS OF REVIEWER 2
Comment
Response

Dear reviewer, thank you for your highly valuable comments. We incorporated the majority of your comments in the new version of the manuscript. Unfortunately, we could not incorporate all of your comments, since some would have a great impact on the design of our already recruiting study. In these cases, we truly hope we answered your comments to your satisfaction.

1. Will any patient with newly diagnosed synchronous isolated unresectable PM be included in the study? And what is the rationale for recommending e-PIPAC alone in this setting as opposed to systemic chemotherapy or a combination of the two? The explanation provided by the authors in the 'rationale for intervention' is a 'hypothesis' and this should be mentioned. Though the authors state in the introduction that systemic chemotherapy procedures poorer results in isolated PM as compared to other metastatic sites, systemic chemotherapy does produce good results in selected patients and even a complete response in nearly 10% - there are no established criteria for identifying the responders and non-responders though. In the experimental study (ref 20) quoted by the authors, it has been shown that systemic chemotherapy produced a similar reduction in PCI compared to PIPAC. Systemic chemotherapy would have the additional benefit of acting on micrometastatic disease and thus delaying or preventing other distant metastases. How do the authors justify using e-PIPAC monotherapy? It would be useful if the authors could state the harms/disadvantages they anticipate with PIPAC monotherapy (apart from the side effects of PIPAC itself). The limitations of the study should be mentioned.
We completely agree with the reviewer that the decision to administer ePIPAC-OX as a monotherapy is debatable and interesting. ePIPAC-OX monotherapy could hypothetically stabilize the intraperitoneal disease load with minimal treatment burden, thereby preserving quality of life, which could be very important in this highly palliative setting. According to your comment, we mentioned that the rationale for the intervention is a hypothesis in the new version of the manuscript. Please see TRACK CHANGE #5.
We completely agree with the reviewer that, compared to PIPAC monotherapy, systemic chemotherapy or a combination of systemic chemotherapy and PIPAC could have better results in terms of tumour response, but these treatment strategies are more likely to interfere with quality of life in the palliative phase. We also completely agree with the reviewer that ePIPAC-OX monotherapy could have important disadvantages, limitations, and harms for patients, especially in patients with synchronous PM and those without prior palliative systemic therapy. In our opinion, the most important of these are undertreatment and subsequent systemic progression or progression of the primary tumour. Therefore, the authors decided to incorporate frequent clinical and radiological evaluations to detect such progression in a sufficiently early stage. Moreover, patients need to be informed by a medical oncologist about the potential consequences of postponing or discontinuing their standard palliative treatment (often: systemic chemotherapy) prior to enrolment. Conclusively, the investigators feel that these controlled circumstances justify ePIPAC-OX as a monotherapy in this setting. To address this topic, we added a 'Discussion' paragraph at the end of the manuscript which includes the most important limitations/harms of this study together with its strengths according to your comments. Please see TRACK CHANGE #18. Thank you very much for these highly valuable comments.

2. The authors should specify if the following patients will be included or excluded:

In general, we deliberately chose broad eligibility criteria for this feasibility/safety study. These broad eligibility criteria will create a heterogeneous study cohort and thereby impede survival analyses, but it will hopefully give us an idea which patients may benefit the most from PIPAC therapy. We added the broad eligibility criteria as a limitation in the new 'Discussion' paragraph. Please see TRACK CHANGE #18.

a. History of prior cytoreductive surgery for colorectal PM

By not mentioning this specific criterion, we automatically imply that patients who received prior cytoreductive surgery for colorectal PM may be included in this study, provided that there are no contraindications for a safe laparoscopy (e.g. extensive adhesions due to prior cytoreductive surgery), which is an exclusion criterion. Therefore, we did not change the manuscript according to this comment, but we hope it is an appropriate answer to your comment..

b. History of prior oxaliplatin HIPEC

By not mentioning this specific criterion, we automatically imply that patients who received prior oxaliplatin HIPEC may be included in this study, provided that there are no contraindications for a safe laparoscopy (e.g. extensive adhesions due to HIPEC) or contraindications for oxaliplatin (e.g. history of severe toxicity), which are both exclusion criteria. Therefore, we did not change the manuscript according to this comment, but we hope it is an appropriate answer to your comment.

c. Synchronous large ovarian metastases

By not mentioning this specific criterion, we automatically imply that patients with synchronous ovarian metastases may be included in this study, provided that there are no symptoms of gastrointestinal obstruction, which is an exclusion criterion. In daily practice, we expect that synchronous large symptomatic ovarian metastases will always be removed before potential enrolment in this study, since this is already standard of care for metastatic colorectal cancer in the Netherlands. Therefore, we did not change the manuscript according to this comment, but we hope it is an appropriate answer to your comment.

d. Signet ring cell carcinomas

By including patients with a carcinoma of colorectal or appendiceal origin, we automatically imply that we also include patients with a signet ring cell carcinoma of the colon/appendix. Therefore, we did not change the manuscript according to this comment, but we hope it is an appropriate answer to your comment.

3. What is the rationale for performing a laparoscopy/laparotomy in all patients? It is possible to diagnose unresectable disease on imaging for many patients.

Diagnostic laparoscopy is a standard tool in the diagnostic work-up for patients with peritoneal metastases of colorectal origin in the Netherlands. Therefore, it is no additional procedure for this particular patient population and we could easily incorporate it in our study protocol. Furthermore, it has the additional benefit of allowing histological/cytological proof of peritoneal metastatic disease, which is an inclusion criterion in this study. However, if diagnostic laparoscopy/laparotomy would not have been standard of care in the Netherlands, we completely agree with the reviewer that imaging is enough to diagnose unresectable disease in at least a part of the patients. We did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

4. What do the authors consider unresectable disease – is it a high PCI (if so, what value?)? 'Unresectable' should be clearly defined.

Unresectable disease is determined at physician's discretion and not defined a priori, since 'unresectable disease' is difficult to define and depends on many factors (e.g. frailty of the patient, location of metastases, small bowel, histology, primary location, differentiation, etcetera, PCI, etcetera). In the new version of the manuscript, we mentioned that the unresectability of the disease is determined by the treating physician. Please see TRACK CHANGE #6.

5. It may be presumed that at least some patients would have received prior FOLFOX chemotherapy. What is the therapeutic rationale for treating such patients with oxaliplatin PIPAC alone?
We completely agree with the reviewer that this is a debatable question. One of the objectives of this study is to evaluate the potential of PIPAC in different patient groups. Currently, it remains unknown whether patients who received prior oxaliplatin-based systemic combination chemotherapy (regardless of response to this therapy) may derive a benefit from PIPAC. In this study, it may be interesting to see whether the administration of – and response to and toxicity of - prior oxaliplatin-based systemic chemotherapy have an effect on the efficacy and toxicity of ePIPAC-OX monotherapy. Therefore, this study may also include patients who received prior oxaliplatin-based chemotherapy, as seen by our broad eligibility criteria. We did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

6. The therapeutic rationale for PIPAC comes from experimental studies which have not considered the morphology of PM. Diffuse carcinomatosis with gross ascites is different from one or more unresectable implants in the pelvis both morphologically and biologically. It will be useful if such information is recorded and reported. It is known that other forms of intraperitoneal chemotherapy do not benefit most patients with tumor nodules measuring >2.5mm but such information is not available regarding PIPAC.
Thank you for your advice. Unfortunately, this information has not been recorded and prospectively reported until now, which would indeed have been very interesting. However, at the end of the study, we will retrospectively obtain these results from radiological images and videolaparoscopy to preliminarily evaluate whether morphology and biology (and tumour nodule diameter) influence the efficacy of PIPAC. Unfortunately, we cannot add this endpoint to the protocol anymore at this stage. Therefore, we did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

7. The criteria for discontinuation need to be specified in more detail. If there is progression after the first or second e-PIPAC, will all three still be administered? The radiological criteria for progression should be specified.
If there is radiological or clinical progression after the first or second ePIPAC-OX, we will immediately stop with further PIPAC-procedures. This is already mentioned in the ‘’Interventions and procedures > ePIPAC-OX’’ paragraph. The radiological criteria for progression are defined according to RECIST or at physician’s discretion in case of RECIST-unmeasurable disease, which is often seen in peritoneal metastatic disease. In the new version of the manuscript, we clarified the radiological criteria for progression. Please see TRACK CHANGE #13.

POINT-BY-POINT RESPONSE TO COMMENTS OF REVIEWER 3
Comment
Response

Dear reviewer, thank you for your highly valuable comments. We truly hope we answered your comments to your satisfaction.

1. P9, L30: ‘’incisions may be additionally sutured’’. This is a pivotal safety issue in PIPAC, so please rephrase to e.g. ‘’the external fascia may be additionally sutured’’. The problem is the risk of subcutaneous necrosis due to chemotherapy, if only the skin is closed around the trocar.
We rephrased the sentence to ‘’the external fascia may be additionally sutured’’, which indeed better describes this pivotal safety issue in PIPAC that we also perform in clinical practice. Please see TRACK CHANGE #11.

2. P10, L32-34: You don't include histological progression (according to PRGS) as reason for discontinuation?
No. Since there is no literature on the prognostic value of the PRGS until now, we decided not to include the PRGS as a reason for discontinuation of PIPAC treatments. Instead, we use the 'regular' progression parameters in oncology (clinical and radiological progression). Since radiological progression is often difficult to measure in peritoneal metastatic disease, we decided to additionally include macroscopic progression (increase in peritoneal cancer index or ascites volume) as a reason for discontinuation. Of course, we will collect all histological regression samples and analyse them afterwards to evaluate (in this and future studies) whether a progressive PRGS should indeed be a reason for discontinuation, and whether PRGS may be a better prognosticator for oncological outcomes than the conventional oncological parameters we use now. We did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

3. P11, L1: This reviewer finds it rather unethical to continue a local treatment of the peritoneum if the patient has systemic disease progression, even if there is no systemic alternative.
We totally agree with the reviewer that this is a debatable (and also uncommon) situation. We incorporated this possibility, which has been approved by the central ethics committee, for the particular group without systemic treatment options that develop an (often asymptomatic) single metastasis in an extraperitoneal organ while having (often symptomatic and clearly lethal) extensive intraperitoneal disease. In these patients with predominantly peritoneal disease, repetitive PIPAC could potentially provide additional quality of life over supportive care by stabilizing the intraperitoneal disease burden without major toxicity. Again, we totally agree with the reviewer that it is a debatable situation. However, we hope this study will provide more information about the value of repetitive ePIPAC-OX in this specific situation, although we realise that this situation is highly uncommon/rare. We did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

4. P12, L12-13: How do you plan to quantify ''amount of adhesions and technical difficulties''?
Adhesions are scored with the Zühlke score, which is mentioned in the ''Interventions and procedures > ePIPAC-OX'' paragraph. We emphasized/rewrote it in the new version of the manuscript for clarification. The way of quantifying 'technical difficulties' is not specified a priori, but recorded descriptively after each ePIPAC-OX. We emphasized/rewrote it in the manuscript for clarification. We also changed 'technical difficulties' to 'procedure-related mistakes and difficulties', since we think it is a more appropriate term. Please see TRACK CHANGE #10, #12, #14

5. P12, L17-18: How do you separate the reporting of organ-specific toxicity from the four weeks CTCAE reporting (which should also include blood-samples?)?
Thank you for this valuable comment. It is indeed difficult to separate the reporting of organ-specific toxicity from the CTCAE reporting. Therefore, we removed organ-specific toxicity as a specific endpoint and we will incorporate the organ-specific toxicity in the main toxicity endpoint according to CTCAE. Please see TRACK CHANGE #2, #8, #15, #16

6. P13, L11-19: A sample-size of 20 is a bit low if you want to perform 60 procedures in this highly-palliative setting. As you have been recruiting patients since 2017, you probably know if it is enough.
Thank you for your advice. The mean number of three PIPAC procedures was based on the study by Demtröder et al (Colorectal Dis, 2016). If we indeed see that the mean number of PIPAC procedures is lower in this highly palliative setting, we will ask the ethics committee for expansion of the study cohort to a number sufficient to complete 60 procedures in total. We did not change the manuscript according to this comment, but we hope it is an appropriate answer to your question.

7. P13, L32-34: Does this sentence imply that you don't evaluate histopathological (PRGS) or radiological response before study completion? Please clarify.
We don't evaluate histopathological regression (PRGS) before study completion, since we don't use it as a criterion for (dis)continuation, as mentioned in the answer to your comment #2. Regular radiological response (according to RECIST criteria) is evaluated in the study centres during the study period and used as a criterion for (dis)continuation. Please see TRACK CHANGE #13. Additionally, we will collect all radiological images after the study to evaluate whether we are able to develop a better/other method to quantify radiological response in (extensive) peritoneal disease.

8. P5, L33: Past tense? Then received.
Thank you. We changed it to 'received'. Please see TRACK CHANGE #3.

9. P6, L7-8: ePIPAC-OX or (e)PIPAC-OX. Please decide and uniform throughout manuscript.
Thank you. We uniformed it to 'ePIPAC-OX' throughout the manuscript. Please see TRACK CHANGE #4.

10. P7, L12-13: Upper Normal Limit abbreviated as UNL not ULN.
In our opinion, 'upper limit of normal' is the most appropriate term, which is abbreviated to 'ULN' in our manuscript. We clarified this abbreviation by explaining it the first time it appears in the text. Please see TRACK CHANGE #7.

11. P8, L8-9: These are cancer patients with a high risk of thromboembolic events. Why don't you use thromboembolism prophylaxis?
We totally agree with the reviewer that this is a debatable topic. We decided not to give the standard thromboembolism prophylaxis (LMWH, 4-6 weeks after abdominal surgery for oncological disease) regularly to patients in the study for several reasons:
- We expected patients to be mobile shortly after the procedure;
- Patients are in a highly palliative setting, and daily subcutaneously administered thromboembolism prophylaxis could interfere with quality of life in this setting;
- Patients are operated every 5-6 weeks, which means that they almost continuously need to have thromboembolism prophylaxis in the palliative phase.

Taken together, we thought and decided that the risks of not giving thromboembolism prophylaxis are less important than the harms/discomfort of its regular administration in this highly palliative setting. Of course, we use thromboembolism prophylaxis if we expect immobility of a patient, for example due to a prolonged hospital stay due to postoperative complications. In the manuscript, we clarified that this prophylaxis is not regularly administered, instead of not administered. Please see TRACK CHANGE #9

VERSION 2 – REVIEW

REVIEWER	Martin Graversen Odense PIPAC Center, Department of Surgery, Odense University Hospital, Denmark
REVIEW RETURNED	03-Jun-2019

GENERAL COMMENTS	Good job!

REVIEWER	Aditi BHATT Zydus Hospital, Ahmedabad, India
REVIEW RETURNED	03-Jun-2019

GENERAL COMMENTS	I thank the authors for their very elaborate yet precise responses to my comments. I agree with their decision to not incorporate all the changes and with all explanations provided. Despite some limitations, the merits of this study are many as very clearly brought out in the discussion. Going back to comment 2, would like to add that though it is presumed that such patients will be included, specific mention of certain clinical situations offers greater clarity to the readers. Though resection of ovarian metastases prior to PIPAC or systemic chemotherapy is in the Dutch Guidelines, not all readers may be aware of it. The same for a staging laparoscopy. The authors may consider including this in the methodology but it is not absolutely essential. I extend my best wishes to the authors for a successful completion and look forward to the results of this study.

VERSION 2 – AUTHOR RESPONSE

Comment by Reviewer #2: I thank the authors for their very elaborate yet precise responses to my comments. I agree with their decision to not incorporate all the changes and with all explanations provided. Despite some limitations, the merits of this study are many as very clearly brought out in the discussion. Going back to comment 2, would like to add that though it is presumed that such patients will be included, specific mention of certain clinical situations offers greater clarity to the readers. Though resection of ovarian metastases prior to PIPAC or systemic chemotherapy is in the Dutch Guidelines, not all readers may be aware of it. The same for a staging laparoscopy. The authors may consider including this in the methodology but it is not absolutely essential. I extend my best wishes to the authors for a successful completion and look forward to the results of this study.

Response by authors: We agree that specific mention of certain clinical situations offers clarity to the readers. Therefore, we incorporated the specific eligibility criteria / clinical situations that you mentioned in your previous comments #2 and #3 in the Methods section of the manuscript. Please see the Track Changes in the Methods section on page 6.