Author's response to reviews

Title: Peri-operative chemotherapy in the management of resectable colorectal cancer pulmonary metastases

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Author's response to reviews: see over
To the Editor,

RE: Reply to reviewers comments for Manuscript 2026934755725714 - Peri-operative chemotherapy in the management of resectable colorectal cancer pulmonary metastases

Many thanks to both reviewers and the editors for your comprehensive review of our manuscript and helpful feedback. Please find the reviewers comments addressed individually below:

Reviewer 1

Different values for survival parameters or PET concordance are all given without referring to the level of significance. In regard of the limited patient sample all comparative values are likely non-significant, however it should be mentioned.

- In this retrospective cohort with the limitation of small numbers and no strict time point at which the PET was performed, attaching statistical significance (or more likely-lack thereof) would place inappropriate value on the results. We have added an explanation in the discussion as follows: These concordance rates were exploratory and hence only described in absolute values, the limited sample size precluded any formal statistical testing.

Background:

second paragraph: number >2 might be more appropriate (ref6), as >1 was only univariate (ref5), cut off value for CEA might be added. Inoue, M., M. Ohta, et al. (2004). "Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma." Ann Thorac Surg 78(1): 238-244 might be added with a high number of patients and two additional factors unilateral and Dukes A.

- This has been changed in the manuscript (paragraph 2, page 3) in line with the reviewer’s recommendations.

third paragraph: If CELIM is cited maybe Boxer trial would fit better than NO66/BEAT (Wong, R., D. Cunningham, et al. (2011). "A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection." Ann Oncol 22(9): 2042-2048.)

- We have added the BOXER trial as a reference and updated the CELIM reference given the long term follow up was reported this year.

Methods:

Multidisc. meeting periop CT for DFI<2y and (instead of or) malignant nodules

- This has been changed in the manuscript

Discussion:

third paragraph:

Although I fully agree with the authors about the feeling of using periop CT in this situation, neither OS nor RFS data are better or higher than for the upfront surgical approach. The abstract is fine. In the
discuss low morbidity supports the use of periop CT although no difference in survival was shown? That should be rephrased. The OS in both groups is very good, maybe similar problem as to be presented at ASCO for the EORTC trial in liver mets.

- We agree and have changed this paragraph to further clarify the meaning.

Last part of last sentence should be rephrased: “but resection is also a feasible option”.
- Likewise, this has been rephrased.

fourth paragraph:
Downsizing in resectable lung mets is not an issue for neoadjuvant CT, but besides assessing response in vivo, gain information about the course of disease, e.g. lung mets as the first sign of rapid overall progression is an important issue.

- We have altered this paragraph to incorporate the points made by the reviewer.

sixth paragraph: Were toxicity with bev noted or not? What is meant by besides the known side effects, what grade etc.?

- We have clarified this paragraph in the manuscript. No toxicities occurred in patients who received bevacizumab in our cohort, but we were attempting to acknowledge the reported increase in surgical complications noted in other studies when bevacizumab was administered preoperatively.

PET: In regard of the low number of patients with PET positivity (N=39), which are further divided into two groups either with or without prior treatment and the discussion about value of PET in neoadjuvant treated liver mets of colorectal origin and the likely not significant difference between the concordance rates I dont think one could make anything out of the obtained data, besides the potential exclusion of extrahepatic mets, although there is no group of patients in this evaluation available who were not resected due to extrahepatic spread. However, I would not say „higher rate of concordance“ in the discussion. What is exactly meant by „did not appear to impact FDG avidity of the lesions“ with only 12 pretreated patients which might have had completely different patterns of disease or did cases were matched. Overall I would rather completely avoid to discuss the value or results of PET out of this evaluation and refer to available guidelines and reviews (e.g. Chan, K., S. Welch, et al. (2011). “Evidence-based Guideline Recommendations on the use of Positron Emission Tomography Imaging in Colorectal Cancer.” Clin Oncol (R Coll Radiol.).)

- We recognise the primary use of PET in this population is to exclude extra-pulmonary disease, and have made this point in the discussion. It is widely understood that many nodules identified on CT which are resected are subsequently discovered to be benign. With this in mind, we aimed to assess whether PET was additionally useful in identifying malignant versus non-malignant lesions and could compare this to histology given all visible nodules were resected. We have further clarified this in the discussion.

- While only 39 patients had a positive PET, this represented 81% of the group who underwent PET. We do highlight the limitations of our study in the discussion with respect to the small numbers and deliberately do not make any new recommendations regarding our observations of PET concordance.

- We have avoided a discussion about any additional value of PET in neoadjuvant treatment of liver mets beyond current guidelines as these can be identified as malignant far more readily by CT and MRI and hence are uncertain as to the point above regarding liver metastases.

Several issues are more interesting and should be discussed:
lymph node resection (meanwhile recommended, hence only performed in 19 patients, likely due to included patients since 1997 or?) Furthermore, the only remaining prognostic factor, which is not commented in the discussion.

- We have amended the discussion in the protocol to further expand on this point but highlight the changes below.
- Lymph node involvement was the only significant prognostic factor found in our cohort but only in univariate analysis. The numbers were too small to compare lymph node involvement between the perioperative chemo vs no chemo groups or to perform a multivariate analysis. Certainly, as the reviewer
has pointed out, the more recent procedures almost routinely involved a lymph node resection whereas earlier procedures did not, which could be impacted on by numerous confounding factors hence our caution at over-stating the value of this result.

- As we reported none of the factors significant for outcomes relating to perioperative chemotherapy we have not discussed any of these in the discussion at length, rather focusing on points relating to the impact of perioperative chemotherapy in this group.

What happened to the patients with re-resection and what impact of periop CT was seen (only casuistics).

- We have described the follow up of those re-resected in figure 3 and toxicity from periop CT and surgical complications are included in tables 3 and 4. We have not formally compared the impact of perioperative CT in this group or separated these patients when reporting toxicity or surgical complications given the numbers are in the order of single figures.

The issue of histological response might be discussed a bit more compared to liver metastases, especially in regard of the noted imaging response before resection.

- For the purposes of reporting, when reviewing the pathology, we only recorded presence of viable tumour, and in surrounding tissue, presence of pulmonary eosinophilia, interstitial fibrosis and/or inflammation unrelated to the locale of the tumour. Which we have described in the methods section.

- Histological response is a difficult topic to address in pulmonary CRC metastases, as the presence of necrosis and, to a lesser extent, fibrosis are features seen in metastatic colorectal carcinoma. However, the extent of these changes being up to 80% likely reflects partial response to chemotherapy prior to surgery in some cases.

- We have added to the results section more about the pathology and a sentence in the discussion about this.

- We are currently preparing a manuscript relating to evaluation of a histological tumour grading system looking in more detail at fibrosis and necrosis in a larger cohort however it is difficult, from current imaging modalities to know whether a pulmonary lesion is definitely malignant prior to neoadjuvant chemotherapy and in this situation if only scar tissue is found at surgery the histopathologist cannot reliably report as to whether there was prior tumour present, or the abnormality is simply a benign, fibrosed lesion.

Discretionary comments:
Background:
first paragraph: A reference with current targeted treatment e.g CRISTAL with an OSR@5years of about 10% might be added.
- We have elected to include survival figures in comparable groups to ours where possible but acknowledge that the survival in overall metastatic CRC is poor, despite the advent of targeted therapies.

Discussion:
fourth paragraph:
In regard of response rates you might add 66% for FOLFOXIRI and 64% from COIN KRAS wt population. References for CRISTAL/OPUS might be updated.
- The range of response rates have been altered to incorporate these studies. As we are quoting response rates, rather than survival we have kept the original papers for Crystal and Opus.

Reviewer 2
Background: I fully agree that DFI, number and size of lesion, CEA level or lymph node involvement are reported as negative factor in literature. Nevertheless the data available are very heterogeneous and there is a wide number of reports, that could not find any benefit in survival for these prognostic factors [see reference 3, Pfannschmidt J et al]. Please consider this.
- We agree and have now acknowledged this in a statement within paragraph 2 of the background.
Methods/results: Amongst others one selection criterion was “...complete resection of all deposits feasible...”. How many patients had progressive disease during chemotherapy and became unresectable? And in how many patients did you see a downsizing of the pulmonary lesions? Please discuss this.

- The authors agree that data on those who PD and cannot undergo resection would be invaluable. Unfortunately, the methods of selection we had to use (including any patient who had undergone a pulmonary resection, rather than any patient with pulmonary only mets who underwent chemotherapy) has not allowed us to collect data on those who were became unresectable- this is described in paragraph 1 of the methods section (page 5).

- With respect to downsizing-we have reported in our response rates in table 5, however, our cohort had no patients where a pulmonary metastasectomy was not planned prior to the chemotherapy (ie unresectable patients who were downsized by chemotherapy to the point of being operable) as we wanted to assess the role of truly ‘neoadjuvant’ chemotherapy. Again, we recognise this would be an interesting cohort to evaluate in future studies given the disease control rate we observed of 92%.

Results: In how many of the resected pulmonary lesions did you find vital tumour or just tumor necrosis? Please discuss this.

- We have amended the results section to further explain this and have clarified below.
- None of the malignant lesions had tumour necrosis only, in either group and only a minority had >75% necrosis. We looked only for ‘presence of viable tumour’ as stated in our methods and did not record additional features for this paper. We are currently preparing a manuscript focusing on evaluation of a scoring grade for pulmonary CRC metastases in these patients by examining the tissue again in a larger cohort for more features, including tumour necrosis.

Discussion: Having received neoadjuvant chemotherapy for the primary tumour and second line treatment for hepatic metastases, do you think it is useful to give chemotherapy to patients with lung metastases as a “third line” option? According to your data will you consider to generally recommend adjuvant chemotherapy after pulmonary metastasectomy from CRC?

- Patients with metastatic CRC and good performance status are routinely offered multiple lines of chemotherapy, especially now with targeted therapies being available and improving survival. There is no randomised evidence to support the use of multiple resections (hepatic, then lung) however, our data suggests that the morbidity and mortality are extremely low in this situation and while it is uncertain as to whether this is curative, we feel it is reasonable, in the scenario where patients have had perioperative/adjuvant treatment for their primary tumour, then second-line treatment associated with a potential liver resection to offer chemotherapy to patients with lung metastases third line chemotherapy providing they have previously had limited toxicities and a prior response to therapy.

- Based on this data, we continue to offer perioperative chemotherapy at our institution to those patients being considered for lung resection, especially in those patients with a disease-free interval of less than 2 years between diagnosis of primary tumour and presentation of lung metastases.

Appendix: Surgical approach. Every surgeon is familiar with the problem of intraoperative nodule detection. You detected on average 25 % more nodules by palpation than by CT scan. The question remains, how many of these nodules that were additionally detected by palpation were also malignant lesions and not only benign lesions discovered by accident?

- This is an important point and the data would be useful, however, we do not have the information in our cohort in order to answer this question with any degree of accuracy, even if compared to the CT scans as while the resection specimens are labelled according to their anatomical site (right or left, and lobe), it was not recorded as to whether they were palpated or identified preoperatively on the histological specimen or operative notes, hence we do not feel the data is robust enough to include in the manuscript as it would be entirely speculative. This is certainly an aspect our group are now considering exploring in a prospective fashion.

Various: An abbreviation list at the beginning of the manuscript might be useful
Thank you for this comment. We have ensured that every abbreviation is defined within the manuscript when first used and have used conventional abbreviations where possible.

Please accept our revised manuscript with the changes tracked.

Kind regards,

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