Author’s response to reviews

Title: Colorectal cancer liver metastases - a population-based study on incidence, management and survival

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Version: 1 Date: 11 Jun 2017

Author’s response to reviews:

Dear reviewers, Armin Wiegering and Stefan Loeb

Thank you for giving us the opportunity to benefit from the thoughtful comments made by you. The comments were all very helpful in strengthening the clarity of this article.

We have made major revisions according to the comments and are now resubmitting the manuscript “Colorectal cancer liver metastases – a population-based study on incidence, management and survival”.

We submit an annotated copy, named CRCLM 2008_R, with the track changes feature to identify all edits. We hope that our revised manuscript meets the high standards of BMC Cancer, and are looking forward to your response.

Yours sincerely,

Jennie Engstrand

M.D., Ph.D
Reviewer #1:

1) The result section has to be re-written as it is very confusing. Especially it is unclear when the liver metastasis occurred (syn vs, met.).

We acknowledge this severe limitation and have to our best re-written the result section. All changes are indicated in the annotated copy but to summarize the major changes made, we have to some extent altered the order of the text and added subheadings. We have also clarified whether the metastases were detected synchronously or metachronously.

We also removed some data on intrahepatic metastatic pattern among patients with less than 20 metastases measuring less than 30 mm as these results might be perceived as out of the context and most likely contribute to the feeling of confusion when reading the result section. Originally, we thought these results to be of interest as it gives the reader an idea of how many patients that potentially could be treated with thermal ablation as a method to extend resectability. But since the main focus is metastatic pattern and survival in right-sided versus left-sided and a discussion on ways to increase resection rate is not a topic of this manuscript, we choose to deleted that section (page 8, line 3).

Since we consider the results from supplementary table 1 important, we have included that table as a main table (Table 4) (page 9, line 8).

At the E-AHPBA Congress held 2 weeks ago, I presented some results from this manuscript and also some additional analyses made after this manuscript was submitted. The results, illustrated in Figure 5 and outlined in the text on page 11, line 15-20 (result section) and page 13, line 23 (discussion) were received with interest by the audience which is why I included it in the manuscript and hope you also consider it as a valuable contribution.

I also opted to add the following to the result section (page 9, line 2-4) and the corresponding discussion (page 13, line 21-25).
Patients with liver metastatic left-sided cancer were more often resected as compared to patients with liver metastatic right-sided cancer (30.8% versus 14.2%, p=0.005).

This was also true in the present study, where patients with liver metastatic right-sided cancer were resected for their liver metastases less often and had an intermediate survival as compared to patients resected for liver metastases from a left-sided cancer and patients not resected at all. However, tumour site was not significantly associated with the likelihood of undergoing a resection in the multivariate logistic regression analysis.

2) Also some sentence does not fit to the figures. e.g. "The 1- and 5-year survival of patients with liver metastases treated with resection, palliative chemotherapy or BSC were 92.8% and 48.6%, 58.1% and 2.2% and 8.2% and 0.0% respectively, counting from the date of diagnosis of liver metastases as outlined ..."

The text was re-written as we fully understand why the sentence is misinterpreted and we thank the reviewer for giving us a clear example of the ambiguity of the result section (page 11, line 6-9).

The 1- and 5-year survival of patients with liver metastases treated with resection was 92.8% and 48.6%, respectively. Patients treated with palliative chemotherapy had a 1- and 5-year survival of 58.1% and 2.2%, respectively, while patients receiving best supportive care (BSC) had a 1-year survival of 8.2% and no 5-year survivors (Figure 3).

3) Over all I recommend major revision

We sincerely hope that the above mentioned changes are considered as satisfying major revision
Reviewer #2:

1) The advantage of a nation-wide data registry on stage IV colorectal disease is the large number of patients being collected for scientific readouts. What is the reason for analysing only one year (2008?)

This is a very well made comment. The reason for only including colorectal cancer diagnosed during one year (2008) was that the primary aim, metastatic pattern, could not be answered by information from the register. The Swedish colorectal cancer register only provides data regarding the primary tumour. Any information on diagnosis of liver and extrahepatic metastases had to be collected by review of patient electronic records. Since the presence of metastases is documented as yes or no, we further had to review each image for each patient to count, measure and determine the number and segmental distribution for each patient. We could have used the Swedish inpatient care register to collect information on diagnosis (date and organ type) of metastatic disease but that would not have given us any information on the metastatic pattern (number, size etc.). Even though it is a poor excuse, the choice of one year was primarily for logistic reasons.

The reason for choosing a historic cohort (2008) was that the same cohort was used for another study, namely re-evaluating the resectability of liver metastases (accepted for publication in The Oncologist, Epub ahead of print: “The Impact of a Hepatobiliary Multidisciplinary Team Assessment in Patients with Colorectal Cancer Liver Metastases: A Population-Based Study”). For ethical reasons, re-evaluation of a more recent cohort could not be done.

2) Less than 50% of cases have been discussed in multidisciplinary liver teams. Do these patients better resp. worse in outcome or have been treated differently? (tumour-free, overall survival or chemotherapy protocols?) This is in my opinion one of the most important facts that could dramatically change preoperative work-up SOPs for patients with colorectal liver metastases.

Again we agree that managing patients with colorectal cancer liver metastases within a liver specific MDT is of outmost importance. The focus on this specific topic was deliberately left out of this manuscript since it’s the main objective of another study on that specific topic, as mentioned in the reply to your comment 1. As you can see in the Kaplan-Meier survival estimate below (please see the attached response letter to view the figure), and as an answer to your
question whether patients discussed at a liver MDT do better or worse, patients discussed at the liver MDT had a 3 yr OS of 47.3% vs 3.3% and a 5 yr OS 33.6% vs 0% and median survival 34.7 mo vs 5.7 mo (p<0.001). In our cancer network, no patients undergo liver resection or ablation if not discussed at a liver MDT, which explains the survival differences.

We regretfully can’t include this figure in the manuscript since a similar one is already in the accepted manuscript.

To clarify that liver resection was only possible for patients discussed at the liver MDT, we added the following (page 8, line 20-21): No patients treated outside of a liver MDT conference were subject to liver resection.

Additional changes

When carefully reading through the manuscript yet once again, we noticed the following errors that we would like to correct:

2. Replacement of > to ≥ in table 2, 3, 4, 5B.
3. Figure 4. Midgut ->right-sided cancer and hindgut->left-sided cancer

Once again, thank you for your valuable feedback.