Author's response to reviews

**Title:** The CAIRO4 study: The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer - a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG).

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**Author's response to reviews:** see over
To: Doctor Dafne Solera  
Executive Editor  
BMC Cancer

Dear Dr. Solera,

On behalf of the co-authors, we thank you for the positive comments from the reviewers on our paper: “The CAIRO4 study: the role of surgery of the primary tumour with few of absent symptoms in patients with synchronous unresectable metastases of colorectal cancer – a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG)”. We are pleased to resubmit a revised version of our manuscript.

We would like to draw your attention to the fact that we have, in the meantime, expanded the CAIRO4 study internationally. There are now 5 Danish hospitals participating in the CAIRO4 study. This has been added to the chapter on study population accordingly. As dr. Yilmaz, who is the principal investigator in Denmark, has contributed to the protocol as well, we would like to add her to the list of authors of this publication.

Below we have addressed each comment separately.

In response to the review of dr. Kim, dated May 13th:

1. “The authors should define “asymptomatic” disease more accurately. Who would decide whether the patient is asymptomatic or not, and based on what, such as physical examination, or history taking.”
   The decision on whether or not a patient requires immediate intervention is left to the discretion of the local treating physician.

2. “Who would decide resectability of extracolonic metastasis?”
   The decision of resectability is left to the discretion of the local tumorboard meeting. We have included this in the methods section.

3. “When to perform colonoscopy: before primary surgery or chemotherapy?”
   Performing a colonoscopy is not part of the inclusion criteria of the study and/or part of the study protocol. All patients in who colorectal cancer has been histologically proven, can be included in the study. The Dutch national guideline states that the preferred technique to diagnose a colorectal carcinoma is a colonoscopy, but inclusion in the study does not depend on this.

4. “In the sample size, drop rate may be considered.”
   The sample size is based on the number of events (deaths). There are 218 events needed to detect a difference of 13 versus 19 months. With a monthly accrual of 12 patients, a total of 180 patients per arm are needed. Follow-up of patients will be continued until at least the 218 events have occurred, and for a minimum of 8 months after the study. With this method, patients who drop out will be accounted for as well.
5. “In the statistical consideration, log rand is misspelled.”
   We have corrected this spelling mistake.

In response to the review of dr. Benoist, dated May 28th:

1. “The authors should give some details about unresectable metastases. Which type of metastases could be included: liver, lung, and peritoneal metastases? Furthermore the authors should clearly define the criteria of non-resectability for each type of metastases, and in particular for liver and lung metastases.”
   Resectability of metastases is left to the discretion of the local treating physician. We have added this to the Methods section. However, all Dutch hospitals have implemented the national guideline, which defines resectability of liver metastases as follows: after resection of all metastases at least 20% of the liver volume should remain in patients without prior systemic therapy and/or liver disease, and 50-60% in patients with chronic liver diseases. Resection of lung metastases is only done in rare occasions and is currently not included in the national guideline. However, if the treating physicians think that a long-term survival is possible after a resection of lung metastases, this should never be denied to the patient in favour of the study. We have also added a sentence stating that there are no exclusion criteria with regard to the side of metastases.

2. “Why should the chemotherapy regimen contain bevacizumab? What is the justification? In 2014, it is relevant to treat patients with WT RAS stage IV colorectal cancer, without EGFR antibodies? It would be more relevant to leave chemotherapy the discretion of the local investigator. I am sure that protocol would be amended concerning this point in future.”
   In the national guideline of The Netherlands the recommended first line treatment in metastatic colorectal cancer patients consists of a fluoropyrimidine containing schedule in combination with bevacizumab. For this study, we did not want to diver from this national guideline. If additional evidence will become available that will necessitate adaptation of the guideline, we will, of course, adapt the protocol of the CAIRO4 study accordingly. Furthermore, given the preliminary data from the CALGB 80405 study (ASCO 2014) there appears to be no difference between upfront treatment with bevacizumab or anti-EGFR in patients with KRAS wildtype tumours in terms of overall survival.

3. “This is probably not a good idea to mix patients with colon and rectal cancer. The problem is so different for quality of life, mortality and morbidity of primary cancer resection and tolerance of chemotherapy after resection.”
   We do agree with the reviewer that there is a substantial difference in both treatment and outcome of colon and rectum cancer. This is the reason that we have included location of the primary tumour (colon / rectum) to the stratification parameters, and only allow patients with rectal cancer with a clinical stage T1-3N0, extramural invasion ≤ 5 millimetres and a distance to the mesorectal fascia of more than 1 millimetre.

4. “In chapter entitled ‘study design’ the term unresectable must be added in the first sentence.”
   The term ‘unresectable’ has been added as requested.

In response to the review of dr. Poultsides, dated June 4th:

1. “Background, second to last paragraph, last sentence: ‘We have reviewed the available literature...’ This entire sentence should be erased. The available literature on this topic is afflicted by considerable selection bias, and this statement is premature. There is substantial
equipoise associated with the research question and the Authors’ attempt to answer it with a randomized trial is commendable.”
The sentence has been removed as requested by the reviewer.

2. “Methods/Design, Study Population, third paragraph: the distinction between which patients with rectal cancer will be included in the study and which will not is vague. The Authors state that “patients with rectal cancer that do not require radiation therapy” can participate in the study. How will this subgroup be defined? Tumours that are T2N0 or less by clinical staging (EUS and/or MRI)? Tumours located in the upper rectum? Furthermore, what circumstances do the Authors have in mind in which asymptomatic or minimally symptomatic patients with rectal cancer and unresectable metastases require radiation? This will indeed be a rare situation. The Authors need to decide a priori whether rectal cancer patients will be included in the study (defined by strict anatomic criteria, such as distance of the tumour from the anal verge by colonoscopy) and, if so, whether separate subset analyses will be performed a priori for colon and rectal cancer patients, respectively.”
We do agree with this reviewer that it is important to recognize the difference between colon and rectal cancers, and to clearly define patients that can be included in the study. For this also, we chose to follow the national Dutch guideline. According to this guideline, patients with cT1-3N0 rectal cancer with extramural invasion with a maximum of five millimetres and a distance to the mesorectal fascia of more than one millimetre do not require radiation therapy. We have added this to the revised document.

3. “Methods/Design, Interventions, Duration of treatment and follow-up, Second paragraph: “Patients will be evaluated every 9-10 weeks for response…” Will a CT scan be obtained every 9-10 weeks? Or will this be a clinical encounter to perform a history and physical, followed by a CT scan if positive findings are noted? This is important to clarify, as PFS is a significant study endpoint.”
All patients will be evaluated according to protocol with CT scanning every 9-10 weeks. This has been clarified in the above mentioned sentence in the revised document.

4. “Methods/Design, Study Objectives: The following secondary endpoints should be additionally recorded: 90-day (in addition to 30-day) postoperative mortality, the number of patients in the surgery arm who never receive chemotherapy, the number of patients in the control (upfront chemo) arm who require stenting or radiotherapy for symptom palliation down the road.”
We would like to thank the reviewer for this suggestion, as we agree that these secondary endpoints are important. We will include these endpoints in the next version of our protocol and we have added them to the revised document as well.

5. “Background, second to last paragraph, second to last sentence: “symptomology” is misspelled.”
The spelling mistake has been corrected in the revised document.

We have corrected this spelling mistake.

7. “Methods/Design, Study Population, first paragraph: The criteria for “unresectable distant metastases” should be defined further. Will a central review of initial cross-sectional imaging be performed by the team of the principal investigator or will resectability of metastatic disease be defined at a local level? How will resectable hepatic disease be defined? How will resectable extrahepatic disease be defined?”
As mentioned above (reviewer 1, question 1 and reviewer 2, question 1) resectability of metastases is left to the discretion of the local treating physician. This has been added to the revised document.

8. “Methods/Design, Study Objectives, second paragraph: It would be helpful to provide the specific methodology of the cost-benefit analysis.”

Although we have planned to perform a cost-benefit analysis, we will decide the specific methodology to estimate costs of treatment after completion of the study. This gives us the opportunity to choose the method that will best correspond with the data and clinical outcome of the study.

We would like to thank you again for taking our manuscript in consideration.

On behalf of the authors,

Sincerely,

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