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).

Version: 2
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Reviewer: Stephane Benoist

Reviewer's report:

The authors propose the design of a randomized phase III study in order to evaluate the benefit of initial resection of primary tumour in asymptomatic patients with synchronous unresectable metastatic colorectal cancer. This is an important question in clinical practice and there is consensus that only results from an ongoing high quality randomized controlled trial will help to answer this question. Overall this is a well written manuscript. A number of issues must be addressed.

Major comments

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,

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 mo relevant to leave chemotherapy the discretion of the local investigator. I am sure that protocol would be amended concerning this point in next future

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.

Minor comments

3) In chapter entitled “study design” the term unresectable must be added in the first sentence.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests