Reviewer’s report

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 Date: 4 June 2014

Reviewer: George A Poultsides

Reviewer’s report:

Major Compulsory Revisions:
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.

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? Tumors that are T2N0 or less by clinical staging (EUS and/or MRI)? Tumors 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 tumor 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.

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.

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.

Minor Essential Revisions:
5. Background, second to last paragraph, second to last sentence:
“symptomology” is misspelled.


Discretionary Revisions:

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?

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

Level of interest: An article whose findings are important to those with closely related research interests

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.