Reviewer 1:

Splenomegaly and thrombocytopenia are commonly attributed to vascular occlusion due to oxaliplatin. The cumulative dose of oxaliplatin in CAPOX w/o cetuximab was higher than that in FOLFOX w/o cetuximab. The dose intensity of oxaliplatin in CAPOX/FOLFOX was also higher than that in CAPOX/FOLFOX with cetuximab. It was difficult to accept this conclusion because there were significant biases.

Reviewer 2: Minor revision

The paper from Victor HF Lee and colleagues is aimed to evaluate the impact of chemotherapy (Capox or Folfox) with or without cetuximab as first line treatment for KRas wild type metastatic colorectal cancer on spleen size, platelet count and liver function.

It is known that oxaliplatin can cause hepatic sinusoidal obstruction and some papers have correlated this injury with increase morbidity and mortality after surgery for hepatic colorectal metastasis in patient treated with preoperative oxaliplatin based chemotherapy (Nakano et all, Ann Surg 2008; Vauthey JN et al, J Clin Oncol 2006).

As stated from the authors in the introduction, the increase in spleen size was recently proven to be a biomarker for such hepatic adverse event after oxaliplatin administration (Overman MJ et al, J Clin Oncol 2010). On the other hand, there are only limited data on the effect of Capox on the spleen size and its related complication as well as the protective effect of adding cetuximab to chemotherapy.

Therefore, the topic of this study could be of interest for Cancer Research Frontiers’ readers.

Certainly the authors know that the main limitation of this study is the small number of subjects. However, the overall manuscript is well written, the introduction provides a good, generalized background of the topic.

The manuscript can be suitable for publication in Cancer Research Frontiers after the following minor criticisms are addressed:

Minor Issues:
• Material and Methods_Patients and Study Design section: could you specify that an informed consent from patients has been obtained?

• Material and Methods_Volumetric Evaluation of Spleen Size section: the statement in fifth line is not clear. Could You explain better what you mean?

• Results_Univariable and Multivariable analysis section: Could you create a table for the results of univariate analysis described in the text?

• Results_Capox plus Cetuximab vs. Folfox4 plus Cetuximab section: What you describe as showed in Figure 2 does not correspond to the figure. Add appropriate figure or change the explanation of the figure in the text.

• Figure 1 a, b, c: add p value in the figure.

• No mention of the NRas status is provided in the text.

Reviewer 3: Major revision

The effect of the association of cetuximab with traditional chemotherapy in the treatment of colorectal cancer is known, as the authors admit. What they emphasize is the impact of CAPOX/FOLFOX with or without cetuximab on on spleen size, platelet count and liver function in patients with KRAS wild-type metastatic colorectal cancer. The work is well done. However, because the use of cetuximab with the chemotherapy regimen does not avoid the onset of adverse effects related to the chemotherapy itself and, in addition, cetuximab is a self-financed drug and not all the patients can afford to buy it, in my opinion the final aim of the manuscript is quite weak.

The following issues need to be tackled:

- the authors should indicate: whether the patients have undergone a biopsy in order to stage the colon cancer; whether the patients have undergone any kind of surgery to resect the tumoral mass or part of it, or if all of them received therapy without surgery.

- the text needs correction, also related to the English writing. I recommend a deep revision, concentrating on proofreading and editing.

Reviewer 4: Major revision

Overall: This is an interesting report regarding the effect of treatment with CAPOX/FOLFOX +/- Cetuximab on spleen size as front line therapy for metastatic CRC. The results are interesting
showing some association between use of capecitabine and higher rates of spleen enlargement, and with the use of cetuximab and lower rates of spleen enlargement. The main limitation of the study lies in the low numbers of patients. Furthermore, there are manuscripts raising questions regarding the clinical significance of this finding. Additional comments are listed below for each section of the manuscript.

1. Title: The title does not represent the actual data within this paper. The study did not assess the impact of these treatments on platelet count or liver function. The main outcome was evaluation of spleen size and its effect on the other measures.

2. Abstract:
   a. Major: The conclusions regarding cetuximab offering protection from splenic enlargement seems too strong for the data presented in the study.
   b. Minor: In the conclusions – the first sentence does not make sense: “CAPOX was associated with more splenic and …”

3. Introduction:
   a. Major:

   - The introduction seems too long with some redundant sections. This includes the section describing the COIN study which could be significantly shortened.

   - Would consider adding some data from the literature regarding the effect of splenic enlargement and why this would be a clinically relevant outcome to look at.

4. Materials and Methods:
   a. Major:

   - This section again appears too long, and could be shortened (for example, there is no need to describe how KRAS mutation analysis was performed; this has no importance for this study).

   - The authors describe a “baseline liver impairment score” it is not clear how this was determined, is there any validation of this marker in the literature?

   - Thrombocytopenia was defined as PLT<150K. It is not clear why the NCI-CTCAE grading method was not used. The CTCAE grade 1 definition for low PLT is <=75K. It is not clear what is the clinical significance of a thrombocytopenia of <=150K.

   - It appears that the change in the size of the spleen was evaluated using serial CTs. However the number of scans varied among patients. There is no timeline associated with the change in spleen size. It would be important to evaluate the change in all patients in a specific time point (like the first disease valuation scan). It is not clear from the text that that was done, and appears that the report is of overall change in spleen size among patients receiving various lengths of therapy.

   b. Minor:
- Are there any other studies that have used this method for evaluating the volume of the spleen. Would be helpful to add references to support the use of this method.

5. Results:

a. Major:

- Overall the section is somewhat confusing, would recommend re-organization of this section to discuss: patient’s characteristics and differences seen between the groups; the data regarding spleen enlargement; CAPOX vs FOLFOX; with/without Cetuximab; the effect of spleen enlargement on PLT and liver dysfunction; and uni/multivariate analysis. It seems that statements regarding these various factors are scattered randomly throughout the text with repetitions of various facts.

- Only 43 patients continued treatment beyond CT time point 1 – this means about 60% of the patients progressed after 12 weeks of FOLFOX/CAPOX in the front line mCRC setting – this number seems very low. It is clear that there were other factors that contributed to this drop, these should be discussed.

- In the uni/multivariate analysis – would separate the analysis of factors contributing to spleen enlargement to one paragraph and then factors contributing to PLT count/liver dysfunction to a separate paragraph.

b. Minor:

- Would add the actual numbers of each group of patients in the text.

- The sentence: “Median increase in spleen size… after treatment…” Not clear what does after treatment means… see previous comment regarding the timing of spleen size evaluation.

6. Discussion:

a. Major:

- The discussion is lacking discussion of major limitations of this study such as: sample size – which limits any definitive conclusions; the study design and the multiple factors that were out of the control of the investigators that affected treatment decisions; the issue of timing of spleen size evaluation;

- The authors discuss a difference noted between the groups with regards to oxaliplatin dose. This is an important point to discuss, however, the data shows that the group that got cetuximab had a lower dose intensity of oxaliplatin compared to their counterparts. Is it possible that this could explain the lower rate of splenic enlargement rather than the use of cetuximab?

- The discussion regarding the difference in number of liver metastases is confusing without any clear conclusions made. Given the very low numbers in each category it is unlikely that this factor will have a major influence over the results, and it would be impossible to stratify based on that.

b. Minor:
The sentence “Therefore, it was reasonable to speculate that capecitabine was the culprit for these splenic, platelet and hepatic sequelae”. Appears too strong, given the low numbers of patients, and the discrepancies noted between the groups. Furthermore, in the multivariate analysis capecitabine dose did not appear to affect PLT count as noted in table 3. The effect of capecitabine on liver function is known.

7. Tables/Figures:

a. Table 1:

- This table includes many factors that are not discussed in the text such as: median ccl; <=50ml/min; alcohol consumption, smoking, etc.), consider trimming down the table and making it less detailed.

- Not clear the difference between: liver only, liver and others, non-liver, and liver metastases.

- The section of number of liver metastases can be condensed to fewer categories.

- In the first part of the table add more text next to <50ml/min (GFR?)

b. Table 2: the line “increase in net spleen size” - not clear, is that number of pt. that had a net increase in spleen size?