Reviewer's report

Title: Different metastatic pattern according to the KRAS mutational status and site-specific discordance of KRAS status in patients with colorectal cancer

Version: 1 Date: 18 May 2012

Reviewer: Oliver Sieber

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Description of work:

Mi-Jung Kim and co-authors report a survey of the mutation status of KRAS codons, 12, 13 and 61 in 143 CRC patients with metastatic CRC. They demonstrate that both the frequency of KRAS mutation and the discordance between the mutation state of the primary and metastatic lesions is related to the site at which metastasis occurs.

The questions posed by the authors were well defined but their findings concerning the transition of cancers from pre-metastatic to a metastatic situation are biased by their selection of cancers for which primary and metastatic tissues were available. Interpretation is also complicated by using two different sources of tissues (resected vs. biopsied samples) to extract DNA, and not re-sequencing samples to confirm results. The authors discuss these deficiencies.

Despite these weaknesses the data appear relatively sound and provide useful information about the association of KRAS mutation status and sites of CRC metastasis.

One critical issue that the authors do not comment on is whether discordance between primary and metastasis relates to metastasis gaining further mutations and whether this differs depending on whether patients were stage IV at presentation or recurrent (See question 1).

The discussion and conclusions are well written and the authors reference previous work appropriately.

Finally, the writing is of good quality and acceptable. The title is well chosen but the abstract could do with rewording (see specific questions below)

Specific questions:

Major Compulsory Revision

1. Of the 12 and 13 KRAS MT cases that had discordant primary and metastasis mutation status, what proportion of each group were in the recurrent group vs the stage IV group. Or in other words, given that KRAS MT was generally associated with lung metastasis, was there a greater number of discordant cases showing a gain of mutation in lung metastases than the other way round? To answer this
question Table 3 should be stratified by whether cases were initially stage IV vs.
patients that recurred

Minor Essential Revisions

Abstract (pg3)
2. KRAS results are presented both for concordance and discordance between
lung metastases and primaries. Perhaps this repetition could be avoided.
3. The conclusion of abstract has a grammatical error with the use of
“concordance”.

Background
4. Well written except for the end of second to last paragraph that could be
slightly re-worded

Methods
5. Re-sequencing of mutations was not performed for confirmation – this should
be considered.
6. Should the word “individual” in line three of stats section be plural?

Results
7. Did not mention the Gly13Cys mutation in the text i.e. numbers of mutations in
text add up to 74 instead of 75 as presented in table 2
8. The section that uses a series of square brackets inside normal brackets is
confusing (pg10, para 2)

Discussion
9. Difference in discordance from biopsy DNA analyses vs. resected sample
DNA analysis is worry (mentioned at top of pg 15). Can the authors provide
further evidence that this did not affect the conclusions?

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
published

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