Reviewer’s report

Title: Impact of Primary Colorectal Cancer Location on the KRAS Status and its Prognostic Value

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Reviewer: Matthew Burge

Reviewer's report:

This paper analyses the prognostic impact of KRAS status by tumour location.

Unfortunately, I find that there are flaws in this paper which need to be addressed.

Specifically:

- Introduction: Authors should detail what is defined by a right and left sided colon cancer. How were transverse colon cancers classified? It's not clear why they also divided the left colon and rectum and compared these 2 entities

  A discussion/reference to RAS mutations outside codons 12 and 13 should take place. Why were these patients excluded? What might their impact on the results be?

Methods: A more detailed description of this study is needed. Was it prospective? Why was there no survival data?

  More detail is needed regarding the types of studies included in the meta-analysis. Were they prospective or retrospective? randomised? An important paper on this topic comes from the QUASAR study:11) Hutchins et al DOI: 10.1200/JCO.2010.30.1366 Journal of Clinical Oncology 29, no. 10 (April 1 2011) 1261-1270. Not cited but it should be.

  The statistical section is inadequate. Was a multivariate analysis performed to take into account confounding prognostic factors? How many patients were included in the meta-analysis of the prognostic impact of KRAS? The study population includes all stages of colorectal cancer hence is very heterogeneous and I can't see how any definitive conclusions can be drawn based on the data presented. The effect size of KRAS appears modest. What were the endpoints? 'Survival time' is inadequate. Overall survival; disease free survival?

  There needs to be justification for the inclusion/exclusion criteria. Why were patients receiving pre-operative chemotherapy/radiotherapy excluded? The target population for this study is not well described
Results: The figures are somewhat confusing and need better explanation. In addition figures 3 and 4 appear to be the wrong way around.

Discussion: I do not agree with the concluding statement that this studies data indicate the crucial importance of categorising CRC by primary side and KRAS status. This is important in metastatic colorectal cancer, but this is already well established. The utility of these same factors in early stage CRC is less.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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