Reviewer’s report

Title: Association between ERCC1 and TS expression levels and disease free survival in colorectal cancer patients in response to oxaliplatin and fluorouracil (5-FU) adjuvant chemotherapy

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Reviewer: Ashwin Ananthakrishnan

Reviewer’s report:

Li et al. examined the association between expression of ERCC1 and TS in influencing survival after oxaliplatin / 5-FU adjuvant therapy in patients with colorectal cancer.

Pharmacogenomics and prediction of treatment response is an important area for clinical practice and research. The authors present a well done study but there are several major limitations which need to be addressed.

Major concerns:

1. Please check your citations carefully. Several of the ones provided appear inappropriate (for example – citation 1 refers to a paper on renal cell cancer, while citation 2 deals only with metastatic colon cancer and is not reflective of the overall survival. The leading statement – colorectal cancer is highly aggressive is also something of an overstatement as outcomes depend on the stage and early stage colon cancer has excellent outcomes.

2. The manuscript would benefit from closer attention to language and grammar. Several sentences are inappropriately constructed – for example, Page 3, end of first paragraph – “There is ,however, no predictive factor of response….” is poorly constructed and erroneous in structure and grammar.

3. A total of 112 patients were included in the present study. Please describe the total patient population with CRC being seen / who underwent surgery during the same time period. What is the generalizability of this cohort? Is the sample representative?

4. Was any power calculation performed a priori? How was the necessary cohort size estimated?

5. Patients were eligible for inclusion if they had stage II or stage III cancer. Yet the results state that tumor metastasis was identified in forty patients – please clarify.

6. Under the different chemotherapy regimens – please rephrase the ‘normal intravenous injection’ to specifically refer to the combination described in the methods. The term ‘normal intravenous injection” is not appropriate. Please do not use phrases like chemo 1, chemo 2, etc. – it would be preferred to refer to the chemotherapy regimen itself.

7. How was TS and ERCC1 expression level quantified? As a continuous
variable? Prior studies have utilized thresholds which may be biologically relevant in classifying patients as high or low expression. Did you attempt this analysis and were signals identified there suggesting a possible threshold effect?

8. Please use standard terminology – Page 7 – what is tubinva, nervinva?

9. It is not clear at all how variables were modeled in the univariate or multivariate analysis and what the reference groups are. For example, stage – what does the hazard ratio represent? Stage III vs. stage II? How about duration? Dose of chemotherapy? Text on page 7 refers to it as univariate analysis while the title of the table is listed as multivariate analysis.

10. A big limitation of this manuscript is the small number of patients within each chemotherapy regimen category. This substantially limits the power to identify an association between TS or ERCC1 expression and DFS.

11. In their discussion – the authors stage that because of HR of 0.818 for TS expression – it may still be predictive of response to chemotherapy. This is not an appropriate claim to make for non-statistically significant results. The univariate p-values are actually close to 1.0 suggesting no effect at all. The discussion should be focused on why they did not identify an effect while previous studies in GI or Gyn cancers may have identified an effect.

Minor points:

1. The title should preferably be free of abbreviations as well. Consider revising so it is appropriate.

2. There is some literature of ERCC1 and response to cisplatin in ovarian cancers. Consider included that in the introduction.

3. In the results, please quantify quality of mRNA in preserved specimens, and if any purification was needed.

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

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.

Declaration of competing interests:

I declare that I have no competing interests