Author's response to reviews

Title: Predictors of Recurrence Free Survival for Patients with Stage II and III Colon Cancer

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Author's response to reviews: see over
April 7, 2014

To Whom it May Concern:

We want to thank the reviewers for their comments. We have addressed the comments line by line. We appreciate their feedback in order to make the document more readable.

Sincerely,

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Reviewer's Report

Title: Predictors of Recurrence Free Survival for Patients with Stage II and III Colon Cancer

Date: 25 December 2013

Reviewer: Craig C Lynch

Reviewer's report:
The authors present a large historical series of stage II and III colon cancer, and have been unable to demonstrate clinicopathological predictors of recurrence.

Major Revisions
Of note, while the authors have obviously strived to maintain as large a cohort as possible, I think this is unhelpful to the data presented:
1. Recurrence is reported as occurring in patients at a range of 6 days to 10 years following surgery. I would question how recurrence can be classified as occurring 6 days after surgery, similarly at 10 years is this not more likely to be a second primary? Given the historical nature of the data, I think those with very short (probably unavailable) follow-up data would be best excluded

This has been addressed. Please review Methods and Results section.

I can make no judgment as to how patients were followed up, how recurrence was identified, or more importantly, excluded. This basic data is obviously important for a predictive model. A description of the follow-up protocol would be useful.

This has been addressed.

2. Mean follow-up of 6 years is stated, but were patients under active surveillance for this long, or does this mean that there was no reported recurrence over this time?

This has been addressed.
3. Recurrence itself is not adequately described; metastatic, nodal, anastomotic, either or any.  

**Addressed**

4. It would be useful to know more about why 30% of stage III patients did not have adjuvant chemotherapy. Also, as this usually occurs 6-8 weeks after surgery, I don't understand how patients can be included who have been followed up for a shorter time than this.

**We agree with reviewer’s thoughtful comment. We have included only patients that show recurrence after the 6-month visit. Patients that were reported with recurrence before that timeframe had underappreciated metastatic disease.**

5. Applying your predictive model to a ‘cleaner’ data set with documented followup for at least 3-4 years would be of more utility.

**This has been addressed.**

We do have long term follow-up on our patients because our site is part of the sites of the National Cancer Database. Each individual is followed closely and events (recurrences) are all reported.

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**Reviewer’s Report**

**Title:** Predictors of Recurrence Free Survival for Patients with Stage II and III Colon Cancer

**Date:** 27 December 2013

**Reviewer:** Dara Kavanagh

**Reviewer’s report:**

1. Is the question posed by the authors well defined?  
The question is very relevant and challenges with regard to recurrence after colon cancer surgery.

2. Are the methods appropriate and well described?  
There is a very detailed description of the statistical methods used but the following clinical aspects need to be outlined

Yes. However, the authors should define more clearly what they mean exactly by a recurrence, local vs regional vs distant. How do they follow patients after colon cancer surgery. What is the interval for endoscopic follow-up and imaging bearing in mind the authors omit CEA staging from the follow-up.

**This has been addressed in the Methods section**

Do the authors have a strict rule whereby all patients operated upon in the 2 centers are followed up at that center for the outlined follow-up period or do patients at remote sites have their surveillance done elsewhere and then provide copies of their surveillance for the databases at the authors institutions. Please expand on this process.

**This has been addressed in the Methods section**
The authors outline that the standardised treatment delivered at the institutions ensures minimisation of heterogeneity in treatment. I fully agree with the authors regarding the benefit of this. Do the authors have a dedicated Multidisciplinary team meeting encompassing the clinician, surgeon, radiotherapist, medical oncologist, radiologist & pathologist which can ensure standardised treatment according to national practice parameters.

This has been addressed in the Methods section.

Were there any changes in chemotherapy treatments over the study period (1995-2013) which could account for differences in recurrences?

The population studied has received 5FU based treatment. Recurrences were adjusted to chemotherapy received.

3. Are the data sound?
Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes.

There are a number of unreferenced statements. I would suggest to the authors that they start the discussion by restating the findings of the study.

This has been addressed. First paragraph of discussion is restatement of the results.

6. Are limitations of the work clearly stated?
Yes. In fact the authors have over-emphasised the negative aspect of CEA. They include a reference form 1990 which alludes to an absence of cost effectiveness in utilising CEA. This can be omitted.

Kievit ref omitted.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

8. Do the title and abstract accurately convey what has been found?
The conclusion of the abstract is a little disappointing and does not really leave a clear message. The conclusion of the main manuscript is well written. Are the authors referring to their provided data or the published literature with the abstract conclusion: ‘Current information is inadequate…….?'

Addressed. Conclusion from original abstract re-entered.

9. Is the writing acceptable?
Overall, the manuscript is well written with very high numbers studied and an acceptable duration of follow-up to capture disease recurrences. The introduction is succinct, well written and outlines the established predictive markers of recurrence in a detailed manner.

Page 8 – there is a difference in lymph node yield between 1995-2001 and 2002 and 2007. Why do the authors think this has occurred? Have the pathologist changed their means of detecting lymph nodes or has the surgery become more radical?

Addressed on page 14

Why is there a significant difference in the differentiation of the tumor in the 2 study periods? Has the interpretation of this pathological entity changed or why do the authors account for this significant change?

We can only speculate that the study of the pathologic specimens has improved over time to explain the differences we see in the study periods. We cannot suggest this, however, from our study results.

Page 10 – paragraph 2, 3rd line – suggest “Most recurrences occurred in the first 2.1 years after surgery.” The only prognostic factor identified was the T Stage”

Addressed.

Page 11. Is there a reference for the SEER data? The authors refer to other studies further down in the same paragraph, yet there is only a single reference.

Addressed. The reviewer is correct. It is a single reference.

Second paragraph.
Line 4. Suggest rewriting as “These findings differ from other studies demonstrating that certain.....”

Addressed.

Last line ‘no event for patients with well differentiated tumors’ please explain this statement.

Addressed.

Page 12 – line 2 – local, regional or distant recurrence.

Addressed.

Furthermore, a c-index of 0.56 indicates that we are just over a coin toss in predicting...Please rewrite this sentence

Addressed.

Page 13 – second last line of first paragraph – change T N to TNM
Addressed.

‘A limitation of our....’ rather than ‘A limitation in our..’

Addressed.

Please adhere to the instruction for authors as outlined for writing references. See example below.
Article within a journal supplement
In press article

Addressed.