Reviewer’s report

Title: Advantages of a multi-state approach in surgical research: How intermediate events and risk factor profile affect the prognosis of a patient with locally advanced rectal cancer.

Version: 0 Date: 06 Jan 2017

Reviewer: Andrew Titman

Reviewer's report:

The paper presents a multi-state model re-analysis of data on survival of patients with locally advanced rectal cancer, starting from time of commencement of chemotherapy. The aim of the paper is to highlight the benefits of using multi-state models rather than standard survival techniques, particularly in relation to demonstrating the benefits for dynamic prediction. Multi-state models clearly are useful for better describing the overall process of survival for rectal cancer patients, therefore the paper makes a useful contribution.

I think the results of the analysis are mathematically valid, my only substantial question is over the choice of the state definitions, particularly in relation to duration of chemotherapy.

Main Comments

- A six state model is assumed. However, three of the states correspond to CTx, with the first relating to less than 6 months on CTx, the second to 6-12 months and the third to completion of 12 months CTx. While it may make sense to assume that the transition intensities to other states will be different in these three states, I don't think it makes sense to model them as separate states. It certainly doesn't make sense to present them as separate states in the stacked plots in Figure 2. The massive drops at 6 and 12 months are due to all patients on CTx at that point switching state in a deterministic way. The correct way to incorporate these effects would be by having a single CTx state and a deterministic time dependent covariate which switches at 6 months and 12 months if the patient is still in that state and which interacts with covariates for the transition intensities out of this state. Discontinuation of CTx, if to be considered random, should be a separate state (or states referring to time of discontinuation).

- Only around 60% of the original dataset is included, due presumably to incomplete recording of duration/timing of chemotherapy. What impact does this have on the validity of the results, i.e. is there any evidence that the data for other subjects in not missing completely at random?
Minor comments/corrections

- Would it be better to call the patients "low risk" and "high risk" rather than "poor risk" and "good risk"?

- p4 l5: allows to adjust the prediction -> allows adjustment to the prediction

- p4 l17: because they allow updating the prognosis of the patient -> because they allow the prognosis of the patient to be updated

- p4 l20: the begin of chemotherapy -> the commencement of chemotherapy

- p5 l2: Aim of this study -> The aim of this study

- p5 l12: Following baseline covariates were considered -> The following baseline covariates were considered

- p5 l4: date of begin -> date of commencement

- Caption for Figure 3a/b: state 0 or 1 -> state 1 or 2.

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

Yes

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

Yes

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

Yes

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:

Needs some language corrections before being published

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