Reviewer’s report

Title: Delay factors in the diagnosis and treatment of symptomatic colorectal cancer

Version: 2 Date: 25 November 2012

Reviewer: Rosemary Tate

Reviewer’s report:

The paper has been very much improved w.r.t. the univariate analyses. However, there has been little change in reporting of the multivariate survival analysis, which was my main concern.

I suggest that the section on survival analysis is removed since the model seems inappropriate and may lead to incorrect conclusions. Also, it does not add very much to the final conclusions. I wonder if it was added as an afterthought since this was originally described as a descriptive study?

If the authors choose to follow my advice and remove the section on survival analysis, then most revisions are very minor. Otherwise major revision is required.

This has been quite difficult and time-consuming to re-review as most of the responses do not show where (or if) changes were made in the text. I have therefore had to hunt around for them. I also found some new changes that were not in the original document, and were not mentioned in the response. In future I would ask the authors to indicate where all changes are made with page and para numbers as is usual for a response.

Detailed comments – I have annotated the relevant sections of my original review and the response with my new comments in capitals

Major revisions:

4. For the Cox model, were the assumptions of proportionality tested and if so what was the result? This needs to be reported. (Alternatively a Poisson model may be more appropriate)

We have changed a little bit the explanation of survival analysis. Including results of proportional test would be long and we thing would not give essential information.

YOU NEED TO SAY WHETHER OR NOT THE PH ASSUMPTIONS WERE MET AS IF THEY WEREN’T THIS MODEL IS NOT VALID.

A multivariate Cox proportional hazard model with time-dependent covariates were performed to allow covariates change their values over time. For example a
patients has a value of hemogram zero until the time the hemogram is done, and 1 after that moment.

IF THE MULTIVARIABLE MODEL IS TO BE INCLUDED, A MUCH MORE THOROUGH REPORTING OF IT IS REQUIRED, BOTH IN THE METHODS AND THE RESULTS. THERE IS VERY LITTLE MENTION OF THESE RESULTS IN THE CONCLUSIONS, SO FOR SIMPLICITY, I SUGGEST IT IS BETTER TO DROP THIS PART ALTOGETHER.

I REMAIN UNCONVINCED OF THE APPROPRIATENESS OF A TIME-DEPENDENT COX MODEL, SINCE MOST OF THE “TIME-DEPENDENT” VARIABLES ARE PART OF THE DIAGNOSIS PROCEDURE. HOWEVER, IF THEY ARE INCLUDED AS TIME-DEPENDENT, THE METHODS TO DO SO AND RESULTS OF HOW THIS TIME RELATES TO THE OUTCOMES NEEDS TO BE EXPLAINED IN MUCH GREATER DETAIL.


THANK-YOU FOR POINTING ME TO THIS (EXCELLENT) ARTICLE BY FISHER AND LIN. CONTRARY TO SUGGESTING THAT THIS METHOD IS APPROPRIATE, THEY WARN AGAINST IT AND, INDEED, EXPRESS MY CONCERNS VERY ELOQUENTLY. PARTICULARLY IN THIS SENTENCE IN THE SECTION ON INTERPRETATION

“IN GENERAL IF TIME-DEPENDENT COVARIATES CAN CHANGE IN RELATION TO HEALTH OR SOME OTHER GENERAL CONCEPT RELATED TO THE ENDPOINT IN THE MODEL, THEN INTERPRETATION IS DIFFICULT AND PRONE TO BE MISLEADING. GREAT CAUTION IS ADVISABLE.”

7. The result that family history of cancer is positively associated with delay seems surprising and counter-intuitive. This result needs checking and further investigation. I note that 45% of patients reported this family history of cancer, which seems rather high – although again this variable is not described, so I can only assume it must relate to non-immediate family and all types of cancer (including very common benign skin cancers?)

There were all type of cancers (not benign skin cancer) we concretely asked for parents, children, spouse, brothers or sisters, any other family member and friends. There are few studies on delay and family history of cancer but when looking to breast cancer screening, some studies show women more reluctant to participate in screening if there is previous familiar or quittances with cancer because fear of some cancer findings is higher.

IN THIS CASE IT IS NOT FAMILY HISTORY THAT YOU ARE LOOKING AT, BUT EXPOSURE TO SOMEONE CLOSE WHO HAS CANCER. PLEASE MAKE THIS CLEAR AS THIS IS SOMETHING QUITE DIFFERENT. ALSO, HAVE YOU CONSIDERED THAT THIS VARIABLE WILL BE RELATED TO AGE, SINCE THE LIKELIHOOD OF THIS HAPPENING WILL INCREASE WITH AGE, AND IN FACT MOST OLDER PEOPLE WILL BE BOUND TO HAVE HAD THIS EXPERIENCE?
8. The results of the Cox regression are very unclear and I’m not really sure why these are included as so little is said about the results. This is the first time symptom duration has been mentioned – presumably you mean symptom diagnosis interval?

We have included some changes in the results of Cox regression to better clarify and eliminated symptom duration.

After multivariate analysis, factors independently associated with a longer SDI and STI in CRC patients were: female gender, not visiting the doctor when he/she felt the first symptoms, the number of GP visits for CRC symptoms before referral, the absence of CRC suspicion in the GP referral letter and not performing the investigations prescribed by hospital doctors. Abdominal occlusion is related to a shorter treatment time interval but not with diagnosis interval (Table 6)"

PLEASE SEE ABOVE THESE CHANGES ARE NOT ENOUGH.

“While there is substantial literature on time duration to cancer diagnosis or treatment, most of it is very old”

THIS IS NOT TRUE, THERE IS SUBSTANTIAL RECENT LITERATURE ON THIS – I MYSELF HAVE WRITTEN TWO RECENT PAPERS, ALSO NEAL ET AL AND MANY OTHERS THAT ARE CITED IN THIS PAPER. PLEASE CHANGE.

Minor revisions
p<0.02 should be changed to actual p-value unless p<0.001
1rst should be changed to first or 1st throughout
In the tables the unit of time should be stated (days)

References 13. The title of ref 53 is incorrect. It should be: Determining the date of diagnosis – is it a simple matter? The impact of different approaches to dating diagnosis on estimates of delayed care for ovarian cancer in UK primary care.

Changed
I SEE YOU HAVE REMOVED THE ABOVE REFERENCE – DID YOU MEAN TO?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests