Author's response to reviews

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

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Author's response to reviews: see over
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Dear editor,

We are pleased to send you the manuscript. ‘Delay factors in the diagnosis and treatment of symptomatic colorectal cancer’ for new consideration after inclusion of referees suggestions. Find enclosed bellow the answers to referees comments. As suggested by reviews we have changed some references and added new ones. We also added an additional table 1.

We are looking forward your answer,

Your sincerely,

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Answers to referee 1

Major compulsory revisions:

Further clarification is needed regarding:

- why was this study done? As they demonstrate there is a considerable body of literature covering this topic - much of it old and poorly conducted.

We tried to better explain why this study was done in the last paragraphs of background

- It would be useful to frame this study in the theoretical frameworks that underpin the literature on time to diagnosis eg. Andersen et al and Walters et al

In the introduction we have included a paragraph about theoretical frameworks, also in the methods we have included a mention of reducing Walkers model entities. Pg1

- Recently, some authors have been trying to move away from the use of the term ‘delay’ which in common English use has a pejorative tone to it. It is therefore unpopular with patients as it implies that they took a deliberate decision to not seek help, which is often not the case.

We agree with you that in spite of very commonly used in the literature, the term delay may result very pejorative for both patients and doctors. We have substituted the term delay for other terms in most of the manuscript. The term delay was left in very few occasions.

- Methods: how was patient pathway data obtained if interviews were not conducted? Did the authors obtain consent to access these data?

When interview was not conducted because patient has died or was unable to answer, and family members could be contacted, we asked permission to the most closed family member for patient inclusion (It was already written in the previous manuscript). In this case we did not have variables from the patient interview but do we have date of onset of the first symptom recorded in primary care clinical records. In this cases, this was the date of the first symptom considered to calculate time intervals (as mentioned in the methods section in the previous manuscript). We have done small changes in order to improve understanding.

- Discussion: This could be a lot shorter. In particular it needs to be clearer about:

It has been shortened
What this study is adding to the literature on this topic, in particular to the systematic literature review conducted by Mitchell et al. I would suggest they only cite high quality literature.

This study was already cited in the previous manuscript.

What associations they have found that may be spurious. For example, confidence in GP and reduced delay – but patients have been interviewed after diagnosis and other work (Browne et al) demonstrates that a long process to diagnosis results in less confidence in the GP. Also, intestinal obstruction and reduced time to diagnosis – diagnosis has to be made within hours, or the patient dies.

We are not convinced that both examples are spurious association. About first example we have done some comments in the discussion section (strengths and limitations) and added references. In the second example however, the association of reduced delay by intestinal obstruction is clear, could be confounded by indication but in our opinion is not a spurious association.

What are the implications of this paper for research and practice?

DONE at the final of the manuscript

REFERENCES


OK


THIS REFERENCE WAS ALREADY INCLUDED IN THE FIRST MANUSCRIPT (REFERENCE 9)


OK
Responses to Reviewer: Peter Murchie

Major Compulsory Revisions
I have very few major concerns.

1. I would like to see a section in the discussion explicitly discussing the current results in the context of international literature.

DONE

2. Could the authors make a comment on why they did not explore rurality, and any views on what this might add if the issue were explored in Spain.

Primary care in Spain organized on geographical accessibility with one health care center by every 10000-15000 inhabitants and with a health center in every population. Each Health Center has a reference Hospital located in about a distance of half an hour from each village. Only Galicia Region is very rural. Zaragoza about 80% of the population lives in the main city. High accessibility to health care has been demonstrated in several studies run in Spain.

We have not included rurality in our work. This is an item not very much explored in studies on this subject. Observed results are contradictory, Robertson et al. Br J Cancer 2004;90,1479-85 not found differences in time to treatment by rural or urban Areas in Great Britain. Robinson et al. Eur J Cancer Clin Oncol 1986;22; did found quicker treatment in those living in URBAN areas.

3. I would like to see a fuller explanation of the use of "non-classical" survival analysis - i.e. what is the justification for not censoring data - within the methods section.

The term “Censored” means that some units of observation are observed for variable length of time but do not experience the event (or endpoint) under study. In this study all patient have experienced the event, because all patient have been diagnosed, and treated (palliative treatment was also considered a treatment).

4. Could the authors please justify the exclusion of tumors diagnosed in private hospitals - I don't understand the rationale for this.

In Spain, some few patients who have been diagnosed of cancer in private hospitals would be treated in public hospitals because private insurance do not pay chemotherapy medication.
We excluded patients diagnosed in private because recruitment of incident cases and access to private clinical records for research from a public agency is extremely difficult.

Minor Essential Revisions.
1. The authors seem to fluctuate between family physician and general practitioner throughout the manuscript. Could they be consistent please?

DONE

2. Page 8 - there is a typo "U-Mann Whitney" should be "Mann Whitney-U."

DONE

3. Page 11 - there is a typo in the second sentence of the second paragraph "general practitioner" should be "general practitioners"

DONE

4. Could the authors define "abdominal occlusion." Is this abdominal obstruction if so that would be the more usual term.

DONE

Discretionary revisions
1. The discussion is lengthy - I wonder if it could be pared back somewhat

It has been shortened

2. My preference is for structured discussions - i) main findings; ii) context with other international literature, iii) strengths and limitations, iv) conclusions, implications and recommendations. Might the authors consider this?

We tried to structure discussion within your recommendations

3. Could the authors refer to general practitioners (GPs) in the abstract - not use family physicians - and then use the abbreviation GP throughout the manuscript. This would help readability.

DONE

3. I suspect some other reviewers or readers may expect reference to, and some limited discussion in context of, the recently published Aarhus statement. This is not a major concern for me, but something the authors might consider to make the paper as current as possible.

A comment has been introduced in the strengths and limitations paragraph
Answers to Reviewer: Rosemary Tate

Reviewer's report:
An interesting paper investigating the factors associated with delay in treatment of colorectal cancer.
This paper needs major revision. The results are important and should be published, but in order to justify the conclusions much more detail is needed about both the measures and the (multivariate) methods. All suggestions are for compulsory or minor essential revisions.

General comments on the statistical analysis
The descriptive statistics (i.e. medians IQR's) seem fine, although the section in the abstract needs rewriting to specify the measures and to detail the (descriptive) methods used.

It is not clear how the measures based on the medical records were extracted (from codes, free text?) or how counts of symptoms were constructed.

The section explaining the multivariate regression is very unclear and needs further explanation.

Also unclear is exactly what is being tested in the Cox regression model.

What questions were being asked for this part of the analysis and why are the events classified as time-dependent since many of them (e.g MRI, CT scan) are part of the diagnosis process which (presumably) occur at the end of the SDI?

The statement “introduced as time-dependent covariates, which allowed consideration of the time at which these occurred” needs to be clarified and also detailed much more in the results section.

Normally with survival analysis the assumptions are tested before committing to a method. Here Cox regression was chosen before the data was obtained, and no results are given for the tests of proportionality.

More detailed comments

Abstract
1. This needs considerable revision
Methods: The measures need to be described more clearly detailing which is the outcome and which are the covariates Cox analysis (and measures for it) should all be described in the methods section.
We have changed it

The phrase “median symptom diagnosis interval” does not really make sense unless SDI is first defined in the methods section
Main paper

Methods

2. This is not a descriptive study as it involves statistical modeling and analysis. It is a cross-sectional study where patient interviews as combined with data from patient notes. More detail is needed on how the primary care measurements were extracted. Was this coded data or free text notes? Were the dates of symptom presentation and diagnosis validated – if so how and if not, can you cite refs that check this? This is important – as explained in ref 53?

   - We changed descriptive by cross-sectional in the abstract and methods section
   - Data in clinical records was text notes
   - We already have not validated date of symptom presentation in primary care and hospital care. But at the moment, we are working in a paper to compare differences in diagnosis interval when using our different data sources to establish symptom onset date (patient, primary care and patient).
   - As expressed in the previous manuscript date of diagnosis was recorded from histology reports (1st positive cancer finding from colonoscopy or surgery) from hospital. This was not obtained from GPs records nor from patient.

3. I note that in the original proposal for this work you planned to compare patient-reported and GP-reported symptoms? Although you cite other authors who have done this, there is no mention of this here? This should be reported.

   This is a broad study with different objectives as can be assessed in the protocol publication. We are planning to publish concordance between the different 3 sources in a next paper. We have done a short comment in the discussion.

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. 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. We consider this model fits well with this type of variables as suggested by Lloyd D, et al. Time-dependent covariates in the Cox proportional-hazards regression model. Ann Rev Public Health 1999;20:145-57.

We thank the suggestion of using a Poisson model is a good alternative to analyze Time-to-event data with time dependant covariate. Both approach are different and we think yield to similar results.

We test the PH assumption, variables which PH cannot be assumed include all intrinsic time-dependent covariates (covariates that changes overtime).

5. Many different types of variables are mentioned, but little detail of how some these were obtained, and/or aggregated, is provided in either this paper or the protocol paper. Some variables e.g. number of visits number of symptoms are only mentioned in the results but are not defined in the Methods. Some have different names in different tables e.g. "Referral mention of CRC" in table 4 is renamed as “CRC suspicion in referral letter” in table 6. (I assume these refer to the same thing, or is this a new variable introduced for the Cox regression?)

Is the same variable, we have unified the terms about the variable.

Much more detail (and consistency) is needed. Some of this detail could be given in an appendix if appropriate.

A new table with more details about variables has been included in an appendix

Results

6. The (bivariate) tables are well presented, although some variables that are shown in Table 6 seem to be missing – e.g. abdominal occlusion, CRC suspicion why is this? Please include, together with the numbers involved.

We apologize but it was a term confusion, abdominal occlusion is abdominal obstruction and Referral mention of CRC is CRC suspicion in referral letter

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?) - another measure that needs more detailed explanation.
There were all types 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.

See appendix table for variable definitions.

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)“

9. In Table 6, all the p-values should be given (NS is not sufficient – do you mean N/A (not applicable)? If so explain why this is so. It is not possible to have a p value of <0.000

We changed <0.000 for <0.001 and eliminated NS, and p values given

Statistical Analysis

10. Please explain what you mean by “In order to avoid outliers”?

In order to avoid symptoms that could not be related to CCR , no more than a 24-month interval between symptom and diagnosis was accepted.

11. The sentence “Most of our patients have to wait median of 4 months” doesn’t make sense and is incorrect. By definition, half the patients have a value greater or equal to the median. The correct statement is “half (or 50% of) the patients have to wait at least 4 months”.

Changed by

After experiencing first CRC symptoms, half of the patients have to wait at least 4 months until diagnosis
Conclusions

Although these conclusions may be correct, I cannot have confidence in them until the measures are better explained and explanation of the analysis is improved.

12. I do not understand this sentence “These findings reinforce the premise that prior experience with cancer in relatives or friends results in longer symptom duration [38]” This ref is from 1988 are there no more recent ones? This result seems quite implausible.

We agree that this sentence is not clear. We have not found recent references of family history of colorectal cancer and diagnosis delay. Also Mitchel et al review only mention this family history of cancer variable in the study of Ratcliffe et al.
Since there is not international comparisons and the discussion is lengthy we eliminated this sentence from the discussion.

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.

While this paper briefly mentions non-recording of symptoms this is not what it is about – please find another ref for this. You may like to cite another of our papers that does show that symptoms often go uncoded and are recorded in the free text