Author's response to reviews

Title: Survival endpoints in colorectal cancer. The effect of second primary other cancer on disease free survival.

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

We are grateful to have the opportunity to resubmit our manuscript to BMC Cancer. We have revised our manuscript according to the excellent advices of the reviewers. For only a few comments we have not made any changes and we have explained why. We do think that this revision has improved the manuscript and we hope that you will now find the manuscript acceptable for publication.

Below you will find our response to the comments of the reviewers. In the manuscript we have highlighted the appropriate changes. Some additional changes motivated by us are also explained and changes made by our reviewer in scientific English can be seen using 'tracked changes'. Please observe changes in the reference numbers due to addition of references as will be mentioned in our answers.

With best regards

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Reviewer: Cornelis Punt

Reviewer's report:
This concerns a paper with data on the effect of endpoint definition in colorectal cancer. The study confirms earlier data that the use of different definitions of endpoints impacts the
outcome of survival, although it has not yet been as clearly demonstrated for second primary cancers. These data are highly relevant for the design of clinical trials and therefore for clinical practice. The number of patients is rather small, however the observed effect was statistically significant. It is confusing that the way in which data (numbers) are presented in the abstract differs from the results section.

Answer:
Good point, in the main text we only referred to the figures and now we have added to p 10 line19-22 the text from the abstract representing the same numbers as in the figures: “DFS for patients with stage I-III disease was 62% after five years if second primary other cancer was not included as an event, compared with 58% if second primary other cancer was included (Figure 2a). However, the difference was larger for stage II (68 vs 60%) than for stage III (49 vs 47%)(Figure 2b).”

The higher number of second primary colorectal cancers in stage II CRC is most likely due to hereditary cancer, however actual data on this are not shown. probably the numbers are too small to show a statistically significant difference. This may be commented upon.

Answer:
Indeed we are focusing on second primary other cancers and only 4 cases of second primary CRC were diagnosed in this cohort as is shown in Table 2. These cases are not included in the calculations. Probably the reviewer is referring to second primary other cancers.

It is unlikely that the higher number of second primary other cancer in stage II can solely be explained by hereditary cancer as the proportion of stage II and III with known first degree relatives with CRC was 10% for both. For better clarity we have added numbers during comparisons of second primary other cancers and heredity for stage II and III (last sentence in results p 11 line 7-11):

“For 283 patients information on heredity was available. No differences were seen between stages in the proportion of patients with first degree relatives with CRC, numbering for stage II 12 (10%) out of 122 and for stage III 9 (10%) out of 91. No differences were seen in the age at diagnosis for patients with and without second primary other cancer.”
Moreover to better clarify if we are discussing second primary other cancer, second primary CRC or both we have added “other” in the Results p 10 line 9; “primary other” in p10 line 12; “primary” p10 line 18; “other” p 11 line 4; and in the Discussion “other” p 13 line 4; “other” p 13 line 13 and “other” p 14 line 9.

To discussion p12 line20-23 we have added: ” This indicates that the second other cancers are likely not therapy-induced. The reason for the greater effect of second primary other cancer on DFS survival in stage II is therefore largely explained by fewer events from other endpoints such as distant metastasis and death from CRC.”

Reviewer : Simone Mathoulin-Pelissier
Reviewer's report:
1. Is the question posed by the authors well defined?
Partly
1.1 Context and definitions of survival endpoints are described; however, an explanation for focusing on second primary other cancer is missing.

Answer:
We have added a sentence in the Introduction p5 line 6-9: “Research on how DFS is affected by the inclusion or exclusion of second primary other cancers as an endpoint in DFS calculations is lacking. Therefore this study was initiated using a population-based cohort with well-documented follow-up data including information on second primary other cancers.”

Moreover the sentence “to understand the effect…” is very short to be understood the meaning of “the effect”. Finally, in the result section, we discovered additional results: multivariate analyses, other endpoints (all according to the paper of Punt).
Answer:
We have changed the sentence to (p5 line 10-12): “The aim was to compare different survival endpoints in patients with primary CRC according to the work by Punt et al [4] (Table 1) and to better understand the relevance of inclusion or exclusion of second primary other cancers as an endpoint in the DFS calculations.”
1.2 The question of survival endpoints is important in cancer trials and this study is an observational study: I think that these particular settings (endpoint and survival definition in observational studies) should be developed

Answer:
Please see our previously added sentence in the introduction p5 line 8-9: “Therefore this study was initiated using a population-based cohort with well-documented follow-up data including information on second primary other cancers.”

Major Compulsory Revisions
1.3 Many sentences in introduction section were unclear; please give more explanations
“meta-analyses are not reliable”: with individual data?

Answer:
We have added to the Introduction p4 line 8-9: “…when studies with different endpoint definitions are being compared”

“Selection of survival endpoints depends on the study question and the information available”

Answer:
We have added to the Introduction p4 line 19-24:” It is important to predefined the endpoints that should be collected during the study design phase since prospectively sampled information is more reliable and complete than information sampled retrospectively. Second primary other cancer is probably more often thought of as a late adverse effect or a competing risk than as a part of a survival endpoint. It can therefore be forgotten in treatment trials when the treatment is not thought to induce second primary other cancers and may not be available for the survival calculations.”

Minor
2. Are the methods appropriate and well described?
Partly
2.1 The methods section should describe where/how the data were abstracted.
We have no information about the whole-population sample related to the data source of “these population based study” (cf. abstract): cancer register or only XX hospitals or both

Answer:
We have added to Patients and methods p6 line 4-11:” The patients were identified through the Regional Cancer Registry which forms the regional report to the Swedish Cancer Registry, to which the reporting is mandated by law and which has a high completeness [7, 8]. It is estimated that more than 99% of all incident colorectal cancers in the county are included in the cohort. The majority of the patients were treated at the Central District Hospital in Västerås. During the time-period for this study patients undergoing surgery for CRC were invited to donate tumour tissue and blood for future studies (n=322) [9]. Information on family history was prospectively collected from 318 patients [10]. “

and we cannot understand the role of “Clinical database for colorectal cancer”.
We have added a reference (nr. 11) in p6 line15, which is electronic source finding information about the Quality registers in Sweden including the one in colorectal cancer:

http://www.kvalitetsregister.se/om_kvalitetsregister/quality_registries

More details about data information collected (and presented in the results and table 3)

Answer:
We have added for better clarity in p6 line 15-16: “…at the Departments of Surgery, Oncology and Pathology at the hospital in Västerås.” Hopefully this together with previously added information is now sufficiently detailed.

and the modality to evaluate quality of data (particularly on survival endpoints) are necessary.

Answer:
Regarding the quality of the present data, survival endpoints were mainly collected from the hospital and pathology records. The hospital records are of high standard and very few
patients in this age group migrate out of Sweden as we show in table 2 with only one patient lost to follow-up. The clinical database is regularly updated against the Regional Cancer Registry, so the survival endpoints collected should be complete.

We have added to Patients and methods p6 line4-7: “The patients were identified through the Regional Cancer Registry which forms the regional report to the Swedish Cancer Registry, to which the reporting is mandated by law and which has a high completeness [7, 8].” and p6line17-23 “Treatment-related death and date of death were available for both colon and rectal cancer patients, but information on locoregional recurrence and distant metastases was available only for rectal cancer patients. This information was double-checked during retrieval of data from hospital records. Other survival endpoints not available in the clinical database were retrieved from hospital records. If patients had moved from the county of Västmanland to another part of Sweden copies of their hospital records were obtained from their local hospital. One patient was lost to follow-up due to emigration.

Major Compulsory Revisions

2.2. The “statistical method” section defined the events and censure according to Punt paper; we have one table (table 1, table 1 is also present in introduction section) and the text. The text is not in accordance with the table (for instance: DFS without distant metastasis? does the term “recurrence” means? (locoregional and distant) ; it necessary to explain it and the different terms using on the table and in the text are confusing. Moreover, censure mentioned in the text is different according to some items (no censure for DFS but for other survival endpoints?)

Answer:
This is partly true. We have now exactly followed the nomenclature of table 1 and added to Statistical methods p7 line13-14: “All observations were censored at loss to follow-up and at the end of the study period (April 15 2010). “ We have removed “at the end of the study period” were it was written later in this paragraph.
We have added in p7 line15-16: “…locoregional recurrences, distant metastases and second primary cancer were ignored.” In p7 line17 “locoregional” and “, distant metastases”. In p7
line 20: we have added”; locoregional recurrences, distant metastases and second primary cancer were ignored.” In p7 line 23 “...and second primary cancer was ignored”. P7 line 25: “...; second primary cancer was ignored”. P7 line25 and P8 line 1-3: “Time to treatment failure (TTF) was measured from the date of surgery to the date of second cancer, locoregional recurrence, distant metastases or death from cancer and treatment-related death; patients were censored at non-cancer related death.”

Minor
2.3 We discover a Cox model without explanation related to an objective in this study.

Answer:
The Cox model was one of the statistical methods used to understand the changes caused by the inclusion and exclusion of second primary other cancers as an endpoint in DFS calculations. We have added to p8 line12-14: “Multivariate analyses were used to explore the magnitude of differences in DFS with and without second primary other cancer as a survival endpoint.”

Minor
2.4 On page 7 last paragraph: the first sentence should moved in the method section (with and without second primary other cancers)

Answer:
Unfortunately we could not understand this comment. No changes made.

Minor
3. Are the data sound?
3.1 The lack of information on population representativeness, data abstraction methods, and record completeness is a weakness.

Answer:
We hope that our previously made additions to the Methods have solved this.

Major Compulsory Revisions
3.2 Moreover we have results without any explanation in the methods section (multivariate analysis for instance)

Answer:
We have as described above added to p8 line12-14: “Multivariate analyses were used to explore the magnitude of differences in DFS with and without second primary other cancer as a survival endpoint.”

Minor
3.3 On page 6, the authors state that they “compare the survival curves of different endpoints”: Why? How? Please explain in method section.
I have the same concern about the analysis by stages: Why? How?
Finally, could you explain why you used all survival endpoints (and survival curves) in these figures related to you main objective?

Answer:
We hope that the aims now described in more detail answer this; we want to compare all survival curves to better understand the relation of different survival curves in the same cohort. We have added to Statistical method p8 line7-8 “Survival curves for all endpoints were plotted to better understand where endpoints stood in relation to one another in this cohort.”

Major Compulsory Revisions
3.4 In the first paragraph of the discussion section, the authors state that the effect of inclusion (or not) of second primary other cancers have an effect on multivariate analyses (“significant changes in the HR for emergency operation”) without any explanation to understand these result.

Answer
This is a consequence of that the multivariate analysis was done by means of Cox models, which also is based on counting events over a specific time period of follow up accounting for censoring – i.e. the same basic information also used in survival analysis. The reviewer correctly points out that we should clarify that this effect pertains to a Cox model. In this study the most pronounced effect was for emergency operation. The reviewer is also right
that this specific effect should not be unduly stressed since it may pertain to other co-
variates in other studies and we have changed the sentence in Discussion p12 line 12-14 to:
“The inclusion of second primary other cancer as an event in DFS did also influence the
results of multivariate Cox models, in our example causing significant changes in the HR for
emergency operation.”

Minor
We have no elements for the study limits in the discussion section.

Answer:
We have added in the Discussion p14 line 19-25 and p15 line 1-3:” The present study is a
population-based observational study, with some of the endpoints retrospectively collected.
This results in an older population with a broader range of stage at diagnosis and less
reliable information on disease recurrence, secondary cancers and causes of death than an
adjuvant treatment trial. Yet a population-based cohort, as in the present study, has the
advantage of limited patient selection, frequently being very large in clinical trials (Soerby et
al, Cancer 2008). However, our study setting represents a real life situation and a population
that would be the recruitment base for clinical studies. Furthermore, the proportion of
patients with second other cancers is, in colorectal cancer, largely independent of age and
disease stage. Therefore we could expect an at least similar effect of second primary other
cancers on DFS survival calculations in an adjuvant treatment trial compared with the
present study. “

Major Compulsory Revisions
4. Does the manuscript adhere to the relevant standards for reporting and data
deposition?
These items are not mentioned in the manuscript.

Answer:
We have followed the checklist of STROBE and believe that we have fulfilled all of its
recommendations. We have added a sentence to methods p7 line 8-9 and added reference nr.
12:” The guidelines for observational studies in epidemiology (STROBE) were followed
during the preparation of the manuscript.”
We have also added “cohort” to patients methods p6 line2 to make the association to a cohort study more clear.

The discussion section, as it currently stands, gives the reader no sense that this research contributes to the literature about what has already been done. There is a need to better clarifying the author’s contribution with this study.

Answer:
We have added p 15 line 4-9:” It is debatable whether second primary other cancer should be regarded as a primary endpoint or as an adverse effect and therefore not included as an event in the main analysis of DFS. To increase clarity Punt recommends that if second primary other cancers are ignored as an event, the survival endpoint should be named RFS. Choice of survival endpoints is an important topic and, to the best of our knowledge, this is the first study to address the use of second primary other cancers in DFS calculations in CRC.”

Minor
6. Are limitations of the work clearly stated?
The authors don't describe any limitations as such

Answer:
Please see our answer above in 3.3 on study limits

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

Answer:
Please see our previously added sentence and references 9 and 10 in Patients and methods, p6 lines 8-11:” The majority of the patients were treated at the Central District Hospital in Västerås. During the time-period for this study patients undergoing surgery for CRC were invited to donate tumour tissue and blood for future studies (n=322) [9]. Information on family history was prospectively collected from 318 patients [10].”
The authors could track the literature about “observational studies and endpoints definition” and “about prognostic factors for CRC with curative intention” (particularly to more understand their results with DFS endpoint)

Discretionary

Answer:
We have thoroughly searched the literature without finding more research on this topic. No changes made.

8. Do the title and abstract accurately convey what has been found?
No.
The abstract results should better describe the population and mains results
The title and the abstract conclusion do not reflect fully the purpose and results of this paper

Answer:
We do think that the title well describes what the study is about, no changes made.

We have made some changes to the abstract: p2 line 9 we have changed:” were used for the analyses” to “was analysed”. We have added p2line 9-11:” Events such as locoregional recurrence, distant metastases, second primary cancers, death, cause of death and loss to follow-up was recorded.” And line 11-12: “..., including DFS, overall survival, cancer-specific survival, relapse-free survival, time to treatment failure and time to recurrence,...” and line 16-19:” DFS was the survival endpoint with most events (n=170) followed by overall survival (n=144) and relapse-free survival (n=139). Fewer events were seen for time to treatment failure (n=80), time to recurrence (n=68) and cancer-specific survival (n=59).” We do believe that the abstract conclusion is in concordance with the title. No changes made.

Minor

9. Is the writing acceptable?
There could be more lively writing of the discussion, which is rather opaque at present.
Please see our previously made changes and we have added to discussion p12 line 21-23:
“The reason for the greater effect of second primary other cancer on DFS survival in stage II
is therefore largely explained by fewer events from other endpoints such as distant
metastasis and death from CRC.“

Reviewer: Amy Downing

Reviewer's report:
Major compulsory revisions
This is an interesting article but I find it difficult to follow in some parts and feel
that the results need to be presented in a clearer way. There is a lot of discussion
around the shape of the curves for figure 1; it would be better to simplify this and
focus on the main, clear differences (it is difficult to know if some of the described
differences are actually significant).

Answer:
We have shortened the sentence in results p 9 line 21: “Similar observation was seen with
the curves for RFS and OS with more events at start for RFS that with time merge with the
OS curve (Fig. 1a).” to “Similar observations were seen with RFS and OS (Fig. 1a).”

The background information also needs to be made clearer. It would help to give some
examples of survival endpoints and how they can differ.

Answer:
Please see our earlier made additions to the Background.

The aims should also be more explicit about the survival endpoints included in the study.

Answer:
We hope that our previous changes of the aims are sufficient. P5 line 10-12.
In the discussion, the authors pick out 2 studies and focus on their endpoint definitions - why these studies? It would be interesting to see a comparison of, say 10, recent studies and the differences amongst them.

Answer:
The purpose of taking one good and one bad example from the literature was to stress the importance of having good definitions of survival endpoints. We would like to refer to Punt et al who makes comparisons of 52 studies in this regard.

Minor essential revisions
Background, paragraph 4: Clarify the statements 'DFS offers earlier presentation of data. Besides, there are more events in DFS than OS.'

Answer:
We have added to the Background p5 line1-2:”…, as events due to disease recurrence by nature occur earlier than death from the disease.” And p5 line 3-4:”…, as events, such as disease recurrence, and second primary other cancers that do not necessarily lead to death are included in DFS but not in OS”

Statistical methods, paragraph 1: TTF is included in Table 1 but not mentioned in the study. Why was this comparison not included?

Answer:
Originally we thought that this study did not fit for this comparison, however all endpoints used in TTF are available so we have added this to the manuscript and figure 1 and table 2. Please see changes in abstract p 2 line 12and 18. Statistical methods p7 line 25 and p 8 lines 1-3: “Time to treatment failure (TTF) was measured from the date of surgery to the date of second cancer, locoregional recurrence, distant metastases or death from cancer and treatment-related death; patients were censored at non-cancer related death.” P8 line 4 “.., TTF..”.. See also additions in Figure 1 a-d and Table 2

Same paragraph: 'CSS was measured from the date of surgery to the date of death in CRC’ - should be 'from CRC'
Answer:
We have replaced “death in CRC” to “death from CRC in abstract p2 line 16 and in statistical methods p7 line 19 and line 22

Results, paragraph 1: Add %s to the descriptive figures

Answer:
Changes have been made, please see results p9 line 4-7.

During these calculations we observed that 15 patients and not 11 had unknown disease stage. This has been corrected in the Results p9 line 6

Discussion: Paragraphs 2 & 3 are related and should be combined.

Answer:
Discussion p 12, paragraph 1 is now line 3-10, paragraph 2 line 12-23.

Discussion, paragraph 5: The sentence beginning ‘ A recent publication has been suggested that...’ does not make sense and should be clarified.

Answer:
Clarification has been made by adding to discussion p13 line 19: “...and comparable with six and seven year OS,...” and “even” has been deleted. The sentence now reads: ” A recent publication has suggested that three year DFS is superior to five year OS and comparable with six and seven year OS, since extended survival due to more effective cancer treatments after disease recurrence is frequently seen [19]”

Figures: Is it possible to reorder the endpoint labels to follow the lines on the graphs (e.g. follow Fig 1a - so that the order would be CSS, TTR...) This may help when trying to follow the differences described in the results.

Answer:
We have done this for Fig 1 a-d.
Figure 2 could be omitted and just described in a sentence or 2 - there are a lot of figures to make sense of and I'm not sure this one is necessary.

We agree and fig 2 has been deleted and to results p 10 line 11 we have added “..of patients without..” and to line13-15:” The cumulative proportion, with standard error, of patients without second primary other cancer after 3 years were 92.5±2.5 for stage II and 98.2±1.2 for stage III and after 5 years these figures were 87.5±2.9 for stage II and 92.9±2.9 for stage III.”

We have changed Figure3a to 2a and Figure 3b to 2b in p10 line 21 and 22. And in Figure 3 is now Figure 2 please see Figure 2.

Discretionary revisions
The abstract does not mention any of the differences between the endpoints, it only focuses on the second primary cancers.

Answer:
That’s true, we have added a sentence to the Abstract p2 line 16-19: “DFS was the survival endpoint with most events (n=170) followed by overall survival (n=144) and relapse-free survival (n=139), fewer events were seen for time to treatment failure (80), time to recurrence (n=68) and cancer-specific survival (n=59).”

**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

Answer:
Changes made by our reviewer in scientific English can be seen using 'tracked changes'.

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