Author’s response to reviews

Title: Impact of comorbidities and use of common medications on cancer and non-cancer specific survival in esophageal carcinoma

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Author’s response to reviews: see over
Ms. Cherry Battad                                         December 24, 2014.
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RE: MS: 1243825290147828

Title: Impact of comorbidities and use of common medications on cancer and non-cancer specific survival in esophageal carcinoma

Dear Editor,

Thank you for reviewing the above-referenced manuscript submitted earlier to your office. We would like to take this chance to express our appreciation to you and colleagues. And we are also very appreciated of the reviewers’ time and effort.

In accord with the Reviewers’ comments and suggestions, the manuscript has been revised accordingly. All the comments have been carefully addressed. All changes have been highlighted with red ink. A point-by-point response has also been prepared and follows this cover letter.

If there are any questions or problems for our re-submission, please feel free to contact me.

Sincerely yours,

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Response to comments of the Editor

The authors collected a lot of data, congratulations to them! However, the results and the interpretation of the results are not so convincing, particularly the multiple testing is not accurately considered in the statistical consideration and the conclusion of the authors. I do agree with the general recommendation of both reviewers.

We think both the editor and reviewers were mostly concerned about the factors that have been integrated in our multivariate analysis.

Actually, we did have put the patients’ general characteristics and treatment factors in univariate analysis as we wrote in the footnote of Table 2. In addition of comorbidities and drugs, age, sex, race, BMI, heavy alcohol use history, smoke at diagnosis, second malignancy, Karnofsky performance scores, tumor histology, tumor location, tumor differentiation, clinical stage, induction chemotherapy, radiation modality and their interactions with surgery were all had been tested in univariable analysis. (See the footnote of Table 2 in page 23 of the revised manuscript).

We have added this description in the ‘Results” section in our revised manuscript (See the 8th to 14th line of page 9 in the revised manuscript), and revised the footnote a little bit to make it clearer. (See the footnote of Table 2 in page 23 of the revised manuscript)

The above variables with either potentially significant main effect or the interaction term \( P<0.10 \) were selected in the multivariable mode.

We have presented the variables that we integrated in multivariable analysis in the footnote of Table 3. In addition of comorbidities and drugs, the interactions of age, race, tumor histology and tumor location with surgery, BMI, smoking at diagnosis, Karnofsky performance scores, tumor location, clinical stage, radiation modality and surgery were also included for the analysis of overall survival; the interactions of race, age, tumor histology and tumor location with surgery, sex, race, age, smoking at diagnosis, tumor histology, tumor length, tumor differentiation, clinical stage, radiation modality and surgery were also included for the analysis of EC-specific death free survival; the interactions of tumor histology and tumor location with surgery, age, Karnofsky performance scores, tumor histology, induction chemotherapy, radiation modality and surgery were also included for the analysis of non-EC specific death free survival. (See the footnote of Table 3 in page 24 of the revised manuscript)

Because of the space limitation, we can’t present all these data in our table. But we will be happy to provide any data if both the editor and reviewers feel necessary.
Response to comments of the Reviewers

Reviewer #1: Wolfgang Eisterer

1. Since in univariate analysis (table 4) there is a strong inverse correlation of smoke at diagnosis and levothyroxine use how does smoke at diagnosis affect OS and ECspec-OS?

Actually, besides comorbidities and medications, we have listed all the other factors that affect OS, EC-specific survival and non-EC specific survival in univariate analysis in the footnote of Table 3, respectively (Please see the footnote of Table 3 in page 24 of the revised manuscript). As the reviewer is interested in the impact value of “smoke at diagnosis”, here we show it in more detail.

In univariate analysis, “smoke at diagnosis” was found to be a significant impact factor on OS (HR=1.26(1.01,1.57)) and a marginal impact factor on EC-specific survival (HR=1.27(0.97,1.66)). However, in multivariate analysis, “smoke at diagnosis” didn’t turn out to be an independent impact factor on OS (HR=1.20(0.97,1.50)) or EC-specific survival (HR=1.17(0.92,1.50)).

Due to the space limitation, we only listed “smoke at diagnosis” as an impact factor in univariate analysis in the footnote of Table 3 (Please see the footnote of Table 3 in page 24 of the revised manuscript) without presenting the detail data in the table.

2. Correlation of AF and Hypothyroidism? (missing in table 4)

There is no significant correlation of AF and Hypothyroidism (P=0.65), we have added this data in revised Table 5 (See the Table 5 in page 27 of the revised manuscript).

3. Did heavy alcohol use at diagnosis affect OS and ECspec-OS?

In univariate analysis, heavy alcohol use at diagnosis was not a significant impact factor on OS (1.18(0.96,1.46)) or EC-specific survival (1.23(0.95,1.59)). Due to the space limitation, we didn’t present these results in the table.

4. How many patients did receive systemic therapy in case of progressive disease during follow-up? was the proportion of later systemic therapy balanced between pts. with levothyroxine use and non-use, since this may affect the outcomes?

There are 170 patients received systemic therapy after progression during follow-up. The proportion of later systemic therapy was balanced between patients with (158/1072, 14.7%) and without levothyroxine use (12/102, 11.8%) (P=0.47). We have added this data in revised Table 5 (See the Table 5 in page 27 of the revised manuscript).
Reviewer #2: Peter C Thuss-Patience

1. p3 line 7 (minor) change consecutively to retrospectively, because consecutively implies a prospective analysis in my understanding, which is not the case.

   The reviewer is right. We have changed “consecutively” to “retrospectively”. Thanks for the good suggestion! (See the 7th line of page 3 in the revised manuscript)

2. P3 line 9 (major) what does it mean “interaction with surgery” please describe later in the text more clearly and exactly which interactions were tested in a multivariate analysis and which not. What is about possible interactions with BMI, ECOG, chemo, time of procedure (1998 versus 2012), age. If you do not test for them please discuss.

   It is a matter of statistical analysis method. The statistical analysis was done by a statistician (Wei Qiao) from Biostatistics Department of our institution. In this way, we can test the impact value of all the potential factors on survival in one cohort while taking the influence of “surgery” into consideration, instead of dividing our patients into two cohorts by receiving surgery or not.

   We have described it in the last paragraph of the “Methods” section, “since receipt of surgery has been recognized as a major prognostic factor for loco-regional EC, the interaction term of each prognostic factor and surgery is included for each variable in the univariable analysis”. Let’s take one of the variables “age” as an example, in our method, we took “age”, “surgery” and “the interaction of age and surgery” all in the univariate analysis.

   Actually, we did test all the variables (as we listed in the footnote of Table 2: comorbidities, drugs, age, sex, race, BMI, heavy alcohol use history, smoke at diagnosis, second malignancy, Karnofsky performance scores, tumor histology, tumor location, tumor differentiation, clinical stage, induction chemotherapy, radiation modality) and their interactions with surgery in univariate analysis. (See the footnote of Table 2 in page 23 of the revised manuscript)

   And the above variables with either potentially significant main effect or the interaction term (P<0.10) were selected in the multivariable mode, which has also been described in the footnote of Table 3. (See the footnote of Table 3 in page 24 of the revised manuscript)

3. (major) One major concern is the following: Hypothyroidism and L-thyroxine:The 1st question is, whether you can really identify hypothyroidism by L-thyroxine use. Many patients might take L-tyhroxine not because of hypothyroidism but because of a benign euthyroid struma. The 2nd big questionmark is that hypothyroidism which is treated with L-thyroxine is no hypothyroidism any more. The patients are euthryroid when they are properly replaced with the hormone. This is very important and puts a big
questionmark over the results. 3rd point is that even if you change the whole correlations from “hypothyroidism” simply to the “use of L-thyroxine” (which would be correct in my view,) L-thyroxine cannot be considered like a normal “drug” like Aspirin or metformine because it is an endogenous hormone which is replaced.

It is true that many patients might take L-thyroxine not because of hypothyroidism but because of a benign euthyroid struma. However, we did not identify hypothyroidism by L-thyroxine use but by the record of past medical history. So, we are sure they had hypothyroidism disease before the anti-cancer treatment. We have added this description in the revised manuscript to make it clearer (See the 14th line of page 6 in the revised manuscript).

Even the total T3 and T4 might be normal after the use of levothyroxine, an elevated serum TSH was still called “subclinical hypothyroidism” according to the guidelines of the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). On the other hand, we took hypothyroidism as a disease not only as a condition, which is just like hypertension. Patients with hypertension will have a normal blood pressure after they take anti-hypertensive drugs, but they are still the patients with a hypertension disease. We think hypothyroidism disease is the same.

The fact is that all the patients had a pre-existing hypothyroidism record in our cohort all regularly took levothyroxine at the same time of receiving anti-cancer therapy. We can’t exclude the influence of levothyroxine on EC prognosis in our study as we mentioned in the discussion section of our manuscript (See the 15th to 18th line of page 13 in the revised manuscript). So we took hypothyroidism/levothyroxine as one variable in our analysis (See the 10th to 11th line of page 7 in the revised manuscript).

4. P3 line 13, 16 (minor): If a HR is described it is not clear whether the factor improves or worsens survival, please write HR for death or for survival

The Reviewer is right. We have revised to make it clear that HR is for death (See the 15th line of page 8 in the revised manuscript).

5. P5 line 2 (major) the distinction between medication and disease is unclear

We mentioned in the “Background” section that the impact value of some comorbid diseases (e.g. diabetes, atrial fibrillation) and some medications (e.g. metformin, statins) on therapy response and/or survival have been reported in patients with esophageal carcinoma. But the relative impact that comorbid disease has on prognosis as compared to the use of certain medications is not well understood.

In our study, we focused on common chronic comorbid diseases, such as hypertension, cardiovascular disease, chronic obstructive pulmonary disease and some metabolic diseases. And for medication, we took regularly-taken and frequently used medications
into analysis.

6. P5 line 15 (minor) You say that staging was done according AJCC 2002. How was stage of disease decided in the patients treated from 1998 to 2002?

It is true that the staging for all patients was done according to AJCC 2002. For patients treated from 1998 to 2002, we did re-staging depending on the detail medical record. In order to make it clear, we revised that sentence into “Staging and restaging was done according to the 6th (2002) edition of the American Joint Committee on Cancer (AJCC) staging manual for esophageal carcinoma.” (See the 22nd line of page 5 in the revised manuscript)

7. P6 line 1 (minor) Do you have information about the kind of operations performed, did all patients receive an esophagectomy?

Yes, we have the information about the kind of operations performed. Not all the patients received an esophagectomy. Totally, we have 1174 patients, 560 cases received surgery after chemoradiotherapy, while the other 614 received chemoradiotherapy but without surgery. For the 560 patients who had surgery, 517 cases received esophagectomy, 37 cases received transhiatal esophagectomy, the other 6 patients received total or subtotal gastrectomy.

8. P6 line 1 (major) Were patients with GE junction carcinoma included. Did they receive a transhiatal extended gastrectomy? This is a factor which may also effect the results.

We did include some patients with distal esophageal carcinoma and GE junction carcinoma. For them, an esophagectomy and a transhiatal extended gastrectomy were performed.

9. P7 line 8-9 (major) “since all patients....” I my view you cannot conclude from the use of L-thyroxine to hypothyroidism (see above)

We did not identify hypothyroidism by L-thyroxine use but by the record of past medical history. It is a similar question with question No. 3, please also see the answer above.

10. P8 line 5 (major) again, which variables are selected for multivariate analysis, please clarify

All the variables that we tested in univariate analysis with either potentially significant main effect or the interaction term (P<0.10) were selected in the multivariable mode. It is a similar question with question No. 2, please see the detail answer above.

11. P9 line 22 onwards (major): Was a multivariate analysis performed for all these
factors (stage, gender, smoking etc). As I understand it was not done, because the number of patients with hypothyroidism is probably too small. Please clarify and discuss

We did have done a multivariate analysis for all these factors (stage, gender, smoking etc). It is a similar question with question No. 2, please see the detail answer above.

12. P10 line 8 (major): As mentioned above, you cannot say “comorbidity hypothyroidism” because the patients were euthyroid.

It is a similar question with question No. 3, please see the answer above for question No. 3.

13. P10 line 16 (major): Which AF was counted as AF: persistent, inter mittend, actual AF at the time of admission or just a history of AF? It would be interesting to know, how many patients with a history of AF were properly treated in terms of either aspirin or anticoagulant use.

As we mentioned above, we took the comorbid information from the past medical record, and all the comorbidities were pre-existing, so all the patients with AF were certainly had a history of AF. And some of them still had an intermittent AF at the time of admission.

The Reviewer is right, many patients with AF in our study were treated with aspirin, but only a few of them used anticoagulant which number was too small to be analyzed. Anyway, AF was an independent impact factor on OS in multivariate analysis after adjusting other factors, including the use of aspirin.

14. P10 line 16 (major): I wonder whether AF was really the reason for a poorer OS or just a surrogate parameter for obesity, coronary artery disease or older age

As we mentioned above (please see the answer to question No. 13), AF was an independent impact factor on OS in multivariate analysis after adjusting other factors, including obesity (BMI), coronary artery disease or older age.

15. P11 line 3-6 (major): For me, the conclusion that this study shows a correlation between hypothyroidism and esophageal cancer is not convincing. As I said above, if you identify the patients via their use of L-thyroxine those patients are euthyroid. Furthermore it is not convincing to me that the results you see are not more dependent on the gender, histology, smoking habit and lower stage of the patient group which took L-thyroxine

As we mentioned above (please see the answer to question No. 3), we did not identify hypothyroidism by L-thyroxine use but by the record of past medical history. First, we
are sure they were hypothyroidism before. Second, we took hypothyroidism as a disease not only as a condition; even they might have a normal T3 and T4 after thyroid hormone replacement, they can still have the hypothyroidism disease.

And again, hypothyroidism/levothyroxine was an independent impact factor on OS in multivariate analysis after adjusting other factors (including gender, histology, smoking habit and stage). Although we can’t exclude the influence of levothyroxine, our data does corroborate previously published studies supporting the protective role of hypothyroidism in certain types of human cancers.

We did realize the limitation of our study as we had listed it in the “Discussion” section of our manuscript (See the 15th to 18th line of page 13 in the revised manuscript). Anyway, at least our results indicate a potential relationship of hypothyroidism and the progression of esophageal cancer, which certainly needs further study to clarify.

16. P11 line 10-16 (minor). This explanation is not so clear to me, please explain in more detail. It is especially unclear how this refers to patients treated with L-thyroxine.

Well, since to date there is no specific study determining the mechanism by which hypothyroidism affect the prognosis of EC, the mechanism is totally unclear. We think we’d better not write anything that is still a speculation, so we deleted that sentence. Thanks for the comment!

17. P11 line 19 (major): It is unclear for me why the use of L-thyroxine should offset the better stage in surgically treated patients. The explanation given regarding the incidence of postoperative low T3 syndrome is especially unclear. Why should patients supplemented with L-thyroxine have a higher incidence of low T3 syndrome. In fact they should be protected against it by the use of L-thyroxine and don’t depend on their own thyroid hormone production.

We didn’t mean that the patients supplemented with L-thyroxine have a higher incidence of low T3 syndrome, but tried to explain that surgical patients had a much higher risk of low T3 syndrome compared to non-surgical patients. And we wrote in the manuscript that it’s “the addition of surgery” but not “L-thyroxine” which might offset the better stage in surgically treated patients (See the 14th to 17th line of page 12 in the revised manuscript). It might be a reason for the survival benefit of hypothyroidism only observed in non-surgery patients.

18. P13 line 8 (major): In my view you cannot really conclude anything in regard to hypothyroidism. You could only say that the use of L-Thyroxin was associated to a different survival.

We admit that we can’t exclude the influence of levothyroxine on EC prognosis in our study. However, we are sure they had hypothyroidism disease before the anti-cancer
treatment, and we did observe an association between hypothyroidism and better OS, which was in accordance with the results of some previous studies. Here, we took hypothyroidism as a disease not only as a condition. We think it is a similar question as question No. 3, please also see the answer above for question No. 3.

19. *Figure 2 (major). The figure is quite unclear; without colours the different graphs cannot really be identified.*

Sorry, we can’t change the original survival curves as they are. Thus, we present it with color to try to make it as clear as we can.

20. *Figure 1 and 2 (minor): include numbers at risk*

We have included the numbers at risk in figure 1 and 2 according to the requirement of the Reviewer (Please see the revised figure 1 and figure 2).

21. *Table 3 (major): As I understand, in a multivariate analysis only the interaction with surgery was investigated. Is this correct? Please explain this a little clearer so that non statisticians can easily understand. If this is correct, interaction to other well known prognostic factors like histology, stage, age, ECOG etc should be checked for. I assume that the numbers (102 – L-thyroxine; 63 AF) are too small for this. Please explain and discuss.*

No, it is not correct. Actually, we did have checked all the other well known prognostic factors. It is a similar question as question No. 2, please see the answer to question No. 2 above.

22. *Table 4 is good (major). It demonstrates that results may not be due to L-thyroxine use but to other well known factors. Please supply a similar table for AF or include in this table*

Thank you for the good suggestion. We have added a similar table for AF (Please see the revised Table 4 in page 25 and page 26 of our revised manuscript).