Reviewer’s report

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

Version: 2 Date: 29 November 2014

Reviewer: Peter C Thuss-Patience

Reviewer’s report:

The authors did a retrospective analysis of 1174 patients, which was a tremendous work. They analysed these patients for factors being associated with OS and describe an association with good survival and hypothyroidism/L-thyroxine use and a poorer survival for patients with atrial fibrillation. These results are interesting.

In my view in the current form I am not totally convinced that these results are nor simply by pure chance and might be due to other factors like stage, histology, age, ECOG, time of diagnosis (1998 versus 2012) etc. For me it is not clear enough which of those factors have been integrated in a multivariate analysis. The patient population investigated seems big (1174) but in fact the number of patients who really have AF or hypothyroidism is small (AF 63, hypothyroidism 102), so the validity of the conclusions and the statistical confirmatory tests should be made clearer. I am not convinced that the use of L-thyroxine can be extrapolated to hypothyroidism, because all patients treated with L-thyroxine will be euthyroid thereafter.

My comments in detail:

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

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.

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 euthyroid 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.

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.

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

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?

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

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.

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)

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

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

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

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

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?

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.

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.

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.

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.

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

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

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.

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.

Overall, it was a nice bit of work to analyse so many patients. Congratulation. I think that there is great potential of this work. In my view in the current form the results are not yet convincing enough.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests