Author's response to reviews

Title: Analysis of a consistent retrospective database of thymic malignancies in a single institution

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Author's response to reviews: see over
Cover Letter

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The Associate Editor
BMC Cancer

Dear Associate Editor:

Thank you for considering our manuscript “Differences in clinical features and outcomes between patients with thymoma and those with thymic carcinoma” (corrected title: “Analysis of the consistent retrospective database of thymic malignancies in the single institution”) for possible publication in BMC Cancer subject to revision.

The reviewers’ comments helped us to improve our manuscript, which we have revised according to the questions posed and recommendations offered by the reviewers.

Replies to Reviewers’ comments:

Reviewer #1 Discretionary Revisions

1. In section 3.3.1, the authors may want to consider using the standard rules for significant figures when reporting data.
   - We have accordingly changed the figures based on the standard rules.

2. The last two sentences of the second paragraph of the discussion may be combined into a single sentence that would be stronger.
   - We have combined these sentences into a single sentence according to your recommendation.

3. The writing could use a closer review and editing prior to publication in an English language journal. Example: Recent biomarker investigations explored c-KIT is a characteristic of thymic carcinoma [19]. For this sentence, investigations are a characteristic. Therefore, the sentence should be: Recent biomarker investigations explored c-KIT are a characteristic of thymic carcinoma [19].
   - We have changed it according to the recommendation of a native English speaker from a commercial company (edanz: http://www.edanzediting.co.jp/).

4. There are other instances when words are made plural that should not be and misspellings and some grammar issues. Although, in general they do not distract too much from the readability of the manuscript except through some sections of the Discussion. Please review and edit.
   - We have had the manuscript edited by a native English speaker from a commercial company (edanz: http://www.edanzediting.co.jp/).
Minor Essential Revisions

1. On the title page the word “adviaced” is used. This is not a word. Did the authors mean “advised”? 
   - Yes, we did. We have corrected it.

2. The term “immunological complications” seems out of place. A more accepted term might be “immunological abnormalities” as not all patients with aplastic anemia or myasthenia have complications, but they are all certainly abnormal.
   - We have substituted “abnormalities” for “complications” in all instances.

3. In the Discussion, the sentence immediately after references 14-16 needs to be re-written. (i.e.: “It seems us to be associated...”)
   - We have had the manuscript edited by a native English speaker from a commercial company (edanz: http://www.edanzediting.co.jp/).

4. In the next to last paragraph of the Discussion, Dr. Weksler’s name is misspelled. There is no “s” on it.
   - We have corrected this error and changed the name to “Weksler”.

5. Additionally, please edit the following sentence as the grammar is poor.
   - We have had the manuscript edited by a native English speaker from a commercial company.

6. Table 1 needs to be re-formatted. There appears to be a line that is skipped making the data for histology not line up. Also, some of the categories run over 2 lines with broken words (i.e: complications).
   - We have corrected the formatting. Our guess is that these problems were caused by changing fonts when converting the document to a pdf from a word file.

7. Same issue for Table 3 on the format. All Tables need to be reviewed and re-formatted to include, but not limited to, title, type, font, alignment, wrap-around, etc...
   - We have corrected the formatting.

8. In the Figure legends section, please re-align. In the pdf reviewed here, there is a free floating 5 that needs to have the portion of the sentence that follows moved to it.
   - We have corrected the figure legends.

Major Compulsory Revisions

1. In section 3.1, the authors describe what appears to be the histologic subtypes of the thymic carcinomas. The authors state there were 68 thymic carcinomas, but in this section there are only 65 listed (42 squamous, 10 neuroendocrine (not 12 like the abstract states), 8 unknown/other, 4 mucoepidermoid, and 1 lymphepithelioma-like).
Can the authors help me understand the missing 3 carcinomas and further explain the "12 neuroendocrine" in the abstract. Then in Table 1, the authors report having 46 squamous cell carcinomas. Also, the authors list only 11 NE tumors in this table.

- We apologize for this confusion and have amended the text. We incorrectly classified the pathologist’s diagnoses of “uncommon type, poorly differentiated adenocarcinoma with neuroendocrine features” as neuroendocrine tumors. Also, the abstract we presented at the European Cancer Congress in 2013 was added to our text and table, causing some confusion.

- We have checked our database to confirm that all numbers are now correct. Because uncommon types were classified as high-grade histology for the multivariate analysis, this analysis was not affected by the error.

2. In section 3.3.2, the 10-year survival for thymic carcinoma is reported as 6.2%, while in the rest of the paper it is 2.3%.

- The correct 10-year survival for thymic carcinoma is 2.3%; we have amended the text accordingly.

3. The sentence in the Discussion that was referenced earlier to be re-written is unclear. What seems to be associated? The authors state “it”. If this refers to the proceeding sentence, then it may mean limitations. Please clarify.

- Is the sentence the reviewers are referring to the one [14-16]? If so, we have corrected it and clarified the association.

4. In the paragraph in the Discussion that begins: Large-scale databases, the second sentence is unclear. Are the authors implying that large databases like the ITMIG only take surgical cases? This is not the case. Also, in the third sentence there is an example of not making a word plural that should be plural “These databases”)

In the final sentence of the same paragraph, the authors seem to imply that databases like the ITMIG may be biased due to limited data and reliability of diagnosis and treatment. In my opinion, it is not exactly that way as the ITMIG database will be likely much larger than any single institutional database.

However, as any database is limited by the quality of the data placed into it and if considered unreliable, it is a function of the data that is submitted to it for inclusion.

- We have misunderstood the “ITMIG database.” We thought it was a database of the North America, JART in Japan, and ESTS in European countries combined together. We checked the spreadsheet of the ITMIG database again; it was an independent database including all patients treated for thymic malignancies by any modality. On the other hand, the JART retrospective database was limited to the surgical cases from 1991 to 2010 in Japan, and our institution was enrolled in the JART study.

Additionally, the ESTS retrospective database was limited to surgical cases (J Clin Oncol 31, 2013 (suppl; abstr 7602)).

We want to emphasize the difference between rare cancer databases and common cancer databases. We have participated in the process of building the retrospective database, and we will cooperate in the process of building the prospective database; we strongly believe the prospective ITMIG database will succeed. However, as we mentioned above, retrospective databases of rare cancers have many potential
problems, which we have pointed out. Although the use of a database of common
cancers from a single institution is thought to be a limitation, databases such as our
database of rare cancer from a single institution with consistent diagnosis and
treatment regimens is very important for the study of rare cancers. We understand
your comments and agree that the function of the database is limited with respect to
quality. We wanted to further comment that rare cancers have a lower reliability of
accurate diagnosis than do common cancers. Therefore, the ITMIG prospective
database is important in that the diagnosis is centrally reviewed by expert
pathologists at the time of registration.
Finally, as mentioned in lines 254 to 277, we would like to emphasize the problem of
performing clinical trials in multi-institutional studies with respect to the fact that
expert pathologists should evaluate rare cancers and participate in the central review
in particular.

5. In Table 1, there are only 14 patients listed under “Complications”. Yet, the abstract
says that there were 26, with all in the thymoma group. Also, the Table shows 1 in the
thymic carcinoma group. The entire Table 1 needs to carefully reviewed for accuracy.
- We have reviewed the text and table and corrected all the errors you have pointed
out. In the abstract, 26 patients were incorrectly classified. The 14 patients cited in
Table 1 is correct.

6. Table 1 and 2 report different data. Example: NE tumors 11 in Table 1 and 12 in Table 2.
- As mentioned above, we have checked our presentation and corrected the number
of patients with NE tumors to 11 throughout.

Reviewer #2: Major Compulsory revisions
1. The aim of this manuscript is not very well stated,
- This study is significant for the following reasons:
  1) The study included a larger number of cases than others involving a single
     institution. Only 5% of published studies evaluated a series of more than 100
     patients.*
     *Detterbeck FC. The international thymic malignancy interest group. J Natl
      Compr Canc Netw. 2013 May 1;11(5):589-93.
  2) An expert pathologist in thymic malignancies (Dr. Hishima) diagnosed all cases
     according to the 2004 WHO Classification. He is the author of the section
describing “thymic squamous carcinoma” in the 2004 WHO Classification (Travis
     W, Brambilla W, Müller-Hermelink H, Harris C. World Health Organization
     classification of tumors. Pathology and genetics of tumors of the lung, pleura,
  3) The data include all treated cases from departments of surgery, medical oncology,
     and radiation oncology, whereas most historical large-scale databases include
     only surgical specimens.

2. The title of the manuscript is not supported by the development of the manuscript.
Which clinical features did the authors look at? Which outcomes besides survival?
We have corrected the title as follows: “Analysis of a consistent retrospective database of thymic malignancies in a single institution”

3. In the paragraph titled “Prognostic factors affecting survival by uni- and multivariate analysis”, it is not clear what the authors’ question is and what their statement mean. There are too many variables and only few deaths (especially in the thymoma group). Review from a statistician would be helpful.

- A statistician has reviewed our material. We repeated the multivariate analysis according to that statistician’s recommendations, which included reducing the number of items analyzed. In the thymoma group, 26 deaths had occurred (there were 199 events in all patients minus 93 in patients who were censored). Therefore, we chose three items to analyze by Cox multivariate analysis, whereas, in the thymic carcinoma group, 50 patients had died and we chose five items to analyze.

4. The discussion is fragmented and it is difficult to understand the intent of the authors. What is the purpose of their study? How are their data comparing to the literature? What is this study showing that is new comparing to the previously reported studies? What are the limitations? I am not even sure the conclusions are relevant. The authors’ conclusions in the abstract are different than the conclusions in the manuscript.

1) The purpose of this study was to clarify the clinical characteristics and outcomes in a single institution. This study is one of the largest reports of thymic malignancies from a single institution. In the present investigation, we speculated that even a single-institution database with consistent diagnosis, management, and treatment regimens is significant for the study of rare cancers.

2) Compared with previous literature, our database is characterized by more advanced diseases and a higher frequency of thymic carcinoma, but similar prognoses.

3) A limitation of our study was the small number of patients with each stage of thymoma or thymic carcinoma. However, this is a common limitation in such studies of small numbers of patients with rare cancers. Additionally, this study was unable to follow up all patients, especially young patients who had undergone complete resection of early-stage cancer or thymoma without immunological abnormalities. Thus, there were more censored patients in the thymoma cohort.

4) We have revised the conclusion at the end of the manuscript according to our statements in the abstract.

Minor Essential Revisions
1. The authors state in the abstract that “The overall 5- and 10-year survival rates were 85.4% and 33.8%, respectively, for thymoma and 71.5% and 2.3%, respectively, for thymic carcinoma”. In the paper however they state that for thymoma “The 5-year and 10-year survival rates were 85.4% and 71.5%”, however for carcinoma “The 5-year and 10-year survival rates were 33.8% and 2.3%, respectively”. The statement in the body of the paper seems more aligned with previously reported survival rates and I think there is a mistake in the abstract. Can the authors comment and correct?
247  - Your comment is correct. The data in the manuscript became confused during the
248  process of editing by a native English speaker from a commercial company. We have
249  checked against the original manuscript and re-analyzed the data in our database. We
250  have also had the manuscript re-edited by a native English speaker from another
251  commercial company.
252  - The correct 5- and 10-year survival rates for thymoma are 85.4 and 71.5,
253  respectively, and for thymic carcinoma 33.8 and 2.3, respectively.
254
255  2. Can the authors give some information about which patients underwent curative versus
256  palliative treatment? I assume patients with more advanced disease underwent
257  palliative treatment, is this correct?
258
259  - Yes, your assumption is correct. Only three patients underwent palliative treatment, all
260  were in the thymoma group. The rest of the patients were treated with curative-intent.
261  - Characteristics of the three patients treated with palliative intent are as follows: one 74
262  year-old, type B2, IVa; survival time more than 17.1 months with chemotherapy; one 26
263  year-old, type B3, IVa, survival time 12.1 months with chemotherapy; and one 81 year-
264  old, type B3, IVb survival time more than 35 months with supportive care.
265  The patients who underwent curative-intent treatment in the thymic group were the
266  patients with chemoradiotherapy for having lymph node metastasis or the patients
267  revealing with pathological lymph node metastasis after surgery.
268  As to the thymic carcinoma group, our group recently published the following paper:
269  Okuma et al. The potency of curative-intent treatment for advanced thymic carcinoma.
271
272  3. How many patients are lost at follow up?
273
274  - Ninety-three patients in the thymoma group and 17 in the thymic carcinoma group
275  were lost to follow-up. In the thymoma group, the censored patients were disease-
276  free 5 or 10 years after surgery, whereas in the in the thymic carcinoma group, they
277  had been admitted to hospices or were still receiving treatment.
278  - We have consulted with a statistician regarding interpretation of our data. The
279  statistician advised us that, given how many patients had been censored in the
280  thymoma group, we had included too many items in the multivariate analysis.
281  Therefore, according to the statistician’s advice, we repeated the multivariate
282  analysis again with fewer items. In the thymoma group, 26 deaths had occurred
283  (there were 199 events in all patients minus 93 in patients who were censored).
284  Therefore, we chose three items to analyze by Cox multivariate analysis, whereas, in
285  the thymic carcinoma group, 50 patients had died and we chose five items to
286  analyze.
287
288  4. There are several misspelled words and the English is not fluent. I recommend the
289  manuscript be reviewed by an English speaking person
290
291  - We have had the manuscript edited by a native English speaker from a commercial
292  company (edanz: http://www.edanzediting.co.jp/).
293
294  We have also changed various expressions and deleted some sentences to avoid
295  redundancy in the revised manuscript. All changes are in red font.
We confirm that all eight authors have approved the above corrections. We apologize to you, the editors and reviewers, for the errors. We hope that you will now find our paper acceptable as an original article for publication in *BMC Cancer*. We look forward to your reply.

Yours sincerely,

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