Peer Review File

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Reviewer A

This is an interesting study utilizing SEER data evaluating the role of clinical pathologic factors on overall survival in > 3800 thymoma patients identified between 1975 and 2017. The authors specifically note that 13% of patients identified have a prior history of cancer (though in limitations they acknowledge that with the limitations of the database, they cannot ascertain when the prior cancer was diagnosed relevant to the thymoma). After propensity score matching, it appears that only prior cancer history is linked to a higher risk of death (though NOT thymoma specific death, but only "other death." Further, Cox regression analysis shows that age (greater or less than 65), separated/divorced/widowed, Masaoka-Koga stage, treatment with no surgery (or no treatment) and prior cancer history were all statistically significantly associated with worsened survival.

The authors state that exclusion from clinical trials of patients with a prior cancer history (ie ~ 13% of the population evaluated in this study) is illegitimate based upon their observation that at least in the > 65 year old group, there is no difference in survival. They advocate for a revision in trial exclusion criteria, and recommend specifically that trials be stratified, according to age, for this variable. The main issue (which the authors acknowledge in the last paragraph of discussion) is that unfortunately they are unable to assess the timing of prior cancer. Indeed, this reviewers reading of most current clinical trials is that prior cancer per se is not an automatic exclusion criteria. Some trials restrict prior cancers only in the last 5 years (ie a patient diagnosed with cancer diagnosed 5+ years ago is not excluded from these trials) and others are even less restrictive allowing investigators to enroll patients with a more recent diagnosis providing it is assessed that the chance of death is less than some established threshold.

Suggestions

• The primary conclusion is somewhat off kilter from the data. While the data are

somewhat interesting (and perhaps not unexpected given the indolent nature of the disease), I believe that topline results that patients with a prior cancer history do worse (dieing from non-thymoma related causes) do not support inclusion of patients with a prior cancer history in clinical trials.

• Unfortunately, the inability to know the timing of prior cancer history make the interpretation of this data rather challenging.

• It might be interesting (if possible) to categorize the types of prior cancers in the 506 patients with this diagnosis in this study.

Response: Thank you very much for the comments on our work and all suggestions for improvement. Indeed, it's a limitation that the inability to know the timing of prior cancer history. The site of prior cancer can be extracted from SEER database, unfortunately the detailed type of prior cancer can not obtain.

Minor points

• In the abstract, line 10, the authors state "of whom 13.22 had a prior cancer history" – I believe they are missing a % sign.

Response: Thank you for your correct. We have carefully improved it.

Reviewer B

In this manuscript the Authors analyze the results of a propensity score matched study assessing the role of previous cancer history on the survival of patients with thymoma. The study was based on the analysis of the data of 3827 patients from the SEER database, 506 with previous cancer history. The results of the study show that prior cancer was associated with lower overall survival, but when the results were stratified according to age, no significant impact of a previous cancer history on overall survival was observed in patients older than 65 years. The Authors therefore conclude that exclusion criteria in studies about thymoma should be defined taking age into consideration, and patients older than 65 years with a previous cancer history should not be excluded from the analysis.

The study addresses an interesting point, but has some significant limitations:

- The primary end point of the study was overall survival, probably due to the lack of

information concerning tumor specific survival, which would have been a more appropriated parameter, since especially in older patients non-neoplastic diseases may have significantly influenced survival

Response: Thank you very much for the comments on our work and all suggestions for improvement. I agree that thymoma specific survival is a more appropriated parameter to assess the survival. But we didn't do that because of the indolent nature of thymoma, the lack of information, and selection bias.

- No data concerning the type of prior tumor and time of previous tumor onset were available

Response: Thank you very much for the comments. It's a limitation that the inability to know the type of prior tumor and time of previous tumor onset.

- Another point to be considered is that data were collected from 1975 to 2017, and treatment results may have significantly changed in this wide interval of time.

Response: Thank you very much for the comments. To decrease the effect of confounding from differences in treatment, propensity score matching (PSM) method was performed.

Reviewer C

Dear Authors,

I read and reviewed with great interest the manuscript you submitted to GS, covering a field of great interest for me.

I would congratulate the authors for the excellent study conducted.

It is based on a huge number of patients for a rare neoplasm.

The methods are good and results convincing.

English language could be improved with minor revisions.

nevertheless I have some minor comments:

- Introduction is too confusing. Please revise and arrange it without repetitions and with clearer sentences.

- The impact of previous cancer history on OS is demonstrated by the authors without confounding bias of patients selection as shown with PSM 1:2. By the way it is not

clear what precise history impact the OS. In other words It is well known that different cancers have different behavior with different treatments. I would better stratify the risk accordingly, in order to better clarify the subtypes of tumors which severely impact on outcome. Please elaborate it.

Best regards

Response: Thank you very much for the comments on our work and all suggestions for improvement. It's a limitation that the inability to know the type of prior tumor. We have carefully improved and modified language.

Reviewer D

Comment 1: The aim of the authors is that the exclusion criteria of thymoma trials should be revised. The authors describe (in the discussion) that their results are similar to Lin et al. Here, the tumor impact on survival is dependent on the influence of the specific tumor entity (cancer biology). However, the authors do not describe which specific extrathymic tumor entities occurred in the thymoma patients, because the information (according to the authors) cannot be derived from the SEER database. Besides, it is not presented whether thymoma patients with a cancer history have an active carcinoma (R0, R1, or R2) or received a curative therapy. For these reasons I do not agree with the authors conclusions. Valid data to support this conclusion are missing.

Response: Thank you very much for the comments on our work and all suggestions for improvement. It's a limitation that the inability to know the type of prior tumor and the treatment for prior cancer.

Comment 2: The authors show (section: results) that there is no difference in OS between thymoma patients with a carcinoma history compared to thymoma patients without a carcinoma history. The authors should carry out further survival analyses, particularly the recommended ones by ITMIG, such as cause specific survival and freedom from recurrence.

Response: Thank you very much for the comments on our work and all suggestions for improvement. The results showed statistically significantly different survival between patients with and without a prior cancer before ($P<0.001$) and after PSM ($P=0.0003$). It's a limitation that the inability to know the time of previous tumor onset and freedom

from recurrence. I agree that thymoma specific survival is a more appropriated parameter to assess the survival. But we didn't do that because of the indolent nature of thymoma, the lack of information, and selection bias.

Comment 3: Furthermore, the impact of age on overall survival is not discussed in the discussion section.

Response: Thank you very much for the comments. The impact of age on overall survival was discussed in the paragraph 2 of discussion section, please kindly check.

Comment 4: Survival analyses based on the WHO classification, Masaoka-Koga classification, treatment categories, and TNM classification should be performed; e.g. within the B1 thymomas with a carcinoma history and B1 thymomas without a carcinoma history (and all other TET types).

Response: Thank you very much for the comments on our work and all suggestions for improvement. We performed Masaoka-Koga stage, WHO histological subtype, and treatment categories. But TNM classification didn't be perform due to lack of information.

Comment 5: The authors describe that all death causes of thymoma patients with a further carcinoma history cannot be traced back to the thymoma. The authors should provide the causes of death of the thymoma patients.

Response: Thank you very much for the comments on our work and all suggestions for improvement. It's a limitation that the inability to provide the causes of death of the thymoma patients.

Comment 6: Databases dedicated to the study of thymoma (ITMIG, ESTS) are more suitable to study such research questions.

Response: Thank you very much for the comments. Though SEER database has many limitations, I believe SEER database also has its advantages.

Comment 7: Thymoma size is not regarded as an established prognostic factor for thymomas and thus should not be used for prognostication in this study. Completeness

of resection and tumor stage should be used.

Response: Thank you very much for the comments on our work and all suggestions for improvement. Lewis JE et al and Roden AC et al demonstrated that large thymoma size has worse OS and is an independent predictor of recurrence and prognosis (4th paragraph of the discussion section). We performed Masaoka-Koga stage and WHO histological subtype. But the information of R0 resection can't obtain from SEER database.

Comment 8: The extrathymic tumor types, extrathymic tumor stage and treatment outcome as well as the time intervall between extrathymic and thymic cancer are the most relevant data to reach the desired conclusion, but are not presented in this study.

Response: Thank you very much for the suggestions for improvement. It's a limitation that we didn't present it.

Comment 9: The study suffers from typical Big Data study issues "stage III/IV were unable to be distinguished because of insufficient clinicopathological data". Needless to say that metastatic disease has to be analysed separately.

Response: Thank you very much for the suggestions for improvement. I agree that metastatic disease has to be analysed separately. It's a pretty good stage base on limited data.