Peer Review File

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Reviewer A

Comment 1: The authors should describe the primary cancer as "lung (number), colon (number), breast (number), and others (number)".
Response: We have done this revision (line 38, page 2; line 138, page 7).

Comment 2: In Figure 1, it is better to show the median age instead of the mean.
Response: We have done this revision (line 124-125, page 6, and Figure 1B).

Comment 3: The authors need to describe the site of malignancy in 5 patients with multiple myeloma who developed second primary malignancy.
Response: We have done this revision (line 134-136, page 6-7).

Comment 4: In Table 2, patient characteristics of multiple myeloma as the second primary malignancy are compared with those of multiple myeloma who developed second primary malignancy, but it is recommended to include those of multiple myeloma alone without other malignancies.
Response: Thank you for your advice. Table 2 demonstrated the characteristics of patients having MM with multiple malignancies. So it did not include those of multiple myeloma alone without other malignancies.

Comment 5: How did the authors extract the case of myeloma without other cancers (n=16) in Table 3 (and possibly Figure 3)?
Response: We adopted simple random sampling among 773 MM patients without other cancers(16 patients with MM as the second primary malignancy and 5 patients as the first primary malignancy excluded). This method can randomly select a certain number of samples from the population to ensure that each sample has the same chance of being selected in the sampling process.

Comment 6: It is needed to discuss more for the reasons of the poor prognosis in patients with multiple myeloma as the second primary malignancy.
Response: Thank you for your advice. We have done this revision (line 271-277, page 13).

Reviewer B

Comment 1: The discussion is overly focused on cataloging previous similar studies and does not adequately address weaknesses of the study or underlying biology.
Response: Thank you for your advice. We have done this revision (line 260-263, page 12; line 271-277, page 13;).

Comment 2: Table 3 and the Results paragraph that describes the data is confusing: 16 out of 794 myeloma patients had previous cancer diagnoses, but Table 3 only looks at a small 16 patient sample of the 778 remaining patients without prior cancer diagnosis. How was this cohort selected and why?
Response: We adopted simple random sampling among 773 MM patients without other cancers(16 patients with MM as the second primary malignancy and 5 patients as the first primary malignancy excluded). This method can randomly select a certain number of samples from the population to ensure that each sample has the same chance of being selected in the sampling process. We have done this revision (line 161-163, page 8).

Comment 3: With only 6/16 patients receiving bortezomib, 12/16 patients receiving immids, less than half on maintenance, and no stem cell transplants, suggests these patients were relatively under-treated, which could explain the differences in survival. The heterogeneity of treatments is noted by the authors, but it should be made explicitly clear that the results the authors observe may simply be due to under-treatment of patients with previous malignancies.
Response: Although the heterogeneity of treatments exists between 16 patients with MM as the second primary malignancy and 16 MM patients without multiple malignancy, there were no statistically significant differences. And the low relapse rate in this group of patients further suggests that the heterogeneity of treatments did not have a significant impact on the therapeutic effect.

Comment 4: Beyond treatment differences, the underlying scientific question is whether myeloma patients can be stratified meaningfully between those with underlying germline genetic risks or chemotherapy exposure (represented by a history of other cancers) and those with no previous cancer history. This biology should be addressed in the Discussion.
Response: Thank you for your advice. We have done this revision (line 271-277, page 13).

Comment 5: The first sentence of the abstract should be deleted, "As the overall survival of patients with Multiple myeloma (MM) improves, the incidence of second primary malignancy in long-term complications increases.' That sentence suggests that the topic of the manuscript is that cancers that occur secondarily after myeloma diagnosis, which is a related, but separate question.
Response: As the overall survival of patients with Multiple myeloma (MM) improves, the incidence of second primary malignancy in long-term complications increases. Several studies have confirmed this point. We want to emphasize the latter sentence: Howerer, there are limited data regarding MM as a second primary malignancy. And this is the purpose of this research. We have done this revision (line 26, page 2).

Comment 6: Can the authors tell us how many cases of primary myeloma had

subsequent diagnoses of cancer?
Response: Five cases of MM as the first primary malignancy developed second primary malignancy, including cancers of the lung (n=1), kidney (n=1), thyroid (n=1), bile duct (n=1), and vocal cord (n=1). We have done this revision (line 134-136, page 7).

Comment 7: Similarly, the paragraph that starts with, "With improvements in survival, a relatively new clinical challenge that has emerged is the risk of long-term complications, especially in second malignancy cases" suggests the paper will examine malignancies after a primary myeloma diagnosis. This is confusing. The authors might address this by discussing underlying genetic risks which may contribute to secondary malignancies, whichever comes first.
Response: We want to emphasize the latter sentence: However, there is limited data regarding MM as a second primary malignancy. And this is the purpose of this research.

Comment 8: This study did not control for referral or detection biases so a strong conclusion that incidence is increasing may have several explanations. In the abstract conclusion, "This retrospective study indicate that the incidence of MM increased annually" should be reworded to reflect uncertainty. Grammatically it should be "indicates," but "suggests…may be" would be more appropriate. Data on the aging of the population might support a stronger conclusion.
Response: Thank you for your advice. We have done this revision (line 43-44, page 2).

Comment 9: Similarly in the abstract, "the survival of patients with MM as the second primary malignant was significantly shorter than that of those without multiple malignancies," should be qualified to reflect uncertainty due to differences in treatment.
Response: Although the heterogeneity of treatments exists between 16 patients with MM as the second primary malignancy and 16 MM patients without multiple malignancy, there were no statistically significant differences. And the low relapse rate in this group of patients further suggests that the heterogeneity of treatments did not have a significant impact on the therapeutic effect. So We still stand by this conclusion.

Comment 10: The conclusion at the end also confuses the issue of which malignancy comes first. Are the authors suggesting screening all patients with cancer for myeloma? Or screening all myeloma patients for other cancers? Either way, this conclusion appears premature. These data are important, mostly to encourage additional work in this area: repeating a similar study matching primary and secondary myeloma cases by treatment for example. Examination of germline risk alleles in myeloma patients is another area of ongoing work.

Response: Thank you for your advice. This study is a retrospective study that demonstrates the incidence and the survival of MM patients as a second primary malignancy in our single center. Early detection and treatment of second primary malignancy may prolong the survival of patients. Of course, the most important thing about this kind of disease is to explore the corresponding pathogenesis, and subsequent studies may involve. We have done this revision (line 279, page 13).

Reviewer C

Comment 1: However, patient numbers are very low in this manuscript.
Response: Thank you for your advice. This is one weakness of this study. Because this study is a single-center retrospective study, the number of MM cases is limited, and the incidence of multiple tumors is low, so the number of multiple malignancies cases analyzed in this study is limited.

Comment 2: In addition, the use of expressions such as secondary primary malignancy (either following myeloma or myeloma following other diseases) is not always fully clear.
Response: Patients with multiple primary malignancies can be divided into two categories; synchronous multiple primary malignancies, which are defined as the occurrence of the second malignancy after the first malignancy within 6 months, and metachronous multiple primary malignancies, which are defined as the occurrence of the second malignancy after more than 6 months from the first malignancy. Thank you for your advice. We have done this revision (line 101-103, page 5).

Comment 3: Some definitions are unclear, e.g. groups in Table 3 (both containing 16 patients).
Response: We want to select the same number of cases with MM as the second primary malignancy. The 16 patients with MM who had no multiple malignancies were chosen from the 773 patients cohort(16 patients with MM as the second primary malignancy and 5 patients as the first primary malignancy excluded) by simple random sampling.

Comment 4: Language proofreading required.
Response: The manuscript has been edited by TopEdit.

Comment 5: Abstract: "The incidence of MM showed an annual upward trend, increasing from 9.3% (2009–2011) to 10.8% (2015–2017). Why were 2012 and 2014 excluded here?
Response: We can see that the incidence of MM is increasing from Figure 1A. For simplicity, we provided detailed descriptions for the periods 2009-2011 and 2015-2017.

Reviewer D

Comment 1: Make clear that you assess MM primary vs secondary. In the introduction authors mentioned "second primary malignancy (SPM) in patients with MM", and "secondary malignancy after MM".
Response: Thank you for your advice. We have done this revision (line 89-90, page 5).

Comment 2: Results, page 6 ln 118-119. The authors stated increase in mean age of diagnosis from 61.2 to 62 years. It is not a real increase. If apply median age, there will be most likely no difference.
Response: Thank you for your advice. We have done this revision (line 124-125, page 6, and Figure 1B).

Comment 3: Results, page 7 ln 148-150. Lenalidomide and thalidomide both are immunomodulators. Clarify what 12 patient who "were treated with immunomodulators" received.
Response: We have already elaborated on this point in line 156-158, page 8.

Comment 4: Discussion, ln 171. Authors stated that "MM accounted for 10% of hematological malignancies in this study" It is not clear, and is out of concept of the study. Did authors loo at total cancer population or only myeloma patients?
Response: A total of 794 patients with MM were diagnosed among 7,921 patients with hematologic malignancy between 2009 and 2017(line 119-120, page 6). So MM accounted for 10% of hematological malignancies in this study.

Comment 5: Discussion, Ln 183-184. The sentence "The male 5-year survival increased from 24% (1967–1971) to 54% (2012–2016)" is strange. Please, clarify what male 5y survival means
Response: It means that the male patients diagnosed with MM are expected to survive for at least five years after diagnosis.

Comment 6: References have different font and size
Response: Thank you for your advice. We have done this revision (line 305-420, page14-20).

Comment 7: Figure 3. Add patients at risk under the graph with KM curves.
Response: Thank you for your advice. But I don't quite understand what you mean.