Peer Review File

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Comment 1: The title is inaccurate. Please consider "risk factors of RLNM among patients with bone sarcoma and survival of patients with bone sarcoma with RLNM".
Reply 1: The reviewer's comment about the title is greatly appreciated by our author groups. The new recommended title indicates more accurately and clearly the content of the article. We are glad to accept this suggestion. we have modified our text as advised (see Page 1, the title) However, the "RLNM" is an abbreviation not generally used elsewhere and conveys no information without specification. We would like to write it in full words, which aids to catch interest of potential readers of our article. The new title is "Risk factors of regional lymph node (RLN) metastasis among patients with bone sarcoma and survival of patients with RLN-positive bone sarcoma". We hope this new title slightly differing from the suggested one can be accepted by the reviewer. If such a title is not appropriate, please response back and we would like to make any change according to the author's further comment. Changes are highlighted in red in the revised manuscript.
Changes in the text: Page 1, the title

Comment 2: Introduction. More insights are needed for the identification of risk factors of RLNM, I think rare studies of risk factors of RLNM does not make it necessary to do the analysis.
Reply 2: This is a good suggestion. Based on the original version, in the *introduction* part, we introduced in more depth the association of RLNM with survival of patients with different bone sarcomas. We have modified our text as advised (see Page 3–4, line 65–79) and presented the significantly poorer outcome related to RLNM in osteosarcoma, Ewing sarcoma and chondrosarcoma, highlighting the importance of clinical attention on status of RLNM and the need to identified risk factors for RLNM. We hope these modifications could meet the requirements of this comment.
Changes in the text: Page 3–4, line 65–79

Comment 3: Line 36, prevalence is an inappropriate term here. Please consider to use proportion.
Reply 3: Thanks for this useful comment. We have made the correction to this comment (see Page 2, line 36), and we have gone through the whole manuscript to avoid the same inappropriate term.
Changes in the text: Page 2, line 36

Comment 4: I do not think the candidate risk factors of RLNM in the study is adequate. These included variables are most cancer-related, and risk factors for survival of RLNM patients are very general. Whether SEER is allowed for the proposed research topic is questionable due to limited study design.
Reply 4:

a. reply to "I do not think the candidate risk factors of RLNM in the study is adequate. These included variables are most cancer-related**"**
The reviewer raised a general concern that inadequate candidate risk factors were analyzed in our study, which results from the inherent limitation of SEER. This database mainly documents tumor-related information, such as tumor size, tumor type, malignant grade, primary site, metastasis, etc. However, we have included all potential risk factors documented in the database, based on our clinical practice and literature reports. Clinically, these variables are also routinely evaluated. Surgeons can get a general understanding of disease condition of the patients based on the information provided by these variables. So, we think higher clinical reference value can be provided by these limited variables.
b. reply to "risk factors for survival of RLNM patients are very general"
We agree with this comment that risk factors for survival of RLNM patients are very general. In our multiple competing risk regression analysis (more accurate than traditional Cox regression for survival analysis in the presence of competing risk), we found only age, distant metastasis and surgery were associated with survival of patients in the presence of RLNM. However, we found this finding is of great clinical significance. First, tumor type is not a prognostic factor for survival of RLNM, which means that chondrosarcoma, which is greatly less malignant than osteosarcoma and Ewing sarcoma, yields comparable poor survival in the presence of RLNM. Second, tumor size is generally considered to be a prognostic factor for survival of patients with malignant disease. However, it is not a prognostic factor for survival of bone sarcoma with RLNM, indicating that patients with tumor of small size may have equal unfavorable outcome to those with tumor of large size. This further highlighted the importance on examining the status of RLNM, even for pony-size and less malignant bone sarcoma. So, we think, the conclusion that tumor size and type are not prognostic for survival of bone sarcoma with RLNM also provides added valuable information to aid clinical management of this tumor. This point was also discussed more intensively in the "discussion" part (see Page 13, line 278–292).
Changes in the text: Page 13, line 278–292

c. reply to "Whether SEER is allowed for the proposed research topic is questionable due to limited study design".
We admit that SEER has some inherent limitations, which was discussed in the penultimate paragraph. However, the database has covered a high portion of the US population and is widely used for clinical cancer research. Studies about risk factors for RLNM of other cancers has also been published, and similar candidate risk factors for RLNM were presented in these studies (1,2), which further adds to the feasibility of our study design. Besides, before we conducted the analysis, we have made strict inclusion and exclusion criteria (figure 1) to avoid potential bias, and used various statistical methods (combining Cox and Fine-Gray's competing risk analysis, see Page 9, line 199–201) to conduct our analysis. We think these strategies add to the rationality and reliability of our study.
Changes in the text: Page 9, line 199–201

Comment 5: In general, the information generated from the study is very limited despite the research topic is interesting.
Reply 5: We admitted that using SEER with limited variables, many questions could not be answered in our article, such as pre-operative imageological examination of RLNM and the role

of lymphadenectomy on survival of patients with bone sarcoma. Based on available date, we only identified risk factors for RLNM and survival of patients with bone sarcoma with RLNM. However, we think the limited information is valuable for clinical practice. For example, unlike general understanding, we found tumor size and type are not predictive of survival of patients with bone sarcoma with RLNM. It is generally considered that patients with small size and low grade of malignance tend to have better outcome. Nevertheless, according to our study, survival will be equally poor in bone sarcoma with small size and low grade of malignance compared to those with large size and high malignance. We think this finding is of great clinical significance. Usually, most patients with bone sarcoma (Osteosarcoma and Ewing sarcoma) are young people, for whom a long-term survival can be expected after standard treatment. Despite rare incidence, If RLNM is ignored, even in tumor small size and low grade of malignance, the survival might be shortened and the cost will be high. After conducting this study, we have also gained added attention on status of RLNM when surgically resecting bone sarcoma, to avoid ignorance of potential RLNM and unfavorable outcome for the patients.
In addition, based on competing risk, we also found that non-cancer specific death (including those attributed to cardiovascular events, diabetes or suicide), which might be neglected by surgeons after surgery treatment, also contributed greatly to poor overall survival. We highlighted the importance of focus on non-cancer specific death and think that preventing non-cancer specific death will also aid the improvement of overall survival of bone sarcoma patients (see Page 12, line 261–267).
Changes in the text: Page 12, line 261–267

Comment 6: A limitation is the small sample size of this study.
Reply 6: We admitted that the sample size of our study is relatively small, which is a result from the rare incidence of primary bone sarcoma. Unlike lung or breast cancer with high incidence, we identified only about 17000 bone tumor cases from 1983 to 2014 from the database. After excluding patients ineligible (mainly those with unknown status of RLNM) for the purpose of this study, only 10641 patients were finally enrolled. However, compared to several single- or multi-center studies, this sample is greatly larger, and the result is more credible. At present, we are unable to avoid such limitation due to low incidence of bone sarcoma and the inherent limitation of SEER. Of course, we can enroll patients in SEER diagnosed before 1983 to add more cases. However, as some key information, such surgery treatment and RLNM, was not accurately documented (SEER has officially reminded user about these inaccurate documentations and suggests users be cautious when using these data), we chose not to include those patients diagnosed before 1983 to avoid potential bias. We believe that with time going by, more cases will be added to the database, thereby enhancing our finding with adequate number of patients. And we deeply appreciate the work of doctors who shared their bone sarcoma cases to the SEER database. Despite limited sample size, as replied above, we think our findings is of great clinical significance. We have provided in-depth discussion about our finding and believe that it can aid orthopedic surgeons in their clinical practice.

A general reply to the reviewer: These comments from the reviewer are very valuable and are greatly appreciated by us. Some of the precious comments have guided us to improve the quality of the article. We went through the whole manuscript, examining the structure, methods, results and their interpretations after we consulted the comments. We think this revised version is much

better based on the reviewer's comments. We also admit that limitations exist in our study, as pointed out by the reviewer. We have also noted some of the limitations when we prepared the original manuscript, but we are unable to address such issue which comes from the inherent nature (e.g. low incidence) of bone sarcoma and the limitation of SEER database. We have also discussed the limitation in the manuscript, which is also common limitation for most articles using data from the database. Nevertheless, we have used rigorous statistical analyses in addition to traditional methods for survival analysis. We think our findings are useful for clinical practice. And now, doctors in our center have gained more attention on RLNM when treating patients with RLNM based on this study. We hope that our reply could meet the requirements of the reviewer and that this manuscript could be accepted to make more doctors know our findings. If there are other concerns from the reviewer, please point out and we will be glad to make any changes according to further precious opinions.