

Peer Review File

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Reviewer A

Comment 1: The manuscript described the characteristics, incidence, and risk factors for death from fatal pneumonia among patients with primary bone sarcomas using the SEER database. Overall, I think the number of developing pneumonia in the present cohort was very small. Therefore, I wonder if we need to do the screening of pneumonia for a long time.

Reply 1: We appreciate your advice, the observation time was from 1973 and 2016 in our study, this partly account to SEER database, a study including more countries and screening of pneumonia for a long time was need.

Comment 2: Although the authors concluded the careful follow-up is necessary for patients with amputation, there were no patients with amputation in chordoma, which was the most major histology of high mortality rate.

Reply 2: The site of chordomas is frequently the sacral area (55%), followed by the skull region (35%) and the vertebral column region (10%)(1). Amputation is rarely used in the treatments of chordoma patients. However, chordomas itself and spinal surgery for sarcoma also could Injury ability of exercise and increase the risk of dying from pneumonia(2)

Comment 3: I know a lot of patients with an amputation below the knee can gait with an artificial limb. Their activity is very high. Did you analyze the relationship between amputation level and the incident of pneumonia?

Reply 3: Thank you for point out this, At the beginning of this study, we also want to analyze the relationship between amputation level and the incident of pneumonia, but we found that only 7 patients died of pneumonia in all amputations, even including partial upper limb amputation, the results showed that the relationship between amputation level and the incident of pneumonia was statistically unstable, so we gave up the analysis.

Comment 4: I think the authors divide the group according to the cause of pneumonia. Some patients developed it due to myelosuppression during chemotherapy. Others may develop after radiotherapy. The others may develop due to non-sarcoma-related cause. Those should be different characteristic.

Reply 4: I am sorry that the description of the calculation method of SMRs was not clear enough in the previous manuscript, so I would like to describe the calculation method in detail here. The SMRs were estimated as the ratios of

observed to expected number of deaths. The observed number of deaths represents the total number of deaths from fatal pneumonia among patients with malignant bone tumors recorded during the study period; the expected number of deaths represents the number of individuals who died from pneumonia in the general population with the same distribution of age, sex and race/ethnicity. To obtain the expected number of deaths, we derived the stratum-specific mortality rates from fatal pneumonia of the reference general population collected by the SEER program and calculated the person-years of relevant strata in the cancer group. The stratum-specific expected number of deaths was estimated as the product of mortality rate in the reference group and the person-years in the cancer group. The total expected number of deaths was a summation of all the expected number of deaths across the strata. Although there is no detailed described in the SEER database whether pneumonia is caused by tumor, chemotherapy, or influenza, we believe that the SMRs after adjusting various factors (age at diagnosis, sex and race) can also fully represent the differences in the risk of fatal pneumonia between patients with malignant bone tumors and the general population according to these previous studies(3-5).

Reviewer B

Comment 1: Research only on recent patient populations should be needed as the authors emphasized that deaths from other diseases are increasing compared to the recent improved survival rate of cancer patients in the Introduction section.

Reply 1: We agree with your comments, we initially used the latest research cohort data for analysis, but we found that when built a multi-factor analysis model, too few patients data lead to unstable of the model, so we carried out a general analysis of patients at all times and explored the risk of pneumonia death in different years.

Comment 2: The expression " regional, or distant" in clinical stage of bone tumors is very ambiguous.

Reply 2: In accordance with the reviewer's request, we added a detailed description of the definition of clinical stage.

Comment 3: Categorization in surgery, chemotherapy, and radiation is also unclear and improper for accurate analyses.

Reply 3: Records of radiotherapy and chemotherapy are not detailed in SEER database, only limited to whether patients have undergone radiotherapy and chemotherapy. Therefore, we couldn't carry out in-depth research.

Comment 4: It differs from the statistical common sense to describe the survival time as range and average

Reply 4: In accordance with the reviewer's request, we changed description of survival time to median and IQR.

Comment 5: Mortality rate in children with malignant bone tumors is higher than that of the general population should be presented. Likewise, opinions should be given on why the death rate from pneumonia is high in black patients with malignant bone tumor

Reply 5: We appreciate your opinions and have made the corresponding changes in the revision.

Comment 6: However, it is not certain that the ability to walk in the amputation patient group is necessarily inferior to that in patients who did not undergo surgery or had a limb-salvage surgery. This is the most critical point to be considered in revision process.

Reply 6: Although we agree with you very much, we couldn't calculate the walk ability in view of the limitations of the SEER database itself. On the one hand, our study not only based common medical knowledge, we also used Fine-Gray Model to prove it. The results showed that amputation significantly increased the risk of dying from pneumonia compared with non-surgery and limb salvage (hazard ratio=0.21; 95% CI [0.06-0.77]; P=0.018 and HR=0.43; 95% CI [0.19-0.93]; P=0.033). On the other hand, our study may mix with some patients with amputation but no change in walk ability such as upper limb amputation, we still concluded that amputation is one of risk factors for pneumonia compared with non-surgery and limb salvage, the impact of amputation on pneumonia will be more pronounced if only aim to lower limbs amputation. So the ability to walk in the amputation patient group is inferior to that in patients who did not undergo surgery or had a limb-salvage surgery.

Comment 7: the result of study seems not to have significant impact on clinicians' practice because the absolute number of deaths from fatal pneumonia is judged to be very small, especially in recent days.

Reply 7: we acknowledge that the number of deaths from fatal pneumonia is small in in patients with malignant bone tumor, but even with the rapid development of multidisciplinary treatments in USA, the risk of death from pneumonia in patients with bone tumors has not decreased to the same extent as in the general population, so it worse in the developing countries. Besides, the

risk of complex infections such as cocci in hospitalized patients increasingly. According to our results: the mortality rate of bone tumor patients dying from pneumonia in 2007-2017 is higher than that of 1996-2006, maybe the mortality will continuously increase, so we hope this article can arouse the attention of clinicians to the pneumonia of bone tumor patients

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