Author’s response to reviews

Title: Ten-year follow-up results of perioperative chemotherapy with doxorubicin and ifosfamide for high-grade soft-tissue sarcoma of the extremities: Japan Clinical Oncology Group study JCOG0304

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Author’s response to reviews:

Dr. Linda Gummlich
Editor
BMC Cancer
Dear Dr. Gummlich,

Thank you very much for your e-mail dated August 20, 2019 with regard to our manuscript (BCAN-D-19-01638) together with the comments from the reviewer. It is our pleasure to resubmit a revised version of our manuscript for publication as an original study in BMC Cancer.

We also appreciate the detailed comments from each reviewer, and have incorporated the suggested changes into the manuscript to the best of our ability. The manuscript has certainly benefited from these suggestions.

The following pages include the responses to each reviewer’s comments. Revisions in the text are marked in red font to make them easier to identify.

We appreciate your time and consideration and hope that our responses are satisfactory. Thank you again for thoroughly reviewing our manuscript.

Please let us know if any additional information is required. We look forward to your decision.
Sincerely,

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Response to reviewer's comments:

Dr. Marcus Lehnhardt (Reviewer 1)

1. Well written article worth publishing on the 10-year results of the JCOG0304 study. The authors correctly limit their conclusions to the absence of a surgical arm with the same strict operative strategy plus adjuvant radiation therapy. Please change the use of singular ("soft tissue sarcoma (STS) is") in the background section of abstract and introduction of the article to plural (soft tissue sarcomas (STS) are") to underscore the heterogeneity of this group of malignancies.

Thank you for your comment. According to the suggestion, we changed the sentence "soft tissue sarcoma (STS) is" in the background section of abstract and introduction of the manuscript to "soft tissue sarcomas (STS) are".

Dr. Scott Michael Schuetze (Reviewer 2)

1. The authors mention that 6 cases of secondary malignancy developed. It may be more accurate that 6 cases of second malignancy or cancer developed. Secondary malignancy usually implies that the cancer was related to the original disease or treatment of the disease. It would be helpful to include the type of cancer that developed in the 6 patients so that the reader may consider whether or not the second cancer may be unrelated to treatment.

Thank you for your important comment. According to your suggestion, we added the description about the types of cancer developed in 6 patients (Page 17, Line 232).
2. Under histologic subtype on page 17 (line 235) and page 20 (line 289), the authors write "undifferentiated, pleomorphic sarcoma". The common in this location is confusing and it would be better to write "undifferentiated pleomorphic sarcoma".

Thank you for your helpful comment. According to your suggestion, we revised the term "undifferentiated, pleomorphic sarcoma" to "undifferentiated pleomorphic sarcoma".

3. It is of interest that the majority of patients did not receive adjuvant or neoadjuvant radiation. Radiation is a currently accepted standard of care. In this trial, radiation was used at discretion of treating physicians after protocol therapy was completed. Only 17% of patients received radiation and local relapse was noted in only 7% of patients. The manuscript would be more interesting, and perhaps more important, if the authors provided more detail on decision to administer radiation (e.g. R1 resection which occurred in 5 patients), and potential impact of no adjuvant radiation on local recurrence. For example, were all cases of local recurrence in patients who did not have radiation (or in patients with R1 resection)? And what was impact of local recurrence on patient survival? I would be interested in the authors thoughts on whether adjuvant radiation may be omitted in patients who receive pre-operative chemotherapy? or in which cases of high-grade, high-risk STS that it would be appropriate to not give adjuvant radiation?

Thank you for your very important comment. Japanese orthopaedic oncologists have a consensus that if the margin of surgical resection of high-risk STS is enough (more than 2 cm of minimum margin), adjuvant radiation would not be necessary, and this is written in the Japanese guidelines of STS treatment. With this procedure, we achieved less than 10% of local recurrence rate without radiation therapy. Since radiation has the risk of edema, fibrosis, joint contracture, fracture and secondary malignancy, we want to avoid radiation if the surgical margin is enough. However, there is no evidence that pre-operative chemotherapy could prevent local recurrence, we did not omit adjuvant radiation in all patients enrolled in our trial. Indeed, no local recurrence was observed in 12 patients treated by adjuvant radiation.

According to your suggestion, we added the description about the indication of radiation and the impact of radiation therapy and local recurrence on outcome. The following sentences were added to the text.

“The decision of administration of radiation was depend on discretionary of the treating physicians, thus the details of radiation therapy were not defined in the protocol of JCOG0304.” (Page 13, Line 178).

“In 12 patients treated by adjuvant radiation therapy, no local recurrence was observed. All 5 patients who had local recurrence were treated by negative margin in surgical resection and one out of the five patients had died.” (Page 16, Line 221).