Author’s response to reviews

Title: Clinical implications of determination of safe surgical margins by using a combination of CT and 18FDG-positron emission tomography in soft tissue sarcoma.

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Dear Editor;

Thank you very much for your valuable comments on our prepublication paper. We will comprehensively modify our paper in accordance with the reviewer’s comments and requests, and resubmit the revised paper.

Our replies to the reviewer’s comments are as follows.

Reviewer #1

• Reference literature for determining tumor borders using 18F-FDG

To describe the determination of borders of solid tumors using radiotherapy, we added the review (5) as a reference. Our literature study revealed that there is no previous report on the efficacy of FDG-PET/CT for determining surgical margins of solid tumors.

We used conventional contrast-enhanced MRI for determining the borders of sarcomas. Moreover, we decided surgical margins for sarcomas according to their distance from tumor borders determined by contrast-enhanced MRI. Accordingly, we have revised the Methods for easy understanding.

• 18F-THYMIDINE

We agree with the reviewer’s comment. Unfortunately, however, 18F-thymidine is not yet commonly used in our institution. Therefore, in the present study, we used 18F-FDG. We have included the following description in the Discussion.

In recent years, FLT-PET using fluorothymidine (FLT) as a tracer has been performed to differentiate between inflammatory and tumor lesions. Thymidine is
one of the elements present in the DNA, and its incorporation into cells is known as an indicator for cellular proliferation. FLT is an analog of thymidine. FLT is phosphorylated by a thymidine salvage pathway; however, it is not incorporated into nuclei. Malignant tumors show rapid cell proliferation and enhanced nucleic acid synthesis. Because the accumulation rate of FLT in inflammatory sites is considered to be lower than that of FDG, FLT might be more useful for determining the surgical margins of tumors.

- Perivascular evaluation
  We have deleted this part.

Reviewer #2

- As the reviewer has pointed out, this study has a key limitation in that the number of cases is small at the present stage. We have added the following description about limitations to the Discussion.

A limitation of this study is that the number of cases is as small as 7. This is because the incidence of sarcoma is overwhelmingly low compared with that of cancer; therefore, it was difficult to design a large-scale study since our study was limited to subcutaneous sarcomas. In the present study, SUV-max can vary greatly among tumors of the same type. It is desirable to examine a larger number of cases to determine whether the cut-off SUV-max level can be uniformly set at 1.0 in all cases including those with tumor the center of which has a low SUV-max. Hence, at the present stage, our study results may be presented as a case report. In the future, we need to collect a variety of cases from multi-institutions as well as a single institution and further accumulate reliable data.

- The title has been changed as follows.
  Clinical implications of determination of safe surgical margins by using a combination of CT and 18FDG-positron emission tomography in soft tissue sarcoma.

- Section of Materials and Methods
  According to the reviewer’s opinion, we have reworded the Materials and Methods for improved understanding.

As we have described in the response to Reviewer #1, the important point is that our study used conventional contrast-enhanced MRI for determination of sarcoma borders. In addition, we decided surgical margins according to distances from tumor borders determined by contrast-enhanced MRI.

We have made the following corrections and additions.

For these cases, we determined tumor borders by using conventional contrast-enhanced MRI, and resection was planned to secure surgical margins between 3 and 5 cm from tumor borders determined by contrast-enhanced MRI. We selected 2 directions without biological barriers from among sagittal, axial, and coronal directions in tumor borders determined by preoperative
contrast-enhanced MRI, and we measured SUV values of soft tissues that were indicated to be outside the tumor borders by contrast-enhanced MRI. SUV data by preoperative FDG-PET/CT were analyzed using VISIO KEOPSYS VIEWER (CODONICS: USA). In other words, we determined that the regions of interest (ROI) were at a distance of 5 cm and 1-cm interval from the tumor borders by contrast-enhanced MRI, and measured their SUV-max value (Figure 1). After extensive resection of the tumors, we performed mapping of neoplastic cells using whole area histological specimens of the resected tissues and compared with the preoperative SUV values (Figure 2).

We found many reports on radiotherapy plans using FDG-PET. However, to the best of our knowledge, there have been no reports on evaluation of the efficacy of FDG-PET/CT for determining the surgical margins for solid tumors. Therefore, we consider that our report is very new.

Your evaluation of our revised manuscript would be much appreciated.

We look forward to your favorable reply.

Respectfully yours,

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