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# Prognostic Stratification of Standard Responders to Neoadjuvant Chemotherapy in Patients with Osteosarcoma Using $^{18}$F-FDG PET/CT Imaging

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**Introduction:** We aimed to identify a new biomarker using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) parameters to identify osteosarcoma patients with standard response after neoadjuvant chemotherapy (NAC).

**Patients and Materials:** Fifty-four patients with conventional osteosarcoma (age ≤39 years) were included in this study. All patients underwent $^{18}$F-FDG PET/CT before (PET1) and after NAC (PET2). We measured PET parameters, including maximum, average, and peak standardized uptake value (SUVmax, SUVave, and SUVpeak); metabolic tumor volume (MTV); and total lesion glycolysis (TLG). Their changes (ΔPET = PET2/PET1) were also examined. The patients were classified into 4 groups based on the histological tumor necrosis rate (TNR): G0 (<50%), G1 (50 to < 90%), G2 (90 to < 100%), and G3 (100%). G0 and G1 patients were enrolled in the standard responder (SR) group (n = 35), while G2 and G3 patients were enrolled in the good responder (GR) group (n = 19). We examined the correlation between changes in each $^{18}$F-FDG PET/CT parameter and TNR as well as overall survival (OS) and progression-free survival (PFS) among the 4 groups. In the SR group, the median value of ΔSUVmax was calculated and correlated with prognostic stratification.

**Results:** The changes in each PET parameter were correlated with TNR, with SUVpeak showing the strongest correlation. Moreover, in the SR group, there were no differences in OS or PFS between G0 and G1. Patients in the SR group were stratified into 2 groups according to the median ΔSUVmax value (0.62). Patients with ΔSUVmax < 0.62 had significantly better OS ($P < 0.01$) and PFS ($P = 0.02$) in comparison with patients with ΔSUVmax ≥ 0.62. In multivariate analyses, ΔSUVmax showed a correlation with OS in the SR group.

**Discussion:** This study revealed that ΔSUVmax may confirm the preoperative stratification of the prognosis be a predictive biomarker for patients in the SR group. Moreover, the preoperative identification of patients with a worse prognosis in the SR group has a significant impact on improving the clinical outcomes of patients with osteosarcoma.

**Level of Evidence:** Prognostic studies, Level III. See Instructions for Authors for a complete description of levels of evidence.

## Introduction

Osteosarcoma is one of the first solid tumors for which neoadjuvant chemotherapy (NAC) proved to be beneficial. Despite significant improvements in survival and the introduction of NAC, treatment options and clinical outcomes have not changed over several decades[1]. The histologic response to NAC is reported to be the most important prognostic factor in osteosarcoma, and patients with whose tumor necrosis rate (TNR) is >90% (good responders: GR) have better outcomes than those a TNR of < 90% TNR (standard responders: SR)[2-7]. The Huvos grade has been widely used to histologically evaluate TNR in resected specimens[8]. However, the Huvos grade

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**TABLE I Patient Characteristics Based on Huvos Grade**

| Huvos Grades | G0 | G1 | G2 | G3 | p |
|---|---|---|---|---|---|
| Number | 16 | 19 | 15 | 4 | |
| Median age (years) | 15 | 14 | 15 | 13.5 | 0.665 |
| Median tumor size (mm) | 85.5 | 99 | 83 | 105.5 | 0.784 |
| Median F/U period (months) | 62 | 88 | 125 | 156 | 0.468 |
| Median TNR (%) | 15 | 70 | 95 | 100 | |
| Sex | | | | | 0.973 |
| Male | 10 | 13 | 10 | 3 | |
| Female | 6 | 6 | 5 | 1 | |
| Location | | | | | 0.878 |
| Femur | 8 | 12 | 10 | 3 | |
| Tibia | 5 | 5 | 4 | 1 | |
| Humerus | 0 | 2 | 0 | 0 | |
| Fibula | 1 | 0 | 1 | 0 | |
| Clavicle | 1 | 0 | 0 | 0 | |
| Radius | 1 | 0 | 0 | 0 | |
| Metastasis | | | | | 0.43 |
| M0 | 14 | 19 | 14 | 4 | |
| M1 | 2 | 0 | 1 | 0 | |
| Final status | | | | | <0.001* |
| CDF | 9 | 11 | 12 | 4 | |
| NED | 0 | 4 | 0 | 0 | |
| AWD | 0 | 1 | 0 | 0 | |
| DOD | 10 | 0 | 3 | 0 | |

AWD = alive with disease, CDF = continuous disease-free, DOD =, dead of disease, F/U = follow-up, TNR = tumor necrosis rate, and NED = no evidence of disease. *Significant difference.

has some disadvantages, including 2-dimensional and subjective evaluation and the inability to predict TNR preoperatively.

Recently, fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) has been performed preoperatively to evaluate the histologic response to NAC and the prognosis of many types of cancer, sarcoma, and lymphoma[9-15].

To improve clinical outcomes in osteosarcoma, intervention for patients with a worse prognosis is needed. However, to the best of our knowledge, there are no reports targeting the further stratifying the SR group. Therefore, we aimed to identify a new biomarker using $^{18}$F-FDG PET/CT parameters to identify patients with a worse prognosis in the SR group of patients with osteosarcoma.

## Material and Methods

### *Ethical Considerations*

The study was approved by our institution's Ethics Review Board (#2024-060) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

### *Patients and Methods*

We retrospectively reviewed the records of patients with conventional osteosarcoma aged younger than 39 years who were treated with NAC and surgery. All patients underwent $^{18}$F-FDG PET/CT before and after NAC. In all patients, the diagnosis of the primary tumor and the TNR of the resected specimens were assessed by pathologists at our institution. The definition of tumor necrosis includes tumors with histological necrosis and/or fibrosis of the tumor cells. The histologic response to NAC was evaluated based on the Huvos grade and classified into 4 groups: G0 (TNR: <50%), G1 (50 to <90%), G2 (90 to <100%), and G3 (100%)[8]. In addition, patients with TNR >90% (G2 and G3) were enrolled in the GR group, and those with TNR <90% (G0 and G1) were enrolled in the SR group.

Fifty-four patients were enrolled in this study. Their medical records were retrospectively analyzed. Data were extracted from each patient's records. Patients underwent $^{18}$F-FDG PET/CT at 2 time points: pre-NAC (PET1) and post-NAC (PET2). Overall survival (OS) and progression-free survival (PFS) were defined as the duration between initial treatment and death and local recurrence or distant metastases. Clinical parameters with prognostic effects were analyzed, and univariate and multivariate analyses were used to identify factors associated with clinical outcomes.

### *$^{18}$F-FDG PET/CT*

After fasting for at least 4 h, the blood glucose levels were measured in all patients before infection with $^{18}$F-FDG. All patients had a serum glucose level of 200 mg/dl before the scan. PET images were obtained 1 h after an injection of $^{18}$F-FDG using a PET/CT scanner (Discovery600, GE Healthcare). PET images were reconstructed using an ordered subset expectation maximization algorithm (AW Server; GE Healthcare).

### *Semiquantitative Analysis*

SUV was defined as the activity concentration (Bq/mL) divided by the injected activity (Bq), normalized to body weight. SUVmax was obtained from the volume of interest (VOI) covering the entire tumor. SUVave and SUVpeak were also calculated for the same VOI. MTV was determined using a threshold of 42% SUVmax. Total lesion glycolysis (TLG) was defined as the product of SUVave and MTV. Changes in SUV parameters were defined as ΔSUV = SUV2/SUV1, ΔMTV = MTV2/MTV1, and ΔTLG = TLG2/TLG1.

### *Statistical Analysis*

The correlation between the TNR and each $^{18}$F-FDG PET/CT parameter was assessed using a linear regression analysis. OS and PFS were estimated using the Kaplan-Meier method, and the log-rank test was used to assess the differences in survival[16]. Differences and correlations were considered to be statistically significant at $p < 0.05$. All statistical analyses were performed using EZR (ver. 1.53; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing). EZR (Easy R) is a

modified version of R Commander designed to add statistical functions that are frequently used in biostatics[17].

## Results

### *Clinical Characteristics of the Patients*

Patient characteristics are given in Table I. Of the 54 patients, 19 (35.2%) were enrolled in the GR group and 35 (64.8%) were enrolled in the SR group. According to the Huvos grade, 16 patients (29.6%) were in G0, 19 (35.2%) in G1, 15 (27.8%) in G2, and 4 (7.4%) in G3. There were no significant differences in sex, age at the primary tumor diagnosis, primary tumor size, location, follow-up period, or distant metastasis at the time of the primary tumor diagnosis. In G0, 10 of 19 patients (52.6%) died of the disease, while in G3, all patients were disease-free at the final follow-up. NAC regimens consisted of methotrexate, doxorubicin, and cisplatin (MAP) (n = 34), with fewer patients receiving MAP plus ifosfamide (IFO) (n = 6), doxorubicin and cisplatin (AP) (n = 1), and AP plus IFO (n = 13). There were no significant differences in the ΔSUVmax among these groups (p = 0.362) or between patients treated with or without IFO (p = 0.648).

### *Correlations Between the Tumor Necrosis Rate and Semiquantitative $^{18}$F-FDG PET/CT Parameters*

The TNR was negatively correlated with ΔSUVmax (R = −0.66, p < 0.001), ΔSUVave (R = −0.61, p < 0.001), ΔSUVpeak (R = −0.77, p < 0.001), ΔMTV (R = -0.57, p = 0.004), and ΔTLG (R = −0.69, p < 0.001) (Fig. 1).

### *Prognosis*

In all 54 patients, the 5-year and 10-year OS rates were 80.8% and 70.3%, respectively. Five-year and 10-year PFS were 66.0% and 66.0%.

Although there was no significant difference in OS between the GR and SR groups (p = 0.11), the GR group showed a trend toward improved survival. PFS was significantly better in the GR group than in the SR group (p = 0.03) (Figs. 2-A and 2-B). In the SR group, there were no significant differences in OS or PFS between G0 (p = 0.08) and G1 (p = 0.873) (Figs. 2-C and 2-D).

The median ΔSUVmax in the SR group was 0.62, which was significantly higher than that in the GR group (0.33, p < 0.001). The 5-year and 10-year OS rates were 100% and 85.1% (95% CI 52.3-96.1%), respectively, in patients with

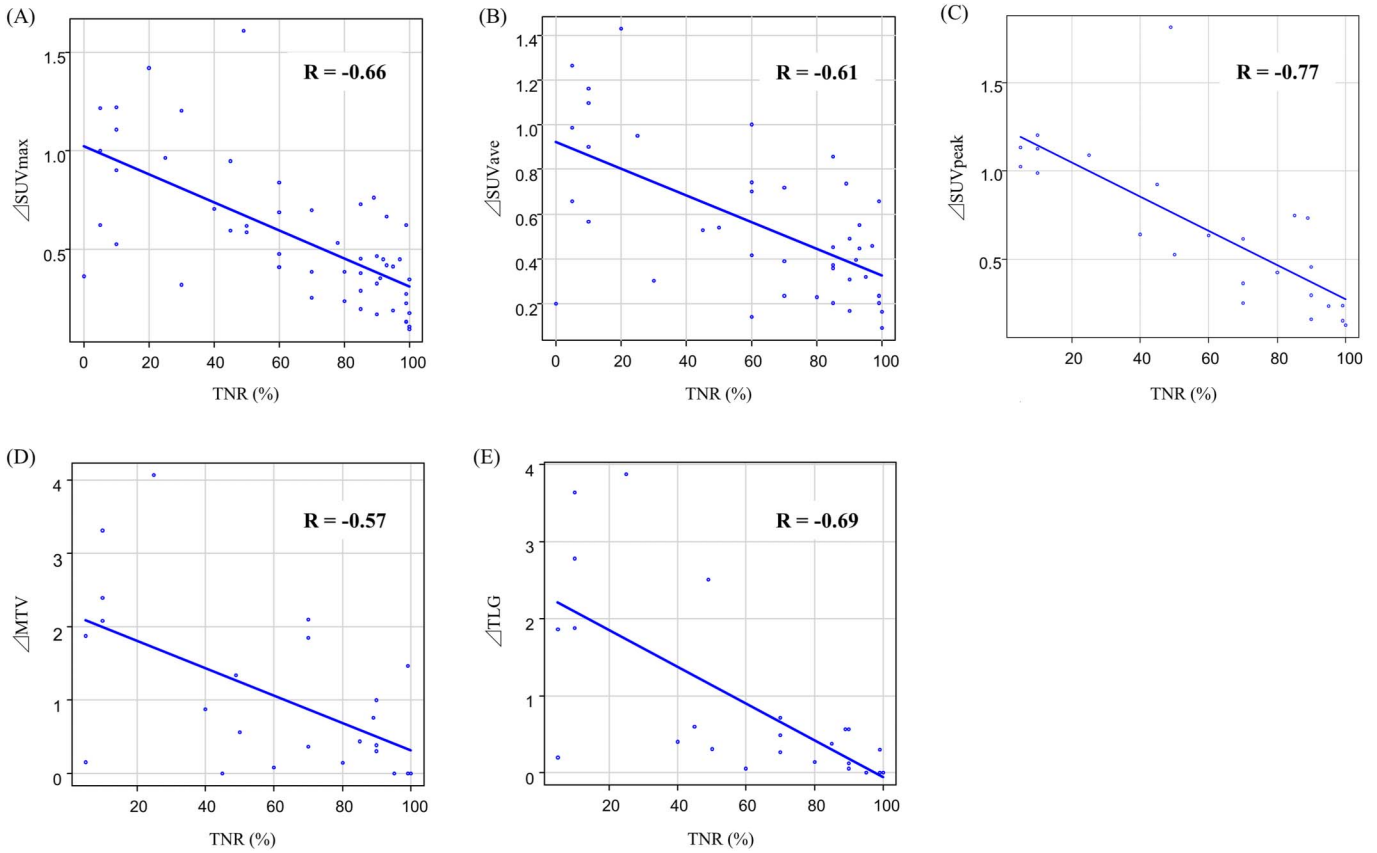


Fig. 1

Correlations between $^{18}$F-FDG PET/CT parameters and tumor necrosis rate. **Fig. 1-A** SUVmax, (**Fig. 1-B**) SUVave, (**Fig. 1-C**) SUVpeak, (**Fig. 1-D**) metabolic tumor volume, and (**Fig. 1-E**) total lesion glycolysis. CT = computed tomography, $^{18}$F-FDG = $^{18}$F-fluorodeoxyglucose, PET = positron emission tomography, and SUV = standardized uptake value.

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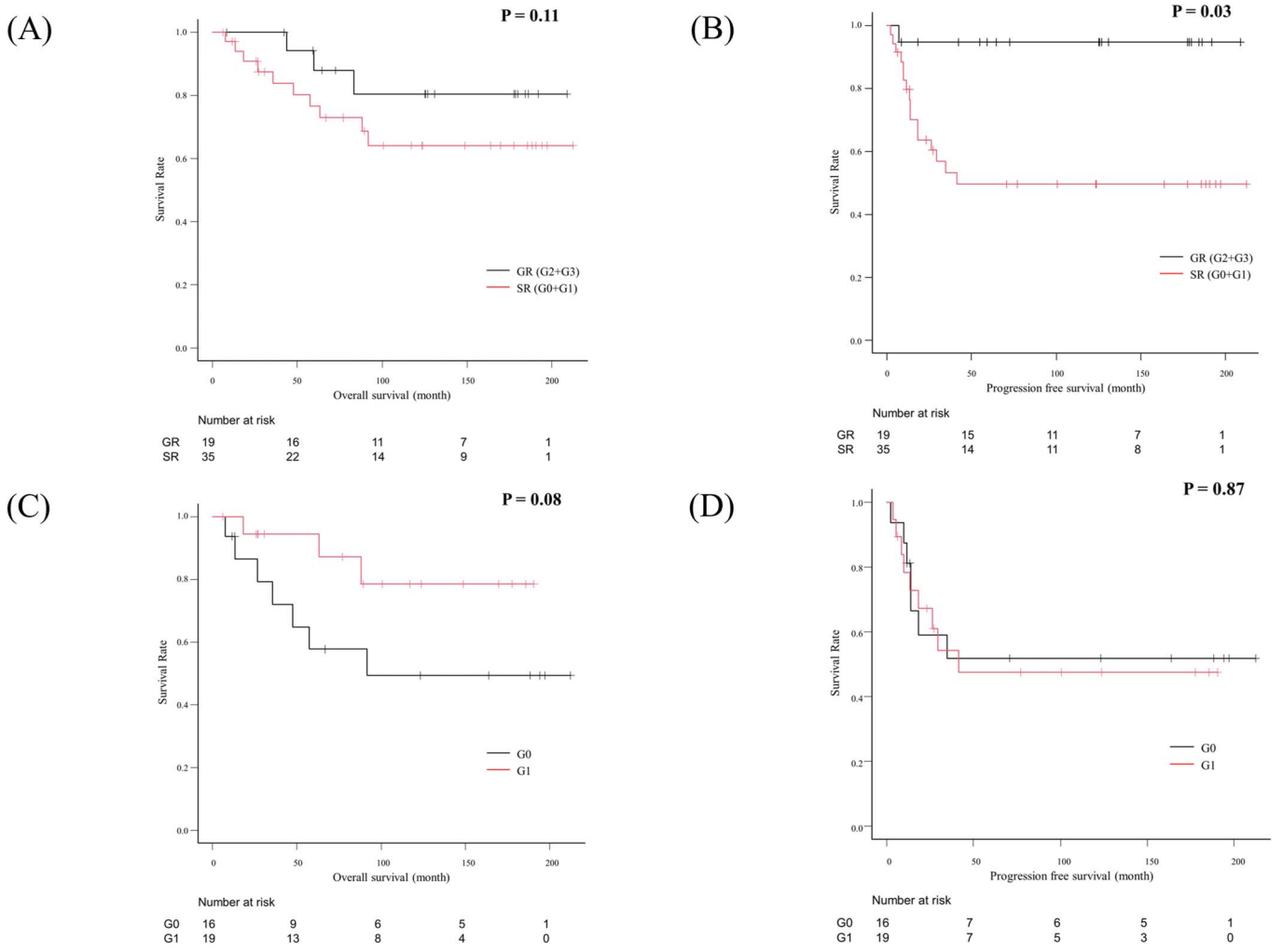


Fig. 2

Kaplan-Meier survival plots of (**Fig. 2-A**) OS and (**Fig. 2-B**) PFS for the GR and SR groups, and (**Fig. 2-C**) OS and (**Fig. 2-D**) PFS for G0 and G1. GR = good responder, OS = overall survival, PFS = progression-free survival, and SR = standard responder.

ΔSUVmax <0.62, and 51.8% (95% CI 24.3-73.6%) and 41.4% (95% CI 15.3-66.1%) in patients with ΔSUVmax ≥0.62. The 5-year and 10-year PFS rates were 69.1% (95% CI 40.7-85.9%) and 69.1% (95% CI 40.7-85.9%), respectively, in patients with ΔSUVmax <0.62, and 28.4% (95% CI 9.0-51.9%) and 28.4% (95% CI 9.0-51.9%) in patients with ΔSUVmax ≥0.62). In the SR group, patients with ΔSUVmax <0.62 had significantly better OS ($p < 0.01$) and PFS ($p = 0.02$) than those with ΔSUVmax ≥0.62 (Fig. 3).

The prognostic factors in the SR group are given in Table II. Cox proportional hazards models revealed that ΔSUVmax ≥0.62 was the only factor significantly associated with worse OS, while tumor size ≥87 mm and M1 were significantly associated with worse PFS.

## Discussion

Osteosarcoma was one of the first solid tumors for which NAC was beneficial. Although survival has improved since the introduction of NAC, the treatment options and clinical outcomes have not changed over several decades[1]. Many reports have shown that the GR prognosis is better than that of SR[2-7], and standard responders are considered to have different treatment options after surgery. However, EURAMOS-1 results showed that adding IFO and etoposide to postoperative chemotherapy did not improve event-free survival in the SR group[18]. Therefore, it is necessary to identify SR patients with a worse prognosis and develop them with novel therapeutic approaches. However, to the best of our knowledge, there are no reports targeting the SR group or stratifying it. This is the first study to suggest stratifying the SR group by SUVmax changes, which is difficult using a conventional pathological evaluation. These results suggest that SUVmax may be a new predictive biomarker to stratify the prognosis of the SR group.

Prognostic factors for patients with osteosarcoma include metastatic disease, primary location, tumor size,

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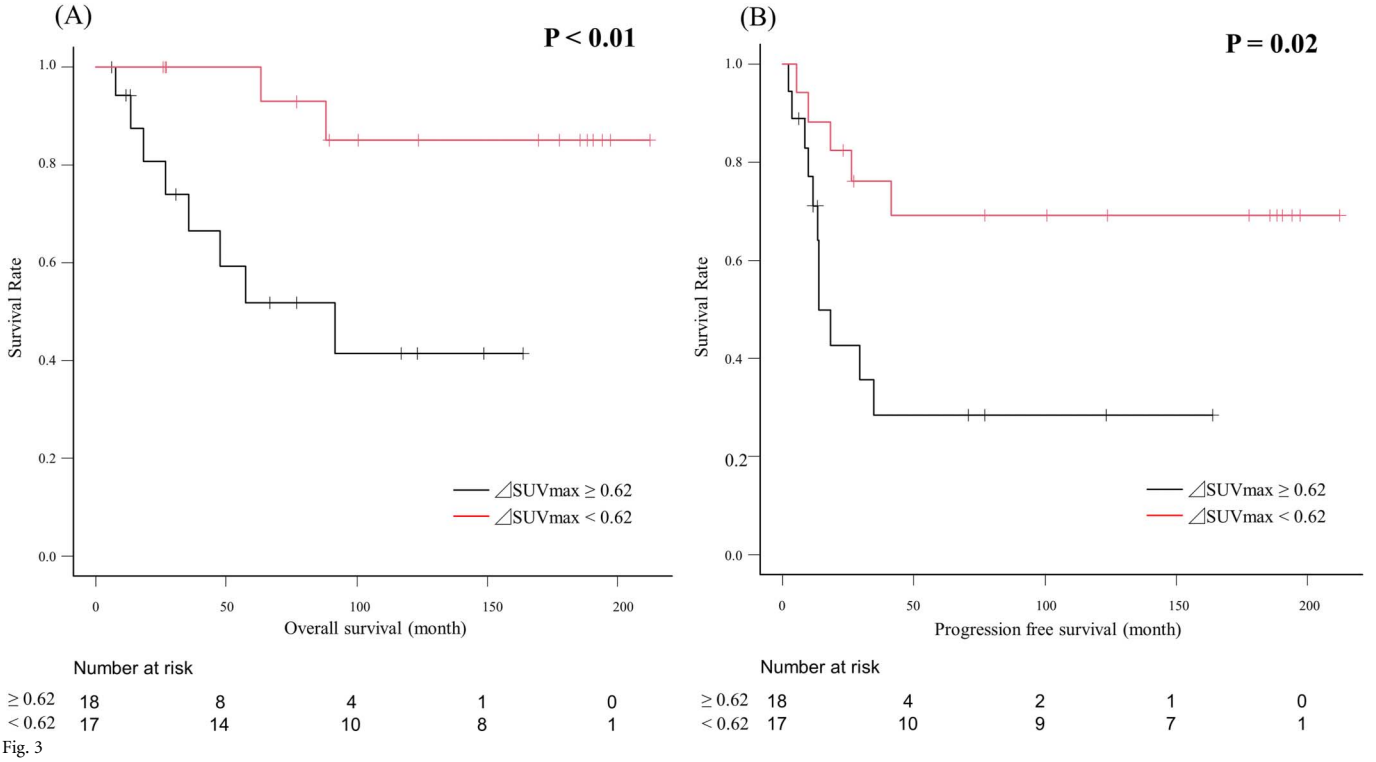


Fig. 3

Kaplan-Meier survival plots of (**Fig. 3-A**) OS and (**Fig. 3-B**) PFS for ΔSUVmax ≥ 0.62 and < 0.62 in the SR group. OS = overall survival, PFS = progression-free survival, and SR = standard responder.

TNR, and surgical remission[3]. In particular, TNR of >90% is reported to be the most important prognostic factor in patients with osteosarcoma to improve outcomes[2-7]. However, there are no reports on prognostic factors in the SR group alone. The Huvos grade is important in categorizing GR and SR groups, but could not stratify the prognosis in the SR group. Moreover, disadvantages of the Huvos grade include 2-dimensional and subjective evaluation and the inability to predict TNR preoperatively.

Recently, $^{18}$F-FDG PET/CT has been frequently used to determine the diagnosis, staging, and response to chemotherapy in many types of cancer, sarcoma, and lymphoma[9-15]. $^{18}$F-FDG PET/CT has the advantages of being a 3-dimensional and objective evaluation that is able to predict the TNR preoperatively, unlike the Huvos grade.

In osteosarcoma, $^{18}$F-FDG PET/CT parameters have also been reported to be useful for predicting histologic responses to NAC or clinical outcomes. The predictors of histologic response to NAC have been reported to be SUVmax and TLG[4], SUVmax[19,20], and MTV and TLG[21]. Similar to this study, $^{18}$F-FDG PET/CT parameters correlated with histologic response to NAC. To the best of our knowledge, there are no reports of correlations between SUVpeak and histologic response to NAC. SUVmax has some advantages because of its simplicity of determination, but concerns remain regarding the effect of image noise on the SUVmax of a single pixel. SUVpeak has superior repeatability and stability in comparison with SUVmax and is less sensitive to image noise[22]. However, due to changes in the equipment used in the current study, SUVpeak could only be measured in 24 cases.

Regarding the correlation between $^{18}$F-FDG PET/CT parameters and the prognosis, Costelloe et al. reported that SUVmax and TLG were associated with OS and PFS[4]. Im et al. reported that SUVpeak, MTV, and TLG are predictive of OS and event-free survival[23]. Other reports have also shown that SUVmax and MTV affect the prognosis[24-26]. However, none of these reports evaluated the prognostic factors in the SR group alone. This study revealed that ΔSUVmax was the only prognostic factor for OS in the SR group. In this study, when the SR group was stratified by the ΔSUVmax at a cutoff value of 0.62, we also observed a significant difference in TNR ($p = 0.01$). However, the TNR is subject to pathologist variability and is considered a relatively subjective parameter. Therefore, ΔSUVmax can be used as a new predictive biomarker to stratify the prognosis of patients in the SR group.

This study has several limitations. First, the sample size was relatively small because osteosarcoma is a rare cancer. Second, the follow-up period was relatively short owing to the retrospective nature of the study and the inclusion of recent cases. Finally, owing to changes in $^{18}$F-FDG PET-CT equipment during the follow-up period, not all $^{18}$F-FDG PET/CT parameters could be detected in all patients.

## Conclusion

Various parameters of $^{18}$F-FDG PET/CT are useful in assessing the histological response to NAC in osteosarcoma.

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**TABLE II Poor Prognostic Factors in the SR Group**

| | | OS | | | | PFS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | Multivariate | | | Univariate | Multivariate | | |
| | Number | 5-Year (%) | p | p | HR 95% CI | 5-Year (%) | p | p | HR 95% CI |
| Age (year) | | | 0.09 | | | | 0.737 | | |
| <14 | 15 | 84.4 | | | | 56.9 | | | |
| ≥14 | 20 | 70.2 | | | | 44.4 | | | |
| Tumor size (mm) | | | 0.124 | | | | 0.004* | 0.007* | 0.158 |
| <87 | 17 | 85.7 | | | | 73.9 | | | 0.041-0.601 |
| ≥87 | 18 | 67.3 | | | | 26.5 | | | |
| TNR (%) | | | 0.084 | | | | 0.447 | | |
| <50 | 16 | 57.7 | | | | 45.2 | | | |
| ≥50 | 19 | 94.4 | | | | 60.2 | | | |
| Sex | | | 0.995 | | | | 0.447 | | |
| Male | 23 | 76.1 | | | | 45.2 | | | |
| | 12 | 77.1 | | | | 60.2 | | | |
| Location | | | 0.659 | | | | 0.11 | | |
| Femur | 20 | 78.1 | | | | 42.9 | | | |
| Tibia | 10 | 85.7 | | | | 74.1 | | | |
| Others | 5 | 50.0 | | | | 25.0 | | | |
| Metastasis | | | 0.001* | 0.068 | 4.81 | | 0.007* | 0.009* | 12.69 |
| M0 | 33 | 81.9 | | | 0.891-25.98 | 52.9 | | | 1.868-86.22 |
| M1 | 2 | NA | | | | NA | | | |
| SUVmax | | | 0.009* | 0.046* | 0.194 | | | | |
| <0.62 | 17 | 100 | | | 0.039-0.970 | 69.1 | 0.016* | 0.138 | 0.429 |
| ≥0.62 | 18 | 51.8 | | | | 28.4 | | | 0.141-1.311 |

CI = confident interval, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, SR = standard responder, SUV = standard uptake value, and TNR = tumor necrosis rate. *Significant difference.

In the SR group, ΔSUVmax was one of the prognostic factors. The rate of change in SUVmax may be a new biomarker for stratifying standard responders among patients with osteosarcoma. Novel therapeutic approaches to identify groups of patients with osteosarcoma who are predicted to have a poorer prognosis and to improve their clinical outcomes are currently needed, and the evaluation of the chemotherapy response by $^{18}$F-FDG PET/CT may provide a breakthrough. ■

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## References

**1.** Harrison DJ, Geller DS, Gill JD, Lewis VO, Gorlick R. Current and future therapeutic approaches for osteosarcoma. Expert Rev Anticancer Ther. 2018;18(1):39-50.

**2.** Wardelmann E, Haas R, Bovée J, Terrier P, Lazar A, Messiou C, LePechoux C, Hartmann W, Collin F, Fisher C, Mechtersheimer G, DeiTos A, Stacchiotti S, Jones R, Gronchi A, Bonvalot S. Evaluation of response after neoadjuvant treatment in soft tissue sarcomas; the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recommendations for pathological examination and reporting. Eur J Cancer. 2016;53:84-95.

**3.** Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, Kotz R, Salzer-Kuntschik M, Werner M, Winkelmann W, Zoubek A, Jürgens H, Winkler K. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol. 2002;20(3):776-90.

**4.** Costelloe CM, Macapinlac HA, Madewell JE, Fitzgerald NE, Mawlawi OR, Rohren EM, Raymond AK, Lewis VO, Anderson PM, Bassett RL Jr., Harrell RK, Marom EM. 18F-FDG PET/CT as an indicator of progression-free and overall survival in osteosarcoma. J Nucl Med. 2009;50(3):340-7.

**5.** Bacci G, Bertoni F, Longhi A, Ferrari S, Forni C, Biagini R, Bacchini P, Donati D, Manfrini M, Bernini G, Lari S. Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity. Histologic response to preoperative chemotherapy correlates with histologic subtype of the tumor. Cancer. 2003;97(12):3068-75.

**6.** Bacci G, Mercuri M, Longhi A, Ferrari S, Bertoni F, Versari M, Picci P. Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. Eur J Cancer. 2005;41(14):2079-85.

**7.** Hauben EI, Weeden S, Pringle J, Van Marck E, Hogendoorn P. Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. Eur J Cancer. 2002;38(9):1218-25.

**8.** Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med. 1977;101(1):14-8.

**9.** Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, Schwartz LH, Zucca E, Fisher RI, Trotman J, Hoekstra OS, Hicks RJ, O'Doherty MJ, Hustinx R, Biggi A, Cheson BD. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27):3048-58.

**10.** Kaneta T, Takahashi S, Fukuda H, Arisaka Y, Oriuchi N, Hayashi T, Fujii H, Terauchi T, Tateishi U, Kubota K, Hara T, Nakamoto Y, Kitajima K, Murakami K. Clinical significance of performing 18F-FDG PET on patients with gastrointestinal stromal tumors: a summary of a Japanese multicenter study. Ann Nucl Med. 2009;23(5):459-64.

**11.** Anderson CD, Rice MH, Pinson C, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. J Gastrointest Surg. 2004;8(1):90-7.

**12.** Kluge R, Schmidt F, Caca K, Barthel H, Hesse S, Georgi P, Seese A, Huster D, Berr F. Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. Hepatology. 2001;33(5):1029-35.

**13.** Shvarts O, Han KR, Seltzer M, Pantuck AJ, Belldegrun AS. Positron emission tomography in urologic oncology. Cancer Control. 2002;9(4):335-42.

**14.** Hillner BE, Siegel BA, Liu D, Shields AF, Gareen IF, Hanna L, Stine SH, Coleman RE. Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. J Clin Oncol. 2008;26(13):2155-61.

**15.** Tateishi U, Hosono A, Makimoto A, Nakamoto Y, Kaneta T, Fukuda H, Murakami K, Terauchi T, Suga T, Inoue T, Kim EE. Comparative study of FDG PET/CT and conventional imaging in the staging of rhabdomyosarcoma. Ann Nucl Med. 2009;23(2):155-61.

**16.** Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457-81.

**17.** Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl. 2013;48(3):452-8.

**18.** Marina NM, Smeland S, Bielack SS, Bernstein M, Jovic G, Krailo MD, Hook JM, Arndt C, van den Berg H, Brennan B, Brichard B, Brown KLB, Butterfass-Bahloul T, Calaminus G, Daldrup-Link HE, Eriksson M, Gebhardt MC, Gelderblom H, Gerss J, Goldsby R, Goorin A, Gorlick R, Grier HE, Hale JP, Hall KS, Hardes J, Hawkins DS, Helmke K, Hogendoorn PCW, Isakoff MS, Janeway KA, Jürgens H, Kager L, Kühne T, Lau CC, Leavey PJ, Lessnick SL, Mascarenhas L, Meyers PA, Mottl H, Nathrath M, Papai Z, Randall RL, Reichardt P, Renard M, Safwat AA, Schwartz CL, Stevens MCG, Strauss SJ, Teot L, Werner M, Sydes MR, Whelan JS. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol. 2016;17(10):1396-408.

**19.** Benz MR, Czernin J, Tap WD, Eckardt JJ, Seeger LL, Allen-Auerbach MS, Dry SM, Phelps ME, Weber WA, Eilber FC. FDG-PET/CT imaging predicts histopathologic treatment responses after neoadjuvant therapy in adult primary bone sarcomas. Sarcoma. 2010;2010:1-7.

**20.** Davis JC, Daw NC, Navid F, Billups CA, Wu J, Bahrami A, Jenkins JJ, Snyder SE, Reddick WE, Santana VM, McCarville MB, Guo J, Shulkin BL. (18)F-FDG uptake during early adjuvant chemotherapy predicts histologic response in pediatric and young adult patients with Osteosarcoma. J Nucl Med. 2018;59(1):25-30.

**21.** Kong CB, Byun BH, Lim I, Choi CW, Lim SM, Song WS, Cho WH, Jeon DG, Koh JS, Yoo JY, Lee SY. (1)(8)F-FDG PET SUVmax as an indicator of histopathologic response after neoadjuvant chemotherapy in extremity osteosarcoma. Eur J Nucl Med Mol Imaging. 2013;40(5):728-36.

**22.** Lodge MA, Chaudhry MA, Wahl RL. Noise considerations for PET quantification using maximum and peak standardized uptake value. J Nucl Med. 2012;53(7):1041-7.

**23.** Im HJ, Zhang Y, Wu H, Wu J, Daw NC, Navid F, Shulkin BL, Cho SY. Prognostic value of metabolic and volumetric parameters of FDG PET in pediatric Osteosarcoma: a hypothesis-generating Study. Radiology. 2018;287(1):303-12.

**24.** Franzius C, Bielack S, Flege S, Sciuk J, Jürgens H, Schober O. Prognostic significance of (18)F-FDG and (99m)Tc-methylene diphosphonate uptake in primary osteosarcoma. J Nucl Med. 2002;43(8):1012-7.

**25.** Sato J, Yanagawa T, Dobashi Y, Yamaji T, Takagishi K, Watanabe H. Prognostic significance of 18F-FDG uptake in primary osteosarcoma after but not before chemotherapy: a possible association with autocrine motility factor/phosphoglucose isomerase expression. Clin Exp Metastasis. 2008;25(4):427-35.

**26.** Byun BH, Kong CB, Park J, Seo Y, Lim I, Choi CW, Cho WH, Jeon DG, Koh JS, Lee SY, Lim SM. Initial metabolic tumor volume measured by 18F-FDG PET/CT can predict the outcome of osteosarcoma of the extremities. J Nucl Med. 2013;54(10):1725-32.