Prediction of Poor Responders to Neoadjuvant Chemotherapy in Patients with Osteosarcoma: Additive Value of Diffusion-Weighted MRI including Volumetric Analysis to Standard MRI at 3T

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Abstract

Objective

To evaluate the added value of diffusion weighted image (DWI) including volumetric analysis to standard magnetic resonance imaging (MRI) for predicting poor responders to neoadjuvant chemotherapy in patients with osteosarcoma at 3-Tesla.

Methods

3-Tesla Standard MRI and DWI in 17 patients were reviewed by two independent readers. Standard MRI was reviewed using a five-level-confidence score. Two-dimensional (2D) apparent diffusion coefficient ($\text{ADC}_{\text{mean}}$) and 2D ADC$_{\text{minimum}}$ were measured from a single-section region of interest. An ADC histogram derived from whole-tumor volume was generated including 3D ADC$_{\text{mean}}$, 3D ADC$_{\text{skewness}}$, and 3D ADC$_{\text{kurtosis}}$. The Mann-Whitney-$U$ test, receiver operating characteristic curve with area under the curve (AUC) analysis, and multivariate logistic regression analysis were performed.

Results

There were 13 poor responders and 4 good responders. Statistical differences were found in posttreatment and percent change of both 2D ADC$_{\text{mean}}$ and 2D ADC$_{\text{minimum}}$, posttreatment 3D ADC$_{\text{mean}}$, and posttreatment 3D ADC$_{\text{skewness}}$ between two groups. The best
predictors of poor responders were posttreatment 2D ADC\textsubscript{mean} and posttreatment 3D ADC\textsubscript{skewness}. Sensitivity and specificity of the 1\textsuperscript{st} model (standard MRI alone), 2\textsuperscript{nd} model (standard MRI+posttreatment 2D ADC\textsubscript{mean}), and 3\textsuperscript{rd} model (standard MRI+posttreatment 2D ADC\textsubscript{mean}+posttreatment 3D ADC\textsubscript{skewness}) were 85% and 25%, 85% and 75%, and 85% and 100% for reader 1 and 77% and 25%, 77% and 50%, and 85% and 100% for reader 2, respectively. The AUC of the 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} models were 0.548, 0.798, and 0.923 for reader 1 and 0.510, 0.635, and 0.923 for reader 2, respectively.

Conclusion
The addition of DWI including volumetric analysis to standard MRI improves the diagnostic accuracy for predicting poor responders to neoadjuvant chemotherapy in patients with osteosarcoma at 3-Tesla.

Introduction
Nonmetastatic osteosarcoma is currently treated with neoadjuvant chemotherapy before surgery [1, 2]. The histologic response after resection reflects the efficacy of neoadjuvant chemotherapy [3]. If the treatment response could be assessed earlier, this information may help avoid ineffective chemotherapy and determine surgical timing [4, 5].

Magnetic resonance imaging (MRI) and fluorine-18 fluorodeoxyglucose (\textsuperscript{18}F FDG) combined positron emission tomography (PET)/computed tomography (CT) using maximum standardized uptake value (SUV\textsubscript{max}) have been used to assess osteosarcoma during neoadjuvant chemotherapy. \textsuperscript{18}F FDG PET/CT assesses the glucose metabolism and calculates the metabolic activity of tumor by SUV [6]. Change of SUV after neoadjuvant chemotherapy in osteosarcoma has been demonstrated to be useful in predicting treatment response [7–9]. However, the delineation of tumor margins on \textsuperscript{18}F FDG PET/CT is difficult and monitoring responses is problematic when the uptake is increased by inflammation or reactive fibrosis [6, 8]. Viable tumors showed strong enhancement without a decrease in tumor size in several previous studies on standard MRI [10–12]. However, standard MRI has limited ability to assess treatment responses because treated lesions sometimes show remnant contrast enhancement and often increase in size despite pathological response.

Posttreatment changes, such as tumor necrosis or a reduction in cell density, cause expansion of the extracellular diffusion space [13]. Diffusion-weighted imaging (DWI) can measure these changes as an increase in apparent diffusion coefficient (ADC) after neoadjuvant chemotherapy. For the osteosarcoma, many studies have assessed the treatment response to neoadjuvant chemotherapy using ADC values; however, the results of previous reports are inconsistent [6, 10, 14–17]. This inconsistency may be attributed to the several differences in techniques of DWI sequences among studies and/or region of interest (ROI) measurement to reflect the whole tumor heterogeneity in a single section. The value of the whole-tumor volume analysis of the ADC map to evaluate the treatment response of osteosarcoma has not been fully demonstrated in the literature, which may complement these limitations [18–20].

Therefore, we hypothesized that DWI including a volumetric analysis may improve the diagnostic performance for predicting poor responders to neoadjuvant chemotherapy in patients with osteosarcoma at 3T.
Materials and methods

Patients

The Seoul St. Mary’s Hospital Institutional Review Board approved this retrospective study and waived the need for informed consent. Thirty-five consecutive patients with osteosarcoma were admitted between March 2009 and May 2017. The inclusion criteria were: (a) conventional osteosarcoma, (b) no identified metastases, (c) 3T MRI including DWI after neoadjuvant chemotherapy, (d) and histologic specimen analysis after surgery. Eighteen patients were excluded for the following reasons: parosteal osteosarcoma (n = 2), telangiectatic osteosarcoma (n = 1), metastatic disease (n = 3), and omission of neoadjuvant chemotherapy (n = 12). Finally, 17 patients (mean age, 17 years [range, 10–53 years]; 13 males) were included (Fig 1). Neoadjuvant chemotherapy was decided using the Children’s Cancer Group (CCG)-7921 regimen A in 12 patients [21]. Four patients did not receive Methotrexate (MTX) at secondary cycle by the monitoring of plasma concentrations. One patient received only one cycle of CCG-7921 regimen A and one cycle of ifosfamide and etoposide because of progressively increasing size. The median interval was 10 days (range, 1–37 days) between neoadjuvant chemotherapy and posttreatment MRI, 109 days (range, 78–166 days) between pretreatment and posttreatment MRI, and 4 days (range, 1–25 days) between posttreatment MRI and surgery. Tumors were located in the femur (n = 9), tibia (n = 4), humerus (n = 3), and scapula (n = 1). Histological subtypes were osteoblastic osteosarcoma (n = 13), fibroblastic osteosarcoma (n = 3), and chondroblastic osteosarcoma (n = 1).

MRI protocols

All 17 patients underwent posttreatment MRI including DWI. Among them, 11 had pretreatment MRI including DWI, while the other 6 patients had only pretreatment standard MRI.

![Flow diagram of the study](https://doi.org/10.1371/journal.pone.0229983.g001)

Fig 1. Flow diagram of the study. MRI = magnetic resonance imaging.

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with no DWI. MRI was performed using a 3T scanner (MAGNETOM Verio; Siemens Healthineers, Erlangen, Germany) with various coils depending on the anatomic region. MRI protocols included longitudinal fat-suppressed (FS) turbo spin-echo (TSE) T2-weighted imaging (T2WI), axial TSE T1-weighted imaging (T1WI), axial TSE T2WI with and without FS, and longitudinal and axial FS contrast-enhanced TSE T1WI. T1WI (TR/TE = 680–870 msec/11–21 msec, turbo factor = 3, number of excitations = 1) and T2WI (TR/TE = 4000–5600 msec/63–83 msec, turbo factor = 13, number of excitation = 1) was obtained with 3–5-mm slice thickness, no interslice gap, an 80–220-mm field of view (FOV), and 512 × 256 matrix size.

DWI was acquired in the axial plane using a single-shot echoplanar imaging sequence. The DWI parameters were as follows: TR/TE, 5000–8700 msec/71–85 msec; FOV, 80–220 mm; slice thickness, 3–5 mm; no interslice gap; matrix size, 80 × 56–128 × 108; EPI factor, 56; and number of excitations, 3–5. Diffusion-sensitizing gradients were applied sequentially in 3 orthogonal directions with four \( b \) values (0, 300, 800, and 1400 sec/mm\(^2\)) in 14 patients and intravoxel incoherent motion DWI with 9 \( b \) values (0, 25, 50, 75, 100, 200, 300, 500, and 800 sec/mm\(^2\)) in the other 14 patients. Pixel-based ADC maps were created based on monoexponential fitting using common \( b \) values of 0 and 800 sec/mm\(^2\) using commercial software and a workstation (Leonardo MR Workplace; Siemens Healthineers, Erlangen, Germany).

**MRI analysis**

Standard MRI analysis for treatment response was performed independently by 2 musculoskeletal radiologists (W.H.J, S.K.L, with 17 and 2 years of experience in musculoskeletal radiology) who were blinded to the patients' clinical histories, MRI reports, surgical findings, and histopathological results. Standard MRI of treatment responses were assessed using a 5-level confidence score: 0, definite good response; 1, probable good response; 2, equivocal; 3, probable poor response; and 4, definite poor response. In the review of standard MRI, pre- and posttreatment images were available for all patients. Therefore, both images were analyzed simultaneously. According to Lang et al. [22], there was no significant difference on T2WI between viable and necrotic tumor tissue because the T2 relaxation times were similar. Therefore, we used contrast-enhanced T1WI to evaluate the viable tumor. When there was an intense enhanced portion at most of area of tumor without interval decrease in extent of enhanced area and size reduction on a posttreatment image, it was considered a definite poor response (score 4) on standard MRI [10–12]. If most of area of tumor was enhanced, despite interval decrease in extent of enhanced area, it was considered a probable poor response (score 3). When the heterogeneous enhancement remained on tumor, despite interval decrease in extent of enhanced area, it was considered an equivocal case (score 3). If most of area of tumor was not enhanced on the posttreatment image, it was considered a probable good response (score 1). When there was little enhancement with size reduction on the posttreatment image, it was considered a definite good response (score 0).

For the single-section ROI of the DWI analysis, the same two readers independently reviewed the DWI with display of standard MRI for the correlation of the solid portion in a picture archiving and communication system. If present, pretreatment DWI was also referenced and analyzed. Two readers independently drew two freehand ROI on a single representative section: 1) mean ADC obtained from the single-section ROI (2D ADC\(_{\text{mean}}\))–ROI that contained the largest area of the tumor except for the peripheral most portions to avoid partial-volume effects. The representative axial slice was carefully selected with reference of standard MRI in order to avoid any necrosis, cystic change, hemorrhage, and sclerosis that might affect the ADC values; and 2) minimum ADC obtained from the single-section ROI (2D ADC\(_{\text{minimum}}\))–ROI located in the lowest signal intensity (SI) within the solid portion of the
tumor on the ADC map that presented as a hyperintense SI on DWI with a \( b \) value of 800 sec/mm\(^2\). To select the lowest ADC value, small ROI (minimum area, 0.5 cm\(^2\)) were drawn 3–5 times and the minimum was recorded [23].

For the whole-tumor volume analysis, the other reader (S.A.I) who was blinded to the patients’ clinical histories, MRI reports, surgical findings, and histopathological results reviewed the DWI using the MR OncoTreat software (provided by Siemens Healthineers, Erlangen, Germany). A freehand ROI was drawn along the border of the tumor on DWI with a \( b \) value of 800 sec/mm\(^2\) on each tumor-containing slice including the solid portion, necrosis, cystic change, hemorrhage, and sclerosis. And then, the software automatically computed the ADC histograms. The mean ADC obtained from the ADC histogram of whole-tumor volume (3D \( ADC_{\text{mean}} \)) was recorded. Skewness and kurtosis were also generated from the ADC histogram of the whole-tumor volume, which reflected the shape of the histogram. Skewness obtained from the whole-tumor volume (3D \( ADC_{\text{skewness}} \)) represents the asymmetry of the ADC value distribution around the mean. A negative skewness indicates that most of the data are concentrated on the right (left-skewed curve). Kurtosis obtained from the whole-tumor volume (3D \( ADC_{\text{kurtosis}} \)) represents the peak and size of the data distribution. A normal distribution shows a skewness of 0 and kurtosis of 3 [24, 25].

The percent change in parameters was calculated if available. The formula used was as follows: Percent change = \[
\frac{\text{Parameter}_{\text{posttreatment}} - \text{Parameter}_{\text{pretreatment}}}{\text{Parameter}_{\text{pretreatment}}} \times 100.
\]

**Pathological analysis**

One pathologist (C.K.J) assessed degree of tumor necrosis using the 4-grade system of Huvos [3, 4]. The resected tumor was fixed in a 10% formaldehyde solution and a representative complete central slab of the specimen was entirely embedded in a grid-like manner. The representative tissue slab was selected and assessed macroscopically, which should reflect the response level of the whole tumor [26]. Based on the histologic analysis, a good responder was defined as >90% tumor necrosis.

**Statistical analysis**

Interobserver agreement for the single-section measurement was evaluated by the Bland-Altman method [27], while the comparison of data between two groups was performed using Mann-Whitney U-test. Diagnostic performances were analyzed using receiver operating characteristic (ROC) curve with areas under the curve (AUC). Sensitivities and specificities were calculated. To examine independent predictive parameters for predicting poor responders, multivariate logistic regression analysis was used. Values of \( P < 0.05 \) were considered statistically significant. All statistical analyses were performed using SPSS Statistics (IBM Corporation, Chicago, IL, USA) and MedCalc (MedCalc, Mariakerke, Belgium).

**Results**

There were four good responders (mean age, 17 years [range, 15–20 years]; 3 males) and 13 poor responders (mean age, 16 years [range, 10–53 years]; 10 males) \( (P > 0.05) \).

**Standard MRI analysis of treatment response**

Standard MRI after neoadjuvant chemotherapy showed significant non-enhancing portions within tumors (score 1) in three patients for reader 1 and in 4 patients for reader 2. Among them, only 1 patient was a good responder on pathological analysis for both readers.
MRI after neoadjuvant chemotherapy showed significant enhancement within the tumors (score 3 or 4) of 11 patients for both readers. Among them, 10 patients were identified as poor responders on pathological analysis for both readers and only 1 patient was a good responder on pathological analysis. The standard MRI showed equivocal (score 2) results for three patients for reader 1 and for 2 patients for reader 2. Two of each were good responders on pathological analysis. Table 1 summarizes the result of a 5-level confidence score for treatment response on standard MRI for both readers.

**Table 1. Results of standard MRI analysis and diagnostic performance for treatment response of osteosarcoma.**

| 5-confidence level       | Reader 1 Poor responder (n = 13) | Good responder (n = 4) | Reader 2 Poor responder (n = 13) | Good responder (n = 4) |
|---------------------------|---------------------------------|------------------------|---------------------------------|------------------------|
| Score 0, definitely good response | 0                               | 0                      | 0                               | 0                      |
| Score 1, probably good response | 2                               | 1                      | 3                               | 1                      |
| Score 2, equivocal        | 1                               | 2                      | 0                               | 2                      |
| Score 3, probably poor response | 9                               | 1                      | 10                              | 0                      |
| Score 4, definitely poor response | 1                               | 0                      | 0                               | 1                      |

**Table 2. Comparison of 2D ADC measurement for treatment response of osteosarcoma.**

| Parameters                  | Poor responder                  | Good responder                  | P     |
|-----------------------------|---------------------------------|---------------------------------|-------|
| Pretreatment 2D ADC<sub>minimum</sub> | n = 9 [870;956]                | n = 2 [999;1127]                | 0.555 |
| Reader 1                    | 955 [813;1268]                  | 939 [765;1112]                  | 0.813 |
| Reader 2                    | 1130 [1065;1426]                | 1180 [1011;1349]                | 0.478 |
| Pretreatment 2D ADC<sub>mean</sub> | n = 9 [955;1127]               | n = 2 [1130;1426]               | 0.813 |
| Reader 1                    | 1179 [1076;1585]                | 1248 [1001;1495]                | 0.637 |
| Reader 2                    | 1195 [1017;1384]                | 1613 [1575;1751]                | 0.024*|
| Posttreatment 2D ADC<sub>minimum</sub> | n = 13 [1195;1384]              | n = 4 [1613;1751]               | 0.089 |
| Reader 1                    | 1099 [998;1481]                 | 1660 [1531;1656]                | 0.024*|
| Reader 2                    | 1531 [1311;1964]                | 2025 [1843;2182]                | 0.089 |
| Posttreatment 2D ADC<sub>mean</sub> | n = 13 [1099;1481]              | n = 4 [1531;1656]               | 0.089 |
| Reader 1                    | 1439 [1232;1968]                | 2151 [2081;2426]                | 0.017*|
| Reader 2                    | 1395 [1131;1964]                | 2025 [1843;2182]                | 0.089 |
| Percent change 2D ADC<sub>minimum</sub> | n = 9 [30;17:38]               | n = 2 [60;44:77]                | 0.099 |
| Reader 1                    | 19 [-3;21]                      | 72 [51;93]                     | 0.034*|
| Percent change 2D ADC<sub>mean</sub> | n = 9 [19;21]                   | n = 2 [72;93]                   | 0.034*|

DWI and ADC map analysis of treatment response

A pretreatment DWI was lacking for 6 patients. For reader 1, the posttreatment 2D ADC<sub>minimum</sub> and posttreatment 2D ADC<sub>mean</sub> were significantly lower in poor responders than in good responders.
responders \( (P = 0.024 \text{ and } P = 0.017, \text{ respectively}) \). In 11 cases with available pretreatment DWI, significantly different percent changes between good and poor responders were found in 2D \( \text{ADC}_{\text{mean}} \), 80.0% vs. 9.5% for reader 1 and 2D \( \text{ADC}_{\text{minimum}} \), 71.9% vs. 19.0% for reader 2 \( (P = 0.034 \text{ for both}) \). Comparisons of pretreatment, posttreatment, and percent change of ADC values derived from single-section ROI (2D ADC) between the two groups are summarized in Table 2. Interobserver agreement for 2D \( \text{ADC}_{\text{minimum}} \) showed that the mean difference (bias) and the 95% confidence interval (CI) of the mean difference (limits of agreement) were -43.27 \( \mu m^2/sec \) (-259.96, 173.42) at pretreatment and 11.47 \( \mu m^2/sec \) (-281.12, 304.44) at posttreatment. Interobserver agreement of posttreatment 2D \( \text{ADC}_{\text{minimum}} \) was superior to that of pretreatment 2D \( \text{ADC}_{\text{minimum}} \) (Fig 2). For 2D \( \text{ADC}_{\text{mean}} \), -27.36 \( \mu m^2/sec \) (-205.42, 150.69) at pretreatment and 68.05 \( \mu m^2/sec \) (-224.79, 360.90) at posttreatment were identified. Interobserver agreement of pretreatment 2D \( \text{ADC}_{\text{mean}} \) was superior to that of posttreatment 2D \( \text{ADC}_{\text{mean}} \) (Fig 2).

The whole-tumor volume analysis revealed significantly lower posttreatment 3D \( \text{ADC}_{\text{mean}} \) in poor responders than in good responders \( (P = 0.042) \). Poor responders demonstrated significantly higher posttreatment 3D \( \text{ADC}_{\text{skewness}} \) than good responders \( (P = 0.017) \). However,
there was no statistical significance in 3D ADC_kurtosis ($P > 0.05$). Comparisons of pretreatment, posttreatment, and percent change of ADC values derived from whole-tumor volume (3D ADC) between the two groups are summarized in Table 3.

**ROC analysis of treatment response**

There was no statistical significance in AUC in the 5-level confidence scores of the standard MRI between the two readers (reader 1, 0.740, $P = 0.157$; reader 2, 0.606, $P = 0.533$). The ROC analysis of standard MRI for treatment response is summarized in Table 1.

Posttreatment and percent change of 2D ADC_min and 2D ADC_mean showed statistically significant AUC for reader 1, while the same parameters except percent change of 2D ADC_mean showed statistically significant AUC for reader 2 ($P < 0.05$) for discriminating between good and poor responders (Figs 3 and 4). The ROC analysis of ADC values derived from single-section ROI (2D ADC) with optimal cutoff values is summarized in Table 4.

Posttreatment and percent change of 3D ADC_mean and posttreatment 3D ADC_skewness showed statistically significant AUC ($P < 0.05$) for treatment response (Fig 5). The ROC analysis of ADC values derived from whole-tumor volume with optimal cutoff values is summarized in Table 5.

**Multivariate logistic regression analysis for predicting poor responders**

Based on the stepwise multivariate logistic regression analysis, the best predictors for poor responders were posttreatment 2D ADC_mean (odds ratio, 0.999; 95% confidence interval, 0.986–1.002) of reader 1 and none of reader 2 among ADC values obtained from the single-section ROI and posttreatment 3D ADC_skewness (odds ratio, 62.08; 95% confidence interval, 0.62–6221.71) among ADC values obtained from the whole-tumor volume.

Three prediction models were designed as follows: 1st model, standard MRI alone; 2nd model, standard MRI combined with posttreatment 2D ADC_mean; and 3rd model, standard MRI combined with posttreatment 2D ADC_mean and posttreatment 3D ADC_skewness. Each of the models showed sensitivity and specificity as follows: 85% and 25%; 85% and 75%; and 85% and 100% for reader 1 and 77% and 25%; 77% and 50%; and 85% and 100% for reader 2, respectively. Each of the models showed the following AUC values: 0.548, 0.798, and 0.923 for reader 1; and 0.510, 0.635, and 0.923 for reader 2, respectively. Each of the models showed the following AUC values: 0.548, 0.798, and 0.923 for reader 1; and 0.510, 0.635, and 0.923 for reader 2, respectively. (Fig 6). Other model of standard

Table 3. Comparison of 3D ADC measurement for treatment response of osteosarcoma.

| Parameters         | Poor responder | Good responder | $P$  |
|-------------------|----------------|----------------|------|
| Pretreatment 3D ADC_mean | $n = 13$ | $n = 4$ |      |
| Pretreatment 3D ADC_skewness | 0.3 [−0.5; 0.7] | 0.4 [-0.7; 1.5] | 0.814 |
| Pretreatment 3D ADC_kurtosis | 4.7 [4.0; 5.8] | 5.4 [4.0; 6.8] | 0.637 |
| Posttreatment 3D ADC_mean | 1574.3 [1309.6;1864.2] | 2053.6 [1967.2;2224.6] | 0.042* |
| Posttreatment 3D ADC_skewness | -0.0 [-0.4; 0.4] | -0.9 [-1.2; -0.8] | 0.017* |
| Posttreatment 3D ADC_kurtosis | 3.6 [3.0; 4.9] | 5.1 [4.2; 5.5] | 0.258 |
| Percent change 3D ADC_mean | 10.6 [-2.4;20.4] | 69.8 [28.1;111.5] | 0.099 |
| Percent change 3D ADC_skewness | -67.5 [-81.7; -21.3] | -31.2 [-153.6;91.3] | 1.000 |
| Percent change 3D ADC_kurtosis | -21.9 [-42.6;23.4] | -1.7 [-49.8;46.4] | 0.637 |

3D ADC, apparent diffusion coefficient values derived from whole-tumor volume.

*indicates statistical significance.

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MRI combined with posttreatment 3D ADC skewness also showed sensitivity and specificity of 85% and 100% with AUC of 0.923, same as 3rd model.

Discussion

Our study showed that the addition of DWI including a volumetric analysis to standard MRI improved the diagnostic accuracy for determining poor responders to neoadjuvant chemotherapy among osteosarcoma patients. Among the parameters obtained from single-section ROI, posttreatment mean ADC was the best independent predictor for poor responder. On the other hand, posttreatment skewness of ADC obtained from whole-tumor volume in addition to posttreatment mean ADC obtained from single-section ROI were helpful for less experienced readers.

Osteosarcoma is the most common type of malignant bone tumor with a peak incidence in the second decade of life [28]. It arises within bone and may metastasize to lung [19]. A combination of surgery and chemotherapy is the choice of treatment, which improved the survival rates [29]. However, there are still 20 – 30% of patients with poor curative effect of limb salvage surgery, and the extent of tumor necrosis to neoadjuvant chemotherapy has been known to be the most important prognostic factor in patients with localized disease [20]. Traditionally, the therapeutic effectiveness of chemotherapy was assessed by comparison of tumor size before and after therapeutic intervention [30]. However, for the osteosarcomas, there was a specific issue; the tumor size showed little changes after neoadjuvant chemotherapy [12, 31], despite
successful chemotherapy. The reason was that the chemotherapy on osteosarcomas has only affected on the mineralized matrix of tumor [10]. According to Lang et al. [22], signal intensity (SI) changes on T2WI are sometimes nonspecific because both viable and necrotic tissues can demonstrate similar SI. The main reason for misinterpretation based on standard MRI could be related to the granulation tissue or fibrosis being interpreted as viable enhancing solid portions [12, 31, 32]. If the treatment response to neoadjuvant chemotherapy cannot be accurately evaluated, it will have an adverse effect to surgical planning, adjuvant chemotherapy selection, and prognostic judgement [20]. Therefore, it is necessary to find an effective and quantitative method to evaluate the treatment response.

DWI may help differentiate granulation/fibrotic tissue from viable tumors [10, 14, 16, 22]. In previous studies, the treatment response of osteosarcoma was assessed with DWI using single-section ROI (2D ADC) on a representative axial image [6, 10, 14, 16, 20, 22]. ADC measurement reduces the number of misleading cases by using parameters including percent changes of 2D ADC and posttreatment 2D ADC values. Many previous studies have reported that ADC difference and ADC ratio were greater in good responders than in poor responders [6, 10, 14, 15]. One study reported that the ADC_{mean} showed a significant correlation with treatment response as the best predictor of treatment [17]. However, another study showed that the significant difference between good and poor responders was not in ADC_{mean} ratio; rather, it was in ADC_{minimum} ratio [16]. ADC_{minimum} ratio well reflects not only the highest cellular portions but also the treatment response in a similar context of SUV_{max}, which represents the point of highest
metabolic activity in a tumor [8, 33]. This inconsistency may be attributed to differences in experience and interpretation, ROI methods, MRI vendors, and MRI parameters among readers and studies for reflecting whole-tumor heterogeneity from single-section analysis. This inconsistency could also be due to reader experience since assessments using ADC with a single-section ROI may have low reproducibility in less experienced readers [18]. Furthermore, DWI interpretation of poor responders with extraosseous myxoid component or with the chondroblastic osteosarcoma subtype, in which ADC values were similar to those of tumor necrosis [34]. Therefore, we thought that ADC mean could better reflect the tumor heterogeneity than ADC minimum value and found that ADC mean was the best independent predictor for poor responders among the parameters obtained from single-section ROI.

Whole-tumor volume analysis of the ADC map may complement these limitations of single-section ROI measurement [18]. One study reported that ADC mean ratio, skewness, and kurtosis derived from whole-tumor volume were well correlated with the therapy-induced response [19]. Another report demonstrated that posttreatment ADC mean derived from whole-tumor volume in good responders was higher than that of poor responders [20]. In our study, posttreatment 3D ADC skewness derived from whole-tumor volume analysis of the ADC histogram was helpful for predicting poor responders, especially less experienced readers or patients with no available pretreatment DWI or the chondroblastic osteosarcoma subtype. Like our results, Wang et al [20] reported significant differences in ADC mean and peak of the ADC histogram after neoadjuvant chemotherapy between good and poor responders. However, Wang et al [20] analyzed ADC histograms visually and did not use quantitative measurements such as ADC skewness or ADC kurtosis. Based on our study findings, quantitative ADC histogram analysis derived from whole-tumor volume may allow easy and quick perception of treatment response because a negative skewness of ADC value derived from whole-tumor

Table 4. Diagnostic performances of 2D ADC measurement for treatment response.

| Parameters              | Cutoff | Sensitivity | Specificity | AUC   |
|-------------------------|--------|-------------|-------------|-------|
| Pretreatment 2D ADC<sub>minimum</sub> |         |             |             |       |
| Reader 1                | ≤ 956  | 78%         | 50%         | 0.639 |
| Reader 2                | > 765  | 78%         | 50%         | 0.556 |
| Pretreatment 2D ADC<sub>mean</sub> |         |             |             |       |
| Reader 1                | > 1011 | 89%         | 50%         | 0.667 |
| Reader 2                | > 1001 | 78%         | 50%         | 0.611 |
| Posttreatment 2D ADC<sub>minimum</sub> |         |             |             |       |
| Reader 1                | ≤ 1442 | 85%         | 100%        | 0.885 |
| Reader 2                | ≤ 1481 | 77%         | 75%         | 0.788 |
| Posttreatment 2D ADC<sub>mean</sub> |         |             |             |       |
| Reader 1                | ≤ 2079 | 85%         | 75%         | 0.904 |
| Reader 2                | ≤ 1783 | 69%         | 75%         | 0.788 |
| Percent change 2D ADC<sub>minimum</sub> |         |             |             |       |
| Reader 1                | ≤ 37.73| 78%         | 100%        | 0.889 |
| Reader 2                | ≤ 39.3 | 100%        | 100%        | 1.000 |
| Percent change 2D ADC<sub>mean</sub> |         |             |             |       |
| Reader 1                | ≤ 34.73| 100%        | 100%        | 1.000 |
| Reader 2                | ≤ 40.51| 100%        | 50%         | 0.778 |

2D ADC, apparent diffusion coefficient values derived from single-section regions of interest.
AUC, areas under the curve.
* indicates statistical significance.

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volume after chemotherapy is related to a higher proportion of tumor necrosis in good responders, causing ADC histograms to have a right-sided peak.

We demonstrated the feasibility of posttreatment DWI for assessing treatment response. A similar result that post-neoadjuvant chemotherapy ADC value in good responders was significantly higher than that of poor responders was noted in one study of osteosarcoma [20]. These results suggested that treatment efficacy could be evaluated without comparison of the initial examination.

There were several limitations to our study. First, it was a retrospective study and, therefore, subject to selection bias. Second, a small number of patients from a single institution was included. Third, pretreatment DWI was not available for 6 of the 17 patients; thus, the evaluation using percent change was limited. Fourth, we used only two common $b$ values of 0 and 800 sec/mm$^2$ because protocols have changed in our institution. And finally, histopathological whole-tumor mapping of specimens was not performed as in other studies.
In conclusion, the addition of DWI including a volumetric analysis to standard MRI may improve the diagnostic performance of predicting poor responders to neoadjuvant chemotherapy in patients with osteosarcoma at 3T. Posttreatment mean ADC obtained from single-section ROI and posttreatment skewness of ADC obtained from whole-tumor volume may be the best predictors for poor responders in patients with osteosarcoma.

Table 5. Diagnostic performances of 3D ADC measurement for treatment response.

| Parameters          | Cutoff     | Sensitivity | Specificity | AUC  |
|---------------------|------------|-------------|-------------|------|
| Pretreatment 3D ADC$_{\text{mean}}$ | >943.24    | 89%         | 50%         | 0.667|
| Pretreatment 3D ADC$_{\text{skewness}}$ | ≤1.45      | 89%         | 50%         | 0.556|
| Pretreatment 3D ADC$_{\text{kurtosis}}$ | ≤6.33      | 89%         | 50%         | 0.611|
| Posttreatment 3D ADC$_{\text{mean}}$ | ≤2039.17   | 85%         | 50%         | 0.846*|
| Posttreatment 3D ADC$_{\text{skewness}}$ | >-0.82     | 85%         | 100%        | 0.904*|
| Posttreatment 3D ADC$_{\text{kurtosis}}$ | ≤4.9       | 77%         | 75%         | 0.692|
| Percent change 3D ADC$_{\text{mean}}$ | ≤45.1      | 89%         | 50%         | 0.889*|
| Percent change 3D ADC$_{\text{skewness}}$ | >-153.65   | 100%        | 50%         | 0.500|
| Percent change 3D ADC$_{\text{kurtosis}}$ | ≤39.43     | 100%        | 50%         | 0.611|

3D ADC, apparent diffusion coefficient values derived from whole-tumor volume.
AUC, areas under the curve.
* indicates statistical significance.

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Fig 6. ROC comparison between three prediction models for both readers. AUC is increased by adding parameters to standard MRI. The 1$^\text{st}$ model: standard MRI alone, the 2$^\text{nd}$ model: standard MRI with posttreatment 2D ADC$_{\text{mean}}$, the 3$^\text{rd}$ model: standard MRI with posttreatment 2D ADC$_{\text{mean}}$ and posttreatment 3D ADC$_{\text{skewness}}$. Post- = posttreatment; 2D = single-section ROI; 3D = whole-tumor volume; ROC = receiver operating characteristic; AUC = areas under the curve.

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Supporting information

S1 Dataset. (XLSX)

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Contact: https://www.siemens-healthineers.com/en-au/magnetic-resonance-imaging/magnetom-world/clinical-corner/clinical-talks/tumor-therapy-assessment-with-oncotreat.html.

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