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Research Paper

Prediction and evaluation of neoadjuvant chemotherapy using the dual mechanisms of ^{99m}Tc-MIBI scintigraphy in patients with osteosarcoma

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ABSTRACT

Purpose: To investigate the feasibility of applying the dual imaging mechanisms of ^{99m}Tc-MIBI scintigraphy in predicting and evaluating the response to neoadjuvant chemotherapy in patients with osteosarcoma.

Materials and methods: Thirty patients with osteosarcoma who underwent both pre-and post-chemotherapy ^{99m}Tc-MIBI scintigraphy were enrolled in the study. In each patient, the tumor to background ratio (T/B), tumor washout rate (WR) of MIBI and the alteration rate (AR) of tumor uptake after chemotherapy was calculated, respectively, on MIBI scintigraphy before or after chemotherapy. Based on the tumor necrosis rate histologically confirmed by tumor resection after chemotherapy, the diagnostic performance of MIBI scintigraphy was assessed in predicting tumor response with the WR of pre-chemotherapy imaging, as well as evaluating tumor response with the AR of both pre-and post-chemotherapy imaging.

Results: On pre-chemotherapy MIBI imaging, no statistical difference was found in T/B values between patients with good response and those with poor response, but the WR in patients with good response was significantly lower. Tumor WR was negatively correlated with the tumor necrosis rate ($r = -0.510$, $P = 0.004$). When WR $\leq$ 25% was taken as the threshold for predicting good response, a sensitivity of 100%, a specificity of 91.7% and an accuracy of 95.8% would be yielded. On post-chemotherapy imaging, T/B values both on early and delayed phases were significantly lower in responders and AR of tumor uptake was significantly higher in these responders. When AR $\geq$ 38% was used as the threshold for a good response, a sensitivity of 91.7%, a specificity of 94.4% and an accuracy of 93.3% would be yielded. The diagnostic coincidence rate between WR for predicting chemotherapy response and AR for evaluating chemotherapy response was 90.0% (kappa = 0.789, $P < 0.001$).

Conclusion: ^{99m}Tc-MIBI imaging is a useful tool for the evaluation of neoadjuvant chemotherapy in patients with osteosarcoma, and its dual mechanisms could be simultaneously used in predicting and evaluating tumor response to chemotherapy.

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor in China, which usually occurs in adolescents and has a high degree of malignancy. Its diagnosis, treatment and prognosis have always been a hot point concerned by clinicians. In the past, the five-year survival rate of patients was only about 20 − 30% with surgery alone. However, with the development of neoadjuvant chemotherapy, the chance of patients to retain limb function has experienced an increase and the five-year survival rate has also increased to 65 − 70% [1–3]. Clinical studies have found that tumor response to chemotherapy was closely related to the prognosis of patients [4,5], and timely monitoring the tumor response to chemotherapy is of great significance for the selection of reasonable treatment and the evaluation of prognosis. Currently, the tumor necrosis rate from the post-chemotherapy surgical resection is used as the "gold standard" for evaluation of neoadjuvant chemotherapy response [6,7]. But this method is cumbersome to some extent and it cannot be monitored real-time and applied in non-surgical patients. It was reported that ^{99m}Tc-MIBI can be used not only as a tumor avid imaging agent to evaluate tumor chemotherapy response [8,9], but also as a multidrug-resistant gene expression imaging agent to predict tumor drug resistance [10,11]. However, there is no evidence that the dual mechanisms can be used to predict and evaluate tumor chemotherapy response at the same time. In order to evaluate the feasibility of applying the dual imaging mechanisms of MIBI in predicting and evaluating the response to neoadjuvant chemotherapy, in this study, we prospectively investigated a group of patients with osteosarcoma who underwent both pre-and post-chemotherapy ^{99m}Tc-MIBI scintigraphy.

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2. Materials and methods

2.1. Study subjects

Among the inpatients diagnosed with osteosarcoma through puncture biopsy or open biopsy and prepared for neoadjuvant chemotherapy during November 2013 and October 2017, those meeting the following four conditions were selected as the study subjects: (1) completed the APMI program formulated by our hospital regularly (doxorubicin 60 mg/m^2, cisplatin 100 mg/m^2, high-dose methotrexate 8–12 g/m^2, ifosfamide 2 g/m^2); (2) obtained ^{99m}Tc-MIBI scintigraphy twice within one week before the beginning of chemotherapy and one week after the end of chemotherapy, respectively; (3) complete tumor resection specimens could be obtained after chemotherapy; (4) postoperative follow-up of at least one year was obtainable. A total of 30 patients, including 26 males and 4 females, were enrolled in the study, with age ranging from 6 to 38 years (mean age: 15.1 ± 5.7 years). All patients underwent tumor resection within one month after chemotherapy (mean time interval: 15.1 ± 4.5 days).

2.2. ^{99m}Tc-MIBI scintigraphy

Optima NM/CT 640 (GE Healthcare, USA) or Philips Precedence 6 (Philips Medical Systems, Netherlands) was used for ^{99m}Tc-MIBI scintigraphy. After intravenous injection of ^{99m}Tc-MIBI (provided by Isotope & Radiation Co., Ltd., Beijing, China; adult dose: 740 MBq, children dose: 250 μCi/kg), early and delayed planar images were acquired at 15 min and 90 min, respectively. In addition to visual analysis, the region of interest (ROI) around the lesion was drawn manually, and an identical ROI was placed on the contralateral normal limb as a background (Fig. 1) for the image analysis. The tumor to background ratio (T/B) was calculated on the mean counts according to the ROIs. Tumor MIBI washout rate (WR) was measured on pre-chemotherapy imaging, by using the following formula: WR (%) $= \frac{T/B\ 15\ min - T/B\ 90\ min}{T/B\ 15\ min} \times 100$. Tumor alteration rate (AR) of T/B value was calculated based on the pre-chemotherapy and post-chemotherapy images.

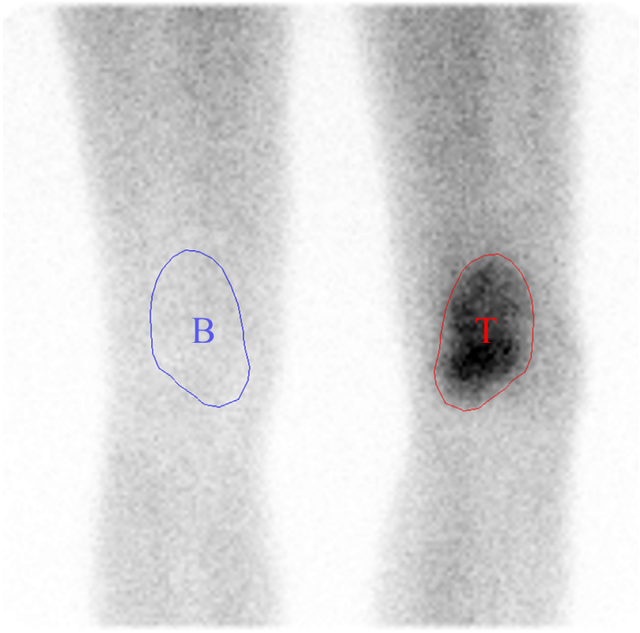

Fig. 1. ROIs of the tumor and the background.

2.3. Evaluation of tumor necrosis rate

All patients underwent the tumor resection after chemotherapy. The tumor was divided along the maximum section, and the section was divided into 20–40 small pieces by grid. The tumor necrosis rate of each small piece of the specimen was calculated, and the arithmetic average was carried out to represent the whole tumor necrosis rate. Based on the Huvos grading system, tumor necrosis rate was divided into four grades [12]: Grade I, rare or no tumor necrosis was observed, 0–50% necrosis; Grade II, tumor cells were partially necrotized and regional viable tumor cells were found, 50 − 90% necrosis; Grade III, a few viable cells remained and only scattered tumor cells were observed, 90 − 99% necrosis; Grade IV, there were no viable tumor cells. According to the previous studies [13–16], chemotherapy response was considered as good when tumor necrosis rate was greater than or equal to 90%, and as poor when tumor necrosis rate was less than 90%.

2.4. Data analysis

According to the necrosis rate of tumor tissues surgically removed after chemotherapy, patients in this group who received neoadjuvant chemotherapy were divided into the response group and poor-response group. Tumor WR of MIBI was used as an indicator to predict the tumor response before the chemotherapy, and AR of tumor uptake of MIBI as an indicator to evaluate the response after chemotherapy. The difference between response group and poor-response group in WR and AR was observed, and the correlation was analyzed between tumor necrosis rate with WR and AR. The receiver operating characteristic (ROC) curves were generated to determine the cut-off values that offered the highest sum of sensitivity and specificity of WR and AR, and the diagnostic efficacy was evaluated, respectively. In addition, based on the clinical follow-up results, the value of tumor necrosis rate, WR and AR for the patient prognosis were analyzed, respectively.

2.5. Statistical analysis

Using SPSS16.0 (SPSS Inc. Released in 2007) software, quantitative parameter differences between the two groups were analyzed with Student *t*-test. The correlation between different variables was evaluated using the Pearson correlation analysis. And the ROC curves were used for diagnostic performance analyses. In addition, using MedCalc (version 11.4.4.0) software, Kaplan–Meier survival curve was performed to compare the progression-free survival rate between different groups of patients by single-factor analysis. All statistical analysis results were considered statistically significant with $P < 0.05$.

3. Results

All the 30 patients with osteosarcoma in this study had single lesions, located at the distal femur (22), proximal tibia/fibula (5), proximal humerus (1), distal tibia (1) and middle femur (1), respectively. The pathological examination results of tumor resection showed 17 cases of conventional type, 6 cases of osteoblast type, 4 cases of chondroblast type, 2 cases of giant cell type, and 1 case of fibroblast type. According to the tumor necrosis rate, 12 patients with tumor necrosis rate ≥90% were responders, including 7 cases of conventional type, 3 cases of osteoblast type and 2 cases of giant cell type. 18 patients with tumor necrosis rate <90% were poor responders, including 10 cases of conventional type, 4 cases of chondroblast type, 3 cases of osteoblast type and 1 case of fibroblast type.

3.1. Pre-chemotherapy MIBI scintigraphy predicting the response to chemotherapy

Before chemotherapy, there was no statistical difference between the response group and poor-response group in the tumor uptake of

Table 1
Semi-quantitative analysis of MIBI scintigraphy before chemotherapy in patients with osteosarcoma.

	Response group (n = 12)		Poor-response group (n = 18)		Statistical parameters	
	Range	Mean ± SD	Range	Mean ± SD	t	P
Early T/B value	1.42–8.12	3.31 ± 2.19	0.80–6.33	3.49 ± 1.72	0.252	0.803
Delayed T/B value	1.15–6.49	2.53 ± 1.58	0.56–4.09	2.28 ± 1.14	−0.497	0.623
WR (%)	9.2–43.8	21.2 ± 8.5	25.5–52.3	33.8 ± 8.0	4.066	<0.001

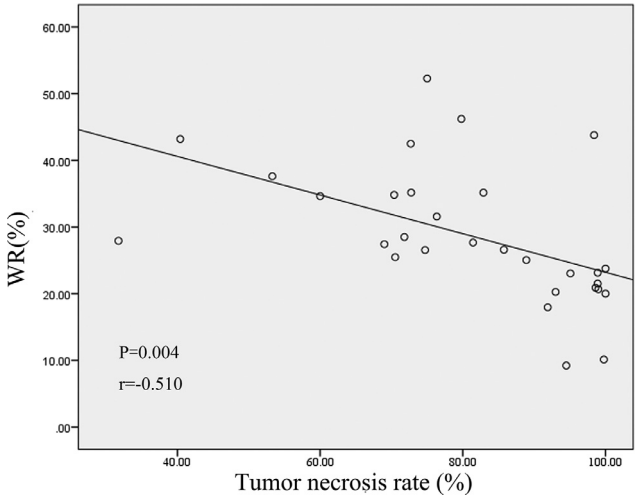

Fig. 2. Pearson correlation analysis between tumor washout rate (WR) and tumor necrosis rate.

MIBI on both early and delayed phases. However, tumor washout rate in the response group was significantly lower compared with the poor-response group (Table 1). It was found that the WR was correlated negatively with the tumor necrosis rate ($r = -0.510$, $P = 0.004$) (Fig. 2). ROC curve analysis based on tumor necrosis rate showed that when WR ≤ 25% was taken as the prediction threshold for good chemotherapy response, the maximum area under the curve (AUC) was 0.926 ($P < 0.001$). The predictive sensitivity, specificity and accuracy were 100.0%, 91.7% and 95.8%, respectively.

3.2. Pre-and post-chemotherapy scintigraphy evaluating the response to chemotherapy

Semi-quantitative analysis results of MIBI scintigraphy before and after chemotherapy were listed in Table 2. Although there was no statistical difference in tumor MIBI uptake before chemotherapy between the two groups, tumor MIBI uptake was significantly lower and AR was greater after chemotherapy in the patients of response group. Pearson correlation analysis showed that AR on both early and delayed phases had a moderately positive correlation with the tumor necrosis rate ($r = 0.630$, $P < 0.001$; $r = 0.611$, $P < 0.001$) (Fig. 3). ROC analysis based on the tumor necrosis rate showed that when AR ≥ 38% after chemotherapy was taken as the threshold for good response, the maximum AUC was 0.931 ($P < 0.001$), and a sensitivity of 91.7%, a specificity of 94.4% and an accuracy of 93.3% would be yielded. On MIBI scintigraphy, a diagnostic coincidence rate of 90.0% (kappa = 0.789, $P < 0.001$) was achieved between the WR to predict the tumor response to chemotherapy and the AR to evaluate the response.

3.3. Clinical follow-up results

By the end of November 2018, the follow-up duration of patients in this study was 14–59 months (39 ± 8 months). Among them, 11 patients (36.7%) with tumor recurrence or metastasis after treatment (including 1 death) were considered as disease progression. The other 19 patients (63.3%) without recurrence or metastasis were considered as no disease progression. Kaplan–Meier survival curve analysis showed that the patients with tumor necrosis rate ≥90% had significantly higher disease progression-free survival rate than those with tumor necrosis rate <90%; meanwhile, patients with tumor WR less than or equal to 25% before chemotherapy or tumor uptake of MIBI decreased more than or equal to 38% after chemotherapy also had a better prognosis (Fig. 4).

4. Discussion

Although the introduction of neoadjuvant chemotherapy into the treatment of osteosarcoma improved the survival rate of patients, local recurrence or metastasis still occur in about 30−40% patients [17], which is related to the poor efficacy of tumor chemotherapy. The necrosis rate of tumor tissue after chemotherapy can directly reflect the tumor response to chemotherapy, and it is considered as an important indicator for the prognosis of patients with osteosarcoma [6]. However, it can only be obtained after tumor resection, and its procedure is quite complex. With the popularization and application of PET/CT in oncology, the role of ^{18}F-FDG PET/CT in the evaluation of chemotherapy for osteosarcoma has been gradually recognized by clinicians [18–20]. The tumor avid single-photon imaging agent, ^{99m}Tc-MIBI, can also be used for tumor chemotherapy evaluation [8,9]. Radionuclide imaging evaluation can be achieved by analysis of the changes in tumor uptake before and after chemotherapy.

^{99m}Tc-MIBI scintigraphy is relatively economical and easy to operate, and it has been used in the evaluation of chemotherapy for lung cancer, breast cancer, as well as bone and soft tissue tumors, with the reported sensitivity of 80−100% and specificity of 89−100% [8,9,21].

Table 2
Semi-quantitative analysis of MIBI scintigraphy before and after chemotherapy in patients with osteosarcoma.

		Response group (n = 12)		Poor-response group (n = 18)		Statistical parameters	
		Range	Mean ± SD	Range	Mean ± SD	t	P
Pre-chemotherapy scintigraphy	Early T/B value	1.42–8.12	3.31 ± 2.19	0.80–6.33	3.49 ± 1.72	0.252	0.803
	Delayed T/B value	1.15–6.49	2.53 ± 1.58	0.56–4.09	2.28 ± 1.14	−0.497	0.623
Post-chemotherapy scintigraphy	Early T/B value	0.77–2.59	1.46 ± 0.63	0.60–4.10	2.90 ± 1.25	4.159	<0.001
	Delayed T/B value	0.74–2.32	1.25 ± 0.50	0.52–3.21	1.87 ± 0.70	2.661	0.013
Alteration rate (AR) after chemotherapy	Early phase AR (%)	31.8–77.9	49.6 ± 13.3	−77.1–65.9	8.85 ± 37.7	−4.208	<0.001
	Delayed phase AR (%)	10.8–77.0	44.2 ± 13.5	−64.8–44.8	9.37 ± 32.0	−4.096	<0.001

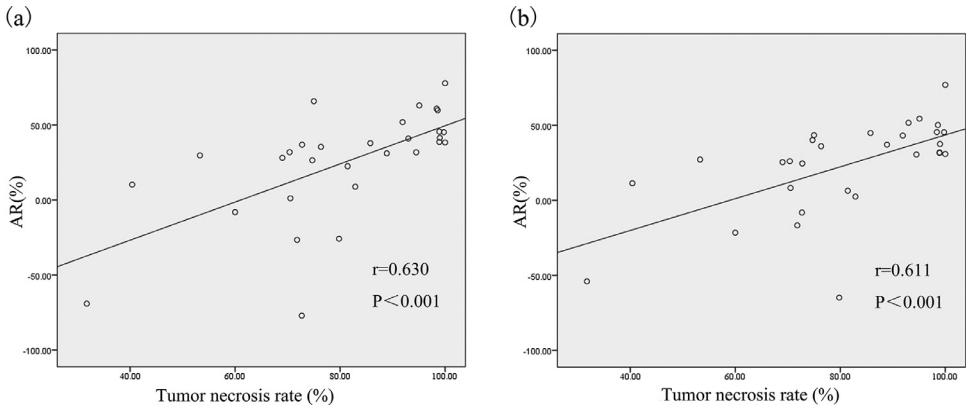

Fig. 3. Pearson correlation analysis between the alteration rate (AR) of tumor MIBI uptake after chemotherapy and the tumor necrosis rate on early phase images (a) and delayed phase images (b).

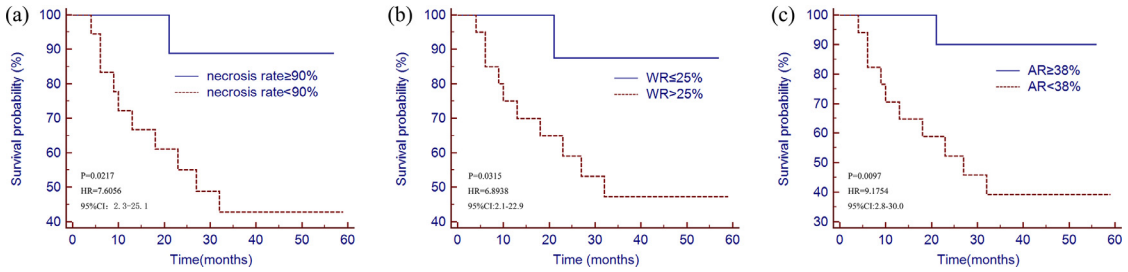

Fig. 4. Results of Kaplan–Meier curve analysis for the progression-free survival rate of patients.

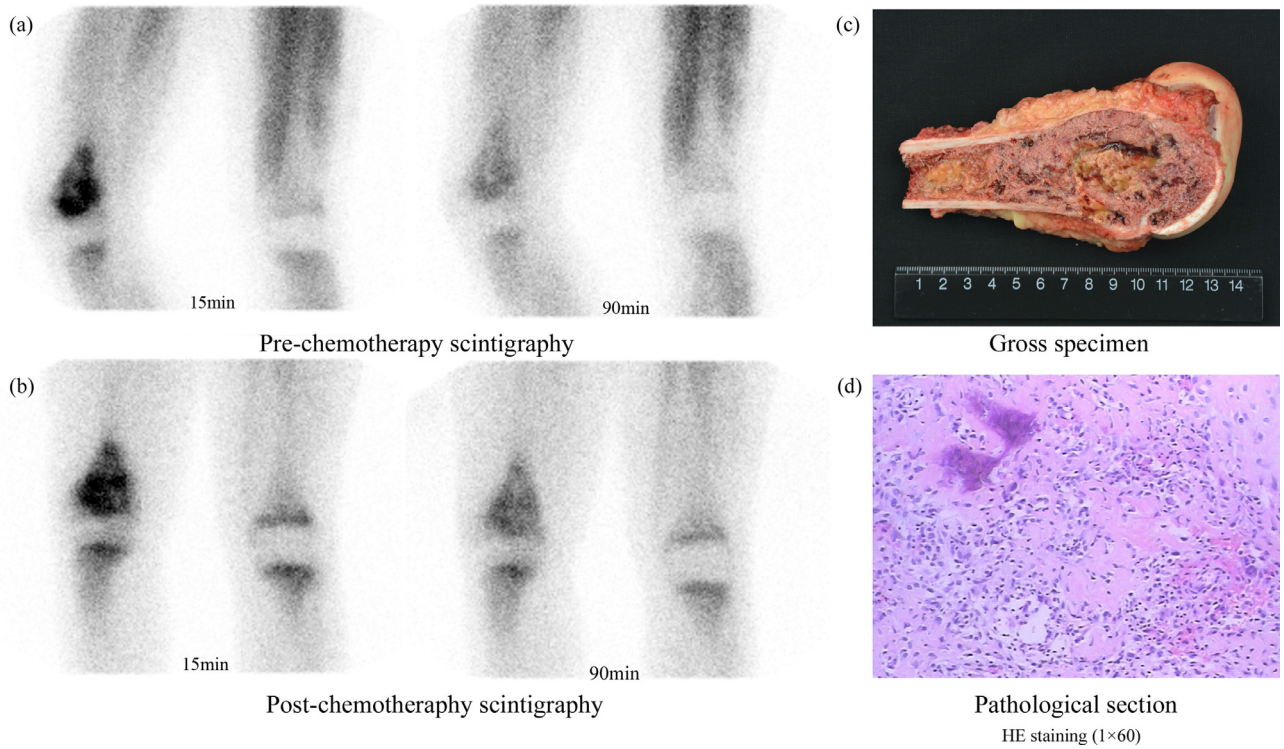

Fig. 5. A 13-year-old boy with osteosarcoma in the right distal femur. On pre-chemotherapy MIBI imaging (a), the tumor uptake was intense in the early phase (T/B = 2.80) and decreased in the delayed phase (T/B = 1.78, WR = 36.4%). On post-chemotherapy MIBI imaging (b), intense uptake in the lesion was also observed (early phase T/B = 2.41; delayed phase T/B = 1.81). Tumor gross specimen removed surgically after chemotherapy showed much residual tumor tissue (c and d), and the total pathological necrosis rate was 79.8%. The patient developed pulmonary metastasis and bone metastasis 4 months after surgery.

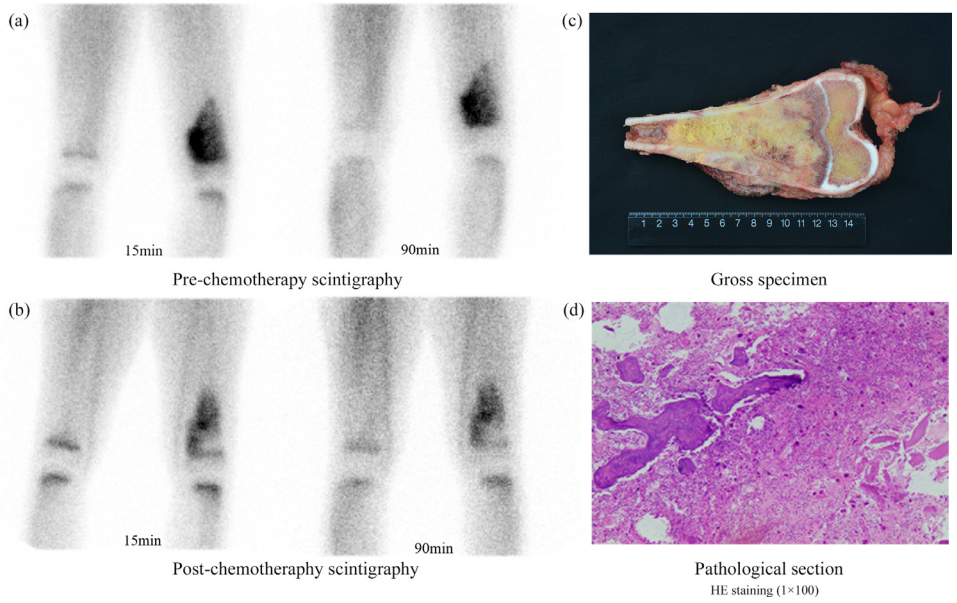

Fig. 6. A 7-year-old boy with osteosarcoma in the left distal femur. On pre-chemotherapy MIBI imaging (a), the tumor showed intense uptake in both early phase (T/B = 3.22) and delayed phase (T/B = 2.76). No significant washout of MIBI was observed (WR = 14.3%). On post-chemotherapy MIBI imaging (b), the lesion uptake was reduced significantly (early phase T/B = 1.93; delayed phase T/B = 1.79). Tumor gross specimen removed surgically after chemotherapy showed much adipose tissue (c and d). The total pathological necrosis rate was 91.9%. The patient remained in the state of disease progression-free with a follow-up of two years.

For osteosarcoma, it was confirmed that the AR in tumor MIBI uptake before and after chemotherapy was a good indicator for chemotherapy response, with the reported sensitivity of 85 − 100% and specificity of 69 − 95%, respectively [22–26]. Our study further proved that when tumor uptake decreased ≥38% after chemotherapy was taken as the indicator for a good response, a sensitivity of 91.7%, a specificity of 94.4% and an accuracy of 93.3% would be yielded.

A poor tumor chemotherapy response is often associated with overexpression of P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) in tumor cells encoded by the multidrug resistance gene (MDR-1), which can efflux chemotherapy drugs out of tumor cells and thus reduce the effect of chemotherapy. MIBI is also a transport substrate for both P-gp and MRP and can be transported out of tumor cells. Therefore, the response to tumor chemotherapy can be predicted according to the washout rate of MIBI in tumor from the early and delayed images. This imaging mechanism has been elucidated in breast cancer, lung cancer and hematological diseases [10,11,27,28]. It has also been proved that a rapid washout of MIBI is related to a higher expression of MRP in osteosarcoma, while its clinical diagnostic efficacy has not been evaluated yet [29,30]. In our study, when WR ≤ 25% was set as the threshold for prediction of a good chemotherapy response, a sensitivity of 100.0%, specificity of 91.7% and accuracy of 95.8% would be achieved, respectively.

Previous studies have been focusing on a single mechanism of MIBI imaging, but in our study, the dual mechanisms of MIBI imaging were applied to the evaluation of neoadjuvant chemotherapy response in the same group of patients with osteosarcoma. Furthermore, the results showed that the lower tumor WR of MIBI before chemotherapy indicated to a good response to chemotherapy, whereas the higher tumor WR indicated a poor response to chemotherapy (Figs. 5 and 6). It was also demonstrated that the tumor washout rate ≤25% before chemotherapy or tumor uptake of MIBI decreased ≥38% after chemotherapy would be predictable of a better outcome in patients with osteosarcoma. Compared with the relative studies on ^{18}F-FDG PET/CT, with the reported sensitivity of 58 − 100% and specificity of 69 − 100% [19,31–34], the diagnostic value of MIBI scintigraphy is not inferior, although the spatial resolution limitation of SPECT may affect the depiction of lesions. Therefore, it is feasible to apply the dual mechanisms of MIBI imaging to the evaluation of neoadjuvant chemotherapy response for osteosarcoma, and it could be considered as an alternative examination method for the evaluation of tumor necrosis rate. Considering the high coincidence rate (90.0%) between the pre-chemotherapy imaging and pre-and post-chemotherapy imaging, it is also feasible and clinically acceptable to use pre-chemotherapy imaging alone in the evaluation of treatment.

5. Conclusions

It can be concluded from the results of this study that either the MIBI imaging before treatment alone or both the pre-chemotherapy imaging and post-chemotherapy imaging can be used for evaluation of response to neoadjuvant chemotherapy in patients with osteosarcoma. The former method is simple and economical as for predicting the curative effect of chemotherapy and prognosis of patients. The latter has an additional role in prediction, evaluation and prognosis. High coincidence rate between the two methods has been achieved. Conclusively, it is feasible to use the dual mechanisms of MIBI imaging for the evaluation of neoadjuvant chemotherapy response in patients with osteosarcoma at the same time, and it could be considered as an alternative examination for tumor necrosis rate.

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Conflict of interest

The authors declare no conflict of interest.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients provided written informed consent for the use of their medical reports for research.

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