Research Article

A Cohort Study to Evaluate the Efficacy and Value of CT Perfusion Imaging in Patients with Metastatic Osteosarcoma after Chemotherapy

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Objective. A case-control study was conducted to explore the efficacy of cohort study and value of CT perfusion imaging in patients with metastatic osteosarcoma after chemotherapy. Methods. Eighty patients with metastatic osteosarcoma treated in our hospital from March 2020 to December 2021 were divided into two groups. According to their different treatment methods, the chemotherapy+antiangiogenesis group had 36 cases and the chemotherapy group had 44 cases. All patients were scanned by 64-slice spiral CT before and after treatment. The differences of tumor volume and perfusion parameters before and after treatment were compared, and the correlation between perfusion parameters and tumor microvessel density (MVD) was analyzed. The receiver working curve (ROC curve) was used to evaluate the efficacy of the two groups after chemotherapy. Results. Blood flow (BF), blood volume (BV), Pallak blood volume (PBV), and time to start (TTS) in the antitumor angiogenesis+chemotherapy group were significantly lower than those before treatment (P<0.05). Microvessel density was positively correlated with PS, BF, BV, and PBV (P<0.05). The reduction rate of BV and BF in the remission group after treatment was significantly higher than that in the nonremission group. When the BV and BF decline rates were 47.37% and 21.53% and the areas under the curve were 0.968 and 0.916, respectively, the diagnostic effect was the best. When the decrease rate of BV was 47.48% and the decrease rate of BF was 21.55%, the sensitivity was 94.72% and 89.56% and the specificity was 91.31% and 91.31%. Conclusion. The reduction rate of BV and BF in CT perfusion imaging is of high value in evaluating the efficacy of radiotherapy and chemotherapy in patients with NSCLC and can provide more objective basis for observing the changes and judging the prognosis of osteosarcoma after treatment.

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor, which usually occurs in puberty. The tumor appears at the site of rapid bone growth, accounting for about 19% of all bone tumors [1–3]. Osteosarcoma usually occurs in the metaphysis of the long bone, most commonly around the knee joint. Axial bone and craniofacial bone are mainly seen in adults [4]. Patients with clinically detectable lung metastasis account for about 20% and 25% of the total diagnosed osteosarcoma [5]. Osteosarcoma usually requires multidisciplinary treatment, including surgery, chemotherapy, and radiotherapy. Although significant progress has been made in the detection and treatment of osteosarcoma in the past 20 years, the survival rate of patients with operable osteosarcoma has been improved by chemotherapy [6, 7], but the 5-year survival rate of patients with metastatic diseases is about 20% [8, 9]. Tumors are heterogeneous from patient to patient, and choosing the appropriate individualised treatment, particularly in children and adolescents, remains a key challenge. Therefore, identifying new generation markers of metastatic and prognostic phenotypes is important for the diagnosis and treatment of osteosarcoma.
Tumor angiogenesis, the process of forming new capillaries from preexisting blood vessels, plays a key role in the development and progression of solid tumors. The rich vascular network provides sufficient oxygen and nutrients to tumor cells, and it is also a gateway for tumor metastasis, so the ability of angiogenesis is considered to be one of the markers of tumor aggressiveness. Tumor neovascularization plays an important role in the occurrence, development, invasion, and metastasis of osteosarcoma [10, 11]. Understanding angiogenesis in osteosarcoma can help predict the prognosis of the tumor.

CT perfusion imaging (CTPI) is a noninvasive functional imaging method [12, 13]. Its theoretical basis is the nuclear medicine radioactive tracer dilution principle and the central volume law. The selected layer is scanned continuously at the same time as the mean transit time is injected intravenously, and the region of interest (ROI) is selected according to the preset criteria. The time-density curve (TDC) of each pixel in this layer is obtained according to this curve. The different mathematical models can be used to accurately reflect the hemodynamic changes of tissues and organs, so as to evaluate the perfusion state of tissues and organs. After contrast injection, the TDC of arteries and tissues is plotted horizontally in time and vertically in enhanced CT values, i.e., the change in iodine accumulation, reflecting the change in tissue perfusion. The CT perfusion volume of local tissue can be obtained by measuring the amount of iodine accumulation in local tissue and the perfusion parameters such as blood flow (BF) and blood volume (BV), which means that mean transit time (MTT) and permeability-surface area product (PS) can be calculated, respectively [14].

The pathophysiological basis of CTPI is that the first-pass enhancement of the tumor is mainly caused by the appearance of the mean transit time in the blood vessel and the first discharge into the extravascular space after injection of iodine contrast agent. The subsequent tumor enhancement is a common result of the appearance of the contrast agent in the intravascular and extravascular space. In the subsequent phase, the mean transit time reenters the vascular system and the contrast agent in the tumor extravascular space is cleared, resulting in the tumor enhancement returning to the baseline level [15–17]. BF (mL/(min·g)) refers to the blood flow through a certain amount of tissue vascular structure per unit time, which is affected by blood volume, draining vein, lymphatic reflux, and tissue oxygen consumption [18]. BV (mL/g) refers to the volume of blood in the tissue vascular system, reflecting tissue blood perfusion and the number of functional capillaries. In addition, BV is related to the size of blood vessels and the number of open capillaries [19]. MTT (s) mainly reflects the average time of contrast media passing through vascular structures (arteries, veins, venous sinuses, and capillaries). The passage time varies with different paths, so it is expressed by average transit time and mainly reflects the time of contrast media passing through capillaries [20]. PS (mL/ (min·g)) refers to the unidirectional transport rate of mean transit time into the intercellular space through the capillary endothelium, reflecting the characteristics of vascular endothelial cell integrity, intercellular space, and wall permeability within the tumor. The capillaries of malignant tumors are often immature and the permeability is increased, and the mean transit time enters the tissue space more and faster through capillaries [21].

Currently, computed tomography (CT), positron emission tomography (PET-CT), and magnetic resonance imaging (MRI) are often used to assess the efficacy and prognosis of radiotherapy and chemotherapy. Among them, conventional CT examinations are mainly used to evaluate the efficacy of treatment by the change in tumor volume before and after treatment. Contrast-enhanced scans cannot reflect the blood supply to the tumor through the degree of tumor necrosis and microangiogenesis. CT perfusion imaging techniques can obtain tumor perfusion parameters and show a high evaluation value [22]. Previous studies have pointed out that CT perfusion can evaluate angiogenesis in patients with metastatic osteosarcoma so as to understand the malignant degree of the tumor, guide clinical treatment, and evaluate prognosis [23]. Based on this, this study analyzed the value of CT perfusion imaging in evaluating the efficacy of metastatic osteosarcoma after chemotherapy.

2. Materials and Methods

2.1. General Information. Eighty patients with metastatic osteosarcoma treated in our hospital from March 2020 to December 2021 were divided into two groups according to their different treatment methods. The chemotherapy+antiangiogenesis group had 36 cases, and the chemotherapy group had 44 cases. All cases were scanned by 64-slice spiral CT before and after treatment. In the chemotherapy+antiangiogenetic group, there were 20 males and 16 females, who were aged from 18 to 54 years old with an average age of 42.83 ± 4.23 years. There were 10 cases of superior fibula, 17 cases of inferior femur, 5 cases of superior tibia, 1 case of ilium, 2 cases of superior humerus, and 1 case of inferior humerus. In the chemotherapy group, the age ranged from 19 to 55 years with an average age of 43.21 ± 4.46 years. There were 13 cases of superior fibula, 20 cases of inferior femur, 6 cases of superior tibia, 1 case of ilium, 2 cases of superior humerus, and 2 cases of inferior humerus. CTP was performed again after treatment in both groups, followed by surgical resection, and pathological data of the tumor were obtained. The pathological data of the tumor were detected by CTPI twice. The interval between the two CTPI examinations was 21-77 days, with an average of 54.12 ± 12.95 days. During the follow-up to December 31, 2021, there was no loss of follow-up. There was no statistical significance in the general data of the two groups. This study was approved by the Medical Ethics Association of our hospital, and all patients signed informed consent.

Selection criteria were as follows: (1) the patient was diagnosed with primary bone tumor by histological or cytological examination; (2) without cognitive, language, and intellectual impairment, with basic reading and writing ability; (3) patients with measurable tumor lesions; (4) agreed to accept continuous follow-up and be able to answer telephone follow-up; (5) chest scan ruled out distant metastasis of the chest or other parts; and (6) there was no serious compound injury and vascular and nerve injury.
Exclusion criteria were as follows: (1) patients with severe heart, liver, and renal insufficiency; (2) patients whose general condition could not tolerate the examination; (3) patients refused to participate in the research; (4) those who received radiotherapy, chemotherapy, and operation before perfusion examination; (5) patients with secondary bone tumor; and (6) patients with history of iodine allergy.

### 2.2. Methods

#### 2.2.1. Treatment Scheme

Chemotherapeutic drugs include adriamycin 30 mg/m² (d1-d3), cisplatin 120 mg/m² (d4), methotrexate 10-12 g/m² (d1), and isocyclophosphamide 3 g/m² (d1-d5). The antitumor angiogenesis drug is recombinant human vascular endothatin (Endu) 15 mg/d (d1-d5).

#### 2.2.2. Inspection Method

Siemens 64-layer helix CT was used. First of all, routine CT scanning was performed. The scanning plane was selected according to the location of the lesion, and the largest slice of the tumor was selected as the standardized section for CTPI. CTP was performed again after chemotherapy, referring to the selected level before treatment. In the selected layer, the same layer dynamic scanning was carried out by using the same layer movie scanning mode and the scanning parameter is 100kV 5 mm 80 mA. The image was reconstructed by layer thickness 5 mm, and 120 (30 × 4) layer images were obtained.

#### 2.2.3. Image and Data Processing

The perfusion image was transmitted to the workstation, and the data were processed and analyzed by Siemens perfusion software. The whole tumor was selected as RO on the cross-sectional view, and the perfusion parameters such as blood flow (BF), blood volume (BV), Permeability-Surface area product (PS), time to start (TTS), and time to peak (TTP) were calculated. Load the raw venous phase data into Siemens Volume software, and set the CT threshold for volume measurement—200-2000 HU. The tumor boundary was manually corrected, and the computer automatically calculated the diameters and volumes.

#### 2.2.4. Determination of Tumor Microvessel Density

All specimens were fixed with formaldehyde, embedded in paraffin, and sliced. CD34 staining was performed according to the instructions of the SP kit after dewaxing, ethanol dehydration, and thermal repair antigen treatment. The standard of tumor microvessel density (MVD) indicated that the dense area of tumor blood vessels was found by 40x light microscope, and the number of microvessels was calculated under 200x visual field. Five visual fields were calculated in each section, and then, the average value was taken as MVD.

### 3. Results

#### 3.1. CTPI Parameters before and after Treatment in the Antitumor Angiogenesis + Chemotherapy Group

First of all, we compared the CTPI parameters before and after treatment in the antiangiogenesis-chemotherapy group. After treatment, the BF, BV, PBV, and TTS decreased significantly. The data were statistically analyzed by SPSS25.0 software. The data was expressed as $\bar{x} \pm s$. The paired sample $t$-test was used to compare the curative effect and CTPI parameters before and after treatment. The Spearman rank correlation test was used for CTPI parameters and MVD after treatment. Moreover, the independent $t$-test was used for comparison between groups after treatment. According to the results of curative effect evaluation and CT perfusion parameters, the receiver operating characteristic curve (ROC curve) was drawn to evaluate the efficacy of CT perfusion imaging in chemotherapy in patients with metastatic osteosarcoma. $P < 0.05$ means that the difference is statistically significant.
in the chemotherapy+antiangiogenesis group (P < 0.05). However, the increase in PS and the decrease in TTP were not obvious, and there was no statistical difference (P > 0.05). All the results are shown in Table 1.

### 3.2. CTPI Parameters of Patients in the Simple Chemotherapy Group before and after Treatment.

We compared the CTPI parameters of patients in the simple chemotherapy group before and after treatment. BF and PBV in the chemotherapy group decreased, and BV, PS, TTS, and TTP increased compared with those before treatment. However, there was no significant difference (P > 0.05). The tumor volume of the two groups increased after treatment, but there was no significant difference between the two groups (P > 0.05). All the results are shown in Table 2.

### 3.3. Correlation Analysis between MVD and Perfusion Parameters.

We analyzed the correlation between MVD and perfusion parameters. MVD was positively correlated with PS, BF, BV, and PBV (R = 0.753, 0.792, 0.576, and 0.844, respectively, P < 0.05). There was no correlation with TTS and TTP (r = -0.051, -0.146; P > 0.05). All results are shown in Table 3.

### 3.4. Therapeutic Effect of Patients in the Two Groups.

We analyzed the treatment effects of the two groups of patients. In the antiangiogenesis+chemotherapy group, 8 (22.22%) patients had CR (38.89%), 14 patients had PR, 8 (22.22%) patients had SD, and 6 (16.67%) patients had PD. In the chemotherapy group, 6 (13.64%) patients had PD, 17 (38.64%) had PR, 9 (20.45%) had SD, and 12 (27.27%) had PD. All results are shown in Figure 1.

### 3.5. BV and BF Reduction Rates between Patients with Remission and Those without Remission after Treatment.

We compared the BV and BF reduction rates of remission and nonremission patients after treatment. After treatment, the BV and BF reduction rates of remission patients were 45.00% for CR, 40.00% for PR, 35.00% for SD, and 30.00% for PD in the antiangiogenesis+chemotherapy group, compared to 35.00% for CR, 30.00% for PR, 25.00% for SD, and 20.00% for PD in the chemotherapy group. All results are shown in Figure 1.
We analyzed the Osteosarcoma by CT Perfusion Imaging. In Figure 2 and Table 5, the sensitivity was 94.72% and 89.56%, respectively, and the rate was 47.48% and the BF reduction rate was 21.55%, the AUC was 0.968 and 0.916, respectively. When the BV reduction rate was 47.37% and 21.53%, respectively. In addition, the AUC curve of chemotherapy in patients with metastatic osteosarcoma. Note: BF: blood flow; BV: blood volume.

| Group           | N   | BV (mL/100 g⁻¹) | Reduction rate (%) | BF (mL/min-100 g⁻¹) | Reduction rate (%) |
|-----------------|-----|-----------------|--------------------|---------------------|--------------------|
| Remission       | 62  | 7.06 ± 0.41     | 52.12 ± 14.42      | 38.76 ± 10.15       | 28.94 ± 9.62       |
| Not alleviated  | 18  | 6.87 ± 0.57     | 16.39 ± 8.67       | 38.64 ± 9.55        | 36.11 ± 10.18      |
| t               | 1.578 | 6.178 | 9.975 | 0.045 | 2.748 | 7.657 |
| P               | >0.05 | <0.01 | <0.01 | >0.05 | <0.01 | <0.01 |

Note: BF: blood flow; BV: blood volume.

### Figure 2: ROC curve of CT perfusion imaging to evaluate the efficacy of chemotherapy in patients with metastatic osteosarcoma. Note: BF: blood flow; BV: blood volume.

higher than those of nonremission patients without statistically great difference ($P < 0.05$). All results are shown in Table 4.

#### 3.6. The Efficacy of Chemotherapy in Patients with Metastatic Osteosarcoma by CT Perfusion Imaging

We analyzed the efficacy of CT perfusion imaging in evaluating the efficacy of chemotherapy in patients with metastatic osteosarcoma. The results of the ROC curve showed that the diagnostic efficacy was the best when the reduction rate of BV and BF was 47.37% and 21.53%, respectively. In addition, the AUC curve was 0.968 and 0.916, respectively. When the BV reduction rate was 47.48% and the BF reduction rate was 21.55%, the sensitivity was 94.72% and 89.56%, respectively, and the specificity was 91.31% and 91.31%. All the results are shown in Figure 2 and Table 5.

### 4. Discussion

The formation of neovascularization in a tumor is the key to tumor growth and metastasis [25, 26]. The mechanism of tumor radiotherapy and chemotherapy is that radiotherapy and chemotherapy destroy tumor blood vessels and inhibit the formation of tumor blood vessels, so as to block tumor nutrition, inhibit the growth of tumor cells, and kill tumor cells. Tumor microvascularization is a precursor of tumor progression. Understanding tumor vascular status by means of detection can be used to evaluate the early and objective curative effect [27]. Understanding the angiogenesis of osteosarcoma in vivo will be helpful to choose the appropriate treatment scheme, observe the therapeutic effect, and predict the prognosis of the tumor. The traditional methods to evaluate tumor vessels mainly rely on pathological sections, including the determination of MVD [28] and the expression of vascular endothelial growth factor [29]. With the development of CT equipment and related software, CT diagnosis has evolved from a single morphological judgment to a new stage of functional diagnosis or both morphology and function. Blood volume and vascular permeability analysis of the whole lesion of a tumor can provide information on the hemodynamics of tissues and organs and has been widely used in clinical disease diagnosis, efficacy evaluation, and prognosis assessment [30].

CT perfusion imaging is a noninvasive imaging method that provides qualitative and quantitative information on tumor angiogenesis. The dynamic changes of the contrast agent in the tumor tissue structure and blood vessels are detected, and perfusion parameters are calculated by hemodynamic modelling. The main evaluation indicators include BV, BF, PTT, and peak enhancement parameters [31]. Some studies have pointed out that CT perfusion parameters have obvious characteristics and the distribution of CT perfusion parameters can objectively reflect the physiological changes of the tumor, thus indicating the degree of differentiation of lung cancer [32]. Traditional microvessel density can only indicate the existence of neovascularization in a certain area, while CT perfusion imaging can reflect tumor vascular blood flow characteristics and microvessel density, which is helpful to evaluate the curative effect. The changes of CT perfusion parameters are related to the ultrastructural abnormalities of tumor vessels. Among them, the values of BV and BF are related to the decrease in microvessel density and the degree of microvascular lumen in tumor tissue, which provide a theoretical basis for the clinical application of perfusion imaging and evaluate the curative effect [33].
With CTPI quantitative measurement of tissue perfusion absolute value, relative blood volume, capillary infiltration, and leakage (extracellular) space, these parameters reflect the microphysiological changes consistent with tumor angiogenesis [34]. CTPI examination of the tumor can not only show the whole picture of the lesion through BF and BV images, reflecting the overall enhancement through TDC, but also understand the distribution of microvessels in the tumor by comparing the BF and BV values of the peripheral area and the central area [35, 36]. In the results of this group, MVD was positively correlated with BF, BV, PBV, and PS, but not with TTP and TTS, indicating that BF, BV, PBV, and PS could reflect the changes of microvessels and blood supply of osteosarcoma to some extent. The related studies have confirmed that CTPI quantitative measurement has good repeatability [37].

After treatment, tumor growth is inhibited and cancer cells are necrotic; on the other hand, the application of antiangiogenic drugs reduces tumor neovascularization and the blood supply to the tumor is reduced [38]. In the chemotherapy plus antiangiogenesis treatment group, BF, BV, and PBV decreased significantly after treatment, suggesting that the blood supply of tumor tissue decreased after treatment, which to some extent reflected the effectiveness of tumor antiangiogenesis therapy. PS has no significant change, which may be due to the formation of a large number of arteriovenous collateral circulation in malignant tumor, blood directly from the artery to the vein without capillary exchange, so the change of PS is not significant [39]. Lee et al. performed perfusion imaging in 25 patients with upper respiratory tract squamous cell carcinoma before and after induction chemotherapy [40]. The results also showed that the tumor BF and BV decreased significantly after treatment. In this study, there was no significant difference in all perfusion parameters before and after treatment in the chemotherapy group. The possible reason is that the effect of chemotherapeutic drugs on cancer cells itself has little effect on tumor vessels. Lin and Liang reported that 24 patients with lung cancer were treated with CTPI before and after chemotherapy and radiotherapy [41]. The results showed that there was no significant change in BF and BV after treatment. In this study, there was no statistical significance in the change of tumor volume between the two groups, so it could be considered that the change of tumor volume lagged behind the change of perfusion parameters.

The changes of CT perfusion parameters are related to the ultrastructural abnormalities of tumor vessels. Among them, the values of BV and BF are related to the decrease in microvessel density and the degree of microvascular lumen in tumor tissue, which provides a theoretical basis for the clinical application of perfusion imaging and evaluates the curative effect and predicts tumor metastasis or recurrence [42–45]. This study showed that there were significant changes in CT perfusion parameters BV, BF, and TTP before and after treatment, which confirmed that the changes of tumor tissue microvessels after radiotherapy and chemotherapy could be reflected by CT perfusion parameters. However, there was a significant difference in the reduction rate of BV and BF between remission and nonremission patients, and the decrease rate of BV and BF was higher in remission patients. According to the reduction rate of BV and BF in remission and nonremission patients, it was found that the diagnostic efficiency was the best when the reduction rate of BV was 47.37% and that of BF was 21.53% and the AUC was 0.968 and 0.916, respectively. When BV reduction rate was 47.48% and BF reduction rate was 21.55%, the efficacy of curative effect evaluation was the best with sensitivity of 94.72% and 89.56%, respectively, and specificity of 91.31%. The cut-off value, sensitivity, and specificity of BV and BF reduction rate are higher than those of the scholar Si Xiao San in evaluating the efficacy of chemotherapy in patients with metastatic osteosarcoma by CT perfusion imaging. The reason may be related to the chemotherapy regimen adopted by the patients in this study, and the difference in curative effect among patients is more significant. There are some limitations in this study. First, the sample size of this study is not large, and it is a single-center study; so bias is inevitable. In future research, we will carry out multicenter, large-sample prospective studies, or more valuable conclusions can be drawn.

To sum up, there are significant changes in CT perfusion parameters in patients with metastatic osteosarcoma before and after chemotherapy. The reduction rates of BV and BF can be used to evaluate the efficacy of radiotherapy and chemotherapy in patients with metastatic osteosarcoma and guide clinical treatment, which has high clinical value. However, a large number of cases and long-term follow-up are needed for further research. Although the sample size in this group is limited and the software used is only four layers of perfusion, the results have suggested that CTPI can dynamically reflect the changes of tumor blood supply, which can provide reference and new ideas for the clinical treatment of osteosarcoma.

### Table 5: The efficacy of chemotherapy in patients with metastatic osteosarcoma by CT perfusion imaging.

| Index               | Area under the curve | Sensitivity degree (%) | Specificity (%) | Youden index | Critical value | 95% CI     |
|---------------------|----------------------|------------------------|----------------|--------------|----------------|------------|
| BV reduction rate   | 0.968                | 94.72                  | 91.31          | 0.861        | 47.48          | 0.925–0.999|
| BF reduction rate   | 0.916                | 89.56                  | 91.31          | 0.809        | 21.55          | 0.821–0.999|

Note: BF: blood flow; BV: blood volume.

### Data Availability

No data were used to support this study.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.
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