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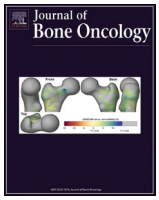

Research Paper

Imaging evaluation of blood supply changes after chemotherapy of osteosarcoma and its correlation with tumor necrosis rate

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HIGHLIGHTS

- The changes in the tumor blood supply represented by the CT enhancement rate is a new evaluation method of the chemotherapy effect on osteosarcoma.
- The blood supply changes based on CT evaluation are related with tumor necrosis rate.
- The evaluation based on CT enhancement rate can be a reference for evaluating the chemotherapy effect of osteosarcoma.

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ABSTRACT

Background: Analysis of the tumour necrosis rate is an important method to evaluate the effect of neoadjuvant chemotherapy for osteosarcoma. However, at present, there is no specific imaging method to evaluate this effect. The purpose of this study was to evaluate the changes in blood supply after chemotherapy by measuring the CT enhancement rate and to analyse the correlation between the CT enhancement rate and the tumour necrosis rate.
Methods: Patients with primary osteosarcoma of the extremities treated in our institute from 2016 to 2017 were analysed retrospectively. In total, 103 eligible patients were enrolled in the study, including 67 males and 36 females, with an average age of 17.7 (6–54) years. Sixty cases had tumour sites in the femur, 25 in the tibia, 10 in the humerus, and eight in other sites. All patients received neoadjuvant chemotherapy including methotrexate, cisplatin + doxorubicin and ifosfamide before surgical treatment. All patients underwent enhanced CT examination of the same tumour site before and after the neoadjuvant chemotherapy protocol. The CT value before and after chemotherapy was measured and the enhancement rate was calculated. The change in the CT enhancement rate after chemotherapy was analysed. Changes in the CT enhancement rate were compared between patients with a tumour necrosis rate greater than 90% and those with one <90%.
Results: The average CT enhancement rates before and after chemotherapy were 1.68 (median 1.63, range 1.00–2.51) and 1.39 (median 1.28, range 1.00–2.83), respectively ($P < 0.01$). The average CT enhancement rate after chemotherapy decreased by 15.0% (median 16.7%, range −27.5–53%): 75 cases exhibited a decrease, three cases remained unchanged, and 25 cases exhibited an increase. The average enhancement rate before chemotherapy was 1.75 (median 1.68, range 1.18–2.51) in the group with a necrosis rate >90% and 1.62 (median 1.52, range 1.00–2.41) in the group with a necrosis rate < 90% ($P = 0.068$). The average CT enhancement rate after chemotherapy was 1.20 (median 1.21, range 1.00–1.53) in the group with a necrosis rate > 90% and 1.53 (median 1.43, range 1.00–2.83) in the group with a necrosis rate < 90% ($P < 0.01$). The enhancement rate of the group with a necrosis rate > 90% decreased by 29.0% (median 28%, range −2.3–53%) ($P < 0.01$); the enhancement rate of the group with a necrosis rate < 90% decreased by 3.8% on average (median 0.7%, range −27.5–44.5%) ($P = 0.225$).
Conclusion: After receiving neoadjuvant chemotherapy, most patients with osteosarcoma of the extremities exhibited reductions in the CT enhancement rate. In cases where the tumour necrosis rate was greater than 90%, the tumour blood supply was significantly reduced. This suggests that imaging evaluations based on the CT enhancement rate can be used as a reference for evaluating the preoperative effect of chemotherapy for osteosarcoma.

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1. Introduction

Osteosarcoma is a highly malignant primary bone tumour. Its main histological feature is that the tumour cells can directly undergo osteogenesis [1]. Osteosarcoma usually occurs in the bones of the extremities; the most common sites include the distal femur, proximal tibia, proximal humerus and proximal femur. Although the incidence of osteosarcoma is very low, the recurrence and metastasis rates are high [2,3]. Amputation was the main surgical treatment in the early years. However, with the wide application of preoperative neoadjuvant chemotherapy and postoperative adjuvant chemotherapy, the limb salvage rate and survival rate of osteosarcoma patients have significantly improved [4,5]. The effect of chemotherapy is an important factor in determining the patient's oncological prognosis. Importantly, the survival rate of patients is closely related to the effect of chemotherapy [6]. Therefore, evaluation of the effect of chemotherapy, especially the effect of preoperative neoadjuvant chemotherapy, is crucial for judging the patient's prognosis and adjusting their treatment plan. At present, the most objective method for evaluating the chemotherapeutic effect and tumour prognosis is the analysis of the tumour necrosis rate [6,7]. Huvos [8] first described the osteosarcoma necrosis rate as a histological evaluation method in the 1970 s, and this method has been used ever since. However, the tumour necrosis rate is not widely used in all musculoskeletal tumour institutions, especially in developing countries and regions. This is due to various reasons, including: the operation steps are complex and difficult to carry out in certain conditions; heterogeneous tumours are difficult to evaluate and treat surgically; it takes a long time to obtain the post-operative results, which delays post-operative treatment; there is a significant financial burden for the patient. Thus, the identification of an imaging evaluation method related to the tumour necrosis rate which can provide a measure of the change to the tumour blood supply after chemotherapy has become an important direction of research.

Enhanced CT of the tumour site is a routine preoperative examination performed for bone tumours, including osteosarcoma; it does not add an additional burden to patients, it produces no damage and it can be performed in a timely manner [9,10]. CT can provide insight into the type of bone destruction and bone strength at the tumour site in order to predict the risk of pathological fracture [11,12]. Enhanced CT includes the bone window, soft tissue window and soft tissue enhancement window at the tumour site, which can provide insight into the status of bone destruction and the degree of mineralization within the tumour. Enhanced CT can also display the tumour blood supply, the relationship between the tumour and the blood vessels, and the tumour range in the bone and soft tissue [13]. As a tumour with high blood circulation, osteosarcoma shows a high enhancement rate on enhanced CT [14]. Thus, in this research, enhanced CT was performed before and after preoperative chemotherapy to evaluate the effect of chemotherapy. The purpose of this study was to analyse the changes in the tumour blood supply, represented by the CT enhancement rate, before and after neoadjuvant chemotherapy for limb osteosarcoma and to examine the correlation between the CT enhancement rate and the tumour necrosis rate. It was hoped that this research would provide a simple and effective quantitative method for the evaluation of the chemotherapeutic effect in osteosarcoma.

2. Materials and methods

2.1. Patient enrolment

The inclusion criteria were as follows: primary single osteosarcoma of an extremity; clear evaluable lesion before and after chemotherapy; obvious soft tissue mass before and after chemotherapy; tumour showing obvious enhancement in CT before chemotherapy; standard neoadjuvant chemotherapy scheme completed; tumour necrosis rate of the resected specimen was examined after chemotherapy. The exclusion criteria were as follows: history of treatment for embolism or other treatments that may affect tumour blood supply; pathological fractures or other situations that lead to significant tumour bleeding before or during chemotherapy; history of local tumour radiotherapy; the type or dose of preoperative chemotherapy was adjusted for various reasons; the patient did not receive enhanced CT examination before/after chemotherapy due to an allergy to the enhanced contrast agent or other reasons.

According to the above criteria, 103 cases of limb osteosarcoma who were treated at our institute from 2016 to 2017 were included in this study (35 patients were excluded after the application of the inclusion and exclusion criteria). The sample comprised 67 males and 36 females, with an average age of 17.7 (6–54) years. The tumour sites included the femur in 60 cases, the tibia in 25 cases, the humerus in 10 cases, the fibula in three cases, the radius in three cases and the ulna in two cases. All patients received four cycles of preoperative chemotherapy including methotrexate (1st), cisplatin + adriamycin (2nd), ifosfamide (3rd) and methotrexate (4th). All patients underwent enhanced CT examination of the tumour site before and after preoperative chemotherapy.

2.2. Imaging evaluation

All patients underwent an enhanced CT examination of the tumour site before chemotherapy at our hospital. After four cycles of neoadjuvant chemotherapy, each patient again underwent an enhanced CT examination of the same site in the same CT machine. The dose of contrast agent and the scanning time of the two CT examinations were consistent. The CT value was measured on the axial cross-section of the tumour, with a 3 mm interval between each measured slice. Then, the average CT value of all slices was calculated. The operator adjusted the system to the tumour level that needed to be measured and selected the target area for measurement. Then, the imaging system automatically displayed the average CT value of that area. The necrosis or ossification area was excluded, and the remaining solid tumour area was selected for measurement. Before and after chemotherapy, the plain and enhanced CT values of the same area at the same level of the tumour were measured. The CT enhancement rate was calculated as follows: CT enhancement rate = enhanced CT value/plain CT value.

2.3. Statistical analysis

SPSS 20.0 was used for data analysis. The plain and enhanced CT values of the tumour before and after neoadjuvant chemotherapy were calculated, and the average CT enhancement rate of the tumour was calculated. The continuous data were compared by t-tests, and the discrete data were compared by chi-square tests or the Fisher's exact probability method. A *t*-test was used to compare the CT enhancement rate of all cases before and after neoadjuvant chemotherapy. According to the Huvos method [8], the tumour necrosis rate was calculated and divided into two groups: greater than and<90%. The differences in the CT enhancement rate between the groups and before/after chemotherapy were compared. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Overall results of the CT enhancement rate

The average CT enhancement rate of all cases was 1.68 (median 1.63, range 1.00–2.51) before neoadjuvant chemotherapy and 1.39 (median 1.28, range 1.00–2.83) after neoadjuvant chemotherapy; there was a significant difference in the CT enhancement rate before and after chemotherapy ($F = 40.813$, $P < 0.01$) (Fig. 1).

The average decrease in the CT enhancement rate of all cases was 15.0% (median 16.7%, range −27.5–53%) after chemotherapy: 75 cases

exhibited decreases, with an average decrease of 25.2% (median 23.8%, range 0.6–53%); three cases remained unchanged; 25 cases exhibited increases, with an average increase of 13.6% (median 12.9%, range 0.7–27.5%) (Fig. 2).

3.2. Grouping according to the tumour necrosis rate

After neoadjuvant chemotherapy, 46 patients had a tumour necrosis rate greater than 90% and 57 patients had a tumour necrosis rate<90%.

The average age of the patients with a necrosis rate greater than 90% was 19.8 (7–54) years, while for those with a necrosis rate<90%, the average age was 16.0 (6–49). There was no statistically significant difference in age between the groups (F = 3.789, P = 0.054). The group with a necrosis rate greater than 90% comprised 30 males and 16 females, while the group with a necrosis rate<90% comprised 37 males and 20 females. There was no significant difference in the gender distribution of the two groups (chi-square = 0.001, P = 0.974). In the group with a necrosis rate greater than 90%, the tumour sites included 28 cases in the femur, 10 cases in the tibia and eight cases in other sites. For the group with a necrosis rate<90%, the tumour sites included 32 cases in the femur, 15 cases in the tibia and 10 cases in other sites. There was no significant difference in the distribution of tumour sites between the two groups (chi-square value = 0.318, P = 0.853). While there were no significant differences in age, gender and tumour site between the two groups, the P value of the age comparison was very close to being statistically significant (Table 1).

3.3. Comparison of the CT enhancement rate as a function of the tumour necrosis rate

Comparison of the initial CT enhancement rate pre-chemotherapy: the average enhancement rate was 1.75 (median 1.68, range 1.18–2.51) in the group with a necrosis rate greater than 90% and 1.62 (median 1.52, range 1.00–2.41) in the group with a necrosis rate<90%. There was no significant difference between the two groups (F = 3.415, P = 0.068) (Table 1).

Comparison of the CT enhancement rate post-chemotherapy: the average enhancement rate was 1.20 (median 1.21, range 1.00–1.53) in the group with a necrosis rate greater than 90% and 1.53 (median 1.43, range 1.00–2.83) in the group with a necrosis rate<90%. There was a significant difference between the two groups (F = 35.645, P < 0.01) (Figs. 3 and 4) (Table 1).

In the group with a necrosis rate > 90%, the average enhancement rate decreased by 29.0% (median 28%, range −2.3–53%), to a level that was significantly lower than that before chemotherapy (F = 111.098, P < 0.01). In the group with a necrosis rate < 90%, the enhancement rate decreased by 3.8% on average (median 0.7%, range −27.5–44.5%), and there was no significant difference compared with that before chemotherapy (F = 2.028, P = 0.157). There was a significant difference in the rate of reduction in the enhancement rate between the two groups (with different necrosis rates) after chemotherapy (F = 53.421, P < 0.01) (Fig. 5).

In the group with a necrosis rate > 90%, the reduction in the enhancement rate was greater than 20% in 33 cases (33/46, 71.7%), greater than 30% in 21 cases (21/46, 45.7%), greater than 40% in 13 cases (13/46, 28.3%) and greater than 50% in six cases (6/46, 13.0%); only two cases (2/46, 4.3%) did not exhibit a reduction in the enhancement rate. In the group with a necrosis rate < 90%, the reduction in the enhancement rate was greater than 20% in 15 cases (15/57, 26.3%), greater than 30% in nine cases (9/57, 15.8%), greater than 40% in one case (1/57, 1.8%) and greater than 50% in no cases; 26 cases (26/57, 45.6%) did not exhibit reductions in the enhancement rate and 23 cases (23/57, 40.4%) exhibited increases in the enhancement rate (Fig. 6).

4. Discussion

With progress in our understanding of oncology and oncological treatment, the survival rate of osteosarcoma patients has gradually improved. However, the survival rate is in a bottleneck period, with no significant breakthroughs in recent years [3,4]. Despite receiving standardized comprehensive treatment in a timely fashion, a small number of patients still experience tumour recurrence or metastasis, and even eventually die from the disease. For these patients, standardized preoperative and postoperative chemotherapy cannot prevent tumour progression, and this may be related to tumour resistance to chemotherapy [6,7]. Therefore, both doctors and researchers, as well as patients and their families, remain concerned and want to know the tumour's sensitivity to chemotherapy and the chemotherapeutic effect as soon as possible, so that the treatment plan can be adjusted, and the tumour prognosis can be judged. In our clinical work, we found that osteosarcoma has a relatively rich tumour blood supply, which is reflected in obvious enhancement in enhanced CT. The degree of tumour enhancement will change after chemotherapy, but there are obvious individual differences. This study focused on whether the above phenomenon can objectively reflect the chemotherapeutic effect. To this end, this study evaluated, for the first time, the effect of preoperative chemotherapy for osteosarcoma based on the enhancement rate of enhanced CT pre- and post-chemotherapy. The degree of change in the enhancement rate was evaluated and compared with the gold standard, that is, the tumour necrosis rate.

First, the CT enhancement rate of osteosarcoma was measured and calculated before chemotherapy. The results showed that osteosarcoma lesions had high enhancement rates, with an average baseline rate of 1.68 before treatment; the highest enhancement rate was about 2.5. This highlights the rich blood supply of osteosarcoma, which is in line with the biological characteristics of this highly malignant tumour. An abundant blood supply is necessary for the rapid growth of a tumour. Then, the same method was used to measure the CT value of each osteosarcoma after neoadjuvant chemotherapy. The results revealed that

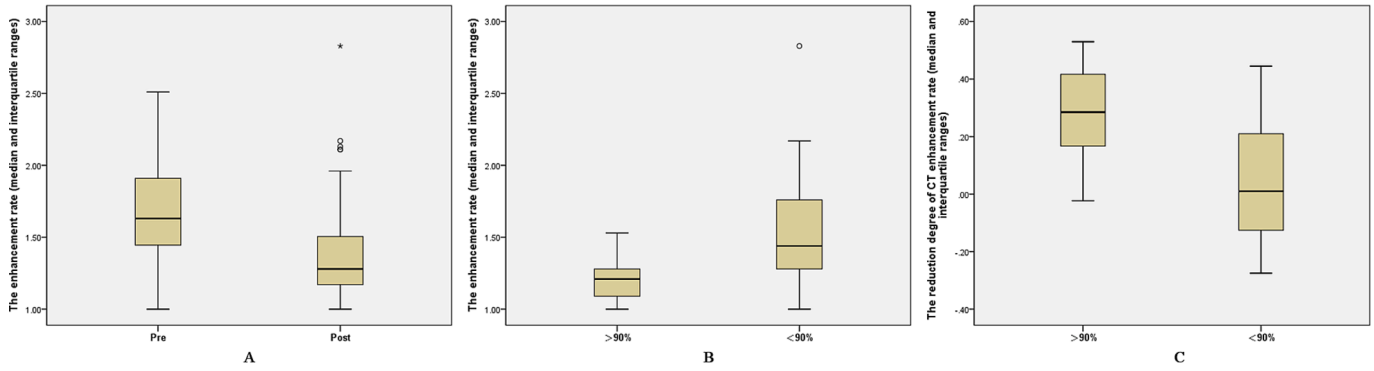

Fig. 1. Comparison of the mean CT enhancement rate before and after chemotherapy.

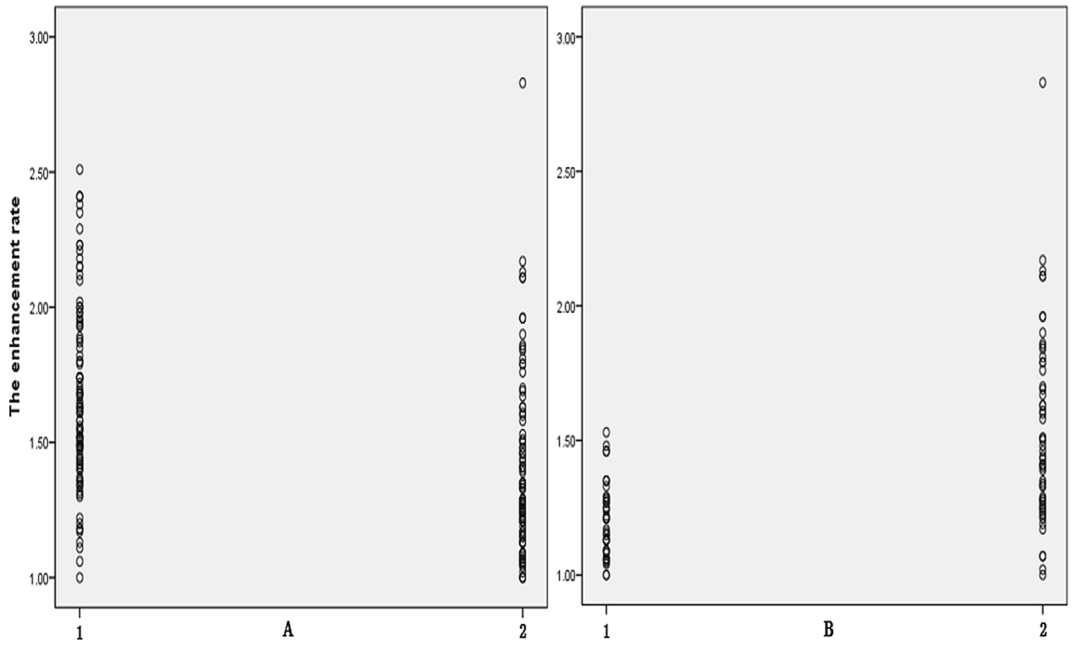

Fig. 2. Individual distribution of the CT enhancement rate before and after chemotherapy (1 for pre-chemotherapy, 2 for post-chemotherapy).

Table 1
General characteristic and measurement results in different necrosis rate groups.

Characteristic		Tumor necrosis rate > 90% (n = 46)	Tumor necrosis rate < 90% (n = 57)	P value
Age (mean)		19.8 (7–54)	16.0 (6–49)	0.054
Gender	Male	30	37	0.974
	Female	16	20	
Tumor site	Femur	28	32	0.853
	Tibia	10	15	
	Others	8	10	
CT enhancement rate (mean)	Pre-chemotherapy	1.75 (1.18–2.51)	1.62 (1.00–2.41)	0.068
	Post-chemotherapy	1.20 (1.00–1.53)	1.53 (1.00–2.83)	<0.01
The decreasing of CT enhancement rate (mean)		29.0% (-2.3% to 53%)	3.8% (-27.5% to 44.5%)	<0.01

the overall average enhancement rate after chemotherapy was significantly reduced. The overall average reduction was 15% and the largest reduction was more than 50%. The results also showed that, although most of the cases exhibited a decrease in the enhancement rate, nearly one-quarter (25/103) of the cases exhibited an increase. Therefore, there is a need to further study whether the characteristics of the above changes in the enhancement rate have certain regularity and significance, especially in relation to the effect of chemotherapy. Previous studies [6–8] have suggested that the necrosis rate can reflect the chemotherapeutic effect and the tumour prognosis of patients. Therefore, whether the CT enhancement rate is related to the tumour necrosis rate, and whether it can replace the tumour necrosis rate to a certain extent, has important clinical significance. The focus of this study was on the analysis of the correlation between the CT enhancement rate and the tumour necrosis rate.

This study included 46 cases with a necrosis rate greater than 90% and 57 cases with a necrosis rate lower than 90%. There was no significant difference between the two groups in terms of age, gender and tumour site distribution; thus, the two groups were matched well. There was no significant difference in the CT enhancement rate between the two groups before chemotherapy, suggesting that the initial CT enhancement rate cannot provide a good indication of the effect of chemotherapy or even the prognosis of the tumour.

However, after neoadjuvant chemotherapy, the average CT enhancement rates of the group with a necrosis rate above 90% and the group with a necrosis rate below 90% were 1.20 and 1.53, respectively. Importantly, there was a significant difference between the two groups. The results indicated that the CT enhancement rate of tumours with a necrosis rate above 90% exhibited a greater overall reduction. Thus, the CT enhancement rate after chemotherapy was consistent with the tumour necrosis rate. Moreover, the highest enhancement rate was observed in the group with a necrosis rate above 90%. After chemotherapy, the enhancement rate of this group was 1.53, only reaching the average level in the group with a necrosis rate below 90%. These data further verify the large gap in the overall distributions of the CT enhancement rates between the two groups. The intra-group comparison before and after chemotherapy showed that the enhancement rate of the group with a necrosis rate above 90% was significantly reduced (an average decrease of 29%), while the enhancement rate of the group with a necrosis rate below 90% exhibited no significant change (an average decrease of 3.8%). This result indicates that the decrease in the CT enhancement rate was related to the increase in the tumour necrosis rate, and the decrease in the CT enhancement rate can reflect necrosis of tumour tissue. The mechanism underlying this relationship between the CT enhancement rate and the tumour necrosis rate is unclear and requires further study. Our preliminary hypothesis is that effective chemotherapy can inhibit the growth of the tumour, which leads to the necrosis of tumour tissue and the inhibition of the blood supply to the tumour to a certain extent. This manifests as a reduction in CT enhancement and an increase in sclerosis in the tumour tissue. Liu et al. [15] reported that CT can be applied to compare the radiomics of non-tumorous bone regions of interest versus tumour regions, and this may improve the prediction of the tumour's pathological response to chemotherapy. However, the calculation process and evaluation method are relatively complex, and the underlying mechanism is unclear.

Enhanced MRI (magnetic resonance imaging) is another routine preoperative imaging analysis performed in osteosarcoma. Some authors [16,17] have used MRI to judge the effect of preoperative chemotherapy for osteosarcoma by measuring the change in the tumour volume and enhancement degree before and after chemotherapy. The

measurement method is similar to the current study. Although some progress has been made in the use of MRI for this purpose, there are several obvious limitations. For example, the imaging principle of MRI is relatively complex, the image sequence is variable, and the grayscale display and measurement technology of MRI are not convenient for routine application. Moreover, the comparability of pre- and post-treatment MRI measurements is poor. The imaging principle of enhanced CT, as applied in the current study, is completely different to that of MRI. The imaging principle of CT is relatively simple, and the grey value of CT images directly reflects the enhancement rate of the tumour, meaning that it is convenient for measurement and comparison. Therefore, compared with MRI, the current evaluation method based on enhanced CT is easy to implement and can be widely used.

Functional imaging methods based on tumour metabolic activity can also be used to evaluate chemotherapeutic effects. Several studies have reported that the effect of chemotherapy for osteosarcoma can be judged by bone scans [18,19] or PET-CT [20]. Although bone scans can reflect the degree of active bone metabolism, they are easily impacted by other factors. Moreover, the image clarity is poor, so it is difficult to accurately select the measurement target area. PET-CT can be used to evaluate the effect of chemotherapy by comparing the maximum SUV value of the tumour site before and after chemotherapy. However, these scans are not recommended for routine examination of osteosarcoma due to their high price. Multiple examinations before and after chemotherapy will significantly increase the economic burden for patients. Moreover, the imaging quality and clarity of enhanced CT images, as used in the current study, are higher than those of bone scans and PET-CT. The measurement area and level can be accurately selected, and the CT value can be accurately matched and compared. The price of CT is also lower than that of MRI and PET-CT. Thus, it is more suitable for clinical application and comparison of multiple examinations.

GCTB (giant cell tumour of bone) is a primary bone tumour with a rich blood supply. We have also carried out studies of the CT enhancement rate in GCTB [21–23]. Our measurement results [23] showed that the initial average CT enhancement rate was 2.01, which exceeds the initial enhancement rate of osteosarcoma in this study. After treatment with denosumab, the CT enhancement rate of GCTB was significantly reduced, and the plain CT value was significantly increased. This indicates a significant increase in lesion sclerosis. Histological examination showed that osteoclast-like multinucleated giant cells in GCTB had almost disappeared and mononuclear stromal cells were significantly reduced after treatment [21,22], which is similar to the necrosis of tumour cells in osteosarcoma after chemotherapy. Thus, our series of studies show that examination of the CT enhancement rate of bone tumours is not only limited to the numerical analysis of images; imaging data can be combined with histological data so as to provide an early, simple and non-invasive basis for judging the chemotherapeutic effect in bone tumours.

This study has some limitations that should be noted. First, this was a retrospective case analysis, not a prospective study. The images and histological data were obtained retrospectively, and clinically significant results were observed. Second, the number of enrolled cases was relatively limited due to the low incidence of osteosarcoma. Although the absolute value of the number of cases was limited, this study, as a single-centre case analysis, contained a large number of cases compared with previous reports. Larger samples can be targeted in future research.

In conclusion, this study examined the chemotherapeutic effect and blood supply changes in osteosarcoma with the hope of identifying a simple and feasible quantitative evaluation method. Enhanced CT was used to evaluate the change in the enhancement rate of osteosarcoma before and after neoadjuvant chemotherapy. The results indicated that the average tumour enhancement rate of all cases was significantly reduced after chemotherapy, but there were large individual differences. The above results suggest that there is a certain correlation between changes in the CT enhancement rate and changes in the tumour necrosis rate. Thus, the CT enhancement rate is worthy of further study and analysis as an index to judge the effect of chemotherapy. In the future, prospective studies with larger samples should analyse the accuracy and specificity of this evaluation method and determine if it follows a similar prognostic pattern as the necrosis rate for determining the survival rates of patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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