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Thallium-201 Scintigraphy to Assess Effect of Chemotherapy in Osteosarcoma

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Imaging results in patients with high-grade osteosarcoma of the extremities were reviewed to determine whether scintigraphic appearance correlated with histologic response to preoperative chemotherapy. **Methods:** Histologically, the percent tumor necrosis in specimens from 30 patients were classified into three grades: grade 1 = necrosis less than 60%, grade 2 = 60%–89% necrosis and grade 3 = diffuse necrosis greater than 90% based upon whole transverse sections. Scintigraphically, we analyzed ^{201}Tl uptake before and after preoperative chemotherapy. The changes in the tumor-to-background ratio were defined by an alteration ratio. **Results:** Of the 11 patients with a grade 1 response, the ratio showed −67.1% ± 45.4% (mean ± s.d.). Of the 9 patients with a grade 2 response, the ratio showed 37.9% ± 29.9% of the 10 patients with a grade 3 response the ratio showed 105.5% ± 12.4%. The ratios correlated well with the histologic grades ($p < 0.0001$; analysis of variance). **Conclusion:** Thallium-201 scintigraphy accurately assesses the effect of chemotherapy on osteosarcoma.

Key Words: thallium-201-chloride; osteosarcoma; preoperative chemotherapy

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The survival rate of patients with high-grade osteosarcoma of the extremities during the past two decades has dramatically improved since intensive chemotherapy was introduced (*1–4*). In addition to postoperative adjuvant chemotherapy, neoadjuvant chemotherapy, adopted as a combination of pre- and postoperative chemotherapy, has recently been commonly used to treat patients with primary osteosarcoma (*4*). Although whether the neoadjuvant chemotherapy itself has further improved the survival rate is controversial, the 5-yr survival rate for patients with osteosarcoma receiving this therapy has reached approximately 60%–70% (*4–7*).

Recent reports indicate that the degree of tumor necrosis following preoperative chemotherapy is likely to be an indicator of the prognosis for patients with primary osteosarcoma (*7–9*). It is now accepted that the patients whose tumors have more than 90% necrosis have a better prognosis than those with less than 90% necrosis (*6,8–11*). A means of quantitative analysis of tumor necrosis prior to surgery, however, has not yet been established. To evaluate the effects of chemotherapy, we performed ^{201}Tl-chloride scintigraphy in patients with osteosarcoma both before and after preoperative chemotherapy and analyzed the images. We evaluated correlations among scintigraphic appearance, histologic degree of tumor necrosis and prognosis.

MATERIALS AND METHODS

Patients

From June 1983 to September 1994, 30 patients diagnosed with high-grade osteosarcoma of the extremities were studied with ^{201}Tl

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scintigraphy both before and after preoperative chemotherapy. No patient had distant metastasis prior to their initial treatment. The study group consisted of 21 men and 9 women, mean age 15 yr (range 9–34 yr). Seventeen patients had tumors in the femur, nine in the tibia, two in the fibula and one each in the humerus and radius, respectively. The diagnosis was made by a combination of plain roentgenograms and histologic sections of biopsy specimen stained with hematoxylin and eosin (H&E). The patients were treated with intensive chemotherapy and surgical treatment for primary lesions. Follow-up periods ranged from 10.4 to 144.2 mo (mean 62.7 mo).

Image Acquisition

All studies were performed using a gamma camera with a data processing computer. Scintigraphy was performed as follows: a 3-mCi dose (111 MBq) ^{201}Tl-chloride was administered intravenously, and scintigraphic images were obtained 2–3 hr postinjection. The patients were instructed to rest during the studies. A low-energy, parallel-hole collimator was used and image data were obtained in a 64 × 64 matrix for 5 min. Images were obtained twice: the first scan was obtained before the initial treatment and a follow-up scan was performed after completion of preoperative chemotherapy.

Region of Interest Placement

For quantitative evaluation, image data counts from the spot images were stored in the computer. Two equally sized regions of interest (ROI) were placed on each image: the first one was over the tumor and the second one on the same level of contralateral area as the background. Care was taken in positioning and sizing the ROIs to maintain identical conditions both before and after preoperative chemotherapy. For each ROI, the average counts per pixel were calculated by the computer.

Data Analysis

The tumor-to-background count ratio (TBR) was calculated by dividing the average counts per pixel of the tumor (T) by the those of the background (BG). Excluding the background activity, the TBR was determined as follows: TBR = (T − BG)/BG. We compared the prechemotherapy TBR (TBR1) with the postchemotherapy TBR (TBR2), and the change was defined as an alteration ratio as follows:

$$\text{alteration ratio (\%)} = (\text{TBR1} - \text{TBR2})/\text{TBR1} \times 100.$$

The results of the alteration ratio were divided into three groups: Group 1 = the ratio less than 0%, increased isotope accumulation in the tumor signifying no effect of preoperative chemotherapy, Group 2 = 0%–99%, no change or a moderate decrease of isotope signifying a minimal or moderate chemotherapeutic effect, and Group 3 = the ratio greater than 100%, disappearance of accumulation, below the background level in certain cases signifying a beneficial effect of chemotherapy.

Chemotherapy and Surgery

Every patient was treated with preoperative chemotherapy. Twenty-six of 30 were treated with high-dose methotrexate combined with rescue by citrovorum factor, cisplatin and doxorubicin administered intravenously. Four patients received cisplatin intra-arterially. The median duration of the preoperative chemotherapy was 2.8 mo.

All the primary lesions were surgically removed within 2 wk after chemotherapy. Limb-sparing resections were done in 20 selected patients in whom a wide margin could be obtained without damage to major neurovascular bundles. Alternatively, wide or radical amputations were performed in 10.

Pathologic Examination

Representative transverse segments were divided into 25 paraffin-embedded blocks on average, each block was cut into 5-μm sections and stained H&E. An entire series of transverse sections of the specimen was examined microscopically to assess the effect of preoperative chemotherapy. We used the data of Huvos et al. (*12*) to define tumor necrosis. The area of tumor necrosis was determined for each histologic section and was mapped life-size onto a paper on which the specimen had been traced (*13*). The percent necrosis was calculated from the area of necrosis relative to that of the entire tumor. Depending on the percent tumor necrosis, the tumors were classified into three grades: grade 1, necrosis less than 60%; grade 2, 60%–89% necrosis; and grade 3, diffuse necrosis greater than 90%.

Finally, the alteration ratios were compared with the histologic grades of necrosis to determine whether the scintigraphic changes correlated with the histologic response to chemotherapy.

Statistical Analysis

The survival data were analyzed by Kaplan-Meier methodology. The variation in survival among subgroups of patients was tested by a log-rank test. Analyses of variance were conducted for comparison between the alteration ratios and the histologic grades. Differences among subgroups were tested by the Kruskal-Wallis test. All probability values less than <0.05 were significant.

RESULTS

Before chemotherapy, tumor images in all patients had greater isotope uptake than did the related background and correctly corresponded to the location, shape and size of the tumor itself. After chemotherapy, the images in 10 patients visually showed enlarged tumor size and significantly increased tracer accumulation. Five of the ten patients had particularly increased peripheral uptake in the tumor (marginal uptake) and three had invasion into the epiphyses. The images in three other patients demonstrated no definite change. In 17 of 30 patients, the images showed diminution in the tumor volume and decreased isotope accumulation. TBR1 values ranged from 0.15 to 3.30 (mean 0.69), whereas the TBR2 ranged from −0.11 to 1.72 (mean 0.34). The alteration ratios ranged from −146.4% to 137.1% (mean ± s.d., 21.9 ± 80.6). Ten of 30 patients were classified as Group 1, 12 as Group 2 and 8 as Group 3.

Histologically, 11 tumors were classified as grade 1, 9 as grade 2, and 10 as grade 3 (Table 1).

Scintigraphic Appearance and Histologic Grading

Of 11 patients with grade 1 response, 10 were classified as Group 1 and 1 as Group 2. All nine patients with a grade 2 response were classified as group 2. Of 10 patients with a grade 3 response, only 2 were classified as Group 2 and 8 as Group 3 (Table 2). The ratios obtained due to ^{201}Tl uptake changes were significantly different for each histologic grade ($p < 0.0001$) (Fig. 1).

Prognosis and Histologic Grading

Fourteen patients have remained disease-free, and one died from an unrelated cause. The remaining 15 patients have had a metastasis. Five are presently alive and disease-free after treatment for their metastases, and 10 have died. The 5-yr disease-free survival rate (5-yr DFSR) of all the patients was 48.9%. The 5-yr DFSR in those patients with grade 1 response was 27.3%; in those with grade 2 response 51.9%; and in those with grade 3 response, 75.0%. There was a significant difference in the DFSRs between patients with a grade 1 response and those with a grade 3 response ($p < 0.05$), and between those patients with a grade 1 or 2 response and those with a grade 3 response ($p < 0.01$).

Representative Cases

Case 1 (Table 1, Patient 27). A 23-yr-old man was diagnosed with high-grade osteosarcoma of the left distal tibia (Fig. 2). A

TABLE 1
Scintigraphic and Histologic Results

Patient no.	Age (yr)	Sex	Tumor site	Change in ^{201}Tl scan†	Alteration ratio	% Tumor necrosis	Current status
			Grade 1 response*				
1	15	F	Proximal tibia	Worse	−146%	35	Dead
2	25	M	Distal humerus	Worse	−111%	20	CDF
3	14	M	Distal femur	Worse	−94%	30	Dead
4	11	M	Distal femur	Worse	−80%	30	Dead
5	13	F	Distal femur	Worse	−73%	40	Dead
6	12	M	Diaphyseal femur	Worse	−70%	40	Dead
7	9	F	Proximal tibia	Worse	−61%	30	CDF
8	14	F	Proximal tibia	Worse	−58%	40	Dead
9	15	M	Distal femur	Worse	−52%	40	Dead
10	17	M	Proximal tibia	Worse	−21%	40	ANED
11	17	M	Proximal tibia	No change	28%	32	ANED
			Grade 2 response*				
12	16	M	Distal femur	No change	1%	84	DOU
13	21	M	Proximal tibia	No change	4%	60	CDF
14	20	M	Distal femur	Improved	19%	60	CDF
15	17	M	Distal femur	Improved	31%	66	ANED
16	14	M	Distal femur	Improved	36%	60	ANED
17	30	M	Proximal tibia	Improved	48%	75	Dead
18	17	M	Diaphyseal femur	Improved	49%	70	Dead
19	13	F	Diaphyseal femur	Improved	54%	88	CDF
20	9	M	Distal femur	Improved	99%	75	CDF
			Grade 3 response*				
21	12	F	Diaphyseal radius	Improved	91%	90	CDF
22	13	M	Distal fibula	Improved	98%	92	ANED
23	34	M	Proximal femur	Improved	100%	99	Dead
24	16	M	Distal femur	Improved	101%	96	CDF
25	14	M	Proximal tibia	Improved	103%	95	CDF
26	12	M	Distal femur	Improved	103%	96	CDF
27	23	M	Distal tibia	Improved	104%	99	CDF
28	15	F	Proximal fibula	Improved	105%	99	CDF
29	25	F	Proximal femur	Improved	113%	85	CDF
30	13	M	Distal femur	Improved	137%	95	CDF

*Grade 1, necrosis less than 60%; Grade 2, 60–89% necrosis; Grade 3, necrosis greater than 90%.
†Visual change on ^{201}Tl scan. Worse, an enlargement of tumor size and increase in accumulation; Improved, decrease in accumulation.
CDF = continuous disease-free; ANED = alive with no evidence of disease; DOU = died from an unrelated cause.

follow-up scan showed considerable reduction in isotope accumulation with tracer levels the same as background (Fig. 2C). The alteration ratio was 104% (Group 3). Histologically, there were no viable cells and the fibrous region dominated over the tumor (Fig. 2D). This patient was classified as grade 3 response and is now disease-free 15 mo after the initial surgery.

Case 2 (Table 1, Patient 6). Figure 3 illustrates radiographic findings in the case of a 12-yr-old boy with osteosarcoma of the left diaphyseal femur. Even after multidrug chemotherapy, the tumor evidently showed the malignant progression. The alteration ratio was −70.0% (Group 1) (Fig. 3B, C). Histologic analysis showed that the remnants of viable tumors were widespread in both the intra- and extra-medullary tumor compartments (Fig. 3D). This patient was classified as grade 1

TABLE 2
Relationship between Scintigraphic Appearance and Histologic Grade

	Histologic grade (% Tumor necrosis)		
	Grade 1 <60%	Grade 2 60%–89%	Grade 3 ≥90%
Group 1 (Alteration ratio < 0%)	10	0	0
Group 2 (Alteration ratio 0%–99%)	1	9	2
Group 3 (Alteration ratio ≥ 100%)	0	0	8

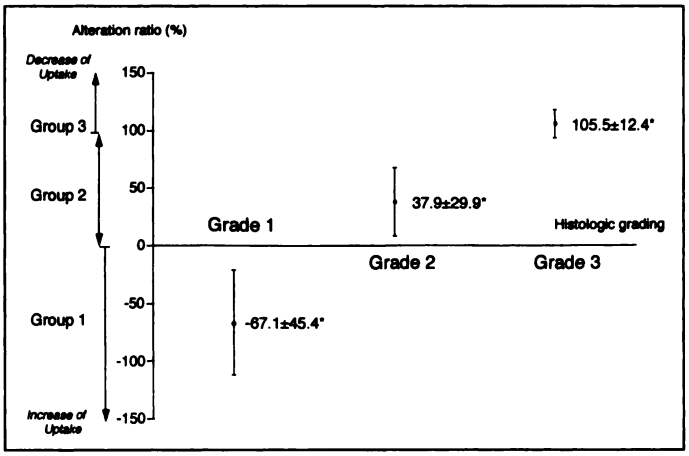

FIGURE 1. Correlation between the alteration ratio in ^{201}Tl uptake and histologic grade. The ratios (mean ± s.d.) are significantly different in each grade ($p < 0.0001$; analysis of variance).

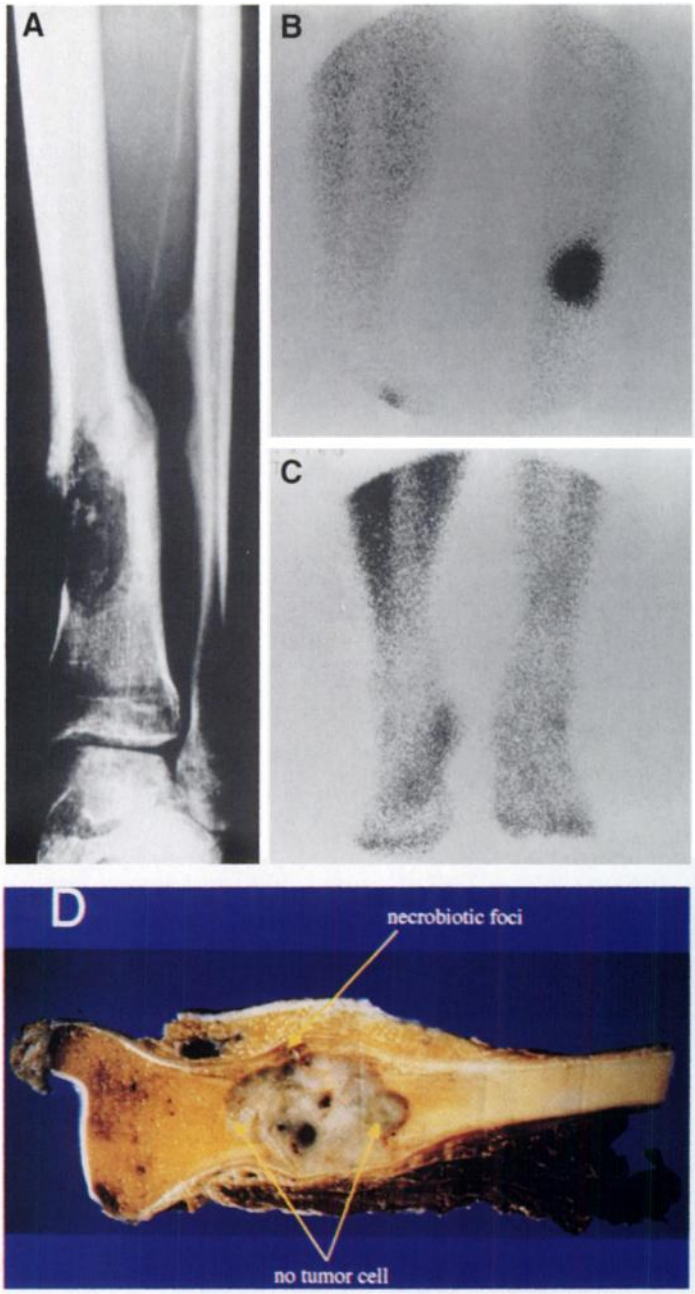

FIGURE 2. Group 3 patient with good response to chemotherapy. (A) High-grade osteosarcoma of the left distal tibia (Patient 27 in Table 1). Pathologic fracture is found. (B) The first scan shows the hot spot: TBR1 value is 0.46. Follow-up scan after treatment with six courses of methotrexate and two courses of doxorubicin plus cisplatin. (C) Considerable reduction with the same level as the background is seen. The TBR2 value is −0.02, and the alteration ratio is 104% (Group 3). (D) Histologically, the percent tumor necrosis: 99% (grade 3).

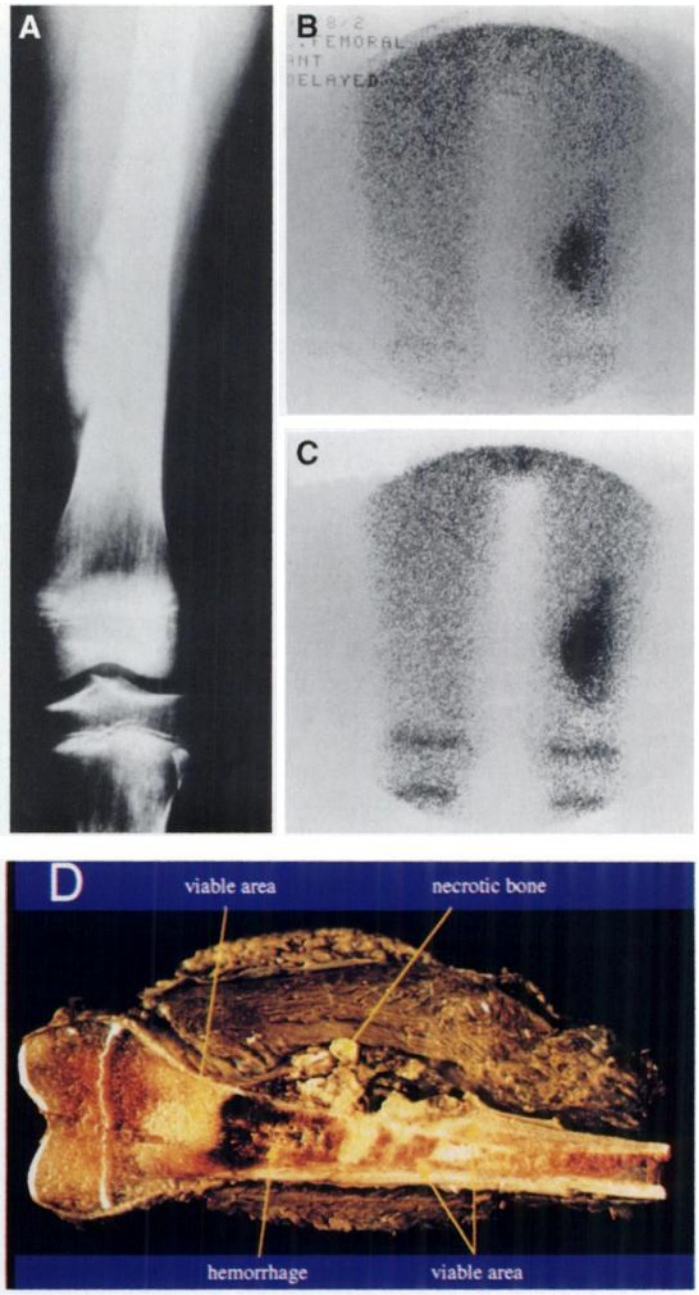

FIGURE 3. Group 1 patient with no response to chemotherapy. (A) High-grade osteosarcoma of the left diaphyseal femur (Patient 6 in Table 1). (B) First scan: the TBR1 value is 0.19. (C) Follow-up scan after treatment with one course of methotrexate and four courses of doxorubicin plus cisplatin: TBR2 value is up to 0.33 and the ratio is −70.0% (Group 1). (D) Histologically, only 40% necrosis is present, which is probably not associated with chemotherapy (grade 1).

response. A pulmonary metastasis developed within 12 mo, and the patient died 34 mo after initial surgery.

DISCUSSION

After introduction of intensive chemotherapy coupled with aggressive surgical treatment, the survival of patients with primary osteosarcoma has improved dramatically (*1–9*). Current clinical studies have demonstrated that the curability of osteosarcoma depends mainly on the response to chemotherapy, and the most powerful prognostic factor is the extent of tumor necrosis (*6–11*). Older imaging methods such as conventional radiography, CT and bone scintigraphy are important for the initial diagnosis and staging the tumor, but changes demonstrated on these studies are difficult to quantify and do not always reflect alterations in tumor activity (*14*). Therefore, we have needed an additional technique to demonstrate localization of viable tumor accurately (*9*). From this point of view, ^{201}Tl scintigraphy is strongly recommended for clinical evaluation of osteosarcoma.

Thallium-201 rapidly clears from the circulation, and it is considered a suitable substance for scintigraphic imaging. In addition, it has less accumulation in benign neoplasms, inflammatory lesions and remodeling bone production than ^{67}Ga. Thus, ^{201}Tl scintigraphy has been used commonly since the 1980s as a major functional imaging tool in clinical oncology (*15*). It has been useful both in localizing and diagnosing several malignant neoplasms, such as thyroid cancer, lung cancer, breast cancer and bone and soft-tissue sarcomas (*16–29*).

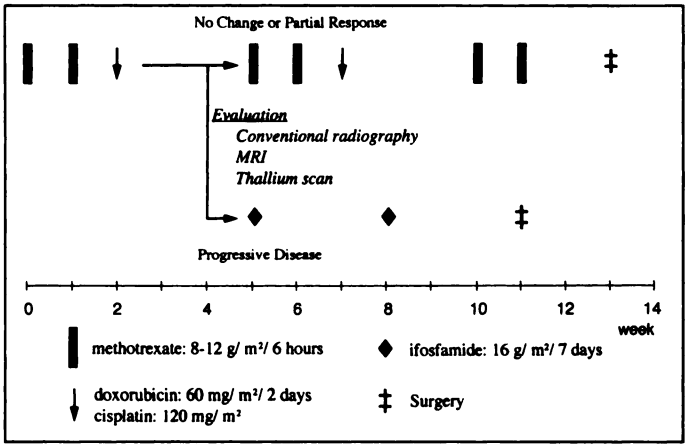

FIGURE 4. A current preoperative chemotherapy regimen for primary osteosarcoma from 1994. Additional thallium scan is applied after the initial cycle of chemotherapy.

Previous studies indicate that ^{201}Tl scintigraphy more accurately reflects viable tumor burden in brain and bone. Kaplan et al. (*30*) have shown that ^{201}Tl offered accurate correlation with viable tumor in patients with brain tumors. The Cedars-Sinai Medical Center (Los Angeles, CA) group recently has evaluated the effect of preoperative chemotherapy on malignant bone sarcomas using ^{201}Tl (*26–29*). In their reports, they compared the degree of accumulation in the tumor lesions with that in the background and heart, and visually classified those results into five grades. In our current study, the degree was evaluated by using alteration ratios calculated from the background activity. Thus, these ratios correlate well with the histologic responses to chemotherapy and often are good prognostic indicators.

We determined the current therapeutic regimen for primary osteosarcoma based on the results of ^{201}Tl scintigraphy before, during and after preoperative chemotherapy (Fig. 4). Four weeks after starting chemotherapy, the patients are evaluated for their response using conventional radiography, MRI (including enhancement with gadolinium) and ^{201}Tl scintigraphy. If these drugs are successful in terminating tumor growth, the patients are treated with the same drugs until surgical intervention. For those patients with an enlarged tumor at evaluation, these drugs should be replaced by another drug, and surgical treatment must be executed rapidly. We expect that ^{201}Tl scintigraphy will be of great use in the noninvasive prediction of the response of osteosarcoma to chemotherapy in the early stage of treatment.

CONCLUSION

Thallium-201 scintigraphy accurately assesses chemotherapeutic response on osteosarcoma and is a simple, easy and reliable tool for preoperative evaluation of patients with osteosarcoma.

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