

Osteosarcoma after Preoperative Chemotherapy : Tissue Characterization with Specimen MR and the Role of Enhanced MR Imaging¹

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Purpose : To evaluate the role of enhanced MR imaging in monitoring tumor response to preoperative chemotherapy for osteosarcomas.

Materials and Methods : Forty-seven patients (30 males and 17 females, with a mean age 17 years ; range 8-44 years) with osteosarcomas were included in this study. We obtained spin echo T1-, T2-, and enhanced T1-weighted images before and after preoperative chemotherapy and in all patients correlated changes in MR parameters with histopathologic response. We also obtained 19 specimen MR images, correlating these with histopathologic results in order to estimate tissue specific signals. Patients with more than 10% viable tumor in the resected specimen were considered poor responders (n= 26), while those with 10% or less viable tumor were considered good responders (n= 21).

Results : Four distinct patterns of signal intensity corresponded, respectively to dead bone and dense fibrosis (low on T1- and T2-weighted images), viable tumor cells (intermediate on T1- and high on T2-weighted images), necrosis (low on T1- and high on T2-weighted images), and hemorrhage (high on T1- and T2-weighted images), but a wide range of overlap was noted. In all four groups, viable tumor cells remained. Increased tumor volume, stable or increased edema and enhancement were good predictors of poor response (predictive values of 83%, 77%, and 89%, respectively). Decreased enhancement was the only reliable predictor of good response (predictive value, 73%). Changes in tumor margin, homogeneity, signal intensity, and joint effusion did not correlate with histopathologic response.

Conclusion : Signal intensities do not reflect histologic nature. Enhanced MR imaging is a useful predictor of tumor response to preoperative chemotherapy.

Index words : Bone neoplasms, MR

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Magnetic resonance (MR), contrast enhancement

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Preoperative intra-arterial chemotherapy and limb-salvage surgery for the treatment of osteosarcoma has led to marked improvement in long-term patient survival (1-3). The most accurate prognostic factor is the percentage of tumor necrosis after chemotherapy (4). The most useful imaging modality for predicting tumor

necrosis is magnetic resonance (MR) imaging and the role of this in monitoring the effect of preoperative chemotherapy has been reported (5-8), as has the use of dynamic contrast-enhanced MR imaging for the detection of residual viable tumor cells (9-17). This study was performed in order to estimate tumor signal intensities by correlation with specimen MR images and pathologic mapping, and to evaluate the role of gadopentetate-enhanced MR imaging in the determination of tumor response to chemotherapy by correlating MR images with histopathologic response.

Materials and Methods

Patients

Forty-seven patients (30 males and 17 females, mean age 17 years ; range 8-44 years) with biopsy proven osteosarcomas were included in this prospective study. Tumors had developed in the femur (n= 27), tibia (n= 12), humerus (n= 4), fibula (n= 3), and radius (n= 1). Before treatment, all patients had undergone MR imaging and tissue diagnosis, and were then treated with three cycles of high dose methotrexate (8-12g/m² of body surface, twice per cycle at weekly intervals), as well as adriamycin (60mg/m²) and intra-arterial cisplatin (12mg/m²) at three-weekly intervals. The two last-mentioned were not included at last cycle. After treatment, patients underwent limb salvage surgery (n= 42) or amputation (n= 5). None underwent pre-operative radiation therapy.

MR Imaging

Before treatment, all patients underwent MR imaging involving the use of a 1.0T superconductive MR unit (SMT 100X, Shmadzu, Japan). In all cases, the imaging protocol used was spin echo T1- (500/20/2-4 TR/TE/excitation) and T2-weighted imaging (2000/80/2), followed by enhanced imaging (Gd-DTPA 0.1mmol/kg), with a slice thickness of 10mm (interslice gap of 2mm) in the axial and longitudinal planes. Matrix was 256 × 256, and field of view 15-20cm. Postchemotherapy MR images were obtained within one week of surgery using the same protocol. We also performed specimen MR imaging (n= 19; spin echo T1 and T2-weighted, with slice thickness of 5mm and interslice gap of 1mm) in the longitudinal section within an hour of resection. Two radiologists without knowledge of the histopathologic findings evaluated the results of MRI.

Tumor volume

Tumor volume was measured on axial and longitudinal enhanced T1-weighted images using the formula: volume = $\pi/6 \times \text{height} \times \text{width} \times \text{length}$. Tumor volume ratio was defined as tumor volume after treatment divided by tumor volume before treatment. Changes in tumor volume were classified as increased (ratio greater than 1.05), stable (ratio between 0.95 and 1.05), or decreased (ratio less than 0.95).

Tumor margin

Extraosseous and intraosseous tumor margins were evaluated on T2-weighted axial and enhanced T1-weighted longitudinal images, respectively. In defining tumor margin as well, moderately, or poorly defined, extra- and intraosseous peritumoral edema was excluded.

The margin was 'well defined' when its entirety was sharply delineated, while 'poorly defined' indicated that less than half the margin was delineated. Changes in tumor margin were scored as 'improved' or 'not improved'.

Homogeneity

Tumor homogeneity as seen on T2-weighted images, was described as homogeneous or inhomogeneous. Changes in homogeneity were scored as 'more homogeneous', 'unchanged', or 'less homogeneous'.

Signal intensity

Areas of signal intensity were categorized in one of four ways : 1) area of high signal intensity on T1 and T2-weighted images ; 2) area of low signal intensity on T1 and T2-weighted images ; 3) area of low signal intensity on T1-weighted images and high signal intensity on T2-weighted ; 4) area of intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted. Changes in areas of signal intensity were classified as 'increased', 'unchanged', or 'decreased'.

Edema

Soft tissue edema was demarcated as an area of poorly defined but homogeneous high signal intensity in soft tissues, as seen on T2-weighted images, and with a feathery appearance, following the facial planes, and without focal mass effect. Intraosseous edema was defined as a poorly delineated area of homogeneous signal intensity adjacent to the tumor with intermediate signal intensity on T1-weighted image and high signal intensity on T2-weighted, relative to the signal intensity of nor-

mal bone marrow (18). Because pre-enhancement T1 and T2-weighted longitudinal images were not available, however, the extent of intraosseous edema could not be evaluated in all patients. Thus, only the extent of soft tissue edema was evaluated, though this and soft tissue edema could not always be differentiated.

The extent of edema were scored as decreased, unchanged, and increased.

Enhancement

Degree of enhancement was classified as 'none', 'weak', or 'strong'. Weak enhancement indicated that signal intensity of the tumor was lower than that of fat, and strong enhancement that it was the same or higher than that of fat. Degree of enhancement was scored as 'decreased', 'unchanged', or 'increased'.

Joint effusion

When joint effusion was noted on T2-weighted images, changes were scored as 'decreased', 'unchanged', or 'increased'.

Histopathology

All 47 resected specimens were sectioned in the same plane as preoperative MR and divided into 1cm × 1cm pixels, each of which was evaluated quantitatively for necrosis or residual viable tumor. In five of 19 cases with specimen MR, radiologists and a pathologist jointly performed a point-by-point correlation between the specimen MR image and histopathologic findings. Patients with more than 10% of viable tumor in the resected specimen were considered poor responders, while those with less than 10% were considered good responders. Thus, 21 of 47 patients were good responders, while the remaining 26 were poor.

Statistical Analysis

To determine whether initial tumor volume correlated significantly with histopathological response, the Spearman test was applied, while for changes in tumor, volume and margin, homogeneity, signal intensity, edema, joint effusion, and enhancement, the χ^2 test for 2 × 2 tables was used. P values less than 0.05 were considered significant. For those parameters which correlated significantly with histopathological response, diagnostic indices (sensitivity, specificity, and predictive values) were calculated.

Results

Tumor Volume

Initial mean tumor volume of good responders and poor responders was 171.3cm³ and 281.3cm³, respectively. Initial tumor volume and histopathologic response correlated significantly (P= 0.03). A tumor volume of less than 100cm³ successfully predicted a good response in 67% of patients, while larger tumors predicted a poor response in 63%.

Changes in tumor volume were evaluated in all patients and correlated significantly with histopathological response (P= 0.03). Decreased or stable tumor volume was found in both good and poor responders (90% and 62%, respectively). Only two good responders showed increased tumor volume (tumor volume ratio, 1.45 and 2.18). The predictive value of decreased or stable tumor volume for good response was 54%, while that of increased tumor volume for poor response was 83%. Sensitivity and specificity were 90% and 38% respectively (Table 1).

Table 1. Statistical Data for the Parameters Correlating Significantly with Histopathologic Response

Parameters and Change at MR Imaging	Histopathologic response		Sensitivity	Specificity	Positive Predictive	Negative Predictive
	Good	Poor			Value	Value
Tumor Volume			90%	38%	54%	83%
No increase	19	16				
Increase	2	10				
Total	21	26				
Edema			74%	65%	61%	77%
Decrease	14	9				
No decrease	5	17				
Total	19	26				
Enhancement			90%	71%	73%	89%
Decrease	19	7				
No decrease	2	17				
Total	21	24				

Tumor Margin

Tumor margin was evaluated in all patients, and in all cases the intraosseous margin was well defined both before and after chemotherapy. Extraosseous tumor margin improved in 27 patients (12 good responders, 15 poor responders), and changes in the margin did not correlate with histopathologic response ($P=0.93$).

Homogeneity

Homogeneity was evaluated in all patients. Thirteen tumors (27%, six good responders and seven poor responders) became more homogeneous, 14 tumors (30%, six good responders and eight poor) became less homogeneous, and 20 tumors (43%, nine good responders and 11 poor responders) were unchanged. There was no significant difference between good and poor responders ($P=0.87$).

Signal Intensity

Comparison with specimen MRI and histopathology is shown in Figure 1: 1) low signal intensity on T1- and T2-weighted images corresponded to dead bone, calcification, and dense fibrosis (viable tumor cells up to 30%), 2) low signal intensity on T1-weighted image and very high signal intensity on T2-weighted corresponded to necrosis and granulation tissue (viable tumor cells up

to 20%), 3) intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted corresponded to viable tumor cells, fibrosis and granulation tissue (viable tumor cells up to 95%); 4) high signal intensity on T1- and T2-weighted images corresponded to hemorrhage (viable tumor cells up to 60%). There was a wide range of overlap between viable tumor, dead bone, fibrosis, granulation, necrosis, and hemorrhage, so tissue characterization on the basis of signal intensity was not possible.

Changes in areas of signal intensity among the four groups were noted, with no significant difference between good and poor responders ($P=0.38$). Areas of low signal intensity on T1- and T2-weighted images increased in nine of 21 good responders (43%) and 10 of 26 poor responders (38%). Areas of intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted decreased in 12 of 21 good responders (57%) and 15 of 26 poor responders (58%).

Edema

Edema was evaluated in 45 patients. In two patients of good responders, its presence was noted neither before nor after treatment. Statistically significant correlation was found between edema and pathologic response ($P=0.02$). Fourteen of 19 good responders (74%) showed



Fig. 1. A 14-year-old boy with osteosarcoma in the proximal tibia.

A, B. T1-weighted specimen MR image (A) and T2-weighted specimen MR image (B) show well defined heterogeneous intra- and extraosseous mass in the proximal metadiaphysis of tibia.

C. Gross specimen with same plane of specimen MR shows necrosis (large arrow) and hemorrhage (small arrow).

D. Histologic map shows residual viable tumor cells interspersed at background of tumor matrix and granulation tissue (\\), necrosis (/), and hemorrhage (black area). Fine dotted area represents normal marrow.

a decrease in the area of edema, while in five (26%), the area remained stable. In no good responders was an increased area of edema noted. The predictive value of decreased edema for good response was 61%, while that of increased or stable edema for poor response was 77%. Sensitivity and specificity were 74% and 65% respectively (Table 1).

Enhancement

Since two patients were missing, tumor enhancement was evaluated in only 45 cases. Nineteen of 21 good responders (90%) showed decreased enhancement (Fig. 2), and no good responders showed increased enhancement. Only seven of 24 poor responders (29%) showed decreased enhancement (Fig. 3). Change in enhance-

ment correlated with histopathologic response ($P=0.0002$). The predictive value of decreased enhancement for good response was 73%, and that of increased or stable enhancement for poor response was 89%. Sensitivity and specificity were 73% and 89% respectively (Table 1).

Joint Effusion

Joint effusion was evaluated in 30 patients. Five of 14 good responders (36%) and ten of 16 poor responders (63%) showed decreased joint effusion. There was no statistically significant correlation between changes in joint effusion and histopathologic response ($P=0.26$).

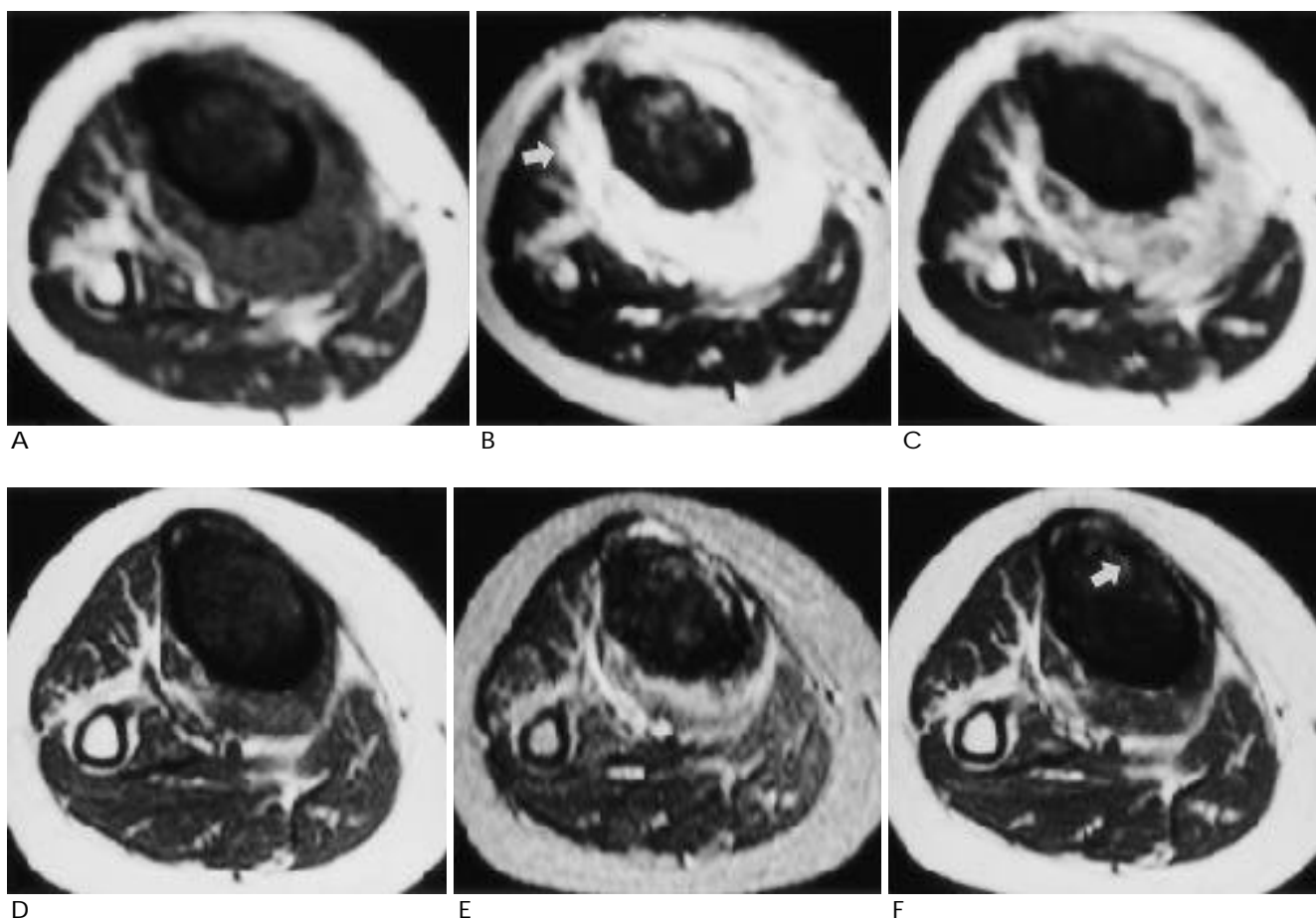


Fig. 2. A 14-year-old girl with osteosarcoma in the proximal tibia.

A-C. Axial MR images obtained before chemotherapy show homogeneous mass involving proximal tibia. Extraosseous mass shows intermediate signal intensity on T1-weighted image (A), high signal intensity on T2-weighted image (B), and strong enhancement after injection of Gd-DTPA (C). Feathery-like peritumoral edema is seen on T2-weighted image (B, arrow). Intramedullary portion shows dark signal intensity on all pulse sequences represents densely calcified osteoid.

D-F. Axial MR images obtained after chemotherapy with same plane of A-C show decrease extraosseous portion of the tumor. Decreased signal intensity and disappeared peritumoral edema are well shown on T2-weighted image (E). Focal and faint enhancement is seen on enhanced MR (F, arrow) compared with pre-enhancement T1-weighted image (D). Overall percentage of tumor necrosis is 96%.

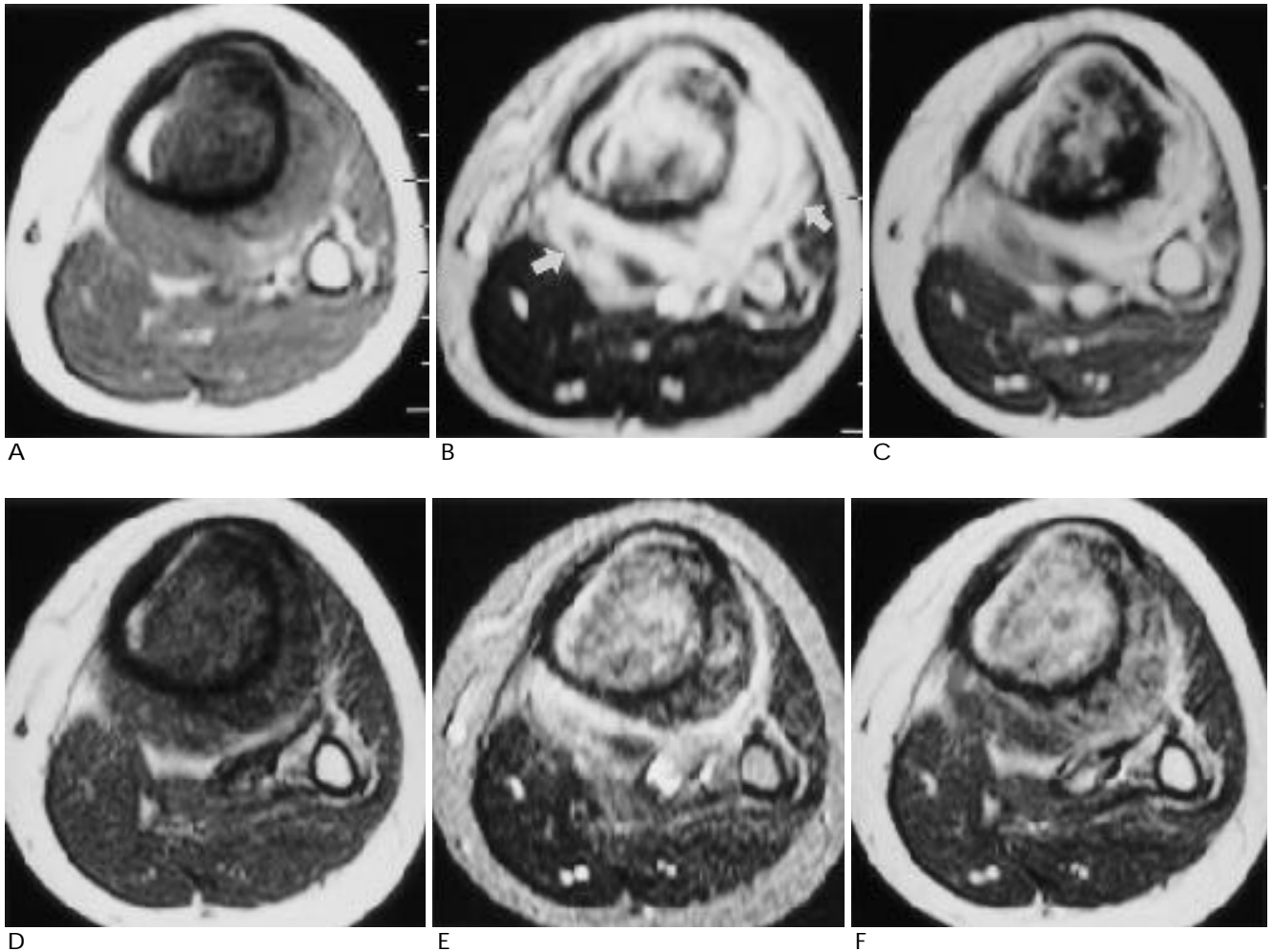


Fig. 3. A 14-year-old boy with osteosarcoma in proximal tibia.

A-C. Axial MR images obtained before chemotherapy show tumor involving proximal tibia. The mass shows intermediate signal intensity on T1-weighted image (A), high signal intensity on T2-weighted image (B), and strong enhancement of intra- and extraosseous components of the mass on enhanced MR (C). Massive peritumoral edema is well demonstrated on T2-weighted image (B, arrows). D-F. Axial MR images obtained after chemotherapy with same plane of A-C show unchanged tumor volume. Signal intensity of the mass decreased on T2-weighted image (E). Markedly decreased peritumoral edema is seen on T2-weighted image, but tumoral enhancement is still noted on enhanced MR (F) compared with pre-enhanced T1-weighted image (D). Overall percentage of tumor necrosis is 50%.

Discussion

Preoperative chemotherapy has improved the disease-free survival ratio of patients with osteosarcoma. The extent of tumor necrosis achieved with preoperative chemotherapy correlates with overall prognosis and thus influences surgical decisions and choices for post-operative chemotherapy (2). Monitoring neoadjuvant chemotherapy by means of MR imaging has been reported (5-8). Dynamic MR study has recently been used to increase the specificity of tissue characterization (9-17). In the present study, we analyzed the parameters of pre- and post-enhancement MR images of osteosarcoma

treated with preoperative chemotherapy. Numerous reports have described the correlation between MR signal intensity and chemotherapeutic effect (5-9).

In order to more precisely identify tissue specific signal intensity, specimen T1- and T2- weighted images were obtained immediately after resection, thus preventing changes in water content. Signal intensities could be roughly categorized, but in all four groups, varying percentages of viable tumor cells remained. Even in group 1, in which, according to pan et al.(b), a dark pattern represented tumor matrix and dense granulation tissue, up to 30% of viable tumor cells remained. In addition, only limited differentiation between group 2 (necrosis over 80%) and group 3 (viable tumor cells up

to 95%) was possible ; this was because technical factors including window selection and volume averaging were involved. Thus tumor necrosis cannot be predicted on the basis of signal intensity alone, and because the appearances of viable tumor, necrosis, edema, fibrosis, granulation tissue, and hemorrhage overlap, changes in signal intensity do not reliably indicate the absence of active disease (5). Moreover, small clusters of active tumor cells were found in areas of dense reactive bones (7). Holscher et al (9) found that increased T2 signal intensity of extraosseous tumor was a good predictor of poor responders, but we did not separately estimate the signal intensity of extraosseous tumor. In addition, neither changes in tumor margin, homogeneity, nor joint effusion are reliable differentiators of good and poor responders.

One of the important parameters predicting poor response was increased tumor volume. Correlation between changes of tumor volume and histopathologic response has been reported (8, 9) and in our study, increased tumor volume was a good predictor of poor response (predictive value 83%). This result is in accordance with that of Holscher et al (8, 9), noted that decreased or unchanged tumor volume in both good and poor responders. There were only two good responders with increased tumor volume, and one of these showed massive postchemotherapy tumor bleeding. The extent of tumor necrosis was also affected by initial tumor volume. Quintana et al (19) found that the proportion of good responders was 75% for small tumors (< 100cm³) and only 25% for large tumors. We also found that differences in initial tumor volume between good responders (171.3cm³) and poor responders (281.3cm³) was statistically significant, so initial tumor volume was an important prognostic factor.

Another important parameter predicting poor response is unchanged or increased edema (predictive value, 77%). We did not, however, evaluate intraosseous peritumoral edema, and this could be a weak point of our study. Soft tissue edema was defined as an area of poorly defined but homogeneous high signal intensity in soft tissues, as seen on T2-weighted images, and homogeneous enhancement with a feathery appearance, following the facial planes and without focal mass effect. During our study, discrepancies in interpretation were resolved by consensus. Pan et al (6) found that peritumoral edema decreased following chemotherapy, but they did not perform statistical analysis. Holscher et al (8) reported that increased or stable peritumoral edema

was a good predictor of poor responders (predictive value, 85-89%) and this is in accordance with our results. Three years later, however, they obtained contradictory results after one cycle of chemotherapy (9), and believed this outcome was related to changes in the degree of edema occurring later in the course of chemotherapy.

In addition, decreased contrast enhancement is a sound predictors of good response (predictive value, 73%), while increased or unchanged enhancement is a good predictor of poor response (predictive value, 89%). Seeger et al (20) found that gadopentetate dimeglumine did not help define the tumor margin of osteosarcoma ; instead it obscured differentiation of tumor from normal marrow or tumor infiltration of perineurovascular fat. In this study, enhanced MRI also obscured the differentiation of intraosseous tumor from normal marrow, though on pre-enhanced T1-weighted images these could be distinguished. Differentiation of extraosseous tumor from surrounding muscle, however, was better demonstrated on enhanced MR than on T2-weighted images, in which the tumor margin was obscured by peritumoral edema. Because viable tumor and nonviable highly vascularized granulation tissue showed similar high signal intensities, static Gd-DTPA-enhanced MR images were not reliable for the assessment of response (10). It has been reported that dynamic MR images usually differentiate viable tumor from vascularized granulation tissue, and for this reason they have been proposed as a way of monitoring response to chemotherapy (9-17). We too found thought that dynamic MR images superior to static enhanced MR images, but this method involves relatively complex manipulation of quantitative data and seems unlikely to be adopted as routine radiologic practice. Baere et al. (21) therefore suggested a simpler method, namely enhanced subtraction MR images, but they treated too few cases. Although our results are derived from a subjective and qualitative method, enhanced MRI is very helpful for the differentiation of group 2 and 3 signal intensities. Even in group 3 cases, peripheral enhancement of cystic or necrotic areas was seen. Fourteen of 21 good responders (67%) and only one of 26 poor responders (4%) failed to show enhancement on post-chemotherapy MRI.

In conclusion, it is hard to characterize different tissue components on the basis of signal intensity alone, but enhanced MR images usefully predict response to preoperative chemotherapy.

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