Assessment of the preoperative chemotherapy of bone sarcomas using anatomical and functional methods of visualization: development of the decisive rule and comparative analysis.

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Purpose

Bone sarcomas represent approximately 1% of malignant neoplasms in adults. Although advances in chemotherapy and surgery have improved prognosis, sarcomas still are fatal in up to half of patients. Histologic response has been shown to be a "gold standard" in the evaluation of neoadjuvant chemotherapy, it is considered to be the main prognostic factor and the criterion defining the postoperative treatment. Due to the Huvos grading system based on the percentage of post-treatment necrosis bone sarcomas are categorized as showing good (# 90% of necrosis) or poor (# 90% of necrosis) responses. To avoid the patient to continue on ineffective chemotherapy protocol there is a need in imaging method which reliably determines success or failure of preoperative chemotherapy prior to surgery and pathologic analysis of tumor.

Different imaging methods (from "classic" plain radiography and three-phase bone scintigraphy to "modern" technologists such as dynamic contrast-enhanced MRI (DCE-MRI) and FDG PET/CT) were offered in the past few decades to assess the effectiveness of preoperative chemotherapy in bone sarcomas.

Purposes of our study were:

1. To increase the informativeness of different imaging methods in assessment of the preoperative chemotherapy of bone sarcomas by developing differential criteria ("decisive rule") of good and poor response to the treatment.

2. To define and to compare the values of informativeness of plain radiography, MRI, DCE-MRI and three-phase bone scintigraphy in the evaluation of chemotherapy in patients with bone sarcomas in the middle and after preoperative chemotherapy.
Methods and Materials

Case selection
To develop and verify the "decisive rule" for different methods of visualization we analyzed the data of 114 patients, 25 (22%) female and 89 (78%) male, with a biopsy proven bone sarcomas. 92 (80%) patients had an osteosarcoma; 12 (11%) patients had a Ewing sarcoma; 5 (4%) patients with malignant fibrous histiocytoma, 3 (3%) - with fibrosarcoma, 1 with mesenchymal chondrosarcoma (1%) and 1 patient with round-cell liposarcoma (1%). Most frequently the tumors were located in the knee joint zone - 77 (68%) cases. The age of the patients varied from 14 to 58 years (mean, 23 years).

The patients were examined before, in the middle and at the end of the preoperative treatment.

Chemotherapy and Surgical Technique
Depending on the histological type of the tumor all patients received from four to six cycles of neoadjuvant chemotherapy. 111 patients (97%) underwent limb-sparing surgery with wide resection of the tumor. 3 patients were treated with amputation.

Pathology

Histologic Grading of Response
The tumors were systematically evaluated with a semiquantitative Huvos Tumor Necrosis Grading System. In every case, we determined the percent areas of viable tumor, necrotic tumor, fibrous/hyalinized stroma and acellular tumor osteoid such that the sum of these components was equal to 100%. Based upon the results, the tumors were categorized as having a good response (Grade III-IV pathologic response) when # 90% of necrosis was present and a poor response (Grade I-II pathologic response) for # 90% of necrosis (Fig. 1 on page 7). The quantity of good and poor responders were equal - 57 patients.

Imaging studies

Plain radiography
To develop and verify the decisive rule for plain radiography we analyzed radiograms of 109 patients. Plain radiography was obtained in the middle and after preoperative chemotherapy at different time periods. Plain radiography was performed in two projections.
**MRI**

MR imaging was performed with a 1.5T system (Siemens Magnetom Avanto), we analysed the data of 96 patients. In all instances, a combination of T2 WI and sequences with fat suppression (T2, Pd or STIR) in both the longitudinal and transverse planes and T1 WI in the transverse plane was used. On the bases of these images the tumor volume and the maximum transversal tumor dimension were assessed on all diagnostic stages. The volume of the tumor was calculated as the product of all dimensions multiplied by the coefficient of 0,52 for spherical or irregular-shaped tumors or 0,76 for cylindrical-shaped tumors.

**DCE-MRI**

In 39 patients after standard MRI examination a single-slice DCE-MRI sequence was performed followed by static postcontrast T1-weighted sequences. The dynamic imaging was performed with a fast low-angle shot sequence (FLASH 2D), with 100-200 images at a single slice (15 mm), with temporal resolution 1,5-3 s. The slice was located through the largest sectional area of the lesion exhibiting a reproducible and representative intra- and extramedullary tumor component. As the contrast medium we used 15 ml of Omniscan, Nycomed. On the post-processing for each patient four regions of interest (ROI) were manually selected, which were located: in the artery (ROI1), in the whole tumor (ROI2), in the earliest enhancing part of the lesion (ROI3) and in the muscle (ROI4). We evaluated the following DCE-MRI parameters: the pattern of enhancement, the type of the time-intensity curves (TIC) (Fig. 2 on page 7), the start of the enhancement compared with the artery, steepest slope per second of TIC of ROI2 and ROI3 [1], and the mean signal intensity (SI) of ROI2.

**Three-phase bone scintigraphy**

In 51 patients three-phase bone scintigraphy was performed. Immediately after intravenous bolus injection of $^{99m}$Tc-technephor, dynamic images of the tumor site and unaffected contralateral region were obtained, followed by a 2-5-minute static bone image obtained 3 hours later. For imaging gamma cameras ZLC-75, E. Cam and Symbia (Siemens) were used. For dynamic study, 40 images were acquired at 1 second per image, followed by 30 images acquired at 10 seconds per image. On the post-processing stage using 3 PHASE BONE program (Siemens) two ROIs were selected, one covering the tumor and another one mirrored over normal tissue of the contralateral site of the body. Time-activity curves were reconstructed within the selected ROIs. A blood pool ratio was calculated by dividing the counts of the tumor curve by the counts measured on the unaffected site at the same time. A similar ratio was calculated in the skeletal phase. The ratios obtained on the different stages of preoperative chemotherapy were
compared in dynamic to identify relative increase or decrease of the level of accumulation technetium in the tumor.

**Statistics, multifactor analysis, decisive rule**

The statistical analysis of the different radiological symptoms was made by STATISTICA program (v. 7.0, Statsoft Inc., USA), the calculation of the weighted coefficient (WC) of each statistically significant symptom was performed using the software "ASTA" invented at the N.N. Blokhin Cancer Research Center (Moscow). "ASTA" besides different statistical programs uses probabilistic mathematical techniques based on Bayes' theorem. In multifactor analysis, statistically significant signs acquire WC, which determine the frequency of occurrence of these symptoms in a group of patients with good and poor response. Subsequently, on the basis of the WCs the decisive rule was created separately for each method of visualization. The threshold of total WCs (TWC) was "0" for every imaging method except three-phase bone scintigraphy, TWC of symptoms with "+" value was categorized as having a poor response, on the other hand TWC with "-" value was showing a good response to chemotherapy. TWC for three-phase bone scintigraphy was +34.

In our study sensitivity characterized a prediliction of good response to treatment, whereas specificity - a group of patients with poor response.

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<table>
<thead>
<tr>
<th>Grade</th>
<th>% of necrosis</th>
<th>Histological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-49</td>
<td>Little or no apparent effect</td>
</tr>
<tr>
<td>II</td>
<td>50-89</td>
<td>Some areas of histologically viable tumor, but also areas of acellular tumor osteoid, necrotic and/or fibrotic material</td>
</tr>
<tr>
<td>III</td>
<td>90-99</td>
<td>Predominant areas of change attributable to chemotherapy, with only scattered foci of histologically viable tumor</td>
</tr>
<tr>
<td>IV</td>
<td>100</td>
<td>No histological evidence of viable tumor</td>
</tr>
</tbody>
</table>

**Good response** ≥ 90% (Grade III-IV)

**Poor response** ≤ 90% (Grade I-II)


Fig. 2: Types of time-intensity curves.

Results

Plain radiography

To develop the decisive rule for plain radiography we used the data of 93 patients which were examined on every three diagnostic stages. The symptoms associated with good response to chemotherapy and their WCs according to the decisive rule are: the structure of the tumor turns to be cellular-trabecular (-179), complete consolidation of pathologic fracture (-101), partial recovery of the cortex (-101), sclerosis around the intramedullary tumor component (-98), complete assimilation of the periosteal reaction (-78), formation of complete periosteal "shell" around the extramedullary tumor component (-69), appearance of foci with a structure of normal medullary bone in the tumor (-40) (Fig. 3 on page 11). The symptoms associated with poor response to chemotherapy and their WCs according to the decisive rule are: extending destruction of the cortex (+208), appearance or extension of aggressive non-assimilated periosteal reaction (+138), partial periosteal "shell" around the extramedullary tumor component (+110), absence of changes in the periosteal reaction (+69), partial formation of cellular-trabecular structure in the tumor (+25), partial assimilation of periosteal reaction (+17). Informativeness of the decisive rule was checked on patients who were examined only on two diagnostic stages. The sensitivity of the plain radiography using the decisive rule in the middle of the treatment was 33%, the specificity - 82%. At the end of the preoperative treatment the value of the sensitivity increased up to 71% the specificity decreased to 63%.

MRI

We evaluated the data of 90 patients with MRI which were examined on different stages of preoperative chemotherapy to develop the decisive rule. The symptoms associated with good response to chemotherapy and their WCs according to the decisive rule are: appearance of foci with a structure of normal fatty medullary bone in the tumor (-125), decrease of cystic component (-101), appearance (-51), extending (-66) or formation (-109) of well-defined margins of the tumor, vanishing the surrounding soft tissue edema (-56), increasing of the zones with high (-35) or low (-29) signal intensity (Fig. 4 on page 11). The symptoms associated with poor response to chemotherapy: preservation of surrounding soft tissue edema (+226), ill-defined borders of the tumor (+145), no change in the cystic component of the tumor (+85), preservation (+56) or increasing (+40) of hemorrhages, appearance (+69) or increasing (+29) of bone marrow edema and absence of changing in the structure of the tumor leading to preservation of signal intensity (+51). Informativeness of the decisive rule was checked on patients examined before and in the middle of chemotherapy, and in the middle and after chemotherapy. The sensitivity of MRI using the decisive rule in the middle of the treatment was 50%, the specificity - 80%. At the end of the preoperative treatment the values of the sensitivity and specificity increased up to 93% and 83% correspondingly.
For the changes of the tumor maximum dimension and the volume we obtained the following results: 50% decrease of the maximum tumor size (-62) and the volume (-40) characterize the group with a good response, absence of these criteria is associated with a poor response to treatment. The sensitivity of these criteria in the middle of the treatment was 50%, the specificity - 82%. At the end of the preoperative treatment the value of the sensitivity increased up to 56% the specificity decreased to 67%.

**DCE-MRI**

We analyzed the data of 39 patients with DCE-MRI. For the group of patients with a good response to treatment the most informative qualitative and semiquantitative DCE-MRI signs according to developed decisive rule are: lobular pattern of enhancement (-41), type I and II TIC of the whole tumor with WCs (-41) and (-12), and for the earliest enhancing part of it (-41) and (-10), correspondingly (Fig. 5 on page 12); for the patients with poor response: diffuse pattern of enhancement (+97), type III, IV and V TIC of the whole tumor with WCs (+21), (+57) and (+16), and for the earliest enhancing part of it (+79), (+34) and (+43), correspondingly. Prospective residual tumor tissue often located in the center of the lesion (WC +26). The sensitivity of these criteria by the end of the preoperative treatment was 68%, the specificity - 55%. The following results were obtained for the quantitative criteria of poor response to chemotherapy: the start of the enhancement of the tumor earlier then 3 seconds after the arrival of contrast in the artery, steepest slope of TIC of the whole tumor> 6%/s, steepest slope of TIC of the earliest enhancing part of the tumor> 10%/s, and the mean signal intensity of the tumor 40. The absence of these criteria was associated with a good response to treatment.

**Three-phase bone scintigraphy**

The data of 32 patients with three-phase bone scintigraphy examined before and after preoperative chemotherapy was used to develop the decisive rule. Unlike previously described imaging methods the threshold for the decisive rule was (+34), the TWC >34 was associated with poor response and < 34 - with good response to treatment. The decrease of accumulation of technetium in the tumor always correlated with a good response to treatment but with the different WCs. For the good responders the following signs are characteristic: decrease of the blood pool ratio in the whole tumor less than 250% (-57) and relative decrease of accumulation more than 40% (-66), or from 0 to 40% (-23) on blood pool phase; decrease of skeletal ratio less than 400% (-140) (Fig. 6 on page 13). Informativeness of the decisive rule was checked on patients examined before and in the middle of chemotherapy, and in the middle and after chemotherapy. The sensitivity of these criteria in the middle of the treatment was 87%, the specificity - 69%. At the end of the preoperative treatment the values of the sensitivity and specificity increased up to 88% and 70%, correspondingly.

*Comparative analysis of different diagnostic methods*
The use of the decisive rule both for plain radiography and three-phase bone scintigraphy in 20 patients with poor response and in 27 patients with good response increased the specificity to 83% and the sensitivity to 94%.

The use of the decisive rule both for MRI and DCE-MRI in 5 patients with poor response and in 5 patients with good response increased the sensitivity to 100%, but decreased the specificity to 80%.

The use of the decisive rule both for MRI and three-phase bone scintigraphy in 11 patients with poor response and 16 patients with good response increased the specificity to 87% and the sensitivity to 94%.
Fig. 3: Radiograms of osteosarcoma of the femur before, in the middle and at the end of the chemotherapy. During the chemotherapy the foci with cellular-trabecular structure and the partial periosteal "shell" appear. Before surgery the "shell" encloses the tumor, which became denser and fully transformed into cellular-trabecular structure. The decisive rule on the final diagnostic stage shows a good response to the treatment (TWC: -322), which was confirmed histologically (Grade III pathologic response).

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**Fig. 4:** MRI of osteosarcoma of the femur before and at the end of the chemotherapy. Appearance of foci with a structure of normal fatty medullary bone and the increasing of the zones with high signal intensity are the signs of good response to treatment after chemotherapy. The decisive rule on the final diagnostic stage shows a good response to the treatment (TWC: -160), which was confirmed histologically (Grade III pathologic response).

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**Fig. 5:** DCE-MRI of osteosarcoma of the femur before and at the end of the chemotherapy. Type I TIC of the whole tumor and the earliest enhancing part of it are the signs of good response to treatment after chemotherapy. The decisive rule on the final diagnostic stage shows a good response to the treatment (TWC: -82), which was confirmed histologically (Grade III pathologic response).

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Fig. 6: Three-phase bone scintigraphy of osteosarcoma of the femur before, in the middle and at the end of the chemotherapy. TWCs on the middle diagnostic stage (-123) and at the end of chemotherapy (-80) less than threshold for decisive rule (+34) for good responders. The result was confirmed histologically (Grade III pathologic response).

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Conclusion

1. In the middle of the preoperative treatment anatomical methods (plain radiography, MRI), based on qualitative features showed higher values of specificity (predilection of poor response - grade I-II pathologic response). After treatment sensitivity (predilection of good response - grade III-IV pathologic response) of plain radiography and MRI increases and exceeds the specificity.

2. Functional methods (three-phase bone scintigraphy and DCE-MRI) show higher values of sensitivity, thus better predict good response to treatment.

3. The combination of anatomical and functional methods improves the quality of evaluation of the treatment in patients with bone sarcomas in the middle and after therapy.

4. The use of the decisive rule will improve and simplify the evaluation of the preoperative chemotherapy of bone sarcomas using different imaging techniques especially for young radiologists. Moreover these criteria can be used in the educational process.
References


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