Perspective approaches in the evaluation of the preoperative chemotherapy of bone sarcomas using plain radiography.

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Authors: A. Bludov, Y. Zamogilnaya, N. Kochergina, A. Nered; Moscow/ RU
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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 Tumor Necrosis Grading System based upon 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.

Plain radiography is the first imaging method which was used to assess the effectiveness of preoperative chemotherapy in bone sarcomas. Review of the literature shows a wide range of sensitivity (from 50 to 91%) and specificity (from 33 to 87%) of plain radiography.

**The purposes** of our study were:

1. To clarify the radiographic signs in assessment of the preoperative chemotherapy of bone sarcomas.
2. To develop diagnostic and differential criteria (decisive rule) of poor and good response to the neoadjuvant treatment.
3. To compare the informativeness of developed criteria in the middle and after preoperative chemotherapy.
Methods and Materials

Case selection

To develop and verify the decisive rule for plain radiography we analyzed radiograms of 109 patients with bone sarcomas confirmed by biopsies. 91 patients (83.5%) with osteosarcoma, 9 patients (8.3%) with Ewing sarcoma/PNET, 4 patients (3.7%) with malignant fibrous histiocytoma, 1 patient with mesenchymal chondrosarcoma (0.9%) and 1 patient with round-cell liposarcoma (0.9%). All the patients were treated with systemic neoadjuvant chemotherapy (without preoperative radiotherapy) and primary surgical excision at our institution with post-treatment histological analysis of response.

Chemotherapy and Surgical Technique

Depending on the histological type of the tumor all patients received from four to six cycles of neoadjuvant chemotherapy. 108 patients (99%) underwent limb-sparing surgery with wide resection of the tumor. Only 1 patient was treated with amputation.

Pathology

Gross

The specimens were dissected in the conventional manner. Following measurement, the tumors were serially transected. We fully analyzed one section of the tumor's greatest dimension which was divided into separate segments. In each segment estimation of percent necrosis and residual tumor was recorded. Final histologic response was determined as the sum of the results in all of the segments. Additionally multiple sections were taken from different parts of the tumor as well as from the margins.

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) when # 90% of necrosis was present and a poor response (Grade I-II) for # 90% of necrosis Fig. 1 on page 5.

Imaging studies

The patients were examined on three diagnostic stages: before, in the middle and at the end of the course of the preoperative chemotherapy (before surgery). Plain radiography
was obtained in the middle and after preoperative chemotherapy at different time periods. 61 patients (56%) were examined both in the middle of chemotherapy and before surgery. 48 patients were examined only on two stages: before and in the middle of the chemotherapy - 16 patients, and before and at the end of the therapy - 32 patients.

Statistics, multifactor analysis and decisive rule

The statistical analysis of the radiographic symptoms was made by STATISTICA program (v. 7.0, Statsoft Inc., USA), the calculation of the weighted coefficient 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 weight coefficients, which determine the frequency of occurrence of these symptoms in a group of patients with good and poor response. Subsequently, on the basis of weight coefficient of each radiographic symptom the decisive rule was created for both groups of patients, with good and poor response.

For making the decisive rule in our study we used the data of 61 patients which were examined on every three diagnostic stages (before, in the middle and at the end of the preoperative chemotherapy). The decisive rule was checked on two groups. The first one ("middle-stage" group) consisted of the data of 77 studies of the patients examined in the middle of the treatment (16 patients who were examined before and in the middle of the therapy + 61 patients who were examined on three diagnostic stages). The second group ("end-stage" group) consisted of the data of 93 studies of the patients examined at the end of the treatment (32 patients who were examined before and after the therapy + 61 patients who were examined on three diagnostic stages).
Fig. 1: Huvos Tumor Necrosis Grading System (Smith J., Heelan R.T., Huvos A.G. et al. Radiographic changes in primary osteogenic sarcoma following intensive chemotherapy: radiological pathological correlation in 63 patients. Radiology. 1982, No. 143, p. 355-360)

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Results

Developed decisive rule with weight coefficients of radiographic symptoms of the bone tumors during neoadjuvant chemotherapy is illustrated in Table 1.

Table 1. Decisive rule with weight coefficients of radiographic symptoms of the tumor during neoadjuvant chemotherapy.

<table>
<thead>
<tr>
<th>#</th>
<th>Radiographic signs</th>
<th>Weight coefficient</th>
<th>Radiographic signs</th>
<th>Weight coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No increasing of plastic component</td>
<td>-24</td>
<td>Increasing of plastic component</td>
<td>+27</td>
</tr>
<tr>
<td>2</td>
<td>No increasing of lytic component</td>
<td>-7</td>
<td>Increasing of lytic component</td>
<td>+59</td>
</tr>
<tr>
<td>3</td>
<td>Presence/extension of peripheral sclerotic rim in the bone</td>
<td>-98</td>
<td>Absence of peripheral sclerotic rim in the bone</td>
<td>+13</td>
</tr>
<tr>
<td>4</td>
<td>Enlarged surrounding soft tissue mass remains without any dynamic</td>
<td>-21</td>
<td>Increasing of the enlarged surrounding soft tissue mass</td>
<td>+230</td>
</tr>
<tr>
<td>5</td>
<td>Decreasing of enlarged surrounding soft tissue mass</td>
<td>-41</td>
<td>Absence of foci with the structure of trabecular bone in the tumor</td>
<td>+3</td>
</tr>
<tr>
<td>6</td>
<td>Appearance/enlargement of foci with the structure of trabecular bone in the tumor</td>
<td>-40</td>
<td>Absence of foci with cellular-trabecular structure in the tumor</td>
<td>+7</td>
</tr>
</tbody>
</table>
or most of the tumor transforms into trabecular bone

<table>
<thead>
<tr>
<th>8</th>
<th>Appearance/enlargement of foci with cellular-trabecular structure in the tumor</th>
<th>-69</th>
<th>No reparation of the cortex</th>
<th>+12</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>The whole tumor appears cellular-trabecular</td>
<td>-179</td>
<td>Further destruction of the cortex</td>
<td>+208</td>
</tr>
<tr>
<td>10</td>
<td>No change of the cortex</td>
<td>-2</td>
<td>No assimilation of periosteal reaction</td>
<td>+46</td>
</tr>
<tr>
<td>11</td>
<td>Partly reparation of the cortex</td>
<td>-101</td>
<td>Non-assimilated periosteal reaction remains without any dynamic</td>
<td>+69</td>
</tr>
<tr>
<td>12</td>
<td>Complete assimilation of periosteal reaction</td>
<td>-78</td>
<td>Partial assimilation of periosteal reaction</td>
<td>+17</td>
</tr>
<tr>
<td>13</td>
<td>Presence of complete periosteal &quot;shell&quot; enclosing the periphery of the extra-osseous component</td>
<td>-69</td>
<td>Appearance or extension of the new non-assimilated periosteal reaction</td>
<td>+138</td>
</tr>
<tr>
<td>14</td>
<td>Increasing of the extension of the periosteal</td>
<td>-56</td>
<td>Presence of the partial periosteal</td>
<td>+110</td>
</tr>
</tbody>
</table>
By marking the radiographic signs in the table and summarizing the coefficients we can make the decision of the result of the chemotherapy. The sum of weight coefficients of radiographic symptoms with "+" value is categorized as having a poor response, on the other hand the sum with "-" value is showing a good response to chemotherapy. Threshold 0.

As we can see from Table 1 on the radiograms of good responders the following signs can be seen:

- presence/extension of peripheral sclerotic rim in the bone
- decreasing of enlarged surrounding soft tissue mass
- appearance/enlargement of foci with the structure of trabecular bone in the tumor or the most of the tumor transforms into trabecular bone
- appearance/enlargement of foci with cellular-trabecular structure in the tumor or the whole tumor appears cellular-trabecular
- partial reparation of the cortex
- complete assimilation of periosteal reaction
- increasing of the extension or presence of complete periosteal "shell" enclosing the extra-osseous component
- partial/complete consolidation of the pathologic fracture

An example of good response is shown on Fig. 2 on page 11.

Radiological signs associated with poor response according to decisive rule are:

- increasing of lytic component
- increasing of the enlarged surrounding soft tissue mass
- further destruction of the cortex
• no assimilation of periosteal reaction or non-assimilated periosteal reaction remains without any dynamic
• appearance or extension of the new non-assimilated periosteal reaction
• presence of the partial periosteal "shell" on the periphery of the extra-osseous component

An example of poor response is shown on Fig. 3 on page 11.

Basing on the data in Table 1 the sensitivity (probability of good response) and specificity (probability of poor response) of plain radiography in the middle and at the end of preoperative treatment were calculated and summarized in Table 2. The sensitivity of the plain radiography using the decisive rule on the "middle" diagnostic stage was 81.6%, the specificity was 64.1%. Positive predictive value (PPV) was 78.1 % and negative predictive value (NPV) - 68.9 %. At the end of the preoperative treatment the values of the sensitivity and specificity increased up to 85.4% and 68.9% correspondingly with PPV of 81.6 % and NPV of 74.6%.

Table 2. Significance of plain radiography using decisive rule on the both diagnostic stages

<table>
<thead>
<tr>
<th>Radiologic response</th>
<th>Pathologic response</th>
<th>Number of examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor (Grade I-II)</td>
<td>Good (Grade III-IV)</td>
</tr>
<tr>
<td>&quot;MIDDLE&quot; DIAGNOSTIC STAGE (IN THE MIDDLE OF THE NEOADJUVANT CHEMOTHERAPY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor response</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Good response</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Number of examinations</td>
<td>45</td>
<td>32</td>
</tr>
</tbody>
</table>

SENsitIVITY 81,6%
Confidence interval (69,3% - 93,9%)
SPECIFICITY 64,1%
Confidence interval (49,05% - 79,15%)
Positive Predictive Value (PPV) 78,1%
Confidence interval (63,78% - 92,42%)
Negative Predictive Value (NPV) 68,9%
Confidence interval (55,4% - 82,4%)
### FINAL DIAGNOSTIC STAGE (AT THE END OF THE COURSE OF TREATMENT)

<table>
<thead>
<tr>
<th>Poor response</th>
<th>41</th>
<th>7</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good response</td>
<td>14</td>
<td>31</td>
<td>45</td>
</tr>
</tbody>
</table>

Number of examinations 55 38 93

#### SENSITIVITY

<table>
<thead>
<tr>
<th></th>
<th>85,4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence interval</td>
<td>(75,4% - 95,4%)</td>
</tr>
</tbody>
</table>

#### SPECIFICITY

<table>
<thead>
<tr>
<th></th>
<th>68,9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence interval</td>
<td>(55,4% - 82,4%)</td>
</tr>
</tbody>
</table>

#### Positive Predictive Value (PPV)

<table>
<thead>
<tr>
<th></th>
<th>81,6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence interval</td>
<td>(68,9% - 84,3%)</td>
</tr>
</tbody>
</table>

#### Negative Predictive Value (NPV)

<table>
<thead>
<tr>
<th></th>
<th>74,6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence interval</td>
<td>(63,1% - 86,1%)</td>
</tr>
</tbody>
</table>
Fig. 2: 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. 3:** Radiograms of osteosarcoma of the fibula before and at the end of the chemotherapy. At the end of chemotherapy the size of the soft tissue mass is the same, the bone and the cortex destruction still persist. The character of periosteal reaction stays the same. Poor response according to decisive rule (TWC: +122), Grade I pathologic response.
Conclusion

Developed diagnostic criteria showed high informativeness of the following radiographic signs in the predilection of good response to chemotherapy (# 90% of necrosis): appearance or enlargement of foci with the cellular-trabecular structure in the tumor, reparation of the cortex, consolidation of the pathologic fracture, and appearance of foci with the structure of trabecular bone in the tumor. For patients with poor response (# 90% of necrosis) typical symptoms are: increasing of enlarged surrounding soft tissue mass, appearance or extension of non-assimilated periosteal reaction or when non-assimilated periosteal reaction remains without any dynamic, further destruction of the cortex and presence of the partial periosteal "shell" on the periphery of the extra-osseous component.

The sensitivity of the plain radiography using the decisive rule on the "middle" stage was 81.6%, the specificity was 64.1%. Positive predictive value (PPV) was 78.1 % and negative predictive value (NPV) - 68.9 %.

At the end of the preoperative treatment the values of the sensitivity and specificity increased up to 85.4% and 68.9% correspondingly with PPV of 81.6 % and NPV 74.6%.

The use of the decisive rule will improve the evaluation of the preoperative chemotherapy of bone sarcomas using plain radiography especially for young radiologists. Moreover these criteria can be used in the educational process.
References

Personal Information

Alexander Bludov,
Department of Diagnostic and Interventional Radiology, Musculoskeletal Division, N.N. Blokhin Cancer Research Center RAMS, Moscow, Russia.
bludov1982@gmail.com

Yanna Zamogilnaya,
Resident at Department of Diagnostic and Interventional Radiology, Musculoskeletal Division, N.N. Blokhin Cancer Research Center RAMS, Moscow, Russia.
yzamogilnaya@gmail.com

Natalia Kochergina, Prof., Dr.Dr.h.c., M.D., Ph.D.,
Department of Diagnostic and Interventional Radiology, Musculoskeletal Division, N.N. Blokhin Cancer Research Center RAMS, Moscow, Russia.

Anastasia Nered,
Resident at Department of Diagnostic and Interventional Radiology, Musculoskeletal Division, N.N. Blokhin Cancer Research Center RAMS, Moscow, Russia.