Principles of orthopedic treatment for malignant bone tumors in children

Zasady postępowania ortopedycznego w złośliwych nowotworach kości w wieku rozwojowym

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Abstract

Primary bone sarcomas are not frequent entities, but constitute important issue especially in pediatric population. Advances in chemotherapy and diagnostic modalities allowed limb saving resections of malignant bone tumors became leading surgical option. To be successful the treatment of primary bone tumors should be conducted in dedicated centers by experienced team of specialists. Nevertheless, the rules of such treatment should be known widely to improve diagnosis, medical care over oncologic patient and communication between specialists. In this review paper the authors present current rules of surgical approach to bony malignancies in children and adolescents.

Key words: malignant bone tumor, pediatric, surgery, biopsy.

Streszczenie

Złośliwe nowotwory układu ruchu są rzadkimi, lecz istotnymi klinicznie chorobami, szczególnie w populacji pediatrycznej. Postępy w skuteczności leczenia chemioterapeutycznego oraz poprawa możliwości diagnostycznych spowodowały zastąpienie amputacji operacjami oszczędzającymi kończyny w chirurgicznym leczeniu guzów kości. Choć leczenie tych chorób powinno być prowadzone w specjalistycznych centrach, wiedza o zasadach postępowania w złośliwych nowotworach kości powinna być szeroko znana, dla poprawy procesu diagnostycznego, opieki nad pacjentem onkologicznym i ułatwienia komunikacji między medycznymi profesjonalistami. W niniejszym przeglądzie autorzy przybliżają zasady chirurgicznego postępowania w złośliwych nowotworach układu ruchu u dzieci i młodzieży.

Słowa kluczowe: złośliwy nowotwór, kości, leczenie chirurgiczne, biopsja.

Introduction

Primary malignant bone tumors – osteosarcoma, Ewing sarcoma and chondrosarcoma, are rare entities, accounting for about 1% of all malignancies but remain an important issue especially in the high – functioning pediatric population with long life expectancy [1]. Among childhood cancers incidence rates, osteosarcoma and Ewing sarcoma are eighth (2,4%) and ninth (1.4%). Other frequent pediatric malignancies are: leukemia (30%), nervous system cancers (22.3%), neuroblastoma (7.3%), nephroblastoma (5.6%), non-Hodgkin lymphoma (4.5%), rhabdomyosarcoma (3.1%), and retinoblastoma (2.8%)[2]. In a very young group of patients (aged 0-5 y) neuroblastoma metastases to long bones may also be found.

Surgery for bone sarcomas is challenging, especially in the pediatric population, due to the growth potential of the bones and frequently their small size. The need for reconstruction of post-resection gaps in children, and management of growth cessation of the limb when the physeal plate needs to be sacrificed in order to maintain oncologic margins, makes orthopedic treatment complex and difficult.

In the 80’s of the previous century amputation or disarticulation was the main surgical option, and overall treatment results were poor with a 5-year survival rate of 10-20%. In the last 4 decades there was a significant improvement in the treatment results, mostly due to advances in contemporary diagnostic modalities and chemotherapy for primary bone sarcomas. Currently, the treatment includes neo-adjuvant (preoperative) chemotherapy, definite surgical tumor excision and adjuvant (postoperative) chemotherapy. Radiotherapy is sometimes needed in cases of small cell sarcomas. Nowadays the 5-year survival rate has increased to 70% [1,3,4].

These improvements justify the replacement of amputations by limb-saving resections as the preferred surgical option in orthopedic oncology management. Limb-salvage tumor resections allow for preservation of the functional limb after safe oncologic resection but require a reconstruction of the post-resection bone gap with biologic material, endoprosthetics or dedicated 3D printed implants [3,4].
For modern orthopedic oncology treatment to be successful, it is necessary to treat children with malignant bone tumors in dedicated medical centers, which offer a full spectrum of diagnostic and therapeutic modalities, by a team of professionals experienced in pediatric oncology and orthopedics and to follow certain principles to establish the diagnosis and for further medical management.

In this publication we would like to review the current guidelines and modern trends in the surgical approach to bone malignancies in children and adolescents.

**Biopsy**

Biopsy is crucial for establishing a proper diagnosis and therefore for proper treatment. This procedure provides pathologic tissue for histologic analysis, allowing for tumor recognition, staging and prognosis. It should, however, be the last step in the diagnostic process, preceded by careful anamnesis, clinical exam and broad imaging of the investigated lesion and detection of possible metastases using classic radiography, CT, MRI, bone scan (other options include PET, PET/CT) [1,4,5].

The biopsy site should be planned by a team of specialists including a pathologist, radiologist and orthopedic surgeon with experience in musculoskeletal malignancies and chosen based on future surgical approach for a radical procedure. Therefore, it should preferably be performed by a surgeon who will do the final tumor resection. Biopsy, that is done improperly (i.e. via transverse incision, close to important neurovascular structures or with violation of uninvolved anatomical compartment) poses a significant risk not only for establishing a proper diagnosis but also for successful limb salvage surgery and may even make it impossible (Figs. 1,2) [5].

Biopsy types include oligo- and open procedures:

1. Fine-needle aspiration biopsy is performed with needles less than 1,2 mm diameter. It can be used to gain material for cytologic studies, but does not permit analysis of tumor architecture, therefore it has a limited role in bone tumor diagnosis.

2. Core-needle biopsy is performed with needles with a diameter greater than 1,2 mm which allows for tissue sampling for histological studies, immunohistochemical or molecular testing. It may be done manually or...
with dedicated power tools. Core-needle biopsy may be done freehand or under CT or US guidance, which allows for precise sampling especially in cases of deep tumor localizations. A disadvantage of core-needle biopsy is the risk that the obtained material will not be representative for proper microscopic assessment.

3. Open (incisional) biopsies are performed through as small as possible longitudinal incisions located in line with future surgical approach for tumor resection and are the preferred method of tissue sampling in cases with high suspicion of malignancy. The biopsy scar and canal (this principle is the same for needle biopsies) needs to be removed together with the tumor itself during definite surgery, due to contamination of the biopsy tract with neoplasm cells. The specimen should be taken from active part of the tumor – most frequently from its periphery, and not the center which usually is necrotic. Tumor imaging (MRI, bone scan) helps to determine which part of the tumor is metabolically active and suitable for biopsy. If a tumor has spread outside the bone, a representative specimen can be taken from the invaded soft tissues only, without the need to violate the bone cortex. In intra-compartmental bone lesions it is necessary to open the bone preferably using a round window rather than rectangular or a longitudinal window rather than transverse, to decrease the risk of fracture around the biopsy site. Bacteriology swab should also be done routinely to rule out infection [5].

Electrocautery should not be used before taking specimen to avoid thermal injuries of the biopsy material, but it is crucial to perform meticulous hemostasis before wound closure as wound hematoma may spread neoplasm cells into surrounding soft tissues. The wound should be closed with narrow sutures, not enlarging the scar. If drainage is needed, it should be in line with biopsy incision, not aside. Repeating biopsy through a different approach is contraindicated. In dedicated centers immediate intraoperative frozen section may be done freehand or under CT or US guidance, which allows for precise sampling especially in cases of deep tumor localizations. A disadvantage of core-needle biopsy is the risk that the obtained material will not be representative for proper microscopic assessment.

Surgical resections of malignant bone tumor

The aim of surgery is to remove the tumor completely with sufficient safe margins of surrounding tissues to minimize the risk of local recurrence. Limb salvage surgery is possible when the tumor can be removed with clear margins leaving the residual limb functional [6,7]. Before planning surgery for malignant bone tumor, the following questions need to be answered:

1. What is the staging of the tumor?
2. What is the age and prognosis for the patient?

Staging

The classic concept of onco-orthopedic staging is based on compartmentalization of the tissues surrounding the tumor and was proposed by Enneking. The classification is based on local extent of the tumor – whether it is confined to anatomic compartment – which is an anatomic space, being an obstacle for tumor invasion surrounded by a natural anatomic barrier i.e. cortex, physis, articular cartilage, joint capsule, intercostal membranes and fascias. Anatomic barriers are classified as strong or weak barriers, depending on how they resist neoplasm invasion (Tab. 2)[8].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Site</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>low</td>
<td>intra-compartment</td>
<td>no</td>
</tr>
<tr>
<td>IB</td>
<td>high</td>
<td>intra-compartment</td>
<td>no</td>
</tr>
<tr>
<td>II A</td>
<td>low</td>
<td>extra-compartment</td>
<td>no</td>
</tr>
<tr>
<td>II B</td>
<td>high</td>
<td>extra-compartment</td>
<td>no</td>
</tr>
<tr>
<td>III A</td>
<td>low</td>
<td>intra &amp; extra-compartment</td>
<td>yes</td>
</tr>
<tr>
<td>III B</td>
<td>high</td>
<td>intra &amp; extra-compartment</td>
<td>yes</td>
</tr>
</tbody>
</table>

Enneking's staging is based on three factors including local tumor invasion within one or more compartments, its malignancy (low vs high grade) and presence of metastases (Tab. 3).

Depending on the compartment concept oncological resections can be classically divided as follows (Fig. 3):

1. Radical resection: resection of the tumor with entire compartment(s) invaded. This type of resection resulted frequently in amputations or disarticulations.
2. Wide resection: resection of the tumor with surrounding healthy tissue, clear from tumor invasion.
In the last decades, advances in chemotherapy and precise imaging reduced the needs for radical resections and made wide resections a golden standard. Limb-sparing surgery became a leading option in malignant bone tumor treatment. Nevertheless, one should be aware that amputations, or rotationplasty are still needed in selected situations or tumor localizations [1,3,4,7] (Fig. 4).

In this case wide resection would be the treatment of choice. Marginal and intralesional resection are forbidden in malignant tumors.

Limb salvage resections can be further divided depending on the tumor localization in relation to the neighboring joint(s) into intra-articular and extra-articular (Fig. 5).

1. Intra-articular resections: performed when tumor does not invade the joint cavity or joint capsule.
2. Extra-articular resection: resection with the joint enblock is needed when the joint is invaded by the tumor.
3. Joint-saving extra-articular resection: possible if neighbouring epiphysis and joint are free of tumor invasion, with metaphyseal or shaft tumor localization, especially in children with open physes.

Oncologic margin

Oncologic or surgical margin is defined as a coat of tissues surrounding the tumor and free from tumor cells. In case of bone tumors, the oncologic margin includes bones and soft tissues. The aim of surgery is to resect the tumor en-block with adequate margins – the surgeon can’t see the neoplasm during surgery. Inadequate margins carry a risk of a local recurrence. As the outcome of treatment depends on this, the evaluation of surgical/oncologic margin is a part of the postoperative specimen investigation and can be classified into three types (Tab. 4). The optimal surgical margin should be maximally oncologically safe (R0) and at the same time should cause as little damage to the limb and its function as possible [9-12].

Adequate margins are important in local tumor control, however what is an adequate margin is still debatable and usually individually tailored. It is agreed that MRI, especially in T1 sequences obtained after neo-adjuvant chemotherapy is currently a golden standard tool allowing to assess and plan adequate margin with 1-2 cm accuracy in both osteosarcoma and Ewing sarcoma [13-16]. Traditionally soft tissue margins were believed to measure few centimeters to provide oncological safety, but decreasing soft tissue margins from i.e. 50 mm to 15 mm did not worsen the overall results [13].

Response to chemotherapy

Response to chemotherapy was found to be even more crucial factor influencing the risk of local recurrence and prognosis of treatment result [13,14]. This is defined as a reaction of neoplasm tissue to the preoperative oncologic treatments. Good response to neo-adjuvant chemotherapy should result
in tumor necrosis, decrease in volume, demarcation of tumor pseudo-capsule. In cases with good response to chemotherapy the oncologic margin can be minimized even to ca. 2 mm: Jays L. et al. proposed a classification of prognosis based on two factors: surgical margin of 2 mm and response to chemotherapy (Tab. 5). They concluded that risk of local recurrence depends mostly on response to chemotherapy and that type 2b (poor reaction to chemotherapy and inadequate margin) has a 20 times greater risk of local recurrence when compared to type 1a [15].

Table 5. The Birmingham classification.

<table>
<thead>
<tr>
<th>Type</th>
<th>Response to chemotherapy</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>≥ 90%</td>
<td>&gt; 2 mm</td>
</tr>
<tr>
<td>1b</td>
<td>≥ 90%</td>
<td>≤ 2 mm</td>
</tr>
<tr>
<td>2a</td>
<td>&lt; 90%</td>
<td>&gt; 2 mm</td>
</tr>
<tr>
<td>2b</td>
<td>&lt; 90%</td>
<td>≤ 2 mm</td>
</tr>
</tbody>
</table>

The weak point is that it is not possible to perform a quantitative assessment of the response to the neo-adjuvant chemotherapy. Qualitative assessment is usually done via evaluation of the clinical improvements of the patient’s status – decrease in tumor mass, pain and levels of tumor markers in lab-tests; or radiographically, using MRI and classic x-rays: decrease in tumor volume with increased ossification, presence of pseudocapsule, and reduction of the reactive zone. The definite information on tumor response to chemotherapy is possible only after tumor resection and pathologic examination of the specimen (mapping) revealing percentage of necrosis and active neoplasm tissue is done. Good reaction is stated when necrosis constitutes over 90% of resected tumor in osteosarcoma cases and 100% for Ewing sarcoma [17]. Recently, new imaging tools were investigated to make the MRI based accuracy of tumor necrosis assessment more reliable, and to allow more precise planning of the surgical margins [18].

**Surgical planning of the tumor resection**

How to perform resection of the tumor is crucial for successful surgery and include assessment of several points:
1. What is the relation of the tumor to the surrounding crucial structures – neurovascular bundles, soft tissues, viscera?
2. Which structures need to be sacrificed in order to maintain adequate margin?
3. Is vascular reconstruction needed?
4. What are the levels of osteotomies to maintain safe oncological margin within the bone?
5. Is it possible to save the limb and perform limb – salvage resection?
6. Is it possible to save the neighboring joint?
7. What is the optimal approach and skin incision including the biopsy tract?
8. What is the optimal post-resection bone gap reconstruction?

MRI performed shortly before surgery, after neo-adjuvant chemotherapy, remains a crucial tool for surgical planning of the tumor resection. It is important to perform imaging not only of the whole region (bone) with the tumor but also the entire limb to detect any possible local metastases or skip lesions. In cases of small cell sarcomas, such as Ewing or PNET initial invasion also needs to be assessed in surgical planning (Fig. 6, 7)[16].

Fig. 6. Pre-operative planning of resection of the distal femur osteosarcoma. The tumor invaded the epiphysis, physeal plate is already closed. Intra-articular resection is recommended. Incision planned with biopsy scar removal.

Fig. 7. Pre-operative planning for Ewing sarcoma of proximal tibia and shaft. Knee saving extra-articular resection was possible.

Surgical resection of bone tumor always needs to include the whole biopsy scar and tract preferably as one unit with the tumor (Fig. 6). The resected tumor must be surrounded by a safe margin of at least 2 mm in tumors with good reaction to neo-adjuvant chemotherapy, depending also on the anatomical region. In most cases however the preferable soft tissue safe margin should be at least 5-10 mm of tissues covering the tumor. This means, that wide resection evolves more into marginal resection in suitable cases. When it comes to bony margins, there are again no
strict recommendations, however in long bones (shaft) it is considered ca. 10 mm from reactive zone of the tumor and/or 30 mm from tumor itself, but this needs consideration of the overall size of the bone and age of the patient, especially in young children [19]. In metaphyseal regions, when the tumor invades the joint, epiphysis or joint capsule, the joint need to be resected with the tumor using extra-articular resection with the neighboring joint en block.

If the tumor does not invade the epiphysis (especially in children with active physisal plates), the neighboring joint can be saved via i.e. trans-epiphysal resection leaving minimal epiphysis with articular surface, suitable for adequate reconstruction (i.e. 10 mm in case of the knee) (Fig. 7) [20].

Resections around the pelvis and shoulder girdle are more complicated both in planning, surgery, and reconstruction. When good reaction to neo-adjuvant therapy is noted, limb salvage procedures in the form of internal hemipelvectomies are possible (Fig. 8). The basic types of pelvic resections are presented in table (Tab. 6). It should be noted, that due to difficult anatomy, it is frequently challenging to plan and obtain the desired oncologic margin. Therefore, the overall survival prognosis is poorer when compared to tumors in peripheral localizations [21,22].

In the shoulder girdle, depending on primary tumor localization (in skeletally immature patients most frequently in proximal humerus) resection may include extraarticular resections with scapular glenoid, intraarticular resection or scapulectomy. Different possibilities of oncologic limb saving resections around shoulder girdle were classified by Malawer into six types (Tab. 7) (Fig. 9)[23].

### Table 6. The Enneking–Dunham classification of tumor resections around the pelvis. Depending on tumor localization and invasion, combinations of above types are adopted, and may include sacroiliac joint or hip joint.

<table>
<thead>
<tr>
<th>Type</th>
<th>Region of pelvic resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>iliac wing</td>
</tr>
<tr>
<td>II</td>
<td>periacetabulum</td>
</tr>
<tr>
<td>III</td>
<td>pubic rami</td>
</tr>
<tr>
<td>IV</td>
<td>sacrum</td>
</tr>
</tbody>
</table>

### Table 7. The Malawer classification system for surgical resections around shoulder girdle.

<table>
<thead>
<tr>
<th>Type</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>intra-articular, Proximal humerus</td>
</tr>
<tr>
<td>II</td>
<td>partial scapulectomy, shoulder preserved</td>
</tr>
<tr>
<td>III</td>
<td>intra-articular scapulectomy</td>
</tr>
<tr>
<td>IV</td>
<td>extra-articular scapulectomy with proximal humerus, shoulder joint sacrificed</td>
</tr>
<tr>
<td>V</td>
<td>extra-articular proximal humerus resection with glenoid, shoulder joint sacrificed</td>
</tr>
<tr>
<td>VI</td>
<td>extra-articular proximal humerus resection with total scapulectomy</td>
</tr>
</tbody>
</table>

Fig. 8. Enneking-Dunham basic hemipelvectomies.

Fig. 9. The Malawer classification of resections around shoulder girdle.
Reconstructions

Detailed presentation of options in reconstruction of post-resection gaps is beyond the scope of this manuscript. All bone gaps need to be filled to provide supporting function of the skeleton and a functional limb. In general, reconstruction options may be divided into mechanical or biological, each having their advantages and disadvantages and possible complications [1,3,4,6,7].

Mechanical options employ a broad array of endoprostheses: modular, custom made or growing, which are used in patients with significant growth remaining. In the pelvis or shoulder girdle, less frequently in limbs, custom made 3D implants may be used for reconstructions. Patient specific instruments (PSI) used as guides for osteotomies not only improve surgical margins but also help to fit reconstruction material to the host bone [21].

Biologic reconstruction includes several techniques i.e. fibular autografts (pedicled, vascularized or free), massive allografts or combinations of both. Osteoarticular allografts are less frequently used due to a high rate of joint complications. Induced membrane two-step technique of allografts or combinations of both. Osteoarticular allografts are less frequently used due to a high rate of joint complications. Induced membrane two-step technique makes an interesting option in shaft reconstructions [3].

In children, residual, post-resection limb length discrepancy is managed via several options including expandable prosthesis reconstruction, bone lengthening, or contralateral leg growth modulations or shortening.

Conclusion

Surgery for malignant bone tumors, especially in a growing skeleton is challenging on each step, from biopsy, via planning, tumor resection and adequate reconstruction. Therefore, it should be a domain reserved for experienced orthopedic surgeons in dedicated centers. Nevertheless, the rules of diagnosis and treatment should be known widely, to improve the diagnosis process, care over the oncological patient and communications between specialists.

References