ONCOLOGICAL PRINCIPLES IN SPINAL TUMOR SURGERY

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Surgical intervention remains the cornerstone of the treatment of patients with spinal tumors. The presented literature review includes also the authors' personal experience in the treatment of tumors. Pain relief, local control of a neoplasm growth and preservation of body functions are the main goals of this pathology treatment.

Treatment of spinal tumors is based on the biology, location and extent of the neoplasm. If surgical treatment is indicated, en-bloc resection is the preferred method. This operation is based on the complete removal of the tumor in a single block entirely covered by a shell of healthy tissue. This surgical procedure can be challenging due to the proximity of the neural structures. Moreover, achieving clean resection margin around the tumor often requires the sacrifice of adjacent anatomic structures. A more comprehensive approach requires a combination of surgery, systemic therapy and radiotherapy to improve outcomes in patients with advanced spinal tumors.

The fulfillment of oncological principles is fundamental to achieving best treatment outcomes for spinal tumors.

Key Words: oncology, spine, tumor, en-bloc resection, margin of resection.

Please cite this paper as: *Zaborovskii NS, Ptashnikov DA, Mikhaylov DA, Smekalenkov OA, Masevnin SV. Oncological principles in spinal tumor surgery. Hir. Pozvonoc. 2021;18(2):64–72. In Russian.*

DOI: http://dx.doi.org/10.14531/ss2021.2.64-72.

Usually, there are primary and secondary tumors of the spine. Primary tumors are caused by bone, adipose, fibrous, and nerve tissues. Also, they can be formed from nerve sheaths, or adjacent paravertebral soft tissues and lymphatic vessels. Secondary (metastatic) tumors enter the spine hematogenically or lymphatically from distant cancerous foci [1]. Primary tumors are subdivided into benign and malignant. A benign tumor does not have metastatic propensity, while a malignant tumor can potentially metastasize. The updated WHO classification [2] highlights a group of intermediate tumors (with locally aggressive growth) which has the potential for malignancy (Fig. 1).

The classification of secondary spinal tumors into metastatic and conditionally-contact ones is prompted by the primary tumor localization. The first variant is caused by spinal metastasis as a result of dissemination of the primary tumor from another organ or vertebra. A special variant here is "skip" metastases inside the tumorous vertebra. The second variant is the tumor invasion into the spine, which is located primarily in the paravertebral organs and tissues.

In the population, primary spinal tumors are less common than metastatic ones [3]. At this point, the most common are patients with metastases of breast cancer (25.7 %), kidney cancer (10.6 %) and lung cancer (6.3 %). These individuals are subject to surgical treatment for spinal tumor lesions. Patients with primary malignant tumors are mainly suffering from multiple myeloma (5.5 %), plasmacytoma (1.5 %) and chordoma (1.4 %). A giant cell tumor prevails in patients with intermediate tumors with locally aggressive growth (2.8 %). Meanwhile, the ratio between primary malignant and secondary spinal tumors which are being surgically treated is 10.2 and 59.0 %, respectively [4].

Decision-making principles in the surgical treatment of spinal tumors

Today, spinal tumor surgery focuses on determining the prediction, indications, compliance with oncological principles and techniques. There are 3 steps to develop a treatment strategy (Fig. 2).

The first step measures are aimed at the diagnosis and staging of the tumor. The diagnosis is established upon the comparison of the clinical picture, the data of laboratory and instrumental diagnostic techniques and the results of pathohistological and molecular genetic study of the biopsy specimen. Clinical and pathological staging is based on the anatomical system of primary tumor registration, malignancy determination, the degree of regional spread and metastasis presence. The second step requires an *ex consilio* decision on the patient's treatment plan. The order of drug administration, radiation therapy, and surgeries is specified. The third step in cases of impossibility of starting or inefficiency of conservative treatment is a surgery.

Staging of spinal tumors

Staging of spinal tumors involves determination of local spread of the tumor in the affected vertebra, the general spread of the disease in the patient's body, as well as the definition of malignancy degree. These criteria are applicable to both primary and secondary tumors.

Traditionally, Enneking et al. [5] classification principles is used to evaluate the bone tumors . Even though the Enneking system does not consider the presence of a continuous epidural compartment for spinal column tumors, its concept appears to be extremely useful for staging tumor lesions of the spine [6]. The system stages are based on the features of the tumor margin, the lesion aggressive behavior, extraosseous growth, and the presence of metastases.

The stages of benign and malignant tumors are different within the Enneking classification. The system of benign tumor staging contains three categories: latent (S1), active (S2) and aggressive (S3). The classification is based on the radiographic features of the tumor margin. The borders with clear edges show a dormant course (latent stage), while the indistinct borders are the result of the tumor growth into the bone and a more aggressive lesion (active stage). The borders are even more indistinct at the aggressive stage. According to the WHO classification, most intermediate tumors are included in the S3 stage according to Enneking. The metastases are uncommon in osteoblastoma and giant cell tumors [7] and might be caused by malignancy or an incorrect initial assessment of histology.

The staging system of malignant tumors considers the degree of malignancy (G), local spread (T), as well as the presence or absence of metastases (M). The system consists of 3 stages: stages I and II are based on the degree of malignancy of the tumor. Due to the rapid tumor growth in stage II, the pseudocapsule of the reactive tissue is low-graded. It includes gaps, and tumor cells may be located outside of it ("skip" metastases). The above mentioned stages are divided into two subcategories (A, B) in terms of the local spread of the tumor (extraosseous growth). Stage III is any tumor with distant metastasis. The Enneking system was initially developed for primary tumors. Nevertheless, in our opinion, the most of secondary tumors may also be classified as stage III. Meanwhile, a solitary metastasis found after a long period without disease progression can be treated with limitations as stage I or II.

Treatment modalities

Systemic treatment. A systemic therapy is an integral part of the comprehensive treatment of malignant and metastatic tumors.

Hanahan and Weinberg [8] arranged the key features of tumor cells (therapeutic goals) and targeted agents. Previously, the arsenal of chemotherapists consisted mainly of chemotherapy. Today, molecular genetic analysis of tumor tissues has provided a boon to the rapid development of different types of systemic therapy.

Molecular genetic analysis has revolutionized the management of metastatic tumors, namely breast cancer, renal cell carcinoma, melanoma, and lung cancer [9, 10]. We are also witnessing the progress in the systemic therapy field of inoperable/recurrent chordomas and other primary spinal tumors [11, 12]. The understanding of the biology of bone tissue diseases has resulted in the bone modifying agents' development like bisphosphonates and denosumab. These drugs prevent bone destruction and are widely used in bony spread as an additional therapy. [13]. Bone modifying agents are also used in primary tumors. Denosumab, for example, efficiently controls the giant cell tumor growth [14–16].

Frequently, a systemic therapy is an independent treatment option. In combination with other modalities, it is used in neoadjuvant or adjuvant mode. In case of a good tumor response, neoadjuvant systemic therapy forms a dense pseudocapsule. This pseudocapsule acts as a distinct boundary of tumor growth, providing a clean resection margin during the surgery. Additionally, a systemic therapy

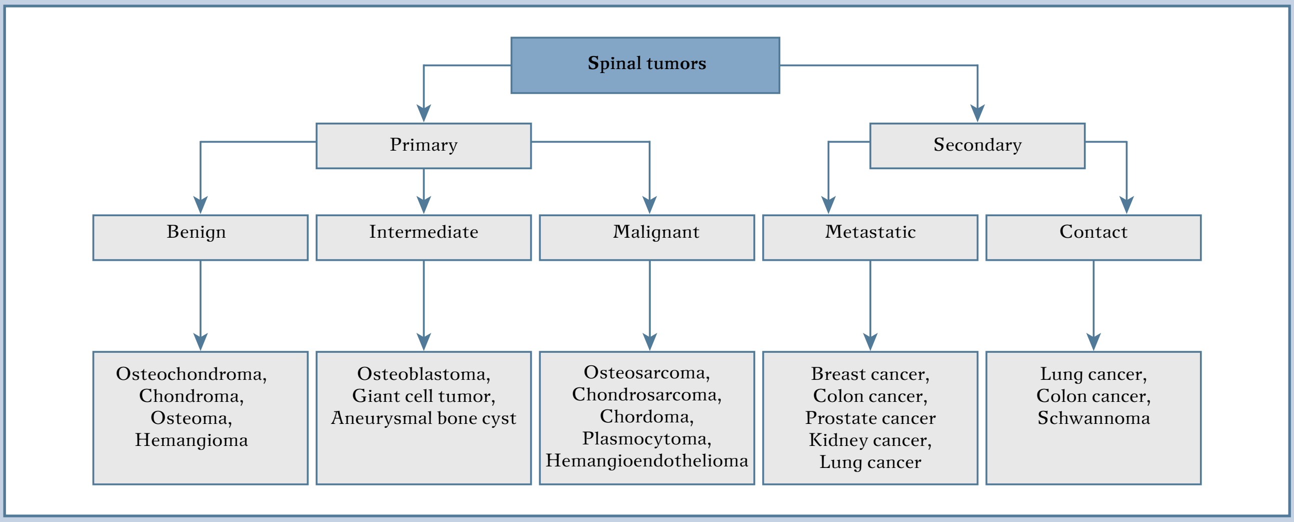

Fig. 1
General principles for the classification of spinal tumors

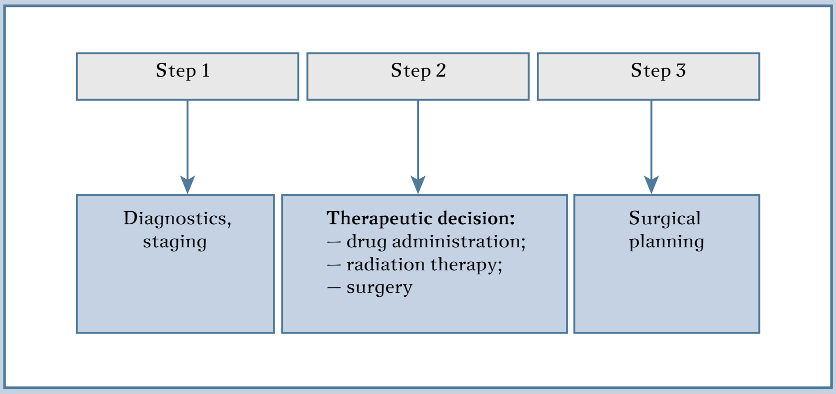

Fig. 2
The decision-making process in spinal tumor surgery

prevents the dissemination risk of the neoplastic process. An adjuvant systemic therapy is performed in the presence of a residual tumor or with metastasis.

Radiation therapy. The ionizing radiation damages the DNA of cells. The radiation can also induce apoptosis inside tumor cells, which is true for lymphoid and hematopoietic tissues. Cells are most sensitive to radiation in the M and G2 phases of the cell cycle and are least sensitive in the later part of the S-phase, probably due to the greater ability to DNA repair in the presence of paired chromatids [17].

Different types of radiation therapy are used in isolation or in combination with other treatment options. The purposes of local radiation therapy in the spinal tumor treatment are palliative care, prevention of local disease progression and subsequent pathological fracture, as well as control of the progression or elimination of nervous structure compression. Meanwhile, radiotherapy methods can be used after resection of tumors to achieve local control. It is possible if radiosensitive structures, such as the spinal cord, are separated from tumor burdens.

The histology of the tumor defines a different sensitivity to radiation therapy (Table) [18]. Specialized methods of radiation therapy help to overcome radioresistance. They are stereotactic radiation therapy and proton therapy.

The place of surgical treatment

The treatment and elimination of symptoms are the aims of spinal tumor surgery. While our efforts are aimed at cure, we often have to realize that occasionally we can achieve the best results for the patient only with palliative care [19]. The indications for spinal tumor surgery should be carefully considered, and the treatment must be performed using a multi-disciplinary approach. Traditional indications for surgery include the following:

– a primary malignant or locally aggressive tumor;
– the spine instability associated with a pathological fracture;
– a progressive neurological impairment;
– a radioresistant tumor with an active growth;
– the need for an open biopsy;
– pain syndrome that is resistant to other treatment options.

While determining the indications for surgery, other specific goals may be assigned, depending on the particular clinical situation.

The life expectancy prediction of such patients is important. However, a long-term prediction is limited [20, 21]. Any predictive system faces two extremes: insufficient accuracy or generalization. The forecast precision depends on the therapeutic possibilities developed for each nosology. At the same time, patients with spinal tumors are an enormous aggregation of unique cases where it is difficult to identify the common features. Thereby we come to the understanding that everything comes down to evaluating the patient's ability to safely undergo the surgery to the required extent.

The concept of compartments and anatomical barriers

The vertebra is a single limited anatomical area (compartment) surrounded by margins (anatomical barriers). The tumor growing inside the vertebral body has a margin with healthy tissues. Benign tumors (Enneking S1, S2) are enclosed by a capsule. Malignant and locally aggressive tumors (Enneking S3, I, II, III) are covered with a membrane of reactive tissue (pseudocapsule). If the tumor grows rapidly, the pseudocapsule is thinned and has gaps. The tumor cells may be located outside of it and are prone to overcoming anatomical barriers. The following tissues act as anatomical barriers to tumor growth outside the vertebra: an anterior longitudinal ligament, a posterior longitudinal ligament, a periosteum outside and adjacent to the spinal canal, a yellow ligament, an interspinous ligament, a supraspinal ligament, a cartilaginous end plate, and a fibrous ring. The periosteum and the posterior longitudinal ligament are the weakest anatomical barriers. The anterior longitudinal ligament, the cartilaginous end plate and the fibrous ring are much stronger barriers [22]. A study by Sasagawa et al. [23] revealed that extraossal tumor growth is most often observed vertically along the lateral sections of the posterior longitudinal ligament; less often - vertically along the lateral surfaces of the vertebral body. It is a rare occurrence that adjacent vertebrae are affected due to tumor invasion through intervertebral discs.

If a tumor grows beyond the vertebra, adjacent compartments are affected, which considerably complicates the tumor resection within healthy tissues. According to Enneking et al. [5], an extraosseous growth is found in stage S3 (aggressive) in benign tumors and corresponds to stages IB, IIB in malignant tumors. The adjacent compartments include many anatomical structures. It is vital to highlight the spinal canal space and its contents. An epidural compartment is surrounded by vertebrae. It extends from the foramen magnum to the sacrum and contains the spinal cord with membranes and nerves. Regarding oncological features, it is the presence of the epidural compartment and its functionally significant contents that is the greatest distinction of the spine as an anatomical area. The dura mater is a strong anatomical barrier to tumor growth. In practice, however, there are cases of tumor invasion through the membranes of the spinal cord. Murakami et al. [24] assume that this situation occurs in aggressive tumors, in which the pseudocapsule is absent or poorly expressed due to rapid growth.

Types of surgeries

Historically, the methods used in the spinal tumor treatment have followed the general orthopedic and neurosurgical principles. However, the long-term result depends most on compliance with oncological principles. The surgery in oncology can be radical and palliative, depending on the degree of spread of the tumor process, the volume and nature of the intervention (Fig. 3). A radical surgery involves the excision of the tumor along with the affected organ. Nevertheless, in relation to spinal tumors, radical surgeries are limited due to the presence of a continuous epidural space extended from the skull to the sacrum. Though there are reports of spinal cord transection for more radical treatment [25], functional losses after such surgeries are obviously catastrophic. Enneking et al. [5] identified the resection types of bone tumors for each stage of the tumor process. The current model allows for the dividing of operations into appropriate and non-compliant with Enneking principles. Later, these principles were adapted for spinal tumors by Boriani et al. [26].

During oncological surgeries, it is essential to comply with the principles of radicalism and ablastics. Considering the tumor borders and the resection margin, surgeries are divided into two large categories: extralesional and intralesional. An extralesional excision is performed by en-bloc resection. An intralesional excision involves resection of the tumor in parts. It is generally recognized that the margin of the tumor resection is a strong predictive risk factor for local recurrence. An intralesional resection is connected with a high frequency of local recurrence for the majority of primary bone tumors, including chordoma [27], chondrosarcoma [28], osteosarcoma [29] and Ewing's sarcoma [30]. A recurrence in the surgery area enhances the complexity of the repeated operation by an order of magnitude [31].

En-bloc-resection (French: en bloc – a single whole, in a block, all together). This technique means the resection of the tumor without exposing its surface, by a common block with the covering healthy tissues. The resection margin extends beyond the tumor borders, which corresponds to the oncological principles of radicality. This also prevents the tumor cells from migrating and leaving them in the wound, which corresponds to the principles of ablastics.

At the surgery planning stage, en-bloc resection may be marginal and wide-margin resection. A wide-margin resection indicates that there is a dense anatomical barrier (for example, fascia, pleura, etc.) or a sufficient number of tissues that are not affected by the tumor (a wide margin) between the tumor border and healthy tissues. A marginal resection is performed when the planned margin passes along the tumor growth border. During surgery, there is a high risk of the damage to tumor membrane and wound contamination by tumor cells – accidental transgression (violation of the tumor margin), which can be found in 14.1 % of cases [32]. Meanwhile, as noted above, in highly malignant tumors, pathological cells can also be located outside the tumor borders. Finally, marginal resection is associated with a higher risk of local recurrence compared to wide-margin resection [33]. However, a marginal resection is often used in a spinal tumor surgery. This is due to the frequent presence of an epidural soft-tissue component [4].

The peculiarity of en-bloc resection of a spinal tumor is a need to unlink the bone elements surrounding the spinal canal during the surgery. Based on the tumor location, a safe window is planned to access the spinal canal contents without transgression. Boriani [34] distinguished 7 types of en-bloc resection of spinal tumors, based on the WBB anatomical classification. A special characteristic of this approach is a clear differentiation of the surgery into stages depending on the tumor location in the vertebra. Several step-by-step approaches can be used during the procedure.

An en-bloc resection of a tumor does not always involve the complete excision of a vertebra. An example is a tumor located in the vertebral arch. Additionally, a type of en-bloc resection is a sagittal osteotomy through the vertebral body when the tumor is located in the left or right part of the vertebra. If the resection margin is adequate, the left part of the vertebral body can fulfill an osteoinductive function during the bone fusion formation.

Nevertheless, it is worth recognizing that, despite the oncological caution, the practice expansion of using modern diagnostic methods (PET, CT, MRI), spinal tumors are often diagnosed at the advanced stages. The tumor affects the vertebra totally, including the body, arch and processes. If it happens, there is no safe window consisting of healthy tissues. If the spinal canal contents are preserved, the tumor excision will result in an intentional transgression – en-bloc resection with tumor margin violation.

Intralesional resection implies a violation of the tumor margin integrity (intentional transgression). In most cases, the tumor is resected by piecemeal. En-bloc resection can also be intralesional, if the tumor margin were violated during the surgery. Intralesional resection without combined treatment for locally aggressive and malignant tumors is accompanied by a high risk of local reccurence.

Table

Tumors in the descending order of their sensitivity to radiation therapy

Myeloma
Lymphoma
Germ cell tumor
Ewing's sarcoma
Rhabdomyosarcoma
Small cell carcinoma of lung
Follicular thyroid cancer (uncured)
Prostate cancer
Breast cancer
Medullary thyroid cancer (uncured)
Myxoid liposarcoma
Synovial sarcoma
Leiomyosarcoma
Non-small-cell lung cancer (with EGFR mutation and sensitive to targeted therapy)
Renal cell carcinoma (against the background of antiangiogenic therapy)
Colon cancer
Non-small-cell lung cancer (without EGFR mutation)
Cancer of unknown primary
Thyroid cancer (radioactive iodine resistant)
Malignant fibrous histiocytoma
Renal cell carcinoma (without antiangiogenic therapy)
Melanoma
Renal cell carcinoma (radio - and drug-resistant)
Chordoma
Osteosarcoma
Chondrosarcoma

It is divided into 2 types regarding the tumor borders.

1. A subtotal resection (intracapsular resection, debulking). The tumor is partially removed. The residual pathological tissue is macroscopically determined. This technique is widely used to provide palliative care to patients with spinal cord compression (decompression surgery). It can be combined with radiation therapy (separation surgery) [35].

2. A total resection (extracapsular resection, gross tumor resection) means the tumor is resected by piecemeal within healthy tissues. This technique can be justified if en-bloc resection is technically impossible (the spread or localization of the tumor), or if the patient refuses to sacrifice certain anatomical structures and loss of function.

An adequacy of the tumor resection margin

A degree of surgery radicality is usually denoted by R letter in oncology. This symbol indicates the presence or absence of a rest (residual) tumor after treatment and is a prognosis factor: Rx – there is not enough data to determine the residual tumor; R0 – there is no residual tumor; R1 – the residual tumor is determined microscopically; R2 – the residual tumor is determined macroscopically.

The resection balance between a sufficiently wide margin to achieve local control and a minimum margin width to preserve function. An adequate resection margin is a developing term. Originally, the recommended margin of more than 5 cm for the resection of malignant bone tumors [5] decreases with time. The current research in this area considers a margin of 1 cm or less to be acceptable [34, 36]. Keys et al. [37] reported no differences in terms of local recurrence at the resection margin of 2 mm or more, if the tumor responds well to neoadjuvant chemotherapy. Andreou et al. [38] suggest that the clear margin of resection (R0) is more significant prognostically than the width of margin. This surgical development has become possible due to the progress in the field of radiation diagnostics. MRI as an imaging method of soft tissue structures helps to clearly determine the tumor growth borders. This is especially important in the spinal tumor surgery, where, due to unique anatomical features, there is often no stock of healthy tissues.

The adequacy of resection margin also depends on the tumor histology. The biological behavior of bone tumors is different. For example, Ewing sarcoma, even after neoadjuvant chemotherapy, is usually poorly delimited microscopically (the presence of viable cells in the scar), which makes it difficult to reach the R0 resection with a small width of margin [39]. However, the tumor response to neoadjuvant and adjuvant therapy is the most important data for marginal resection planning. For example, in osteosarcoma, even at the R0 resection, the frequency of local recurrences is higher in the case when the tumor does not respond well to chemotherapy [38]. In other words, an adequate resection margin with a good response is not adequate with a poor tumor response to drug therapy.

The various tumor sensitivity to radiation therapy is also essential. There are different prognoses for R1 resection of osteosarcoma and Ewing sarcoma, which is very sensitive to postoperative radiation therapy. The current advances in proton therapy are likely to change the concept of an adequate resection margin for chordoma and chondrosarcoma in the future. The encouraging results for the local control of these tumors were achieved in cases where complete surgical resection was not possible [40, 41]. Eventually, the progress in the field of systemic and radiotherapy forces the concept of an adequate resection margin to develop and be dependent on the

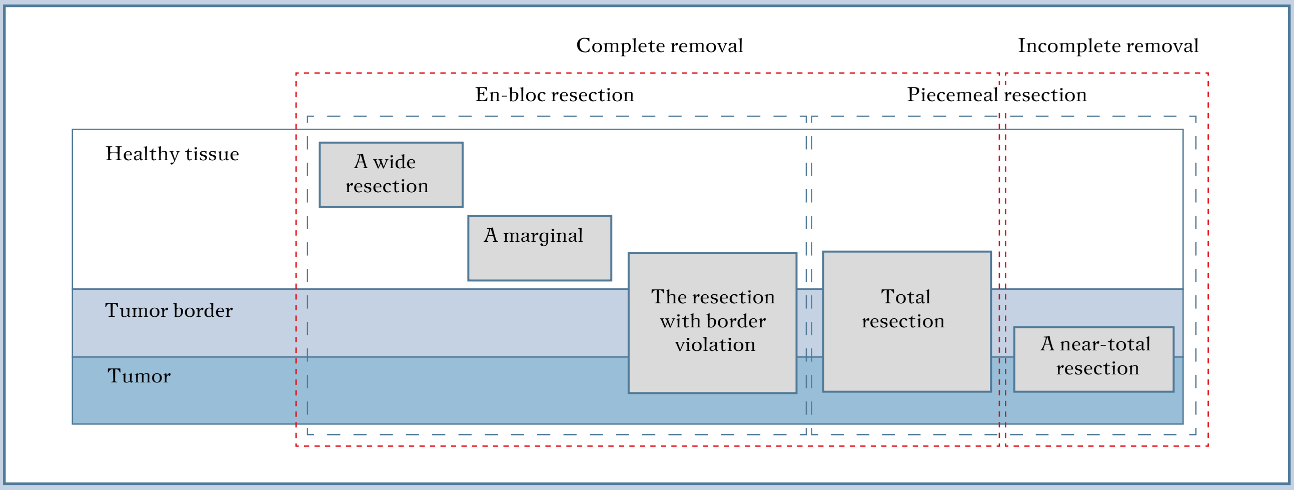

Fig. 3
Surgery types depending on the volume, method and margin of resection

molecular genetic characteristics of the tumor. This means that an inadequate resection margin may be suitable if it is consistent with the overall treatment strategy.

Conclusion

In contrast to the surgical treatment of traumatic injuries, deformities or degenerative diseases, the spine tumor surgery requires a multidisciplinary approach to assess the pathology nature and possible treatment options. It is important to observe the oncological principles that are the treatment basis. A histological diagnosis is essential for comprehending the malignancy and the probability that the tumor will respond to drug or radiation therapy. The distributional pattern of the disease in the spine and in the body determines the surgical treatment option. The tumor resection margin affects the prediction and treatment strategies of the patient after the surgical stage.

The study had no sponsorship. The authors declare no conflict of interest.

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Received 17.07.2020
Review completed 12.02.2021
Passed for printing 24.02.2021

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