

What are metastases?

Metastasis - also known as metastatic spread - is a process in which malignant cells or cell groups are transported by a variety of different means from the primary tumor (for instance a malignant tumor of the lungs, breast, uterus, kidney, stomach, or prostate) to other tissues or organ systems, such as the liver, the large tubular bones or the vertebrae. They begin to grow a tumor at the new location. This is called a metastasing primary tumor with, for example, liver, bone, or vertebral metastases.

Which malignant primary tumor types disseminate their metastases into the spinal column or other bones?

The most important malignant tumors that disseminate metastases to the vertebrae or other bones are:

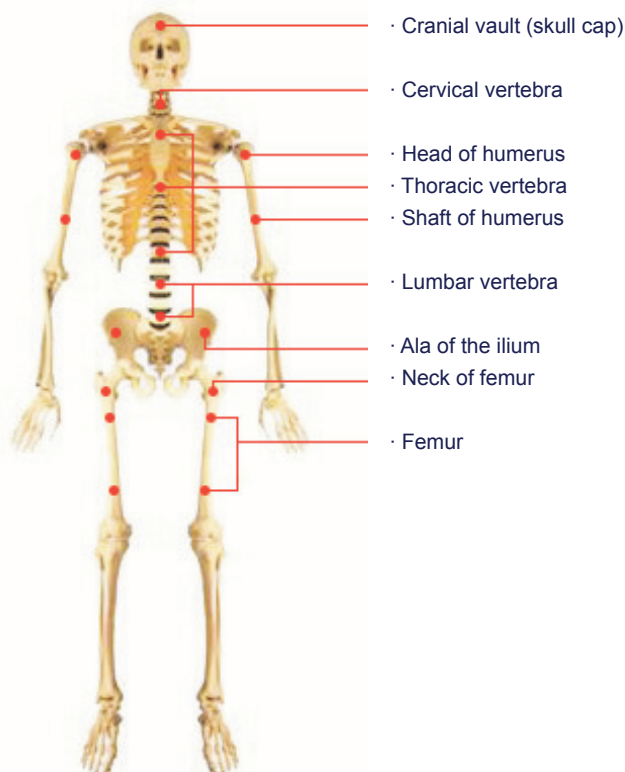
- Mammary carcinoma (female breast cancer)
- Prostate carcinoma (cancer of the prostate gland)
- Bronchial carcinoma (lung cancer)
- Thyroid carcinoma
- Hypernephroid renal carcinoma (kidney cancer)
- Skin cancer
- Stomach cancer
- Cervical cancer (portio carcinoma)

Where can bone metastases occur?

Bone metastases occur frequently:

- in the skull cap
- in the spinal column
- in major tubular (long) bones (thigh upper arm)
- in the iliac alae

• Frequent localizations of bone metastases



How can bone metastases develop?

The exact pathogenesis of metastases is not yet understood. One possible mechanism is tumor cell embolization that finds a favorable milieu in the young bony substance of the spine (spongiosa) for the nidation of tumor cells and further tumor growth.

The primary tumor outside of the spinal column gives off tumor cells, which then circulate in the bloodstream. From the bloodstream, these tumor cells can enter the bone marrow, where the tumor cells bind to the bony walls as cell groups. These malignant cell groups are called micrometastases. The normal balance in healthy bone is determined, among other factors, by a balanced activity level of the osteoblasts, which are responsible for building up bone tissue, and the osteoclasts, responsible for breaking it down.

The micrometastases disturb this balance, allowing the tumor cell groups to penetrate into the bone and destroy it. The most frequent bone metastases are osteoclastic (bone breakdown) metastases that destroy the bone by tumor growth and dissolution (osteolysis).

How does tumor tissue from a malignant primary tumor outside the spinal column get to the vertebrae (metastatic pathways)?

Metastasis from a primary tumor can take one of a number of different routes:

- hematogenic - through the vascular system
- lymphogenic - through the lymphatic vessel system
- per continuitatem - by virtue of simple further growth of the primary tumors into the surrounding tissues

Vertebral metastases are disseminated mainly via the hematogenic pathway.

There are several different types of hematogenic dissemination of metastases:

· Pulmonary type

A primarily malignant lung tumor disseminates its metastases through the pulmonary veins into the left heart. From there, the metastases from the primary tumor enter the blood vessels of the system circulatory system, e.g. into the liver, bones, brain and other organs.

· Hepatic type

A malignant liver tumor releases tumor cells after it has perforated the hepatic venous system. From there, the cancer cells get into the lungs, which then further disseminate the tumor cells via the pulmonary metastatic route.

· Portal vein type

The portal vein (vena portae) collects the venous blood from the stomach, pancreas, spleen, small intestine, and parts of the large intestine, and transports this blood to the liver. If any of these organs has a malignant tumor, tumor cells can arrive at the liver via this route, then spread throughout the body (hepatic type).

· Vena cava type

The upper and lower vena cava collects the venous blood from the body and transports it to the right atrium. If the vena cava drainage areas include a malignant tumor, tumor cells can travel by this route through the right side of the heart to the lungs, then spread from there to create further metastases (pulmonary type).

- Vertebral metastasis type

Drainage of the venous blood from the vertebrae is accomplished by the Batson venous plexus, a fine network of valveless veins consisting of the plexus venosus vertebralis externus and internus. After passing through the Batson venous plexus, the venous blood from the cervical and thoracic spine is transported to the upper vena cava (vena cava superior), and the venous blood from the lumbar spine, sacrum and coccyx is transported through the Batson plexus to the lower vena cava (vena cava inferior), and from there to the right half of the heart.

Primary tumors of the lung, breast, prostate, kidneys, and gastrointestinal tract are vascularly connected with the Batson plexus of the vertebrae. Increased pressure in the vascular system, e.g. caused by coughing, pressing or sneezing, may cause the blood flow to reverse in the Batson venous plexus, where the blood is not carried away from the vertebrae, but is rather “pressed” from the above-named organs into the vertebra. Direct dissemination of tumor cells from a primary tumor in these organs to the vertebrae can result from this mechanism.

What symptoms can metastases cause?

The type and severity of the symptoms depend on metastasis spread and location. Since the presence of a tumor does not cause specific symptoms, it can prove difficult to differentiate back pain caused by tumor or metastasis disease from pain deriving from other causes, such as diseases of the spinal column involving wear, simply because the symptoms may be similar.

- General symptoms, e.g.

- Fever
- Weight loss
- Nocturnal sweating
- Exhaustion
- Drop in performance

- Pain with different causes and qualities

- Dull constant pain at level of tumor
- Periosteal pain (periosteum) caused by raising and stretching of the periosteum as a result of the destruction of the cortical layer (outer wall of the vertebra) by the tumor
- Local pressure or percussion pain
- Pain at rest
- Stress-dependent pain
- Nocturnal pain
- Painful spinal column movement restrictions
- Lymph node enlargement

- Neurological disturbances due to compression of the spinal cord or spinal nerves

- Radicular symptoms resulting from pressure exerted by the tumor on the spinal nerve roots. Compression of the posterior spinal nerve root results in sensory defects in the corresponding area of distribution with painful dysesthesias (impairment of sensation). Pressure on the anterior spinal nerve root causes sensomotor defects with paralyses and atrophy of the muscles in the corresponding areas of distribution.

- Paraplegic symptoms
Rapid metastatic growth may cause acute, complete paraplegia, the neurological effects of which always depend on the level of the vertebra affected by the tumor metastasis. Motor or sensory defects noted in the clinical examination provide an early indication of the level of the vertebral tumor.
Pressure on the posterior white columns of the spinal cord results in disturbances in depth sensitivity and gait, and changes in sensation of pain and temperature.
If the pyramidal (corticospinal) tract is damaged by tumor pressure on the spinal cord, a muscular weakness may develop in the legs accompanied by a sense of tiredness and temporary paralytic symptoms.
- Dysfunctions of bladder and colon function
- Sexual dysfunction
- Changes in reflexes (enhanced, reduced, absent)

- Instability of affected mobile segment due to
 - Increasing destruction of the vertebra affected by tumor disease
 - Pathological fracture of the destabilized vertebra

- Symptoms deriving from the organ systems in which the primary tumor is located and metastatic spread to the spinal column (gynecological symptoms, gastrointestinal symptoms, abnormalities in the urogenital system, lungs, thyroid gland and prostate).

How are metastases of the spinal column diagnosed?

Bone or vertebral metastases are often diagnosed while examining the region of a known primary tumor located outside the spinal column or “incidentally” within the framework of an x-ray examination to clarify “back pain.” It is important to do a complete diagnostic workup so that the dignity (benign/malignant) and type of the primary tumor (location outside of spine or primary bone tumor?) can be confirmed. This information then serves as the basis for any further therapy. The following examination methods can be used to obtain an exact diagnosis:

- Medical history and clinical examination
 - Onset and nature of symptoms? (acute/gradual onset)
 - Did the symptoms occur without any apparent cause?
 - Accident traumas in medical history?
 - Any history of spinal column or back symptoms?
 - Is spinal mobility restricted?
 - Where is the pain?
 - Describe the quality of the pain (dull, burning, continuous, intermittent, dependent on stress load or postural position)?
 - Any soft tissue swelling?
 - Unintentional weight loss?
 - Did the clinical examination of the organ systems reveal any abnormalities?
 - Any notable lymph node swelling?

- Neurological examination
 - Are there any sensory or motor dysfunctions?
 - Does patient limp in an attempt to relieve pain, or due to paralysis, or leg shortening?
 - Are there any signs of bladder, colon or sexual dysfunction?
 - Are the muscles normal or is muscular atrophy evident?
 - Have the reflexes changed?

- Instrumental imaging diagnostics

- Conventional x-ray images

Conventional x-ray images in 2 planes with oblique or direct images may provide valuable initial information for an first diagnosis.

It is possible to assess the location and spread of the tumor, the nature of the bony structure of the vertebra, and the height of the intervertebral space. The location of the tumor within the vertebra provides initial evidence of its dignity (benign/malignant), since benign processes, with the exception of hemangioma and eosinophilic granuloma, are usually found in the posterior portions of the vertebrae and malignant tumors are usually found in the anterior portions.

- Computer tomography (CT)

Using this layered imaging technique, tumorous changes in the bony vertebral structure can be visualized. Different sectional image layers are combined to create three-dimensional reconstructions of local findings. Computer tomography is used in precision puncturing of the suspicious tissues or for imaging of narrowed spinal canal sections with the help of a contrast agent (CT myelography).

- Magnetic resonance tomography (MRT, MRI)

Magnetic resonance tomography is highly suitable for assessing the location of the tumor in relation to the spinal cord and spinal nerves, possible infiltration of neighboring soft tissues, and mass displacement or ingrowth of the tumors into vessels in fine-layered images.

This technique is now considered the most useful of all for diagnosing tumor diseases, and also for differential diagnostics to distinguish them from other diseases of the spinal column. Another important field of application for MRT is in monitoring after surgery, radiation therapy, or chemotherapy on a vertebral tumor.

- Nuclear medicine examination methods

- 3-phase skeletal scintigraphy

In this method, the patient is injected with a radioactive marker (technetium-99m methylene diphosphonate) that then accumulates in bones at areas where metabolic activity levels are elevated. The entire bony skeleton is portrayed and the areas with elevated metabolic levels are clearly distinguishable from normal structures, thus providing an overall simultaneous view of all areas with raised metabolic activity levels.

This method is nonspecific, i.e. any and all areas of high-level bony metabolism are shown.

Differentiation between benign and malignant tumors, active arthrosis, or an infection of a vertebra can only be obtained using the other diagnostic methods.

- Positron emission tomography (PET)

Preceded by administration of a radioactively marked substance, this method renders increased levels of metabolic activity in the body (e.g. the elevated metabolic levels in a tumor) visible. Modern PET devices are coupled with CT scanners. This "two-in-one scanner" creates images using both CT and PET technology that are then compiled by computer to create an image that provides the needed information.

- Single photon emission computer tomography (SPECT)

This nuclear medicine examination method, combined with spiral computer tomography and the administration of various agents with low-level radioactivity, can make changed metabolic processes in the body down to the molecular level visible. This combination of the two methods unifies the data obtained in the SPECT examination with the layered spiral CT images, allowing for the exact localization of regions of the body with pertinent anomalies.

- Myelography

With the injection of a contrast agent into the spinal canal, myelography can make changes that are narrowing or compressing the spinal nerves (e.g. tumor compression, intervertebral disc prolapse) visible.

The contrast agent is distributed throughout the entire spinal canal by shifting the position of the patient on the examination table. A dynamic examination in motion can be done using fluoroscopy. Myelography is usually followed by a CT scan.

- Angiography

If a precise image of tumor vascularization is required as a basis for surgical planning and MRT and CT cannot provide reliable results, a contrast agent-based image of the arterial vessels can be obtained by this method, proving exact information concerning the vascularization of the tumor and the position of the tumor in relation to major vessels.

- Sonography

An ultrasonic examination, of the abdominal cavity in particular, provides for a rapid indication of the possible presence of liver tumors, kidney or adrenal tumors, or suspected lymph node changes along the major vessels of the abdominal cavity.

- Biopsy and examination of tissues at the cellular level

In a biopsy, various methods are employed to remove tissue from a suspicious area. These tissue samples can then be examined under a microscope.

This examination method facilitates a reliable assessment of the dignity (benign or malignant) of a tumor, so that further therapeutic steps can then be taken.

There are various biopsy methods:

- Closed methods

In fine needle or punch biopsy, a small amount of the suspected tissue is removed under anesthesia.

By examining this tissue sample under a microscope, it is possible to arrive at an exact histological (microscopic structure of tissue) diagnosis (tumor type, benign/malignant).

These punctures are minimally invasive in nature and are usually done under CT monitoring.

- Open methods

Excision or incision biopsy involves partial or complete removal of tissue portions altered by tumor activity under anesthesia, followed by histological analysis of the tissue.

- Laboratory diagnostics

Laboratory diagnostics are generally not suited to the confirmation of the presence of a tumor. Some laboratory parameters are nonspecific, i.e. they can also be changed by other diseases.

- Blood sedimentation rate (BSR)

- C-reactive protein (CRP)

- White blood cell count (leukocytes)

These inflammation parameters can be elevated in tumor diseases, but this may also be the case with other kind of infection.

Tumor markers are proteins that occur in low concentrations in blood plasma, where they can be measured.

They are produced by tumor cells, but sometimes by normal cells as well.

While elevated concentrations of various tumor markers may be an indicator of the potential presence of certain type of tumor, this evidence is not conclusive.

Known tumor marker include:

- Alpha-fetoprotein (AFP) as an indicator for hepatic (liver) carcinoma

- Neuron-specific enolase (NSE) as an indicator for a parvicellular bronchial carcinoma or neuroendocrine tumors

- Prostate-specific phosphatase (PSA) as an indicator for prostate carcinoma

- Monoclonal antibodies from the group of cancer antigens (CA) may, depending on the existing CA type, provide evidence of tumors of the mammary glands, the pancreas or the stomach.

- Carcinoembryonal antigen (CEA) is an indicator for tumors of the gastrointestinal tract.

How is diagnostic staging of bone tumors and bone metastases done?

Once a tumor is found in a bone or other organ, the treating physician must quickly gain an overall picture that includes the following factors in order to classify the newly found tumor according to stage (grading):

- Dignity, i.e. is the tumor benign or malignant?
Final confirmation of this can be obtained by microscopic analysis of a tissue sample at the cellular level (histology).
- In this analysis, the status of the tumor cell groups can be determined, i.e. to what extent the tumor cell groups deviate from healthy, differentiated cells. This procedure is known as tumor grading. It provides valuable information as to the aggressiveness, growth, and metastatic spread potential of the tumor. The grades are classified from G1 (well differentiated) to G4 (undifferentiated). The more undifferentiated tumor tissue is, the more malignant the tumor is.
- Tumor location and spread
CT and MRT scans can be used to determine the location and spread of the tumor and its relation to adjacent tissue structures.
- Are metastases from the tumor present in other organ systems (lungs, liver, bones)?
Whole body skeletal scintigraphy, MRT, and CT reveal whether, and where, metastatic spread has taken place. Accurate knowledge concerning these factors is decisive for developing an individual therapeutic strategy and the prognosis of the course of the tumor.

Is there a system to classify malignant bone tumors or bone metastases (TNM classification)?

The TNM system is used for all malignant tumors with the exception of leukemia and malignant lymphomas. This system can be used to assess individual cases of tumor disease.

The TNM system is internationally standardized. It provides support to practicing physicians after diagnosis and throughout the course of the disease by defining a “common language”:

The three letters stand for:

- | | |
|------------------|--|
| · T (tumor) | Tumor extent or size of primary tumor |
| · N (node) | Are there any lymph node metastases? |
| · M (metastasis) | Has metastatic spread from the primary tumor occurred? |
| · G (grading) | How is the differentiation of the tumor tissue graded? |

The letters T, N, M and G are further differentiated by adding numbers that provide information as to the size of the tumor (T1-T4), the existence and number of lymph node metastases (N0-N3), presence or absence of metastatic spread to other organ systems (M0 or M1) and the degree differentiation (grade) of the tumor tissue (G1-G4).

If it is not possible in the diagnostic process to provide reliable information on one of the three factors in the TNM system or grading, the letter X is added.

“MX” would therefore signify that no reliable data on the presence of metastases can be provided.

Example of TNM classification of a primary bone tumor of the spinal column:

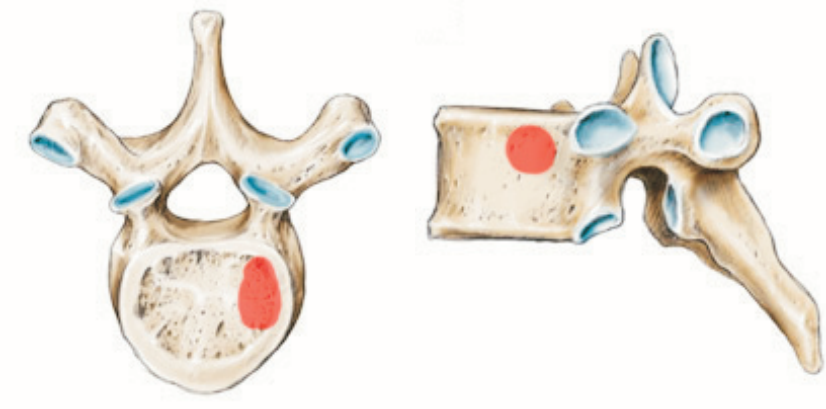
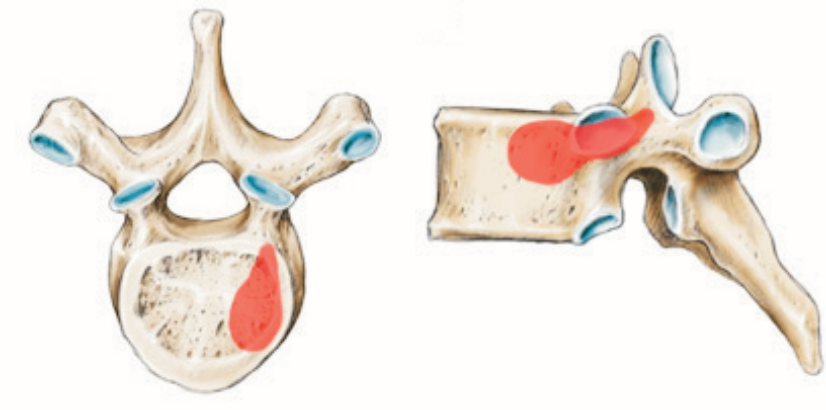

T1N1M1G4 would mean:

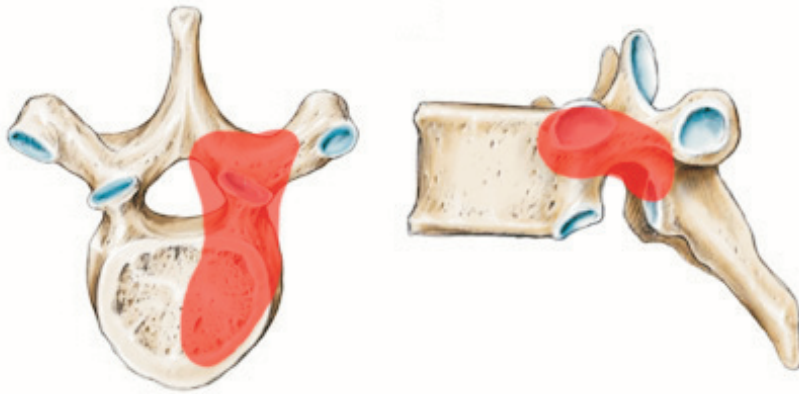
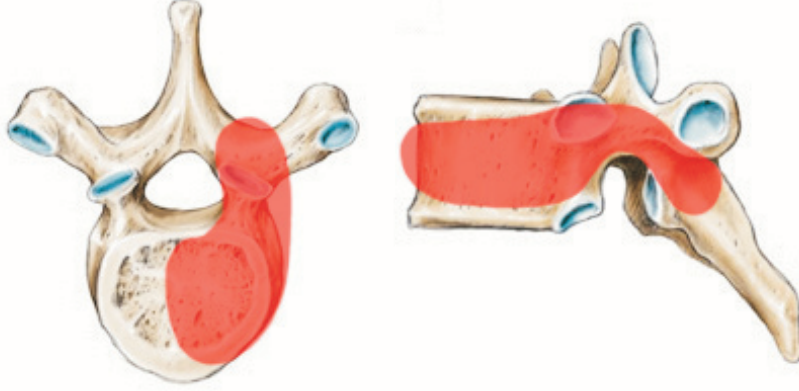


- T1: The tumor has broken through the corticalis (hard bony outer wall) of the vertebra and is infiltrating the adjacent tissue
- N1: Regional lymph node metastases are present
- M1: Confirmed metastatic spread of the tumor to lungs, liver, or other bones
- G4: The tumor tissue is undifferentiated, i.e. highly malignant

Is there a classification system that designates the location of a vertebral metastasis in relation to surrounding structures, providing a surgeon with information for planning a possible surgical procedure?

The Tomita classification system divides metastases of the spinal column into 7 subtypes based on their localization. The combination of this information with a specially developed score provides guidelines for projected therapeutic objectives and possible surgical procedures.

- Tomita classification of localization of vertebral metastases

Tumor invasion within the bony margins of the vertebra		<p>Type 1 Tumor invasion of the vertebral body</p>
		<p>Type 2 Tumor invasion of the vertebral body with spread to pedicles</p>
		<p>Type 3 Tumor invasion vertebral body with spread to pedicles and vertebral arches</p>

<p>Tumor invasion with perforation through the bony margins of the vertebra</p>		<p>Type 4 Tumor invasion of the vertebral body, pedicles and vertebral arches, with epidural spread</p>
		<p>Type 5 Tumor invasion of the anterior and posterior columns with perforation into the paravertebral space</p>
		<p>Type 6 Tumor invasion of 2-3 vertebrae</p>
<p>Multisegmental tumor invasion within and outside of the bony margins of the vertebra</p>		<p>Type 7 Multisegmental tumor invasion with varying localization</p>

In the score system introduced by Tomita in 2001, three parameters of the existing tumor disease are evaluated with points. The total of all points can then provide guidelines for therapeutic objectives and possible surgical procedures.

The three evaluation parameters for the metastatic disease to be assessed are:

1. Malignancy grade of the primary tumors:

- Slow growth tumor (e.g.: carcinoma of the female mammary gland, the prostate, or the thyroid gland)
- Moderate growth tumor (e.g.: carcinoma of the kidney or cervix uteri)
- Rapid growth tumor: (e.g.: carcinoma of the lungs, liver, stomach, large intestine, and tumor of unknown situs.)

2. Visceral metastases in the lungs, liver, kidneys, or brain:

- No visceral metastases
- Visceral metastases can be treated by surgery or transarterial embolization
- Untreatable visceral metastases

3. Bone metastases:

- Solitary or isolated metastases of the spinal column
- Multiple bone metastases (solitary or isolated metastases of the spinal column together with other bone metastases or multiple spine metastases with or without bone metastases).

These three parameters are assigned points to produce a score:

Points	Prognosis	Factors	Factors
	Primary tumor	Visceral metastases	Bone metastases
1	Slow growth	None (0)	Solitary
2	Moderate growth	Treatable	Multiple
3	Rapid growth	Not treatable	None (0)

In this evaluation method, 2-10 points can be scored. The point score provides surgeons with helpful strategic information concerning therapeutic objectives and possible surgical approaches.

Points	Therapy objective	Surgical strategy
2,3	Long-term local control	Broad or marginal removal
4,5	Medium-term local control	Marginal or intralesional removal of metastases
6,7	Short-term palliation	Palliative surgery
8,9,10	Terminal care	Supportive treatment

With initial scores of 2-3, where the tumor tissue can be removed broadly or up to the edge of the healthy tissue (marginal), local improvement can be presumed over the long term. These findings have the best prognosis.

With scores of 4-5 points, indicating marginal or intralesional (inside the tumor boundaries) removal of the metastasis tissue, improvement over the medium term is to be expected.

With a score of 6 or 7 points, only palliative (alleviating and protective) procedures are undertaken to stabilize collapsed vertebrae or prevent imminent paraplegia by means of decompression surgery.

Only a short-term improvement of the tumor disease can be achieved using these methods.

Patients with scores between 8 and 10 points are usually not operated on.

How are metastases of the spinal column treated?

Once a tentative diagnosis "metastasis in the spinal column" has been reached, the dignity (benign/malignant), exact localization, existence of any further metastases in other organ systems, and the cellular structure of the tumor must be clarified.

If a malignant tumor is confirmed, a therapeutic strategy must be drawn up based on the findings at hand. Since tumor disease always comprises a complex clinical picture, the individual therapeutic strategy must be developed by a team of specialists. The cooperation of these specialists in this interdisciplinary tumor conference ensures the patient the highest possible level of therapeutic quality based on their specialist skills and knowledge. The participants in the tumor conference include surgeons as well as specialists for tumor chemotherapy (oncologists) and radiotherapy, radiologists and pathologists.

The main pillars of vertebral tumor treatment are:

- Radiotherapy
- Chemotherapy
- Pain therapy
- Tumor surgery

Malignant tumor diseases of the spinal column cannot always be healed despite surgery and supportive radiotherapy and chemotherapy.

In the spinal column in particular, the surgeon encounters limitations presented by the anatomical situation (spinal cord, spinal nerves, vascularization) when it comes to radical surgery. That is to say: not every tumor can be radically removed in the oncological sense of the word.

Tumor surgery of the spinal column adapted to the individual findings may, however, help improve the quality of life of the patient to a significant degree.

- Tumors in favorable locations can be removed completely (curative, "healing" treatment)
- If a vertebra is or threatens to become destabilized by the tumor growth, the risk of neurological defects or paraplegic symptoms may be eliminated.
- Pain can be reduced by removing the tumor or reducing the tumor mass

Metastases of the spinal column must principally be considered just like benign or malignant tumors. Once a metastasis has been confirmed, it must be determined whether a monolocular or multilocular manifestation is present, since this is of preeminent importance when selecting a surgical procedure. In monolocular manifestation, the same criteria as for the treatment of benign or malignant tumors should be applied: Removal of tumor as radically as possible, if feasible en-bloc-resection. We know that such radical metastasis surgery can clearly reduce local recidivation. We also know that radical metastasis surgery, in combination with adjuvant chemotherapy and radiotherapy, is far superior to radiotherapy alone.

In cases of advanced metastatic spread, such radical measures are of course only of limited usefulness. In such cases, pain treatment and the maintenance of the stability of the spinal column in particular, are of primary importance. The therapeutic concept must therefore be formulated by a group of physicians from the disciplines involved in the tumor therapy. We also know that aggressive surgical treatment of metastases cannot lengthen the patient's life, but can improve the quality of life by a significant margin. This should always be the guideline for intervention, and above all determine the level of intervention, since a tumor patient with a limited life expectancy should also be allowed to profit from the advantages surgery has to offer.

If surgery does prove necessary, a number of methods of tumor removal and subsequent stabilization of the mobility segment are available.

Here is a list of some of the surgical methods used frequently in our department in treatment of malignant vertebral tumors:

Tumors of the cervical spine:

- Transoral dens resection with dorsal spondylodesis
- Dorsal decompression with cervical fusion
- Ventral corpectomy with cervical spondylodesis

Tumors of the thoracic and lumbar spine:

- Corpectomy with dorsal spondylodesis

Tumors of the sacrum (os sacrum)

- Sacrum surgery with special instrumentation

What is oncological follow-up?

Malignant tumors must be monitored at regular intervals after conclusion of treatment.

Generally speaking, control follow-up examinations are carried out at 3-month intervals during the first 2 years after a tumor diagnosis is reached.

Biannual checkups follow in the 3rd to 5th years, with annual checkups beginning in the 6th year.

A number of techniques are employed in these examinations (CT, MRT, scintigraphy, ultrasound, clinical, and neurological examination) to determine whether the patient's overall condition has remained stable or if tumor growth has resumed.

Regular checkups facilitate rapid intervention should tumor growth reoccur.