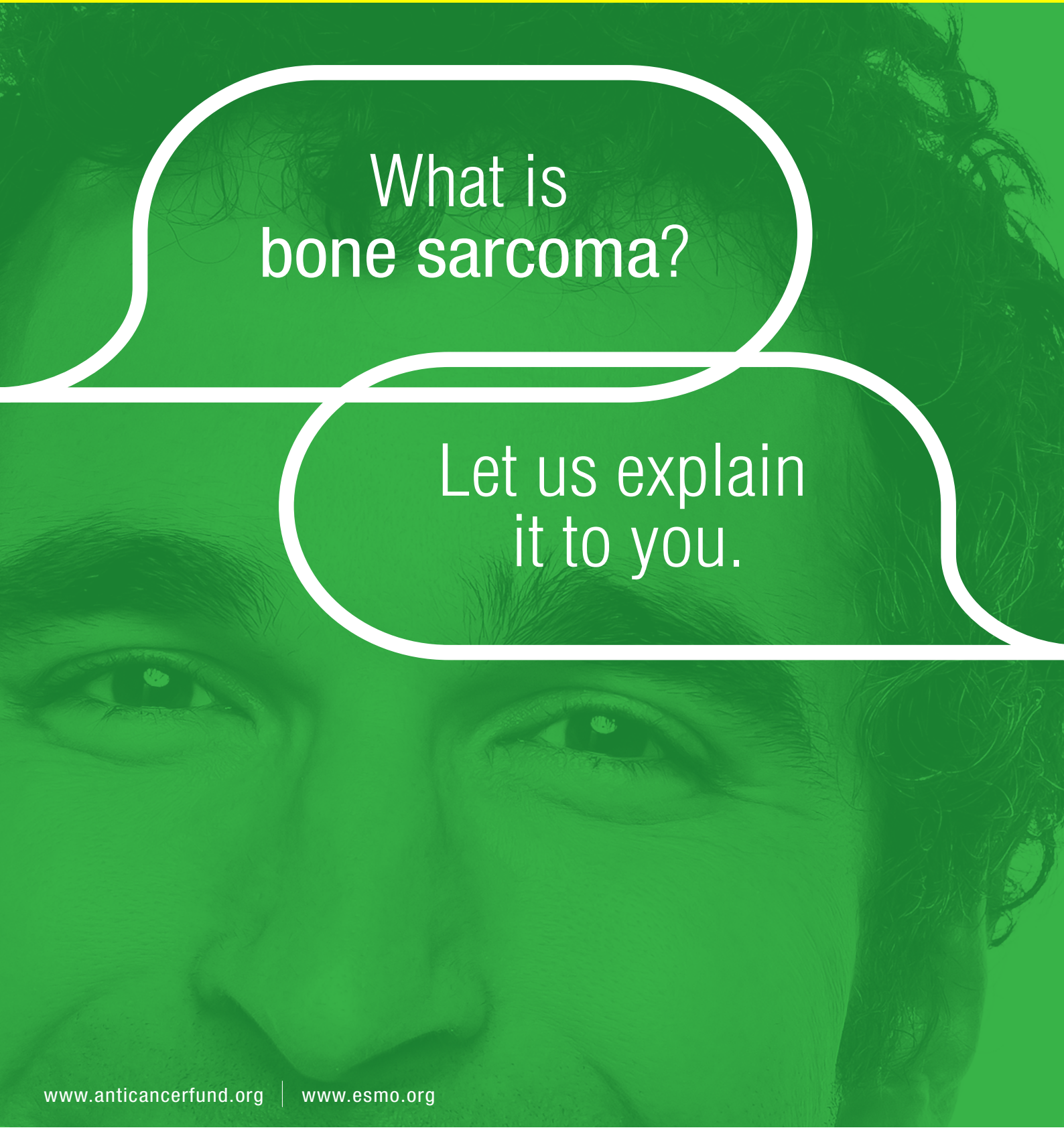
Bone Sarcoma



What is bone sarcoma?

Let us explain it to you.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

ESMO/ACF Patient Guide Series

based on the ESMO Clinical Practice Guidelines

BONE SARCOMAS: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of bone sarcomas and treatment choices available. We recommend that patients ask their doctors about what tests or types of treatments are required for their type and stage of disease. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of bone sarcomas. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the leading author of the clinical practice guidelines for professionals. It has also been reviewed by patient representatives from ESMO's Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

More information about the European Society for Medical Oncology: www.esmo.org

For words marked with an asterisk, a definition is provided at the end of the document.

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FACTSHEET ABOUT BONE SARCOMAS

Definition of bone sarcomas

- Bone sarcomas are a group of malignant tumours* that may originate in any part of the body where bones are found, i.e. the skull, limbs and girdles*, the spine and the ribs. Malignant tumours contain cells which can spread to and damage other tissues and organs.

Diagnosis

- Unfortunately, bone sarcomas* may not present symptoms for a long time and the symptoms will depend on the part of the body which is affected. Bone pain is the most commonly reported symptom at diagnosis. Sometimes, it is possible to feel a mass/swelling located deeply in the involved bone and occasionally a fracture/break may occur.
- Radiological tests*, which use different types of energy to create images of the inside of the body, the images determine the extent of a bone sarcoma and establish if the cancer has spread to other parts of the body, this is called metastases*.
- A small piece of the tumour (biopsy*) must be obtained for examination in the laboratory to confirm the diagnosis and get more details about the type of bone sarcoma.

Treatment

- Localised sarcomas* are confined to the primary site* and have not spread to nearby tissues or to other areas of the body.
  - Removal of the tumour by surgery is the standard treatment
  - Radiotherapy* (the use of radiation to treat cancer)
  - Chemotherapy* (drugs that kill and/or limit the growth of cancer cells).

Radiotherapy and chemotherapy can be used separately or together before and/or after surgery. They can sometimes be used to increase the chance of complete cure and reduce the risk of cancer returning.

- Advanced bone sarcomas have spread from the primary site* to other parts of the body. This is known as metastatic or locally advanced tumour.
  - The main treatment is the use of chemotherapy* and molecularly targeted therapy*. The choice of drug will mainly depend on the clinical condition of the patient and on the type of bone sarcoma.
  - Radiotherapy,* either during or after chemotherapy,* may be used to relieve symptoms and control metastases.
  - Surgery may be used to relieve symptoms (such as pain) and may be curative in some cases.

Follow-up

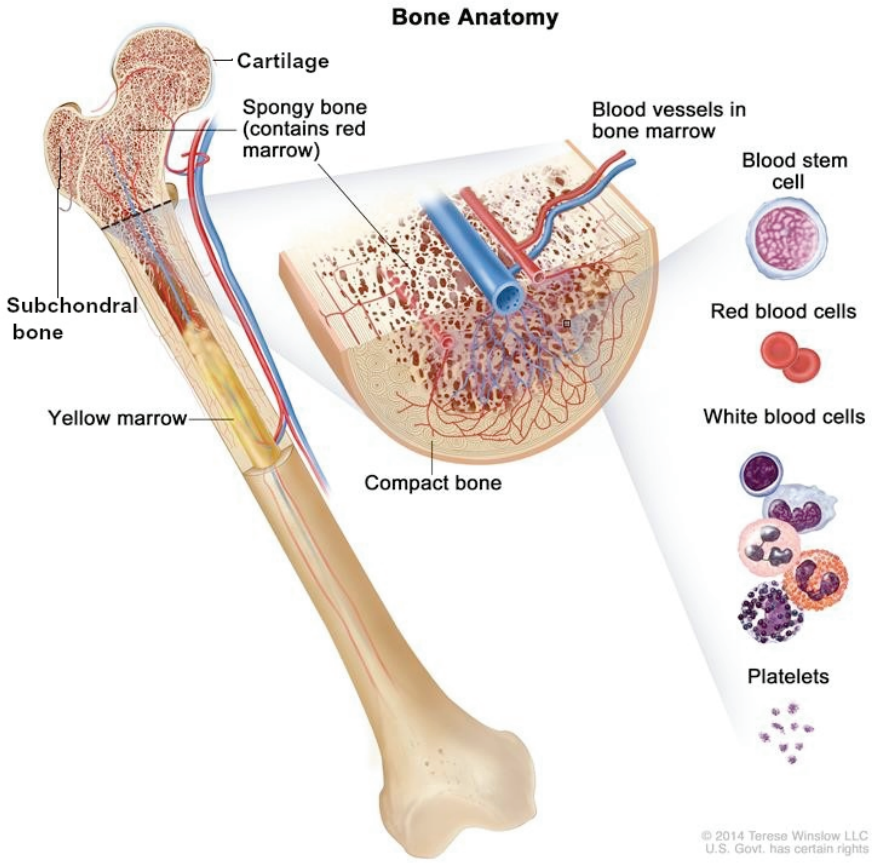
- Follow-up appointments include physical examination, blood tests and radiological examination*; they will be done regularly for several years.
- The follow up investigations for bone sarcomas depends on the location, the size and the aggressiveness of the tumour. The frequency of follow up will depend on the grade of your sarcoma.

DEFINITION OF BONE SARCOMAS

Bone sarcomas are a diverse group of malignant tumours* that originate in the bones. Bones consist of three types of tissue: the cortical bone (the hard, rigid outer part of the bone), the cancellous bone ("spongy" tissue inside the bone containing the bone marrow), and subchondral bone (the smooth bone tissue of the joints lying under articular cartilage*). The periosteum, a layer of fibrous tissue, covers the outside of the bone. Cartilage, a firm, flexible and elastic type of connective tissue, surrounds the subchondral tissue to form a cushion around the joints. Articular cartilage is the tissue that covers the ends of bones where joints are formed.

Bone Anatomy

There are different types of bone sarcomas and the most common are osteosarcoma* (also known as osteogenic sarcoma), Ewing sarcoma, chondrosarcoma, giant cell tumour of the bone, and chordoma.



Anatomy of the bone. The bone is made up of compact bone, spongy bone, and bone marrow. Compact bone makes up the outer layer of the bone. Spongy bone is found mostly at the ends of bones and contains red marrow. Bone marrow is found in the center of most bones and has many blood vessels. There are two types of bone marrow: red and yellow. Red marrow contains blood stem cells that can become red blood cells*, white blood cells*, or platelets*. Yellow marrow is made mostly of fat.

ARE BONE SARCOMAS COMMON?

Bone sarcomas are rare tumours, accounting for less than 1% of malignant tumours*. There are various types of bone sarcomas. The incidence of bone sarcomas depends on the type of bone sarcoma. Incidence refers to the number of new cases diagnosed in a defined time period, generally 1 year. However, it is important to know bone metastases*(bone lesions resulting from the spread of cancer cells from other tumours, e.g. lung, prostate, breast etc.) to a different part of the body are seen more frequently. Bone metastases are not bone sarcomas, unless the primary tumour* is a bone sarcoma. This guide concerns tumours that primarily started in bones, not metastases from other cancers.

Osteosarcoma* is the most frequent type of primary tumour* of bone. It is estimated that there are 2 to 3 new cases per million people every year; adolescents, particularly around the age of 15 to 19, are the most commonly affected age group.
Chondrosarcoma is the most frequently occurring bone sarcoma type of adulthood, with 2 new cases per million people diagnosed every year. The most common age at diagnosis is between 30 and 60.
Ewing sarcoma is the third most common bone sarcoma. It occurs more frequently in children and teenagers, in whom it is usually diagnosed around 15 years of age, but it also occasionally occurs in adults. It may involve any bone, and soft tissues as well, but it is more common in the limbs (50%) and pelvic bones (25%), the ribs and vertebral column/spine may also be affected. Osteosarcoma* and Ewing sarcoma are more common in males than in females.
Giant cell tumour of the bone represents 5% of all primary bone tumours*. It most commonly occurs between 21 and 30 years old and it is more frequent in women.
Chordoma is a very rare malignant bone tumour*, it is diagnosed in one out of one million people every year. Common sites of origin are the sacrum *(50%), the skull-base* (30%) and the spine (20%). It is most frequently diagnosed in people at 60 years old. Skull-base* lesions, however, generally affect a younger population, appearing in most cases around 50 years old, but it has also been reported in children.
Due to their rarity and the frequent need for combinations of different therapies, all patients suspected of having bone sarcoma should be referred to centres with expertise in the treatment of this type of tumour, involving dedicated pathologists*, radiologists*, orthopaedic surgeons*, radiation oncologists*, medical oncologists* and paediatric oncologists*.

WHAT CAUSES BONE SARCOMAS?

Currently, it is not clear why bone sarcomas occur. Some risk factors* have been identified. A risk factor* increases the risk of cancer, but is neither necessary nor sufficient to cause it. A risk factor is not a cause in itself.

Some people with these risk factors* will never develop bone sarcomas and some people without any of these risk factors* may nonetheless develop a bone sarcoma.

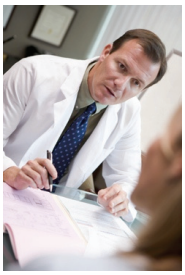
Some risk factors* for bone sarcoma have been identified and the main ones are the following:

- Genetic predispositions*: both inherited* and acquired* conditions may be associated with a bone sarcoma.
    - *Li-Fraumeni syndrome*: an inherited* genetic condition caused by a mutation* of a tumour suppressor gene* (p53), which is a gene that helps to protect cells from becoming cancerous. Patients with this rare syndrome are more likely to develop several types of cancers, including bone sarcomas.
    - *Hereditary RB (retinoblastoma)*: a familial syndrome in which all the cells of the body have a mutation* in the RB1 gene. Patients usually develop malignant tumours* of the retina (layer of nerve tissue in the back of the eye, it receives images and sends them to the brain through nerves, so images can be processed) in both eyes during infancy and these children also have an increased risk of developing bone or soft tissue sarcomas*, including osteosarcoma*. A familial syndrome is a hereditary predisposition to a pattern of different tumour types and sites.
    - *Hereditary multiple exostoses*: (also known as multiple osteochondromatosis) is a rare inherited* musculoskeletal* disorder which causes short stature and deformities. In this condition, each osteochondroma has a very small risk of developing into a bone sarcoma (most often a chondrosarcoma).
    - Other rare inherited* conditions, including *Werner syndrome* (hereditary disorder marked by rapid aging that starts in adolescence), *Rothmund–Thomson syndrome* (hereditary disorder that affects the skin, the bones, eyes, nose, hair, nails, teeth, testes, and ovaries) and *Bloom syndrome* (disorder marked by height that is shorter than average, a narrow face with redness and a rash, a high-pitched voice, and fertility problems), have also been linked to an increased risk of osteosarcoma*.
- Paget's disease of the bone: a disorder characterised by abnormal growth of new bone cells. The affected bones are fragile and misshapen and more likely to break than normal healthy bones. Bone sarcomas (mostly osteosarcomas*) develop in about 1% of people with Paget's disease, usually when many bones are affected. It mostly affects people older than 50.

- Ionizing radiation*: exposure to ionizing radiation*, such as X-rays and radiotherapy, can increase the risk of bone sarcomas even in absence of other risk factors*. Rarely, bone sarcomas can arise following exposure to radiation given to treat other cancers and often start in the area of the body that has been treated with radiation. The risk increases with the treatment dose and decreases with age. The average time between radiation exposure and diagnosis of a bone sarcoma is about 10 years. However, radiation exposure is a very rare cause of bone sarcomas.

Osteosarcoma* risk is higher in children and teenagers with Down's syndrome. There are other factors that have been suspected to be associated with an increased risk of bone sarcomas, but the evidence for these is inconsistent.

HOW ARE BONE SARCOMAS DIAGNOSED?



Bone sarcomas might not cause symptoms for a long time, and inflammation (swelling and redness) will only be present if the tumour has progressed through the cortical bone. Symptoms depend on the size and location of the tumour. Bone pain is the most common symptom: it usually begins with a feeling of tenderness in the affected bone, which gradually progresses to a persistent ache. In some cases, the tumour can also weaken the bones causing spontaneous fractures or fractures after a minor injury or fall. Nerve problems can be present due to constriction of the nerves by the tumour. Less common symptoms can include fever, unexplained weight loss, fatigue/tiredness or anaemia* (a reduction in the number of red blood cells in the blood). Bone sarcomas may also be found by chance during an investigation of other symptoms or during a routine operation.

The diagnosis of bone sarcomas is based on the following examinations:

1. **Medical History and Clinical Examination.** Your doctor will begin by taking your complete medical history, asking when the symptoms began, how they have changed over time and he/she will also check for the presence of any risk factors*. Your doctor will then perform a complete physical examination, including the area where there is inflammation, swelling and/or pain: it's important to evaluate the size, thickness of the swelling, its location and mobility, and the relation of swelling to the involved bone. Occasionally, this swelling may be painful or tender, but it may also be painless.

2. **Radiological examination*.** A wide range of imaging techniques used to look inside the body are used to determine the extent of bone sarcoma and to establish the presence or absence of distant metastatic disease*.

   - **Bone X-rays*:** X-rays of the bone should always be the first test done since they can help to determine damage to the bones caused by cancer, new bone growth or a bone fracture. Doctors can often recognise a bone tumour such as osteosarcoma* based just on X-rays* of the bone but other imaging tests might also be needed.

   - **MRI:** Magnetic Resonance Imaging (MRI) uses magnetic fields and radio waves to create a series of detailed pictures of the tissue of the body. MRI of the affected bone, all other tissues surrounding it and the adjacent joints is the best imaging test for diagnosis of extremities (arms and legs) and pelvic tumours and is an effective way of assessing the size and spread of any cancer inside the bones or in the surrounding soft tissues.

- **CT scan***: Computed Tomography scan (CT-scan*) is an X-ray* technique that produces detailed pictures of the inside of the body. You may be asked to drink a liquid called oral contrast and you may also receive contrast liquid injected into your veins. This helps the organs or tissues to show up more clearly and it also allows visualisation of calcifications (deposits of calcium) or bone destruction. CT scans* can also be performed to check if bone sarcoma has spread to the lungs or other organs. Chest X-rays* may also be taken for this purpose.

- **PET scan**: Positron Emission Tomography (PET) scan is mainly used to find out if the sarcoma* has spread to other parts of the body. It uses a substance that contains glucose*, which is injected into the patient. This radiolabelled glucose*-based substance is absorbed by cancerous cells which are less able to eliminate it than normal tissues, so it remains "trapped" in cancerous tissues, making them visible. PET scans can also be used to examine the effect of the treatment on tumours, so that cancer regression or progression is seen thanks to the radiolabelled glucose-based substance aforementioned.

- **Bone scintigraphy**: a type of scan using a radiolabelled* substance to find out whether other bones are affected. The radiolabelled* substance travels to areas of bone changes, which appear brighter and indicates possible spread of the tumour.

3. **Histopathological examination*.** Histopathological examination*, the examination of tissues under a microscope, is made on a biopsy* or a piece of tissue after removal of the whole tumour by surgery. Only the histopathological* assessment of the tumour will disclose whether the tumour is a bone sarcoma, and what type. It will also provide the "malignancy grade", which is a score of the aggressiveness of the cancer cells. Grades are explained in more detail later in the text.

   A biopsy* is performed to take a small piece of the tumour, which is then examined under a microscope to look for cancer cells. Different types of biopsies may be used: needle biopsies and surgical biopsies.

   - Fine needle / Core needle biopsy*: cells of the tumour are removed using a needle. A local anaesthetic is injected to numb the area before the biopsy* is taken and several samples may be taken. The doctor may use imaging techniques such as ultrasonography or a CT scan* to visualize and guide the needle into the right place if the tumour is located deeper within the body.

   - Incisional / Excisional biopsy*: under anaesthesia*, surgical instruments are used to remove a piece of tissue from the tumour ("incisional"), or the entire tumour ("excisional").

When a biopsy* is taken through an incision, to be sure that the biopsy* location is adequate and that the characteristics observed in that piece of tissue are likely to be similar to the characteristics of the whole tumour, it is recommended to make X-rays* of the biopsy* location and sometimes undertake another sample in case more material is required. In aggressive tumours, the biopsy* track must be considered to be contaminated with tumour and must be removed together with the resection of the tumour sample to avoid local recurrences, including the possible channels through which drains have been placed. Biopsy* tracks should be clearly marked by means of a small incision or ink tattoo to ensure that the location can be recognised at the time of the definitive procedure.

4. **Blood Test.** A blood test is performed to check the general health status of the patient, and to explore the function of the liver, kidneys and blood cells. In some osteosarcomas*, abnormalities in the blood, such as an increase in enzymes called alkaline phosphatase and lactate dehydrogenase, can be detected. Enzymes are proteins that speed up chemical reactions in the body.

What is important for patients to know in order to receive an optimal diagnosis?

Patients should be referred to expert orthopedic surgeons to get an appropriate biopsy*. Even if a biopsy* is only meant to help with the diagnosis, it is a surgical procedure in itself which may affect successive treatment. An accurate assessment of the biopsy* incision site is essential; it must be planned taking into account another surgical procedure may be performed in the same area to remove the rest of the tumour. In addition, biopsy* haemostasis must be very accurate to avoid haematomas which could contain tumoural cells and, therefore, increase the risk of recurrence. If a biopsy* is not performed in the appropriate manner, it may disseminate the tumour or make the surgical approach for its resection more complex; in other words, when the biopsy* is planned, the possibility of a subsequent tumour resection must be taken into account.

WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?

Doctors will need to consider many factors related to both the patient and the tumour in order to choose the best treatment plan for the patient.

Relevant information about the patient

- General well-being
- Personal medical history
- History of cancer in the patient's family
- For women, menopause* status, which in some cases requires taking a blood sample to measure the level of hormone levels.
- Results from the clinical examination by the doctor
- Results from blood tests

Relevant information about the tumour

- **Results of the biopsy***

A tumour sample obtained from a biopsy* will be examined in a laboratory. This examination is called histopathology. The second histopathological* examination involves the examination of the whole tumour after surgical removal. It is very important to confirm the results of the biopsy* and to provide more information on the tumour. These should include:

- **Histological type**
  - **Osteosarcoma***, also known as osteogenic sarcoma, is the most common primary bone tumour*, and usually arises in long bones of the limbs, the femur being the most common site. Its hallmark is the production of a substance called malignant osteoid extra-cellular matrix in the bones affected, this is observed in the laboratory when bone samples are analysed under the microscope. Several different type of osteosarcoma are known. Bone sample analysis gives insight to the type and the prognosis of a given case of osteosarcoma.
  - **Chondrosarcoma** is the second most common bone tumour, and is characterised by the presence of cartilage. These tumours occur mainly in the axial skeleton (parts of the skeleton that are not the arms and legs), with the pelvic girdle* and the ribs being the most common sites. They range from low- to high- grade tumours: the higher the grade, the higher the risk of tumour spread. The histopathological* subtypes include: conventional, mesenchymal, clear cell, and dedifferentiated chondrosarcoma.
  - **Ewing sarcoma** is the third most common primary bone tumour* (second in children and adolescents), usually characterised by the presence of a specific genetic alteration. The most common sites of occurrence are the pelvis, ribs and long bones of the limbs (arms and legs).

- **Giant cell tumour of the bone** usually arises at the extremity of long bones, around the knee. It is generally considered a benign bone tumour, though with a tendency to bone destruction and frequent local recurrences. Transformation into cancer and spread to other organs is extremely rare.
- **Chordoma** is a rare tumour arising from the vertebrae of the spine or from remnants of the notochord*, a structure which forms the spine in a developing baby in the womb. It is characterised by a high rate of local recurrences, but metastatic spread is uncommon.
- Other histotypes, such as fibrosarcoma, leiomiosarcoma, etc., are most commonly found in soft tissues and are exceptionally rare as primary bone tumours*.
- Other tumours that may arise in bone include multiple myeloma, non-Hodgkin lymphoma* and bone metastasis* from primary tumours* in other locations, but since they are not treated like primary bone sarcomas*, they will not be discussed here.

- **Grade**
  - The grade of a tumour indicates how "aggressive" the tumour looks when analysed under a microscope by a pathologist*. The grading system generally distinguishes four malignancy grades: grade 1-2 (low), and grade 3-4 (high). The lower the grade, the better the prognosis*.

- **Molecular profiling:** Doctors may ask for additional information about the characteristics of the tumour. This relies on examination of structures (such as chromosomes* or genes) and molecules (such as proteins) of the cells. These analyses may be performed either to confirm or clarify the histological type of bone sarcoma, or to provide additional information about the prognosis* of the disease, or to help make decisions about the treatment. This is especially important with regard to the use of targeted therapies* that work by binding to and inhibiting the function of a specific protein or cellular structure known to be involved in the growth and progression of cancer.

- **Staging***

Doctors use staging* to assess the extension of the tumour in the body, which is an important indicator of prognosis*. The most widely used staging* system for bone sarcomas is the TNM system. The combination of T (size of the tumour and invasion of nearby tissue), N (involvement of lymph nodes*), and M (metastasis* or spread of the tumour to other organs of the body), will classify it into one of the stages shown in the table below. For bone sarcomas, the TNM staging* also takes into account the malignancy grade (G), which is a very important prognostic factor. Tumour burden and the presence of detectable distant disease are the two main factors which are taken into consideration in the clinical staging* of these diseases.
The stage is fundamental in order to make the right decision about what treatment to use. The lower the stage, the better the prognosis*.

The table below presents the different stages for bone sarcomas. The definitions are somewhat technical, so it is highly recommended that patients ask their doctor for more detailed explanations.

Stage	Definition
Stage IA	*The tumour* - *is categorised as grade 1 or 2 (low-grade);* - *is no more than 8 cm in its greatest dimension;* - *has not spread to lymph nodes* or to other parts of the body.*
Stage IB	*The tumour* - *is categorised as grade 1 or 2 (low-grade);* - *is more than 8 cm in its greatest dimension or is located in different parts of the same bone;* - *has not spread to lymph nodes* or to other parts of the body.*
Stage IIA	*The tumour* - *is categorised as grade 3 or 4 (high-grade);* - *is not more than 8 cm in its greatest dimension;* - *has not spread to lymph nodes* or to other parts of the body.*
Stage IIB	*The tumour* - *is categorised as grade 3 or 4 (high-grade);* - *is more than 8 cm in its greatest dimension;* - *has not spread to lymph nodes* or to other parts of the body.*
Stage III	*The tumour* - *is categorised as grade 3 or 4 (high-grade);* - *is located in different parts of the same bone;* - *has not spread to lymph nodes* or to other parts of the body.*
Stage IVA	*The tumour* - *has spread to the lungs.*
Stage IVB	*The tumour* - *has spread to nearby lymph nodes* or distant sites other than lungs.*

Though this classification is universally accepted, doctors usually refer to and plan the treatment upon the diagnosis of *localised* and *metastatic* disease.

WHAT ARE THE TREATMENT OPTIONS?

Planning treatment involves an inter-disciplinary team of medical professionals. This usually implies a meeting of different specialists, called multidisciplinary opinion* or tumour board review. In this meeting, the planning of treatment will be discussed according to the relevant information mentioned before.

The treatment will usually combine therapies that:

- affect the tumour locally, such as surgery or radiotherapy*
- affect the tumour cells present in other locations in the body through systemic therapy, such as chemotherapy*

The treatment choice will depend on the type and stage of the tumour and also considering the risk to the patient.

Treatment plan for localised disease

Bone sarcomas are localised when they are still confined to the primary site and have not spread to nearby tissues or to other areas of the body. At this stage, the main therapeutic goal is to remove the whole tumour by surgery whenever possible. Radiotherapy* and chemotherapy* can also be used to increase the chance of definitive cure or reduce the risk that the tumour comes back.*

Treatment for localised forms of bone sarcomas include options that aim to act locally in the region affected by disease.

Surgery

Most frequently, surgery is the standard treatment method used for localised bone sarcomas. As bone sarcomas are rare, surgery should be performed by a surgeon who specialises in treating this type of tumour. The goal of most bone sarcoma surgery is complete resection without leaving anything behind (microscopically negative margins*), thereby reducing the risk of local recurrence. Today, it is rare to resort to amputations for limb bone sarcomas since currently it is often possible to remove only the tumour and some of the surrounding tissue using a conservative approach, known as “limb-sparing” surgery, possibly with the contribution of other treatment modalities, including chemotherapy*.

The completeness of the surgical resection can be defined by several terms:

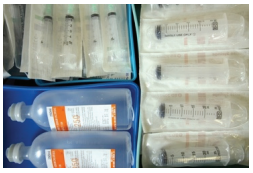
- "R0" resection means complete removal of all the tumour according to the analysis of the tissue margins* done by a pathologist* using a microscope;
- "R1" resection indicates that the margins* of the resected parts shows the presence of tumour cells when viewed microscopically;
- “R2" resection indicates a macroscopic residual disease (which means that a portion of tumour visible to the naked eye could not be removed by surgery).

Small bone sarcomas can usually be effectively removed by surgery alone and curettage*. Cryosurgery* (the use of extreme cold to destroy abnormal tissue) can also be an option in selected cases. R1 and R2 resection may need additional treatment by surgery or another option is to treat the resected margin* containing tumour cells with radiation and possibly chemotherapy*.

Radiotherapy*

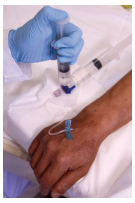
In bone sarcomas, radiotherapy* may be used before (neo-adjuvant) surgery (to shrink the tumour size and allow it to be removed completely) or after (adjuvant) surgery (to kill any remaining tumour cells); it may be considered in case of positive margins* or in case of residual macroscopic disease (when a portion of the tumour visible to the naked eye is still present). In selected cases, radiotherapy* may be performed instead of surgery to achieve local control of the disease.
Over the years, radiotherapy* techniques and radiotherapy* machines have improved and it is now possible to target external radiotherapy* more accurately. These new techniques deliver higher doses of radiation to the tumour with less damage to surrounding healthy tissues. New radiation therapy techniques, like proton/ion beam radiotherapy, may be considered for some types of bone sarcomas. The difference between conventional and proton/ion beam radiotherapy* is that high molecular weight particles, such as carbon ions and protons (hadrons), release almost all of their energy at the spot they are aimed at, and not throughout their course like X-rays do. This causes less damage to surrounding healthy tissues.

Chemotherapy*



Chemotherapy* may be considered alone or in combination with radiotherapy*, and before or after surgery for localised disease. It is strongly considered in these 2 situations:

- In osteosarcoma*, chemotherapy* has a very well established role in preventing local and distant relapses*, and it is usually given both pre-operatively and post-operatively for a cumulative period of 6-10 months.
- In Ewing sarcoma, chemotherapy* is usually given every three weeks, pre-operatively and post-operatively, for about 10-12 months with regimens including at least 5-6 different drugs. It may be used in combination with radiotherapy*.



Chemotherapy* is not routinely used in localised chondrosarcomas, and is not an option in chordoma and giant cell tumour of the bone.

Treatment plan for advanced disease

Bone sarcomas are advanced when they have spread from where they started to other parts of the body. This is known as the metastatic phase. At this stage, the main therapeutic goal is to control the disease, leading to a better quality of life for patients by improving their symptoms.

Advanced disease is not treated exactly the same way every time in different patients. The best treatment strategy requires careful and individual consideration of the different options by a multidisciplinary team.

Occasionally, surgery may be considered in metastatic disease to relieve symptoms and may be curative in some cases, mainly when lung metastases are relatively few and slow growing and are not accompanied by metastases that are located in organs other than the lungs.

Radiotherapy* may also be given to relieve symptoms and control metastases, in particular bone metastases.

However, the main treatment approach in case of advanced disease is the use of systemic therapy, which includes both chemotherapy* and molecularly targeted therapy* (drugs which target specific proteins or cellular structures known to be involved in the growth and progression of cancer). Each type of drug works differently, but all alter the way a tumour cell grows, divides and repairs itself.

Chemotherapy*

Chemotherapy* is the mainstay of treatment for advanced disease, as the drugs administered enter the bloodstream and reach tumour cells throughout the body. The most commonly used chemotherapeutic drugs in bone sarcomas are doxorubicin* and other anthracyclines*, cisplatin*, ifosfamide*, cyclophosphamide*, gemcitabine*, docetaxel*, etoposide*, methotrexate*, irinotecan*, vincristine* and other vinca alkaloids*.

Chemotherapy drugs can be given alone or in combination, and may be given as an outpatient* or as an inpatient* with admission to hospital for a few days. Chemotherapy* is given in cycles of treatment and the chemotherapy* regimen usually consists of a number of cycles given over a set period of time: the number of cycles depends on the type, site and size of bone sarcoma and how it is responding to the drugs.

Targeted therapy

Targeted therapy may also be used to treat advanced disease. These therapies work by binding to a specific protein or cellular structure involved in tumour growth and progression. Side effects are different from the side effects of the traditional chemotherapy*, and depend on how the drug affects your body.

Radiotherapy*

Radiotherapy* may be considered to relieve symptoms or prevent complications in patients with advanced disease, for example in the case of bone metastases or pain.

Surgery

Surgery to remove metastases may be considered depending on their location and on the history of the disease. For example, this would be the case when lung metastases appear a long time after initial treatment and when the surgeon considers that the metastases can be completely removed.

Treatment according to types of bone sarcoma

The management of the different types of bone sarcoma also varies according to the type. These differences are explained below.

Osteosarcoma*

Osteosarcoma* is the most common primary bone tumour*. These tumours can occur in people of any age, but is most common in children and young adults between the ages of 10 and 30. They usually arise in long bones of the limbs, like the femur, and commonly around the knee. In adults, it occurs typically in the spine, girdles* and skull.

Osteosarcoma* is primarily treated by surgery and almost all patients will also receive chemotherapy* to reduce the risk of local and distant relapse*. Doxorubicin*, cisplatin*, methotrexate*, ifosfamide*, and etoposide* are used in different combinations, before and/or after surgery for about 6-10 months. In young patients, additional treatment to boost the immune system, called adjuvant immunomodulatory treatment, together with mifamurtide may be proposed, given weekly for about one year.
There is no indication for radiotherapy* in osteosarcoma* but in some cases, when complete resection is not feasible, standard radiation treatment or new radiotherapy* techniques, like proton beam/carbon ion radiotherapy*, may be considered.
If the osteosarcoma* has spread to the lung, the lung metastases may be removed surgically in selected cases and the surgery may be curative.

Ewing sarcoma

Ewing sarcoma is the third most common primary bone tumour* (second in children and adolescents). It's usually characterised by the presence of a specific genetic change in cells, this change causes that a gene called EWS is moved to a different position on a different chromosome* – this activates the gene, and this contributes to cells becoming cancerous. Ewing sarcoma can occur in any bone, most commonly affected are the pelvis, the chest wall, and the long bones of the limbs (femur and tibia). However, it can also develop in the soft tissues surrounding the bone or joint and this type of Ewing sarcoma is known as extraosseous (extra meaning outside and osseous meaning bone). Some patients can be diagnosed with metastatic disease (mainly in the lungs, bones or bone marrow) at diagnosis and are usually treated with the same treatment approach as patients with localised disease.
Ewing sarcoma is usually treated with a combination of chemotherapy*, surgery and/or radiotherapy*. The treatment includes 3–6 cycles of initial combination chemotherapy* (to shrink the tumour and make it easier to remove surgically), followed by local therapy (surgery and/or radiotherapy*). Chemotherapy* will almost always continue after surgery or radiotherapy*, with another 6–10 cycles of treatment over a total period of 10–12 months.
Radiotherapy* can be used before surgery to shrink the tumour, with chemotherapy*, and to lower the risk of the cancer recurring after surgery. Surgery can be difficult if bone sarcoma develops in certain sites of the body, for example in the pelvis or the spine. In this case, radiotherapy* may be used as the main treatment.

High-grade spindle/pleomorphic sarcoma of bone

These represent between 2% and 5% of primary bone tumours* and some risk factors* like Paget's disease, bone necrosis* or history of previous irradiation have been identified for the occurrence of these kinds of bone sarcomas.
They are treated the same way as osteosarcoma*: often the patient is first treated with chemotherapy* to shrink the tumour followed by surgery. In some cases, chemotherapy* is also given after surgery. Radiotherapy may be considered after surgery if there is suspicion that some tumour was left behind or instead of surgery when the tumour is inoperable.

Chondrosarcoma

Chondrosarcoma is a tumour of the cartilage and is more common in adults, usually occurring in people over the age of 50. They are usually slow growing tumours and they are most commonly found in the bones of the head and trunk, in the pelvis and the ribs and may arise from benign (non-cancerous) bone lesions known as enchondromas and osteochondromas. They can be low- to high-grade sarcomas*: the higher the grade, the higher the risk of tumour spread. The majority are low-grade and non-metastasising* tumours. Surgery is the main treatment, and curettage* is appropriate in low-grade conventional chondrosarcomas.

Chondrosarcomas in the skull are hard to treat because complete surgical tumour removal is difficult, and the tumours may cause serious side effects. Radiotherapy* can be used instead, and since chondrosarcomas are relatively resistant to photons (particles that contain energy), high doses or new radiotherapy* techniques, like proton beam/carbon ion radiotherapy*, may be considered.
Chemotherapy* and radiotherapy* are not routinely used to prevent the risk of local and distant relapse*. However, chemotherapy* can be used to treat some special types of chondrosarcoma, i.e. dedifferentiated and mesenchymal chondrosarcoma, which are particularly responsive to chemotherapy* and may be treated as osteosarcoma* or Ewing sarcoma respectively.

Giant cell tumour of the bone

Giant cell tumour (GCT) is a rare tumour of the skeleton which occurs most commonly at the extremity of long bones, usually around the knee. Although it is generally considered a benign bone tumour, its behaviour is locally aggressive with a tendency to bone destruction and frequent recurrences. Malignant transformation and spread to other organs are extremely rare.
GCTs are mainly treated with surgery, ranging from curettage* to en-bloc excisions (removal of a tumour and surrounding tissues, virtually without sparing much of the potential healthy tissue around). If a GCT spreads to other organs, the lungs are most commonly affected and in some cases the lung metastases can be removed surgically. GCT which cannot be removed surgically or that has spread to other tissues can be treated effectively with denosumab*.

Chordoma

A chordoma is a rare type of tumour that develops from embryonic remnants of the notochord*, which is a structure that forms the spine in a developing baby in the womb. They can present at any age, but mainly affect people aged 40-60; childhood chordomas are very rare. They can be found in any part of the spine, most commonly in the sacrum* (50%), at the skull base* (30%) or in the neck, the upper and lower back (20%). They grow slowly and rarely spread to other parts of the body. If they spread, the most commonly affected places are the lungs, the liver, bone and skin. They are characterised by a high rate of local recurrence. Surgery is the main treatment for this disease and in many cases it is very difficult to remove the tumour completely. Other types of treatment like radiotherapy* may be considered if the tumour has spread into surrounding tissues. Radiotherapy* can be given after surgery or alone if surgery is not feasible or if the tumour comes back after initial treatment and further surgery is not possible. Palliative radiotherapy* (therapy aimed at improving the quality of life of the patient rather than curing their illness) is also sometimes used to relieve symptoms such as pain, especially in bone metastases. Newer radiation methods, such as proton beam therapy, can be effective in treating chordoma. Chemotherapy* is not an option in treating chordomas but it may sometimes be given to control a tumour that has recurred or has spread elsewhere in the body. Targeted therapy* with imatinib* may be considered in advanced chordomas.

In general, bone sarcoma treatment involves a treatment plan that can be modified depending on the specific histologic subtype and also the stage of the disease. The treatments listed below have their benefits, their risks and their contraindications*. It is recommended that patients ask their doctors about the expected benefits and risks of every treatment in order to be informed about the possible consequences of the treatment. For some treatments, several possibilities are available and the choice should be made according to the balance between benefits and risks.

Why clinical trials* are important?

The aim of clinical trials* is to try to find new treatments for cancer and find out if new cancer treatments are safe and effective or better than the standard treatment. Patients who take part in a clinical trial* may receive the standard treatment or be among the first to receive new therapy options. The purpose of clinical trials* includes testing new ways to stop cancer from recurring, reducing the side effects of cancer treatment, and looking for better ways to prevent, screen or diagnose a tumour. Trials help to extend our knowledge about cancer, improve current treatment options and develop new treatments, now and for future patients. You are encouraged to ask your doctor whether there are any clinical trials in which you could be enrolled.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENTS?

Risks and side effects of surgery

General risk of surgery
Minor surgery and biopsies usually pose less risk than major surgery: pain, infections at the site of biopsy* and reaction to the local anaesthesia* are possible.

Risks in major surgical interventions are shared by all surgical interventions performed under general anaesthesia*. These complications are infrequent and include deep vein thrombosis* (the formation of a blood clot in a deep vein of the extremities or lower pelvis), heart or breathing problems, bleeding, infection, or reaction to the anaesthesia*. Doctors will take the most appropriate steps to minimise any risks. Before any surgery, you should be clearly and carefully informed by the medical team about the possible risks.

Resection of a tumour in the arm or leg
After your operation you may have a tube in the wound to remove any fluid that collects in the area of the operation; the drainage tube will be removed once fluid has stopped draining. Immediately after surgery, your pain will be controlled with strong pain medications which will be given systemically.

Amputation
The consequences of the surgical resection depend on its extent, as to whether it involves the removal of parts of bone or an entire segment and surrounding soft tissues. It is not always possible to preserve the entire limb, even with a reconstruction, and occasionally amputation of part of the limb may be necessary.

- Some people experience pain that appears to come from the part of the limb that has been amputated, known as phantom pain. Your medical team tries to treat this very special form of pain and several types of treatment may be necessary: anticonvulsants*, antidepressants* and opioids can help relieve pain from nerve damage or to attempt to block pain signals.
- Rehabilitation begins shortly after surgery. The goal of rehabilitation is to help the patient return to the maximum level of function and independence possible, while improving the overall quality of life, physically, emotionally, and socially. A physiotherapist* will tell you how to exercise to strengthen your trunk (torso), arm, and leg muscles in order to prepare the remaining part of the limb for use of an artificial limb, called a prosthesis.

Resection of a tumour in the spine or pelvic girdle* or chest wall
The consequences of the surgical resection depend on the extent and site of the operation. A resection of a tumour located in the ribs is usually followed by minor or no consequences. A resection of a tumour located in the vertebral column or pelvic girdle* may involve nerve damage and functional deficits depending on the nerve involved. Rehabilitation helps to recover these deficits and improves the functional outcomes of the treatment.

Risks and side effects of radiotherapy*

During radiotherapy*, side effects may occur in organs that are directly targeted, but also in healthy organs that lie close to the region irradiated. Side effects may be more intense when radiotherapy* is administered together with chemotherapy*. Radiotherapy* in addition to surgery may also increase the risk of surgical complications and may cause problems with wound healing. Major improvements in radiotherapy* techniques and machines have been made during the last decades and severe side effects are now very rare.
Most side effects of radiotherapy* disappear gradually once the course of treatment has ended. For some people, however, they may continue for weeks or even longer. The radiotherapy* team will support you during this treatment period.

Immediate side effects
Since radiotherapy* is a local treatment, its side effects are local too. The most frequent general side effects of radiotherapy* are:

- Skin reactions (redness, soreness and/or itchiness) after three to four weeks of having external radiotherapy*, but these usually settle down two to four weeks after the treatment has finished. However, the treated area may remain slightly more pigmented than the surrounding skin.
- Dysphagia or difficulty swallowing due to inflammation of the oesophagus is frequent during radiotherapy* directed to the neck or chest areas.
- Nausea and vomiting, diarrhoea: some people find that their treatment makes them feel sick; this is most common when the treatment area is near the stomach or bowel.
- Hair loss can occur when the head is irradiated.
- Fatigue is a common side effect and may continue for some time after treatment finishes.
- Sore mouth and inflammation of the mucous membranes lining the mouth (oral mucositis*): your mouth may become sore or dry, or you may notice small ulcers during this treatment. This is common when the treatment area is near the oral cavity. It's very important to keep the oral mucosa* well hydrated and your teeth clean during the course of the entire treatment.

Long-term side effects
It is rare to develop severe, long-term side effects after radiotherapy*. However, long-term side effects can greatly affect the quality of life in some patients. Some possible long-term side effects are:

- long-term changes in the skin;
- occurrence of lymphoedema*, a swelling that occurs when the lymph nodes* and vessels are damaged by radiotherapy*;
- bowel incontinence*, bladder incontinence*, infertility and early menopause* in women when the pelvis is irradiated. If there is a risk of infertility following radiotherapy*, your doctor will discuss all the options with you and suggest available support before your treatment. It may be possible for men to store sperm and women to store eggs for future use;
- neuropathic pain (pain due to nerve damage) when major nerves are present in the irradiated field.

Radiotherapy* is associated with a slightly increased risk of developing a second tumour many years after treatment. The type and the dose of the radiotherapy* will be carefully planned to reduce the risk.

Risks and side effects of chemotherapy*

Side effects of chemotherapy* are well known, even if progress has been made in managing them using adequate supportive measures. They will depend on the drugs administered, on the doses and on individual factors. If a patient has other medical problems some precautions may have to be taken and/or adaptation of the treatment will be made. Please tell your health care team about your previous experiences and medical history.
Listed below are the side effects that are known to occur with one or several of the chemotherapy* drugs currently used for bone sarcomas. The nature, frequency and severity of the side effects vary for every chemotherapeutic drug combination used.

The most frequent general side effects of chemotherapy* are:

- Risk of infection: chemotherapy* works by interfering with the ability of cells to grow or reproduce and can reduce the number of white blood cells* (which help fight infection), a condition known as leucopoenia. A blood test will be performed before having chemotherapy* to check the number of white blood cells*.
- Bleeding: chemotherapy* can reduce the number of platelets*, which help the blood to clot. Sometimes a platelet* transfusion is needed if your platelet* count is low.
- Anaemia*: chemotherapy* can reduce the number of red blood cells*, this may make you feel tired and breathless. A blood transfusion may be needed if your red blood cell* count is low.
- Nausea and vomiting: effective antiemetic drugs* can be used to prevent, or reduce this side effect.
- Sore mouth: your mouth may become sore or dry, or you may notice small ulcers during treatment. Keeping your mouth moist and cleaning your teeth regularly can help to reduce the risk of mucositis*.
- Hair loss: not all chemotherapy* drugs cause hair loss; hair may be lost completely or may just thin. If your hair does fall out, it will almost always grow back over a period of 3-6 months once the chemotherapy* has finished.
- Fatigue: feeling tired is a common side effect of chemotherapy*.
- Fertility: as there is a risk of infertility, your doctor will discuss all the options and available support with you before your treatment.

A local reaction may occur at the site of venous access for drug administration into the vein. Local tissue might also be damaged if the drug leaks from the vein in the surrounding tissue. Your health care team will give you more information if you happen to be receiving such a drug.

More specific side effects may occur depending on the specific chemotherapy* drugs used. Not all available chemotherapy* drugs will be used during the course of your disease. The type of chemotherapy offered will depend on the type of bone sarcoma and the side effects will depend on the specific drug(s) used. Your health care team will inform you before you start chemotherapy about the specific side effects that could be expected from the drugs you will receive.

- Doxorubicin* and epirubicin* can cause damage to the heart muscle. Therefore, assessment of heart function is important before therapy with these two drugs; the chance of heart problems depends on the dose of this drug and the patient's condition prior to treatment. Heart problems may happen even if the patient does not have any risk factors*. These drugs can make the skin more sensitive to sunlight and cause redness in areas where the patient has had radiotherapy* in the past. Urine may turn red or orange for a few days after treatment. This is not blood and is due to the colour of the medication.
- Ifosfamide* may cause kidney problems in some patients resulting in blood in the urine and bladder pain. In some cases, it may also cause neurotoxicity* resulting in sleepiness, hallucinations and confusion.
- Cisplatin* and methotrexate* can cause damage to the kidneys. Therefore, blood tests will be done before and during treatment to monitor renal function. Extra fluids before and after chemotherapy* will be given intravenously* to help protect your kidneys. Methotrexate* may also cause mucositis*. An antidote will be administered together with fluids after the infusion to help protect normal cells.
- Cyclophosphamide* may cause bladder damage with bladder irritation causing discomfort when passing urine. Treatment can affect kidney and liver function but this is usually mild and will return to normal after treatment. At high doses, cyclophosphamide* can cause damage to the lungs or the heart. Development of a second cancer is a rare side effect.
- Etoposide* can cause a temporary drop in blood pressure (transitory hypotension) and mucositis*.
- Vincristine* and other vinca alcaloids* may cause abdominal cramps, and nerve damage (known as peripheral neuropathy), characterised by tingling and numbness.

Risks and side effects of targeted therapy

Denosumab* and imatinib* are the only targeted therapies* used in bone sarcomas.

- The principal side effects of denosumab* are diarrhoea, muscle-skeletal pain, drop in the level of phosphates (hypophosphatemia) and calcium (hypocalcemia) in the blood. Therefore, it is important to take calcium and vitamin D supplements during treatment. Osteonecrosis* of the jaw is a rare side effect of denosumab*. Preventive oral care can reduce this risk and a dental evaluation is recommended before starting treatment.
- Imatinib* may cause dizziness, diarrhoea, nausea and vomiting, muscle cramps, bleeding problems, blurred vision, oedema* (most frequently around the eyes or in the legs) and numbness or tingling in the hands, feet, or lips. Imatinib* can also cause neutropenia, reducing the number of white blood cells* which help to fight infections.

Most of these side effects can be treated with appropriate medications or dose adjustments, therefore it is very important to tell your doctor about any discomfort you feel.

HOW CAN PATIENT SUPPORT GROUPS HELP?

By Markus Wartenberg of the Sarcoma Patients EuroNet Association (www.sarcoma-patients.eu)

On the day of the diagnosis, whether you are a patient in the doctor's office, or a carer present to hold a family member's hand or comfort a friend, a sarcoma* diagnosis is a new, unplanned, and sometimes scary experience. Suddenly, there is a great deal to learn, understand, and cope with. Fortunately, patients and caregivers are often not alone. There are people in the same situation who have never heard the word "sarcoma"* before and have many questions to ask, that are waiting for results to find out what type of sarcoma they have and the treatment options available. In some European countries, patients with sarcomas* have come together and founded patient support and advocacy groups. Mostly these are not for profit organisations founded by patients and their relatives - for patients. Their mission is to work together with leading sarcoma* experts, the research industry, health insurance companies, other patient groups and other representatives of the healthcare system to optimise information, treatment and research situations for patients with a sarcoma*, a gastrointestinal stromal tumour (GIST)*, a desmoid tumour or a specific type of bone cancer. The most important areas of their work are:

- Improving the patient's level of information and competence (help them to help themselves)
- Securing access to innovative therapies and improving the quality of treatment
- Supporting sarcoma* research
- Advocating in the national health policy environment

Meanwhile, numerous studies show that timely treatment in interdisciplinary sarcoma* centres significantly change the results and prognoses among many patients. Hence, the international treatment guidelines (ESMO and NCCN) and the European sarcoma* patients' organisations maintain that sarcoma* - on account of its rarity - should be treated by experienced doctors and centres.

Unfortunately, many patients who live a long time with the "sarcoma"* diagnosis spend a lot of time being treated in non-specialist centres before getting in contact with experienced sarcoma* experts. These patients could have received better care sooner if they had been referred to the appropriate sarcoma centres. This much is painfully clear: had they been informed earlier of the existence of sarcoma* centres, or if their doctors had referred them to these experts, their disease would have been diagnosed earlier, and they would have received better treatment. Several patients would have better prognoses today.

If a sarcoma* is suspected or diagnosed, it may be useful to get a second opinion from another doctor before embarking on surgery or long-term, extensive treatment. In addition, it never hurts to seek independent, secondary findings, such as in an experienced sarcoma* centre, if the patient has reasonable doubts about the initial diagnosis and/or does not feel well-advised. A second opinion can exclude the possibility of misdiagnoses, check over therapy options, and possibly introduce new/different treatment options. Sarcoma* patient support groups are very experienced when it comes to the national sarcoma* expert landscape. They know where the sarcoma* experts/centres are located in a country and they can help patients to find the best support for a second opinion, a very rare sarcoma* subtype, for a special treatment option or a clinical study.

If a patient would like to have more information about his/her situation, or if they just need someone to talk to, it could be extremely valuable to contact a national sarcoma* patient support group.

For a list of sarcoma* support groups and charities in different countries, visit the Sarcoma Patients EuroNet Association's group locator page at http://www.sarcoma-patients.eu.

WHAT HAPPENS AFTER THE TREATMENT?

Follow-up with doctors

Regardless of the goal of the therapy, you will have regular follow-up appointments for several years after treatment. The usual practice will include a physical examination to look for any signs of tumour recurrence, blood tests to check your general conditions and possible treatment side effects. Depending on primary location* and bone sarcoma type, your doctor may ask for radiological examination* of that area, as well as of areas where the tumour could recur. This appointment is an important time for you to talk about any new symptoms or changes you notice and any questions or problems you have.
At first, the appointments will be every few months. They will gradually become less frequent and the gap between them will get longer because the risk of the tumour coming back gets steadily lower over time. Generally, in high-risk bone sarcomas a recurrence* would appear in the first two to three years after treatment; low-risk sarcomas* may relapse* later.
The routine follow-up depends on tumour grade, tumour size and tumour site. The optimal time schedule for routine follow-up is unknown, however, the routine follow-up after treatment for intermediate or high-grade bone sarcoma is more intensive than for low-grade ones.

Returning to normal life

Returning to normal life is one of the main objectives in the treatment of bone sarcomas. You are encouraged to tell your doctor about any worries, troubles of feelings about going home, or back to work or school. Make sure you discuss them with your health care team in advance so that help can be organised. Some patients may also find support from ex-patient groups or patient-targeted information media. Expert psychological advice may also be very useful.

What if the tumour comes back?

Bone sarcomas can come back in the same area as the initial tumour. This is called a local recurrence. Patients with an isolated local recurrence* may be offered surgery again to remove the tumour, but may also receive additional treatment.
Bone sarcomas can also come back in organs and parts of the body other than the initial site. This process is called metastasis*. In bone sarcoma patients, metastases mainly occur in the lungs, other bones than the primary tumour* and liver. Since metastases, especially at an early stage when they can be removed, may not cause any symptom, your doctor will pay special attention to these sites during the follow-up.
In patients previously treated with systemic drugs, further treatment options with chemotherapy* or targeted therapy may be considered.
Radiotherapy* may be applied to relieve symptoms or prevent complications related to the tumour.
It is important that every tumour recurrence* is evaluated by a multidisciplinary expert team, to select the most appropriate treatment modality or the most appropriate combination of treatments.

It may also happen, as a late effect of some therapies used for bone sarcomas, that a new secondary cancer appears. If a secondary cancer is suspected, your doctor will order a set of examinations to analyse the type of secondary cancer and its extent. Most appropriate options for management should be discussed within the multidisciplinary team responsible for your care, taking into consideration the previous treatments applied for bone sarcoma.

DEFINITIONS OF MEDICAL TERMS

Acquired (condition)
It refers to a condition that did not exist at birth, non-hereditary; but it developed after birth.

Anaemia
Condition characterised by the shortage of red blood cells* or haemoglobin, an iron-containing protein that carries oxygen from the lungs to the whole body; this process is diminished in this condition. Symptoms of anaemia include tiredness and shortness of breath.

Anaesthesia
Reversible state of loss of awareness, induced artificially by the employment of certain substances known as anaesthetics, in which the patient feels no pain, has no normal reflexes, and responds less to stress. It can be complete or partial and allows patients to undergo surgery or other invasive procedures.

Anthracyclines
A class of antibiotic drugs used in chemotherapy* to treat a wide range of cancers.

Anticonvulsant
A drug or other substance used to prevent or stop seizures or convulsions. Also called antiepileptic.

Antidepressant
A drug used to treat depression.

Antiemetic drug
An agent that prevents or reduces nausea and vomiting that may be associated with anticancer therapies. Antiemetic drugs include granisetron, metoclopramide, and ondansetron.

Articular cartilage
A smooth tissue that covers the ends of bones where they come together to form joints. Articular cartilage in joints makes it easier to move. It allows the bones to glide over each other with very little friction.

Biopsy
The removal of cells or tissues for examination by a pathologist*. The pathologist* may study the tissue under a microscope or perform other tests on the cells or tissue. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

Bladder incontinence
Inability to control the flow of urine from the bladder (also called urinary incontinence).

Bowel incontinence
Inability to control the escape of stool from the rectum (fecal incontinence).

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, depending on the location of the cancer.

Cisplatin
A drug used to treat many types of cancer. Cisplatin contains the metal platinum. It kills cancer cells by damaging their DNA and stopping them from dividing. Cisplatin is a type of alkylating agent.

Clinical trial
A research study conducted with patients to evaluate whether a new treatment is safe (safety) and whether it works (efficacy). Clinical trials are performed to test the efficacy of drugs but also non-drug treatments, such as radiotherapy* or surgery, and combinations of different treatments.

Contraindication
Condition or symptom that prevents the administration of a given treatment or procedure to the patient. Contraindications are either absolute, meaning the treatment should never be given to patients with this condition or symptom, or relative, meaning that the risk can be outweighed by the benefits in some patients with this condition or symptom.

Chromosome
An organised structure which encodes genes which are the body's code for characteristics such as hair colour or gender. Human cells have 23 pairs of chromosomes (46 chromosomes in total). Cancer or leukaemia cells often have a chromosomal abnormality which is a change to their chromosomes, such as a chromosomal duplication or an extra chromosome (47 chromosomes) or have a chromosomal deletion or a loss of a chromosome (45 chromosomes). A chromosomal or genetic inversion is when no extra chromosomes are added or deleted, but instead a portion is backwards.

Cryosurgery
Cryosurgery (also called cryotherapy) is the use of extreme cold produced by liquid nitrogen (or argon gas) to destroy abnormal tissue. Cryosurgery is used to treat several types of cancer, and some precancerous or noncancerous conditions.

CT scan / Computed Tomography scan
A form of radiography in which body organs are scanned with X-rays* and the results are processed by a computer to generate images of parts of the body.

Curettage
This is a medical procedure used to remove tissue. An instrument called a curette is used to scrape or scoop out the tissue to be removed.

Cyclophosphamide
A drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. It is also used to treat some types of kidney disease in children. Cyclophosphamide attaches to DNA in cells and may kill cancer cells. It is a type of alkylating agent. Also called CTX.

Dactinomycin
Dactinomycin, also known generically as actinomycin D, is the most significant member of actinomycines, which are a class of polypeptide antitumour antibiotics isolated from soil bacteria of the genus Streptomyces. It is one of the older anticancer drugs, and has been used for many years.

Deep vein thrombosis
The formation of a blood clot in an extremity or lower pelvis. Symptoms may include pain, swelling, warmth, and redness in the affected area. Also called DVT.

Denosumab
A drug used to prevent or treat certain bone problems. It is used to prevent broken bones and other bone problems caused by solid tumours that have spread to the bone. It is also used in certain patients to treat giant cell tumour of the bone that cannot be removed by surgery. It can be used to treat osteoporosis (a decrease in bone mass and density) in postmenopausal women who have a high risk of breaking bones. Denosumab is also being studied in the treatment of other conditions and types of cancer. It binds to a protein* called RANKL, which prevents RANKL from binding to another protein* called RANK on the surface of certain bone cells, including bone cancer cells. This may help keep bone from breaking down and cancer cells from growing.

Docetaxel
Docetaxel belongs to the group of anticancer medicines known as taxanes*. Docetaxel prevents cells from destroying the internal 'skeleton' that allows them to divide and multiply. With the skeleton still in place, the cells cannot divide and they eventually die. Docetaxel also affects non-cancer cells, such as blood cells, which can cause side effects.

Doxorubicin
A drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. Doxorubicin comes from the bacterium Streptomyces peucetius. It damages DNA and may kill cancer cells. It is a type of anthracycline* antitumour antibiotic. Also called doxorubicin hydrochloride and hydroxydaunorubicin.

Etoposide
Etoposide is an anticancer drug that damage cancer cells directly (cytotoxic) which belongs to the topoisomerase inhibitor chemotherapy* drug class. Topoisomerases are proteins required for the unwinding of DNA when cells copy their DNA. Etoposide drug blocks this process and means that cancer cells can't divide. It is given intravenously* or orally in capsule form.

Epirubicin
A drug used together with other drugs to treat early breast cancer that has spread to lymph nodes*. It is also used and studied in the treatment of other types of cancer. Epirubicin is a type of anthracycline* antibiotic. Also called epirubicin hydrochloride.

Fibroblast
A connective tissue cell that makes and secretes collagen proteins.

Gastrointestinal stromal tumours (GIST)
A type of tumour that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant.

Gemcitabine
The active ingredient in a drug that is used to treat pancreatic cancer that is advanced or has spread. It is also used with other drugs to treat breast cancer that has spread, advanced ovarian cancer, and non-small cell lung cancer that is advanced or has spread. It is also used or studied in the treatment of other types of cancer. Gemcitabine blocks cells from making DNA and may kill cancer cells. It is a type of antimetabolite.

Genetic predisposition
An inherited increase in the risk of developing a disease. Also called genetic susceptibility.

Girdle
Either of two more or less complete bony rings at the upper or lower end of the trunk, they support the arms and legs i.e. shoulder and pelvic girdles.

Glucose
Glucose is a monosaccharide sugar that occurs widely in plant and animal tissue. It is the major energy source of the body.

Histopathologic/histopathology
The examination and study of tissue and cells using a microscope. Tissue obtained from the body by biopsy* or surgery is placed in a fixative and transported to the laboratory. Here, it is cut into thin sections, stained with various dyes and then studied under a microscope.

Ifosfamide
A drug that is used with other drugs to treat germ cell testicular cancer that has not responded to previous treatment with other drugs. It is also used and studied in the treatment of other types of cancer. Ifosfamide attaches to DNA in cells and may kill cancer cells. It is a type of alkylating agent and a type of antimetabolite.

Imatinib
Imatinib is a protein-tyrosine kinase inhibitor. This means that it blocks some specific enzymes known as tyrosine kinases. These enzymes can be found in some receptors on the surface of cancer cells, including the receptors that are involved in stimulating the cells to divide uncontrollably. By blocking these receptors, imatinib helps to control cell division.

Inherited (condition)
In medicine, describes the passing of genetic information from parent to child through the genes in sperm and egg cells. Also called hereditary.

Inpatient
A patient whose care requires a stay in a hospital. As opposed to an outpatient*.

Intravenous(ly)
Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein. Also called IV.

Ionizing radiation
A type of radiation made (or given off) by X-ray* procedures, radioactive substances, rays that enter the Earth's atmosphere from outer space, and other sources. At high doses, ionizing radiation increases chemical activity inside cells and can lead to health risks, including cancer.

Irinotecan
Irinotecan is a drug used for the treatment of cancer. Irinotecan prevents DNA from unwinding by inhibition of toposisomerase I. In chemical terms, it is a semisynthetic analogue of the natural alkaloid campthothecin.

Lymph nodes
A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (the fluid that circulates throughout the lymphatic system) and they store lymphocytes (a type of white blood cell). They are located along lymphatic vessels. Also called lymph glands.

Lymphoedema
A condition in which extra lymph fluid builds up in tissues and causes swelling. It may occur in an arm or leg if lymph vessels are blocked, damaged, or removed by surgery.

Lymphoma
Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called Reed-Sternberg cell. The other category is non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin and non-Hodgkin lymphomas can occur in children and adults, and prognosis* and treatment depends on the stage and the type of cancer.

Malignant tumours
Malignant tumours, also called cancers, are composed from malignant transformed cells that usually divide rapidly and have a tendency to spread to other parts of the body.

Margin
The edge or border of the tissue removed in cancer surgery. The margin is described as negative or clean when the pathologist finds no cancer cells at the edge of the tissue, suggesting that all of the cancer has been removed. The margin is described as positive or involved when the pathologist finds cancer cells at the edge of the tissue, suggesting that not all of the cancer has been removed.

Medical oncologist
A doctor who specializes in diagnosing and treating cancer using chemotherapy*, hormonal therapy, biological therapy, and targeted therapy. A medical oncologist is often the main health care provider for someone who has cancer. A medical oncologist also gives supportive care and may coordinate treatment given by other specialists.

Menopause
The time of life when a woman's ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50. A woman is said to be in menopause when she hasn't had a period for 12 months in a row. Symptoms of menopause include hot flashes, mood swings, night sweats, vaginal dryness, trouble concentrating, and infertility.

Metastasis
The spread of cancer from one part of the body to another. A tumour formed by cells that have spread is called a metastatic tumour or a metastasis. The metastatic tumour contains cells that are like those in the original tumour.

Methotrexate
Methotrexate, also known as MTX, is an antimetabolite and antifolate drug. It acts by inhibiting the metabolism of folic acid, which is important for cells to make DNA. It is used in treatment of cancer as well as for rheumatoid arthritis and severe skin conditions, such as psoriasis.

Mitosis
The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes* from the parent cell. This process allows the body to grow and replace cells.

Mucositis
A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth.

Multidisciplinary opinion
A treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient. In cancer treatment, a multidisciplinary opinion may include that of a medical oncologist (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), and a radiation oncologist (who provides cancer treatment with radiation). Also called tumour board review.

Musculoskeletal
Relating to the system that moves the body and maintains its form, composed by bones, muscles, joints, tendons and ligaments.

Mutation
A change in the sequence of base pairs in the DNA that makes up a gene. Mutations in a gene do not necessarily change the gene permanently.

Necrosis
Refers to the death of living tissues.

Negative margin
The edge or border of the tissue removed in cancer surgery. The margin is described as negative or clean when the pathologist* finds no cancer cells at the edge of the tissue, suggesting that all of the cancer has been removed. The margin is described as positive or involved when the pathologist* finds cancer cells at the edge of the tissue, suggesting that all of the cancer has not been removed.

Neurotoxicity
The tendency of some treatments to cause damage to the nervous system.

Notochord
A notochord is a structure which forms the spine in a developing baby in the womb. It appears in embryos as a small flexible rod made from one of the three layers of cells of embryos cells. The notochord has many functional and developmental functions. The most commonly cited functions are as a site of muscle attachment, vertebral precursor, and as a midline tissue that provides signals to the surrounding tissue during development.

Oedema
An abnormal collection of fluid beneath the skin or in a body cavity.

Oral mucosa
The moist, inner lining of the mouth. Glands in the mucosa make mucus (a thick, slippery fluid). Also called mucous membrane.

Oral mucositis
A complication of some cancer therapies in which the mucosal lining of the mouth becomes inflamed. Often seen as sores in the mouth.

Orthopaedic surgeons
A surgeon who specializes in diagnosing and treating injuries and diseases of the musculoskeletal* system. This includes the bones, joints, tendons, ligaments, and muscles.

Osteonecrosis
A disease where bone tissue dies because the blood supply to the bone is impaired.

Osteosarcoma
A cancer of the bone that usually affects the large bones of the arm or leg. It occurs most commonly in young people and affects more males than females. Also called osteogenic sarcoma.

Outpatient
A patient who visits a health care facility for diagnosis or treatment without spending the night. Sometimes called a day patient.

Paediatric oncologist
A doctor who specializes in treating children with cancer.

Pathologist
A doctor specialized in histopathology*, which is the study of diseased cells and tissues using a microscope.

Phantom limb pain
The sensation of pain or other unpleasant feelings in the place of a missing (phantom) limb.

Physiotherapist
A health professional trained to evaluate and treat people who have conditions or injuries that limit their ability to move and do physical activities. Physiotherapists, also called physical therapists, use methods such as exercise, massage, hot packs, ice, and electrical stimulation to help strengthen muscles, relieve pain, and improve movement. They also teach exercises to help prevent injury and loss of motion.

Platelet
Small cell fragments that play a fundamental role in the formation of blood clots. Patients with a low platelet count are at risk of severe bleeding. Patients with a high count are at risk of thrombosis, the formation of blood clots that can block blood vessels and result in stroke or other severe conditions, and can also be at risk of severe bleeding because of platelet dysfunction.

Positive margin
The edge or border of the tissue removed in cancer surgery. The margin is described as positive or involved when the pathologist* finds cancer cells at the edge of the tissue, suggesting that all of the cancer has not been removed.

Primary (bone) tumour (cancer/sarcoma)/site/location
A term used to describe the original, or first, tumour in the body. Cancer cells from a primary cancer may spread to other parts of the body and form new, or secondary, tumours. This is called metastasis. These secondary tumours are the same type of cancer as the primary cancer. Also called primary tumour.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence*.

Radiation oncologist
A specialist treating cancer with radiation. He or she is different from a radiologist* - another specialist who performs imaging tests to diagnose and follow up on different conditions.

Radiolabelled
Tagged with a radioactive substance. Once injected in the body, the progress of the substance can be followed through the body with a detector.

Radiological examination (test)
A test that uses imaging technology (such as radiography, ultrasound*, computed tomography* and nuclear medicine) to visualize organs, structures and tissues within the body to both diagnose and treat diseases.

Radiologist
A doctor who specializes in the diagnosis of disease and injury with the use of imaging devices such as those used for X-rays*, CT scans* or MRIs* (magnetic resonance imaging).

Radiotherapy
A therapy in which radiation is used in the treatment of cancer always oriented to the specific area of the cancer.

Recurrence
Cancer or disease that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen at the same location as the original (primary) tumour or in another area of the body. Also called recurrent cancer or disease.

Red blood cell
The most common type of blood cell. It is the substance that makes the blood appear red. The main function of these cells is the transport of oxygen.

Relapse
The return of signs and symptoms of cancer after a period of improvement.

Rhabdomyosarcoma
A type of sarcoma* that usually begins in muscles that are attached to bones and that help the body move (skeletal muscles). Most rhabdomyosarcomas develop in children, but they can also occur in adults.

Risk factor
Something that increases the chance of developing a disease. Some examples of risk factors for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to radiation or certain chemicals, infection with certain viruses or bacteria, and certain genetic changes.

Sacrum
The large, triangle-shaped bone in the lower spine that forms part of the pelvis. It is made of 5 fused bones of the spine.

Sarcoma
A cancer of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.

Staging
Performing exams and tests to learn about the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment strategy.

Skull base
Bottom part of the skull where the brain rests and at the same time it is the body ridge behind the nose and eyes.

(Molecularly) Targeted therapies
A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific proteins or cellular structures known to be involved in the growth and progression of cancer. Targeted therapy may have fewer side effects than other types of cancer treatments.

Taxane*
Taxanes are drugs that are used to treat cancer as they block cell growth by stopping mitosis* (cell division). Taxanes interfere with microtubules (cellular structures that help move chromosomes* during mitosis*). They are known as mitotic inhibitors or antimicrotubule agents.

Tumour suppressor gene
A type of gene that makes a protein called a tumour suppressor protein that helps control cell growth. Mutations* (changes in DNA) in tumour suppressor genes may lead to cancer. Also called antioncogenes.

Vinca alkaloids
Vinca alkaloids are a set of anti-mitotic and anti-microtubule alkaloid agents originally derived from the vinca plants. Vinca alkaloids are used in chemotherapy for cancer. Acting upon tubulin, they prevent it from forming into microtubules, which are cellular structures that help move chromosomes* during mitosis* and are a necessary component for cellular division.

Vincristine
The active ingredient in a drug used to treat acute leukaemia. It is used in combination with other drugs to treat Hodgkin disease, non-Hodgkin lymphoma*, rhabdomyosarcoma*, neuroblastoma, and Wilms tumour. Vincristine is also used and studied in the treatment of other types of cancer. It blocks cell growth by stopping cell division. It is a type of vinca alkaloid* and a type of antimitotic agent.

White blood cell
Cells of the immune system that are involved in the body's defence against infections.

X-ray
X-rays are a form of radiation used to take images of the inside of objects. In medicine, X-rays are commonly used to take images of the inside of the body.

The ESMO / Anticancer Fund Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types. These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org

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