Cancer Association of South Africa (CANSA)

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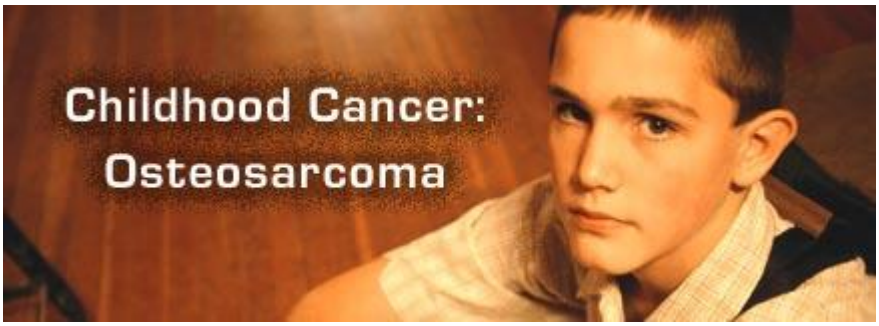
Fact Sheet
on
Childhood Osteosarcoma

Introduction

Osteosarcoma is one of the most common type of bone cancer, and a very common type of cancer in children. Although other types of cancer can eventually spread to parts of the skeleton, osteosarcoma is one of the few that actually begin in bones and sometimes spread (or metastasise) elsewhere, usually to the lungs or other bones.



[Picture Credit: Osteosarcoma]

Because osteosarcoma most often develops from osteoblasts (those cells that make growing bone), it usually affects teenagers who are experiencing a growth spurt. Boys are more likely to develop this disease than girls, and most cases of osteosarcoma involve the knee.

Most osteosarcomas arise from random and unpredictable errors in the DNA of growing bone cells during times of intense bone growth. There currently isn't an effective way to prevent this type of cancer. But with the proper diagnosis and treatment, most kids with osteosarcoma do recover.

Williams, L.A. & Spector, L.G. 2019.

BACKGROUND: Males have worse survival for childhood cancer, but whether this disparity exists among all childhood cancer types is undescribed.

METHODS: We estimated sex differences in survival for 18 cancers among children (0-19 years) in Surveillance, Epidemiology, and End Results 18 (2000-2014). We used Kaplan-Meier survival curves (log-rank *P* values) to characterize sex differences in survival and Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between sex and death for each cancer type. We used an inverse odds weighting method to determine whether the association between sex and death was mediated by stage of disease for solid tumors.

RESULTS: Males had worse overall survival and a higher risk of death for acute lymphoblastic leukemia (HR = 1.24, 95% CI = 1.12 to 1.37), ependymoma (HR = 1.36, 95% CI = 1.05 to 1.77), neuroblastoma (HR = 1.28, 95% CI = 1.09 to 1.51), osteosarcoma (HR = 1.29, 95% CI = 1.08 to

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1.53), thyroid carcinoma (HR = 3.25, 95% CI = 1.45 to 7.33), and malignant melanoma (HR = 1.97, 95% CI = 1.33 to 2.92) (all log-rank *P* values < .02). The association between sex and death was mediated by stage of disease for neuroblastoma (indirect HR = 1.12, 95% CI = 1.05 to 1.19), thyroid carcinoma (indirect HR = 1.24, 95% CI = 1.03 to 1.48), and malignant melanoma (indirect HR = 1.28, 95% CI = 1.10 to 1.49). For these six tumors, if male survival had been as good as female survival, 21% of male deaths and 13% of total deaths after these cancer diagnoses could have been avoided.
CONCLUSIONS: Consideration of molecular tumor and clinical data may help identify mechanisms underlying the male excess in death after childhood cancer for the aforementioned cancers.

Osteosarcoma

Osteosarcoma (also called osteogenic sarcoma) is a cancer of the bone that destroys tissue and weakens the bone. Osteosarcoma develops from immature bone cells that normally form new bone tissue. Osteosarcoma most often starts in the bones around the knee joint, at the lower end of the femur (thigh bone) or the upper end of the tibia (shin bone).

[Picture Credit: Osteosarcoma 2]

The second most common place is in the humerus (upper arm bone close to the shoulder). However, osteosarcoma can develop in any bone in the body. Rarely, it can also occur as a tumour in the soft tissue of the body, outside the bone.

Osteosarcoma is described as either a medullary (central) tumour or a peripheral (surface) tumour. Each has different subtypes. The type and subtype of osteosarcoma is determined by looking at the tumour cells through a microscope. The most common subtype is called conventional central osteosarcoma. The other subtypes are much less common, each accounting for less than 5% of all osteosarcomas.

Medullary osteosarcoma subtypes include:

- Conventional central osteosarcoma
- Telangiectatic osteosarcoma
- Intraosseous well-differentiated (low-grade) osteosarcoma
- Small cell osteosarcoma

Peripheral osteosarcoma subtypes include:

- Parosteal (juxtacortical) well-differentiated (low-grade) osteosarcoma
- Periosteal (low-grade to intermediate-grade) osteosarcoma
- High-grade surface osteosarcoma

Incidence of Childhood Osteosarcoma in South Africa

The South African National Cancer Registry (2017) does not provide any information on the incidence of Osteosarcoma.

Causes of Childhood Osteosarcoma

Osteosarcoma is probably caused by a combination of genetic changes that together cause immature bone cells to become cancer cells instead of developing into bone. The same gene that is commonly abnormal in patients that develop eye tumours called retinoblastoma (the RB gene) may also be associated with osteosarcoma. The RB gene is a 'tumour suppressor' gene that normally controls the growth of cells. When it becomes changed, or mutated, it can no longer control cell growth and tumours can form. Defects in another tumour suppressor gene, P53, can also predispose individuals to osteosarcoma or other cancers. These gene disturbances are very rare.

Despite this information, only a few risk factors for osteosarcoma are known for sure.

- Ionising radiation (X-rays) - there is an increased risk following radiation treatment for a previous cancer. Children who receive X-rays to diagnose a medical condition, such as a broken bone or tooth decay, are NOT at increased risk.
- Genetic syndromes - children with some genetic syndromes are more likely to develop osteosarcoma than other children. The syndromes are hereditary retinoblastoma, Li-Fraumeni syndrome and Rothmund-Thomson syndrome. Children with these genetic conditions are more at risk for osteosarcoma, but these account for only a small fraction of cases. These syndromes usually require medical care, so one would know if one's child had one of them.

According to the current state of medical knowledge, the following things most likely DO NOT increase a child's risk of osteosarcoma:

- Fluoride in drinking water
- Injury to the bone

Further, researchers know that most osteosarcomas develop in people who have no other diseases and no family history of bone cancer. Osteosarcoma may be triggered by an over activity of bone cells. In a very small number of families, siblings of children with osteosarcoma can develop osteosarcoma. These families may be studied to see if a rare genetic defect may be causing the tumour. If such a defect is found, it may help doctors identify other family members that may be at risk and understand the process by which cancer develops in other patients with osteosarcoma.

Symptoms of Childhood Osteosarcoma

Symptoms may be present for weeks, months, or occasionally longer before osteosarcoma is diagnosed. The most common presenting symptom of osteosarcoma is pain, particularly with activity. Patients may complain of a sprain, arthritis, or so-called growing pains. The patient often has a history of trauma, although pathologic fractures are not particularly common. The exception is the telangiectatic type of osteosarcoma, which is commonly associated with pathologic fractures. If pain affects a lower extremity, it may result in a limp.

The patient may have a history of swelling, depending on the size of the lesion and its location. Systemic symptoms, such as fever and night sweats, are rare. Tumoural spread to the lungs rarely results in respiratory symptoms, and such symptoms usually indicate extensive lung involvement. Metastases to other sites are extremely rare; therefore, other symptoms are unusual. Only 15-20% of patients present with metastases, which primarily affect the lungs but can also affect other bones. Manifestations at several bone sites at diagnosis may indicate multifocal sclerosing osteosarcoma.

Osteosarcoma most commonly involves the distal femur (bone of the thigh) and proximal tibia (largest bone in the lower leg), followed by the proximal humerus (bone of the upper arm) and mid and proximal femur. As many as 20% of patients present with tumours of the flat bones of the body including the skull and pelvis. Tumours of the jaw are relatively uncommon.

A diagnosis may not be made right away because the symptoms are common to other health problems.

The following symptoms may be present at the tumour site:

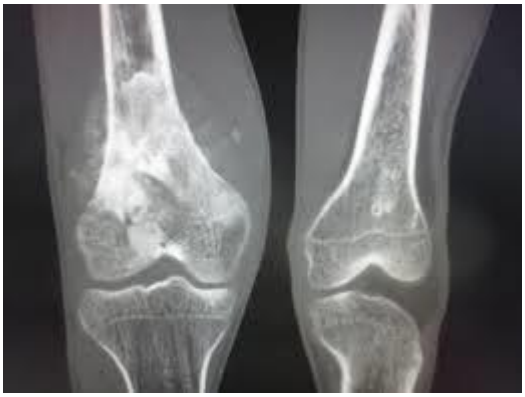
- Chronic pain which may be localised or radiating through parts of the body
- Fatigue
- Fever
- Weight loss
- Anaemia
- Swelling
- Decreased joint motion
- Fracture (broken bone), less common

Physical findings are usually limited to those of the primary tumour site.

- Mass: A palpable mass may be present. The mass may be tender and warm, although these signs are indistinguishable from those of osteomyelitis. Increased skin vascularity over the mass may be discernible. Pulsations or a bruit may be detectable.
- Decreased range of motion: Joint involvement should be obvious on physical examination.
- Lymphadenopathy: Involvement of local or regional lymph nodes is unusual.
- Respiratory findings: Auscultation is usually uninformative unless extensive pulmonary disease is present.

Diagnosis of Osteosarcoma

A delay in diagnosis for childhood osteosarcoma is not uncommon because the symptoms, such as pain and swelling, can be easily mistaken for normal teenager activity.



[Picture Credit: Knee X-ray showing Osteosarcoma]

Many procedures and tests may be performed to see if and where cancer cells are present. If a bone tumour is suspected, it is important that the child is diagnosed and treated by a team experienced in working with children with cancer.

Quite often, your child's primary doctor will have completed some type of X-ray. These exams are often repeated by the specialist who will be looking for specific details of the lump or swelling.

Following an x-ray, a number of other tests may be performed such as:

- CT scan of affected part

- Chest X-ray
- MRI
- Bone scan

The information gained from these tests will help doctors better define the location and size of the cancer, and identify whether it is interfering with other structures in the body. These are helpful pieces of information in making decisions about how to treat the cancer.

In addition to scans, a biopsy will also be performed. During the biopsy, a piece of the tumour is removed and is examined under a microscope by a pathologist to identify the types of cells present. It is imperative that the biopsy be performed by an experienced surgeon with knowledge of sarcomas to assure that the appropriate biologic tests are done on the sample and that the biopsy does not interfere with future surgical planning.

[Picture Credit: Osteosarcoma 3]

Osteosarcomas are described by their location:

- central tumours - arise inside the bone; while
- surface tumours - arise on the outer surface of the bone.

Each type has a number of subtypes. Conventional central osteosarcomas account for the vast majority of osteosarcomas in children and adolescents.

Before treating a tumour, doctors need to know exactly how much of the cancer is present in the body both at the site of the tumour and elsewhere in the body. To evaluate this, a variety of tests may be performed, including scans of other parts of the body, such as the lungs, to see if the tumour has spread.
Doctors use the following terms to describe osteosarcoma and develop treatment plans.

- Localised: the tumour is limited to the bone of origin and the tissue surrounding the tumour; it has not spread to other parts of the body.
- Metastatic: the tumour has spread from where it began to other parts of the body. The most common sites of spread are the lungs or other bones.
- Recurrent: the tumour has come back after treatment. It can recur in the same place that it started, or in another part of the body. The lungs and other bones are the most common sites of recurrent tumours.
- Initial response to therapy: an important prognostic (predictive of treatment success) factor is the patient's response to initial therapy. Patients whose tumour cells have nearly all been eliminated after the initial 10 weeks of chemotherapy have a better outlook than those whose tumour cells do not respond as well to treatment. Investigators are working on finding biological differences that distinguish responsive from unresponsive tumours. If this can be determined at the time of diagnosis, treatment could be targeted better to the tumour and potentially improve the outlook for patients with less responsive tumour types.

Zhang, Z., Liu, C., Liang, T., Yu, C., Qin, Z., Zhou, X., Xue, J., Zeng, H., Lu, Z., Xu, G., Wang, Z., Chen, J., Jiang, J. & Zhan, X. 2020.

Background: In pediatric tumors, immunotherapy exhibits less toxicity than chemotherapy and radiation. The current study aims to identify potential immune targets in immune-related genes of C-C motif chemokine ligand genes (CCLs) and C-C motif chemokine receptors (CCRs) in childhood osteosarcoma (OS) and to explore the underlying molecular mechanisms of childhood OS.
Methods: Firstly, we identified immune-related genes in CCLs and CCRs, these genes were used for functional annotation and interaction analysis. Then, the prognostic value of these genes was evaluated using Kaplan-Meier analysis and multivariate COX regression model. And the potential relationship between risk score and immune infiltrating cells was identified. Finally, gene set enrichment analysis was used to determine the underlying molecular mechanism of OS. Immune-related genes in CCLs and CCRs are inextricably linked.
Results: The results of survival analysis of these genes show that CCL5, CCL8, CCR4, and CCR5 are significantly associated with the prognosis of childhood OS. The combined effect survival analysis shows that the co-high expression of these 4 genes has a good prognosis for childhood OS. A prognostic signature model was constructed based on the 4 genes mentioned above, and the result of time-dependent receiver operating characteristic curves showed that this model was a good predictor of childhood OS 3- and 5-year prognosis. In addition, the risk score of the constructed prognostic signature model was closely related to immune infiltration. We also found that CCL5, CCL8, and CCR5 may affect the prognosis of OS through complex regulation among Toll-like receptor signaling pathway, mitogen-activated protein kinase (MAPK) family signaling cascade, and nuclear factor-kappaB pathway, whereas CCR4 affects the prognosis of OS by regulating eukaryotic translation.
Conclusion: CCL5, CCL8, CCR4, and CCR5 are potential prognostic markers for the prognosis of childhood OS, and the underlying molecular mechanisms of childhood OS have been identified.

Wang, J.Y., Yang, Y., Ma, Y., Wang, F., Xue, A., Zhu, J., Yang, H., Chen, Q., Chen, M., Ye, L., Wu, H. & Zhang, Q. 2020.
"Osteosarcoma (OS) is one of the most common malignant bone tumors in childhood and adolescence. Although great efforts have been made in therapeutic methods for OS, the prognosis is not yet satisfactory and the underlying molecular mechanisms of OS pathogenesis have not been fully explored. Meanwhile, non-coding RNAs, especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), have long been investigated due to their roles as key players in regulating various biological and pathological processes, such as proliferation, apoptosis, cell-cycle, migration, invasion, metastasis, EMT and drug resistance, through targeting their mRNAs transcriptionally or posttranscriptionally. Although, numerous studies have confirmed a complex cross-regulation among lncRNAs, miRNAs and mRNAs, the underlying molecular mechanism has not been elucidated. In this review, we comprehensively summarized the latest research progress of the regulatory relationship among lncRNAs, miRNAs and mRNAs, and highlighted the role of lncRNA-miRNA-mRNA axis in the development of OS to provide novel approaches for cancer diagnosis and treatment."

Grading and Staging of Childhood Osteosarcoma
Grading refers to the appearance of the cancer cells under the microscope, and gives an idea of how quickly the cancer may develop. Low-grade cancer cells are usually slow-growing and less likely to spread.

In high-grade tumours the cells are likely to grow quickly and are more likely to spread. Most osteosarcomas are high-grade, but a type known as parosteal osteosarcoma is usually low-grade.

The 'stage' of a cancer is a term used to describe its size and whether it has spread beyond its original site.

Knowing the particular type and stage of the cancer helps the doctors to decide on the most appropriate treatment. Most patients are grouped depending on whether cancer is found in only one part of the body (localised disease), or whether the cancer has spread from one part of the body to another (metastatic disease).
A commonly used staging for osteosarcomas is described below:

Stage 1A
The cancer is low-grade and is only found within the hard coating of the bone.

Stage 1B
The cancer is low-grade, extending outside the bone and into the soft tissue spaces that contain nerves and blood vessels.

Stage 2A
The cancer is high-grade and is completely contained within the hard coating of the bone.

Stage 2B
The cancer is high-grade and has spread outside the bone and into surrounding soft tissue spaces that contain nerves and blood vessels. Most osteosarcomas are stage 2B.

Stage 3
The cancer can be low-grade or high-grade and is either found within the bone or extends outside the bone. The cancer has spread to other parts of the body, or to other bones not directly connected to the bone where the tumour started.

If the cancer comes back after initial treatment, this is known as recurrent or relapsed cancer.

Treatment of Childhood Osteosarcoma
Treatments for osteocarcoma may involve a combination of therapies including surgery, radiation and/or chemotherapy. In most cases, children receive chemotherapy before surgery (neoadjuvant), a surgical procedure to remove the tumour and additional chemotherapy after surgery (adjuvant). Treatment options will vary greatly, depending on your child's situation. Your child's doctor and other members of your care team will discuss the options with you in-depth. Prompt medical attention and aggressive therapy are important for the best prognosis.

Osteosarcoma surgery - depending on the size and location of the tumour and whether the tumour has spread, the child may receive one of the surgical treatments necessary to combat it including limb salvage surgery, amputation, or a rotationplasty. If the osteosarcoma has spread to other parts of the body, such as the lungs, additional surgery may be required.
Sometimes amputation of the limb is unavoidable if the cancer is affecting the surrounding blood vessels and nerves.

After amputation, a false limb will be fitted and will be regularly adjusted as the child grows. False limbs can work very well. It should be possible for a child to join in with normal activities and even sports.

[Picture Credit: Artificial Limb]

There are two ways that limb-sparing surgery may be done:

- replacing the bone with a prosthesis (a specially designed artificial part)
- replacing the affected bone with bone taken from another part of the body (bone graft).

After this type of surgery, children will usually be able to use their limbs almost normally. However, they are advised not to participate in any contact sports. This is because any damage to the bone graft or prosthesis may require another major operation to repair or replace it.

If a child is growing, the limb prosthesis will need to be lengthened as the bone grows. This may mean there are extra short stays in hospital, although some prostheses can be lengthened as an outpatient procedure.

Chemotherapy for osteosarcoma - chemotherapy is a group of drugs that interfere with the cancer cell's ability to grow or reproduce. Different groups of chemotherapy drugs work in varied ways to fight cancer cells and shrink tumours. Chemotherapy is systemic treatment, meaning it is introduced to the bloodstream and travels throughout the body to kill cancer cells. Chemotherapy can be given orally, as an injection into the muscle or fat tissue, directly to the bloodstream, or with a needle directly into the fluid surrounding the spine.

Prudowsky, Z.D. & Yustein, J.T. 2020.
"Osteosarcoma, the most common bone malignancy of childhood, has been a challenge to treat and cure. Standard chemotherapy regimens work well for many patients, but there remain minimal options for patients with progressive or resistant disease, as clinical trials over recent decades have failed to significantly improve survival. A better understanding of therapy resistance is necessary to improve current treatments and design new strategies for future treatment options. In this review, we discuss known mechanisms and recent scientific advancements regarding osteosarcoma and its patterns of resistance against chemotherapy, radiation, and other newly-introduced therapeutics."

Radiotherapy - radiotherapy may occasionally be given. This treats cancer by using high energy rays to destroy the cancer cells, while doing as little harm as possible to normal cells.

Rehabilitation and supportive care - rehabilitation is an extremely important part of a child's osteosarcoma care. This includes physical and occupational therapy, as well as help adapting to social situations.

Proton therapy - proton therapy is an innovative form of radiation treatment that allows for more precise radiation doses delivered to cancerous tumours. Proton therapy's greatest benefit is that it is less damaging to the surrounding healthy tissue because it delivers most of its energy to a very narrow field at the location of the tumour. Proton therapy is not yet available in South Africa.

Qiu, R., Sun, D., Bai, Y., Li, J. & Wang, L. 2020.
"Osteosarcoma is the most common primary malignant bone tumor in childhood and adolescence. Currently, surgery combined with chemotherapy is the main treatment for osteosarcoma. However, the long-term survival of patients with metastatic osteosarcoma is unsatisfactory. Therefore, new treatment methods to improve the prognosis of patients with osteosarcoma are required. The present study aimed to develop nanocarriers with both tumor targeting and reduction responsiveness abilities, and to improve the therapeutic effect and reduce toxicity by loading traditional small molecule antitumor drugs. The tumor targeting peptide-decorated, doxorubicin (DOX)-loaded mPEG-P(Phe-co-Cys) nanoparticles were developed successfully through the ring-opening polymerization of amino acids. The peptide VATANST (STP) can specifically bind with vimentin, which is highly expressed on the osteosarcoma cell surface, resulting in tumor targeting effects. The nanoparticle is core-shell structured to protect the loaded DOX during blood flow. The disulfide bonds within the nanoparticles are sensitive to the osteosarcoma microenvironment, which has high glutathione (GSH) levels. Under the enhanced permeability and retention and active tumor targeting effects, the STP-decorated DOX-loaded nanoparticles accumulated in tumor tissues. High GSH levels can rupture disulfide bonds, resulting in the controlled release of DOX, which will cause necrosis of tumor cells. The characteristics of the synthesized nanoparticles, DOX release profiles *in vitro* and *in vivo*, cytotoxicity analysis, animal study, and safety evaluation were performed. The nanoparticles could increase the tumor inhibition efficiency against osteosarcoma and reduce the side effects of DOX to major organs. The STP-decorated mPEG-P(Phe-co-Cys) nanoparticles might be a suitable drug delivery system for DOX to treat osteosarcoma."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Brard, C., Piperno-Neumann, S., Delaye, J., Brugières, L., Hampson, L.V., Le Teuff, G., Le Deley, M.C. & Gaspar, N. 2019.

INTRODUCTION: The controversial results on the mifamurtide efficacy associated with chemotherapy, issued from the American INT-0133-study, in localised osteosarcomas, and the underpowered analysis performed separately in metastatic patients, should be clarified to homogenise international use of this promising drug. The European Commission has granted a marketing authorisation to mifamurtide combined with postoperative chemotherapy in localised osteosarcomas but not in metastatic patients, while the Food and Drug Administration (FDA) has denied this authorisation.
METHODS AND ANALYSIS: Sarcome-13/OS2016 trial is a multicentre randomised open-label phase II trial evaluating the survival benefit of mifamurtide administered during 36 weeks in combination with postoperative chemotherapy versus chemotherapy alone, in patients >2 and ≤50 years with newly diagnosed high-risk localised or metastatic osteosarcoma. The main objective is to evaluate the impact on event-free survival (EFS) of mifamurtide on intention-to-treat population. The secondary objectives are to evaluate the impact of mifamurtide on overall survival, to evaluate the feasibility and toxicity of the planned treatment, to correlate biology/immunology with the mifamurtide efficacy/toxicity. With a total of 126 enrolled patients and 51 events, the power is 80% if mifamurtide is associated with an 18% improvement of the 3-year EFS (52%vs70%, equivalent to an HR=0.55), with a one-sided logrank test alpha=10%. As relevant historical data are available (aggregate treatment effect from the INT-0133 trial and individual data from the control group of the Sarcome-09/OS2006 trial), a Bayesian analysis is also planned.
ETHICS AND DISSEMINATION: This study was approved by the 'Comité de Protection des Personnes Ile de France I' (12/06/2018), complies with the Declaration of Helsinki and French laws and regulations, and follows the International Conference on Harmonisation E6 Guideline for Good Clinical Practice. The trial results, even if they are inconclusive, as well as biological ancillary studies will be presented at appropriate international congresses and published in international peer-review journals.
TRIAL REGISTRATION NUMBER: EudraCT 2017-001165-24, NCT03643133.

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Osteosarcoma 2
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Osteosarcoma 3
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