Cancer Association of South Africa (CANSA)

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Fact Sheet on Childhood Sarcoma of Soft Tissue

Introduction

Soft tissue is a broad term often used for mesenchymal tissues that support and surround more well-defined organs and specific tissues. The cells and structures of soft tissue are present throughout the human body. The major cell types of soft tissues are non-epithelial and of mesodermal origin, denoted as 'mesenchymal cells'.

[Picture Credit: Soft Tissue Sarcoma]

In anatomy, soft tissues are the tissues that connect, support, or surround other structures and organs of the body, not being bone. Soft tissue includes tendons, ligaments, fascia, skin, fibrous tissues, fat, and synovial membranes (which are connective tissue), and muscles, nerves and blood vessels (which are not connective tissue).

Soft Tissue Sarcomas

Soft tissue sarcomas are cancerous (malignant) tumours that originate in the soft tissues of the body. Soft tissues connect, support and surround other body structures. The soft tissues include muscle, fat, blood vessels, nerves, tendons and the lining of the joints (synovial tissues). A large variety of soft tissue sarcomas can occur in these areas.

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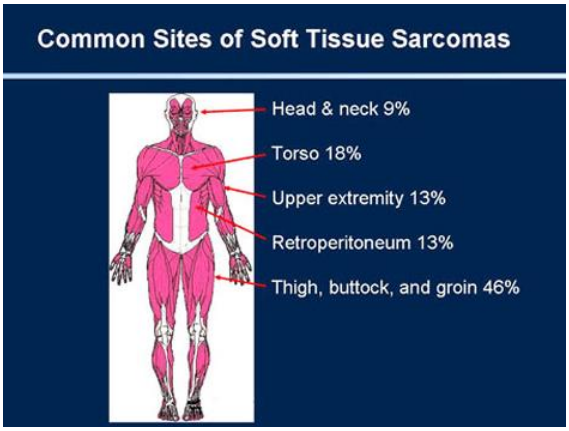
Soft tissue sarcomas are not common. But soft tissue sarcomas are very serious, especially if diagnosed when the disease is more advanced.



[Picture Credit: Soft Tissue Sarcomas]

Although there are various types of soft tissue sarcoma, they generally share similar characteristics, produce similar symptoms and are treated in similar ways.

Tonning Olsson, I., Brinkman, T.M., Wang, M., Ehrhardt, M.J., Banerjee, P., Mulrooney, D.A., Huang, I.C., Ness, K.K., Bishop, M.W., Srivastava, D., Robison, L.L., Hudson, M.M. & Krull, K.R. 2020.
Background: To the authors' knowledge, few studies to date have examined long-term neurocognitive outcomes in survivors of childhood soft-tissue sarcoma.
Methods: A total of 150 survivors (41% of whom were female with a mean current age of 33 years [SD, 8.9 years] and a time since diagnosis of 24 years [SD, 8.7 years]) and 349 community controls (56% of whom were female with a mean current age of 35 years [SD, 10.2 years]) completed comprehensive neuropsychological testing, echocardiography, electrocardiography, pulmonary function tests, endocrine evaluation, and physical examination. Patient-reported outcomes of health-related quality of life (HRQOL) and social attainment were collected. Survivors were compared with norms and controls on neurocognitive outcomes using general linear models, and on HRQOL and social attainment using modified Poisson models. The impacts of treatment and chronic health conditions on outcomes were examined using multivariable general linear models (effect size was expressed as unstandardized β estimates that reflected the unit of change from a mean of 0 and an SD of 1) and modified Poisson models (effect size expressed as relative risks).
Results: Compared with controls and population norms, survivors demonstrated lower performance on measures of verbal reasoning (mean z score, -0.45 [SD, 1.15]; P < .001) mathematics (mean z score, -0.63 [SD, 1.07]; P < .001), and long-term memory (mean z score, -0.37 [SD, 1.14]; P < .001). Cumulative anthracycline exposure (per 100 mg/m^2) was found to be associated with poorer verbal reasoning (β = -0.14 z scores; P = .04), reading (β = -0.09 z score; P = .04), and patient-reported vitality (relative risk, 1.32; 95% CI, 1.09-1.59). Neurologic and neurosensory chronic conditions were associated with poorer mathematics (neurologic conditions: β = -0.63 z score [P = 0.02]; and hearing impairment: β = -0.75 z scores [P < 0.01]). Better cognitive performance was associated with higher social attainment.
Conclusions: Long-term survivors of soft-tissue sarcoma are at risk of neurocognitive problems and poor HRQOL associated with anthracycline treatment and chronic health conditions.

Incidence of Sarcoma of Soft Tissue in South Africa
The National Cancer Registry (2016) does not provide information on Sarcoma of Soft Tissue.

Risk Factors for Sarcoma of Soft Tissue
Some genetic factors and external exposures have been associated with the development of non-Rhabdomyosarcomatous soft tissue sarcoma, including the following:

- **Genetic factors:**

  Li-Fraumeni syndrome: Patients with Li-Fraumeni syndrome (usually due to heritable cancer-associated changes of the *TP53* tumour suppressor gene) have an increased risk of developing soft tissue tumours (mostly nonrhabdomyosarcomatous soft tissue sarcomas), bone sarcomas, breast cancer, brain tumours, and acute leukaemia.

  Familial adenomatous polyposis: Patients with familial adenomatous polyposis are at increased risk of developing desmoid-type fibromatosis.

  ***RB1* gene:** Germline mutations of the *RB1* gene have been associated with an increased risk of developing soft tissue sarcoma, particularly leiomyosarcoma, and the risk appears higher among those younger than 1 year who were treated with alkylating agents.

  ***SMARCB1* gene:** Germline mutations or deletions of the *SMARCB1* (*INI1*) gene are associated with an increased risk of developing extrarenal rhabdoid tumours.

  Neurofibromatosis type 1: Approximately 4% of patients with neurofibromatosis type 1 develop malignant peripheral nerve sheath tumours, which usually develop after a long latency; some patients develop multiple lesions.

  Werner syndrome: Werner syndrome is characterized by spontaneous chromosomal instability, resulting in increased susceptibility to cancer and premature aging. An excess of soft tissue sarcomas has been reported in patients with Werner syndrome.

  Tuberous sclerosis complex: Tuberous sclerosis complex is associated with the development of various tumors showing perivascular epithelioid cell differentiation (PEComas), including lymphangioleiomyomatosis and hepatic and renal angiomyolipomas.

  Adenosine deaminase-deficient severe combined immunodeficiency: Patients with adenosine deaminase-deficient severe combined immunodeficiency have been reported to be at increased risk of developing multicentric dermatofibrosarcoma protuberans, which usually presents at an average age of 8.9 years.

- **External exposures:**

  Radiation: Some nonrhabdomyosarcomatous soft tissue sarcomas (particularly malignant fibrous histiocytoma) can develop within a previously irradiated site.

  Epstein-Barr virus infection in patients with AIDS: Some nonrhabdomyosarcomatous soft tissue sarcomas (e.g., leiomyosarcoma) have been linked to Epstein-Barr virus infection in patients with AIDS.

Lupo, P.J., Luna-Gierke, R.E., Chambers, T.M., Tavelin, B., Scheurer, M.E. Melin, B. & Papworth, K. 2019.
"Perinatal factors have been associated with soft tissue sarcomas (STS) in case-control studies. However, (i) the contributions of factors including fetal growth remain unknown, (ii) these factors have not been examined in cohort studies and (iii) few assessments have evaluated risk in specific STS

subtypes. We sought to identify the role of perinatal and familial factors on the risk of STS in a large population-based birth cohort.

"We identified 4,023,436 individuals in the Swedish Birth Registry born during 1973-2012. Subjects were linked to the Swedish Cancer Registry, where incident STS cases were identified. We evaluated perinatal and familial factors obtained from Statistics Sweden, including fetal growth, gestational age, and presence of a congenital malformation. Poisson regression was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for associations between perinatal factors and STS overall, as well as by common subtypes.

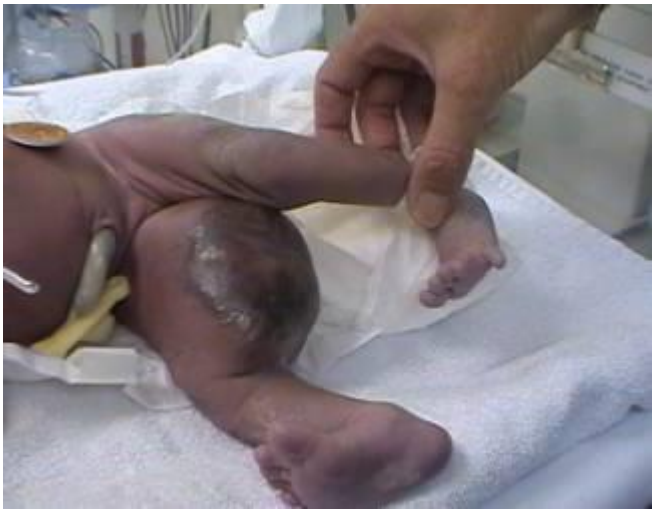
"There were 673 individuals diagnosed with STS in 77.5 million person-years of follow-up. Having a congenital malformation was associated with STS (IRR = 1.70, 95% CI: 1.23-2.35). This association was stronger (IRR = 2.90, 95% CI: 1.25-6.71) in recent years (2000-2012). Low fetal growth was also associated with STS during the same time period (IRR = 1.86, 95% CI: 1.05-3.29).

"Being born preterm was associated with rhabdomyosarcoma (IRR = 1.74, 95% CI: 1.08-2.79). In our cohort study, those with congenital malformations and other adverse birth outcomes were more likely to develop a STS compared to their unaffected contemporaries. These associations may point to disrupted developmental pathways and genetic factors influencing the risk of STS."

Signs and Symptoms of Sarcoma of Soft Tissue

A soft tissue sarcoma usually produces no signs and symptoms in its early stages. As the tumour grows, it may cause:

- A noticeable lump or swelling
- Pain, if it presses on nerves or muscles
- A blockage in the stomach or intestines or gastrointestinal bleeding if the tumour is located in the abdomen or digestive tract



[Picture Credit: Sarcoma of Soft Tissue]

Other signs of soft tissue sarcoma include the following:

- A lump or mass - is the most common soft tissue sarcoma sign. The lump will form in the area in which the tumour is growing, and there may be some pain if it is pressing on a nerve or muscle. Even if the lump isn't painful, if it continues to grow in size, or if it is located deep within an extremity or body cavity, consult your doctor.

- Uncomfortable swelling - is another sign of soft tissue sarcoma, especially when it is located in the arms and legs.

- Limited mobility - can be a symptom of soft tissue sarcoma. Some tumours can restrict motion, such as those found in the hip, knee, shoulder or hands.

- Skin lesions - can occur when a sarcoma tumour breaks through the skin.

Other symptoms may be signs of soft tissue sarcoma, because a sarcoma tumour can form almost anywhere in the body, and can therefore affect a variety of organs.

For example, sarcomas in the abdomen may cause abdominal pain, vomiting or constipation, while sarcomas in the uterus may cause vaginal bleeding and/or abdominal pain. With gastrointestinal stromal tumours (GISTs), you may feel full after eating only very small meals, or you may vomit blood or have dark bowel movements.

Soft tissue sarcomas can occur anywhere in the body, but the most common types of soft tissue sarcomas are gastrointestinal stromal tumours and soft tissue sarcomas that affect the extremities. About 60 percent of soft tissue sarcomas occur in the arms, legs, buttocks, hands or feet. Another 20 percent occur in the chest and abdomen. About 10 percent are found in the head and neck.

Soft tissue sarcomas go by a variety of names, depending on the tissue in which they originate. Examples of some sarcomas and their locations include:

Rhabdomyosarcoma – more common in children, this sarcoma occurs in the skeletal muscle

Leiomyosarcoma – occurs in the smooth muscles – muscles not under voluntary control. Found most commonly in the uterus, gastrointestinal tract or lining of blood vessels.

Haemangiosarcoma – affects blood vessels, especially in areas that have previously received radiation treatment.

Kaposi's sarcoma – a malignancy that occurs in blood vessel walls. Often affects people with immune deficiencies, such as HIV/Aids.

Lymphangiosarcoma – affects the lymph vessels and is sometimes seen in a limb with chronic swelling (lymphoedema). This can be from an area of prior radiation therapy or certain chronic infections.

Synovial sarcoma – tissue around joints such as knees and ankles are affected. Typically occurs in children and young adults.

Neurofibrosarcoma – occurs in the peripheral nerves. The peripheral nervous system (PNS) is the part of the nervous system that consists of the nerves and ganglia outside of the brain and spinal cord.

Liposarcoma – fatty tissue, often in the legs and trunk, is affected.

Fibrosarcoma – fibrous tissue in the arms, legs or trunk may be affected.

Malignant fibrous histiocytoma – a fibrous tissue tumour more likely to occur in the legs.

Dermatofibrosarcoma – grows in the tissue beneath the skin, and often develops in the trunk or limbs.

Diagnosis of Sarcoma of Soft Tissue

The specialist will ask about the patient's general health and any previous medical problems. They will also examine the patient, which will include feeling the area where there is pain or swelling. The patient may be asked to have blood tests and a chest x-ray to check his/her general health.

The doctors will usually ask if they can take a sample of the lump, which will be examined under a microscope. This is known as a biopsy and is the only way to tell whether the lump is a cancerous or non-cancerous (benign) tumour. The patient may have other tests and scans to assess the lump before a biopsy. A biopsy can be done in two ways: a core needle biopsy or a surgical biopsy.

Core needle biopsy - This is when a sample of cells is removed from the lump using a needle. Several samples may be taken.

Before the biopsy is taken, a local anaesthetic is injected to numb the area. If the lump is near the surface of the body and can easily be felt, the doctor will probably just feel it to guide the needle in. If the lump is deep within the body (such as in the abdomen) or is harder to feel, the doctor will use an ultrasound scan or sometimes a CT scan to guide the needle into the right place.

A pathologist (a doctor who specialises in diagnosing disease by looking at body tissue and cells) will look at the cells under a microscope to see whether they are benign or cancerous. If the lump is a sarcoma, further tests may be done on the sample to try to find out exactly what type of sarcoma it is.

Sometimes, particularly with children, the biopsy is done under a general anaesthetic while the patient is asleep.

For most people, a core needle biopsy will show whether the lump is a sarcoma or not. However, sometimes not enough cells are collected to give a clear answer, and then a surgical biopsy is needed.

Surgical biopsy - This is far less commonly used. It will only be done if a core needle biopsy does not give a definite result. A surgical knife (scalpel) is used to open the area and remove a tissue sample from the lump. If the lump is small enough, all of it may be removed.

A surgical biopsy may be done under a local or general anaesthetic, depending on the position of the lump and how deep it is within the body. As with a core needle biopsy, the sample will be sent to the laboratory so that it can be tested. Often a large number of studies will be done even on a very small sample.

It can take up to ten days to get all the results. This can be a worrying time, but it is very important that an accurate diagnosis is made so that the most appropriate treatment can be given. If the lump turns out to be benign, the patient may not need to have any more treatment. If it is cancer, the doctor will discuss the treatment options with the patient and his/her parent(s) or guardian(s).

Grading and Staging of Sarcoma of Soft Tissue

The grade of a cancer gives an idea of how quickly it might grow. Doctors examine the cancer cells under a microscope and see how they compare with normal cells. The grade helps the doctor decide if the patient needs further treatment after surgery.

- Grade 1 or low-grade or well differentiated - The cancer cells look similar to normal cells and usually grow slowly and are less likely to spread.
- Grade 2 or moderate- or intermediate-grade - The cancer cells look more abnormal and are slightly faster-growing.
- Grade 3 or high-grade or poorly differentiated - The cancer cells look very different from normal cells and may grow more quickly.

Grading of soft tissue sarcomas can sometimes be difficult, especially for the less common types. The stage of a cancer describes its size and whether it has spread beyond its original area in the body.

Several different staging systems may be used for soft tissue sarcomas. Two of the most commonly used systems are a number staging system and the TNM staging system.

Elmanzalawy, A., Vali, R., Chavhan, G.B., Gupta, A.A., Omarkhail, Y., Amirabadi, A., Shammas, A. 2020.

Background: Soft-tissue sarcomas in children are a histologically heterogenous group of malignant tumors accounting for approximately 7% of childhood cancers. There is a paucity of data on the value of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) for initial staging and whether PET influenced management of these patients.

Objective: The aim of this analysis is to assess the use of ^{18}F-FDG PET exclusively, and as a supplement to cross-sectional imaging in comparison to typical imaging protocols (CT and magnetic resonance imaging [MRI]) for initial staging as well as therapy planning in pediatric soft-tissue sarcoma patients.

Materials and methods: The list of ^{18}F-FDG PET/CT performed for soft-tissue sarcoma between March 2007 and October 2017 was obtained from the Hospital Information System database. Twenty-six patients who had received ^{18}F-FDG PET, MRI and/or CT at initial diagnosis were included in the study. ^{18}F-FDG PET and concurrent diagnostic CT and MRI at initial staging were independently reviewed to note the number of primary and metastatic lesions detected by each modality. A chart review was conducted to collect information on final diagnosis, staging and treatment plan.

Results: During the study period, 26 patients (15 females) ages 1.3-17.9 years (median age: 6 years) had received ^{18}F-FDG PET/CT at initial diagnosis of soft-tissue sarcoma. Diagnostic CT was available for comparison in all 26 patients and MRI was available in 18 patients. The mean interval between cross-sectional imaging and ^{18}F-FDG PET was 5.9 days (range: 0-30 days). All 26 primary lesions were equally detected by ^{18}F-FDG PET compared to CT and MRI. From 84 metastatic lesions, 16 were detected by PET as well as CT and MRI, 12 by ^{18}F-FDG PET only (included mainly lymph node metastases) and 56 by CT and MRI only (included mainly lung metastases). ^{18}F-FDG PET changed therapy planning in 5 patients out of 26 (19%) by showing additional lesions not detected by CT and MRI.

Conclusion: ^{18}F-FDG PET proved to be a valuable tool for precise initial staging of pediatric soft-tissue sarcoma patients, especially in detecting lymph node metastasis, and could be included in their initial work-up. Given the relative rarity and heterogeneity of this group of tumors, additional investigations are required to definitely establish a role for ^{18}F-FDG PET in the initial staging and therapy planning of soft-tissue sarcoma in the pediatric population.

Treatment of Sarcoma of Soft Tissue

For small, localised sarcomas, surgery is the main treatment and may cure the disease. The patient is likely to have radiotherapy afterwards if your surgeon could not completely remove the sarcoma and

a wide border of healthy tissue with no cancer cells. The radiotherapy helps to stop the cancer coming back.

If the patient has a larger tumour that has not spread, he/she may have radiotherapy or chemotherapy before surgery. This treatment is designed to shrink the sarcoma so that the patient will not need so much surgery. This is only done with particular types of sarcoma such as rhabdomyosarcoma and Ewings sarcoma. Some types of sarcoma do not respond so well and are less likely to shrink.

If the sarcoma has spread, for example to the lungs or liver, the may have surgery to remove the areas of spread. This can help to relieve symptoms and keep the cancer under control for longer. The patient may also have chemotherapy, radiotherapy or any combination of these 3 types of treatment. People with a type of sarcoma called gastrointestinal stromal tumour (GIST) may have the biological therapy drug imatinib (Glivec). If that stops working the doctor may recommend another biological therapy drug called sunitinib (Sutent).

Sandler, G., Yokoi, A. & Hayes-Jordan, A. 2019.
PURPOSE OF REVIEW: Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) is a rare subgroup of malignancy in childhood that is composed of a variety of soft tissue and bony tumors. Prognosis for resectable localized disease is usually good and improved with systemic treatment. However, survival from locally advanced and metastatic disease remains poor. There have been numerous preclinical and clinical studies to define histopathology, biology, and genetic alteration of sarcomas. The purpose of this review is to clarify the progress in the management of NRSTS.
RECENT FINDINGS: Genomic analysis, including the use of next-generation sequencing, has revealed fusion transcripts or specific genetic alterations which provide diagnostic biomarkers and potential targets for novel therapies.
SUMMARY: Most cases are sporadic, but some are associated with genetic predispositions. Most present as a painless mass and diagnosis is frequently delayed because of a low index of suspicion. There is a wide array of histopathological subtypes. Investigations usually involve core, incisional or excisional biopsy for tissue diagnosis, and cross-sectional and nuclear imaging for staging. Management of pediatric sarcoma is largely dependent on the patient's histopathological diagnosis, age, disease stage, and co-morbidities but usually involves a combination of systemic and local therapies. Preclinical studies and phase I/II trials of newer targeted therapies are ongoing.

Surgery

An operation to remove the tumour is the main treatment for most soft tissue sarcomas. The aim of the surgery is to remove as much of the cancer as possible. As well as removing the cancer, the surgeon will remove a good border of surrounding healthy tissue. This is to try to make absolutely sure that they take away the whole sarcoma. The border is usually a few millimetres and is called a healthy margin or clear margin. This means the cancer is less likely to come back in that area. At the same time, the surgeon tries to take away as little healthy tissue as possible, so that the impact of the surgery is as small as possible.

In the past, surgery for sarcomas in the arm or leg often meant removing the affected limb completely (amputation). But there have been big improvements in surgical techniques, such as being able to re-attach tiny blood vessels (microvascular surgery). Or sometimes surgeons repair the operation site with muscle from other parts of the body (a muscle flap) and skin grafts. These improvements mean that amputation can now be avoided in most people and may have limb sparing surgery instead. Fewer than 1 in 20 people diagnosed with sarcoma need amputation these days. Unfortunately, the size and

position of a soft tissue sarcoma in the arm or leg may still mean that amputation is needed in some people.

Surgery is used to remove stage 1, 2 and 3 sarcomas. If surgery to remove a sarcoma is too difficult because of its position in the body, the patient may have radiotherapy instead of surgery. In some areas of the body, radiotherapy may also be difficult because of the risk of damage to vital organs.

Many people have radiotherapy after surgery to try to kill off any remaining sarcoma cells and reduce the risk of the sarcoma coming back. Whether a person needs radiotherapy or not depends to some extent on the grade and size of the sarcoma. Radiotherapy may not be necessary after surgery if the person has:

- A low grade sarcoma
- A very small sarcoma
- A sarcoma that is near the body surface (superficial) and not buried deep in the tissues

In some situations, surgery may also be used to remove sarcoma that has spread to other parts of the body (stage 4). This is most often done when the sarcoma has spread to the lungs or liver. There are also specialist surgical techniques to destroy sarcoma that has spread to the lung or liver.

Radiotherapy

Radiotherapy uses high energy rays to kill cancer cells. A patient may have radiotherapy before or after surgery for sarcoma, or on its own as the main treatment.

Treatment before surgery is called neo adjuvant treatment. The aim is to shrink the tumour so that it is easier to remove. If the treatment is successful, the patient may be able to have a smaller operation than it would otherwise have been. Doctors call this ‘down staging’ the sarcoma.

But doctors use radiotherapy for sarcoma mostly after surgery, to kill off any cancer cells that may have been left behind. They call this adjuvant radiotherapy. If the patient has radiotherapy after surgery, he/she usually begin their treatment between 6 and 12 weeks after operation. This gives the area time to heal before the radiotherapy starts. Radiotherapy treatment may last for up to 7 weeks. The exact time will depend on the type, size and position of the sarcoma.

Sometimes, radiotherapy may be the main treatment for sarcoma – for example with Ewing’s tumours, the patient may have radiotherapy to try to cure the sarcoma. But otherwise radiotherapy is usually used when the position of the cancer makes surgery to remove it too difficult. In this situation, radiotherapy is used to try to control the sarcoma and slow its growth.

Doctors also use radiotherapy to treat symptoms or try to control a sarcoma that has already spread or has come back since it was first treated.

Chemotherapy

Chemotherapy means having anti-cancer drugs. For sarcoma, chemotherapy is mostly used to treat:

- Ewing's sarcomas
- Embryonal or alveolar rhabdomyosarcoma

- Children or young adults with sarcoma
- Sarcomas that have spread

It is not yet clear how helpful chemotherapy is in other situations. A patient may be asked to join a clinical trial if they are offered chemotherapy. Some studies have shown that chemotherapy does not help to reduce the chance of most types of sarcoma coming back after surgery. So chemotherapy is not standard treatment after surgery.

The chemotherapy drugs that doctors most often use to treat soft tissue sarcomas are injected into a vein or given through a drip. The patient may have a single chemotherapy drug or a combination of two or more drugs.

Chemotherapy for soft tissue sarcoma can sometimes be given before surgery to try to shrink the cancer. This may make it easier to remove but is not standard treatment. This is called neoadjuvant chemotherapy. Occasionally people have chemotherapy to shrink their sarcoma before surgery using a technique called isolated limb perfusion. This is a way of giving chemotherapy into just one arm or leg.

Chemotherapy can be used to treat symptoms or try to slow down a cancer that has already spread or has come back since it was first treated. Doctors call this palliative chemotherapy. Research is continuing to try to improve the success of this type of treatment.

Biological therapy

Biological therapy drugs work by stopping a series of chemical reactions that make the cancer cells grow and divide. People with gastrointestinal stromal tumours (GISTs) that have spread may have a biological therapy drug called imatinib (Glivec). Studies have shown that imatinib can work very well at controlling the growth of GISTs for several years or more.

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/

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Sarcoma of Soft Tissue
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Soft Tissue Sarcomas
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