Cancer Association of South Africa (CANSA)

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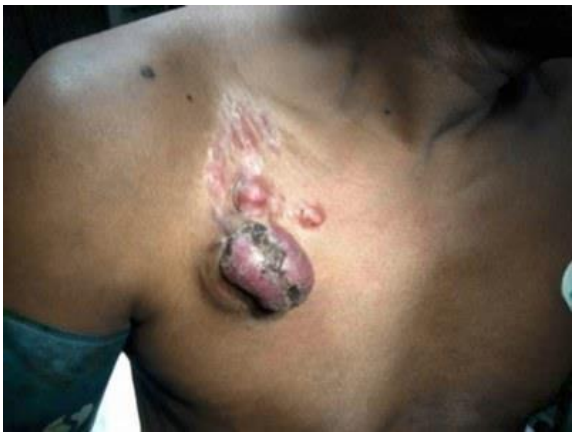
Fact Sheet on Dermatofibrosarcoma Protuberans

Introduction

A sarcoma (from the Greek σάρξ *sarx* meaning "flesh") is a cancer that arises from transformed cells of mesenchymal origin. Malignant tumours made of cancellous bone, cartilage, fat, muscle, vascular, or haematopoietic tissues are, by definition, considered sarcomas. This is in contrast to a malignant tumour originating from epithelial cells, which are termed carcinoma. Human sarcomas are quite rare. Common malignancies, such as breast, colon and lung cancer, are almost always carcinoma. (Wikipedia).



[Picture Credit: Dermatofibrosarcoma Protuberance]

Dermatofibrosarcoma Protuberance

Dermatofibrosarcoma Protuberans (DFSP) is a rare type of cancer, a soft tissue sarcoma that develops in the deep layers of skin. It is sometimes described as having tentacles that can grow into surrounding fat, muscle and even bone. DFSP is most commonly found on the torso, but can also be seen on the arms, legs, head and neck. It has a tendency to recur in the same location after it is removed. However, it only spreads to other parts of the body in about 5% of cases.

DFSP most often starts as a small, firm patch of skin, approximately one to five centimetres in diameter. The skin is occasionally flat or depressed. It can be purplish, reddish or flesh-coloured. The tumour typically grows very slowly (over months to years) and can become a raised nodule.

DFSP tends to affect people between the age of 20 and 50, but it has been diagnosed in people of all ages. The tumours affect black patients about twice as much as white patients. (The Liddy Shriver Sarcoma Initiative).

Rare Variants of Dermatofibrosardoma (DFSP)
There are several variations of DFSP that can be identified under a microscope:

Bednar tumours (pigmented DFSP) - contain dark-coloured cells called melanin-containing dendritic cells. Melanin is the substance that gives skin its colour. As a result, this type of tumour may contain various colours, including red and brown. Bednar tumours account for approximately 1%-5% of all DFSP cases.

Myxoid DFSP - tumours contain an abnormal type of connective tissue that is called myxiod stroma. This type of tumour is uncommon, presents a diagnostic challenge and is important to recognise in order to prevent both under- and over-treatment.

Giant cell fibroblastoma - referred to as juvenile DFSP because it typically affects children and adolescents, is characterised by giant cells in the tumour. It appears to be histologically similar to DFSP and in rare instances can be found within the same tumour in conjunction with DFSP, resulting in a hybrid lesion.

Rarely, the tumours involved in the different types of DFSP can have regions that look familiar to fibrosarcoma, a more aggressive type of soft tissue sarcoma. In these cases, the condition is called Fibrosarcomatous (FS) DFSP. These tumours are more likely to metastasise than tumours in the other types of DFSP.
(British Association of Dermatologists; The Liddy Schriver Sarcoma Initiative)

Incidence of Dermatofibrosarcoma Protuberance in South Africa
The National Cancer Registry (2012) does not provide any information regarding the incidence of Dermatofibrosarcoma Protuberance in South Africa.

Causes and Risks for Dermatofibrosarcoma Protuberance (DFSP)
The cause is unknown, but an injury to the affected skin may be a predisposing factor. Recent advances show tumour cells carry abnormal chromosomes within the tumour cells - t(17;22)(q22;q13) - resulting in the fusion gene COL1A1-PDGFB. This encodes a protein that causes the tumour to grow.

DFSP is rare, and affects less than 1 person in every 100 000 inhabitants per year, It usually presents in early or middle adult life between 20 and 59 years of age, but all ages can be affected. The tumour is rare in children. Males are affected slightly more frequently than females. There would appear to be a racial predilection towards individuals who are classified as black.

Dermatofibrosarcoma protuberans is associated with a rearrangement (translocation) of genetic material between chromosomes 17 and 22. This translocation, written as t(17;22), fuses part of the COL1A1 gene from chromosome 17 with part of the PDGFB gene from chromosome 22. The translocation is found on one or more extra chromosomes that can be either the normal linear shape or circular. When circular, the extra chromosomes are known as supernumerary ring chromosomes. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure. Other genes from chromosomes 17 and 22 can be found on the extra chromosomes, but the role these genes play in development of the condition is unclear. The translocation is acquired during a person's lifetime and the chromosomes containing the

translocation are present only in the tumour cells. This type of genetic change is called a somatic mutation.
(DermNet NZ; The Liddy Shriver Sarcoma Initiative; Genetics Home Reference).

Diagnosis of Dermatofibrosarcoma Protuberance (DFSP)
Although routine imaging is not necessary, magnetic resonance imaging (MRI) may be helpful to evaluate the gross local extent of the tumour and may be important in preoperative planning for larger tumours. As with many other soft tissue tumours, T1-weighted images demonstrate low signal characteristics while T2-weighted images exhibit higher signal. While MRI can adequately delineate the bulk of the tumour, it does not define microscopic tumour extension. Furthermore, it does not clearly define recurrent lesions or lateral infiltration which is typical of this entity. In patients with prolonged or recurrent DFSP or when sarcomatous changes are evident (DFSP-FS (see below)) a CT of the chest should be obtained to evaluate for pulmonary metastases. A CT scan of the local area may be useful if bony involvement is suspected.

Diagnosis is made using either a core needle or an open incisional biopsy. While the role of fine needle aspiration is established in cases of recurrent disease, initial biopsies should be larger samples that demonstrate the histologic architecture of the tumour.

A core needle biopsy (or core biopsy) involves removal of a very small amount of tumour and is performed by inserting a hollow needle through the skin and into the organ or abnormality to be investigated. The needle is then advanced within the cell layers to remove a sample or core. This procedure takes a few minutes to perform and may be undertaken in an outpatient setting.

An incisional biopsy removes only a portion of the tumour for the pathologist to examine. An incisional biopsy is generally reserved for tumours that are larger and offers the pathologist a larger specimen with which to work. This type of biopsy has a slightly higher diagnostic success rate and is usually carried out in the operating room.

An excisional biopsy involves removal of the entire tumour and is typically reserved for very small lesions in which an incisional biopsy or a core needle biopsy is not practical. It is usually performed in cases where removing the entire lesion along with a narrow margin of normal tissue is easily accomplished and tolerated by the patient. This is also often performed in the operating room.
(British Association of Dermatologists; The Liddy Shriver Sarcoma Initiative).

Prognosis of Dermatofibrosarcoma Protuberance (DFSP)
Because DFSP rarely spreads, this cancer has a high survival rate. Treatment is important, though. Without treatment, DFSP can grow deep into the fat, muscle, and even bone. If this happens, treatment can be difficult.
(American Academy of Dermatology).

Treatment of Dermatofibrosarcoma Protuberance (DSFP)
Currently, conventional chemotherapy is rarely used in the treatment of dermato-fibrosarcoma protuberans (DFSP). Limited case reports have not shown any significant value of conventional chemotherapy in the treatment of DFSP.

Radiation therapy (RT) has had a limited role in the past, but, recently, it has been used as an adjunct to surgery. Radiation therapy may be recommended for patients if the margins of resection are positive or for situations in which adequate wide excision alone may result in major cosmetic or functional deficits. Postoperative adjuvant RT may reduce the risk of recurrence when clear surgical margins are not confident. The complete radiation therapy dose ranges from 50-70 Gy. Overall, the risk of severe complications from RT is low. Close follow-up care after radiation therapy is warranted because some DFSP tumours may become more aggressive.

Based on the knowledge that constitutively activated PDGFB-PDGFR-beta signalling pathway plays a central role in the proliferation of DFSP tumour cells, the development of molecularly targeted therapy holds promise as an additional treatment option. Originally approved for the treatment of chronic myelogenic leukaemia, imatinib mesylate has been found to have significant therapeutic value in the treatment of DFSP. Imatinib is a potent and specific inhibitor of several protein-tyrosine kinases, including the platelet-derived growth factor (PDGF) receptors.

On October 19, 2006, the US Food and Drug Administration granted approval for imatinib mesylate (Gleevec) as a single agent for the treatment of DFSP. Imatinib mesylate is indicated for the treatment of adult patients with unresectable, recurrent, and/or metastatic DFSP. The recommended oral dose is 800 mg/d.

With limited clinical data to date, a response rate of approximately 65% has been achieved among DFSP patients treated with imatinib. A small subset of DFSP patients lacking the classic t(17,22) gene aberration seems to have no response to imatinib.

Neoadjuvant imatinib therapy for DFSP has been proposed in recent studies. Using imatinib as a preoperative therapy agent in locally advanced or recurrent DFSP may decrease tumour load, promote tumour cell apoptosis, and subsequently reduce the extent of surgery. Caution should be used when applying such a therapeutic strategy, because the potential exists for creating a skip area wherein discontiguous tumour may obscure the accurate pathology assessment of surgical margins.
(Medscape).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

<u>Types of Clinical Trials</u>
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is

processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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