Cancer Association of South Africa (CANSA)

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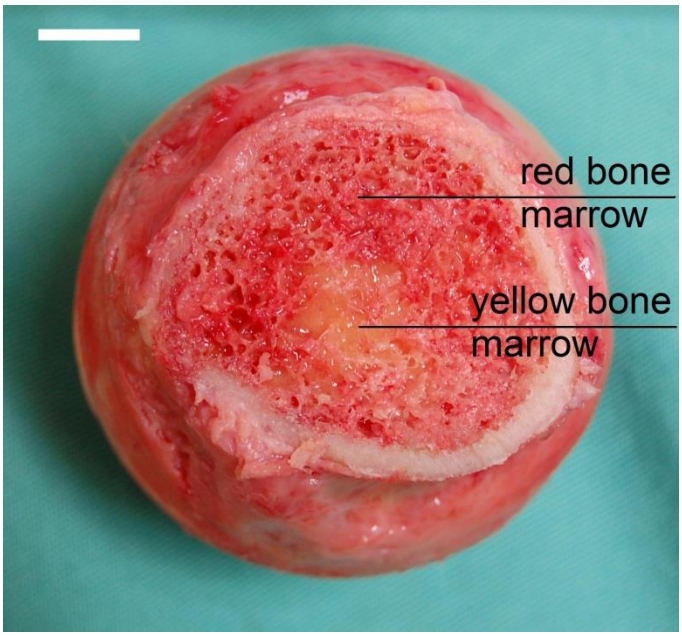
Fact Sheet
on
Multiple Myeloma

Introduction

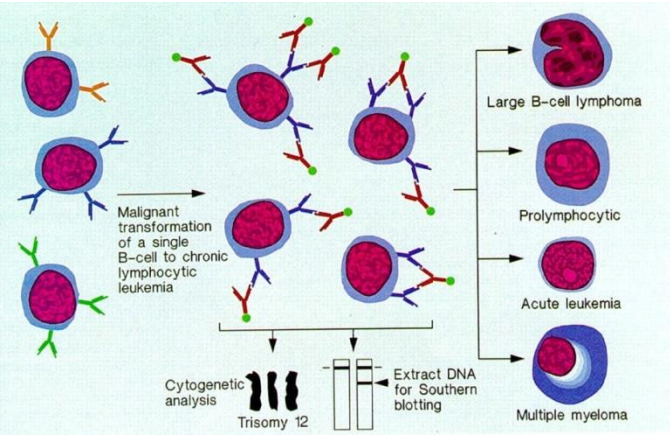
Multiple myeloma, also known as myeloma, is a haematologic cancer, or cancer of the blood.



[Picture Credit: Bone Marrow]

Multiple myeloma develops in the bone marrow, the soft, spongy centre of most bones. Myeloma typically occurs in bone marrow with the most activity, in the marrow in the spine, pelvic bones, ribs and area of the shoulders and hips. Many blood cells are produced in the bone marrow; myeloma affects plasma cells, cells that produce immunogobulins (antibodies) that help fight infection and disease.

[Picture Credit: Malignant Myeloma Cells]



In multiple myeloma, normal plasma cells transform into malignant myeloma cells and produce large quantities of an abnormal immunoglobulin called monoclonal (M) protein. The malignant cells also crowd out and inhibit the production of normal blood cells and antibodies in the bone marrow. In addition, groups of myeloma cells cause other cells in the bone marrow to remove the solid part of the bone and cause soft spots in the bone. These soft spots, also called osteolytic lesions, and other signs

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Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

of bone loss are common with myeloma, although they do not occur in all individuals with myeloma.

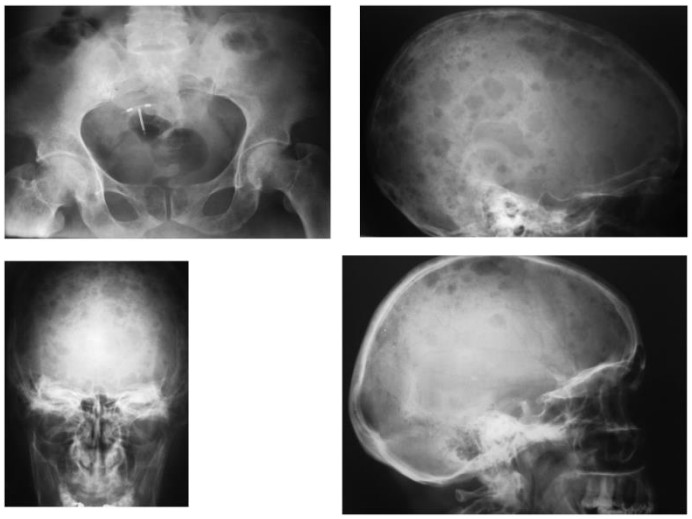
Kumar, S.K., Raikumar, V., Kyle, R.A., van Duin, M., Sonneveld, P., Mateos, M.V., Gay, F. & Anderson, K.C. 2017. Multiple myeloma. *Nat Rev Dis Primers*. 2017 Jul 20;3:17046. doi: 10.1038/nrdp.2017.46.

"Multiple myeloma is a malignancy of terminally differentiated plasma cells, and patients typically present with bone marrow infiltration of clonal plasma cells and monoclonal protein in the serum and/or urine. The diagnosis of multiple myeloma is made when clear end-organ damage attributable to the plasma cell proliferative disorder or when findings that suggest a high likelihood of their development are present. Distinguishing symptomatic multiple myeloma that requires treatment from the precursor stages of monoclonal gammopathy of undetermined significance and smouldering multiple myeloma is important, as observation is the standard for those conditions. Much progress has been made over the past decade in the understanding of disease biology and individualized treatment approaches. Several new classes of drugs, such as proteasome inhibitors and immunomodulatory drugs, have joined the traditional armamentarium (corticosteroids, alkylating agents and anthracyclines) and, along with high-dose therapy and autologous haemopoietic stem cell transplantation, have led to deeper and durable clinical responses. Indeed, an increasing proportion of patients are achieving lasting remissions, raising the possibility of cure for this disease. Success will probably depend on using combinations of effective agents and treating patients in the early stages of disease, such as patients with smouldering multiple myeloma."

Osteolytic Lesions

Osteolytic lesions, also called osteoclastic lesions or lytic lesions (for short), are characteristic areas of damage caused by myeloma. When myeloma invades bone tissue, it causes weak areas to form. In addition, the myeloma cells release chemicals that also lead to bone breakdown. The result is lesions with a specific 'punched-out' appearance that may occur in any bone in the body, but are most often noted in the spine, skull, pelvis and ribs.

[Picture Credit: Osteolytic Lesions]



Incidence of Multiple Myeloma in South Africa

According to the National Cancer Registry (2014) the following numbers of Myeloma cases were histologically diagnosed in South Africa during 2014. Histologically diagnosed means that a specimen (biopsy) was taken and forwarded to a recognised laboratory where a specially trained pathologist confirmed a diagnosis of cancer.

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	172	1:969	0,47%
Asian males	2	1:3 282	0,22%
Black males	71	1:1 770	0,64%
Coloured males	14	1:971	0,34%
White males	84	1:390	0,41%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	175	1:1 090	0,46%
Asian females	6	1:849	0,52%
Black females	74	1:1 830	0,46%
Coloured females	34	1:568	0,83%
White females	61	1:567	0,37%

The frequency of histologically diagnosed cases of Myeloma in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	0	1	9	29	44	49	29	11
Asian males	0	0	0	1	0	1	0	0
Black males	0	0	6	15	22	17	7	3
Coloured males	0	0	0	2	6	4	1	1
White males	0	0	3	10	16	25	21	7

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	0	2	5	18	39	54	43	11
Asian females	0	0	0	1	0	2	3	0
Black females	0	2	3	10	18	18	14	4
Coloured females	0	0	2	4	6	10	8	3
White females	0	0	0	3	15	19	17	4

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Symptoms of Multiple Myeloma

Myeloma may not cause any symptoms in the early stages of the disease. Occasionally, it is diagnosed following a routine blood test before any symptoms develop. When symptoms do occur, they are mostly caused by a build-up of abnormal plasma cells in the bone marrow, and by the presence of the para-protein in the blood.

Bone pain - The most common symptom of myeloma is bone pain. About 70% of people complain of lower back pain, or pain in their ribs. The pain happens because too many abnormal plasma cells are crowding out the bone marrow, which can damage the bone. Other bones may be affected too, such as the skull or pelvis.

Kim., C., Bhatta, S., Cyprien, L., Fonseca, R. & Hernancez, R.K. 2018.
"Skeletal-related events (SREs) are common bone complications in multiple myeloma (MM). However, there are few real-world reports of their incidence. In this study, a database of oncology electronic health records was linked to administrative claims data. Patients identified were aged ≥18 years and newly diagnosed with MM, had ≥1 clinic visit within 1 month of diagnosis, and ≥1 year of follow-up after diagnosis. The study period was January 1, 2011 to December 31, 2016. 343 patients were included, 35% of whom had a baseline history of any SRE. During a median follow-up of 25.7 months, 34% of patients experienced SREs after diagnosis. Median time to SRE was 167 days. Among patients experiencing an SRE, 68% had an SRE within the first year. The incidence rate of SREs at 1 year following MM diagnosis for patients with baseline history was 103/100 person-years (PY) versus 16/100PY for patients without baseline history. SRE incidence rates within 3 months of initiating a line of therapy increased with subsequent lines (line 1: 81/100PY, line 2: 118/100PY, line 3: 150/100PY). Risk of SREs was similar across different anti-MM regimens, including proteasome inhibitor-based regimens. These results highlight the importance of continued surveillance and management of MM-associated bone disease."

Other symptoms may include:

- tiredness and fatigue due to a lack of red blood cells (anaemia)
- kidney problems, which are caused by the para-proteins produced by the myeloma cells. They can also cause tiredness and anaemia
- repeated infections, particularly chest infections, due to a shortage of normal antibodies
- loss of appetite, feeling sick, constipation, depression and drowsiness, which are caused by too much calcium in the blood (hypercalcaemia)
- unexplained bruising and abnormal bleeding, for example nosebleeds or bleeding gums, due to a reduced number of platelets in the blood
- weight loss

If a person has any of these symptoms, it is important to see a doctor as soon as possible. Many of these symptoms can also occur in other conditions - most people with these symptoms will not have multiple myeloma.

Causes and Risk Factors for Multiple Myeloma
No cause for myeloma has so far been identified. Some research has suggested possible associations with a decline in the immune system, specific occupations, exposure to certain chemicals (heavy metals), and exposure to radiation. Exposure to herbicides, insecticides, petroleum products, heavy metals, plastics, and various dusts including asbestos also appear to be risk factors for the disease. However, none of these associations is strong, and in most cases, multiple myeloma develops in individuals who have no known risk factors.

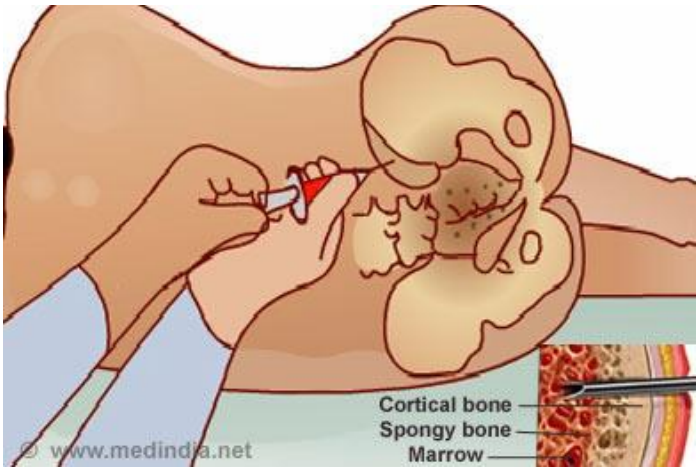
Genetic factors may also be involved in the development of multiple myeloma. Learn more about genetic abnormalities in multiple myeloma. Researchers believe that multiple myeloma is most likely the result of several factors acting together. The most significant risk factor for multiple myeloma is age, as 96% of cases are diagnosed in people older than 45 years, and more than 63% are diagnosed in people older than 65 years.

Diagnosis of Multiple Myeloma
The following tests may be done to diagnose multiple myeloma:

A blood test called serum protein electrophoresis separates the blood proteins and can detect the presence of monoclonal proteins (M proteins) — referred to as an "M spike" — in the blood.

Other tests may include:

- Imaging - X-rays of the skeleton can show whether the bones have any thinned-out areas (osteolytic lesions), common in multiple myeloma. If a closer view of the bones is necessary, the doctor may use magnetic resonance imaging (MRI), computerised tomography (CT) scanning or positron emission tomography (PET) scanning.
- Bone marrow examination - the doctor may also conduct a bone marrow examination (biopsy) by using a needle to remove a small sample of bone marrow tissue. The sample is then examined under a microscope to check for myeloma cells. A portion of the sample is also tested for chromosome abnormalities using tests such as fluorescence *in situ* hybridisation (FISH).



[Picture Credit: Bone Marrow Biopsy]

- Tests may also be done to measure the rate at which the plasma cells are dividing.

Staging of Multiple Myeloma
Staging is the process of finding out how much the cancer has advanced. It is important for treatment options and prognosis.

Treatment of Multiple Myeloma
Because currently there is no known cure for multiple myeloma, understanding the standard treatments - and the treatment options - is critical in attempting to prolong survival and maintain the patient's overall functional ability and quality of life. Aspects of importance in the treatment of multiple myeloma may include:

- Which patients with multiple myeloma are candidates for an approach known as ‘watchful waiting’, where the progress of the disease is monitored carefully but no specific treatment is required
- The various phases in the treatment of multiple myeloma for patients whose disease has progressed to the point where treatment becomes necessary. These treatment phases are grouped into the following categories:
  - initial or induction chemotherapy
  - consolidation therapy
  - maintenance therapy
  - salvage therapy

- The role of stem cell transplantation in the management of patients with multiple myeloma, including the risks and benefits of this procedure
- The treatment options available to patients with multiple myeloma who experience a relapse or recurrence of the disease after initially having gone into remission
- The role of plasmapheresis - the direct removal of abnormal antibody proteins from the bloodstream - in the management of patients with multiple myeloma
- A detailed overview of the risk of infections in people with multiple myeloma, including practical recommendations for reducing the risks of developing potentially life-threatening bacterial, viral, and fungal infections
- The treatment options that are available for the management of patients with multiple myeloma who develop myeloma bone disease - areas of bone destruction caused by multiple myeloma that significantly increase the risk of developing pathologic fractures
- The prognosis (outlook) for people with multiple myeloma and important prognostic factors that have a significant impact in predicting the overall chances of recovery and survival
- The role of complementary therapies in the management of people with multiple myeloma
- Quality of life issues such as sleep disorders, fatigue, weight loss, and psychological stress that often confront people with multiple myeloma and tips for how to minimize their impact and better cope with these important issues

If one has multiple myeloma and is not experiencing any symptoms, he/she may not need treatment. However, the doctor will regularly monitor the patient's condition for signs the disease is progressing. If it is, the patient may need treatment. If one is experiencing symptoms, treatment can help relieve pain, control complications of the disease, stabilise the condition and slow the progress of the disease.

Treatments for Multiple Myeloma may Include:
Though there's no cure for multiple myeloma, with good treatment results one can usually return to near-normal activity.

Chemotherapy. Chemotherapy may be given orally or given through an intravenous (IV) injection. Chemotherapy is often given in cycles over a period of months, followed by a rest period.

Corticosteroids. Corticosteroids, such as prednisone and dexamethasone, have been used for decades to treat multiple myeloma. They are typically given in pill form.

Stem cell transplantation. This treatment involves using high-dose chemotherapy along with transfusion of previously collected immature blood cells (stem cells) to replace diseased or damaged marrow.

Stadtmauer, E.A., Pasquini, M.C., Blackwell, B., Hari, P., Bashey, A., Devine, S., Efebera, Y., Ganguly, S., Gasparetto, C., Geller, N., Horowitz, M.M., Koreth, J., Knust, K., Landau, H., Brunstein, C., McCarthy, P., Nelson, C., Qazilbash, M.H., Shah, N., Vesole, D.H., Vij, R., Vogl, D.T., Giralt, S., Somlo, G. & Krishnan, A. 2019.
PURPOSE: Single-cycle melphalan 200 mg/m^2 and autologous hematopoietic cell transplantation (AHCT) followed by lenalidomide (len) maintenance have improved progression-free survival (PFS) and overall survival (OS) for transplantation-eligible patients with multiple myeloma (MM). We designed a prospective, randomized, phase III study to test additional interventions to improve PFS

by comparing AHCT, tandem AHCT (AHCT/AHCT), and AHCT and four subsequent cycles of len, bortezomib, and dexamethasone (RVD; AHCT + RVD), all followed by len until disease progression.
PATIENTS AND METHODS: Patients with symptomatic MM within 12 months from starting therapy and without progression who were age 70 years or younger were randomly assigned to AHCT/AHCT + len (n = 247), AHCT + RVD + len (n = 254), or AHCT + len (n = 257). The primary end point was 38-month PFS.
RESULTS: The study population had a median age of 56 years (range, 20 to 70 years); 24% of patients had high-risk MM, 73% had a triple-drug regimen as initial therapy, and 18% were in complete response at enrollment. The 38-month PFS rate was 58.5% (95% CI, 51.7% to 64.6%) for AHCT/AHCT + len, 57.8% (95% CI, 51.4% to 63.7%) for AHCT + RVD + len, and 53.9% (95% CI, 47.4% to 60%) for AHCT + len. For AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len, the OS rates were 81.8% (95% CI, 76.2% to 86.2%), 85.4% (95% CI, 80.4% to 89.3%), and 83.7% (95% CI, 78.4% to 87.8%), respectively, and the complete response rates at 1 year were 50.5% (n = 192), 58.4% (n = 209), and 47.1% (n = 208), respectively. Toxicity profiles and development of second primary malignancies were similar across treatment arms.
CONCLUSION: Second AHCT or RVD consolidation as post-AHCT interventions for the up-front treatment of transplantation-eligible patients with MM did not improve PFS or OS. Single AHCT and len should remain as the standard approach for this population.

Radiation therapy. This treatment uses high-energy penetrating waves to damage myeloma cells and stop their growth.

Treatments for relapsed or treatment-resistant multiple myeloma

Most people who are treated for multiple myeloma eventually experience a relapse of the disease. In some cases, none of the currently available, first line therapies slow the cancer cells from multiplying. If the patient experiencea a relapse of multiple myeloma, the doctor may recommend repeating another course of the treatment that initially helped. Another option is trying one or more of the other treatments typically used as first line therapy, either alone or in combination.

Kehrer, M., Koob, S., Strauss, A., Wirtz, D.C. & Schmolders, J. 2017.
Background: Multiple myeloma is a haematological blood cancer of the bone marrow and is classified by the World Health Organisation (WHO) as a plasma cell neoplasm. In multiple myeloma, normal plasma cells transform into malignant myelomacells and produce large quantities of an abnormal immunoglobulin called monoclonal protein or M protein. This ultimately causes multiple myeloma symptoms such as bone damage or kidney problems. The annual worldwide incidence of multiple myeloma is estimated to be 6-7/100,000 and accounts for 1% of all cancer. In Germany, there are about 6,000 cases of newly diagnosed multiple myeloma per annum. In the current era of new agents, such as immunomodulatory drugs and proteasome inhibitors and antibodies, enormous progress has been achieved in the therapy of multiple myeloma. In orthopaedics, it is essential to be able to recognise the of alarming symptoms of multiple myeloma in clinical routine and to be aware of basic diagnostic features to confirm this disease. Surgical treatment of myeloma-related bone lesions - such as stabilisation of pathological fractures - is an important domain of tumour orthopaedic surgery.
Methods: A comprehensive literature search was performed in PubMed using the keywords "multiple myeloma" and "diagnostic" or "therapy". This served to evaluate the available primary and secondary literature on the current status of the diagnostic testing and therapy of multiple myeloma. Systematic reviews, meta-analyses and clinical studies as well as international recommendations in therapy were included until the spring of 2016.

Results: There are now very sensitive screening methods for the diagnosis of multiple myeloma. Accurate diagnosis is generally based on several factors, including physical evaluation, patient history, symptoms, and diagnostic testing results. The standards for initial diagnostic tests are determined by blood and urine tests as well as a bone marrow biopsy and skeletal imaging, such as X-rays, CT scans and MRI scans. Major and minor criteria are required to confirm the diagnosis of multiple myeloma and help to determine the classification and staging of multiple myeloma, and whether it is smoldering myeloma (asymptomatic), symptomatic myeloma, or a monoclonal gammopathy of undetermined significance (MGUS). Multiple myeloma treatment options have increased significantly over the last 10 years. Standard of basic myeloma treatment consists of high dose chemotherapy in combination with autologous stem cell transplantation. Several factors may determine multiple myeloma treatment, such as age and general health, results of laboratory and cytogenetic (genomic) tests as well as symptoms and disease complications. After evaluation of these factors, an individual and often multimodal treatment plan is created and implemented in interdisciplinary cooperation. Conventional treatment options have to be evaluated for older patients (> 70 - 75 years), who are not eligible for high dose chemotherapy and autologous stem cell transplantation due to their age and/or severe comorbidities. It is essential to include supportive therapy in the integral treatment concept, in order to control pain or retain function or mobility. Supportive drugs such as bisphosphonates but also radiation therapy and orthopaedic surgery may be required in order to manage complications of the disease as well as side effects of treatment.
Conclusion: Current studies show promising results in the treatment of multiple myeloma, due to new agents such as immunomodulatory drugs, proteasome inhibitors and antibodies, which may improve prognosis and survival rate among myeloma patients in the future. However treatment algorithms have become more complex and expensive.

Immunotherapy:
Treating Multiple Myeloma by means of immunotherapy is still in its infrancy.

Htut, M. 2019. Immunotherapeytic approaches for Multiple Myeloma: where are we now? *Curr Hematol Malig Rep*. 2019 Jan 21. doi: 10.1007/s11899-019-0492-z. [Epub ahead of print]
PURPOSE OF REVIEW: The treatment landscape for multiple myeloma has evolved rapidly with the availability of multiple new drugs; however, although patient survival has improved, the disease remains incurable. Multiple myeloma is characterized by the unregulated growth of malignant plasma cells accompanied by immune dysfunction as well as disrupted immune surveillance mechanisms. Here, we analyze clinical modalities, with a focus on monoclonal antibodies and adoptive cellular therapy that enhance patients' immune systems and overcome these defects.
RECENT FINDINGS: Early clinical trials with PD-1 inhibitors were promising, but randomized phase III trials with immunomodulatory drugs showed increased toxicities. Monoclonal antibodies targeting surface antigens led to substantial clinical efficiency in relapsed myeloma. Chimeric antigen receptor (CAR) T cell therapy for multiple myeloma represents a significant advance, as exciting and dramatic responses in early clinical trials have been seen. Immunotherapeutic approaches are promising and can augment or replace the current standard of care, with the potential to offer extended survival for myeloma patients.

Treating Complications of Multiple Myeloma
Because multiple myeloma can cause a number of complications, one may also need treatment for those specific conditions.

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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Ms Stacy Erholtz
https://www.google.co.za/search?q=Ms+Stacy+Erholtz&source=lnms&tbm=isch&sa=X&ei=S7eaU9X5HK-v7Aba5YH4Bg&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=4df2T2uKhj37LM%253A%3BgXM8ecwVmZ7pgM%3Bhttp%253A%252F%252Fi2.cdn.turner.com%252Fcnn%252Fdam%252Fassets%252F140518151715-newsroom-intv-stacy-erholtz-cancer-survivor-00010306-story-top.jpg%3Bhttp%253A%252F%252Fwww.cnn.com%252F2014%252F05%252F15%252Fhealth%252Fmeasles-cancer-remission%252F%3B640%3B360

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National Cancer Institute
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Osteolytic Lesions
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