Cancer Association of South Africa (CANSA)

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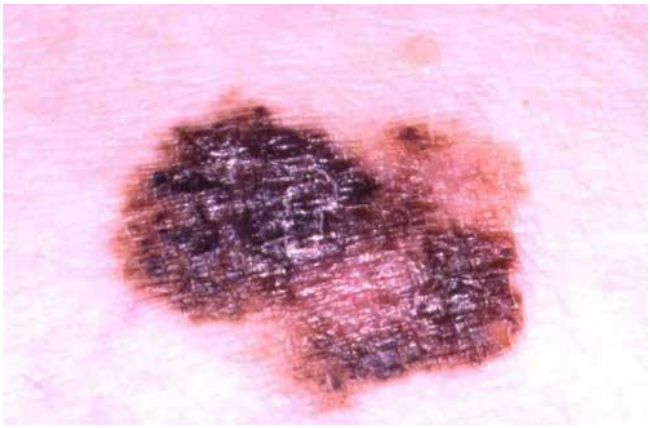
Fact Sheet on Malignant Melanoma of the Skin

Introduction

Malignant melanoma of the skin, (sometimes referred to as only melanoma) is the most dangerous form of skin cancer.



[Picture Credit: Melanoma Picture]

These cancerous growths develop when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation from the sun or tanning beds) triggers mutations (genetic defects) that lead the skin cells to multiply rapidly and form malignant tumours. These tumours originate in the pigment-producing melanocytes in the basal layer of the epidermis. Melanomas often resemble moles. Some melanomas develop from moles. The majority of melanomas are black or brown, but they can also be skin-coloured, pink, red, purple, blue or white. Melanoma is caused mainly by intense, occasional UV exposure (frequently leading to sunburn), especially in those who are genetically predisposed to the disease.

Lodde, G., Zimmer, L., Livingstone, E., Schadendorf, D. & Ugurel, S. 2020.
"Malignant melanoma is an aggressive skin cancer that originates from cells of the melanocytic lineage and is associated with an invasive growth pattern and early spread. Besides endogenous risk factors such as fair skin type or genetic disposition for the formation of multiple nevi, exposure to ultraviolet light is the most important exogenous risk factor. Treatment of patients with primary tumors includes the complete excision of the primary lesion with appropriate safety margins and in patients with an increased risk of metastasis sentinel lymph node excision. Prognostically significant parameters are the Breslow invasion depth, ulceration of the primary lesion, and sentinel lymph node status. Systemic therapy plays an important role in the adjuvant setting and for inoperable tumors. Depending on the indication and the molecular profile of the tumor tissue, immune checkpoint inhibitors or targeted kinase inhibitors can be used and may result in a significant prolongation of survival times."

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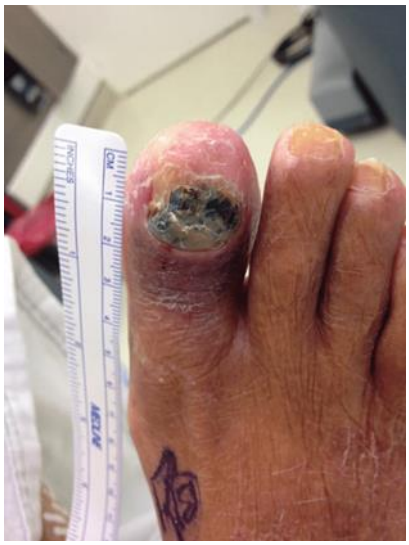
Laudicella, R., Barotto, L., Minutoli, F., Baldari, S. & Jagaru, A. 2020.
Background: Cutaneous malignant melanoma is a neoplasm whose incidence and mortality are dramatically increasing. 18F-FDG PET/CT gained clinical acceptance over the past 2 decades in the evaluation of several glucose-avid neoplasms, including malignant melanoma, particularly for the assessment for distant metastases, recurrence and response to therapy.
Objective: To describe the advancements of nuclear medicine for imaging melanoma with particular attention to 18F-FDG-PET and its current state-of-the-art technical innovations.
Methods: A comprehensive search strategy was used based on SCOPUS and PubMed databases. From all studies published in English, we selected the articles that evaluated the technological insights of 18FFDG- PET in the assessment of melanoma.
Results: State-of-the-art silicon photomultipliers based detectors ("digital") PET/CT scanners are nowadays more common, showing technical innovations that may have beneficial implications for patients with melanoma. Steady improvements in detectors design and architecture, as well as the implementation of both software and hardware technology (i.e., TOF, point spread function, etc.), resulted in significant improvements in PET image quality while reducing radiotracer dose and scanning time.
Conclusion: Recently introduced digital PET detector technology in PET/CT and PET/MRI yields higher intrinsic system sensitivity compared with the latest generation analog technology, enabling the detection of very small lesions with potential impact on disease outcome.

Iglesias-Pena, N., Paradela, S., Tejera-Vaquerizo, A., Boada, A. & Fonseca, E. 2019.
"Cutaneous melanoma (CM) causes more deaths than any other skin tumor, and incidence and mortality rates have risen in recent years, especially in patients of advanced age. There are differences in the biological behavior of CM tumors in the elderly as well as differential management of the disease, evidently influenced by such factors as limited life expectancy, the high incidence of concomitant conditions in older patients, and issues of quality of life unrelated to CM itself. We review relevant current literature on the epidemiology, etiology, pathogenesis, and immunology of CM as well as research on the clinical features, prevention, and management of these tumors in the elderly."

Incidence of Skin Cancer Among Individuals of Colour
Most skin cancers are associated with ultraviolet (UV) radiation from the sun or tanning beds, and many people of colour are less susceptible to UV damage thanks to the greater amounts of melanin in the skin of individuals with a darker skin. Melanin is the protective pigment that gives skin and eyes their colour, however, people of colour can still develop skin cancer from UV damage.



[Picture Credit: Acral lentiginous melanoma]

Additionally, certain skin cancers are caused by factors other than UV - such as genetics or other environmental influences - and may occur on parts of the body rarely exposed to the sun. For example, darker-skinned people are more susceptible to acral lentiginous melanoma (ALM), an especially virulent form of melanoma (the deadliest type of skin cancer) that typically appears on the palms of the hands and soles of the feet.

Acral lentiginous melanoma (ALM) accounts for about 5% of melanoma cases, and is a leading cause of skin cancer deaths. The disease initially appears as a bruise or nail streak on the skin. Most patients do not notice ALM until it has already begun to spread aggressively throughout the body. Bob Marley was killed from this form of malignant tumour under his toenail. ALM (also called subungual melanoma) affects people of Asian or African descent more than any other race or ethnicity.

Laikova, K.V., Oberemok, V.V., Krasnodubets, A.M., Gal'chinsky, N.V., Useinoa, R.Z., Novikov, I.A., Temirona, Z.Z., Gorlov, M.V., Shyed, N.A., Kumeiko, V.V., Makalish, T.P., Bessalova, E.Y., Fomochkina, I.I., Esin, A.S., Volkov, M.E. & Kubyshkin, A.V. 2019.
"Skin cancer has always been and remains the leader among all tumors in terms of occurrence. One of the main factors responsible for skin cancer, natural and artificial UV radiation, causes the mutations that transform healthy cells into cancer cells. These mutations inactivate apoptosis, an event required to avoid the malignant transformation of healthy cells. Among these deadliest of cancers, melanoma and its 'younger sister', Merkel cell carcinoma, are the most lethal. The heavy toll of skin cancers stems from their rapid progression and the fact that they metastasize easily. Added to this is the difficulty in determining reliable margins when excising tumors and the lack of effective chemotherapy. Possibly the biggest problem posed by skin cancer is reliably detecting the extent to which cancer cells have spread throughout the body. The initial tumor is visible and can be removed, whereas metastases are invisible to the naked eye and much harder to eliminate. In our opinion, antisense oligonucleotides, which can be used in the form of targeted ointments, provide real hope as a treatment that will eliminate cancer cells near the tumor focus both before and after surgery."

Incidence of Malignant Melanoma of the Skin in South Africa
The National Cancer Registry does not provide any information regarding the incidence of Malignant Melanoma of the Skin. The National Cancer Registry of 2017 provides combined statistics of all forms of Malignant Melanoma independent of where in the body it occurs.

According to Krige (2010) there are distinct differences in malignant melanoma of the skin between black and white populations regarding the incidence, anatomical distribution, histogenetic types of melanoma, stage at presentation and prognosis.

In South Africa, the incidence of malignant melanoma is 15 times less among dark skinned individuals than in among the white population. In fair or light-skinned populations, more than 90% of melanomas occur in sun-exposed skin whereas 60% of melanomas among Africans arise in non-sun-exposed skin, involving in particular, plantar, palmar, subungual (under the nail) and mucosal surfaces.

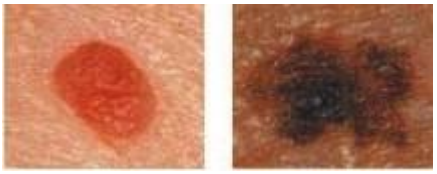
The volar and subungual areas are the most common anatomical sites of malignant melanoma in black populations, with 70% of malanomas found on the lower limb and 90% of melanomas on the leg occurring below the ankle. These views are supported by Hudson & Krige (1995).

The ABCDE of Malignant Melanoma of the Skin

Moles, brown spots and growths on the skin are usually harmless — but not always. Anyone who has more than 100 moles is at greater risk for melanoma. The first signs can appear in one or more atypical moles. That is why it is so important to get to know one's skin very well and to recognize any changes in the moles on your body. Look for the ABCDE signs of melanoma, and if you see one or more, make an appointment with a physician immediately.

A - Asymmetry

Should one draws a line through the picture of the mole on the right, the two halves will not match.

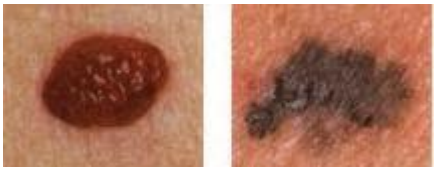


B - Border

The border of the mole on the right is uneven. The edges may be scalloped or notched.

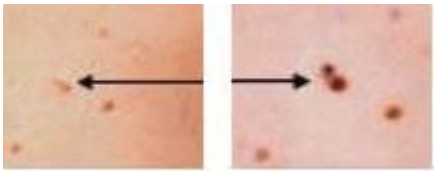
C - Colour

Having a variety of colours is another warning signal. A number of different shades of brown, tan or black could appear. A melanoma may also become red, blue or some other colour.



D - Diameter

Melanomas usually are larger in diameter than the size of the eraser on an ordinary pencil (6 mm), but may sometimes be smaller when first detected.



E - Evolving

Any change — in size, shape, colour, elevation, or another trait, or any new symptom such as bleeding, itching or crusting — points to danger.

Other warning signs are:

- A sore that does not heal
- A new growth
- Spread of pigment (colour) from the border of a spot to surrounding skin

- Redness or a new swelling beyond the border
- Change in sensation – itchiness, tenderness, or pain
- Change in the surface of a mole – scaling, oozing, bleeding, or the appearance of a bump or nodule

Metastatic Melanoma
"Metastatic" means that the melanoma has spread to one or more parts of one's body. It is also referred to as 'advanced' or 'Stage IV' Melanoma.

Although it cannot be cured, it can be treated. Melanoma starts in the cells that make melanin, the pigment that gives colour to one's skin. It can spread anywhere in the body, but it first tends to go to the lymph nodes (a network of glands that fight infection) near where it formed.

From there it can travel to organs like the brain, lungs, liver, and bones, as well as other areas of the skin -- including places far away from where it started (what doctors call the "primary site").

Causes of Melanoma - the sun's ultraviolet (UV) rays are the main cause. Artificial sunlight (such as from tanning beds) can also trigger melanoma of the skin. UV radiation damages the DNA in skin cells, prompting them to multiply rapidly and become cancer. Melanoma can happen after intense UV exposure (think of very bad sunburns), especially in people whose genes put them at risk for the disease. But it can also happen due to everyday UV exposure, without burning, over a long time.

Anyone can get melanoma, including people with dark skin.

- It is more likely if one is white, especially if one has light hair and eyes
- One has had many blistering sunburns, especially as a child or teenager
- One has several large or many small moles, including beauty marks and brown blemishes
- Unusual moles run in one's family
- If anyone in one's family has already had any type of skin cancer
- One's immune system is weak

DeWane, M.E., Kelsey, A., Oliveiro, M., Rabinovitz, H. & Grant-Kels, J.M. 2019.
"There are multiple, genetically distinct pathways that give rise to melanoma. Melanomas on sun-damaged skin (MSDS), including lentigo maligna and desmoplastic melanoma, have distinct genetic profiles and are uniquely linked to chronic ultraviolet exposure. In this article, we discuss the etiologies of lentigo maligna and desmoplastic melanoma, emerging diagnostic adjuncts that might be helpful for accurately identifying these lesions, and the clinical relevance of their frequent co-occurrence. We present unique and overlapping features of these entities and discuss challenges in MSDS management, including margin assessment, excision, and the potential role of nonsurgical therapy. Last, we address the role of immunotherapy in invasive disease. Understanding MSDS as distinct from melanoma arising on intermittently sun-exposed or sun-protected skin will ultimately help optimize patient outcomes."

Parts of the Body Affected by Melanoma - melanoma is often found on the belly, back, head, or neck in men, and on the arms and legs in women. But it can happen anywhere on the skin, including places that one might not expect, like the palms of one's hands, fingernails, the bottoms of one's feet, scalp, and even the genitals.

Symptoms - melanomas often resemble moles, and some develop from moles. Most are black or brown, but they can also be skin-coloured, pink, red, purple, blue, or white. Sometimes a change to an existing mole or to normal skin is the first warning sign of advanced melanoma.

Other clues depend on where the cancer has spread to:

- Lymph nodes - they may feel hard, swollen, and painful
- Skin - one may notice hardened lumps under one's skin
- Lungs - one may be breathless or have a cough that does not get better
- Liver - one may feel pain in the right side of the belly (under the lower right ribs) or not have one's usual appetite
- Bones - one may feel an ache in one's bones
- Brain - warning signs may include a headache that does not go away, weakness or numbness in one's arms or legs, seizures, and changes in the personality or mood

Other symptoms can include unexpected weight loss, and feeling very tired or not well in general. All of these symptoms can be caused by other conditions, so it is important to see a doctor to find out what is going on.

Darmawan, C.C., Jo, G., Montenegro, A.E., Kwak, Y., Cheol, L., Cho, K.H. & Mun, J-H. 2019.
"Acral lentiginous melanoma is a distinct subtype of melanoma on acral skin. Patient presentation at later stages and delayed diagnosis by physicians contribute to a worse associated prognosis and survival rate. Despite our progress in understanding the key features of this disease, the diagnosis of early-stage acral melanoma is still challenging. It is essential to integrate clinical, dermoscopic, and histologic findings in the diagnosis of acral lentiginous melanoma. In addition, molecular studies can be helpful. In this review, we have summarized our current understanding of this disease entity from articles that were published between 1969 and 2018. We have outlined clinical and dermoscopic features as well as pathologic and molecular findings regarding acral melanoma and have presented an algorithm for diagnosis. Understanding and integrating these characteristics may assist clinicians in the early detection of acral melanomas."

Screening for Malignant Melanoma of the Skin
Consider the following screening options:

- *Skin examinations by a trained professional* - during the skin examination the professional person will conduct a head-to-toe inspection of the skin. This may include an examination with the use of a Dermascope. This type of examination is currently offered by the Cancer Association of South Africa (CANSA).

- *Skin examinations done at home* - a self-examination may help in determining where moles, freckles and other skin marks are on the skin. One can then, on a regular basis, inspect one's skin with the purpose of noticing any changes. It is best to do this standing in front of a full-

length mirror while using a hand-held mirror to inspect hard-to-see areas. Be sure to check the fronts, backs and sides of the arms and legs. In addition, check the groin, scalp, fingernails, soles of the feet and spaces between the toes. It is often helpful to get a family member to assist in checking hard-to-see areas.

Diagnosing Malignant Melanoma of the Skin

Sometimes malignant melanoma of the skin can be detected simply by looking at the skin, but the only way to accurately diagnose melanoma is by doing a biopsy. In this procedure, all or part of the suspicious mole or growth is removed, and a pathologist analyses the sample under a microscope.

Where Melanoma may Spread to in the Body

Should Melanoma spread (metastasise) it will most probably spread as indicated below:

Cancer Type:	Main Sites of Metastasis (Spread)
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung
Colorectal	Liver, lung, peritoneum (lining of abdomen)
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum (lining of abdomen)
Pancreas	Liver lung, peritoneum (lining of abdomen)
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum (lining of abdomen), ovaries
Thyroid	Bone, liver, lung
Uterus	Bone, liver, lung, peritoneum (lining of abdomen), vagina
Non-melanoma skin cancer	Very rare: lymph nodes, lung, bone (if in head/neck region)

Treatment of Malignant Melanoma of the Skin

The best treatment for each individual patient depends on the stage of the malignant melanoma, age and overall health of the patient.

Treating early-stage melanomas

Treatment for early-stage melanomas usually includes surgery to remove the melanoma. A very thin melanoma may be removed entirely during the biopsy and require no further treatment. It may, however, be necessary for the doctor to remove the melanoma as well as a small border of normal skin and a layer of tissue beneath the skin. For people with early-stage melanomas, this may be the only treatment needed.

Treating melanomas that have spread beyond the skin

If the melanoma has spread beyond the skin, treatment options may include:

Surgery - surgery is used to remove affected lymph nodes. If the melanoma has spread to nearby lymph nodes, the surgeon may remove the affected nodes. Other additional treatments, before or after surgery, may also be recommended by the treating doctor.

Wollina, U. & Brzezinski, P. 2019.
Cutaneous melanoma is an aggressive neoplasia of melanocytes. Prognosis is dependent on tumor stage. Stage IV melanoma is characterized by the occurrence of distant metastases. Response of metastases to classical chemotherapy is limited and toxicity of treatment is high. In recent years, new developments in immunotherapy and targeted therapies improved prognosis of stage IV melanoma patients with better tolerability of treatment. There is no dispute about surgical treatment of primary melanoma. But what is the value of metastasectomy in the era of new systemic treatments? This review aims to discuss available data for surgical removal of distant metastases for several organs and tissues. The available evidence suggests that for selected patients with possible complete resection of all tumor metastases, metastasectomy remains an effective treatment option with a benefit in overall survival.

Puza, C.J., Bresslet, E.S., Terando, A.M., Howard, J.H., Brown, M.C., Hanks, B., Salama, A.K.S. & Beasly, G.M. 2019.
Background: The emergence of immune checkpoint inhibitors (ICIs) has improved survival for patients with metastatic melanoma. The types of disease-response patterns to ICI therapy can be more complex relative to traditional chemotherapy and include mixed responses, pseudoprogression, and oligoprogression. The potential benefit of surgery after incomplete response to ICI therapy has not been explored. The purpose of this study was to explore outcomes of surgery after ICI therapy in patients with metastatic melanoma.
Methods: A retrospective study was conducted at two centers and included patients with melanoma who underwent surgery after treatment with monotherapy or combination therapy with anti-programmed cell death protein (PD) 1 and/or anti-cytotoxic T-lymphocyte associated protein (CTLA)-4 checkpoint blockade.
Results: Of 25 patients, nine received anti-CTLA-4 therapy, eight received anti-PD-1 therapy, and eight received both anti-CTLA-4 and anti-PD-1 therapies before surgery. Five patients were treated in the adjuvant setting and developed new lesions, whereas 20 patients were treated for metastatic disease and underwent surgery for persistent disease on imaging after ICI therapy. Twenty-five patients underwent 30 operations without complications. Twenty-seven of 30 masses were confirmed to be melanoma on pathology, one was a desmoid tumor and two were necrosis. At a median follow-up of 14.2 months, 2 patients died, 8 were alive with a known disease, and 15 continued to have no further evidence of disease.
Conclusions: Surgery was well tolerated in this cohort of patients receiving ICI therapy for melanoma. Surgery may benefit select patients with an oligoprogressive disease after ICI therapy. After a mixed response, surgery remains the only definitive method to render some patients free of disease.

Chemotherapy - chemotherapy uses drugs to destroy the cancer cells. Chemotherapy can be given intravenously, in pill form or both so that it travels throughout the body. Chemotherapy can be given via a vein in the arm or leg in a procedure called isolated limb perfusion.

Goggins, C. & Khachemoune, A. 2019.
"Electrochemotherapy (ECT) is a treatment modality that combines low-dose chemotherapy with electroporation, thereby enhancing cytotoxicity. ECT was first utilized in the treatment of metastatic

head and neck cancer. Today it is used as a local treatment for the cutaneous and subcutaneous metastases of a variety of cancers, including melanoma. In addition, recent evidence indicates that ECT in combination with immunotherapy can lead to a systemic tumor response. This review aims to summarize the efficacy of ECT in the treatment of metastatic melanoma, with a specific focus on the combination of ECT with immunotherapy."

Radiation therapy - this treatment uses high-powered energy beams, such as X-rays, to kill cancer cells.

Biological therapy - biological therapy boosts the immune system to help the body fight the cancer.

Targeted therapy - targeted therapy uses medications designed to target specific vulnerabilities in cancer cells.

Reducing the Risk for Malignant Melanoma of the Skin

Many cases of skin cancer, including malignant melanoma, can be prevented by following the following precautions:

- Avoid midday sun. Avoid the sun when its rays are the strongest. For most places, this is between about 10:00 and 15:00. Because the sun's rays are strongest during this period, try to schedule outdoor activities for other times of the day, even in winter or when the sky is cloudy.

- Use a good quality sunscreen. Use a broad-spectrum sunscreen, preferably one with the CANSA Seal of Recognition.

- Wear protective clothing. Sunscreens don't provide complete protection from UV rays, so wear tightly woven clothing that covers your arms and legs and a broad-brimmed hat, which provides more protection than a baseball cap or visor does.

- Avoid tanning beds. Tanning beds emit UV radiation, which can increase the risk of skin cancer.

- Become familiar with the skin so changes can be noticed easily. If anything unusual is noticed, make an appointment with a doctor and point it out to him/her.

- Refer to the *CANSA Fact Sheet on Solar Radiation and Skin Cancer* – available on CANSA's Website: www.cansa.org.za

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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Melanoma Picture
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