

Review on Melanoma Skin Cancer Treatment by Cold Atmospheric Plasma

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Abstract— Melanoma is known as the most serious type of skin cancer and the risk of melanoma seems to be around people under 40, especially women. Warning signs of skin cancer can help ensure that cancerous changes are discovered and cured before cancer has spread. Melanoma can be cured successfully if it is detected early. In this review, we discussed the causes, risk factors and prevention methods of melanoma skin cancer, which may lead to early detection of melanoma among people. In addition, this review also shows the stages of melanoma and how to treat melanoma skin cancer. We also highlighted the new suggested skin cancer treatment using cold atmospheric plasma.

Index Terms— Melanoma Skin Cancer; New Melanoma Treatment; Possible Side Effects Melanoma Treatment; Stages Of Melanoma.

I. INTRODUCTION

Skin cancer is the most widely recognized cancer type. According to Malaysia's Third National Cancer Registry (2003-2005) which reveals that skin cancer is the most common cancer growth in Malaysia, representing 2.6% of all cases [1]. Unlike various types of cancer, skin cancer is not widely considered in Malaysia, and there is little awareness among the general population. The World Health Organization (WHO) reports that the occurrence of skin melanoma cancer has evolved over the last decade [1]. The case of melanoma infection will increase 132,000 cases a year.

A. Overview of Melanoma Skin Cancer

Melanoma is a type of skin cancer that usually starts in a certain type of skin cell. It is a disease in which cancer cells form in melanocytes. Melanocytes are cells that make melanin and it's found in the lower part of the epidermis. Melanin is a pigment that gives the skin a natural color. When the skin is exposed to sunlight or any artificial light, melanocytes make more pigment and cause the skin to become dark.

Melanoma skin cancer can grow anywhere on the skin, however they may start in storage space (middle and back) in men and women's legs. Neck and face are another normal places that melanoma can grow.

Melanoma skin cancer will grow deeper into human skin. This causes melanoma has several stages from the epidermis to the dermis of human skin. The treatment of melanoma is in accordance with its respective stages.

Melanoma skin cancer occurs more frequently in people with fair skin. For people without a history of skin cancer in their families, no studies have been done to test the

helpfulness of routine screening for melanoma. Dermatologists do not recommend skin cancer examinations, but because melanoma is a serious, sometimes deadly disease, early detection and treatment is very important. The dermatologist can perform a test called 3-D photography to screen the entire body[2]. Everyone has the risk of melanoma, but the increased risk relies upon a few factors which are sun exposure, number of moles on the skin, type of skin and family history (genetics).

Being exposed to the sun is dangerous to the skin, and can promote skin cancer, including melanoma[2]. The best way to avoid melanoma is to decrease the duration that we are exposed to the sun. There are two categories of moles which are normal moles and atypical moles [2]. Atypical moles can be a sign of melanoma, and situates us at increased risk of melanoma.

As with all skin cancers, people with more fairer skin are at high risk. Genetics plays a major role in melanoma skin cancer. Approximately one in every 10 patients detected has family members with a history of melanoma skin cancer. If our parents, siblings or children have melanoma, we are in a family that is easy to have melanoma skin cancer [2]. If melanoma skin cancer are present in our family, we can protect ourselves and our children with great caution to discover early warning signs and find cancer when it is easiest to treat.

B. Stages of Melanoma Skin Cancer

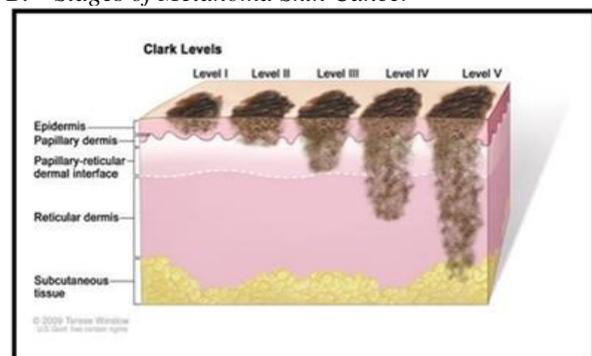


Figure 1: Stages of melanoma skin cancer. Adapted with permission from National Cancer Institute by Terese Winslow. Copyright (2009)

Classifications for melanoma skin cancer are called stages as shown in Figure 1. Stage referring to the thickness of melanoma skin cancer has spread. Staging is used to determine the treatment. Early melanoma skin cancer, stage I cancer means the melanoma cancer cells are not penetrating under the skin surface. The melanoma skin cancer cells are

only in the surface of the skin, while stage II means there is melanoma skin cancer cells are in the layer under the epidermis [3]. Stage III means the melanoma skin cancer cells are throughout the dermis and touching on the next layer down (the reticular dermis) [3]. More advanced melanoma skin cancer (Stages IV and V) has extended into the deep dermis and has grown into the layer of fat under the skin respectively.

II. TREATING MELANOMA SKIN CANCER

The treatments recommended by dermatologist depends on the stages of melanoma skin cancer. This section discusses the treatments that will be considered for each stage of melanoma. Usually, stage I and II are treated by the surgery. It will remove cancer as well as a part of normal skin around it [3]. For some patients with stage II and their lymph nodes containing cancer, they may be advised to use an adjuvant therapy after surgery [3]. Other drugs or vaccines are also recommended to support the treatments for stage II.

Stage III patients require the removal of primary cancer along with the lymph nodes [3]. Adjuvant therapy can also help maintain some cancer from coming back. Another option is to provide radiation therapy to areas where the lymph nodes are removed, especially if many areas contain cancer[3]. Stage IV and V melanoma skin cancer are often difficult to treat because it already spread to the lymph nodes or another part of the body[3]. It often is treated by surgery or radiation therapy.

Immunotherapy can also help patients with stage IV and V live longer. High doses seem to be effective but it also has worse side effects [3]. In addition, chemotherapy can also help but other treatments are usually tried first. Although chemotherapy shrinks cancer, it usually begins to grow again in a few months [3]. Although an advanced stage of melanoma skin cancer is hard to treat, people or cancer patients respond well to the treatment and survive for years after diagnosis.

III. POSSIBLE SIDE EFFECTS FROM SUGGESTED MELANOMA SKIN CANCER TREATMENT

For melanoma skin cancers treatment, there are a few suggested treatment such as surgery, immunotherapy, targeted therapy, chemotherapy and radiation therapy[22]. Each of the treatment will be used according to suitable stages of melanoma skin cancer. If not suitable, there will be a possible side effect faced by the patients.

A. Surgery

Surgery is the primary treatment option for most melanoma skin cancer that usually treats the initial stage of melanoma. Many patients are not interested in this choice as it may leave scarring even though it helps ensure that cancer has been removed or not left the cancerous cells behind. In some cases, this is painful especially for wide excision. However, some doctors feel it can prolong the life of the patient and at least avoid the pain that may be due to increased cancer.

B. Immunotherapy

Stimulating your own immune system to recognize and destroy cancer cells more effectively and also known as immunotherapy is one of the choices of melanoma treatment[22]. This option uses several types of drugs and

keeps the cancer cells from attacking normal cells in the body. The most common side effects of this drug include fatigue, diarrhea, skin rash and itching[22]. For patients, especially women may be required to undergo this choice as it may damage their skin and this is the reason why patients do not want to undergo surgery.

C. Targeted Therapy

Targeted therapy used the drug to target melanoma cells which makes it different from normal cells[22]. This option works differently from the chemotherapy process and also has less severe side effects such as fatigue and hair loss[22]. Although it provides some common side effects but can sometimes have serious effects including heart rhythm problems, severe liver problems and allergic reactions[22]. Targeted therapies are the least preferred method of treating melanoma as a result of potentially serious side effects.

D. Chemotherapy

Chemotherapy is a common option for treating cancer including skin cancer[3,22]. It uses a drug that kills cancer cells. Drugs are injected into the veins or taken by the mouth as a pill. They move through the blood flow to all parts of the body and attack cancer cells that have spread out of the skin. It does not work but it can relieve symptoms or extend life to some patients. Similar to immunotherapy and targeted therapy, chemotherapy also provides some side effects such as hair loss, diarrhea and fatigue[3,22]. This seems to give a second even for patients to choose this treatment.

E. Radiation Therapy

Radiation therapy uses high-energy radiation such as x-rays or particles to kill cancer cells[22]. Radiation therapy is not often used to treat melanoma on the skin, although it is sometimes used if surgery is not an option for some reasons especially diabetes mellitus patients. Side effects of radiation are usually restricted to areas with radiation. Common side effects may include skin color changes, hair loss, nausea and fatigue[22].

The suggested melanoma treatment showed several advantages and disadvantages toward patients. Then, all melanomas patients need to do the screening process and getting advice or motivation from any dermatological doctors. This can prevent from having any possible side effects from the treatment. However, treatment of melanomas gets more improvement and this can be a solution to prevent any side effect and make melanomas' patients better. Nowadays, many treatments showed its capability to treat melanoma and it also been proving in the clinical trials. One of the advancing melanomas treatment is based on the atmospheric pressure plasma.

IV. NEW TREATMENT FOR MELANOMA SKIN CANCER

Nowadays, there are several alternatives treatment for melanoma skin cancer. In addition, this kind of treatments has their side effects toward patients. In order to avoid the possible side effects, we have another option or alternative that known as cold atmospheric plasma treatment. Cold atmospheric plasma has shown capability in treating cancer cells (lung cancer, bladder cancer tumors (ScaBER) and breast cancer). We suggest treating melanoma using cold atmospheric plasma (CAP) due to the potential application in melanoma treatment. it is also based on the experimental

result that shows the effect of the CAP on various cancer cells that can support the skin cancer treatment[4-30]

Recently, CAP's effects act as a helpful method for anti-cancer treatment including for melanoma skin cancer. Many researchers have studied on the application of the CAP on melanoma skin cancer cells[4-30].

In melanoma skin cancer treatments, Arndt et al. mentioned that cold atmospheric plasma (CAP) could induce the apoptosis of melanoma skin cancer cells. It is because after two minutes of CAP treatment approximately 30% apoptotic cells was achieved[4]. Interestingly, CAP shows high efficacy in promoting apoptosis in melanoma skin cancer cells, compared to anti-tumor agents such as disulfiram, indirubin derivative and isoflavone genistein[4].

Brooks et al. showed that CAP could treat melanoma skin cancer cells through necrosis at higher doses which is 15 s of treatment time. CAP treatment starts the behavior of apoptosis in the cells not through the growth media poisoning in which cells exist but through direct contact with the cell [5].

In addition, Mimbbrera et al. also observed that CAP composed of chemically active species that can be cytotoxic or cause cell death[6]. This active species can cause changes in cellular morphology and cell mobility. When CAP applied on cancer cells, apoptosis was induced due to the active species.

Intracellular reactive oxygen species (ROS) also one of the active species that were induced from the CAP treatment. Sensenig et al. reported that CAP treatment might provide a method to treat melanoma skin cancer by induction of apoptosis[7]. Induction of apoptosis by CAP treatment occurs through the establishment of intracellular ROS. Production of ROS also induced the DNA damage and caused the cell death.

Then, Iseki et al. also investigated that most of the cells become smaller after plasma treatment and these changes are characteristic of apoptotic cells[8]. Cells experienced apoptosis but not necrosis. Most of the cells in the treated region detach from the dish when treated more than 180 s, while the cell in the untreated region remained adherent[8]. Cells around treated region remained attached to the dish. The proliferation rate of the cells also reduced after plasma treatment[8].

Kim et al. detected that cancer cells begin to remove from the surface after plasma treatment[9]. Morphological changes in treated cells may indicate further involvement in cellular metabolic processes with great damage, since cell detachment from ECM can promote apoptosis [9]. Cellular damage is observed depending on plasma doses. Plasma with a low applied voltage causes the cells to burst, cell resistance and apoptosis, while the plasma with the higher voltage leads to the necrosis of cellular characteristics. Cytotoxicity has increased dramatically with increased voltage used, which shows the destruction of membrane cells by plasma [10-13]. Based on the reviews, this demonstrates the ability of cold atmospheric plasma treatment on skin cancer treatment.

A. *Effects and Mechanisms of Action of Cold Atmospheric Plasma on Cancer Cells*

CAP is a gas composed of multiple chemically active species such as reactive oxygen and nitrogen[14,15]. It induces either physical or chemical changes on cell surfaces upon application. Different studies presented various aspects of CAP application in skin cancer treatment such as the role of reactive species that effect on the oxidative stress and cause

cell apoptosis in skin cancer depends on the CAP doses [20, 24, 25, 25, 27]. Oxidative stress may play different roles in the melanoma skin cancer treatments. Melanoma skin cancer cells exhibit oxidative stress which could damage surrounding tissue.

The reactive species also was the key mechanism of plasma effects on the cell that lead to induction of the apoptosis of cancer cells. Apoptosis is a type of programmed cell death, and mitochondria act as the major regulator of apoptosis. Induction of apoptosis is an important issue in cancer treatment. CAP has been studied by the researcher as a possible therapy for induction of apoptosis especially in melanoma skin cancer treatment [16-18].

Cancer cells show a weak antioxidant mechanism compared to normal cells. This property can attack selective cancer cells by CAP which is delivered by reactive oxygen species and reactive nitrogen species, resulting in severe oxidative stress and cell death [16]. Schmidt et al. observed that redox changes due to the CAP's treatment result in changes in cell morphology. Changes in cell morphology can also cause cell apoptosis [10].

When applied directly or indirectly to cancer cells, CAP has been shown to give the effects on oxidative stress and induce cell apoptosis via multiple pathways including reactive oxygen and nitrogen species[16-19]. Therefore, we suggested further investigation of CAP, including the chemical reaction and also the safety of CAP as a therapy for melanoma skin cancer.

V. CONCLUSION

This review provides a better understanding of melanoma skin cancer and its treatment. Additionally, it provides an idea to investigate new melanoma treatments for early detection and avoid the worst cases. Finally, these findings will play a role to improve the treatment of skin melanoma skin using a new and advanced atmospheric plasma device that can be used as a clinical tool to diagnose early melanoma skin cancer.

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