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The A-Z Guide To Non-Melanoma Skin Cancer: Prevention, Detection And Treatment.

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Abstract: Skin cancer is one of the most devastating cancers of the present decade. Non- melanoma skin cancers include basal cell carcinoma(BCC), actinic Keratosis, and squamous cell carcinoma(SCC). Treatment of these are done by using non-invasive methods. Some treatments for non-melanoma carcinoma are such as surgery, cryosurgery, curettage electron section and radiotherapy. BCC arises from uncontrolled proliferation of basal cells which is the foundational layer of the epidermis. Ultraviolet radiation from sunlight, stands as the primary culprit, triggering mutations which disrupt normal cell growth control. Some other contributing factors include genetic predisposition, fair complexion, immunosuppression, and certain syndromes. Food and Drug administration approved various molecular targeting therapies which include Hedgehog inhibitors for BCC, monoclonal antibodies targeting anti-programmed death ligand-1 and anti programmed cell death 1 (PD-1) for MCC and anti-PD-1 for cSCC. Squamous cell carcinoma manifests as diverse skin lesions, commonly appearing on sun-exposed areas like the head, neck, ears, and arms. Early lesions may present as scaly red patches, thick and rough skin, or open sores. Advanced tumors can grow larger which form nodules or ulcerative lesions that may bleed or crust. Diagnosis of SCC involves a combination of clinical examination, dermoscopy, and biopsy. Histopathological analysis confirms the presence and type of squamous cell carcinoma. Treatment depends on various factors like tumor size, location, depth. Surgical excision remains the mainstay, with Mohs micrographic surgery which offering high cure rates for specific cases. Other methods include radiotherapy, chemotherapy, and cryotherapy. Metastatic SCC may require systemic therapy with targeted drugs or immunotherapy. Untreated SCC can grow locally that invade deeper tissues, and potentially metastasize to regional lymph nodes or distant organs.

Index Terms - Skin Cancer, Melanoma, Non-melanoma, Basal cell carcinoma(BCC), Squamous cell carcinoma(SCC), Cryosurgery, Radiotherapy, Monoclonal antibodies, Anti programmed cell death 1 (PD-1), Anti-PD-1, Histopathological analysis.

I. INTRODUCTION

Skin cancer is most common form of cancer and approximately one out of five people suffer from skin cancer anywhere in their lifetime. Basically cancer is the uncontrolled and unorderly growth of normal cells, and the capacity of losing the controlled growth of normal cells is termed contact inhibition of proliferation. There are two main types of skin cancer which are named as non-melanoma skin cancer and melanoma skin cancer and the former is further categorized into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Non-melanoma skin cancer (NMSC) or keratinocyte skin cancer (KSC) is the most common form of skin cancer. As per the statistics presented by the American Cancer Society, the new cases of melanoma skin cancer among all cancers are estimated to be 6% in males and 4% in females in the year 2023 (Hasan et al. 2023).

Melanoma skin cancer occurs due to abnormal proliferation of human melanocytes; pigment containing cells, comprised of 90%, 5% and 1% in skin, eyes, and intestine. Non-melanoma skin cancer (NMSC) are caused by genetic and environmental factors represents approximately 95% of the skin cancers. Generally, Non-melanoma skin cancer encompasses many other cancerous types but these types are mainly divided into two main subtypes:- cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) make up 99% of all NMSCs (Khan et al.2021).

Nowadays Non-melanoma skin cancer is a Public health problem worldwide. According to most recent statistic report, there are annually recognized about 5.4 million cases of BCC and SCC. Certain characteristics, such as light skin, and light colored eyes, freckles are risk factors for the development of Non-melanoma skin cancer. NMSC mostly occurs in various parts of the body such as neck, head, palm, hands and face because of direct exposure to sunlight. In the early stages, NMSC can be 99% curable by surgical excision. Rate of mortality is lower in BCC than in SCC, but BCC covers more than 80% of cases and SCC covers only 20% of cases of NMSC, other types of NMSC cover only less than 1% of cases of skin cancer (Ciuciulete et al. 2022).

2. BASAL CELL CARCINOMA

Basal cell carcinoma (BCC), previously known as basal cell epithelioma. BCC is the most common cancers in Humans. Basal cell carcinoma are usually a slow-growing tumor for which metastases are rare (McDaniel et al. 2022).

On the basis of clinical diagnosis, BCC appears as flesh- or pink-colored, pearly papules with overlying ulceration or telangiectatic vessels.

Stage 1	Tumors < 2cm, limited to the skin
Stage 2	Tumors ≥ 2cm, limited to skin and subcutaneous adipose tissue
Stage 3	Invasion of muscle, cartilage, bone, lymphatics, and perineural invasion
Stage 4	Distant metastases

Types of Basal Cell Carcinoma

- **Nodular**
- **Superficial**
- **Basosquamous**
- **Morphoeic**
- **Pigmented**

2.1. ETIOLOGY

The prime etiological factor in the development of BCC is exposure to UV light, specially the UVB wavelengths. Exposure to ultraviolet is not only the risk factor as 20% of BCC arise in non- sun exposed skin. BCC also occur due to various other factors such as ionizing radiation exposure, immunosuppression, arsenic exposure, and genetic predisposition.

Some of the genetic syndromes associated with an increased risk of BCCs are Xeroderma pigmentosum, basal cell nevus syndrome, Rombo syndrome, and Bazex- Duper- Christol Syndrome.

2.2. HISTOPATHOLOGICAL ANALYSIS

The histopathological analysis of BCC is characterized by aggregates of Basal cells with a small cytoplasm, hyperchromatic nuclei, apoptotic cells, all included in a fibromyxoid stroma.

The BCC histopathological subtypes are classified according to risk of tumor recurrence. BCC having low risk of recurrence are nodular, superficial, pigmented and infundibulocystic. However, high risk are recurrence are micronodular, infiltrating, sclerosing/Morphoeic and Basosquamous BCCs (Niculet et al. 2023).

Nodular BCC is the classic form accounting for 50-79% of all BCCs. Nodular BCC presents microscopically as large nests or islands of malignant basaloid cells with central, haphazard cell arrangement and peripheral palisading, tumor- stroma clefting, mucoid/myxoid stroma with spindle cells, with/without amyloid deposits. The most common sites for nodular BCCs are the face especially nose, cheeks, eyelids, forehead.

Superficial BCC is the second most common subtype. It can appear as a multicentric tumor and sometimes be part of a mixed pattern tumor, with micronodular, nodular, or infiltrating components.

Micronodular BCC is characterized by small islands or nests of malignant tumor cells with infiltrate deep into the dermis. The tumor has a satellite like arrangement of discrete nodules with irregular contours which are lined by a thin margin of stroma and separated by normal dermal collagen.

Infiltrating BCC composed mainly of chords or thin nests of tumor cells (with a thickness of >5-8 cells) with infiltrate deeply, with angulated edges and have an irregular, permeating invasion pattern at the tumor edge.

Morpheaform or sclerosing BCCs constitute 5-10% of BCCs. It is called as sclerosing because of its clinical resemblance to an indurated plaque of localized scleroderma. Lesions present as pink to ivory – white, smooth, scar like, indurated plaques or depressions with ill-defined borders.

Pigmented BCC is a variant of superficial or nodular BCC containing melanin pigment derived from an increased number of dendritic melanocytes within the malignant tumor nests (Dourmishev et al. 2013).

2.3. TREATMENT

The surgical treatment of BCC is the main approach through which the entire tumor mass can be excused. The surgical excision needs to be made with at least 4-mm margins in low- risk BCC and at least 6- mm margins in high- risk should be ensured (Sutedja et al. 2022).

•Curettage and Electrodessication are older techniques, which are recommended in superficial BCC or low-risk tumors, having the downside of not allowing a histopathological examination of surgical margin. These two techniques should not be used in parts of the body having terminal hair growth, such as scalp, axillae, beard area, or pubis because of risk of tumor extension in the hair follicle (Barlow et al. 2006).

•Cryosurgery uses freeze- thaw cycles to destroy the malignant tumor cells and as with Curettage and Electrodessication, doesn't allow the microscopic examination of tumor margins and mostly recommended in low- risk cases such as superficial BCC.

The basic principle of cryotherapy is that freezing cycle with a temperature below zero will result in tissue damage and induction of wound healing. Complications of cryotherapy include pain, bullae, pigmentary changes, nerve damage, alopecia, bleeding and cicatricle tissue. Delayed complications include neuropathy, dyschromia, milia, and abnormal cicatrisation (Kaur et al. 2023).

• Photodynamic therapy, two- step therapeutic approach; it involves the initial local application of a photosensitizing chemical substance (methyl aminolevuinate or aminolevulinic acid), followed by irradiation with the help of light source. It determines oxidative damage in the tumor cells, along with vascular damage, and without having major effects on the surrounding normal tissue; it may be recommended in cases of periocular BCC, having a good function preservation and cosmetic outcome. This technique has high

recurrence rates of up to 30.7% within 5 years, and is mainly recommended for superficial BCC (Collier and Rhodes 2020).

•Radiotherapy is a less frequent treatment approach, being used for unresectable tumors or in cases where surgery is not recommended; brachytherapy and external beam radiotherapy/ teletherapy have been used in the treatment of BCC, having lower recurrence rates as compared with cryosurgery (Yosefof et al. 2023).

a) Soft X- ray (contact) therapy:-

This method entails placing a cone directly onto the irradiation surface, typically with the delivery of the dose at energies of 30-100kV.

Advantages:- This method include a low penumbral dose and easy clinical setup.

Disadvantage:- especially in the definitive setting, are unclarity regarding the subclinical spread, and technical difficulty in measuring the depth of tumor (Grossi Marconi et al. 2016)

b) Electron beam radio therapy:-

Delivered via a linear accelerator at energies of 6-10 MeV and may Target superficial lesions with a therapeutic depth of up to 5 cm. This method is useful in treating relatively large fields and lesions deeper than 1 cm without compromising superficial tissues (Kokurewicz et al. 2019).

c) Mega-Voltage (MV) photon beam therapy:-

Delivered via a LINAC at energies of 6-18 MV. Treatment is mostly planned via CT stimulation. This is the preferred method for the treatment of tumors with a deep-set component or with proximity to critical structures (Zhang et al. 2016).

d) Interventional radiotherapy (brachytherapy):-

Mostly performed with interstitial catheters and on HDR source, or by personalized surface molds. This method is useful for lesions with complex geometry where external beam therapy may result in an inhomogeneous dose distribution, or in proximity to critical structures. Use of this technique of charged particle therapy is becoming more and more widespread in routine. Practice, especially in the setting of re-irradiation. It I is delivered via a particle accelerator and generally planned inversely (Rovirosa et al. 2023).

3. SQUAMOUS CELL CARCINOMA

SCC is the second most common cutaneous malignancy after BCC. SCC has precursor lesions called actinic Keratosis, exhibits tumor progression and has the potential to metastasis in the body. Ultraviolet (UV) solar radiation is the primary risk factor in the development of cutaneous squamous cell carcinoma (CSCC). Excision by surgery is the primary treatment modality for cutaneous squamous cell carcinoma (Howell and Ramsey 2023).

3.1.ETIOLOGY

Ultraviolet solar radiation is the most common cause of squamous cell carcinoma. Whereas, long term exposure to cancer causing chemicals such as tar in cigarettes can also lead to the development of SCC. Some other possible causes include a site of a severe burn scar, and ulcer or sore present for many years and sone types of Human Papillomaviris (HPV) in the genital area. Head and Neck SCC develop from the mucosal epithelium in the oral cavity.

3.2. TREATMENT OF CSCC

(a) Targeted therapy in CSCC

• EGFR (Epidermal Growth Factor Receptor) inhibitors

Targeting to EGFR that inhibits the PI3k/AKT/mTOR and RAs/RAF/ERK signal transduction pathways.

There are following two classes of EGFR inhibitors:-

• Monoclonal antibodies that block the extracellular domain of the receptor (e.g., Cetuximate, panitumu mab),
• Small molecule tyrosine kinase inhibitors (TKIs) that block tyrosine kinase activity and thereby inactivating the downstream cellular pathways (e.g., gefitinib, erlotininb, afatiInib).

Monoclonal antibodies and small molecule tyrosine kinase inhibitors have been evaluated in clinical trials for poor-prognosis CSCC (Chen et al. 2021).

(b) Immunotherapy in CSCC

In immunotherapy, medicines are used to strengthen a patients immune system, which can identify and recognise the cancer cells from the normal cells and it can destroy only the cancer cells (Ansary et al.2022).

Immune checkpoint therapies are the novel drugs initially developed to treat melanoma which mainly targets the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and Programmed cell death (PD-1).

The PD-1/PD-L1 pathway works as an immune checkpoint to halt or turn off the T-cell responses, resulting in protecting normal cells from the attack of T cell and minimizing inflammatory responses. In cancer patients, the PD-1 receptor is expressed in activated T cells and antigens presenting cells, and tumor cells express PD-1 ligand and PD-L1. When PD-1 bind with its ligand then the functionality of T cell decreases, suppress the immune system function, and accelerates cancer cells proliferation (Didona et al. 2018).

4. CONCLUSION

Non-melanoma skin cancers (NMSCs) are the most common malignancy worldwide, of which 99% are BCCs and SCCs of skin. NMSCs are non-lethal and curable by surgery. Both basal cells and squamous cells belong to keratinocytes, therefore sometimes they are termed as keratinocyte cancer. Effective treatment and prevention strategies are crucial in combating skin cancer. Early detection, sun protection measures, regular screening, and lifestyle changes play a vital role in prevention. Treatment options vary depending on the type and stage of skin cancer but may include surgery, chemotherapy, radiation therapy, immunotherapy and targeted therapy. Awareness and education about the risks of UV exposure and the importance of sun safety practices are essential for reducing the incidence of skin cancer and improving the outcomes for those affected.

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