RESEARCH PAPER

A Comprehensive Review of Skin Cancer: Classification, Risk Factors, Diagnosis, and Treatment

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ABSTRACT
Skin cancer is one of the world's most common and rapidly growing cancers, caused by excessive ultraviolet (UV) radiation exposure and environmental risk factors. It includes melanoma and non-melanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which together account for the majority of diagnosed cases. The skin, as the largest organ and first line of defense, is constantly exposed to hazardous agents such as UV radiation, pollutants, and carcinogenic substances, making it extremely vulnerable to Cancer.This study provides a comprehensive overview of skin cancer, including its classification, etiology, pathophysiology, diagnostic tools, and treatment. The molecular mechanisms underlying carcinogenesis are intensively investigated, particularly UV-induced DNA damage and changes in tumor suppressor genes like p53. Furthermore, the role of environmental pollutants, heavy metals, viral infections, and immunosuppression in the progression of skin cancer is examined.Advances in diagnostic techniques, non-invasive imaging modalities like dermoscopy, reflectance confocal microscopy, and optical coherence tomography, have greatly improved early detection and clinical outcomes. Various therapeutic options are investigated, including traditional methods such as surgery, radiation, chemotherapy, and cryosurgery, and novel strategies such as immunotherapy, targeted therapy, photodynamic therapy, and nanotechnology-based drug delivery.Overall, this article emphasizes the diagnosis, prevention strategies, and the development of targeted treatments to improve patient prognosis and reduce the global burden of skin cancer.

Keywords: *Skin cancer, Melanoma, Non-melanoma skin cancer, Skin cancer diagnosis and Treatments*
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1. INTRODUCTION

1.1 Cancer overview:

Cancer is a disease when some body cells proliferate out of control and spread to other body regions. Since the human body is composed of trillions of cells, cancer can begin practically anywhere. It is normal for human cells to divide and develop in order to create new cells when the body requires them. Cells die when they age or sustain harm, and new cells replace them.[1]Cancer was initially identified as a tumor, which is a growing mass of tissue. They could see how it looked, how quickly it expanded, and how it frequently seemed to "bite" into the body. The

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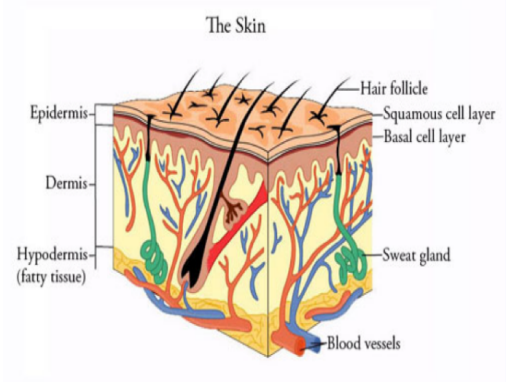
tumors themselves were known to be lethal and occasionally appeared to spread to other areas of the body.[2]

1.2. Skin:

The skin acts as a first-order physical barrier against the environment and covers the entire external surface of the body, making it the largest and most important organ for protection.[3]The skin performs a number of tasks, including temperature regulation, feeling, protection, and vitamin D synthesis. it also supports the immune system and bone health.[4]

The skin, which covers the entire body, is the biggest organ in the human body. Although it has several functions, its main one is to shield internal organs from the outside world, which includes bacteria, viruses, UV rays, dehydration, and chemical and mechanical harm and elimination of waste products.[5]

1.2.1. Anatomy of skin:



Figure(1): Anatomy of skin[71]

The three layers of skin are the epidermis, which is the outermost layer, the dermis, which is the structure beneath it, and the subcutaneous tissue, which is the structure beneath the dermis.[6].

I. The epidermis, the skin's outermost layer, influences skin tone and acts as a waterproof barrier.

II. Beneath the epidermis is the dermis, which is home to sweat glands, blood vessels, lymphatic vessels, hair follicles, and connective tissue.

The hypodermis, the deeper subcutaneous tissue, is composed of connective tissue and fat.[7]

1.3. Skin Cancer:

Skin cancer is a deadly condition that has seriously harmed people's health all over the world. It is one of the prevalent cancers among organ transplant recipients, with a yearly rise in prevalence. Of them, 95% are basal cell and squamous cell carcinomas.[8].According to the World Health Organization, skin carcinoma is the fifth most frequent type of cancer worldwide as of 2020. The American Academy of Dermatology (AAD) revealed in 2022 that 9,500 Americans receive a skin cancer diagnosis every day. Australia and New Zealand have the highest incidence rate of skin cancer outside of the US, followed by northern European nations like Norway and Denmark.[9]

2. Types of skin cancers:

Melanoma	Non melanoma
• Nodular melnoma • superficial spreading melanoam • Lentigo Malinga • Acral lentiginous melanoma	• Basal cell carcinom • Squamous cell carcinoma • Actinic keratosis

Table 1: Classification of skin cancers[72,73,74]

Together, melanoma and nonmelanoma skin cancers make for almost half of all cancers, making them the most prevalent type.

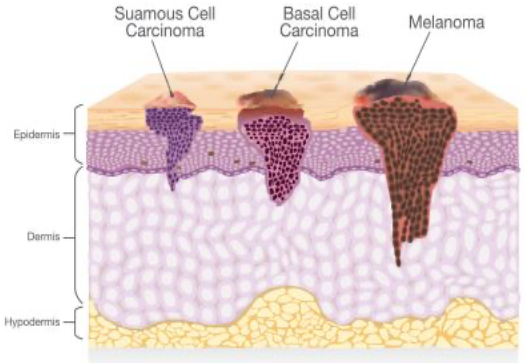


Figure 2: types of skin cancer

2.1. Melanoma:

Melanoma is a potentially lethal cancer that typically affects the skin. The global incidence of melanoma has increased dramatically during the last 50 years. Its prevalence is greater in lower latitude areas and among people with fair skin. Melanoma is more common in older persons, but it is also one of the most common cancers in teenagers and young adults.[10].

2.1.1. Superficial Spreading Melanoma:

The most prevalent type of melanoma in the West is called superficial spreading melanoma (SSM), It frequently appears on areas that are exposed to the sun, such women's legs and men's shoulders and backs.[11]The main characteristics of superficial spreading melanoma include intraepidermal pagetoid spread of melanoma cells (pagetoid in situ melanoma) and/or significant nested growth. Though it can also occur de novo, particularly on the trunk and extremities, this kind of melanoma is frequently linked to melanocytic nevi.[12]

2.1.2. Nodular melanomas:

After the more common superficial spreading melanomas, nodular melanomas (NMs) are the second most common clinical subtype of melanomas, accounting for 14% to 30% of all melanoma cases.[13]Most often, involvement

occurs in the trunk and legs. Nodular melanoma is characterized by rapid growth over weeks to months, which usually results in larger thickness at diagnosis compared to other melanoma subtypes. Clinically, the lesion shows as an elevated, dark brown to black papule or nodule, and ulceration and bleeding are common. [14]

2.1.3. Lentigo maligna:
Lentigo maligna, a subtype of melanoma, usually affects the head and neck area and manifests as an uneven brown macule on skin that has been exposed to the sun for a long time.The gradual growth of lentigo maligna led to its classification as "circumscribed precancerous melanosis," "junctional nevus," and "infective senile freckles."[15].The lesion becomes larger and eventually becomes lentigo maligna melanoma (LMM), often years after it first occurs. Because of this, the majority of authors view LM as a kind of melanoma in situ. Both destructive and surgical techniques are used for treatment; surgical removal is the recommended course of action.[16]

2.1.4. Acral lentiginous melanoma:
Acral lentiginous melanoma (ALM), commonly known as just acral melanoma, is a kind of melanoma that affects the palms, soles, fingers, toes, and nail units of the hands and feet. The Greek word for the highest or topmost part of the limbs (extremities) is where the word "acral" originates.[17].ALM has unique traits, including higher chromosomal changes and low total mutation rates. In comparison to other subtypes of cutaneous malignant melanoma, it is linked to a worse prognosis, more advanced disease, and shorter survival rates. ALM is more common in non-white communities, especially among Black, Hispanic, and Asian people. Its occurrence varies throughout the world.[18]

2.2. Non Melanoma skin cancer(NMSC):
NMSC is the most common cancer among white people, and its incidence increases year after year. About 90% of NMSC are caused by UV radiation exposure, which also suppresses the inflammatory response and causes keratinocytes to undergo malignant transformation.[19].All non-melanoma malignant neoplasms that affect the skin are referred to as NMSC. About 99% of all NMSCs are of the two primary kinds, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Apocrine adenocarcinoma, sebaceous carcinoma, Merkel cell carcinoma, and other uncommon tumors are examples of other NMSCs.There is limited epidemiological data about NMSCs, despite the fact that they are 18–20 times more common than cutaneous melanoma.[20]

2.2.1. Basal Cell Carcinoma:
The most common type of skin cancer, basal cell carcinoma (BCC), typically appears in the head and neck area in 80% of patients, frequently without any prior precancerous lesions. High morbidity is the outcome of BCC's frequent local invasion and tissue damage rather than its uncommon metastases.[21].UV radiation exposure is significantly linked to the emergence of BCC: tumors mostly form on the sun-exposed skin of older people with fair skin types; they are rarely detected on palmo-plantar surfaces or in youngsters, and they never show up on the mucosa. Men are more likely than women to be impacted, and this usually happens after the age of 50. [22]

2.2.2. Squamous cell carcinoma:
The second most prevalent type of skin cancer among white people is SCC.SCC is most frequently caused by UV radiation, although it can also form as a result of ionizing radiation, human papillomavirus, chemical agents, immunosuppression, and persistently wounded or inflamed skin. Invasive SCC can have a variety of clinical manifestations and develop from SCC in situ or from a precursor lesion like actinic keratosis.[23]

The histological subtypes of squamous cell carcinoma includes

2.2.2.1. Keratoacanthoma:
Common cutaneous skin tumors called keratoacanthomas (KA) start in the hair follicles. KA has a benign evolution and can retreat on its own, unlike squamous cell carcinoma.[24]Additionally, KA is more common in older adults, particularly those with prolonged sun exposure or immunosuppression, and it occurs more frequently in men than in women.[25]

2.2.2.2. Desmoplastic melanoma:
Desmoplastic melanoma (DM) is a rare form of spindle cell melanoma that typically appears in older adults with sun-damaged skin.Neoplastic melanocytes' most distinctive histological characteristics are their spindle shape, noticeable desmoplasia, and frequent neurotropism.[26]

2.2.2.3. Sarcomatoid/spindle cell carcinoma:
SpCC can occur in many regions of the body, including the urogenital tract, skin, breast, aerodigestive tract, salivary glands, and gastrointestinal system. . The larynx is the most common location in the head and neck area, followed by the pharynx, oral cavity, and sinonasal tract.[27]

2.2.2.4. Acantholytic carcinoma:
A rare histopathologic variation of SCC known as acantholytic SCC (ASCC) exhibits widespread acantholysis of cancerous epithelial cells, giving the appearance of pseudovascular or pseudoglandular. Therefore, it is also referred to as angiosarcoma-like SCC, pseudovascular adenoid SCC, gland-like SCC, adenoid SCC, and pseudoglandular SCC.[28].A distinctive neoplasm with tumor cell acantholysis is cutaneous adenoid squamous carcinoma (ASCC). Because this lesion might occasionally be difficult to diagnose.ASCC primarily affected the skin on the head and neck in the elderly peoples.[29]

2.2.2.5. Clear cell carcinomas:
Adenocarcinomas, also known as clear cell carcinomas, are uncommon tumors that make up less than 1% of all salivary gland malignancies. These tumors do not

morphologically fit into other types of salivary gland malignancy and have a sizable percentage of neoplastic cells with transparent cytoplasm under a microscope.[30]Globally, oral squamous cell carcinoma (OSCC) ranks as the eighth most prevalent type of cancer.It makes up 96% of all oral cancers and is the most prevalent form to afflict the head and neck area.One very rare histological variation of OSCC is the Clear Cell form (CCOSCC).[31]

2.2.2.6. Bowen's Disease (BD):

Bowen's disease (BD) manifests as a tiny, erythematous, photo-distributed psoriasiform plaque.Bowen's disease is an in situ cSCC that has a 3–5% chance of developing into an invasive SCC.People over 60 are usually affected with BD, while people under 30 and Black people are less likely to have it..[32].Bowen's disease is frequently misdiagnosed at first because the lesions' morphology might be mistaken for other cutaneous conditions. When a patient has a persistent cutaneous lesion that has been previously identified as "atypical" dermatitis, or whose diagnosis is unclear, a skin biopsy should be conducted and Bowen's disease should be investigated.[33]

2.2.2.7. Verrucous carcinoma (VC):

Verrucous carcinoma (VC) is an uncommon type of well-differentiated squamous cell carcinoma that has a limited potential for metastasis, a recidive tendency, and a capacity for local invasion

The following clinical entities can be identified based on the site of the VC:

- ✧ oral florid papillomatosis,
- ✧ epithelioma cuniculatum,
- ✧ papilomatosis cutis carcinoides and
- ✧ Buschke-Löwenstein tumor [34]

3. Etiology and Epidermiology of skin cancer:

In people with fair skin, skin cancer is the most prevalent kind of cancer worldwide.The most common cause of skin cancer is ultraviolet radiation (UV) from sun exposure. Skin malignancies and immunosuppression are brought on by cumulative damage from sunburns and prolonged exposure. Weather, elevation, latitude, altitude, UV light intensity, and ozone depletion all affect how much UV radiation reaches the earth's surface. Skin malignancies are more common in AIDS patients and organ transplant recipients.[35].The idea that viruses could be the cause of cancer dates back as far as the discovery of viruses. Shope and Rous show that malignant progression to skin tumors was produced by either exposing these papillomas to coal tar or infecting a host that does not allow viral replication. The first virus connected to cancer in a mammalian host was the cottontail rabbit papillomavirus, also known as Sylvilagus floridanus papillomavirus.[36]

3.1. Effect of UV rays on skin cancer

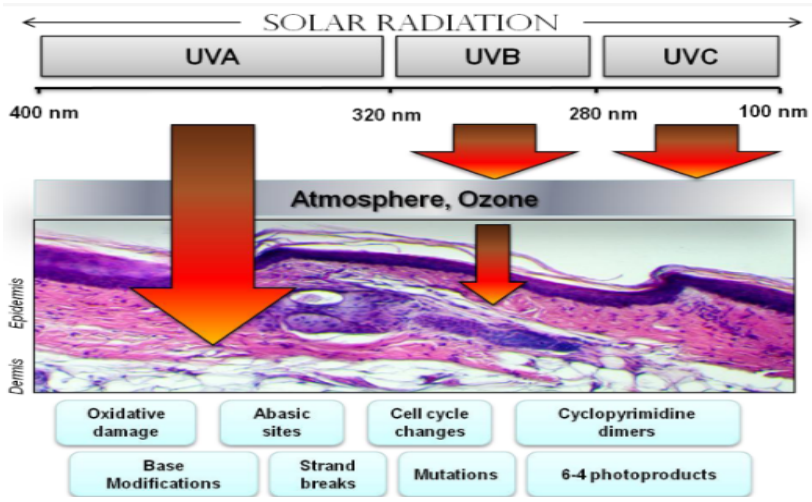


Figure 3: Electromagnectic spectrum of UV radiation[75]

Sunlight provides the primary energy for life on Earth through photosynthesis, yet ultraviolet (UV) radiation from the sun has significant negative impacts. The sun releases UV radiation across a broad spectrum, from the high-energy UVC band (wavelengths below 280 nm; 1 nm=10−9 m) and UVB band (280-315 nm) to the UVA band (315-400 nm), which borders the visible region from 400 to 800 nm.[37]The tumor suppressor gene p53 was one of the genes that caused skin cancer when exposed to sunlight.The p53 point mutations were clearly caused by wavelengths in the UVB range, which are also the wavelengths that most frequently cause animal malignancies . This is due to the fact that UVB radiation produces more dipyrimidine photo-products in the skin's basal layer than UVA radiation (320–400 nm). In isolated DNA, UVC creates these photoproducts even more efficiently than UVB, but the ozone layer filters them out at least 105 times.[38]

3.2. **Psoriasis and Skin Cancer**

One important consideration when treating psoriasis is the potential for skin cancer. Systemic UV treatments for psoriasis may increase a person's chance of developing cancer. Psoriasis sun exposure can exacerbate the chronic inflammatory condition and make it more challenging for immunosuppressive medications to work[39].According to a recent meta-analysis, individuals with psoriasis are more likely than the general population to acquire NMSC, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), Although the association between psoriasis and malignant melanoma (MM) is still debatable due to inconsistent findings from various research[40].

3.3. Environmental Exposure:

We are more vulnerable to environmental pollution. During metabolization, activation, or buildup, pollutants can become extremely dangerous to vital organs, and this is often linked to a serious genotoxic effect. As the skin acts as a barrier between the body and the environment, it is frequently exposed to pollutants right away[41].

3.4. Effect of the Pollutants on the Skin:

The most common external skin stressors that might cause early aging are smoking, UVR, and air pollution. The face, head, neck, and back of the hands are among the areas that are most commonly affected by them. Furthermore, long-term skin exposure to photopollution may hasten the photoaging process and increase the risk of cancer.[42]

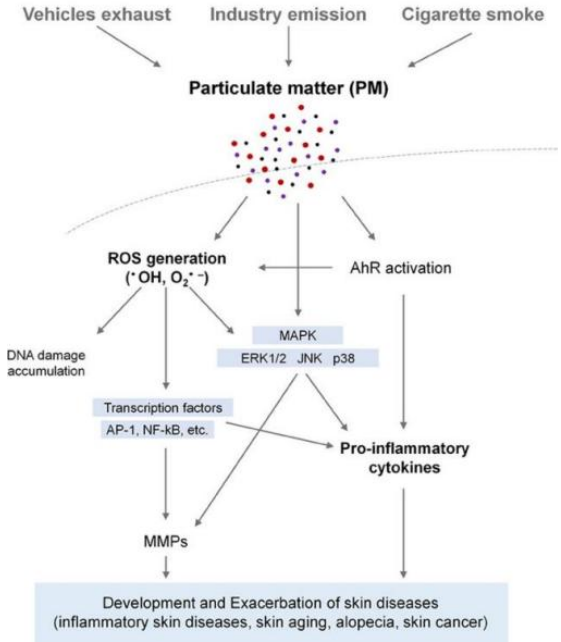


Figure 4: Effect of pollutants on skin[76]

3.5. Virus and Skin Cancer:

According to current estimates, viral infection accounts for 10% of all cancer cases worldwide, with the bulk (>85%) happening in underdeveloped nations. Different kinds of DNA and RNA viruses are known as oncogenic viruses, and they cause cancer through a number of different methods.[43.]HPVs (Human papillomavirus) belong to the Papillomaviridae family (PV) and are tiny, non-enveloped viruses having an icosahedral capsid. So far, about 200 serotypes have been identified. The five major genera of HPVs are α, β, γ, v, and μ. Of them, α-HPV and β-HPV are more strongly associated with human conditions. While β-HPVs are linked to skin infections and cutaneous squamous cell carcinomas, α-HPVs are intimately tied to mucosal and skin infections and have been linked to cervical carcinoma and benign viral warts[44].

3.6. Volatile Organic and Inorganic Compounds:

Carbon is the primary structural atom of a family of gases known as volatile organic compounds (VOCs), which are volatile at room temperature and atmospheric pressure. While weighted quantile sum regression was performed to investigate the connections of mixed co-exposures, binary logistic regression was utilized to thoroughly evaluate the possible relationship between each urine VOC exposure and skin cancer. Particularly in females, several volatile organic compounds (VOCs), most notably mercapturic acid (MA), demonstrated strong associations with the incidence of skin cancer[45].

4. PATHOGENESIS:

4.1. Uv radiation:

UVA radiation (320-400 nm) is 10,000 times less carcinogenic than ultraviolet B radiation (290-320 nm), which has a wavelength that is strongly absorbed by the DNA and a spectrum of mutations that differ from those created by other types of mutagenesis. UVB-induced mutations entail the replacement of nitrogenous bases in two or more successive pyrimidines, most commonly in the transition from cytosine (C) to thymine (T) and the production of thymine dimers (CC → TT). Solar radiation-induced DNA changes only progress to skin cancer if they occur repeatedly and sequentially, thereby entering the

replication stage.Two proto-oncogenes, a proto-oncogene and a tumor suppressor gene, or two alleles of a tumor suppressor can all undergo mutations. Normal genes known as proto-oncogenes can develop into active oncogenes or proteins with novel activities when they undergo mutations. When tumor suppressor genes are altered or removed, they no longer have a detrimental effect on regulating the growth of tumors[46].Pathways that result in UV mutagenesis at CPDs with cytosine. A DNA polymerase avoids the CPD in the error-prone DNA synthesis pathway by inserting an incorrect adenine base across the cytosine, which results in C to T alterations. The CPD that has developed at dipyrimidines containing cytosine is hydrolytically deaminated to uracil in the deamination-bypass pathway. Adenine is incorporated across uracil to enable error-free DNA synthesis past uracil-containing dimers by DNA polymerase eta. Nevertheless, the deamination event fixes the mutation. Double cytosine or 5-methylcytosine deamination events may result in UV-induced CC to TT mutations.[47]

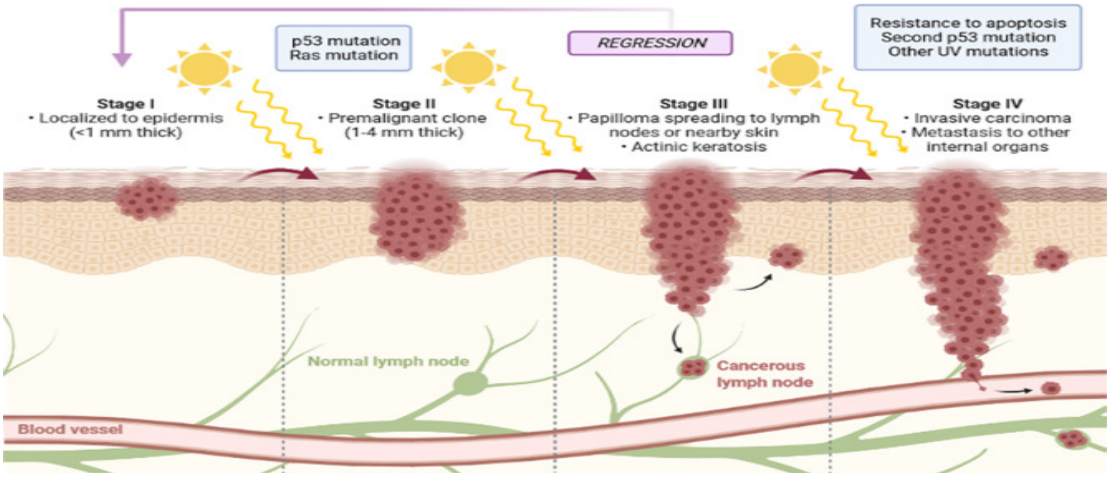


Figure 5: Schematic representation of stages of squamous cell carcinoma[77]

5. DIAGNOSIS OF SKIN CANCER:

5.1 Non-invasive optical technologies:

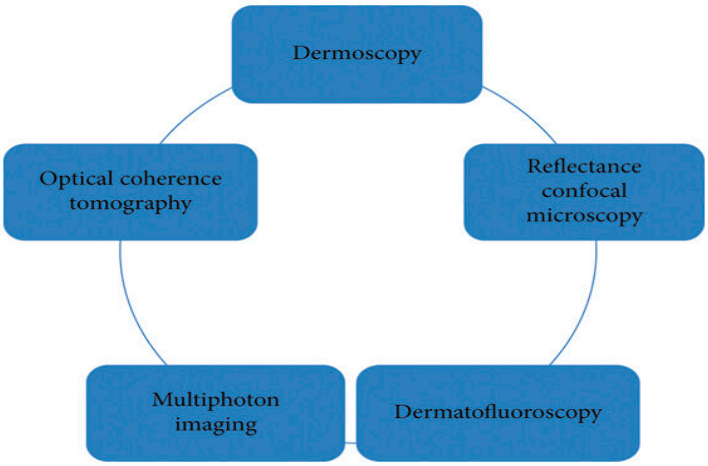


Figure 6: types of diagnosis of skin cancer by non-invasive optical technologies.[78]

Despite the fact that histopathology is the more reliable method of identifying skin cancer, the invasive nature of the operation sometimes makes people reject to have it done. Thus, it is clinically significant to increase diagnostic precision and decrease unnecessary biopsies. There have been significant advancements in the development of technology to support the hunt for a more objective and noninvasive optical type of diagnosis.[48]

Dermoscopy is a useful, non-invasive, and popular method that has significantly increased the diagnostic precision of pigmented skin lesions and, more recently, of non-pigmented skin conditions such skin cancer, inflammatory illnesses, and infectious diseases. It makes it possible to observe the skin in vivo and see morphological structures that are invisible to the human eye in the papillary dermis and epidermis.

5.1.1. Dermoscopy:

Dermoscopy is a useful diagnostic technique for the clinical evaluation of non-melanoma skin cancers (NMSC), including basal cell carcinoma (BCC), Bowen's disease (BD), actinic keratosis (AK), and squamous cell carcinoma (SCC). It has also had a major influence on the early diagnosis of melanoma[49].

5.1.2. Dermatofluoroscopy:
Magnosco GmbH in Berlin, Germany, created Magnosco DermaFC ®, which enables in vivo PSL diagnosis.With a wavelength of 810 nanometers, the device's pulses can penetrate the skin up to 500 micrometers and illuminate a 50 micrometer-diameter area. Its scanning head is capable of measuring individual spots across a 20 by 20 mm area and obtaining a set of melanin fluorescence spectra that indicate the degree of cancer. A score is then generated to help differentiate MMs from other PSLs once all of these spectra have been sorted and analyzed using an automated, objective data processing method. Sensitivity and specificity were 89.1% and 44.8%, respectively, in a prospective, blinded, multicenter trial that identified 476 PSLs using a cutof score of ≥30.[48]

5.1.3. Multi Photon Imaging:
In order to understand the three-dimensional and extremely dynamic mechanisms of tumor growth and progression, multiphoton microscopy has proven to be an effective method. Excellent tissue penetration, low background fluorescence, low phototoxicity, and simple coupling with label-free detection systems are MPM's distinct benefits over other preclinical intravital imaging techniques. MPM is also beginning to be utilized in clinical settings to swiftly and noninvasively diagnosis skin malignancies as a result of these advantages.[50]

5.1.4. Reflectance Confocol Microscopy:
RCM is an optical imaging technique that allows for the vivo visualization of cutaneous lesions down to the depth of the papillary dermis without the need for a biopsy for histological the assessment Through cellular level resolution of 0.5–1.0 μm laterally and 4.0–5.0 μm axially.The use of RCM as a supplemental tool to dermoscopy is especially pertinent in these situations, despite the operator dependence and limited penetration depth. Its high-resolution, non-invasive imaging capabilities may lower the number of needless excisions as well as the risk of missing melanomas.However, there is still a dearth of real-world evidence assessing the additional diagnostic utility of RCM in lesions classified as medium risk—those that most commonly complicate clinical decision-making.[51]

5.1.5. Optical Coherence Tomography:
OCT, or optical coherence tomography, is a novel technique for high-resolution cross-sectional imaging. OCT is comparable to ultrasound imaging, however it uses light instead of sound.Cross-sectional images of tissue structure at the micron scale can be obtained in real time and in situ using OCT. OCT is a type of optical biopsy. OCT can be utilized to guide interventional procedures, minimize sampling errors related to excisional biopsy, and in situations when standard excisional biopsy is risky or impracticable.[49]

6. TREATMENT:
Patients with actinic keratosis, squamous cell carcinoma of the skin, and basal cell carcinoma can get several forms of treatment. A treatment clinical trial is a type of research study that aims to enhance existing cancer treatments or gather data on novel treatments. A novel treatment may take the place of the standard treatment if clinical trials demonstrate that it is superior.[52]

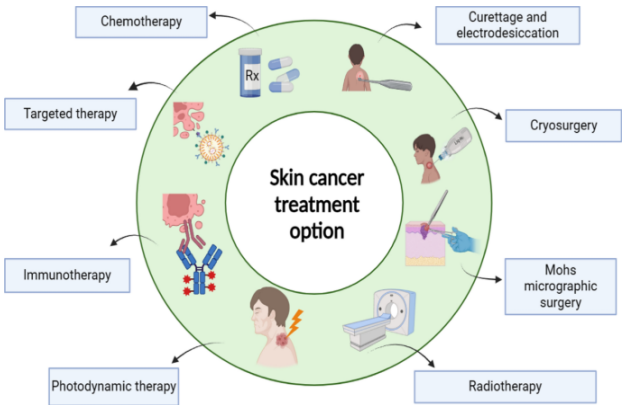


Figure 7: types of treatment for skin cancer[79]

6.1.1. Mohs micrographic surgery:
Mohs micrographic surgery is a precise, tissue-sparing technique for removing skin cancer that bears Frederick Mohs's name. For the treatment of various skin malignancies, such as squamous cell carcinomas (SCC) and basal cell carcinomas (BCC), this surgical method gives significant cure rates.The visible tumour is marked and removed, leaving a margin of 1-2mm. The scalpel is used to make the incision at a 45-degree angle, All lateral and deep exterior regions of the fragment are included in the surgical margins that need to be inspected. "Horizontal" histological sections are made when the fragment is frozen in the cryostat, enabling the examination of all lateral and deep edges.The remaining "roots" of the tumour are removed for further microscopic inspection.[53].

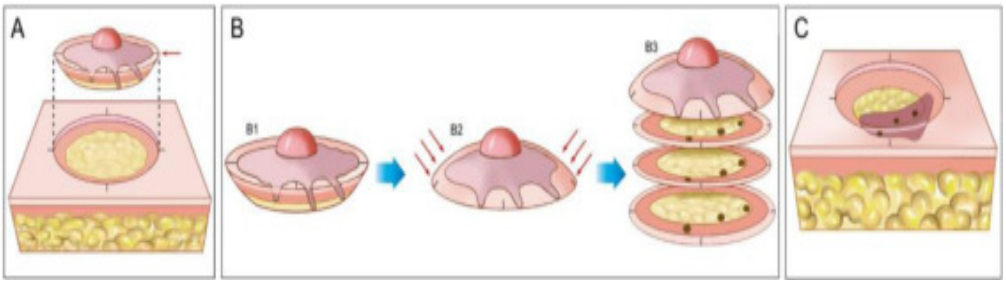


Figure 8: Representation of mohs microscopic surgery[80]

6.1.2. Radiotherapy:

Although more rarely utilized, radiation therapy (RT) is still an essential treatment option for BCC.When it comes to primary therapy, RT has the significant advantage of avoiding reconstructive surgery in important areas such as the lacrimal system, nose, and ears. Many patients with BCC are poor surgical candidates because to advanced age and co-morbidities, making surgery impractical.There has also been hesitation to treat individuals with basal cell nevus syndrome who have a genetic deficiency in the PTCH tumor suppressor gene, as RT may cause further DNA damage, increasing the risk of further tumor growth.[54]

S.no	Therapy type	Energy range	Depth of penetration	Clinical uses
1	**Soft X-ray**	30-100 kv	Up to ~10 mm	Well-demarcated, superficial, symmetrical, and palpable lesions
2	**Electron Beam Radiotherapy**	6–20 MeV	Up to ~5 cm (90% isodose at 20 MeV)	Superficial to moderately deep lesions
3	**Megavoltage (MV) Photon Therapy**	6–18 MV	Deep-seated tumors	Tumors with deep components or near critical structures
4	**Interventional Radiotherapy (Brachytherapy)**	HDR source (dose: 30–50 Gy in 5–10 fractions)	Localized (direct placement)	Complex lesions, near critical structures, or after EBRT failure
5	**Proton Therapy**	Particle beam (protons)	Highly precise (Bragg peak effect)	Re-irradiation cases and tumors needing high precision

Table 2: types of radiation used in the skin cancer therapy[81]

6.1.3. Photo-dynamic therapy:

Photo-dynamic therapy (PDT) is a non-invasive and effective cancer treatment that uses certain wavelengths of light to activate photosensitizers (PS) in an oxygen-rich environment. When the PS is activated by light, it transforms from an excited singlet state to a long-lived triplet state before reacting with ground state (triplet) O2 to produce reactive oxygen species (singlet oxygen and free radicals).The fundamental principle underlying PDT is that when exposed to appropriate light wavelengths, the photosensitizer releases singlet oxygen and other reactive oxygen species, which damage the cell membranes and organelles of cancer cells, eventually leading to apoptosis or necrosis. In contrast to standard chemotherapy and radiotherapy, which use toxic chemicals and ionizing radiation, PDT is considered a relatively safe, FDA-approved anticancer strategy.[55]

6.1.4. Immunotherapy:

Medicines are used in immunotherapy to enhance a patient's immune system, allowing it to distinguish and destroy cancer cells from normal cells with greater efficiency. Immunotherapies, particularly immune checkpoint treatments, are innovative medications that were initially created to treat melanoma and primarily target the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1).Under normal physiological conditions, the immune system—more especially, the T cells—protects our body from external invaders while maintaining normal, healthy cells.

It is known that the PD-1/PD-L1 pathway functions as an immunological checkpoint to prevent or suppress the T cell response, thereby shielding healthy cells from T cell assault and reducing inflammation.[56]

Drug	Target	Indications (NMSC)	Dose	Results
Ipilimumab	CTLA-4	Limited data in cSCC, BCC, MCC	3 mg/kg IV every 3 weeks (4 doses)	Durable remission in some cSCC & BCC cases; ~60% response in refractory MCC (with nivolumab)
Cemiplimab	PD-1	Approved for la-cSCC & m-cSCC; studied in BCC & MCC	3 mg/kg IV every 2 weeks or 350 mg every 3 weeks	cSCC: RR ~47–50%, DCR ~61–65%; BCC: RR 31%, DCR ~80%; limited MCC data
Pembrolizumab	PD-1	cSCC, BCC, MCC	2 mg/kg IV every 3 weeks	cSCC: RR 35–50%; MCC: RR 58%, CR 30%; BCC: variable responses
Nivolumab	PD-1	BCC, cSCC, , MCC	3 mg/kg IV every 2 weeks	MCC: CR 14%, PR 55%; responses observed in cSCC and BCC
Avelumab	PD-L1	Approved for metastatic MCC	800 mg or 10 mg/kg IV every 2 weeks	MCC: RR ~33–39%; 5-year OS ~26%; real-world RR ~64%

Table 3: immunotherapies for skin cancer[82]

6.1.5. Trageted therapy:

6.1.5.1. Cyclooxygenase Cox-2 inhibitors:

Cyclooxygenase (COX), the rate-limiting enzyme for producing prostaglandins (PG) from arachidonic acid, has at least two isoforms: COX-1 and COX-2. COX-1 is constitutively expressed, whereas COX-2 is activated by inflammatory stimuli such as UV radiation exposure. Increasing evidence points to the involvement of COX-2 and its products, particularly prostaglandin E2, in the development of NMSC. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has demonstrated potential therapeutic effect in the prevention of cutaneous neoplasia.Celecoxib, both orally and topically, has been shown in animal experiments to have a chemopreventive effect, suppressing new tumor growth and prolonging tumor latency. These COX-2 inhibitors are promising treatments for cutaneous neoplasia.[57]

6.1.5.2. EGFR Inhibitors (EGFR-i) and Anti-EGFR Antibodies:

From first to fourth generation EGFR inhibitors, significant progress has been made in overcoming resistance and improving therapeutic efficacy.First-generation inhibitors, such as gefitinib and erlotinib, developed the concept of reversible EGFR inhibition. However, they encountered resistance mutations such as T790M.Second-generation inhibitors, including afatinib and dacomitinib, aimed to address this challenge by forming irreversible bonds, but at the cost of increased toxicity. The third generation introduced medications such as Osimertinib, which specifically targets T790M mutations, resulting in increased efficacy and fewer adverse effects. The current development of fourth-generation inhibitors tries to circumvent other resistance mechanisms, such as the C797S mutation, through unique binding techniques.[58]

6.1.5.3. Fibroblast growth factor receptor (FGFR) inhibitors:

Comprehensive genomic profiling is playing an increasingly important role in cancer therapies. As therapy choices for advanced tumors remain limited, patients are increasingly turning to tumor genetic changes as potential targets for cancer treatment. Many malignancies have frequent FGFR changes, such as genetic amplifications, mutations, rearrangements, and fusions. Currently, the FDA has approved two medications: erdafitinib and pemigatinib. Erdafitinib is approved by the FDA for the treatment of metastatic urothelial carcinoma with FGFR2 and FGFR3 changes,whereas pemigatinib is approved for the treatment of unresectable cholangiocarcinoma with FGFR2 mutations.[59]

6.1.5.4. Antibody–Drug Conjugates:

ADCs use monoclonal antibodies to precisely deliver targeted medicines to tumor-associated antigens. However, because antigens can be expressed in non-neoplastic tissue, on-target off-tumor effects may occur, leading to a variety of toxicities. CD44v6, a target antigen for

bivatuzumab mertansine (BM, an ADC containing an antimicrotubule drug) being studied for SCC of the head and neck, is found in healthy squamous epithelium and produces desquamation in up to 80% of patients treated with BM.[60]

6.1.5.5. Nanotechnology based treatment:

A growing number of in vitro and in vivo research indicate that nanotechnology could be useful in the treatment of skin cancer.Due to the improved activity of anticancer medications supplied via nanocarriers, the systemic side effects of chemotherapy are minimized; anticancer agents that display greater effectiveness at lower doses play a crucial role in improving patients' general health.Various nanostructured platforms, such as liposomes, carbon nanotubes, nanomicelles, nanoemulsions, and metal nanoparticles, have been investigated for their potential in improving skin cancer diagnostics and treatment.[61]

6.1.6. Cryosurgery:

Cryoablation typically involves two methods: cryoapplication using various types of cryoprobes and open cryospray .Various types of liquid nitrogen-based cryo equipment: CRYO-02, CRYO-05, and CRYO-01 ELAMED (Russia).[62]This type of surgery usually requires the use of liquid nitrogen, which has a temperature between -346 and -320°F; however, carbon dioxide and argon may also be utilised.Mammalian cells are damaged when cold to -20°C (-4°F).Primary damage begins with the development of ice crystals. Intracellular crystals tear the cell's outer membrane, while ice production outside dehydrates the environment. When organelles are disrupted, cells lose their ability , resulting in cell death.A second freeze/thaw cycle is employed to provide a deadly dosage of cold to all targeted tissues. Pre cooled tissue freezes faster than normal tissue, which leads to more uniform necrosis.[63]

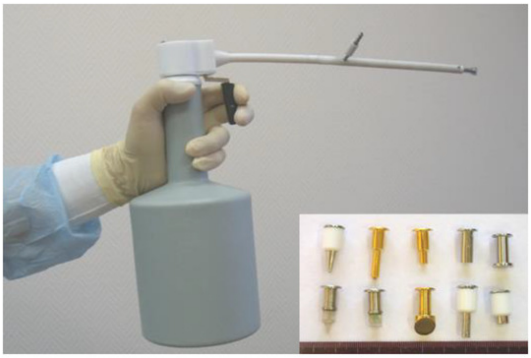


Figure 9: the instrument CRYO-05 with types of cryophobes[83]

6.1.7. Curettage and electrodesiccation:

Curettage and electrodesiccation (CE) is a widely used procedure for destroying benign and malignant cutaneous neoplasms[64].This method starts with washing the area and administering a local anesthetic to numb the lesion. A tiny biopsy is then obtained with tools like scissors, scalpels, or punches. The visible tumor is then treated with electrodesiccation, which use electric current to kill the tissue, and the lesion is gently scraped with a curette to remove any damaged tissue.The majority of the tumor is removed, and the electrodesiccation and curettage procedure is repeated to achieve full removal.[65]

6.1.7.1. Laser therapy:

Laser therapy is a treatment that involves administering a focused light source with a precise wavelength to the tumor. Lasers can be used to cut, burn, or destroy tissues, including NMSCs. Two laser therapies are specifically utilized for BCC: carbon dioxide laser and pulsed contrast laser.[66].Malignant skin tumours can be treated using CO2 laser excision or vaporisation, neodymium:yttrium aluminium garnet (Nd:YAG) laser coagulation, and systemic or topical photodynamic treatment (PDT). CO2 laser vaporisation may be used to treat superficial basal cell carcinomas, actinic keratoses, Bowen's disease, actinic cheilitis, and leukoplakia. However, laser treatment of skin cancers is not yet considered standard therapy and should only be used in chosen patients. Further clinical research is needed to assess the role of laser therapy in this specific condition.[67,68]

6.1.7.2. Chemotherapy :

Natural Chemotherapeutic Agents:

Globally, there are several natural resources for therapeutic purposes that have yet to be fully utilised in the pharmaceutical sector. Natural sources account for about 50% of accessible pharmaceuticals, including 70% of anti-cancer compounds.Currently, there are few organically derived medications available to treat skin cancers, but none have been licensed for topical administration. This may be due to the recognised negative effects of these agents when applied directly to the skin.[69]

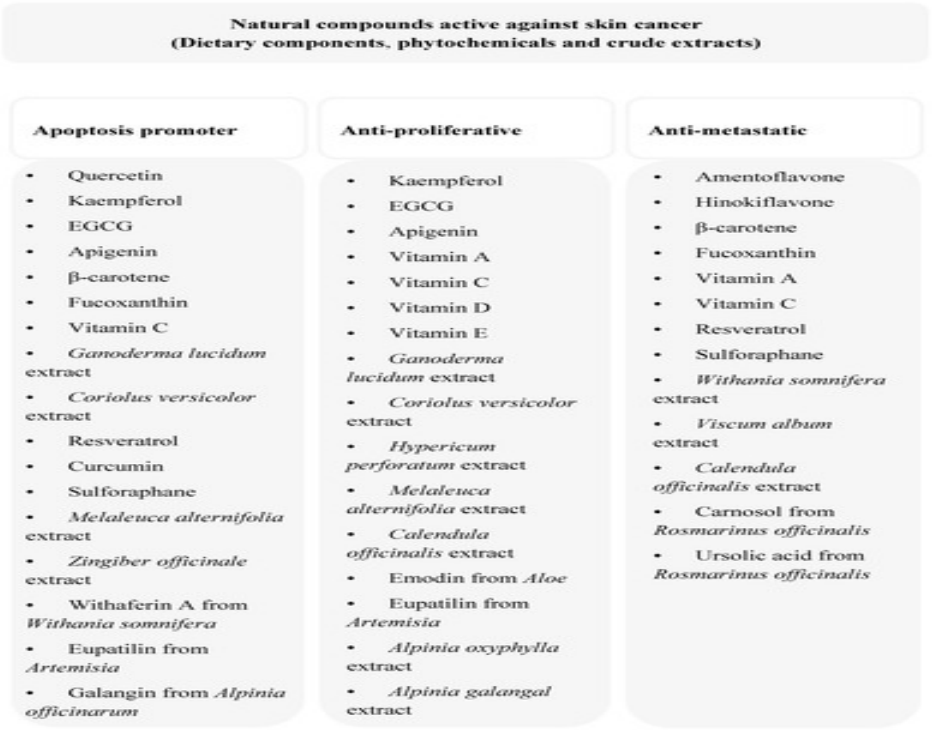


Figure 10: List of natural compounds for skin cancer[84]

Topical Chemotherapy:

Topical pharmacological treatment is a promising technique for localised and early-stage disease since it is self-administered and non-invasive, may cure a wide spectrum of precancerous lesions, and produces better cosmetic results. However, the efficiency of topical medicines is frequently hampered by inadequate drug penetration, due to the barrier role of the stratum corneum (SC).[70]

S.no	Topical treatment	Indication/Dose
1	5-fluorouracil	Basal cell carcinoma 2 times/day for 6 weeks Actinic keratosis 2 times/day for 6 weeks
2	Diclofenac solaraze	Actinic keratosis 2 times/day for 60-90 days
3	Imiquimod aldara	Basal cell carcinoma 5 times/week for 6 weeks Actinic keratosis 3 times/week for 4 weeks
4	MAL metvix (methyl aminolevulinate)	Basal cell carcinoma and Browen disease 2 session

Table 4 : types of topical treatment for the skin cancer[85]

7. CONCLUSION:

Skin cancer remains one of the most common malignancies worldwide, with its incidence continuing to rise due to increased exposure to ultraviolet radiation, environmental pollutants, immunosuppression, viral infections, and other risk factors.Advances in understanding the molecular mechanisms of skin carcinogenesis, particularly UV-induced DNA damage and alterations in tumor suppressor genes, have significantly improved strategies for prevention, diagnosis, and treatment. Modern non-invasive diagnostic techniques such as dermoscopy, reflectance confocal microscopy, and optical coherence tomography enable earlier and more accurate detection, thereby improving patient outcomes.

A wide range of therapeutic modalities are currently available, including surgical excision, Mohs micrographic surgery, radiotherapy, photodynamic therapy, immunotherapy, targeted therapy, chemotherapy, cryosurgery, and laser therapy. Among emerging

approaches, nanotechnology-based drug delivery systems offer promising opportunities to enhance drug penetration, improve therapeutic efficacy, and reduce systemic adverse effects.

Overall, effective prevention through sun-protective measures, early diagnosis, and the integration of innovative targeted therapies are essential for reducing the global burden of skin cancer. Continued research into molecular pathways and advanced therapeutic technologies will further contribute to improved patient survival, treatment outcomes, and quality of life

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