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Skin Cancer Melanoma Advance Research

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Abstract: ***Melanoma is the most deadly type of skin cancer, and its morbidity and fatality rates are rising globally. Melanoma has significant heterogeneity and a high potential for metastasis, which limits the effectiveness of currently available treatments, which were limited to chemotherapy, radiation, and surgery for several years. The creation of novel treatment classes, including immune checkpoint and small molecule kinase inhibitors, has been made possible by advances in our understanding of the pathophysiological mechanisms underlying the illness. Effectiveness is still far from ideal, despite the undeniable improvements in patients' quality of life and survival rates. The primary obstacles are a few negative side effects and resistance mechanisms. As a result, numerous clinical trials looking into novel medications and/or combinations have been prompted by the quest for better alternatives. Drugs' poor stability, quick metabolism, and limited water solubility restrict the clinical potential and medicinal applications of certain substances. Therefore, the investigation of nanotechnology-based approaches is being investigated as the foundation for the widespread use of various nanosystem types in melanoma treatment. The difficulties in comprehending the mechanisms that increase the effectiveness of these nanosystems will be the main focus of future research.***

Keywords: history of melanoma, etiollogy, bilogy of melanoma , reasearch methodology , classification , pathogenesis , risk factors, symptoms, mechanism, treatment(theries),

I. INTRODUCTION

The subject of this review is cutaneous melanoma. This malignancy comprises the great majority of identified cases and has four main subtypes: lentigo maligna melanoma, acral lentiginous melanoma, nodular melanoma, and superficial spreading melanoma.The non-cutaneous variety of melanocytes, however, can also be found in various tissues, including the central nervous system, mucosa, eyes, inner ear, and hair follicle bulbs . Additionally, while being the least prevalent type of skin cancer, melanoma is the most deadly and aggressive . Along with the significant social impact, improved health care's complexity and price have drawn attention.For instance, in the United States, the expenses related to melanoma represent.[1]

This review offers useful treatment algorithms in addition to a thorough summary of contemporary therapies for metastatic melanoma. These algorithms were created to help clinicians navigate the complexities of making decisions in the treatment of aggressive melanoma. taking into account a range of clinical situations, such as patient traits, tumor biology, and previous medical interventions.

In the complicated world of advanced melanoma, where individualized care is essential, these therapy algorithms are very helpful. Based on variables such the existence or lack of BRAF mutations, the occurrence of brain metastases, and the patient's performance condition, they provide an organized method for choosing the best treatment approaches.[2]

Despite being the most deadly of the primary cutaneous neoplasms and having a constantly rising incidence over several decades, 3-year overall survival (OS) rates have

between 2004 and 2009, were largely consistent among the subcategories of stage IV metastatic illness, ranging from 26.4% to as low as 4.7%.1,2 The 5-year survival rate for Americans with stage IV disease at diagnosis is estimated by the SEER database to be 29.8% as of 2018.3 The prognosis for noncutaneous forms of melanoma, such as mucosal and ocular subtypes, is typically significantly worse.Four It is projected that 7,180 melanoma-related deaths and 106,110 new cases of invasive melanoma will occur in the US in 2021.[3] Melanocytes, which are neural crest-derived cells that produce melanin pigment, can undergo malignant transformation to become malignant melanomas . UV light is one of many variables that control the melanogenic activity and behavior of melanocytes. (UVR) as well as biological and chemical mediators, including genetic and molecular regulators, as well as hormonal and non-hormonal ones . In comparison to other malignancies, cutaneous malignant melanomas are the most common type of melanomas, affecting significant segments of the population and having high incidence and mortality rates .

Rarely, melanomas can also arise from other organs, such as the central nervous system (CNS), but they also start from melanocytes of the eye and mucosa, including oral, anorectal, and genitourinary melanomas . In light of the recent World [4]

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II. HISTORY OF MELANOMA -

When Dr. William Norris described a patient with "fungoid disease" in the 1820s, he added that the man's father had also passed away from a related illness, leading him to hypothesize that the illness could
Be heritable in some situations.12, 13 People from families with hereditary melanoma frequently had a lot of moles, according to Norris, who also noted that melanomas developed from moles.
Norris was the first to recommend surgical excision of melanoma lesions with wide margins because the disease tended to recur, the margins were too narrow, and if the cancer had spread, there was little use in doing so.12, 13 Norris' findings were significant because melanoma was not well known at the time, and they were made about 50 years before Mendel's discovery about heredity.[5]

III. BIOLOGY OF MELANOMA

Melanocytes are thought to be the skin's natural defense against damaging radiation. The amplification and expansion of melanocytes are linked to abnormalities in their functions.
These skin insults are pledged by a number of details such as tissue invasion, metastasis, insensitivity to growth inhibitors, cellular apoptosis avoidance, persistent angiogenesis, infinite replicative potential, and growth factor self-sufficiency . Through molecular processes like dotted mutation, deletions, and translocation, or epigenetic mechanisms like microRNA expression and promoter methylation, these factors either drive the events that activate oncogenes or decrease the tumor suppressor genes [6]
Acquired immune deficiency syndrome (AIDS) and other viral infectious illnesses have been linked to skin malignancies. AIDS patients have been found to have a three to five times higher chance of developing non-melanoma skin cancer [21]. Furthermore, it has been shown that hemophiliacs with HIV have an incidence of BCC that is 11.4 times higher than that of the general population. HIV individuals with SSC have a 50% chance of dying between the ages of 6 and 84 months, as well as a significant risk of metastasis and recurrence [22]. Approximately 90% of NMSC in immunocompromised patients and up to 50% in immune competent individuals were found to contain DNA originating from cutaneous or β-HPV types, according to molecular investigations that reveal the complicity. Furthermore, Furthermore, it is thought that these viruses may be indirectly involved in the pathophysiology of NMSC [24]. Patients with xeroderma pigmentosa are more likely to have sunburn, freckles, and juvenile skin cancers, according to the largest documented collection of ocular surface biopsies.
Many signaling pathways linked to the control of gene expression are often dysregulated in a variety of malignancies, including skin tumors that are melanoma and those that are not. One example of this dysregulation is a mutation in the PTCH1 gene, which causes unchecked skin cell proliferation and the development of numerous BCCs in an autosomal dominant condition [26]. Similarly, the most frequently found cause in men is a mutation in the CDKN2A gene, while in women, it is a mutation in the MDM2 gene.[7]

IV. CLASIFICATION OF MALENOMA

A. Cutaneous Melanoma

This cancer can be classified into four main types:

1) Melanoma with superficial spreading: About 70% of cases are of superficial spreading melanoma, which is the most prevalent type of the illness. It usually starts in a mole that already exists.
2) Nodular melanoma: The second most prevalent type, accounting for 15–30% of occurrences, is nodular melanoma. More aggressive and typically developing more quickly than superficial melanomas are nodular melanomas.
3) Lentigo maligna: Usually observed on the faces of fair-skinned women over fifty, lentigo melanoma manifests as broad, flat lesions. About 4% to 10% of instances of melanoma are of this kind, which has a lesser chance of spreading than other forms.
4) Acral lentiginous melanoma: This type of melanoma can develop on the palms, under the nail beds, or on the soles of the feet. They represent up to 60% of melanomas in individuals with darker skin, but only 2% to 8% of melanomas in those with fair skin. Acral lentiginous melanomas have an average diameter of three millimeters and are quite aggressive.

Mucosal Melanoma: Only around 1% of all melanoma cases that are diagnosed are mucosal melanomas. The illness manifests in mucosal tissue that borders hollow organs and bodily cavities. The head and neck region, which includes the mouth, esophagus, and nasal cavity, as well as the rectum, urinary system, and vagina, are the most often affected areas for mucosal melanoma. Even after being identified and treated, mucosal melanomas have a terrible prognosis.

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B. Ocular Melanoma

Melanoma may develop in the eyes because to the presence of melanocytes, which are cells that produce pigments. Learn more about the two kinds of ocular melanoma

1) Uveal Melanoma: This type of cancer of the eye affects the iris, ciliary body, or choroid, which together make up the uvea. Melanocytes, which are pigment cells that give the eye its color, are the source of tumors. These melanocytes are different from the pigment epithelial cells that underlie the retina and do not develop into melanomas.
2) Conjunctival: Melanoma A raised, pigmented or nonpigmented lesion that manifests in adulthood is the hallmark of malignant melanoma of the conjunctiva. 75% of conjunctival melanomas may be linked to primary acquired melanosis.[8]

V. ETIOLOGY

Melanomagenesis, the term for the malignant transformation of melanocytes with subsequent progression to advanced stages, is caused and fueled by environmental, genetic (inherited), constitutional, and epigenetic variables in addition to acquired mutations with the accumulation of genetic alterations that are exacerbated by systemic and local neuroimmunoendocrine variables that impact the disease's course.

We will only give a quick summary of these factors because they have been covered in other review publications.

" Patients with this mutation are more likely to develop superficial spreading melanoma than acral or nodular melanoma [99,103]. The following proteins are encoded by high penetrance genes implicated in telomere maintenance: telomerase reverse transcriptase, telomeric repeat binding factor 2, POT1, POLE, and ACD, respectively.

Interaction protein, DNA polymerase epsilon catalytic component, protection of telomeres 1, and adrenocortical dysplasia protein homolog Germline inactivating mutations in the tumor suppressor gene BRCA1-associated protein 1 (BAP1) cause atypical intradermal melanocytic tumors and a tiny percentage of spontaneous cutaneous melanoma.[4]

A. Hereditary Conditions That Increase the Risk of Melanoma Development

A family history of melanoma is present in 7–15% of melanoma patients [6], and the risk of developing melanoma doubles if a first-degree relative has previously found to have melanoma. Fewer cases are believed to be heritable, with shared sun exposure among family members likely accounting for the majority of the risk. Although the higher risk of melanoma in patients with genetic condition is well established, it is still unclear how these hereditary melanomas differ from sporadic melanomas in terms of their characteristics. Below is a discussion of high penetrance genetic disorders. [9]

VI. PROGNOSIS

According to the American Cancer Society, 106,110 instances of melanoma are expected to be diagnosed in 2021, with a preference for males; 62,260 of these cases willbe ascribed to 43,850 girls and males. Nowadays, the majority of melanoma diagnoses occur between the ages of 55 and 81, with an average age of 65. Risk factors include skin type, a personal history of melanoma, the presence of many atypical or dysplastic nevi, and, however uncommon, inherited genetic abnormalities like those found in familial atypical multiple mole-melanoma (FAMMM) and FAMMM-pancreatic cancer.[4] Therefore, patients should think about genetic counseling if they have a strong family history of invasive melanoma, whether or not they also have pancreatic cancer. Environmental elements that affect melanoma development include excessive sun exposure and UV-based artificial tanning. According to their morphologic characteristics, melanoma can be divided into four main subtypes: superficial spreading (SSM), nodular (NM), lentigo maligna (LM), and acral lentiginous (ALM). The World Health Organization (WHO) updated its melanoma categorization system in 2018 to incorporate histologic, clinical, genetic, and epidemiologic features. [10]

VII. PATHOGENESIS

A staging method for melanoma was suggested by Clark and associates in 1978. It was based on the tumor's thickness and ulceration, as well as whether or not there were lymph nodes or distant spread. This method assisted in the classification of melanoma into distinct stages and the prediction of each stage's prognosis and available treatments. "Breslow's depth," which is the distance between the top of the epidermis' granular layer and the deepest point of tumor invasion, was a more accurate way to assess tumor thickness that was first proposed by Alexander Breslow and associates in 1985. Given that bigger tumors typically have a worse prognosis than thinner ones, Breslow's depth is one of the most significant prognostic variables for melanoma. Balch and associates revised in 1992 (11)

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VIII. MELANOMA SYMPTOMS

Early detection is possible for the majority of melanomas that originate on the skin.
You can identify worrisome moles or skin changes that could be early indicators of melanoma by doing routine skin checks, either with a clinician or on your own.Other signs and symptoms include:

1) A pain that doesn't go away;
2) Skin that is red, swollen, or tender;
3) A mole that leaks or bleeds;
4) Eye darkness, blindness, or loss of vision (12)

IX. REASEARCH METHODOLOGY

The goal of this systematic literature review was to identify and classify the most effective methods for using neural networks (NNs) to detect skin cancer.
Systematic literature reviews gather and examine previous research based on predetermined standards. These assessments assist in identifying what is already understood in the relevant
area of research [10].
Every piece of information gathered from original sources is arranged and examined. The core research question is addressed in a more reasonable, rational, and solid manner after the systematic literature is finished .
Research articles pertinent to SC detection using deep neural network (DNN) approaches made up the population of studies taken into consideration in the current systematic literature review.
1 Framework for Research
The initial step in this systematic review was to define the review framework. It included a general strategy that was adhered to throughout the systematic literature review. The strategy included Planning, data selection and evaluation, and outcomes generation and conclusion are the three layers. [10]

X. TREATMENT

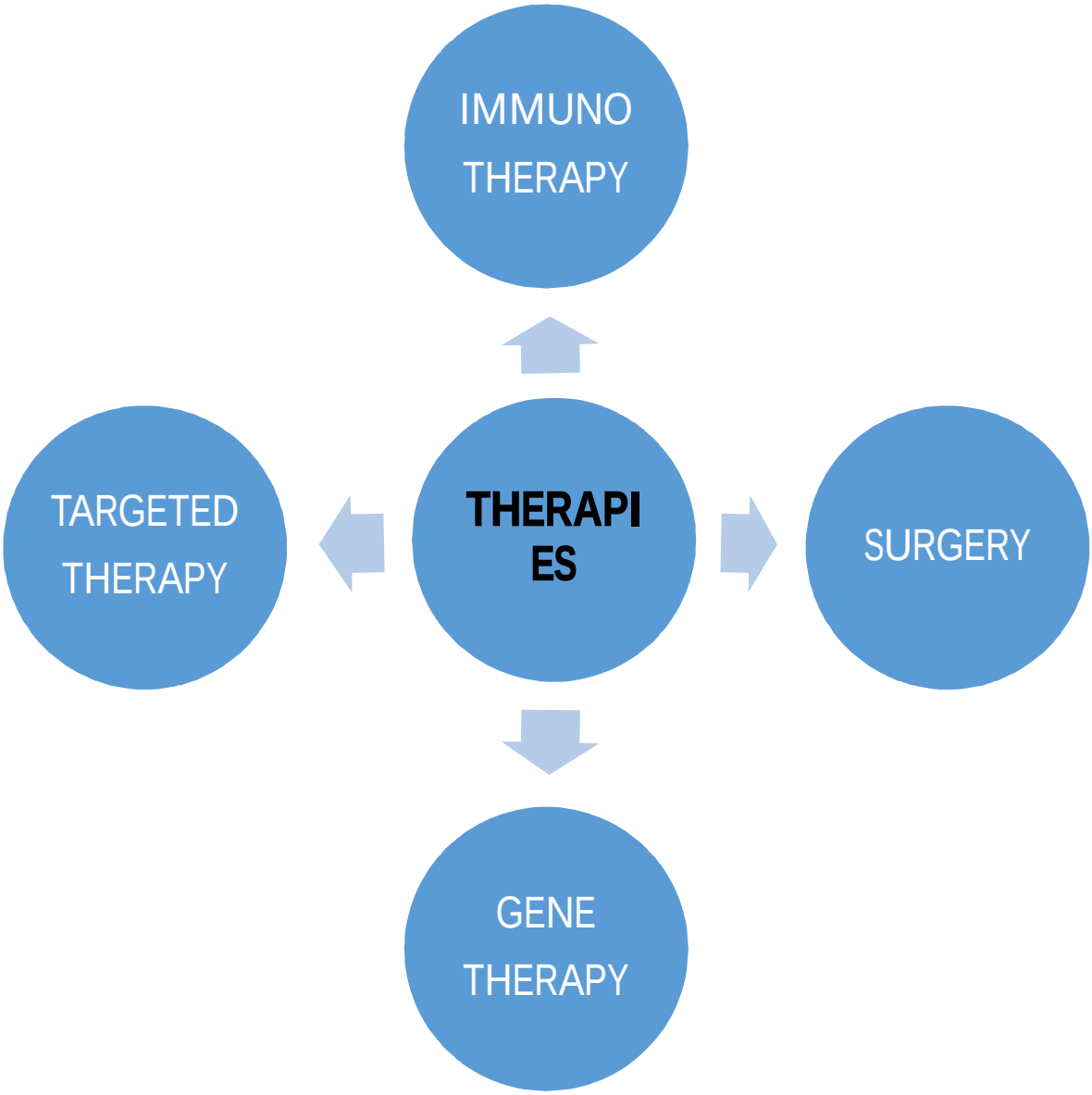
In patients with concealed regional or distant metastases, surgery is the main treatment for cutaneous malignant melanoma with the aim of local control and cure. Following the initial biopsy, a deeper and more extensive excision is carried out to guarantee that the lesion is completely removed. This process lowers the chance of local recurrence and confirms histologically clean margins.
Surgical margins vary according on the stage of melanoma. The resection of a stage T1 melanoma should be broad, leaving a 1-cm surgical margin. However, the recommended size for a T2 melanoma varies from 1 to 2 cm depending on the location of the tumor and functional or esthetic factors. In regions like the face, ears, scalp, and fingers—where both practical and aesthetic considerations are necessary—
The most precise and dependable method of staging for suitable patients with primary melanoma is a sentinel lymph node biopsy (SLNB). 7. To reduce ymphatic channel disruption and maximize mapping accuracy, it should be carried out before to or concurrently with a broad excision of the main tumor when needed. SLNB should be provided to patients with stage T2 melanoma, and discussions about it begin for those with stage T1 melanoma based on other unfavorable features. [14]
Since there are currently few therapeutic salvage techniques available for these individuals, this problem has actually gotten considerably more serious since adjuvant therapy was introduced into clinical practice.
Even though antiPD-1 antibodies have been shown to extend recurrence-free life, between 25% to 30% of patients still repeating within a year. The recurrence pattern, management approaches, and results of patients who experienced recurrence in spite of adjuvant anti-PD-1 medication were examined in a recent study. Melanoma recurrence happened in 17% (147 patients) of the approximately 850 individuals who received treatment. The majority of recurrences (76%), compared to a lesser percentage (24%), happened following adjuvant anti-PD-1 treatment.The timing of recurrence and the therapeutic regimen used affected treatment responses. Crucially, the results indicate that patients who experienced recurrence during PD-1 treatment showed limited activity of additional anti-PD-1 monotherapy (no responses observed), underscoring the potential clinical utility of alternative strategies like ipilimumab (24% responded to ipilimumab alone or in combination with anti-PD-1).[2]

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XI. THERAPIES

A. Surgery

For the majority of melanoma skin cancers, surgery is the main treatment option; it often addresses the early stages of the disease. Even though this option helps guarantee that the cancer has been removed or not, many patients are not interested in it because it may leave scars. This can hurt in certain situations, particularly when there is a large excision. Nonetheless, some medical professionals believe it can help patients live longer and at least prevent suffering that could result from further cancer. (15)



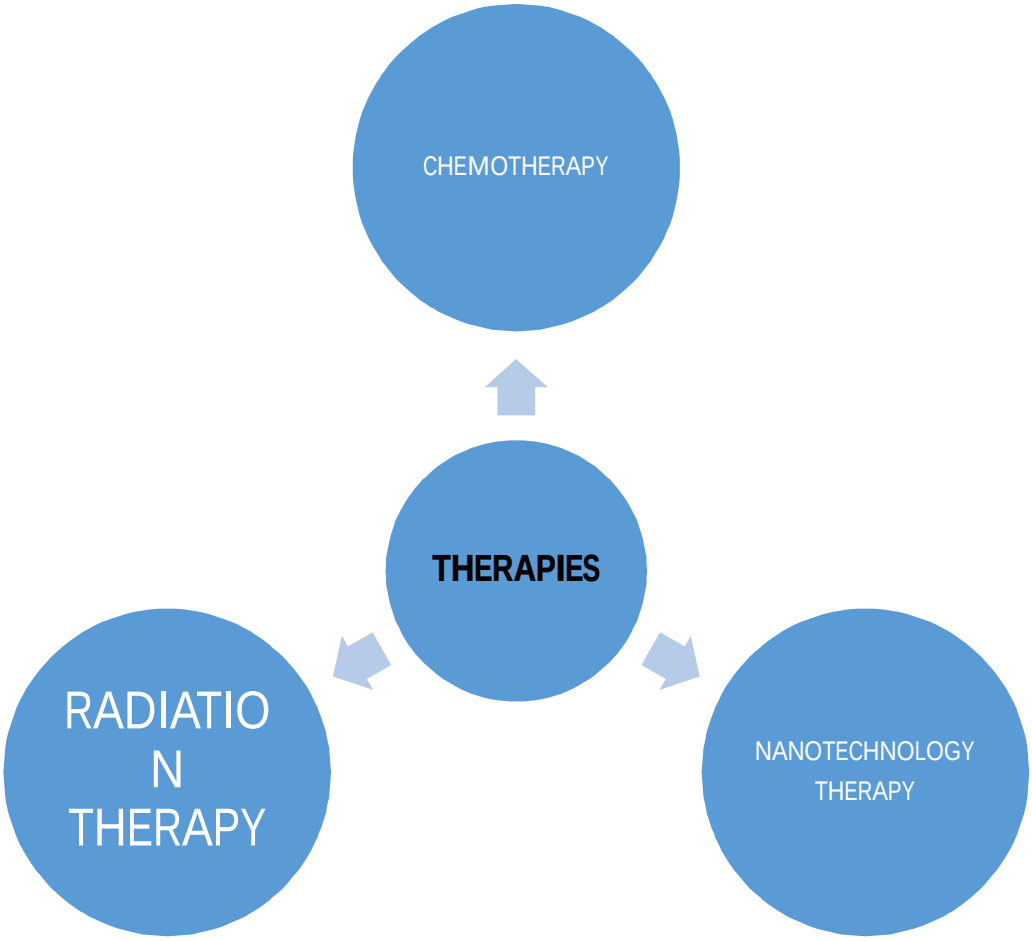


Fig no .1 THERAPIES OF MELANOMA

B. Immunotherapy

Early researchers believed immunotherapy would be useful because of the first reports of lymphocyte infiltration and spontaneous melanoma regression.

help with cancer treatments. Although the initial research on intralesional bacillus Calmette-Guerin or levamisole generated curiosity, long-lasting effects were not observed until the introduction of recombinant human cytokines, interferon-a2 and IL-2, albeit in extremely tiny patient percentages. The development of human-blocking antibodies was made possible by the ground-breaking research on immunological checkpoints (ICs) conducted by Nobel laureates Honjo (programmed cell death protein 1 [PD-1]) and Allison (cytotoxic T-cell lymphocyte [CTLA]4). The first phase I trials involving ICI's anti-CTLA4 drug, ipilimumab, were initiated in 2007.

In March 2011, the FDA approved ipilimumab, an anti-CTLA4 agent, as the first single-agent ICI for the treatment of metastatic melanoma at a dose of 3 mg/kg once every 21 days for four doses62. Later, the drug was licensed in the adjuvant setting at a dose of 10 mg/kg once every three weeks for In October 2015, advanced (stage III) illness was treated with four doses, followed by every three months for a maximum of three years. 63 However, due to established evidence of positive PFS seen with both anti-PD-1 monotherapy or combined anti-CTLA4 and anti-PD-1 regimens, antiCTLA4 monotherapy is not regarded as standard of care in the first-line context. [2]

C. Targeted Therapy

Because melanoma cells differ from normal cells, targeted therapy uses a medication to target those cells . In addition to having less severe side effects such fatigue and hair loss, this approach operates differently than chemotherapy . Even while it has some typical adverse effects, it can occasionally cause more significant ones, such as allergic responses, severe liver issues, and irregular heartbeats . Because of the potentially dangerous side effects, targeted treatments are the least desired treatment option for melanoma.[16]

D. Chemotheropy

1].One popular treatment for cancer, particularly skin cancer, is chemotherapy . It employs a medication that destroys cancer cells. Medications are either administered orally or injected into the veins like a tablet. They target cancer cells that have spread beyond the skin by traveling through the blood supply to every area of the body.

Although it doesn't work, it can help some patients live longer or reduce their symptoms. such immunotherapy and targeted therapy, chemotherapy can cause adverse effects such fatigue, diarrhea, and hair loss . This appears to provide patients a second chance to select this course of treatment.[17]

2]. Dacarbazine For metastatic melanoma, dacarbazine, an alkylating agent that was licensed by the FDA in 1974, is the typical chemotherapeutic drug. According to studies, 2%–6% of patients had a 5-year survival rate, and less than 5% of patients experienced a complete response. 21 Dacarbazine remained the recommended treatment in spite of these findings since alternative single agents or combination chemotherapiesdid not show that patients' OS had improved. 21 Nevertheless, a number of clinical trials are still in progress, either with dacarbazine alone as a comparison or in conjunction with other immunotherapies, targeted treatments, and chemotherapies.

Temozolomide (TMZ) Advanced melanoma has been treated with TMZ, an oral prodrug of dacarba-zine's active metabolite. 21 While there were no changes in OS or objective response rates, TMZ demonstrated a smaller improvement in median progression-free survival (PFS) when compared to dacarbazine.

Electrochemotherapy (ECT) ECT is a treatment that uses high-intensity electric pulses to help transfer medications into cells while also using cytotoxic chemicals like cisplatin and bleomycin. 24,25 ECT has been shown to be successful in treating melanoma nodules that are both cutaneous and subcutaneous. According to a study of the European Standard Operating Procedures for Electrochemotherapy, there were no significant adverse events and an overall response of 85%. [18]

E. Gene Therapy

Gene therapy includes gene alteration, artificially boosted expression, or inhibition of gene expression. Post-transcriptional gene silencing, or mRNA-level gene expression suppression, is possible with RNA interference (RNAi) technology. It is possible to transport antisense oligonucleotides (ASO), micro ribonucleic acid (miRNA), short hair-pin ribonucleic acid (shRNA), and small interfering ribonucleic acid (siRNA) inside the cell to reduce protein turnover by[19]

Barears to gene therapy

• Deterioration within the bloodstream : It is possible for free plasmid DNA to infect malignancies, skeletal muscles, and the liver. However, because DNA is susceptible to deterioration in the bloodstream, it must be appropriately packaged and transported. DOTAP (1,2-Dioleoyl-3-trimethylammonium propane) and DOPE (dioleoylphosphatidylethanolamine) are examples of cationic lipids that have been created as strategies to stop DNA degradation due to nuclease activity. These lipids that are cationic are

Gene therapy applications Scientists from all over the world have been drawn to nucleic acid therapies because of their potential to treat terrible hereditary and acquired genetic illnesses. Gene therapy has been used in clinical trials for a number of malignancies, neurological illnesses, and cardiovascular conditions [. It is less likely that gene therapy will encounter the resistance issue that chemotherapeutics do. Furthermore, this method may serve as a long-term replacement for patients born [19]

F. Nanotechnology Therapy

To enhance general health in Europe and beyond, the fight against cancer must be encouraged. The majority of contemporary research focuses on the early identification and successful treatment of cancerous diseases, but some attempts are also undertaken to enhance patients' quality of life, for example, by pharmacologically lowering pain, which is frequently a natural part of illnesses. Presently, there is no completely successful, minimally invasive anticancer chemotherapy, despite the tremendous advancements in modern medicine, the dynamic growth of pharmacology, and extensive scientific research. A variety of cytostatic medications are

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available for the clinician to select from, each with a distinct mode of action and use in the management of particular tumor types. For example, alkylating cytostatic medications can break down the DNA structure of cancer cells.

Nanotechnology, a new interdisciplinary field of science and technology that deals with the design and construction of objects called nanoparticles, which range in size from 5 to 100 nm, is currently connected with great prospects. Its advancement is crucial to pharmacy and medicine, and it is today one of the most popular scientific disciplines. The great anticancer potential, relatively high durability, and moderate cytotoxicity of nanoparticles to normal cells have made nanotechnology particularly interesting in recent years. By improving the bioavailability, targeting, and delivery of medications to cancer cells at effective concentrations, recent advancements in nanotechnology provide the potential to treat cancer successfully while avoiding the problem of drug resistance.[20]

G. Radiation therapy

The usual course of treatment for patients with initial melanoma has been surgical tumor excision. Melanoma has not seen the widespread use of radiation therapy, which is popular for many other forms of cancer, because skin cancers are typically radioresistant. For the majority of patients, administering therapeutic agents is a more likely course of treatment. For patients with incurable tumors, radiotherapy is still an option. Some patients with early-stage melanoma may also be offered imiquimod cream, a local immunomodulator. Prior to the introduction of targeted therapy in 2011, melanoma patients were treated with dacarbazine, a chemotherapeutic drug that was first used in the 1970s (Table 1). Dacarbazine prevents DNA replication by non-specifically alkylating DNA [16]. In patients receiving dacarbazine, the objective tumor response rate varied from 13 to 20%, with almost all of the responses being partial .. Furthermore, patients experienced significant adverse effects (AE) from dacarbazine. [21]

Radiation therapy, sometimes known as "radiotherapy," is sometimes used to alleviate some of the conditions that melanoma causes. Using radiation treatment is the process of killing cancer cells with high-energy radiation.

Radiation therapy only affects cells in the treated area, making it a local therapy. Melanoma that has progressed to the brain, bones, and other areas of the body is typically treated with radiation therapy.[8]

XII. DIAGNOSIS

Despite significant improvements in patient outcomes due to advancements in immunotherapy and targeted therapy, many melanoma patients continue to experience recurrence cancers (2025, 17, 707 3 of 22). Illness. For the diagnosis of recurrent melanoma, imaging techniques and molecular diagnostics, including circulating tumor DNA (ctDNA), have been studied . There is new promise for a more accurate assessment thanks to molecular characterizations and advanced imaging techniques. Histological and immunohistological methods continue to be the gold standard for the diagnosis, grading, and staging of melanoma, although interest in better diagnostics. [22]

He demonstrated that patients in stages I and II of the disease, who featured thinner melanomas, had a significantly higher likelihood of surviving and a decreased risk of distant and regional metastases. Fourteen This insight made it possible to for smaller resections than were popular at the time, and similar to Clark's approach, it enabled doctors to evaluate the likelihood that the melanoma had spread to the lymph nodes and decide whether or not to remove the lymph nodes (prophylactic lymph node dissection was more likely to be beneficial for patients with a Breslow thickness of 1.5 mm or greater). 12–14. Measurement cutoffs would eventually be modified and added to staging systems, which are still in use today to direct therapy and forecast prognosis; Breslow depth is still one of the most reliable independent indicators of patient outcome. [10]

A. Clinical Diagnosis

Transformed melanocytes give rise to cutaneous melanoma, which can develop anywhere melanocytes have moved during embryogenesis. The central nervous system, eyes system digestive tract and even the gallbladder have been identified as the disease's main locations. Over 90% of melanomas are diagnosed on the skin, and 4% are determined to be metastases without an original site that can be identified. On histological investigation, it is discovered that many melanomas, particularly those in the early stages of growth, have regions of tumor regression (regression is the host immune response to the tumor) that clinically resemble discolored patches in the pigmented lesion. [23]

XIII. RISK FACTOR

Overtreatment of somewhat slow-growing skin malignancies, which can raise screening expenses without providing much additional value. Germany, Australia, Belgium, France, and the United States have all tried early detection programs.

America. According to a recent evidence-based study, there is not enough evidence to support the claim that screening programs are helpful overall. To ascertain whether the identification of thinner primaries results in appreciable drops in the overall melanoma death rate, we await more information from these screening initiatives, particularly Germany's national initiative.[24]

The primary environmental risk factor for the development of melanoma skin cancer is ultraviolet (UV) light radiation from sunlight (4–6). The UV intensity, and specifically the UV-B spectrum, is closely linked to the elevated risk of melanoma from sun exposure . Furthermore, several studies have linked sun exposure timing and patterns to an elevated risk of melanoma. Specifically, a higher risk is linked to severe and sporadic sun exposure, which is typical of sunburn histories, as opposed to a chronic, continuous pattern of sun exposure, which is more commonly linked to actinic keratosis and non-melanoma skin malignancies.[25]

skin cells produce less melanin, a pigment that protects against UV damage, lighter skin is more likely to develop melanoma. Lighter-colored hair and freckles are additional phenotypic risk factors. Several benign nevi (moles), which are usually harmless, are present in some patients. However, a patient's risk of developing melanoma in the future increases with the number of nevi they have. Routine physical examinations are crucial for identifying and monitoring suspected nevi in those with numerous risk factors. [26]

XIV. MECHANISMS AND ROUTES FOR MELANOMA METASTASIS

A. EMT-to-MET Transition

To effectively spread to distant organs, melanoma cells and other cancer cells must take a number of stages. Melanoma cells need to separate from the main tumor first.

Adolescents experience the Epithelial Mesenchymal Transition (EMT), a process that alters the morphology and phenotype of epithelial cells to enable them to move more freely across tissues and reach the bloodstream. Non-EMT tumor cells, as suggested by Tsuji and associates, are tumor cells that have not undergone EMT; they are affixed to EMT tumor cells and "come along for the ride" to distant organs. Active and passive intravasations were proposed by Bockhorn and associates .An very stressful environment causes tumor cells to passively shed during tumor growth in passive intravasation.[27]

Treatment-resistant quiescent in-transit melanoma cells raise the possibility that these cells have transformed into endothelial-like cells and are involved in melanoma recurrence in individuals who have already responded to treatment. Curiously, it has been demonstrated that highly metastatic melanoma cells can create their own vascular tubes, a process known as vascular mimicry, to enhance blood flow to the tumor site and encourage the spread of cancer cells. In order to extravasate into the metastatic niche, it has been suggested that these transdifferentiated quiescent melanoma cells might go through an endothelium to mesenchymal transition (EndMT). Therefore, depending on whether they are active, circulating melanoma cells may successfully develop in the secondary location through at least two different processes.[27]

B. Angiogenesis

Placental growth factor (PlGF), vascular endothelial growth factor A (VEGF-A), and other essential functioning enzymes and adhesion factors have been explored in relation to melanoma.

Angiopoietin (Ang), platelet-derived growth factor (PDGF), interleukin-8 (IL-8), primary fibroblast growth factor (bFGF), urokinase plasminogen activator (uPA), and integrin[28]

The first cytokine to be identified, vascular endothelial growth factor (VEGF), promotes the development of new blood vessels in tumors (Senger (1983). VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factors are among the seven varieties of this gene family (Shibuya, 2011). Thus, the tyrosine kinase receptor family, which includes five subtypes (VEGFR-1, VEGFR-2, VEGFR-3, NRP-1, and NRP-2), includes the VEGF receptor (VEGFR) (Zhao et al., 2021).[28]

C. Exosomes

Cells secrete extracellular vesicles called exosomes, which have a distinct molecular signature that identifies the type of cell they come from. Exosomes might be considered as potential biomarkers for diagnosis and prognosis in a variety of malignancies, including melanoma, due to their easily isolated nature and traceable biological origins. Since they may be extracted from a range of biological fluids, including blood, plasma, urine, and cerebrospinal fluid, they are easily accessible using minimally invasive techniques. It has been demonstrated that exosomes isolated from melanoma cell lines exhibit unique mRNA, miRNA, and protein profiles. Since different exosomal components are markedly changed in cutaneous melanomas, exosome analysis can provide crucial diagnostic and prognostic information. [29]

In this regard, Surman M. et al. discovered elevated exosome concentrations in melanoma patients; however, there was no correlation between these levels and the stage of the disease [134]. In contrast, metastatic melanoma was shown to have a larger concentration of exosomes than non-metastatic instances, according to Boussadia Z. et al. [138]. Although many pathways have been hypothesized, the intricate link between exosomal components and the advancement of melanoma remains unclear. Exosomes, for example, have the ability to transport and modify matrix metalloproteinases (MMPs), change cell adhesion, and stimulate fibroblasts to become cancer-associated fibroblasts, all of which increase the invasiveness of melanoma.[29]

D. Melanoma Biomarkers

The first step in distinguishing a benign nevus from cutaneous melanoma is visual investigation. With the official addition of "E" in 2004 [33], the ABCDE criteria—asymmetry, border irregularity, color variation, diameter (>6 mm), and evolution—are visual criteria for melanoma identification. The left side of Figure 6 illustrates these characteristics. Thomas et al. discovered that combining two criteria results in 89.3% sensitivity and 65.3% specificity, whereas combining three criteria results in 65.55% sensitivity and 80% specificity. Dermatoscopy, often known as dermoscopy, is a technique that uses skin surface microscopy to examine the skin. A seven-point checklist of melanoma used in dermoscopy was presented by Russo et al. and included the following: (I) atypical network (indicating two types of pigment networks); (II) blue whitish veil (irregular area with blue pigmentation); (III) atypical vascular pattern (dotted and hairpin vessels indicating neoangiogenesis); (IV) atypical dots/globules (indicating clumps of melanocytes); (V) irregular streaks (indicating melanocytic nests in rete ridges); (VI) irregular blotches (pigmented keratinocytes or pagetoid melanocytosis); and (VII) regression structures (corresponding to thin epidermis and few melanophages).[30]

E. Oxidative Stress in Melanomagenesis

An imbalance between the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the antioxidant defense systems that counteract them is referred to as oxidative stress [30]. ROS are very reactive chemicals that, if they build up to dangerous quantities, can harm biological macromolecules like proteins, lipids, and DNA. Among the endogenous producers of ROS include cytochrome P450, endothelial nitric oxide synthase (eNOs), cyclooxygenases, lipooxygenases, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase (NOX), and others. Inflammation and UV exposure are examples of exogenous ROS producers [31, 32]. DNA lesions in the form of 8-hydroxy-2′-deoxyguanosine (8-OHdG), lipid peroxidation end products, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), and protein oxidation derivatives, such as advanced oxidation protein products (AOPPs) and advanced glycation end products (AGEs), are biomarkers for oxidative stress.[31]

XV. PREVENTION

Melanoma develops when genetic and (epi)genetic changes build up over time and interfere with homeostatic processes. This leads to unchecked tumor cell growth, invasion, and the lymphatic or hematogenous spread of the tumor cells to other locations. In UV radiation is the main source of alterations on sunexposed skin, including cutaneous melanocytic neoplasms. Consequently, genetic and epigenetic factors that control the rate at which mutations are produced most likely define an individual's susceptibility to melanoma. More research is still needed to determine the exact function of UV light in carcinogenesis, including the relative contributions of UVA and UVB wavelengths. Given the continuous efforts to develop broad-spectrum sunscreen agents that have been authorized by the FDA. The presence of melanomas at cutaneous sites that are not exposed to the sun suggests that UV-independent mutagenesis occurs in melanoma, which is well supported by the available data.[32]

A. Secondary Prevention

Attempts to test for melanoma— Early detection and treatment of pre-lethal melanoma are essential for the effectiveness of early detection as a secondary prevention strategy. This calls for a strategy that: 1) informs at-risk individuals about skin self-examinations and clinical warning indications of melanoma, 2) ensures access to medical professionals who can detect melanoma early on, and 3) leads to the right kind of treatment. Additionally, an ideal early detection program should minimize biopsy of benign lesions and ensure that the advantages of early diagnosis outweigh the risks. Overtreatment of somewhat slow-growing skin malignancies, which can raise screening expenses without providing much additional value. Germany, Australia, Belgium, France, and the United States have all tried early detection programs. America. According to a recent evidence-based study, there is not enough evidence to support the claim that screening programs are helpful overall. To ascertain whether the identification of thinner primaries results in appreciable drops in the overall melanoma death rate, we await more information from these screening initiatives, particularly Germany's national initiative.[33]

XVI. CONCLUSION

UV radiation from sunshine is the main environmental risk factor for the development of melanoma skin cancer (4–6). The increased risk of melanoma from sun exposure is tightly associated with UV intensity, and more especially, the UV-B spectrum (5). Moreover, a number of studies have connected a higher risk of melanoma to the timing and patterns of sun exposure. In particular, a chronic, continuous pattern of sun exposure is more frequently associated with actinic keratosis and non-melanoma skin cancers, whereas intense and intermittent sun exposure, which is typical of sunburn histories, is associated with a higher risk.

Melanoma is a major public health issue these days. Thousands of people worldwide lose their lives to melanoma every year due to its complexity and unpredictable nature. A few examples of variables linked to elevated risk are age, sex, ethnicity, and personal phenotypic characteristics. However, melanoma is a very avoidable condition. Cancer because UV radiation exposure is the main risk factor. Therefore, it is crucial to invest in the population's health literacy.

IHC has become more used as an auxiliary test for melanoma diagnosis within the past 20 years. The creation of reliable, sensitive, and targeted cancer biomarkers in the area of Research is still being conducted on tissue immunohistochemistry. Despite its potential as a diagnostic (and even predictive) tool, this approach has drawbacks.

Because IHC scoring can be arbitrary, creating diagnostic systems that use several biomarkers will necessitate the concurrent establishment of stringent interpretation standards and standardization protocols to guarantee repeatability across pathologists and between laboratories. Newer, more objective, and repeatable techniques are being developed and have the potential to completely change the way malignancies like melanoma are diagnosed, even though IHC is a helpful method for biomarker recognition.

Until the 20th century, when wise clinical observations and developments in molecular biology demonstrated the hereditary basis of melanoma, the disease was still poorly understood and deadly. and environmental elements that contribute to its growth and development. One of the most prevalent and aggressive types of skin cancer nowadays is melanoma, which is also one of the most curable if caught early. The study of mutational profiles was transformed by genomics. From the 1800s until the 2010s, immunotherapies and cytotoxic chemotherapy followed significant advancements in the history of melanoma. Melanoma may have a better future thanks to genetics, which may also lessen the suffering of oncologists who treat largely fatal cases.

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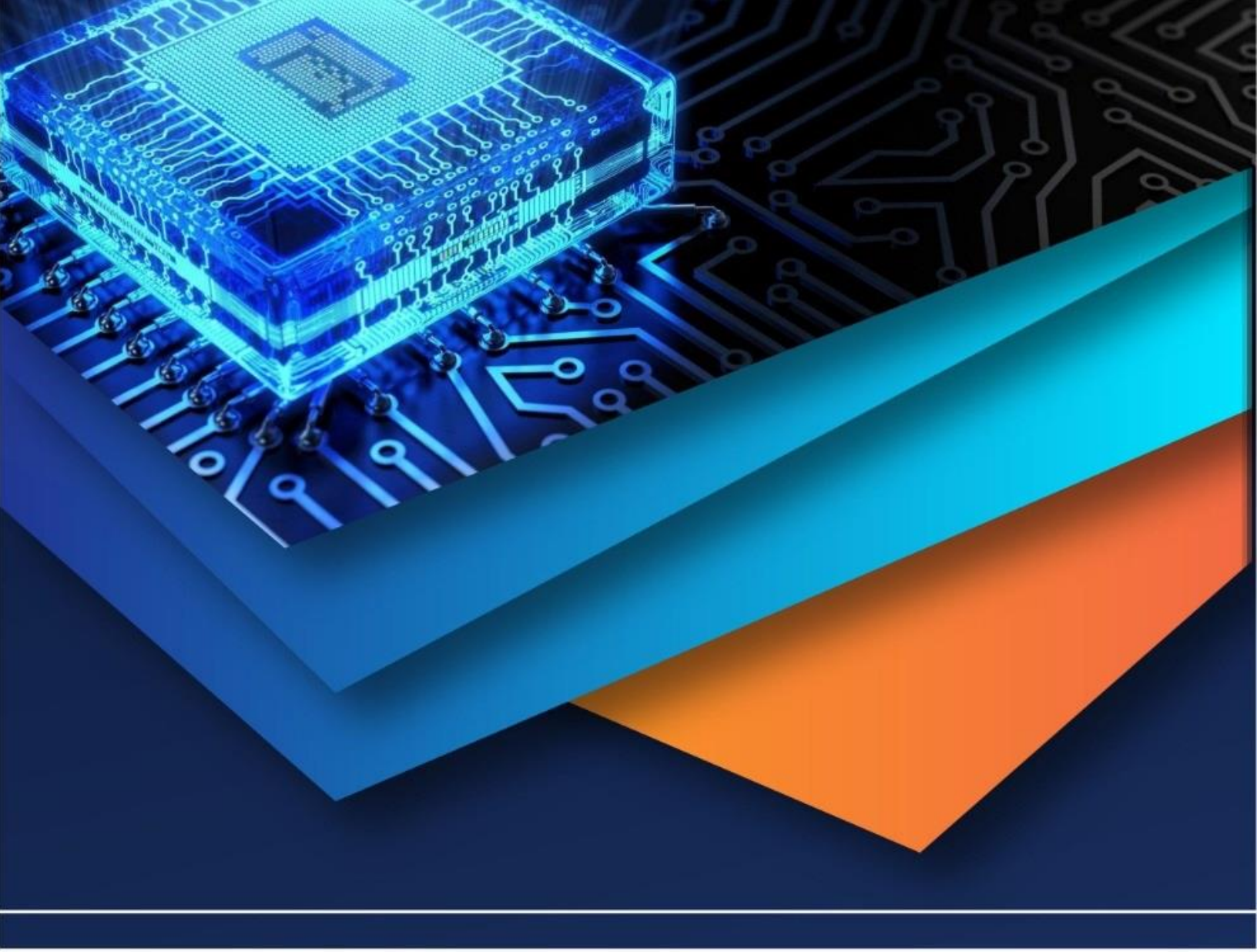
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