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Skin Cancer Cutaneous Squamous Cell

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Abstract: ***Usually due to UV light-induced DNA damage, keratinocytes in the epidermis proliferate abnormally, resulting in cutaneous squamous cell carcinoma (cSCC). Histological assessment is still the gold standard for identifying cSCC, but modern optical imaging diagnostic techniques enable doctors to perform "optical or virtual biopsy" in real time. Presenting a current literature review and advancements in optical imaging diagnostics for cSCC is our aim. Papers published between 2008 and 2022 were thoroughly evaluated using the PubMed, Embase, and Cochrane databases. Out of the 9581 total articles that the search yielded, 136 relevant articles that satisfied screening and eligibility criteria were included in the literature evaluation. This paper highlights the optical imaging techniques currently used to diagnose cSCC.***

The most recent advances in nonsurgical care of SCC were reviewed, despite the fact that surgical excision or Mohs micrographic surgery is still regarded as the gold standard. The review of the literature leads us to the conclusion that modern optical imaging tools, including multiphoton tomography, optical coherence tomography, line-field confocal optical coherence tomography, and confocal microscopy, have transformed real-time diagnostic imaging in dermatology, especially in the field of skin cancer. Rapid diagnosis and therapy beginning are made possible by these gadgets. Patients with multifocal cSCC, for whom many biopsies would be impractical, or high-risk patients (such as those who have received organ transplants or are exposed to prolonged UV radiation) may benefit from the use of modern imaging technologies in the management of cSCC, therefore avoiding needless biopsies. Optical imaging technology, in conjunction with dermoscopy, can enhance diagnostic efficiency by decreasing turnaround time

Keywords: Etiology, Hpv, Dignosis, Riskfactors, Biology And Pathogenesis, Advancetreatment, Theraoputic Aproches In Cutaneous Scc, Management , Prevention

I. INTRODUCTION

A Synopsis The formation of malignant epidermal keratinocytes is a characteristic of CSCC. Long-term exposure to sunlight is one of the most significant factors in CSCC. The activation of the NF-kB, MAPK, and PI3K/AKT/mTOR networks are among the signaling pathways that mediate the overexpression of the epidermal growth factor receptor (EGFR), along with genetic[1].

Between 1990 and 2017, the incidence of SCC rose by almost 310% in 195 countries globally [2]. Understanding the environmental and individual risk factors for cSCC as well as the circumstances that raise the chance of acquiring it can help prevent and detect cSCC early. A history of sunburns as a child or adult, a history of precancerous intraepidermal lesions (such as actinic keratosis-AK-) or Bowen's disease, a history of prior skin cancer, a compromised immune system (such as in patients with leukaemia or lymphoma or those receiving immunosuppressants), and some uncommon genetic disorders (such as xeroderma pigmentosum) are common individual risk factors.cSCC can be brought on by ionizing radiation, artificial ultraviolet radiation (UVR), such as tanning beds, and dermal exposure to certain substances like coal tar or arsenic. The International Agency for Research on Cancer (IARC) has categorized solar UVR exposure as carcinogenic to humans (Group 1), making it likely the most significant risk factor [3]. The paper that follows details a range of diagnostic and therapeutic approaches, from traditional to innovative. The type of treatment employed depends on the location of the tumor, the stage and type of skin cancer, and patient-dependent factors like age, comorbidities, and treatment preferences. Advanced therapeutic options include immunotherapy. 4. With more sophisticated treatment options including immunotherapy and targeted therapy, the management and results of skin cancer treatment are more hopeful. Four Estimates for the United States were proposed in 2012 based on available data. Nodal metastases occurred in around 3% of the estimated 186,157 to 419,543 white individuals with cSCC who received a diagnosis [1].

II. ETIOLOGY

The development of cutaneous squamous cell carcinoma is connected with the following risk factors and etiologies:

UV radiation:The two main risk factors are UVA and UVB.

Other environmental exposures besides UV radiation include ionizing radiation, polycyclic aromatic hydrocarbons, nitrosamines, arsenic, and alkylating chemicals.

Factors related to age, gender, and fair skin.

Iatrogenic, leukemia, and AIDS are examples of immunosuppressed states.

Genetic immunodeficiency syndromes, keratitis-ichthyosis-deafness syndrome, Fanconi anemia, oculocutaneous albinism, xeroderma pigmentosa, dyskeratosis congenita, Rothmund-Thomson syndrome, Werner syndrome, Bloom syndrome, dystrophic epidermolysis bullosa, and epidermodysplasia verruciformis are among the genetic syndromes.

Human papillomavirus, actinic keratosis, porokeratosis, lichen sclerosus et atrophicus, hypertrophic or oral lichen planus, discoid cutaneous lupus erythematosus, and chronic wounds (Marjolin ulcer) are examples of preexisting lesions.

Immunosuppressive medications include voriconazole, vismodegib, and BRAF inhibitors. 5.

III. HPV

It is evident that cSCC and the human papillomavirus (HPV) are connected. Carcinogenesis is facilitated by the constitutive activation of oncogenes such as E6 and E7 found in HPV types 16 and 18, respectively. The most prevalent viral subtype in ungual cSCC is HPV 16, which is detected in 74% of patients. According to a 2016 meta-analysis, additional HPV subtypes 5, 8, 17, 20, and 38 were associated with an increased risk of cSCC in immunocompetent individuals. SOTRs often have HPV types 8, 9, and 15. Interestingly, HPV is not actively transcribed in cSCC, but it promotes carcinogenesis in its early stages. A single Although HPV has been isolated in some CSCCs, no carcinogenic mechanism has been identified to account for the association.1

The retinoblastoma protein (pRb) is bound and broken down by the HPV E7 protein, which stops it from blocking the transcription factor E2F and causes a lack of cell cycle regulation. According to a recent review, the E6 and E7 proteins also interact with a wide range of additional intracellular targets (Munger et al., 2004). It has been demonstrated that cells expressing E6 experience structural chromosomal alterations, while cells expressing E7 develop aneuploidy and accumulate a variety of chromosomal defects (White et al., 1994). Dysregulated cell cycle progression and HPV DNA replication in infected squamous epithelial cells, followed by oncogenesis, are the ultimate consequences of E6 and E7 protein activity. 6.

IV. DIGNOSIS

1) Clinical presentation and diagnosis of the most common kind of cSCCAn actinic keratosis that progresses to a hyperkeratotic state, its base infiltrates, or it becomes ulcerated or sensitive is the most common clinical sign of invasive cSCC. The majority of cSCCs are caused by actinic keratosis, although over a few years of follow-up, the rate at which AKs progress to invasive cSCC seems to be minimal (less than 1/1000 years over a 5-year follow-up). It's interesting to note that AKs with persis tent beta papilloma virus infections appear to experience the progression more frequently. 7.
2) Tumour appearance and location determine the differential diagnosis of cSCC. Small or non-keratotic lesions can be mistaken for amelanotic melanoma, atypical fibroxanthoma, or basal cell carcinoma, despite the fact that SCC is typically easy to identify. Warts and other benign skin lesions, such as HPV-induced papillomas and bowenoid papulosis of the genital area, can be mistaken for cSCC of the genital or extremities at first. Only the patient's medical history can be used to suspect metastatic squamous cell carcinoma, but pseudoepitheliomatous hyperplasia can mimic SCC that develops on chronic inflammation. Usually, pathology findings are malignant adnexal tumours.By displaying diagnostic characteristics like glomerular or hairpin vessels, white circles, and areas devoid of white structures, dermoscopy can help in the differential diagnosis. A definitive diagnosis typically necessitates a biopsy or lesion excision.8

Reflectance Confocal Microscopy

Considering Confocal Microscopy RCM is a noninvasive technique that images the skin in vivo with cellular-level resolution (0.5-1.0 mm in the lateral dimension and 4-5 mm in the axial dimension) using near-infrared laser light at 830 nm. Depending on the wavelength of the laser light used, the imaging depth is limited to 200–300 mm, which is the same as the papillary dermis in healthy skin. This technique produces grayscale horizontal skin photos with a resolution comparable to standard histology 9.

V. RISK FACTORS

1) *Ultraviolet Radiation*

The most common cause of CSCC is exposure to ultraviolet (UV) radiation. Deoxyribonucleic acid (DNA) damage is caused by UV radiation in a number of genes.

Half of CSCCs have been shown to contain mutations in the p53 tumour suppressor gene, which is involved in DNA repair pathways. Cumulative chronic UV exposure, whether from natural or artificial sources, is associated with the establishment of CSCC. Schmitt et al. found in a meta-analysis that people who were exposed to UV light at work had a twofold higher risk of developing CSCC. In a similar vein, another meta-analysis revealed that people who had ever used tanning beds had a 67% higher risk of developing CSCC than people who had never used them.Lastly, a 30-year cohort showed that patients who had received more than 350 psoralen and ultraviolet A (PUVA) treatments had a significantly higher chance of developing CSCC (350-450 vs. 50 treatments, incidence rate ratio [IRR]=6.01, 95% confidence interval [CI] =4.41- 8.20).10

Ionizing Radiation

Radiation Ionization It has been demonstrated that ionizing radiation therapy can cause the development of CSCC. The total accumulated dose is the most significant risk factor, and it has an inverse relationship with the latency period for the development of CSCC.10

2) Genetic Factors

Similarly, many and early cSCCs are a feature of xeroderma pigmentosum, a rare condition that includes a range of hereditary problems in DNA repair, and oculo-cutaneous albinisms, which include a panel of disorders of melanin production. A high rate of cSCC is also linked to other inherited illnesses including epidermodysplasiaverruciformis, a genetic ailment with a fault in the protection against HPV, in addition to genetic syndromes with defects of the protective mechanisms against UVR. Immune suppression, such as that caused by allogeneic organ transplantation, immune-mediated illness treatment, or oncologic conditions like leukemia or lymphoma, is linked to a higher risk of cSCC because it reduces immunosurveillance against HPV and cancer.Although to varying degrees, all immunosuppressive medications, such as chemotherapy, traditional immunosuppressives, or even biologic drugs, affect this risk. Organ transplant recipients are the finest example of iatrogenic immunosuppression, as they are linked to a 65–250-fold rise in .8

Novel Genetic Research in Management of cSCC

Innovative Genetic Studies in the Treatment of cSCCThe subjective character of histological reporting, the absence of a uniform reporting method, and the failure to record risk at the molecular level are some of the drawbacks of clinicopathological factor-based risk assessment and formal staging systems, notwithstanding their usefulness. For stratifying metastatic risk, the 40-gene expression profile (40-GEP) test, clinicopathological risk assessment, and molecular profiling have shown significant prognostic utility. This strategy will encourage personalized risk assessment and enhance results.11

VI. BIOLOGY AND PATHOGENESIS

Our knowledge of the molecular mechanisms underlying the formation of CSCC has advanced significantly, and several genes have been found to be essential for the beginning and maintenance of tumors. However, CSCC has one of the highest median TMBs of any tumor type, meaning that each megabase contains hundreds of mutations. Separating genuine oncogenic alterations from passenger mutations is one of the difficulties in comprehending the molecular mechanisms underlying CSCC. Here, we go over the carcinogenic functions of a few frequently altered genes, including CDKN2A, TP53, and Notch. There are currently no known specific oncogenic drivers of CSCC.CSCC have been identified.Primarily a transcription factor, p53 has the ability to either activate or repress a wide range of target genes. Specifically, nucleotide excision repair (NER) and other DNA repair mechanisms that are critical for repairing UV-induced DNA damage are modulated by p53. TP53 mutations permit continuous, unrepaired UV-induced DNA damage. For instance, individuals with genetically compromised DNA repair systems, such as those with xeroderma pigmentosum who develop NMSCs in childhood, have a markedly increased chance of developing CSCCs.12

ETIOPATHOGENESIS

The development of cSCC is described by the multistage paradigm of malignant transformation. The clinical term "actinic keratosis" refers to a focused keratinization disorder that results from clones of mutant cells inside the epidermis. This condition causes cellular atypia and a focal area of loss of normal architecture. Intraepithelial or in situ neoplasms are caused by atypical keratinocyte growth across the epidermis and usually present as Bowen's disease. The accumulation of extra cellular and mutational processes will lead to invasive growth and, less often, metastasis. The most common genetic defect among cSCCs is a mutation in the tumor suppressor gene p53.7

VII. ADVANCED TREATMENT

Treatment of Primary Site

- The primary goals of treatment for cSCC are to cure the tumor while preserving function and appearance. In patients whose cSCC grows among multiple actinic keratoses and multiple in situ tumors, a number of destructive but blind modalities (cryotherapy, curettage & electrodessication, photodynamic therapy with ALA or methyl ALA) or topical agents (imiquimod 5% and 3.75%; 5-fluorouracil 0.5%, 1%, and 5%; diclofenac 2.75%, ingenolmebutate 0.05% and 0.015%; chemical peels) can be used to "sterilize" the area of cancerization (see EDF guidelines of actinic keratosis). 7.
- Localized Resectable
- Diseases at High Risk Adjuvant therapy is frequently not necessary for the majority of CSCCs since they are tiny, indolent, and surgically resectable. However, patients with resected high-risk localized disease—generally characterized as tumors exhibiting implicated resection margins, depth of invasion exceeding 2–6 mm, substantial perineural invasion, or major nerve involvement—are given consideration for post-operative radiation [2,149]. Large primary tumors and involvement of lymph nodes are further signs.
- Following Surgery, Chemoradiotherapy Since multiple studies have demonstrated a survival benefit, platinum chemotherapy drugs like cisplatin and carboplatin are frequently used in conjunction with postoperative irradiation in patients with mucosal head and neck squamous cell carcinoma (HNSCC). These trials' findings have been extended and used with cutaneous SCC patients. Prior to recently, no conclusive prospective study had been conducted to support its usage in this population.12
- Current treatment modalities
- The European Interdisciplinary Cancer team has rolled out theirlatest guideline on CSCC based on a consensus meeting in
- September 2019. Suggestions were based on systematic examination of the literature, guideline and expert consensus. Surgical excision with postoperative margin evaluation or microscopically controlled surgery (Mohs) are the first-line treatments for primary CSCC. To reduce the risk of local recurrence and metastasis, safety margins containing clinically normal-appearing tissue around the tumor after surgical excision and negative margins as documented in the pathology report are required. There should be no flap replacement until the margin has been cleared definitively. For operable instances, a re-excision should be performed if the margins are affected.13

VIII. NOVEL THERAPUTIC APPROCHES IN CUTANEOUS SCC (Targeted Therapies and Immunotherapies)

1) Surgery

The major goals of treatment are to remove the tumor completely, preserve as much of the surrounding healthy tissue as possible, and achieve favorable cosmetic results. With a five-year cure rate of more than 90%, classic early surgical excision is the preferred treatment for localized stages . The EDF-EADO-EORTC group states that the surgical resection limits are extended up to 10 mm for high-risk tumors and 5 mm for low-risk tumors . Given the higher curability linked to reduced recurrence rates, maximum tissue preservation, and good esthetic results, Mohs microsurgery with margin control may be an alternative for patients with specific anatomical sites or high risk [88]. Four to five percent of SCC patients proceed to more advanced stages: progressed locallymetastatic illnesses (less than 5%) with distant or locoregional metastases; these stages call for additional therapeutic strategies including radiotherapy, chemotherapy, or, more recently, immunotherapy. Because metastatic forms are rare, they present a treatment challenge; a multidisciplinary team of dermatologists, surgeons, radiotherapists, and oncologists must make medical decisions on these patients' care.14

2) Radiation Therapy

High-risk cSCC can be treated with radiation therapy, although the results are typically worse than with surgery. The technique's inability to confirm margins, a crucial consideration when dealing with large or thick tumors, limits the application of radiation therapy. Therefore, older patients with incurable cancers are typically the only ones who receive radiation therapy. However, radiation therapy can produce better functional and cosmetic results at some areas, such the lower lip, and can produce results comparable to those of surgical treatment.15

a) Primary radiation therapy

First-Line Radiation Treatment For tiny, well-defined primary CSCC, primary radiation therapy is an additional therapeutic option; however, it should only be used for individuals who are not candidates for surgery .

According to a systematic evaluation of 761 individuals treated with primary radiation for CSCCs, the disease-related death rate was 9.1% (95% CI, 1.4%-22.8%) and the local recurrence rate was 6.4% (95% CI, 3.0-11.0%).10

b) Adjuvant Radiation Treatment

When high-stage cancers with certain risk characteristics are surgically excised, adjuvant radiation therapy should be taken into consideration. As a salvage treatment for cases not treated with surgery or those with in-transit metastases, radiation is currently advised for CSCC cases with large caliber nerve invasi (> 0.1 mm nerve diameter), cases with doubtful or positive surgical margins, and those with these characteristics. When radiation therapy is used as an adjuvant instead of salvage therapy, treatment outcomes are maximized.10

3) Chemotherapy

Systemic therapies containing cytotoxic agents have been used off-label in advanced cSCC. Although polychemotherapy, 5-fluorouracil, bleomycin, methotrexate, taxanes, gemcitabine, and cisplatin/carboplatin have been shown to be more successful than monotherapy, they are also linked to more severe adverse events. Isotretinoin, interferon, and cytotoxic agents were the treatments employed more than thirty years ago; they were effective against cSCC but had little effect on metastases [93]. Platinum-based chemotherapy was the first line of treatment until the advent of targeted therapy, but it was fraught with significant toxicity and a higher chance of the cancer being treated recurring.14

4) Targeted theorapy

a) Particular Treatments

Inhibitors of CSCC and Sonic-Hedgehog Ironically, medications used to treat melanoma and basal cell cancer (BCC) can trigger CSCC. A smoothened inhibitor (Hedgehog pathway inhibitor) called vismodegib has been approved by the FDA and EMA to treat locally advanced and metastatic BCC. There have been several case reports connecting vismodegib to CSCC, and a retrospective cohort study revealed this increased risk. A later study was disputed by other academics because it was unable to replicate such a correlation. Vismodegib-treated BCCs have also been demonstrated to display squamous metaplasia. But according to some evidence, hedgehog inhibitors may potentially increase the risk of CSCC.16 .

b) BRAF and CSSC Inhibitors

Inhibitors of CSSC and BRAF About 50% of melanomas have a BRAF mutation, and the availability of BRAF inhibitors, namely vemurafenib and dabrafenib, a few years ago, expanded the range of available treatments for this tumor. Compared to dacarbazine, these medications improved PFS and overall survival, but they markedly raised the chance of CSCC. These medications work because they can disrupt the MAPK pathway, which is downstream of constitutive BRAF activity. However, in cells with non-mutated BRAF, BRAF inhibitors may paradoxically increase the MAPK pathway, which is necessary for the establishment of CSCC. 16.

5) NEO Imminotherapy

The effectiveness of ICI in treating individuals with advanced disease has led to initiatives to introduce it into earlier stages of the disease to reduce (a) the morbidity associated with massive tumor resections and (b) the danger of locoregional relapse or metastasis. Clinical and translational uses of neoadjuvant immunotherapy are highly desirable. Tumor and stroma changes can be observed by comparing pretreatment biopsies with the resection specimen. Neoantigens and intratumoral immune cells within the incurable malignancy may also improve immune activation. Furthermore, neoadjuvant studies offer faster evaluation using pathologic response, in contrast to adjuvant research, where survival data may take years to mature. 1.

6.SyatematicTherapy

Systemic Treatment Patients who have metastases or locally progressed SCC in spite of prior treatments may benefit from systemic therapy. Clinical features (location, symptomatic perineural invasion, and tumour size), histological features (poor differentiation, desmoplasia, thickness, and perineural invasion), immunosuppression, and radiological features (bone erosion and radiological PNI) are among the high-risk prognostic factors for cSCC recurrence that were established by European interdisciplinary guidelines (EADO, EDF, and EORTC) in 2020. As a result, these patients require therapeutic protocols.14

IX. MANAGEMENT

The American Academy of Dermatology (AAD) and the National Comprehensive Cancer Network (NCCN) have established standardised guidelines for the management of cSCC. cSCC is stratified into low- and high-risk subgroups to help with management choices . To get an acceptable cosmetic result, the main goal of cSCC treatment is to completely remove a tumour through surgery while preserving healthy tissue . For cSCC, surgery with margin analysis is the primary therapy option. Sectional evaluation for standard excision and complete circumferential, peripheral, and deep margin analysis (CCPDMA) for Mohs surgery and its variations (such as the muffin technique or the Tubingen torte technique) are the two types of margin analysis . Approximately 1% of the tissue sample's marginal surface area can be visually evaluated using sectional evaluation, which uses bread-loafing .17

Through face segmentation, CCPDMA enables histologic evaluation of the entire margin. Standard excision with 4–6 mm margins and postoperative margin evaluation are the first-line treatments for localised, low-risk cSCC . When it comes to the head or neck, immunocompromised patients, recurring illness, aggressive histologic subtypes, or lesions that are 2 mm deep, Mohs surgery is the preferred course of treatment . Liquid nitrogen or cure and electrodessication (C&E) can be used to destroy cSCC in low-risk cSCC or cSCCIS . C&E can be used to treat a CSCC larger than 2 cm, however the recurrence rate is 11.8% . When there is relapse, perineural invasion, or positive margins following excision, radiation therapy may be used.17

Areas near cosmetically sensitive regions, such as the lower eyelid, inner canthus, lip, nose tip, or ear, can benefit from radiation therapy (RT) . For certain patients, the scar created by routine excision or surgery may be a more acceptable cosmetic result because RT frequently results in treatment-related side effects as skin pallor and telangiectasia . Additionally, RT has a worse cure rate than traditional surgical excision . After surgery, RT can be administered as an adjuvant in high-risk cSCC [28,108]. After an 18-month follow-up, 48 cases of cSCCIS with one or more passes were treated with ablative laser therapy (carbon dioxide laser), with a recurrence rate of 6.8%.17

X. PREVENTION

To prevent patients with precancerous lesions from developing invasive cSCCs. Treatments and early detection are crucial. Educating people about sun protection measures, such wearing protective clothing and using sunscreen, is essential. The preventive impact of broad UV-A/B coverage and high SPF sunscreens in avoiding new cSCCs has been amply proven by prospective research. However, studies are still being conducted to ascertain the function of statins, nutrition, vitamin D supplements, and non-steroidal anti-inflammatory medications as chemopreventive agents. It is desirable to treat field cancerization in photodamaged skin in order to prevent the formation of cSCC. 7.

XI. CONCLUSION

Even with a multidisciplinary approach, advanced squamous cell carcinomas are challenging for clinicians to treat. The prevention and identification of early-stage tumours that can result in a great prognosis are equally crucial, but novel treatments are required because advanced tumours frequently do not respond to traditional treatment choices. Although the majority of novel treatments are currently undergoing clinical trials or require approval, their therapeutic benefits are undeniable. As a result, innovative targeted medicines with few adverse effects for patients depend on a deeper comprehension of the pathophysiology of cSCC and the molecular, genetic, and epigenetic factors underlying tumour cell behaviours.

The accuracy of skin cancer diagnosis could be greatly increased by integrating CAD algorithms. The types of AI models utilised, the nationalities of the researchers, the publication years, and the geographic locations of the studies are only a few of the features of research in the field of HSI for skin cancer detection that we have methodically categorised and investigated in this study. The worldwide efforts and various strategies used to use HSI for skin cancer diagnosis are demonstrated by this thorough analysis. Nonetheless, it's critical to recognise the current constraints in this area. Relevant research has noted limitations such low patient involvement and a lack of readily available training datasets and imaging data. These difficulties show how much more cooperation and data sharing are required.

Collaboration to maximise the effectiveness of HSI technologies in the identification of skin cancer. Going forward, improving the early detection and individualised treatment of skin cancer will be made possible by sustained HSI research and innovation as well as a dedication to resolving these limitations. Studies using HSI have shown increased precision in the early identification and distinction of skin cancer forms, including squamous cell carcinoma, basal cell carcinoma, and melanoma.

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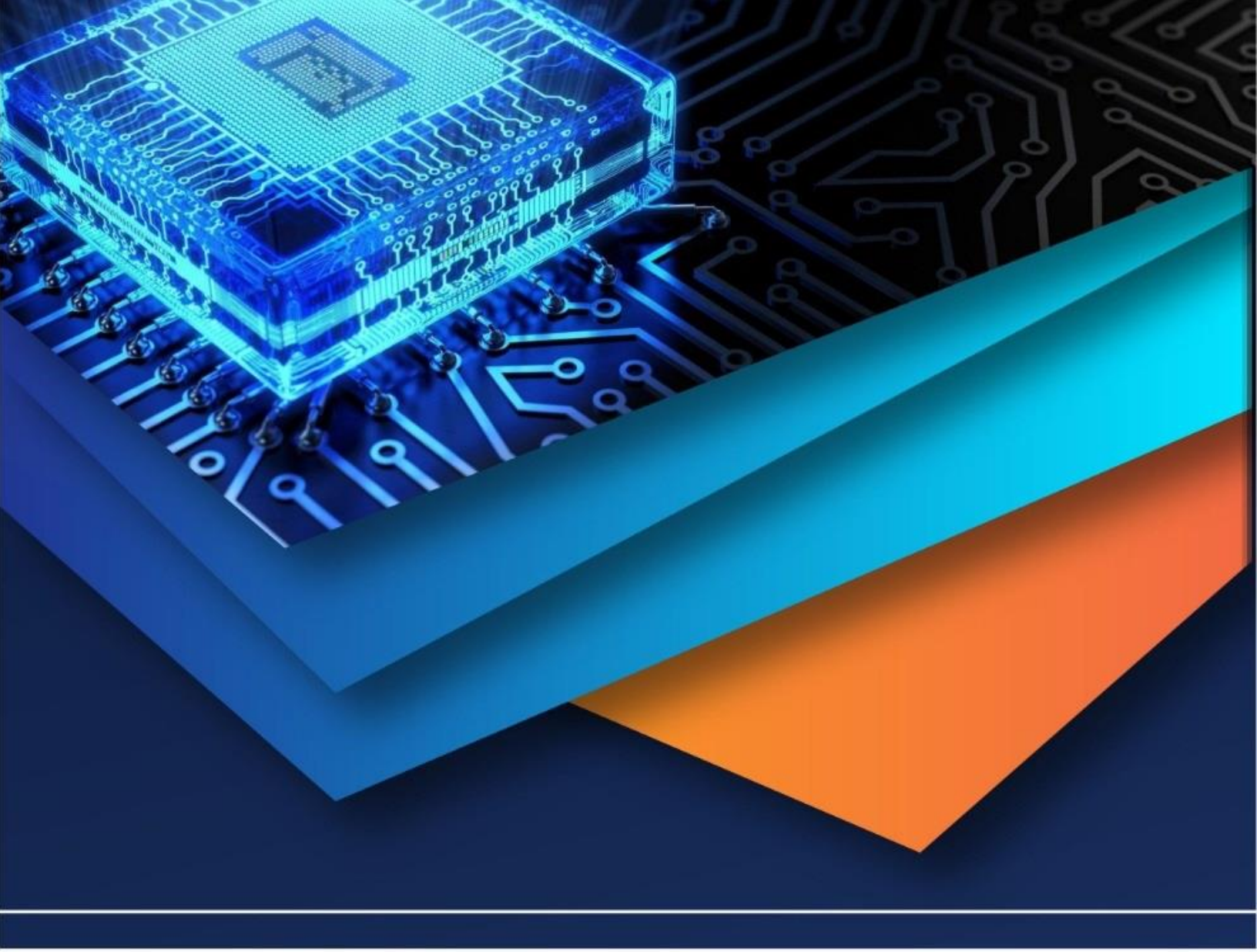

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