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Risk factors and treatment for Non-Melanoma Skin Cancer (N-MSC) in solid organ transplant recipients

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ABSTRACT

Background: Skin cancers that are not melanomas are known as Non-Melanoma Skin Cancers (NMSC), and they are the kind of cancer that is seen in Solid Organ Transplant Recipients (SOTR) the most commonly.

Objective: The purpose of this research is to give the latest information on the prevalence and take better care of NMSC in SOTR.

Results: The occurrence rates during ten years vary widely from country to country, ranging from 24% in Northern Europe to 80% in Australia to 15% in Italy. More than fifty percent of NMSC are found on parts of the body that are directly exposed to sunlight (the head and the palms of the hands, for example). Some risk factors have been discovered, some of which include age at organ transplantation, fair skin, the medication that suppresses the immune system type, cumulative exposure to sunlight, infections caused by viruses, and a variety of biological markers. Patients who have already been diagnosed with an NMSC for the first time have a risk that is 49 times greater of being diagnosed with a second NMSC. All transplanted patients should be advised to self-examine their skin and take measures to protect themselves from the sun. Skin surveillance over an extended period, prompt detection and severe management of any questionable behaviour, diminishing of immunosuppression medications, and switch to m-TOR inhibitors are all potential beneficial approaches for reducing the incidence of NMSC.

Conclusion: NMSC is the kind of malignancy that is seen most often in SOTR. Effective approaches for reducing the prevalence of skin cancer other than melanoma include early detection, education of patients, and change of immunosuppression.

Keywords: basal cell carcinoma, Non-Melanoma Skin Cancer (NMSC), solid organ transplant, squamous cell carcinoma

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INTRODUCTION

Cancer incidence is rising globally as a consequence of changes in the climate, prolonged exposure to sunshine, and personal and societal factors [1]. Due to insufficient reporting, it is difficult to determine the actual incidence of skin malignancies; nevertheless, procedures for prevention and detection are becoming increasingly accurate and successful [2]. Merkel Cell Carcinoma (MCC) that has traditionally included in the category of neuroendocrine tumours despite having a strong tendency to invade lymph nodes represents an odd episode in the overall picture of skin malignancies [3]. Fair skin photo type, prolonged sun exposure, advanced age, suppression of immunity, and infection with HPV are indicators of risk for NMCSs. The majority of NMSCs are found on skin that is more frequently exposed to sunlight, particularly on the hairline, face, and dorsum of the hands [4]. NMSCs make up almost 40% of all skin cancer-related diagnoses, making them very prevalent. The incidence of NMSCs is on the increase due to a population getting older that exhibits significant amounts of cumulative Ultraviolet (UV) radiation and immunosenescence [5]. The impact of skin cancer in the United States needs to be better understood so that evidence-based decision-investment in resources and healthcare planning may be carried out to reduce the prevalence, incidence, morbidity, and death rates associated with skin cancer [6].

Mediated immune reaction, Solid Organ Transplant (SOT) patients are known to be more susceptible to several respiratory viral infections, including influenza [7, 8]. The degree of immunosuppression corresponds with the severity of many infectious illnesses in Solid Organ Transplant (SOT) patients, which led to the first hypothesis that SOT participants may be more prone to severe COVID-19 [9]. Skin cancer is the most prevalent kind of cancer among Solid Organ Transplant Recipients (SOTR). SOTR are at a greater risk of acquiring melanoma and nonmelanoma skin cancers [10, 11].

The paper [12] discusses several viewpoints on skin carcinogenesis and presents updated information on the genetic characteristics of NMSC, potential genes, and novel therapeutics. Healthcare systems have faced difficulties as a result of the worldwide epidemic and the state of the world's health, especially in the diagnosis and treatment of individuals with cancer following the Common Terminology Criteria for Adverse Events (CTCAE), premature skin exposure was categorized. Following at least a year, cosmetic outcomes were assessed using the RTOG scale developed

by the Radiation Therapy Oncology Group (RTOG) [13]. Observational studies were considered appropriate for inclusion if they determined a potential ratio of NMSC in individuals who suffered from psoriasis. We retrieved data from the studies that were included in the meta-analysis, and we used random-effects models for the analysis [14]. A technique for the categorization of melanomas that utilizes deep learning is suggested in the paper. The effectiveness of the suggested modified U-net network in lesions categorization is quite high when used in combination with after-processing approaches [15]. Classification, segmentation, localization, and many more domains have benefited from the use of deep learning. The article examines deep learning methods for separating melanoma instances from other skin lesions in dermo copy and clinical photos [16]. The application's foundation is a Convolutional Neural Network (CNN) that was trained using patient demographic data and clinical imaging data that were both gathered from cell phones [17]. Skin cancer datasets are unbalanced, the paper provides a method for balancing datasets that uses the mutation operator, which is part of the Differential Evolution (DE) algorithm [18]. Three approaches for image categorization were suggested in the article. There are three types of dropouts: Deep Ensemble (DE), Ensemble Monte Carlo (EMC), and Monte Carlo (MC). We offer a unique hybrid dynamic BDL model that accounts for uncertainty and depends on the Three-Way Decision (TWD) model to further resolve the ambiguity that remains after using the MC, EMC, and DE approaches [19]. The study suggested using convolutional Neural Networks and the LeNet-5 architecture to identify image data using deep learning technologies [20]. To identify skin cancer abnormalities from skin imaging data, the study provides a short description of some of the most significant uses of deep learning and few-short learning algorithms [21, 22]. Laser therapy for NMSC underwent a thorough study and systematic review. Recurrence Rate (RR) served as the main result [23]. The research investigate the long-term hazards of primary and recurrent NMSC in OTR, as well as related risk variables [24]. An examination of medical records of patients from a dermato-oncological specialized clinic was the subject of a single-centre, retrospectively cohort research.

MATERIALS AND METHODS

In this section, we discuss in detail about risk factors and treatment for Non-Melanoma Skin Cancer (N-MSC) in solid organ transplant recipients.

NMSC epidemiology in Solid Organ Transplant Recipients (SOTR)

Patients who have had solid organ transplants are in danger of NMSC and Actinic Keratoses (AK), primarily SCC and BCC. Based on geographic latitudes, post transplantation NMSC incidence rates vary, the range in Italy is around 7% following 5 years of life and 9% at 10. A greater prevalence was observed in Northern Europe and Australia. In transplanted communities, the BCC: SCC ratio is inverted; the standardized mortality ratio is 70 times–260 times more for SCC and 10 times–30 times greater for BCC, with a higher risk in men, as contrasted with non-immunosuppressed individuals. A quarter of individuals who are not immunosuppressed have at least one AK, making them widespread in this population as well [25].

People who have had organ transplants are 250 times more likely to get AK than immunocompetent people. With a minimum of 50 AKs, the likelihood of developing an SCC was 12.7 times higher in transplant recipients. In transplant recipients with a history of NMSC, the chance of getting another NMSC is 49 times greater than in those without NMSC. It is uncommon for NMSC to develop in juvenile transplant patients. Minimal information is available, although NMSC is often identified in young adulthood, 12 years to 15 years following transplant. Table 1 provides a review of epidemiological information and risk variables.

Tab. 1. Analysis of risk factors of NMSC

Factors	Definition
A transplant patient's age	Between a period of three years in patients implanted beyond the age of 50 and 8 years in individuals implanted at the age of 40, the mean duration between transplantation and the development of NMSC varies
The kind of implanted organ	The incidence of NMSC in hepatic SOTRs during ten years ranges from 15% to 28% due to more acute suppression of immunity, older age at organ transplantation, and poor leukocyte antigen comparison, heart-related transplant patients and combined pancreatic and transplanted kidneys seem to be at greater risk for NMSC than organ transplant recipients, while there is no universal agreement on this
Continuation of NMSC risk	Within 13 months, 28% to 42% of individuals experiencing their initial SCC will develop a second lesion, and 49% will do so within 3.5 years. In the five years after the first NMSC, up to 100% of those receiving transplants develop additional NMSCs

Pathogenesis and etiology

UV infections of the skin brought on by electromagnetic radiation, immunosuppression, genetic factors, and Human Papilloma Virus (HPV) are the most significant variables regarding NMSC pathogenesis. But the cause of NMSC is a complicated.

Ultraviolet radiation

Considering the prevalence of NMSC, UV light appears to have a major influence is greatest in nations with a lot of sunshine, such as Australia. Additionally, more than half of all NMSC may be discovered on body regions sensitive to the sun, such as the head and hand palms people who have a lighter complexion, blue eyes, red or blond hair, and pale skin are more likely to develop NMSC than people who have a darker complexion. In both groups of patients from Australia and Italy, the total quantity of sun exposure over the lifespan, particularly before organ transplantation, was shown to be a major predictor of the risk of NMSC. Recent research found that sun exposure during leisure activities that were both vigorous and prolonged greatly enhanced the likelihood of acquiring NMSC. In contrast, research that followed participants for 24 months found that frequent use of sunscreen and wearing

of appropriate clothes were beneficial in lowering the incidence of newly diagnosed cases of AK and new NMSC.

Immunosuppressive drugs

The main risk factor for NMSC in SOTRs is drug-induced immunosuppression; however, there are contradictory data as to whether or not some immunosuppressive medicines encourage the formation of NMSC more than others. Even though azathioprine has been shown to enhance the vulnerability of DNA to damage caused by UV light and is mutagenic, its usage is now much less common than it was in the past. In many cases, mycophenolate mofetil (also known as MMF) has taken the position of azathioprine. Those who are treated with MMF seem to have a decreased chance of developing NMSC compared to those who are treated with azathioprine.

It has been shown that calcineurin inhibitors, such as cyclosporine and tacrolimus, reduce the number of Human keratinocytes subjected to Ultraviolet B (UV B) rays that undergo repairs to the DNA and mortality as a result. This results in an accumulation of DNA damage. The chance of developing NMSC was elevated by a factor of 2.8 when cyclosporine was added to a treatment plan that included azathioprine and prednisolone. According to the findings of other research, there is no correlation between the kind of immunosuppressive protocol and the development of NMSC.

This leads credence to the notion that the incidence of NMSC is the result of the level of immunosuppression rather than a particular medication regimen [26]. Prospective research in which individuals were randomly assigned to receive either a normal or low dosage of cyclosporine medication provided evidence in support of the hypothesis that the overall degree of immunosuppression has a role in the establishment of NMSC. The group that took cyclosporine at a modest dosage, increases the general probability of cancer, and the chance of developing skin cancer was dramatically reduced. It has been shown that immunosuppressive treatment with m-TOR blockers may reduce the likelihood of developing posttransplant malignancy, including NMSC.

In mice treated with m-TOR blockers, experimentally produced SCC as compared to animals who received calcineurin inhibitors or antimetabolites, they are much less common, numerous, large, vascularized, and progressing (Azathioprine and MMF). This was in contrast to the results shown in mice treated with calcineurin inhibitors or antimetabolites. Following a diagnosis of NMSC or AK, switching in calcineurin inhibitors to m-TOR slows the development of new lesions, causes a healing process of currently active lesions, and lowers the incidence of NMSC in the future. This occurs in the clinical situation.

Aspects of genetics

A recent study looked at the role that genetic variables play in the development of NMSC in SOTRs and analysed the results. Polymorphisms in the methylenetetrahydrofolate reductase gene have the potential to change the pattern of DNA ethylation, which in turn raises the risk of squamous cell carcinoma. These polymorphisms also have the potential to make DNA more sensitive to the damage caused by ultraviolet irradiation. Variations in the genes that control human pigmentation may alter the production of melanin and, as a result, may contribute to the damage caused by UV radiation to the skin.

P53 tumour protein abnormalities probably contribute to the emergence of anogenital SCC caused by HPV; however, it is uncertain to what degree this protein contributes to the NMSC pathophysiology in SOTRs. The body's the capacity to breakdown the waste materials produced by the damage from oxidation is restricted by a polymorphism in the glutathione-S-transferase genetic family, which leads to greater destruction of DNA and the eventual appearance of NMSC in SOTRs. This is true even after taking into account the patients' ages when they received their transplants. Interleukin-10 and the retinoblastoma gene are two additional factors that have been linked to the development of NMSC.

HPV infection

Individuals with squamous cell carcinoma containing certain beta-PV types on regions exposed to UV light provided primary proof that HPV may have a role in the development of SCC. Associated with the production of certain betaPV genes, it has been discovered that SCC specimens obtained from individuals with no immunity contain betaPV DNA as well as transplant recipients. There is functional evidence to support beta PV's possible involvement as a cocarcinogen when combined with UV light. In case–control investigations, the HPV identification of DNA is related to SCC as well as AK. The link correlation between beta PV contamination and SCC was established in recent case-control research includes the identification of antigens directed against the blood vessels bloodstream containing HPV, providing additional evidence for the function of this viral infection in the pathogenesis of NMSC.

NMSC's methodical approach to SOTRs

Every patient should be urged to do routine self-examinations of their skin and to take general precautions against skin cancer, such as wearing protective clothing and sunscreen, avoiding tanning beds, and not using sunlamps. Even if a patient does not report experiencing any of the symptoms or signs of Non-Melanoma Skin Cancer (NMSC), they should nevertheless undergo proactive monitoring, often known as frequent skin inspection, at least once a year.

The number of follow-up appointments can change depending on the risk factors associated with a particular kind of skin cancer. It has been shown that the use of topical imiquimod on skin regions up to 60 cm^2 is secure and efficient in lowering the number of AKs as well as the size of SCCs, and there were no adverse effects on the systemic immune response that were documented. When there are several lesions, electrodesiccation, and curettage could be performed instead of multiple surgical operations since patients are more likely to tolerate this technique than multiple surgical procedures.

An adequate cure rate may be achieved with aggressive electrodesiccation and curettage when treating suitably chosen low-risk skin cancers. This kind of treatment is also safe. For the management of superficial NMSC that are resistant to more traditional methods including sterilization, electrical surgery, CO_2 laser, oxygen cryotherapy, and topical 5-fluorouracil (5-FU), PDT 64 may be utilized in SOTRs.

It has been said that PDT provides a better cosmetic result and is more effective than 5-FU in achieving total recovery of tumours. The response rate for scalp and face lesions was seen to be 72%,

whereas the response rate for acral lesions was observed to be 40%. Although it has been suggested that prolonged exposure to PDT could inhibit the development of NMSC, there is no widespread consensus in support of this idea.

Any tumour that does not react well to these therapies needs to be removed surgically. It is recommended that surgical treatment for NMSC is carried out following the most recent recommendations and that clean margins are achieved for further histologic analysis.

No standardized enrolment criteria were utilized for selecting participants for the study. Because of these factors, the advantages of SLNB for preventing the course of illness and increasing the chances of survival with SCC are yet unknown and patients need to be closely monitored. People who acquire five to ten SCCs annually may consider systematic chemoprevention alongside retinoids or oral capecitabine.

Acitretin is most successful when administered at a dosage of 20 mg–25 mg per day; however, beginning treatment with a low dose of 10 mg and gradually increasing the dosage by 10 mg increments at intervals of two to four weeks helps reduce the risk of adverse effects and increases patient adherence. Before initiating treatment, a baseline fasting complete blood cell count, a lipid panel, liver function tests, and serum creatinine should be conducted.

Mild adverse effects were seen, such as mucositis, hand-foot syndrome, and muscle pains; nevertheless, more research is required to substantiate the encouraging outcomes shown in this study [27]. Patients who have recurrent NMSC or several NMSCs at the time of the initial consultation may benefit from reducing the amount of immunosuppressive medicine they are receiving or switching to an immunosuppressive regimen that is based on m-TOR. Even when the modification in treatment is made several years after the transplantation, this method is still successful [28, 29].

RESULTS

Between 2015 and 2019, a total of 195 individuals sought our assistance for skin tumours. Of them, 144 patients had malignant tumours, comprising 133 SCC and BCC individuals (Figure 1). This research included 152 cancer events from 27 SCC patients and 102 BCC patients, and 4 individuals with both types of skin cancer. The majority of BCC tumours appeared nodular, infiltrative (33 tumours); the other histological BCC variations were less common. There were only 5 non-keratinizing tumours among the SCC tumours; the other cancers included 11 clearly separated, 18 transition-differentiated, and 3 unclassified being found after SCC grading. During the 5 years, sixteen individuals had two NMSCs with distinct localizations removed. Four hospitalizations for BCC tumours in various head and neck areas were reported in a female outpatient who was 74 years old throughout 2015 and 2019. Table 2 shows the results of age of melanoma patients.

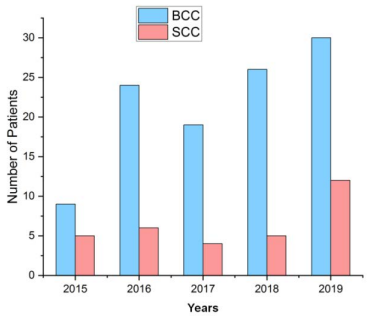

Fig. 1. Patient age distribution for skin cancer

Tab. 2. Results of skin cancer patients' age

Year	Number of Patients	
	BCC	SCC
2015	9	5
2016	24	6
2017	19	4
2018	26	5
2019	30	12

The surgical flaws in the frontal as well as temporal regions produced greater main sealing than membrane reconstructions, while the postoperative defects in the nasal, cheek, and orbital locations often needed flap reconstructions (Figure 2). Table 3 shows the computation analysis of reconstructive surgery.

Statistically meaningful results weren't found a link between the tumour stage and the amount of time needed to conduct surgery, even though the initial stage of NMSC patients were usually clinically cured in less than an hour (Figure 3). Table 4 shows the computation analysis of the stage of the tumour.

But there was additionally an extremely noteworthy relationship between the stage of the tumour and the number of days spent in the hospital. Levels I as well as II were typically treated between one and three days after admission to the hospital (Figure 4). Additionally, there was a statistical relationship between the number of hospital days and the kind of repair, with the main closure and grafts of skin needing fewer days in the hospital than local flap replacement. Table 5 shows the computation analysis of hospitalization days and tumour stage (Figure 5).

Considering a total of five of the six immunosuppressed individuals included in this research being older than 60, immunosuppressed patients also had greater treatment costs when compared

to non-immunosuppressed ones. Table 6 shows the computation analysis of the association between the kind of restoration.

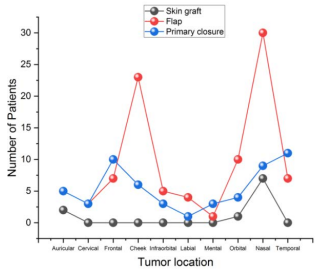

Fig. 2. The relationship between where the tumour is situated and the kind of reconstructive surgery

Tab. 3. Computation analysis of reconstructive surgery

Tumor Location	Number of Patients	
	Skin Graft	Flap
Auricular	2	5
Cervical	0	3
Frontal	0	7
Cheek	0	23
Infraorbital	0	5
Labial	0	4
Mental	0	1
Orbital	1	10
Nasal	7	30
Temporal	0	7

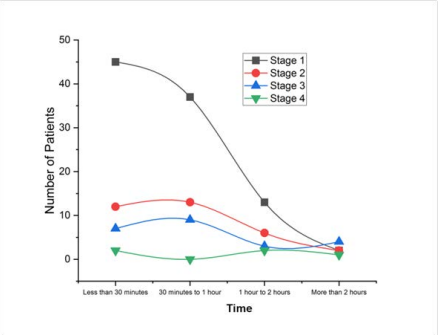

Fig. 3. The time needed for surgery and the stage of the tumour

Tab. 4. Analysis of risk factors of NMSC

Time	Number of Patients		
	Stage 1	Stage 2	Stage 3
Less than 30 minutes	45	12	7
30 minutes to 1 hour	37	13	9
1 hour to 2 hours	13	6	3
More than 2 hours	2	2	4

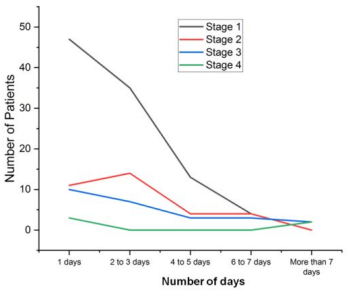

Fig. 4. Hospitalization days and tumour stage are correlated

Tab. 5. Computation analysis of hospitalization days and tumour stage

Days	Number of Patients			
	Stage 1	Stage 2	Stage 3	Stage 4
1 day	47	11	10	3
2 days to 3 days	35	14	7	0
4 days to 5 days	13	4	3	0
6 days to 7 days	4	4	3	0
More than 7 days	0	0	2	2

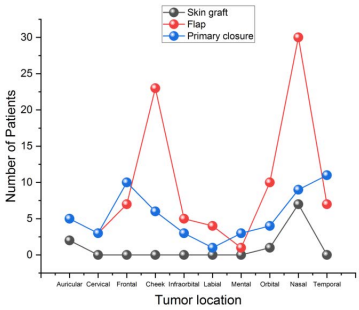

Fig. 5. The association between the kind of restoration

Tab. 6. Computation analysis of the association between the kind of restoration

Days	Number of Patients		
	Skin Graft	Flap	Primary Closure
1 day	5	30	35
2 days to 3 days	3	42	11
4 days to 5 days	2	13	4
6 days to 7 days	0	7	0
More than 7 days	0	3	0

The higher NMSC treatment costs for technological educational institutions and patients with low incomes were in line with earlier studies. Subjects with low incomes and more exposure to occupational pollutants are more likely to acquire NMSC malignancies, and the expense of treatment is higher for them compared to patients with better incomes and educational levels. But we discovered that only expenditures associated with educational formation were statistically significant to be rising.

The cost of treating NMSCs is higher than that of other anatomical areas, especially the abdominal cavity and limbs, but lowers than that of the neck and head mucosal malignancies. The skin is the site of 19% of neck and head malignancies. The cost of treatment for each episode was higher in the area surrounding the orbit primarily because local healing of this structural component presents challenges location [30].

CONCLUSIONS

In SOTRs, NMSC is by far the most prevalent kind of malignancy found. Even if it doesn't metastasis very often, it might cause a large amount of sickness. These skin lesions can be easily identified, making prompt treatment and detection possible. A multidisciplinary strategy that includes the most efficient approach is to educate patients about prior to donating an organ, sunlight exposure, epidermis check, and dermatologic testing, immediately after organ transplantation, and at periodic intervals during follow-up for managing this patient population. Once lesions that might potentially be skin cancer are identified, the patient must be sent to a dermatologist as soon as possible. The treatment of patients who have high-risk superficial cancers must be reduced to the minimum dosage that will allow for graft survival; patients must switch to an m-TOR inhibitor; there must be a collaborative effort involving the oncologist, the radiotherapist, a cosmetic surgeon, and the dermatologist; and it is necessary to negotiate with transplant physicians to lessen the amount of immunosuppressive medication that is administered.

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