

Technical Answers for Real World Problems (TARP)

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Slot: TF2

1. Describe the problem identified for TARP?

The Answer:

AIM:

This project aims to see the reduction in skin cancer in India and world at large. The research papers have found it to be difficult to do so with a very less accuracy. The project represents a good accuracy in finding the skin cancer occurrence and help more and more people.

OBJECTIVE:

The project is about making a Skin Cancer Detector. In India, many people are suffering through skin diseases. Many a times in village's people think it is just a mole and ignore it. Later when it is realised it is already too late to cure and the patients suffer a lot. Some even die. Thus keeping in thought the problem we are making an app which will help in detecting skin cancer through deep learning algorithms and using Generative Adversarial Networking for generating and checking more possible test cases. Thus, it will not only help to have a detection but also able to give a free chat with doctor for fixing an appointment for the skin cancer check-up.

Skin cancer constitutes a small but significant proportion of patients with cancer. Although the presence of eumelanin in dark skin is protective against the development of skin cancer, it is increasingly being diagnosed in the Indian population.

INTRODUCTION:

There has been an increasing concern in print and electronic media regarding increased incidence of cancer in the Malwa belt of Punjab. Various authors have attempted to scientifically correlate the available data with environmental factors. Although skin cancer is a less common malignancy, its incidence is noted to be

progressively increasing over last few decades. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma are the most frequent primary skin cancers. BCC and SCC are together known as Non-Melanomatous Skin Cancers (NMSC). Skin cancers are relatively uncommon malignancies worldwide not ranking among the first ten common cancers, although there has been progressive increase in the skin cancers over last few decades.

Of all the diagnosed cancers in India, less than 1% is skin cancer. Worldwide BCC is the commonest cutaneous malignancy, but in India, SCC is reported to be the most prevalent skin cancer. Skin cancer incidence in India is relatively lower in comparison to the western world, but absolute number of cases is estimated to be significant due to larger population base. In India, skin cancer constitutes less than 1% of all diagnosed cancers. BCC is the commonest skin cancer worldwide, but various studies from India have consistently reported SCC as the most prevalent skin malignancies. Although, the incidence of skin cancers in India is lower as compared to the western world, absolute number of cases is estimated to be significant due to larger population base.

Although the incidence of all types of skin cancers is thought to be lower among Indians due to the protective effect of melanin, there are several smaller reports that NMSCs may be on the rise in India. Conventional thinking is that the incidence of all varieties of skin cancer is lower among Indian due to protective effect of melanin. Though national surveys and cross-country data in India are unavailable, there are several smaller reports that NMSCs may be on the rise in India. A significant number of patients have reported to the Plastic Surgery department in our institution over a year with skin tumors and have undergone required excision and reconstructive surgeries for the same. Similarly, on review of oncological registrations there are significant numbers of new cases reported. A hospital based study in this region reported a paradoxically increasingly trend of BCC with female predilection.

NMSCs arise from keratinocytes. Ultraviolet B radiation (UVB 290-320 nm) derived from sun exposure is a well known agent causing NMSCs. Arsenic, radiation therapy, coal tar and various hydrocarbons are other important aetiological agents. Arsenic, in compound form used in insecticides, pesticides, herbicides and poultry feeds is poisonous and harmful environmental contaminant. In humans arsenic is known to cause skin cancer. Both SCC and BCC arise from keratinocytes. Ultraviolet radiation cause skin derived from sun exposure is well known to be most important cause of skin cancer. Epidemiological data and experimental evidence indicate that UVB radiation (wavelength 290-320 nm) includes the most significant wavelengths for induction of skin cancers. Other important aetiological agents include radiation therapy, arsenic, coal tar and various hydrocarbons. Though pure arsenic is not poisonous, but its compounds that are used as pesticides, herbicides, insecticides

and poultry feeds are poisonous. In fact, arsenic is a very harmful environmental contaminant and in humans this element is known to cause skin cancer.

Major source of human exposure to arsenic is contaminated drinking water. The carcinogenic potential of inorganic arsenic exposure through drinking water is a cause for considerable concern, especially because the hazardous inorganic arsenic is a powerful human multi-site carcinogen. In combination with UVB, arsenic can cause skin cancer. Available data shows an increased level of Arsenic, Selenium and mercury in ground as well as tap water, more than permissible level of United States Environmental Protection Agency (USEPA). High use of pesticides is also well known in Punjab.

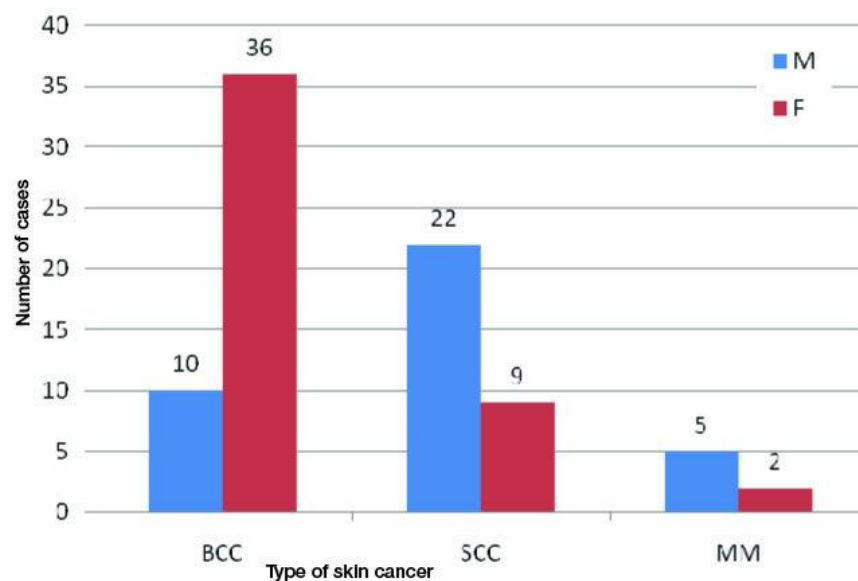
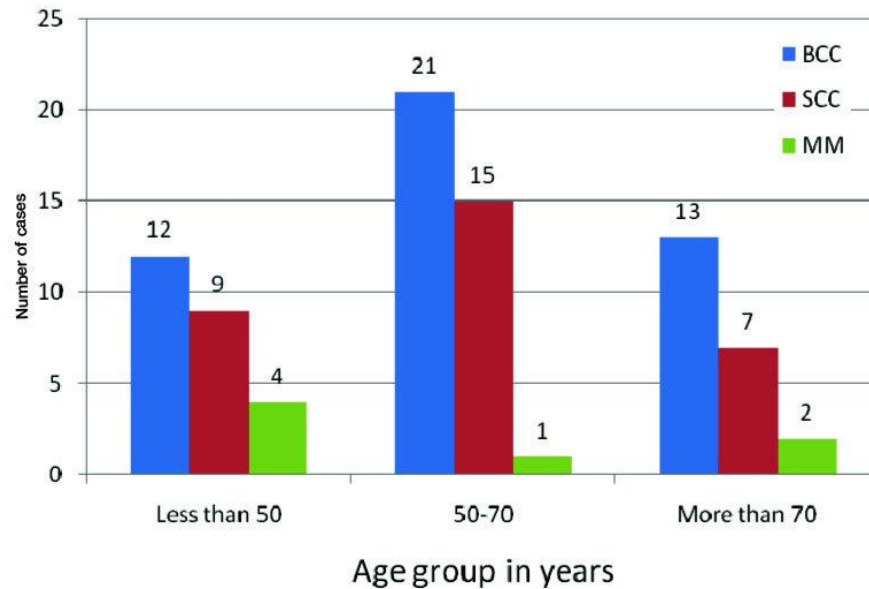


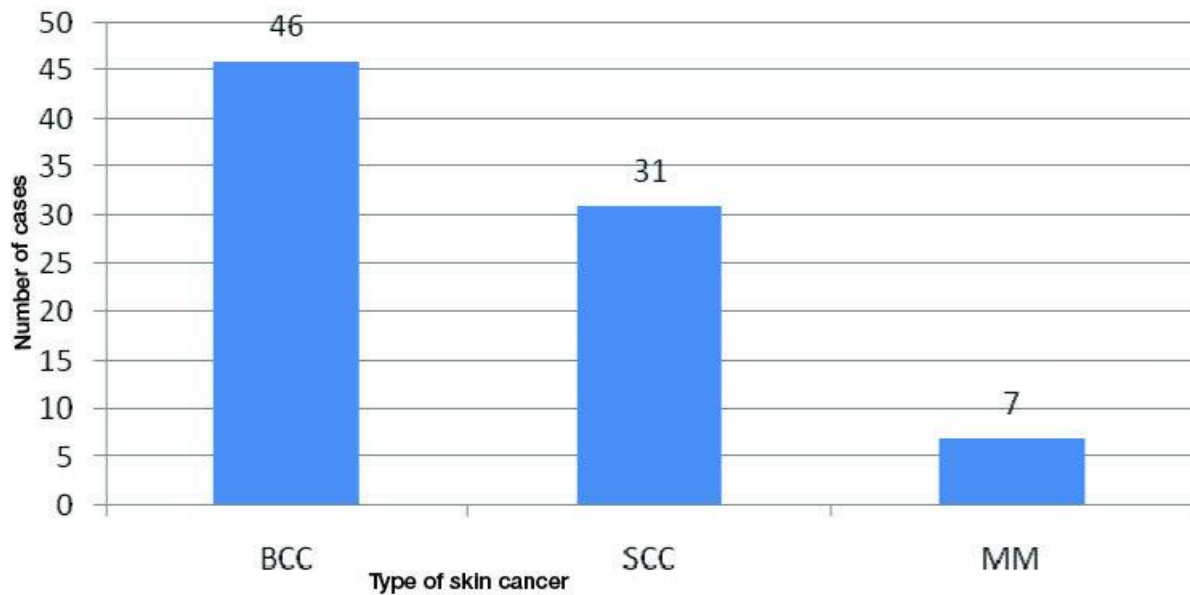
Figure 2: (A) Large superficial BCC involving facial skin. (B) Postresection defect. (C) Late postoperative picture following resection and skin graft

Incidence of skin cancers has been increasing since the last few decades worldwide. Nonmelanoma skin cancer (NMSC) is the commonest variety of cutaneous malignancy. Conventional wisdom has it that the incidence of all varieties of skin cancers is lower among Indians due to the protective effects of melanin. Though national surveys and cross-country data in India are unavailable, there are indirect indications from several smaller reports that NMSCs may be on the rise in India. Reports of quite a few atypical cases lead us to hypothesize that factors other than ultraviolet radiation may be important in the occurrences of these cancers, particularly in the skin types prevalent in India. The descriptive epidemiology and clinical characteristics of squamous and basal cell carcinoma in India, including their variants, are discussed here along with hypotheses on their etiopathogenesis. Novel management techniques currently available in India are also highlighted.

Nonmelanoma skin cancers (NMSCs) consist of, for the most part, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), if tumors of mucous membrane are excluded. These two cancers of skin are the most frequent malignant conditions worldwide. The largest incidence is seen in the White population. The incidence shows an inverse relation with the degree of

pigmentation, presumably due to the protective effect of eumelanin on ultraviolet light (UVL)-induced damage. We shall review here the epidemiology, clinical presentations, etiopathogenesis, and management options of SCC, BCC and their variants, specifically in the context of India.





Descriptive Epidemiology

More than one-third of all cancers in the United States are NMSCs. Smaller surveys suggest that the incidence may have increased by as much as 65% since 1980. BCCs are the commonest cutaneous tumors accounting for approximately 70% of all malignant diseases of the skin. The exact incidence in India is not known. But NMSC is known to be uncommon in Asians. Among dark-skinned individuals, SCC is commoner than BCC. Various studies from India consistently report SCC to be the most prevalent skin malignancy. In dark-skinned people, SCC often occurs in sites that have not been exposed to the sun and is often aggressive. Otherwise, exposure to sunlight is the principal cause of both BCC and SCC. The incidence of SCC increases more rapidly with age and with cumulative sun exposure than does the incidence of BCC. SCC in heavily pigmented skin often arises in association with scarring processes. The incidence of BCC appears to be increasing worldwide. A recent retrospective analysis presented at the American Society for Dermatologic Surgery (ASDS) 2009 Annual Meeting by A Metelitsa *et al* looked at nearly 100,000 patients diagnosed with NMSC and entered into the Alberta Cancer Registry between 1988 and 2007. An evaluation of the data showed an initial overall rapid increase of NMSC rates between 1988 and the mid-1990s, followed by stabilization across the genders that started in 2000. Most of the nonmelanoma cancers were in the head and neck. The study contradicted some previous findings on rising skin cancers among younger people and concluded that NMSC incidence rates were leveling off.

Etiopathogenesis

Both SCC and BCC arise from keratinocytes. Epidemiologic data and experimental evidence indicate that ultraviolet B (UVB) radiation (wavelength

290–320 nm) includes the most important wavelengths for the induction of skin cancer. Depletion of ozone in the atmosphere increases the levels of UVB radiation at the surface of the earth and the risk of skin cancer. Mathematical models suggest an increase of 2-4% in the incidence of tumors for each 1% reduction in the ozone layer, with the increase being larger for SCC than for BCC. Other important etiological agents include radiation therapy, arsenic, coal tar and various hydrocarbons. BCC is the most frequent carcinoma occurring at the region of the body to which radiotherapy is delivered. Human papilloma virus (HPV) may play a role in immunosuppressed patients, particularly in SCC. The role of HPV in BCC is controversial, with an Iranian study failing to find a significant relationship based on immunohistochemical techniques. Patients whose immune status is deficient, particularly organ transplant recipients, are also predisposed to develop these tumors. It has been estimated that renal transplant recipients have a risk of developing cutaneous SCC, which is 18 times that of the general population. These patients develop skin cancer earlier than the normal population. Patients of NMSC are at risk of having a second NMSC, either concurrently or later. In a retrospective study of 456 consecutive patients with NMSC who presented for Mohs surgery, more than 39% either had synchronous multiple NMSCs or had experienced a subsequent (metachronous) NMSC within 2 years of presentation.

Clinical Aspects

Squamous cell carcinoma

According to the unitarian viewpoint of Ackerman, the following conditions are morphological expressions of SCC: actinic keratosis and its analogues, arsenical and radiation keratoses, Bowen's disease and bowenoid papulosis, giant condyloma and verrucous carcinoma, keratoacanthoma, and proliferating tricholemmal cysts.

Most SCCs arise in areas of direct exposure to the sun. Non-exposed areas are occasionally affected, remarkably more often in the heavily pigmented skin. When the genitalia are affected, typically patients in this part of the world are very late in seeking medical attention. A case of Bowen's disease of the periareolar skin causing destruction of the nipple has been reported from North India. Sunlight and arsenic exposure are the usual culprits in the causation of Bowen's disease. Keratoacanthoma has been reported to occur in the suprapubic area and presenting as verruca vulgaris-like lesions. Among other unusual sites, SCC of the leg has been reported in a 26-year-old female patient with Kindler syndrome. SCC of the nail bed, reported in the Indian literature, is not only difficult to recognize, but difficult to treat as well. Carcinoma cuniculatum, a low-grade SCC (verrucous carcinoma) of plantar skin, has been reported to occur on the flanks, leg, face, and palm too in a series of 12 patients. Kangri cancer is, of

course, a well-known pattern of SCC that develops on or over erythema ab igne. It is typically seen to occur on the lower extremities and the abdominal wall following the use or exposure of kangri, an indigenous fire pot tucked in between the thighs to generate warmth during the winter months. This cancer is seen exclusively among the impoverished people of the Kashmir valley, and was reported as early as in 1879. These tumors have an aggressive biological behavior with a substantial risk of loco-regional metastasis in 20-50% cases.



SCC of penis with massive local tissue destruction (courtesy: Dr Aditi Chakraborty)

There are uncommon reports of SCC arising from burns scar and presenting as cutaneous horn, SCC *in situ* arising in smallpox vaccination scar, etc. Tumors arising from scars are usually aggressive, and local recurrences are common. The term “Marjolin's ulcer” has been used for SCCs arising in sites of chronic injury or irritation such as scars, ulcers and sinuses, although Marjolin did not describe the condition with which he is eponymously credited.

In the Indian scenario, development of SCC has been associated with certain dermatological conditions where the pathogenesis is akin to the development of SCC in scars. One of these is discoid lupus erythematosus (DLE). There are numerous Indian reports of SCC developing on chronic DLE lesions despite the easy availability of topical steroids, protective sunscreens, antimalarials and growing awareness levels of patients. Another such condition is lupus vulgaris

(LV). Ten per cent of all long-standing cases of LV undergo malignant change, of which SCC is the commonest. Russian dermatologists have christened this malignant change as “lupus carcinoma”. There are numerous reports from various parts of India on malignant transformation of LV into SCC.

Other uncommon occurrences of SCC on pre-existing dermatological conditions, which have been reported from India include the following: lichen planus (LP) including LP hypertrophicus, necrobiosis lipoidica diabetorum (NLD), lichen simplex chronicus (LSC), psoriasis, chronic lymphedema, and disseminated porokeratosis. Various pathogenetic factors have been ascribed to the malignant transformation in these conditions, *inter alia*, hypoxic status of poorly vascularized cicatricial structures in NLD, chronically irritated skin of LSC, deficiency in afferent lymphatic drainage preventing early recognition of tumor-specific antigen in chronic lymphedema, and overexpression of p53 in the keratinocytes near the cornoid lamella in the porokeratotic lesion.

Other than these, eruptive keratoacanthomas have been described in Hodgkin's disease, verrucous carcinoma in erythema elevatum diutinum, and epidermodysplasia verruciformis with vulval Bowen's disease. SCC and its variants, viz., keratoacanthoma, are seen in increased frequency in patients with xeroderma pigmentosum. Likewise, malignant progression of actinic keratoses to SCC has been reported to occur in increased frequency among albinos from India.

SCCs are found predominantly among older people; they are rare in adolescence and childhood. Clinically, they typically present as shallow ulcers, often with a keratinized crust and elevated, indurated margins.

A few atypical variants find mention in the Indian literature. Centrifugal necrotic keratoacanthoma represents the intermediate state of the spectrum where keratoacanthoma and overt SCC represent the most benign and the most malignant ends, respectively. A very rare variant, sarcomatoid or spindle cell SCC, was described in an atypical presentation of a painful centrofacial erythematous plaque with multiple discharging sinuses and blackish granule-like nasal discharge in a 28-year-old male from eastern India. Probably, this is the first case ever, and the only instance of an NMSC until now, when a primary cutaneous malignancy presented as multiple discharging sinuses. Another case of primary skin cancer, a malignant melanoma, has been reported to present as multiple discharging sinuses, that too from India. Other rare variants of SCC are the adenoid, pseudovascular, clear cell, “signet ring”, pigmented, inflammatory, basaloid, infiltrative, desmoplastic and rhabdoid types.



Erythematous plaque with indistinct margination on the left cheek encroaching upon the left nose with multiple sinuses and the blackish granule-like discharge from the left nostril containing purulent necrotic debris in a case of spindle-cell SCC

Basal cell carcinoma

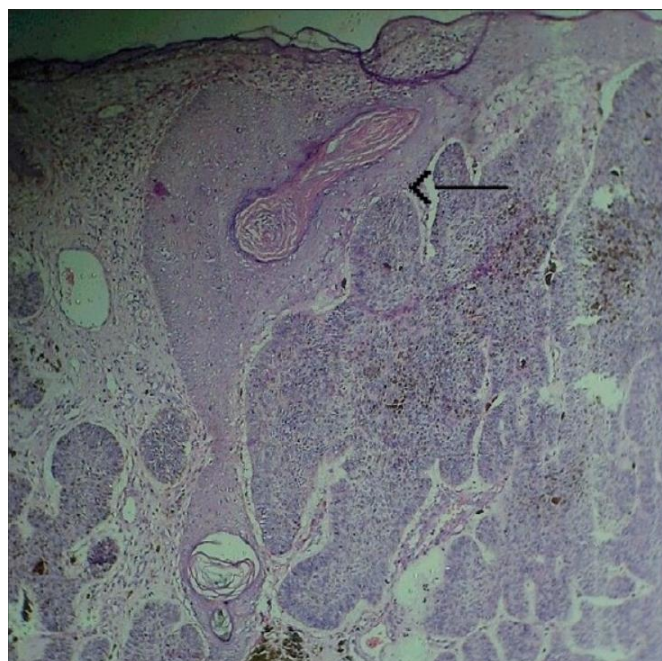
BCCs are found predominantly on areas of skin exposed to the sun. They are rarer in dark-skinned individuals. Up to 80% of all lesions are found on the head and neck, whereas approximately 15% develop on the shoulders, back or chest. There are isolated reports documenting involvement of the lower extremities, the clitoris and the vulva, perianal region, etc. Rare instances of BCC developing in verrucous epidermal nevus, and coexisting with multiple trichoepithelioma have been reported from India. Multiple BCCs may develop in the nevoid basal cell epithelioma (Gorlin's) syndrome. Gorlin's syndrome presents with characteristic facies, pitting of palms and soles, and radiological evidence of osseous abnormalities, including fusion of ribs and vertebrae, lytic lesions of the mandible, and calcification of the falx cerebri. A unique case has been described from eastern India in a 74-year-old man where BCC occurred in a two-decade old lesion of LP. This case possibly represents the first ever of LP transforming into BCC.

BCCs are more common in males, presumably due to greater occupational and recreational exposure to UV light. An Indian series reported an unusual female preponderance. They tend to occur in older people, although they have also been documented in children and young adults.

The clinical presentation of BCC can be quite variable. It may be a papulonodular lesion with a pearly translucent edge, an ulcerated destructive lesion (rodent ulcer), a pale plaque with variable induration, an erythematous plaque with visible telangiectasia, or a partly cystic nodule. Cutaneous horn overlying a nodulo-ulcerative lesion of BCC has been described. Variants with mutilation of the face have also been documented.

Although most BCCs are slow-growing, relatively non-aggressive tumors, a minority have an aggressive behavior with local tissue destruction and rarely, metastasis. Thus, there are rare instances of BCC eroding into the eye. Metastatic BCC has a reported incidence of only 0.0028-0.5%.

There is considerable variability in the morphology of the BCCs, and as a consequence, a number of histopathological subtypes have been defined. BCCs are composed of islands or nests of basaloid cells, with palisading of the cells at the periphery and a haphazard arrangement of those in the centers of the islands. The vast majority of cases show some connection to the undersurface of the epidermis. Islands of tumor cells are surrounded by a stroma, which is newly formed and different from the adjacent dermis. A variable inflammatory infiltrate is usually present. The morphological subtypes include solid (nodular), micronodular, cystic, superficial, multifocal, pigmented, adenoid, infiltrating, sclerosing, keratotic, infundibulocystic, metatypical, basosquamous, and fibroepitheliomatous. Mixed patterns are quite common, and have been reported from India.



Lobules of basaloid cells, stromal separation, connection of tumor lobule with the undersurface of the basal layer of the epidermis (shown with an arrow), foci of melanin incontinence (hematoxylin and eosin stain, magnification $\times 400$)

Punjab is India's one of most prosperous state, largely due to the green revolution. Seventy percent of population is directly or indirectly associated with agriculture. In our study, majority of cases belong to agricultural background with history of prolonged sun exposure while working in the fields.

The role of some environmental factors in the causation of skin cancers was reviewed. UVB radiation is well known as agent inducing non melanoma skin cancers in a dose dependent way. The effects of UVB radiation are enhanced by ozone depletion, which is responsible for an increase in biologically damaging solar UVB radiations reaching the Earth surface . Mathematical models suggest an increase of 2-4% in the incidence of skin tumour for each 1% reduction in ozone layer . But factors other than the mentioned above need to be searched and verified as ozone destruction is most evident over the temperate and Polar Regions, while India is a tropical country.

Ingestion of arsenic, both from drinking water supplies and medicinal preparations is known to cause skin cancers. The association between arsenic ingestion and skin cancer has been documented since the late 19th century. BCC and SCC have repeatedly been reported to be associated with ingestion of arsenic alone or in combination with other risk factors. The compounds of arsenic are used as pesticides, herbicides, insecticides and poultry feeds. Also inorganic arsenic, a metalloid is ubiquitously distributed in nature. Under certain conditions like pH, temperature etc, inorganic arsenic easily dissociates from its soil bound forms and enters the aquifers. For this reason, the major source of human exposure to arsenic is the drinking water of course, the contaminated groundwater. In combination with UVB arsenic can cause skin cancer. Indeed arsenic-UVB interaction provides reasonable explanation for the cases of arsenical cancers in sun exposed skin. Multiple and recurrent skin lesions are associated with cellular immunity dysfunction in chronic arsenism. The main proposed mechanisms regarding arsenic carcinogenicity are induction of chromosomal abnormalities, promotion and oxidative stress.

In a study by Sharma et al., many of the water samples taken from existing hand-pumps, submersible pumps, tube-wells, dug-wells (underground water) and municipal water supply from the south western districts of Punjab were analysed and found to have high content of Arsenic beyond their permissible limits said by WHO along with high variability. Study has revealed that 80% of water samples analysed was having arsenic concentration above the safe limit (10µgm/L) [36].

Management Issues

The lynchpin of management of NMSCs is surgical extirpation of various kinds. This includes non-excisional ablative techniques, conventional surgical excision,

and Mohs micrographic surgery. Regardless of the surgical modality, recurrence is a frequent cause of concern. In a classic study, Rowe *et al.* reviewed all major series of SCC dating back to determine risk factors associated with recurrence and metastasis. The characteristics of “high risk” lesions are diameter greater than 2 cm; depth greater than 4 mm and Clark level IV or V; tumor involvement of bone, muscle and nerve; location on ear and lip; tumor arising in scar; poor differentiation (Broders grade 3 or 4); immunosuppression of patient; and absence of inflammatory infiltrate. Curettage and desiccation is one of the most frequently used surgical modalities for BCC. Cryotherapy is another destructive modality used in BCC, which has been successful in difficult sites like the eyelid.

Among topical therapies, imiquimod 5%, a novel immune modifier, capable of inducing local production of cytokines, has been used successfully in a number of NMSCs, including Bowen's disease and BCC. 5-fluorouracil has been used in the treatment of actinic keratoses as well as BCCs. Topical tazarotene gel (0.05%) has been reported to successfully treat Bowenoid papulosis of the genitalia.

Among physical therapies, photodynamic therapy (PDT) and radiation have been found to be effective. PDT with exogenous δ -aminolevulonic acid increases intracellular production of the endogenous photosensitizer protoporphyrin type IX which preferentially accumulates in tumor cells of BCCs, producing activated oxygen species that destroy the constituent cancer cells. Radiation is a useful adjuvant to excisional surgery in NMSCs. X-ray therapy may be useful in cases of primary BCC. Recently, a cohort of NMSC patients were reported to be successfully managed with plesiotherapy using stepping stone ^{192}Ir HDR source.

Conclusions

NMSC occupies a smaller space in the perception of clinical dermatologists in India than perhaps is its due, mainly because of the supposedly protective effects of eumelanin in the brown skin of the Indian population. As we have seen in this review, not an inconsiderable body of work exists in the Indian literature, which is a testimony to a large variety of cases of NMSC occurring in this country. Many atypical forms of NMSC are seen in our clinical setting, ranging from the archetypal Kangri cancer in Kashmir to unique entities like a sarcomatoid SCC presenting as multiple discharging sinuses (till now possibly the only case of primary NMSC to be reported to present in such a fashion), and a case of LP transforming into BCC, the first such instance of probable malignant transformation of LP into BCC to be reported in the world literature. SCC is predominant in the Indian population rather than the BCC; this is an epidemiological characteristic that sets us apart from the global trend. The Indian clinicians, within the limited parameters set by infrastructural and logistic constraints, have also carried out significant research in management of NMSCs, particularly in the areas of topical therapy and radiation.