Ashish Dwivedi · Anurag Tripathi
Ratan Singh Ray
Abhishek Kumar Singh *Editors*

Skin Cancer: Pathogenesis and Diagnosis

Springer

Skin Cancer: Pathogenesis and Diagnosis

Ashish Dwivedi • Anurag Tripathi •
Ratan Singh Ray • Abhishek Kumar Singh
Editors

Skin Cancer: Pathogenesis and Diagnosis

Springer

Editors
Ashish Dwivedi
Food, Drug & Chemical Toxicology
CSIR-IITR
Lucknow, Uttar Pradesh, India

Anurag Tripathi
Food, Drug & Chemical Toxicology
Indian Institute of Toxicology Research
Lucknow, Uttar Pradesh, India

Ratan Singh Ray
Photobiology Division
Indian Institute of Toxicology Research
Lucknow, Uttar Pradesh, India

Abhishek Kumar Singh
Amity Institute of Neuropsychology and Neurosciences
Amity University
Noida, Uttar Pradesh, India

ISBN 978-981-16-0363-1 ISBN 978-981-16-0364-8 (eBook)
https://doi.org/10.1007/978-981-16-0364-8

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Contents

About the Editors

Ashish Dwivedi is a Scientist in the Division of Food, Drug & Chemical Toxicology, CSIR-IITR, a premier Institute of Toxicology Research in India. He has done his post-doctoral research from the Israel Institute of Technology (IIT), Israel and Colorado University, US on cancer therapy. He has also been awarded a prestigious Dr. D.S Kothari Post-Doctoral Fellowship by UGC. He has done his Doctoral Research from Photobiology Division, Indian Institute of Toxicology Research (IITR), Lucknow. His Doctorate research work was focused on phototoxicity/photosafety assessment of therapeutic drugs, environmental pollutants and nanotized phytochemicals at ambient UV-R exposure. He has more than ten years of research experience in Photo & Dermal Toxicology and published several articles in reputed journals of Photochemistry & Photobiology, Toxicology, Biomaterials, and Hazardous materials.

Anurag Tripathi is working as a Senior Scientist in the Department of Food, Drug and Chemical Toxicology at CSIR-Indian Institute of Toxicology Research. He did his Ph.D. from the School of Biotechnology, Banaras Hindu University. He has 16 years of research experience and published more than 50 research articles in peer-reviewed international journals such as Immunology, Molecular Immunology, Molecular Aspects of Medicine, Toxicology Letters, ACS Nano, Toxicology, and Applied Pharmacology. He is a life member of the Indian Nanoscience Society and serves as an editorial

board member in several prestigious international journals such as Journal of Immunology & Serum Biology, SM Journal of Nanotechnology and Nanomedicine, Journal of Toxicology and Forensic cases and Austin Immunology.

Ratan Singh Ray is a Senior Principal Scientist & Head, Photobiology Division, CSIR-Indian Institute of Toxicology Research, Lucknow. He has twenty-nine years of research experience in the area of Photobiology. He is an active member of various scientific societies including, the Bureau of Indian Standards (Cosmetics Sectional Committee PCD 19), India, American Society for Photobiology, USA, Indian Photobiology Society, India, Society of Toxicology, India. He has published many research articles in reputed journals of Photochemistry & Photobiology, and Toxicology.

Abhishek Kumar Singh is an Assistant Professor at Amity University, Noida. He earned his PhD from CSIR-Indian Institute of Toxicology Research, Lucknow, in 2013. Then, he joined Guru Ghasidas Central University, Bilaspur, as an Assistant Professor in the Department of Biotechnology. His major research interest is to investigate the interplay between autophagy and pro-survival pathways during aging of the brain and aging-induced neurodegenerative disorders. Dr. Singh has more published more than 50 research articles in international journals of high repute and ten book chapters. He is a member of the Indian Academy of Neuroscience, the International Society of Neurochemistry, and the Society of Toxicology India.

Cancer of the Skin: Types and Etiology

1

Shiv Poojan and Ruchi Pandey

Abstract

Skin, the largest organ system in the human body, plays an important role in making a porous barrier to detach internal organs from external stimuli. Genetic or natural mutations in skin cells can cause cutaneous tissue hypethrophic and inflammatory condition or malignant transformation, that accounting for a big number of ailment in human skin which leads to skin cancer developement in the skin cells. Here in this chapter, we are describing the recent details on skin cancer types and their etiology. It also gives a brief idea of skin growth and how mutations or misregulations of these are elaborated in the pathogenesis of skin cancer development.

Keywords

Skin cancer · Basal cell carcinoma · Melanoma · Nonmelanoma keratinocytes · Wounding · Skin tumor · Skin blistering

Abbreviations

AFX	Atypical fibroxanthoma
AK	Actinic keratoses
AS	Angiosarcoma

S. Poojan (✉)
Department of Dermatology & Cutaneous Biology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA
e-mail: shiv.poojan@jefferson.edu

R. Pandey
Center for Translational Medicine, Thomas Jefferson University, Philadelphia, PA, USA

A. Dwivedi et al. (eds.), *Skin Cancer: Pathogenesis and Diagnosis*,
https://doi.org/10.1007/978-981-16-0364-8_1

BCC	Basal cell carcinoma
DFSP	Dermatofibrosarcoma protuberans
DTS	Digital transcriptome subtraction
EB	Epidermolysis bullosa
EMPD	Extramammary Paget disease
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
LAS	Lymphedema-associated angiosarcoma
MAC	Microcystic adnexal carcinoma
MCC	Merkel cell carcinoma
NBCCS	Nevoid BCC syndrome
NMSC	Nonmelanoma skin cancer
OS	Overall survival
PUVA	Psoralen plus UVA
RDEB-SCC	Recessive dystrophic epidermolysis bullosa squamous cell carcinoma
SC	Sebaceous carcinoma
SCC	Squamous cell carcinoma
SEER	Surveillance, epidemiology, and end results
STS	Stewart-Treves syndrome
UPS	Undifferentiated pleomorphic sarcoma
UV	Ultraviolet
WHO	World Health Organization

1.1 Nonmelanoma Skin Cancer

Nonmelanoma skin cancer (NMSC) develops in one out of five Americans throughout their lifetime. It is the most common human cancer; an annual rate assessed more than three million as recorded in 2006 in the USA. It is relatively higher than the frequency of breast cancer, colon cancer, lung cancer, and prostate cancer collectively [1–3]. The recent trends showed more number of NMSC in Australia, Northern America, and Western Europe, due to holidays in sunny places and outdoor activities. Even then incidence is continuing to rise instead of public awareness of the harmful effect of ultraviolet (UV) exposure from the sunlight. Age shift, high ambient solar irradiance and artificial UV exposure are responsible for the increasing frequency of NMSC. Using tanning beds or sunlamps too much can also cause it. It also derives from exposure to different sources of UV, such as artificial tanning. Light skinned people are more susceptible to get skin cancer and people over 40 are at higher risk. Even risk is higher if any in family have had it or had it before. It may also be more possible to get it if you have been exposed often to X-rays, to toxic chemicals (such as arsenic, coal tar, and creosote), or to radioactive substances [4] (Fig. 1.1).

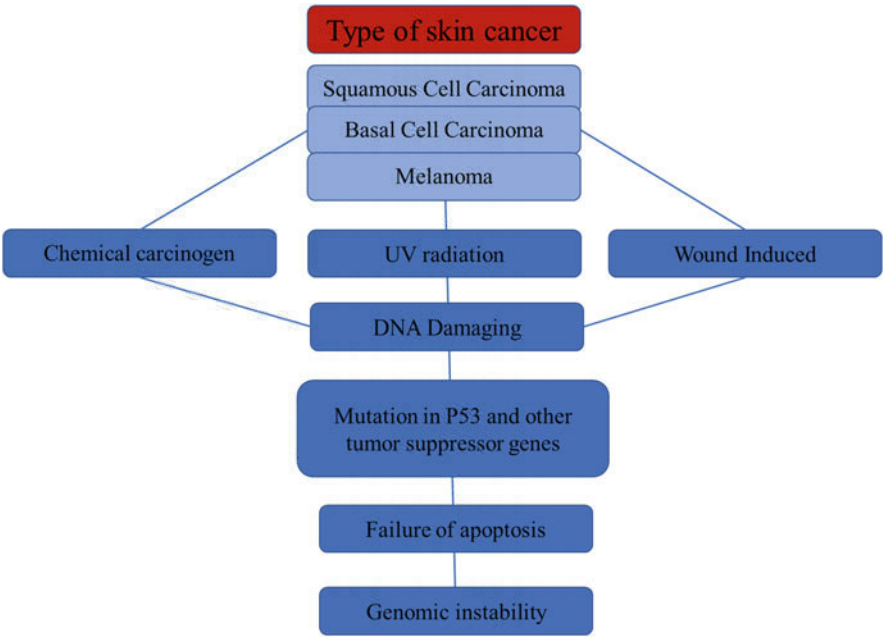

Fig. 1.1 Mechanisms involved in cancer pathogenesis

1.2 Actinic Keratoses

Actinic keratoses (AK) cancer is a very common cancer type that is frequently linked to sun-exposed areas, it affects mostly blond or red-haired, fair-skinned people with green or blue eyes phenotype. AKs signify the initial intraepidermal feature of abnormal growth of keratinocytes and possess the canonical mutations in tumor suppressor genes such as p53, PTCH (Drosophila patched gene) seen in SCC. AK is the earliest lesions with the chance of progression to SCCIS and invasive SCC [4]. Clinically, there are three main patterns seen in AKs: unprompted relapse, perseverance, or progression to invasive SCC [5]. The risk of AK development to SCC has been calculated between 0.025% and 16% per year, and the estimated total risk of malignant transformation for a patient with AKs surveyed for a period of 10 years ranges from 6.1% to 10.2% [6]. AKs are responsible to rise approximately 60–65% of SCCs. Over a period of 12 months, impulsive relapse has been stated in as high as 25.9% of AKs and even 15% relapse rate was distinguished at continuation [4]. Both individual and environmental factors are involved in the etiology of actinic keratoses [4]. Extreme exposure to UV radiation which acts as a complete carcinogen is the main reason for both enhancing and promoting tumor growth [6–8]. Activation of molecular signaling pathways, which are contribted in modifications of regulatory cytokines levels, immunosuppressive properties, faulty

cell differentiation, and apoptosis are mainly caused by UV radiation [7]. Along with the formation of proinflammatory cytokines and initiation of mast cells with the inhibitory factor of macrophage migration, the arachidonic acid pathway mediates the inflammatory process. The outcome of the initiation of these mediators contains lipid peroxidation, growth in intralesional levels of T lymphocytes and Langerhans cells, rise of p53 Bcl-2, and decrease in Fas (cd95) and Fas-ligand, which are crucial early factors in the apoptosis progression of UV-mutated cells [7]. Activation, suppression, and removal of apoptotic mediators such as CD95 cause apoptotic disorders along with some other factors like apoptosis driven by tumor necrosis factor and of pro-apoptotic tumor suppressor genes, or by regulation of p53 apoptotic signal activity [9, 10]. In disease development, important risk factors are related to age, sex, phototypes I and II, previous history of cutaneous neoplasms, prolonged sun exposure and occupational environment are the reasons, that play an important role in actinic keratoses development [11]. The history of previous skin neoplasms is also very significant because it reproduces the connotation of individual genetic factors, which may affect the understanding of UV radiation and the level of exposure of chronic UV radiation during the life of a particular individual [11, 12]. While assessing the impact of occupational sun exposure for the development of actinic keratoses, it was found that workers from outside area are at 2–3 times the higher risk and they were also at higher risk for all cutaneous neoplasms [13, 14]. Subsequently, both condition acute exposure and chronic UV radiation can lead to mutations in the p53 gene and following clonal keratinocyte growth therefore, the incidence of painful sunburn before 20 years of age may represent the beginning events of the carcinogenesis progression and it enhances even more when arsenic or other heavy metal toxicity is present. It is reported, arsenic exposure disrupts the homeostasis of the skin stem cell population in the mice during carcinogenesis [15, 16]. As a result of the carcinogenic effects of UV radiation, patients with prolonged use of general immunosuppressive drugs are a particular risk group for developing cutaneous neoplasias and dysplasias [17]. NMSC is the most prevalent neoplasm observed in 27% population of solid organ transplant patients [17, 18]. Likewise, higher risk of progression in the immunosuppressed patients due to the prevalence of actinic keratoses developed lesions to SCC [19]. Additional features such as facial telangiectasias, ephelides, solar lentigos, cutis rhomboidalis nuchae, solar elastosis, and around ten melanoses on the dorsa of the hands are also considered as a risk phenotype for actinic keratoses development [20, 21].

1.3 Basal Cell Carcinoma

The most common cancer in humans is basal cell carcinoma (BCC), previously known as basal cell epithelioma and mostly arises on sun-damaged skin and rarely develops on the palms and soles or mucous membranes. BCC is usually a slow-growing tumor for which metastases are rare. Although BCC is rarely fatal, in case of inadequate or delayed treatment it can be extremely critical and mutilate niche tissues. Clinical inspection of BCC typically looks as flesh or pink colored

shining papules with covering ulceration or telangiectatic vessels. BCC occurs on the head or neck in majority of cases [22–24]. BCCs are described in the literature with different subtypes and most dermatologists agree on these major, identifiable, clinicopathologic type nodular, superficial, morpheaform, and fibroepithelial structure. Whereas, the occurrence of combinations of these clinical features in patient is also observed with other type of nodular formation in BCC. Variable amounts of melanin may be present within these tumors but otherwise, in majority of cases, BCCs are amelanotic [25]. Typically, lighter-skinned individuals are more prone to BCC and particularly on sun-exposed parts. Mainly nose acquires approximately 30% lesions of BCC. However, BCC can occur anywhere, even without UV exposure by the sun, its occurrence has been observed even on the penis, vulva, scrotum, and perianal areas Effect of BCC is somewhat more observed in men in comparison to women. The younger generation are more vulnerable to the BCC, especially in childhood and adolescence sporadic frivolous sun exposure. Exposure to UVR (UVB has a greater risk than UVA) and overexposure to sun heat (i.e., sunburns) shows substantial risk to develop BCC. Additional aspects such as mutations in regulatory tumor suppressor gene, experiencing ionic radiation, chemicals (arsenic, and PAHs), Psoralen plus ultraviolet A (PUVA) photochemotherapy, and modifications in immune reconnaissance (i.e., organ transplantation, primary hematologic malignancy, immunosuppressive medications, or HIV infection) are involved in the pathogenesis. BCC is considerably more common among childhood cancer survivors, primarily due to prior ionizing radiation treatment with or chemotherapy combination. BCC occurrence found between 20 and 39 years of age in individuals with a history of childhood cancer, and it is more common in cancer survivors, who had received $\geq$35 Gy versus individuals who did not have radiation therapy [26]. The development of BCC can be due to genetic conditions. Comprised within the nevoid BCC syndrome (NBCCS), Bazex syndrome (X-linked dominant; characterized clinically by follicular atrophoderma, hypotrichosis, hypohidrosis, milia, epidermoid cysts, and facial BCCs), Rombo syndrome (structures like to individuals of Bazex syndrome with marginal vasodilation with cyanosis), xeroderma pigmentosum (an autosomal recessive disorder in spontaneous DNA repair, clinically categorized by numerous NMSCs and melanomas), and individual basal cell nevus syndrome, NBCCS has more prevalence in group of BCC disease. NBCCS is a sporadic autosomal leading disorder defined by a mutation in the patched gene (PTCH1) and tendency to numerous BCC and additional tumors, besides a wide range of developmental abnormalities. In this condition, individuals may develop a broad nasal root, marginal intellect, calcification of the falx cerebri, medulloblastomas, odontogenic keratocysts of the jaw, palmar and plantar pits, and several skeletal abnormalities in addition to a few to thousands of BCCs [27]. As BCCs develop most commonly in sun-exposed areas, it shows sun exposure plays a role in tumor development in patients with NBCCS. Usually, the clinical course is benign before puberty; however, lesions may gradually raise and ulcerate after puberty. Individuals with NBCCS are extremely sensitive to ionizing radiation. Several cases of BCCs were reported in children who have gone through treatment with radiation therapy for medulloblastoma. To understand the molecular signature

to the pathogenesis of BCC, a patient with NBCCS has gone through sequencing analysis. This information leads to the behavior of neoplasms in the NBCCS and it confirms a model of carcinogenesis—tumors that develop in cells sustaining two genetic alterations [28]. The first mutational pattern in a TSG is by inheritance, and the second is based on random genetic rearrangement due to inactivation of the normal homologue by environmental mutagenesis factors. Inactivation of the NBCCS, TSG, and PTCH1 is measured and observed main cause of the origin of Intermittent BCCs because of underwent two somatic mutational events. Mutational association with the PTCH1 regulatory gene, which maps to chromosome 9q22.3 was observed with the BCCs studies [29]. In both the sporadic and the hereditary BCCs the loss of heterozygosity at this site is observed. For BCC formation the PTCH1 gene inactivation probably plays a necessary role. The PTCH1 protein is a part of a receptor complex that regulates hedgehog signaling pathway and is a very important regulator of embryonic development and cellular proliferation. Smoothened, a transmembrane receptor for the secreted molecule hedgehog is bound and inhibited by the PTCH1 protein. The inhibitory effects of PTCH1 release Smoothened on the hedgehog binding site and also converts a stimulating signal via GLI transcription factors [20, 30]. Unopposed Smoothened activity and cellular proliferation are permitted by PTCH1 after the loss of function mutation. Therefore, this knowledge of the molecular pathogenesis gives us a ground to develop targeted therapy for BCC with small molecule inhibitors of Smoothened. Some of UV-induced mutations have also been reported in up to 60% of BCCs at the p53 gene [31]. UV light exposure is the prime etiological factor in developing basal cell carcinoma, especially the UVB wavelengths but also the UVA wavelengths. Outdoor workers are significantly at higher risk observed in meta-analysis and sensitivity analysis studies, with an opposite relationship among occupational UV exposure and BCC risk with autonomy. The Fitzpatrick skin type is a suitable marker of the comparative risk of BCC between Whites [25, 32]. UV exposure duration and its intensity also play a role in BCC development along with cumulative UV dose and skin type. Recreational sunlight exposure, use of indoor tanning salons, and UV light therapy may also lead to BCC occurrence. Some other risk factors are obsereved such as intermittent intense sun exposure, sunburning (skin types I or II), blistering in childhood BCC, a fair complexion, ionizing radiation, arsenic exposure, immunosuppression, and genetic predisposition [24]. Some genetic syndromes such as xeroderma pigmentosum, Gorlin Syndrome or basal cell nevus syndrome, Bazex–Dupre–Christol syndrome, and Rombo syndrome are also found to be linked with an increased risk of BCCs. There is no association with diet but smoking also appears to be a risk factor in females [25, 32].

1.4 Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (SCC) is the second most common nonmelanoma skin cancer (NMSC) after BCC. Neoplasm of keratinizing cells is the main cause of SCC that shows malignant characteristics, including anaplasia,

rapid growth, local invasion, and metastatic potential. A recent study of cases of SCC in the USA population on the basis of age-weight incidence ratio is 1.4:1, that predicted high number of SCC burden [33]. Every year in the USA more than 200,000 cases of SCC are diagnosed [34]. And also, a very high number of cases reported in a recent study, the age-standardized incidence rate of SCC in the UK population is 77 cases per 100,000 person-years (PY) [35]. The risk of developing SCC increases more and more with patient age and is highly affected by the amount of ultraviolet (UV) irradiation, exposure based on country latitude and skin phototype of individuals, and is growing with time, expected because of worldwide population aging and improved diagnosis procedures [35, 36]. People of Celtic descent, and same as BCC people with fair complexions, with deprived tanning capability and sensitivity against sunburn, are at increased risk for developing SCC. Conversely, in Blacks SCC most often arises on preexisting inflammatory sites such as scars, burn injuries, or trauma [37]. Patients treated with Psoralen and ultraviolet A radiation (PUVA) or undergoing immunosuppressive therapy following solid-organ transplantation and human papillomavirus (HPV) infections are at increased risk of SCC [36]. Nevertheless, UV exposure for a prolonged period is certainly the main driver of SCC, as observed in the diagnosis and shown at an epidemiologic and molecular level. Mutational signature enrichment shown for C > T transitions at dipyrimidine-sites is related to UVB radiation. In SCC patients, most frequent mutations are in the tumor suppressor gene TP53, but chromosomal rearrangements and as well as genetic alterations have been observed in some other cancer-related genes, such as cyclin-dependent kinase inhibitor 2A (CDKN2A), NOTCH1/2, and RAS [38]. Due to cumulative UV exposure and from a multi-series procedure of accumulation of genetic hits SCC formation occurs. In SCC development another group of genetic disorders is severely observed. Another heterogeneous group of the inherited disorder known as epidermolysis bullosa (EB) is determined by mutations in genes encoding for a building block for cutaneous basement membrane. And during EB skin becomes more fragile and constant blistering shows disease symptoms. Even then defective wound healing is a verse kind of symptoms shown in most EB (sub)types, with fibrosis and inflammation at lesional skin. These features are a way towards serious disease complications, including cutaneous squamous cell carcinomas (SCCs) occurrence. Early and extremely aggressive SCCs (RDEB-SCC) are observed in almost all patients affected with severe recessive dystrophic EB (RDEB) subtype, which is known as the first cause of death in these patients. Less information and the crucial genetic determinants of RDEB-SCC do not thoroughly justify its inimitable behavior as associated with low-risk, ultraviolet-induced SCCs in the population [39, 40].

1.5 Angiosarcoma

Angiosarcoma (AS) is a very rare and extremely aggressive malignant tumor which is also known as malignant hemangioendothelioma, hemangiosarcoma, and lymphangiosarcoma. It originates from lymphatic or vascular endothelial-cell and

makes up less than 2% of all soft tissue sarcomas in humans and mainly affects adult and elderly patients [41–43]. Angiosarcoma is a clinically and genetically heterogeneous subgroup of sarcomas that can occur anywhere in the body [44] with an overall incidence of approximately 0.1 per million/year. Cutaneous lesions are the most common site of angiosarcomas (about 60% of cases), especially the head and neck, and can also found within the soft tissues, bone, visceral organs, and retroperitoneum [41–44]. Currently, four variants of cutaneous AS are recognized including AS of the "head and neck" (also known as idiopathic AS) that accounts for 50–60% of all cases, AS in the context of lymphedema (lymphedema-associated AS [LAS]; Stewart-Treves syndrome), radiation-induced AS, and epithelioid AS. However, these variants are different in presentation but share crucial features, like the clinical appearance of primary lesions, a biologically aggressive nature, and, ultimately poor outcomes [41, 44, 45]. According to the studies, the rates of advanced/metastatic disease at presentation differ from 16 to 44%, and the overall survival (OS) range is from 6 to 16 months [46]. Angiosarcoma can occur at any age and has a similar distribution between males and females. However, cutaneous angiosarcoma has been found preferentially in older male individuals, with a reported median age between 60 and 71 years [47]. While the pathogenesis is often unknown in the majority of developing angiosarcoma cases. Several etiological factors, like radiation, environmental carcinogens, chronic lymphoedema, and genetic syndromes are well known for playing an important role in this disease.

1.5.1 Radiation

Radiation is a defined risk factor for benign and malignant tumor development. In retrospective studies, radiation has been associated with the heightened risk of tumors via radiation-induced gene mutation and concurrent chronic lymphoedema [48, 49]. According to an epidemiology survey, the common sources of radiation are occupational exposure, diagnostic, and therapeutic radiation in patients [50]. As radiotherapy is a significant treatment in early-stage sarcomas, particularly for breast sarcomas, therefore, radiation-induced sarcomas are known as the main subtype of secondary sarcomas [51, 52]. Some studies reported breast sarcomas, induced because of radiation have a long latency period after radiation, the median disease-free interval of which was 5–10 years [51, 53, 54]. Hence, beyond the conventional 5-year oncological follow-up, a long-term follow-up is needed to attain the efficient detection of recurrence [53]. The direct relation between angiosarcoma and radiotherapy has not been fully confirmed, but multiple studies outcomes show that with the increased use of radiotherapy for the treatment of angiosarcoma, the risk of radiation-induced angiosarcoma also increases [55, 56]. The high dose of radiotherapy and the incidences of angiosarcoma are also correlated [57]. However, the overall risk of radiation-induced angiosarcoma is little or negligible as compared to the underlying benefit of radiotherapy.

1.5.2 Chronic Lymphoedema

Chronic lymphoedema is another risk factor for angiosarcoma. Chronic lymphoedema and angiosarcoma have been confirmed for having correlation and called Stewart-Treves syndrome (STS) [58]. The Stewart-Treves syndrome is a very sporadic and fatal thing, which is distinct as angiosarcoma rising in the location of chronic lymphedema. It characteristically presents in women after breast conservative surgery followed by adjuvant radiotherapy. The adjuvant radiotherapy in the treatment of early disease is thought to cause the development of STS [50, 58–60]. Some other potential causes are parasitic infections such as filariasis or Milroy's disease, idiopathic, congenital, traumatic, and filarial lymphedema [61]. Approximately 5% of angiosarcomas comprise STS, and it occurs after 5–15 years of local treatment with radiotherapy and surgery [60]. The prediction of STS is unsatisfying, with approximately 10 months survival rate [59]. There is still an argument about the mechanism between secondary angiosarcoma and some forms of chronic lymphedema. In some cases, the mutation of tumor genes, such as p53 and MYC, was thought to be a feasible cofactor [59, 62].

1.5.3 Environmental Carcinogens

Although a major portion around 75% of hepatic angiosarcomas does not exhibit definite etiology [63]. Environmental carcinogens are well known and common factors to induce cancer in many organs in the body. Skin is the most affected organ from environmental polutant due to open exposure from industrial materials such as vinyl chloride monomer and iatrogenic exposure of colloidal thorium dioxides for the radiological examinations, chronic arsenic ingestion [64, 65]. Occupational exposure is the main risk for this disease and most cases are caused by the same [66].

1.5.4 Genetic Syndromes

Approximately 3% of angiosarcomas are gene-induced, gene-associated diseases such as bilateral retinoblastoma, xeroderma pigmentosa, ollier disease, maffucci disease, recklinghausen neurofibromatosis, and Klippel-Trenaunay syndrome. Familial syndromes are associated with angiosarcoma [67]. Some recent genomic studies showed that the dysregulation of angiogenic pathways played a significant role in etiology of angiosarcomas and some other tumor suppressor genes were found to be associated with angiosarcomas, whereas the clinical significance of these findings still should be elucidated [68].

1.6 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare, cutaneous fibrohistiocytic neoplasm that was first defined by Darier and Ferrand in 1924 and the name DFSP was introduced by Hoffman in 1925. With an annual occurrence of 0.8–5 cases/million population, it consists of approximately 1% of all soft tissue sarcomas. DFSP also constitutes approximately 1% of all sarcomas and <0.1% of all malignancies [69]. The vast majority, about 90% of DFSPs are low-grade sarcomas, whereas the rest are classified as intermediate or high grade due to the existence of a high-grade fibrosarcomatous component (DFSP-FS) [70]. Most commonly DFSP affects patients in their mid-to-late 30s; however, people of any age can be affected. DFSP has also been reported in congenital and childhood cases [71]. A comparative higher incidence has been observed in Blacks than Whites. Gender wide also both men and women are equally affected [72]. DFSP rates are highest among Blacks, with a male-to-female ratio of 1:1 and a 5-year relative survival rate of 99% [2–4]. There are no particular risk factors related to DFSP; it can arise in chronically damaged areas or even on healthy skin. With a high rate of local recurrence DFSP typically follows an indolent clinical course because of its infiltrative behavior, but low metastatic potential. Chromosomal translocation is also associated with DFSP tumorigenesis and leads to the fusion of collagen type 1 alpha 1 (COL1A1) and platelet-derived growth factor subunit b (PDGFB) genes. This fusion protein origins a nonstop beginning of the receptor PDGF receptor b (PDGFRB) tyrosine kinase, which indorses DFSP cell growth [73].

1.7 Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) disease is scarce, originated from the neuroendocrine cell, and has a very aggressive tumor showing similarity with mechanoreceptor Merkel cells. In the USA, MCC is an annual incidence with an estimated rate of 3 people per million of the population [74]. Normally MCC is present in men than women, and it increases in White individuals than Black, MCC average diagnosis rate is 70 years [75]. Neural crest is the driving source of Merkel cells, and it differentiates as a part of the amine precursor uptake and decarboxylation system and it also functions as slowly adapting type I mechanoreceptors [75]. Merkel cell tumor is evident in two distinct forms. First, a virus called Merkel cell polyomavirus participates in the pathogenesis of one form of Merkel tumors, and the second is driven by ultraviolet (UV)-linked mutations [73]. MCC is a primary, cutaneous, and neuroendocrine neoplasm associated with a poor prognosis [76–78]. The mortality rate for MCC disease is greater than 40%, significantly higher than that of melanoma and other cutaneous cancers [77, 79]. Some factors as loss of immune competence, prolonged ultraviolet exposure, and advanced age constitute risk factors for developing MCC [76, 77]. Mechanoreceptor cells (located in the basal layer of the epidermis) with MCC tumor cells that originated from the epidermal progenitors during embryonic development play an essential role in the sensory system of the

skin [78, 80–82]. As a result of its scarcity and its resemblance with other more common neuroendocrine tumors, such as small cell lung carcinoma determining the incidence of MCC has been challenging. Across the regions of the world, the incidence rate of MCC is varied. In the USA in 2018, the incidence rate reported by SEER analysis (surveillance, epidemiology, and end results) was 0.79 per 100,000 [83]. According to the RARECARE database, reported incidence of MCC in Europe, are 0.13 per 100,000 (1995 and 2002) [84]. In the last 20 years in the USA and Europe, the incidence of this neoplasm has quadrupled, perhaps due to systemic immune suppression, increasing UV exposure, and longer lifespan [83]. It is also reported Australia has the highest incidence of 1.6 per 100,000 from 1993 to 2010 [85]. According to a recent study from 2000 to 2013, the incidence of MCC is outpacing that of other cancers with an increase of 95% [86]. The authors of that study have predicted the numbers of newly diagnosed cases would possibly increase from 2488 to 3284 in a leap of years from 2013 to 2025 [86, 87]. It is discovered that integration of polyomavirus genome in the genome of MCC tumor cells increases the tumor insidence. This created a major paradigm shift in the understanding of the etiology of MCC. MCC was chosen and subjected to digital transcriptome subtraction (DTS), a direct sequencing-based method due to its strong association with immunosuppression and because of its epidemiology [88, 89]. Polyomaviruses have also been previously connected to human disease [90]. However, unlike other polyomaviruses, MCV found to be the first polyomavirus and a causative agent, which is convincingly linked to human cancer [91]. World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) classified it as a Group 2A carcinogen due to its compelling evidence of causation [92]. Type of MCC was identified by MCPyV-negative and MCPyV-positive tumor incidence, and MCPyV-negative has a higher number of chromosomal aberrations and UV-specific mutation burden [93–97]. This is reported that virus-negative tumors may be clinically more aggressive [98]. This aggressive nature of MCC tumor has been associated with higher exposure to risk factors, as well as a changed immune system. UV radiation is a risk factor for MCC. The appearance of tumors is more common in skin areas with substantial UV radiation exposure; the incidence of MCC associates with UVB radiation index and other skin cancers subsequent from sun exposure. White patients are frequently affected than other races. Patients with the underlying immunosuppressed condition, such as those with hematologic malignancies, a developed immunodeficiency syndrome (AIDS), autoimmune disease, and a history of solid organ transplant, are at higher risk for developing MCC [94–98].

1.8 Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma (MAC) is a type of skin cancer which is described in literature as aggressive trichofolliculoma, combined adnexal tumor, carcinoma with syringomatous features, malignant syringoma, sclerosing sweat duct carcinoma, sweat gland tumor. MAC was first defined as a separate subject in 1982 by Goldstein

et al. [99]. The origin of MAC is from pluripotent adnexal keratinocytes and it is capable of both eccrine and follicular differentiation. MAC is not clearly observed with pathogenesis but may involve exposure to ionizing and UVR that may lead to the growth of MAC as long as 40 years [100]. MAC is very aggressive and has a high rate of local recurrence with nearby damaging cutaneous appendageal neoplasm but has a low rate of metastasis. It mainly affects White, middle-aged people, though it has been reported in children and Blacks. Comparative to further main cutaneous malignancies, MAC shows a small female prevalence. CD 10 expression is found to have 60% of infiltrative basal cell carcinoma, 31% of microcystic adnexal carcinoma, and 25% of squamous cell carcinoma. The expression of BerEP4 was reported in 38% of microcystic adnexal carcinoma, desmoplastic trichoepithelioma has 57%, infiltrative basal cell carcinoma is 100%, and 38% of squamous cell carcinoma [101].

1.9 Sebaceous Carcinoma

Sebaceous carcinoma (SC) is a type of skin cancer that has variable sites of origin it develops a malignant adnexal tumor, it observed through histologic growth patterns, and clinical presentations. Around 75% of SCs are periocular in location [102]. Periocular SC might arise from Meibomian glands and a few from the glands of Zeis. Eyelids are most frequently involved in SC development, and approximately 25% of cases of SC involve extraocular sites, which might be included in the head and neck, trunk, salivary glands, and external genitalia [103]. Globally SC affects most of the race, but Asian race is more vulnerable to the SC disease. With a noticeable ratio of 2:1, women are affected more commonly than men. SC is associated with sebaceous adenomas, radiation exposure, and Muir Torre syndrome and classically presents in the seventh to ninth decades [104]. As SC shows robust connotation with Muir Torre syndrome, colonoscopy is used to understand the colon cancer incidence. Repetitive genetic screening for Muir Torre in the absence of colon lesions is not commonly observed. Sebaceous carcinoma typically presents in older age mostly after 60 years, on the eyelid, head and neck, and trunk. Diagnosis through deep biopsy is frequently required; also, differential diagnoses that imitate the condition can be omitted with special histological stains [105]. It is quite common to detect false benign conditions, follow-on in inappropriate management. Therefore, this is of utmost importance to uphold a high index of doubt. Notwithstanding earlier reports, sebaceous carcinoma might have occurred with similar frequency in Asians and Whites. Genetic data suggest that there are numerous mutational groups of sebaceous carcinomas, help the way for specific treatment of SC.

1.10 Extramammary Paget Disease

Extramammary Paget disease (EMPD) is a rare cutaneous malignancy condition that occurs mostly on apocrine rich skin of mid-age to older individuals, frequently on the genitalia. Paget disease was described in 1874, by Sir James Paget, also known as mammary Paget disease. This disease reintroduced as extramammary Paget disease (EMPD) of the scrotum and penis in 1889. Although there is a slight female prevalence in Caucasian patients, there is a strong 4:1 male prevalence in Asians [106].

It is histologically similar to Paget disease of the breast, EMPD is another class of disease other than breast cancer with a distinct. Mostly EMPD is a malignant form of cancer from a primary intraepidermal origin which is from eccrine or apocrine glands. It is also associated with internal malignancy in 15% to 30% of cases, usually colon, bladder, or prostate cancer [107] that could lead to secondary EMPD with less prognosis than primary EMPD. Surgical operation is the treatment of choice; nevertheless, procedures tend to be extensive and associated with a high rate of recurrence. EMPD is a slowly red plaque disease that looks like an inflammatory condition and this affects diagnosis delay. Diagnosis requires histopathologic examination and is frequently supported by immunohistochemical analysis. EMPD diagnosis in the patient is evaluated further for malignancy. Data suggested that Mohs micrographic surgery might have superior clinical outcomes and lower recurrence rates. Substitutes therapy, photodynamic therapy, and topicals have been explored and may be suitable in some cases. Patients with EMPD generally have a good prognosis with a 5-year overall survival rate of 75% to 95%. Although mammary and extramammary Paget disease are both characterized by epidermal Paget cells and part a parallel clinical presentation, their exclusivity deceits in anatomical site and histogenesis. Immunohistochemical staining lets for differentiation among primary and secondary EMPD in adding to the various other disease objects that clinically look like this malignancy. Surgical removal is utilized as first-line therapy and the prognosis is frequently favorable. Current developments inside the ground have inspected the expression of chemokine receptors inside tumors, which may be appropriate in decisive prognosis [108].

1.11 Atypical Fibroxanthoma and Malignant Fibrous Histiocytoma

Atypical fibroxanthoma (AFX) is a rare cutaneous soft tissue tumor, atypical fibroxanthoma (AFX) and malignant fibrous histiocytoma were supposed to be two separate parts of the same malignancy. WHO describes AFX as soft tissue sarcomas that identifies cell line beginning in the classification of tumors. As earlier considered, maximum cases of malignant fibrous histiocytoma, were found to be simply a morphologic pattern somewhat a defined pathologic condition [109]. In most of the cases, ultrastructural and immunohistochemical inspection permitted for recognition into distinct histologic subtypes of sarcomas. On that basis updated

classification of the term malignant fibrous histiocytoma is presented as a substitute for undistinguishable pleomorphic sarcoma (UPS). This cancer type is a deep-seated subcutaneous nodule infrequently comes across in the skin; it is mostly seen on the limbs of old aged individuals. UPS has a very poor prognosis that leads to aggressive tumor development. Though surgical excision is the first-line treatment (normally with adjuvant RT), up to 50% of patients may have distant metastasis at the time of initial condition, and the nearest affected organ is the lung. It affects typically the elderly on sun-exposed skin.

Atypical fibroxanthoma presents as a red nodule or plaque, and as frequently AFX effect on the head and neck of sun-exposed people and on the trunk and edges of younger patients [110]. AFX has similar histologic features to undifferentiated pleomorphic sarcoma, and it is less aggressive. Tumor development in the AFX characterized by the time point of the head and neck present during the eighth phase, while tumors connecting the boundaries often present during the fourth phase [111, 112]. The gender ratio is almost to be equal. A very small number of cases are reported with xeroderma pigmentosum. AFX pathogenesis involves UV exposure, ionizing radiation, and abnormal immune host response. The most common mutation with UVR showed TSG p53 mutation. Typically, after ionization radiation tumors might occur after 10–15 years. A high number of AFX incidences occurred in patients with renal transplant and metastatic condition and patient with chronic lymphocytic leukemia [113].

1.12 Carcinoma Metastatic to Skin

The metastatic tumors of the skin are primary tumors same as of the breast, lung, or melanoma; and skin metastases also become sporadic by other primary carcinomas. Metastasis stage of cutaneous visceral carcinomas normally occurs in patients with progressive disease and is linked with a poor prognosis. Cutaneous participation is also seen in the leukemias, with an extensive disparity in the morphology of lesions. Cutaneous metastatic disease is most common in the scalp. It may be helpful to utilize immunohistochemical stains to determine the place of the primary tumor. Management strategies such as prompt consultation with oncologists may help in the pathogenesis of tumor stage determination [114].

1.13 Conclusion

Ultraviolet (UV) light from the sun is the main cause of most skin cancers. DNA damage by UV light predominantly plays important role in skin cancer. Too much sun exposure from an early age is the primary cause of developing basal cell carcinomas (BCCs) or squamous cell carcinoma (SCCs). Sun exposure over a long time can cause both types of skin cancer but it is most common in SCC. People who work outdoors such as farmworkers, builders, and gardeners are more at risk of developing skin cancer. Normally skin cancer comes very late at an age like after

40 and commonly occurs in older age. Though the rising number of incidences is seen in younger. Using sunbeds and sunlamps rises the risk of emerging some skin cancers. Squamous cell carcinoma in situ is also called Bowen's disease. That abnormal growth of cells leads to outer layer of the skin (the epidermis), and these cells do not spread into the deeper layers of the skin. Sometime when Bowens disease left untreated may cause to develop SCC. A weak Immune system is also a prominent factor in developing SCC. Another possible rare cause for nonmelanoma skin cancer is overexposure to certain chemicals, usually at work. Most skin cancer is not genetically transferred on to other family members. Biological families are possible to have the same skin characters that may lead to their risk of developing cancer in the skin. In some cases, such as rare genetic like Gorlin syndrome, epidermolysis bullosa (EB), xeroderma pigmentosum (XP) have a higher risk of developing skin cancer. Persistent ingestion of arsenic in drinking water is associated with a higher risk of skin cancer and bladder cancer, and as it is reported occupational and medical exposure to arsenic has been clearly associated with skin cancer in epidemiological studies.

Conflict of Interest The author declares no conflict of interest.

References

1. Madan V, Lear JT, Szeimies RM (2010) Non-melanoma skin cancer. Lancet 375:673–685
2. Stern RS (2010) Prevalence of a history of skin cancer in 2007: results of an incidence-based model. Arch Dermatol 146:279–282
3. Rogers HW, Weinstock MA, Harris AR et al (2010) Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 146:283–287
4. Berman B, Amini S, Valins W et al (2009) Pharmacotherapy of actinic keratosis. Expert Opin Pharmacother 10:3015–3031
5. Schwartz RA (1997) The actinic keratosis. A perspective and update. Dermatol Surg 23:1009–1019
6. Salasche SJ (2000) Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 42:4–7
7. Rodriguez-Vigil T, Vazquez-Lopez F, Perez-Oliva N (2007) Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation. J Am Acad Dermatol 56:91–95
8. Brash DE, Ziegler A, Jonason AS et al (1996) Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. J Investig Dermatol Symp Proc 1:136–142
9. Ulrich C, Bichel J, Euvrard S et al (2007) Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. Br J Dermatol 157:25–31
10. Tanghetti E, Werschler P (2007) Comparison of 5% 5-fluorouracil cream and 5% imiquimod cream in the management of actinic keratoses on the face and scalp. J Drugs Dermatol 6:144–147
11. Cognetta AB, Howard BM, Heaton HP et al (2012) Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. J Am Acad Dermatol 67:1235–1241

12. Veness MJ (2008) The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities. J Med Imaging Radiat Oncol 52:278–286
13. Krawtchenko N, Roewert-Huber J, Ulrich M et al (2007) A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1- year follow-up. Br J Dermatol 157:34–40
14. Piacquadio DJ, Chen DM, Farber HF et al (2004) Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol 140:41–46
15. Smith S, Piacquadio D, Morhenn V et al (2003) Short incubation PDT versus 5-FU in treating actinic keratoses. J Drugs Dermatol 2:629–635
16. Poojan S, Kumar S, Verma V, Dhasmana A, Lohani M, Verma MK (2015) Disruption of skin stem cell homeostasis following transplacental arsenicosis; alleviation by combined intake of selenium and curcumin. PLoS One 10(12):e0142818
17. Szeimies RM, Karrer S, Radakovic-Fijan S et al (2002) Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol 47:258–262
18. Rivers JK, Arlette J, Shear N et al (2002) Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. Br J Dermatol 146:94–100
19. Weiss ET, Brauer JA, Anolik R et al (2013) 1927-nm fractional resurfacing of facial actinic keratosis: a promising new therapeutic option. J Am Acad Dermatol 68:98–102
20. Lacour JP (2002) Carcinogenesis of basal cell carcinomas: genetics and molecular mechanisms. Br J Dermatol 146:17
21. Wang Y, Wells W, Waldron J (2009) Indications and outcomes of radiation therapy for skin cancer of the head and neck. Clin Plast Surg 36:335–344
22. Clarissa PHR, Renato MB (2019) Actinic keratoses: review of clinical, dermoscopic, and therapeutic aspects. An Bras Dermatol 94(6):637–657
23. Dai J, Lin K, Huang Y, Lu Y, Chen WQ, Zhang XR, He BS, Pan YQ, Wang SK, Fan WX (2018) Identification of critically carcinogenesis-related genes in basal cell carcinoma. Onco Targets Ther 11:6957–6967
24. De Giorgi V, Savarese I, Gori A, Scarfi F, Topa A, Trane L, Portelli F, Innocenti A, Covarelli P (2020) Advanced basal cell carcinoma: when a good drug is not enough. J Dermatolog Treat 31(6):552–553
25. Martens MC, Seebode C, Lehmann J, Emmert S (2018) Photocarcinogenesis and skin cancer prevention strategies: an update. Anticancer Res 38(2):1153–1158
26. Watt TC, Inskip PD, Stratton K et al (2012) Radiation-related risk of basal cell carcinoma: a report from the childhood cancer survivor study. J Natl Cancer Inst 104:1240–1250
27. Epstein EH (2008) Basal cell carcinomas: attack of the hedgehog. Nat Rev Cancer 8:743–754
28. Grossman D, Leffell DJ (1997) The molecular basis of nonmelanoma skin cancer: new understanding. Arch Dermatol 133:1263–1270
29. Situm M, Buljan M, Bulat V et al (2008) The role of UV radiation in the development of basal cell carcinoma. Coll Antropol 32(suppl 2):167–170
30. Lupi O (2007) Correlations between the sonic hedgehog pathway and basal cell carcinoma. Int J Dermatol 46:1113–1117
31. Ziegler A, Leffell DJ, Kunala S et al (1993) Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. Proc Natl Acad Sci U S A 90:4216–4220
32. Kamath P, Darwin E, Arora H, Nouri K (2018) A review on imiquimod therapy and discussion on optimal management of basal cell carcinomas. Clin Drug Investig 38(10):883–899
33. Chahal HS, Rieger KE, Sarin KY (2017) Incidence ratio of basal cell carcinoma to squamous cell carcinoma equalizes with age. J Am Acad Dermatol 76:353–354
34. Karia PS, Han J, Schmults CD (2013) Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States in 2012. J Am Acad Dermatol 68:957–966

35. Venables ZC, Nijsten T, Wong KF, Autier P, Broggio J, Deas A, Harwood CA, Hollestein LM, Langan SM, Morgan E et al (2019) Epidemiology of basal and cutaneous squamous cell carcinoma in the U.K. 2013-15: a cohort study. Br J Dermatol 181:474–482
36. Que SKT, Zwald FO, Schmults CD (2018) Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol 78:237–247
37. Gloster HM Jr, Brodland DG (1996) The epidemiology of skin cancer. Dermatol Surg 22:217–226
38. Inman GJ, Wang J, Nagano A, Alexandrov LB, Purdie KJ, Taylor RG, Sherwood V, Thomson J, Hogan S, Spender LC et al (2018) The genomic landscape of cutaneous SCC reveals drivers and a novel azathioprine associated mutational signature. Nat Commun 9:3667
39. Kim YW, Kim YH, Song Y et al (2019) Monitoring circulating tumor DNA by analyzing personalized cancer-specific rearrangements to detect recurrence in gastric cancer. Exp Mol Med 51(8):1–10
40. Condorelli AG, Dellambra E, Logli E, Zambruno G, Castiglia D (2019) Epidermolysis bullosa-associated squamous cell carcinoma: from pathogenesis to therapeutic perspectives. Int J Mol Sci 20(22):5707
41. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ (2010) Angiosarcoma. Lancet Oncol 11:983–991
42. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF (1996) Angiosarcoma. A report of 67 patients and a review of the literature. Cancer 77:2400–2406
43. Khan JA, Maki RG, Ravi V (2018) Pathologic angiogenesis of malignant vascular sarcomas: implications for treatment. J Clin Oncol 36:194–201
44. Buehler D, Rice SR, Moody JS, Rush P, Hafez GR, Attia S, Longley BJ, Kozak KR (2014) Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. Am J Clin Oncol 37:473–479
45. Mullin C, Clifford CA (2019) Histiocytic sarcoma and hemangiosarcoma update. Vet Clin North Am Small Anim Pract 49:855–879
46. Buehler D (2014) Angiosarcoma outcomes and prognostic factors. Am J Clin Oncol 37:473–479
47. Lahat G, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, Phung TL, Pollock RE, Benjamin R, Hunt KK, Lazar AJ, Lev D (2010) Angiosarcoma: clinical and molecular insights. Ann Surg 251:1098–1106
48. Yin M, Wang W, Drabick JJ, Harold HA (2017) Prognosis and treatment of non-metastatic primary and secondary breast angiosarcoma: a comparative study. BMC Cancer 17:295
49. Verdura V, Di Pace B, Concilio M, Guastafierro A, Fiorillo G, Alfano L, Nicoletti GF, Savastano C, Cascone AM, Rubino C (2019) A new case of radiation-induced breast angiosarcoma. Int J Surg Case Rep 60:152–155
50. Peterson CB, Beauregard S (2016) Radiation-induced breast angiosarcoma: case report and clinical approach. J Cutan Med Surg 20:304–307
51. Virtanen A, Pukkala E, Auvinen A (2007) Angiosarcoma after radiotherapy: a cohort study of 332,163 finnish cancer patients. Br J Cancer 97:115–117
52. Disharoon M, Kozlowski KF, Kaniowski JM (2017) Case 242: radiation-induced angiosarcoma. Radiology 283:909–916
53. Amajoud Z, Vertongen AS, Weytens R, Hauspy J (2018) Radiation induced angiosarcoma of the breast: case series and review of the literature. Facts Views Vis Obgyn 10:215–220
54. Miller R, Mudambi L, Vial MR, Kalhor N, Grosu HB (2017) Radiation-induced angiosarcoma as a cause of pleural effusion. Am J Respir Crit Care Med 196:e10–e11
55. Plichta JK, Hughes K (2017) Radiation-induced angiosarcoma after breast-cancer treatment. N Engl J Med 376:367
56. Alves I, Marques JC (2018) Radiation-induced angiosarcoma of the breast: a retrospective analysis of 15 years' experience at an oncology center. Radiol Bras 51:281–286
57. Seo CJ, Lek SM, Tan GHC, Teo M (2017) Radiation-associated peritoneal angiosarcoma. BMJ Case Rep 2017:217887

58. Pereira ES, Moraes ET, Siqueira DM, Santos MA (2015) Stewart Treves syndrome. An Bras Dermatol 90(Suppl 1):229–231
59. Berebichez-Fridman R, Deutsch YE, Joyal TM, Olvera PM, Benedetto PW, Rosenberg AE, Kett DH (2016) Stewart-Treves syndrome: a case report and review of the literature. Case Rep Oncol 9:205–211
60. Cui L, Zhang J, Zhang X, Chang H, Qu C, Zhang J, Zhong D (2015) Angiosarcoma (Stewart-Treves syndrome) in postmastectomy patients: report of 10 cases and review of literature. Int J Clin Exp Pathol 8:11108–11115
61. Mesli SN, Ghouali AK, Benamara F, Taleb FA, Tahraoui H, Abi-Ayad C (2017) Stewart-Treves syndrome involving chronic lymphedema after mastectomy of breast cancer. Case Rep Surg 2017:4056459
62. Benmansour A, Laanaz S, Bougtab A (2014) Stewart-Treves syndrome: a case report. Pan Afr Med J 19:2
63. Tripke V, Heinrich S, Huber T, Mittler J, Hoppe-Lotichius M, Straub BK, Lang H (2019) Surgical therapy of primary hepatic angiosarcoma. BMC Surg 19:5
64. Chaudhary P, Bhadana U, Singh RA, Ahuja A (2015) Primary hepatic angiosarcoma. Eur J Surg Oncol 41:1137–1143
65. Choi JH, Ahn KC, Chang H, Minn KW, Jin US, Kim BJ (2015) Surgical treatment and prognosis of angiosarcoma of the scalp: a retrospective analysis of 14 patients in a single institution. Biomed Res Int 2015:321896
66. Tran Minh M, Mazzola A, Perdigao F, Charlotte F, Rousseau G, Conti F (2018) Primary hepatic angiosarcoma and liver transplantation: radiological, surgical, histological findings and clinical outcome. Clin Res Hepatol Gastroenterol 42:17–23
67. Blatt J, Finger M, Price V, Crary SE, Pandya A, Adams DM (2019) Cancer risk in Klippel-Trenaunay syndrome. Lymphat Res Biol 17(6):630–636
68. Cao J, Wang J, He C, Fang M (2019) Angiosarcoma: a review of diagnosis and current treatment. Am J Cancer Res 9(11):2303–2313
69. Kampshoff JL, Cogbill TH (2009) Unusual skin tumors: Merkel cell carcinoma, eccrine carcinoma, glomus tumors, and dermatofibrosarcoma protuberans. Surg Clin North Am 89:727–738
70. Abbott JJ, Oliveira AM, Nascimento AG (2006) The prognostic significance of fibrosarcomatous transformation in dermatofibrosarcoma protuberans. Am J Surg Pathol 30:436–443
71. Gu W, Ogose A, Kawashima H et al (2005) Congenital dermatofibrosarcoma protuberans with fibrosarcomatous and myxoid change. J Clin Pathol 58:984–986
72. Monnier D, Vidal C, Martin L, Danzon A, Pelletier F, Puzenat E, Algros MP, Blanc D, Laurent R, Humbert PH, Aubin F (2006) Dermatofibrosarcoma protuberans: a population-based cancer registry descriptive study of 66 consecutive cases diagnosed between 1982 and 2002. J Eur Acad Dermatol Venereol 20(10):1237–1242
73. Arora R, Rekhi B, Chandrani P, Krishna S, Dutt A (2019) Merkel cell polyomavirus is implicated in a subset of Merkel cell carcinomas, in the Indian subcontinent. Microb Pathog 137:103778
74. Haag ML, Glass LF, Fenske NA (1995) Merkel cell carcinoma. Diagnosis and treatment. Dermatol Surg 21:669–683
75. Rockville Merkel Cell Carcinoma Group (2009) Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol 27:4021–4026
76. Hodgson NC (2005) Merkel cell carcinoma: changing incidence trends. J Surg Oncol 89:1–4
77. Becker JC, Stang A, DeCaprio JA, Cerroni L, Lebbe C, Veness M et al (2017) Merkel cell carcinoma. Nat Rev Dis Primers 3:17077
78. Schadendorf D, Lebbe C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M et al (2017) Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 71:53–69