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Cutaneous Malignant Tumors: Clinico-Pathological Study in Bahrain

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ABSTRACT

Introduction: Cutaneous malignancies are in the rise worldwide. They include basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) and Malignant Melanoma (MM). Advance age and exposure to ultraviolet (UV) rays are among the most important risk factors associated with skin malignancies, although various other factors are also implicated.

Aims and Objectives: The aims of this study are to study clinical spectrum with age and sex distribution of cutaneous malignancies in Bahrain; to study clinicopathological variants of each type of these malignancies, describe their pathological stage and predict the prognosis.

Patients and Methods: It is a retrospective analysis of biopsy proven cases of cutaneous malignancies at Salmaniya Medical Complex in the period between January 1, 2016 to January 31, 2021. Medical records of patients were retrieved from ISEHA system. Statistical analysis was done using Microsoft Excel 2019.

Results: 61 cases with cutaneous malignancies were recruited. There was Bahraini nationality (89%) and male preponderance (69%). The most common age group affected was 60–70 years with the mean age of 62.26 year. BCC was the most common malignancy diagnosed (71%) followed by malignant melanoma (16%) and squamous cell carcinoma (13%). Face was the most common site involved (36%). The majority of tumors had a T1 pathological TNM staging (49%). T4 stage tumors were the malignant melanoma cases (12%). The most common presenting symptom was a pigmented lesion (49%), followed by a longstanding ulcer (36%).

Conclusion: Malignant skin neoplasms in Bahrain have male preponderance. The most common clinical presentation of these tumors is a pigmented lesion. Basal cell carcinoma is the most common type. Face and nose are the most common sites involved. Majority of skin cancers in the study are of low pathological stage except malignant melanoma patients who presented with an advance stage.

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Introduction

Malignant skin tumors are among the rare cancers in the world. However, a notable rise in their incidence and prevalence are observed globally. Skin Cancer Deaths are rare as well and a proportional maintenance in its number is due to the early detection and prompt management. According to the latest WHO data published in 2018 Skin Cancers Deaths in Bahrain reached 5 or 0.20% of total deaths. The age adjusted Death Rate is 0.61 per 100,000 of population ranks Bahrain #162 in the world [1].

Cutaneous malignancies include epithelial tumors such as basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) which are also referred to non-melanoma skin cancers (NMSC) and these collectively Form the most common skin cancers world-wide [2]. Malignant Melanoma (MM) is another type of skin cancer which usually has an advance stage on presentation due to the late diagnosis of the initial disease. Other skin malignancies include, cutaneous lymphomas, and sarcomas that have different presenting clinical symptoms and adverse outcome in most instances [2].

Malignant skin adnexal tumors are another group of skin cancers that arise from one of the skin adnexal epithelium lineage and have wide morphological subtypes. Their clinical presenting symptoms, pathological diagnosis and cancer stages are unique and differ a lot from the common malignant skin cancers [2].

Advance age and exposure to ultraviolet (UV) rays is the most important risk factors associated with skin malignancies, although various other factors are also implicated. These essential risk

factors manifested by the higher incidence of skin cancers in sun exposed areas specifically head and neck region [3].

There are many published skin malignancies research data from all over the world. However, seldom information is known about the skin cancers in Bahrain. This study aims to study a clinical spectrum with age and sex distribution of cutaneous malignancies in Bahrain; to study clinicopathological variants of each type of these malignancies; and describe their pathological characteristics along with correlation with the pathological stage of the disease and the patient survival rate.

Materials and Methods

This is a retrospective analysis of clinical and biopsy proven cases of cutaneous malignancies at the main tertiary governmental hospital in The Kingdom Of Bahrain- Salmaniya Medical Complex - in the period between January 1, 2016 to January 31, 2021. Cutaneous malignancies studied in this study are Basal Cell Carcinoma (BCC) and its variants, Squamous Cell Carcinoma (SCC) and its variants and Malignant Melanoma (MM) and its variants. Cutaneous lymphomas, sarcomas and skin adnexal malignancies were not included in this study.

Medical records of patients in ISEHA were assessed with respect to demographic information, clinical examination, and histopathology reports. Statistical analysis was done using mean, proportion, and percentage with the assistance of Microsoft Excel 2019.

Results

Sixty-one cases with cutaneous malignancies were recruited. Most of the malignant skin tumors in our center were diagnosed on excisional biopsy specimens of skin lesions (87%) followed by punch\incisional biopsies (13%). Most of the diagnosed malignancies were in Bahraini nationality patients (89%). And Male predominance (69%). The most common age group affected was 60–70 years (Table 1) with the mean age of 62.26 year.

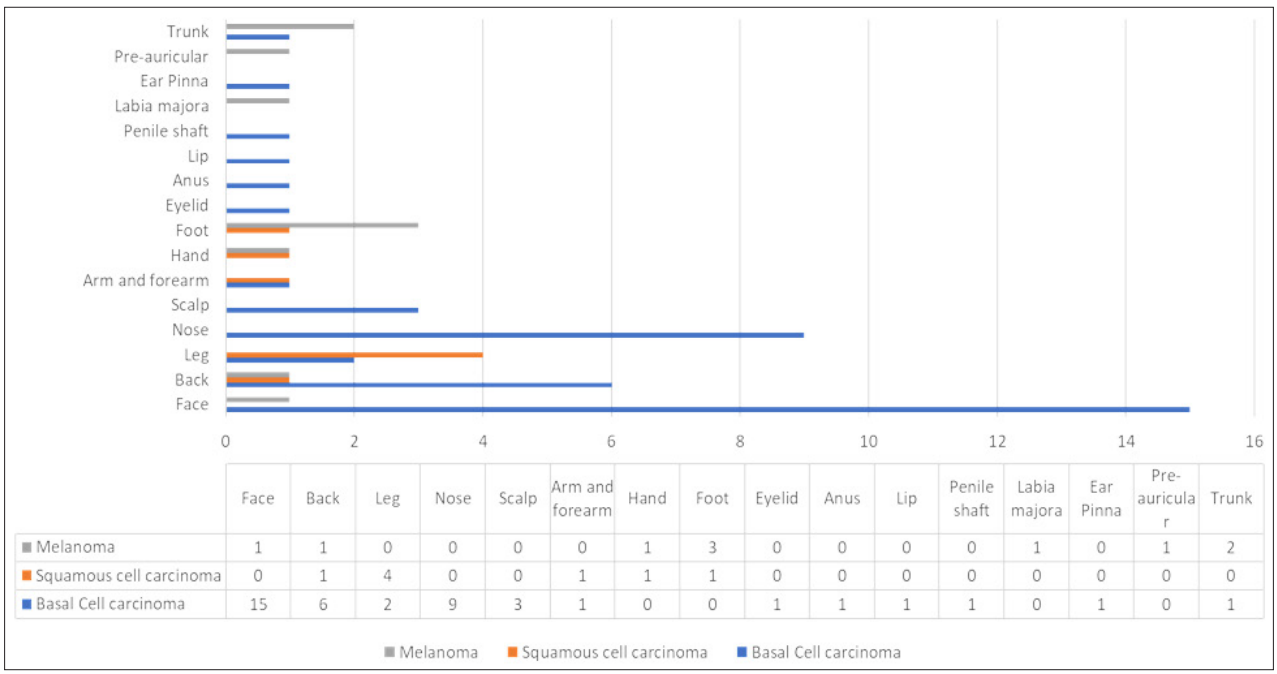
Table 1: Number of Malignant Skin Tumors Distribution according to Age Groups

Age (years)	No.of Malignancy (%)
21-30	2(3%)
31-40	4(7%)
41-50	8(13%)
51-60	13(21%)
61-70	17(28%)
71-80	9(15%)
81-90	8(13%)
`Total	61(100%)

In our study, we found that the most prevalent histological type of cancer was Basal cell carcinoma (BCC) accounting for 43 cases (71%) followed by malignant melanoma accounting for 10 cases (16%) and lastly squamous cell carcinoma which was diagnosed in 8 patients (13%) (Table 2). in accordance with most literature studies, the sun exposed areas were the most frequently affected sites of the body. Hence, head and neck (mainly face) are the most common site involved by various types of skin cancer (36%) followed by nose (21%) and back region (14%) (Figure1) and (Table3).

Table 2: Distribution of Different Types of Malignant Skin Tumors in the Study

Tumor	Malignant	No.(%)
Keratenocytic	BCC SCC	43(71%) 8(13%)
Melanocytic	MM	10(16%)
Total		61(100%)



	Face	Back	Leg	Nose	Scalp	Arm and forearm	Hand	Foot	Eyelid	Anus	Lip	Penile shaft	Labia majora	Ear Pinna	Pre-auricular	Trunk
Melanoma	1	1	0	0	0	0	1	3	0	0	0	0	1	0	1	2
Squamous cell carcinoma	0	1	4	0	0	1	1	1	0	0	0	0	0	0	0	0
Basal Cell carcinoma	15	6	2	9	3	1	0	0	1	1	1	1	0	1	0	1

Figure 1: Histological types of cutaneous malignancies in relation to the site of malignancy. The chart shows the number of each type of skin cancer in relation to the site of the malignancy. The table below the chart shows the exact number of each malignant tumor distributed according to the body site.

When analyzing the data of each histological types of the epithelial malignancies we studied, we found that 26 patients with basal cell carcinoma (BCC) was diagnosed with the nodular type making it the most common subtype of this cancer in our study (62%). Other histological variants of basal cell carcinoma (BCC) were also not uncommon. We found that superficial BCC was diagnosed in 5 patients (12%). We also found that aggressive variants of BCC such as infiltrative BCC, Micronodular BCC, Basosquamous variant and poorly differentiated variant were accounting for 10%, 2%, 10%, 2% and 2% of the cases respectively (Figure 2). Regarding the patient's diagnosed with Malignant Melanoma, we found that they have the nodular type as a relatively common histological type accounting for almost all the cases (80%). We also assessed the l evel of invasion of all the histological subtypes of these epithelial skin malignances and was concluded that in all these surgical specimens, most of these tumors were invading the skin to the level of reticular dermis (80%) followed by the subcutaneous fat and lastly the muscle (7%). All surgical resection specimens' reports were reviewed and their pathological TNM staging were compared as well and show that most of cutaneous malignancies in the study were at a very early stage of diagnosis (pT1 stage) (49%) with the majority of the diagnosed malignancy being nodular type basal cell carcinoma. pT2 stage tumors account for (25%), pT3 stage tumors (14%) and T4 stage tumors were (12%) which were all of the malignant melanoma cases. When reviewing the clinical presentation of these malignancies, we observed that the most common presenting symptom was a pigmented lesion (49%), followed by a longstanding ulcer (36%) and least commonly the patient presented with a mass (8%).

Table 3: Histological types of cutaneous malignancies in relation to the site of malignancy. The table shows the number of each type of skin cancer in relation to the site of the malignancy

Malignancy Site	No. (Total)	Histological type (No.)		
		Basal cell carcinoma	Squamous cell carcinoma	Melanoma
Face	16	15	0	1
Back	8	6	1	1
Nose	9	9	0	0
Leg	6	2	4	0
Scalp	3	3	0	0
Arm and forearm	2	1	1	0
Hand	2	0	1	1
foot	4	0	1	3
Eyelid	1	1	0	0
Anus	1	1	0	0
Lip	1	1	0	0
Penile shaft	2	2	0	0
Labia majora	1	0	0	1
Ear pinna	1	1	0	0
Pre-auricular	1	0	0	1
Trunk	3	1	0	2
Total	**61**	**43**	**8**	**10**

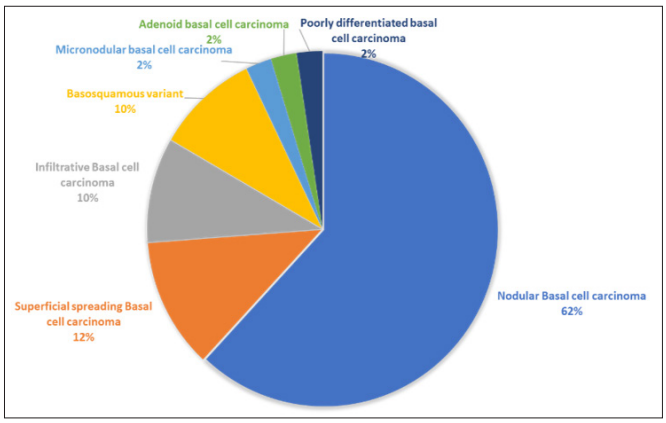


Figure 2: Histological types of basal cell carcinoma in the study. The pie chart shows the percentage of each type of basal cell carcinoma which were diagnosed in the cases included in the study

Discussion

This study examined the rate of cutaneous keratinocytic and melanocytic malignancies with their pathological parameters and their clinical presentations in the main tertiary referral hospital in the kingdom of Bahrain. The results of this study reflect the general pathological and clinical characteristics of the most common cutaneous malignancies among Bahraini population.

Keratinocytic malignancies include Basal cell carcinoma (BCC) and squamous cells carcinoma (SCC) with their variants. Melanocytic malignancies compose of Malignant Melanoma (MM) with its wide range of variants [1, 2].

Advance age and Ultraviolet radiation are common underlying risk factors for both keratinocytic and melanocytic malignancies. As described in the literature, the association between ultraviolet radiation and risk of cutaneous malignancies is well-established. However, it is not possible to conclude a definitive relationship between the amount and duration of sun exposure and skin cancer development, possibly due to the variability in the definition of sun exposure across epidemiological studies [1-3].

Being an extremely prevalent environmental factor, Ultraviolet (UV) radiation's main carcinogennic factor is its ability to damage the genome. Human cells respond to UV-induced DNA damage by activating multiple biological processes including DNA damage checkpoint for cell cycle arrest, DNA repair that is affected by chromatin state, and DNA damage tolerance that may promote survival with mutations. UV light exposure for prolonged periods increases mutation burden. The latter has a tremendous effect on skin cancer development. This process is guided by reactive oxygen species (ROS), continuous inflammation, and immunosuppression. Many recent studies have described the precise molecular and cellular consequences of the chronic exposure to UV irradiation. Hence, Targeting UV-induced DNA damage responses is an effective means to prevent and treat skin cancer [3].

According to a previous published study a decade ago, Skin cancer in Bahrain accounted for 6.7% of all malignancies among Bahraini Arabs with 70.2% of the patients above the age of 60 years [4,5]. Moreover, referring to the latest WHO data published in 2018 Skin Cancers Deaths in Bahrain reached 5 or 0.20% of total deaths [4. The age adjusted Death Rate is 0.61 per 100,000 of population ranks Bahrain #162 in the world [4, 5].

The Incidence of skin cancer in Bahrain comprises from Basal cell carcinoma (BCC), Squamous cell carcinoma and less frequently malignant melanoma [5]. Basal cell carcinoma (BCC), considered the most common human cancer worldwide. Although the mortality from BCC is negligible, this tumor can be associated with significant morbidity and cost. BCC is considered a malignant neoplasm of keratinocyte origin, which mainly originates from the basal cells in the epidermis and the outer root sheath of the hair follicles, which contain pluripotent epithelial cells [6, 7].

Diagnosis of BCC begins with clinical suspicions over a chronic pigmented lesion with recent change in size or nature or an ulcer with prolonged healing. Dermoscopy and, more recently, reflectance confocal microscopy has largely improved BCC diagnosis [7].

Confirmatory diagnosis of BCC is usually made histologically with subcategorization of the specific histological variant of BCC as several histopathological BCC subtypes with different prognostic values have been described. Nodular BCC (NBCC) is the most common subtype of BCC. It is characterized by infiltrative nests of basaloid cells with peripheral palisading of cells and typical artificial clefts around them along with stromal mucin collections [7,8]. This type of BCC is generally considered a low-risk variant unless it has an increase mitotic index or the lesion size is more than 1 cm in high-risk areas (Table: 4) [8,9]. Another low-risk BCC variant is superficial BCC which usually has the best prognosis.

Table 4: Prognostic groups of BCC according to Dandurand et al. [8].

Low-Risk BCC	Intermediate-Risk BCC	High-Risk BCC
Superficial primary BCC	Superficial recurrent BCC	Morpheaform or poor-defined
Nodular primary BCC when: <1cm in intermediate risk area* <2cm in low risk area*	Nodular primary BCC when: <1cm in high risk area* >1cm in intermediate risk area* >2cm in low risk area*	Nodular primary BCC when: >1cm in high risk area*
Pinkus Tumor		Hitological forms aggressive: (Recurrent forms apart from superficial BCC)
*High-risk zones are the nose, periorificial areas of the head and neck; intermediate-risk zones are the forehead, cheek, chin, scalp, and neck; low-risk zones are the trunk and limbs. Aggressive histological forms include micronodular, morpheaform, and metatypical basosquamous forms. Perineural invasion also seems to be a histological sign of aggressiveness.		

Aggressive variants of BCC are the Infiltrating or sclerosing/ morphoeic basal cell carcinoma, Micronodular basal cell carcinoma and the basosquamous variant [8,9]. Moreover, any perineural invasion associated with any histological type of BCC is considered a high-risk factor and can predict more aggressive disease [8, 9]. In our study, the most prevalent cancer hitological type was Basal cell carcinoma (BCC). The nodular BCC was the most common histological type. We found also that all BCC patient's had low disease stage and low pathological staging in terms of the level of invasion and minimal perineural and lymphovascular invasion.

Cutaneous squamous cell carcinoma (cSCC) is the second most common human cancer and is second in incidence only to basal cell carcinoma. Cutaneous SCC typically manifests as a spectrum of progressively advanced malignancies, ranging from a precursor actinic keratosis (AK) to squamous cell carcinoma (SCC) in situ (SCCIS), invasive cSCC, and finally metastatic SCC. In our study, we only included the primary invasive cutaneous squamous cell carcinoma. The latter has few histological subtypes as well such as desmoplastic cSCC and basaloid squamous cell carcinoma which are both considered as aggressive variants. Nevertheless, grading of this type of cancer has a prognostic value. They are usually graded as Grades 1, 2, 3 and 4 Corresponding to well, moderately, poorly and undifferentiated, respectively. A poorly differentiated squamous cell carcinoma is a solitary high-risk feature for skin cancer. In our study, cSCC was the third most common cancer with low pathological staging in terms of the level of invasion, perineural invasion, lymphovasular invasion and lymph nodes involvement [10].

Cutaneous Malignant Melanoma (cMM) develop from a proliferation of intraepidermal melanocytes that may progress through radial (including in situ and microinvasive stages) and vertical growth phases (VGP). The most widely accepted classification of melanoma is based on the presence (eg, superficial spreading, lentigo maligna, or acral lentiginous melanoma) or absence of a radial growth phase (nodular melanoma). Other classification of cMM is either the expansile nodules composed of epithelioid cells, spindle cells, or smaller nevus-like cells. Less common variants of the invasive cutaneous Malignant Melanoma include desmoplastic and neurotropic melanomas and minimal deviation melanoma. Other unusual or rare forms of melanoma are malignant blue nevus, balloon cell melanoma, and clear cell sarcoma [11].

In our research, all cMM patient's had adverse pathological stage and advance clinical outcomes due to the aggressive behavior of the tumor with frequent perineural invasion and deep invasion with nodal involvement. These mutually recurring histological prognostic factors among all these skin cancer types are vital risk factors that affect the long-term management and prognosis of these types of cancer. As it is evident from our study, the level of tumor invasion and the diameter of the tumor, both have a tremendous effect on the staging of these cancers. The deeper the tumor's reach below the skin layers (subcutaneous fat, muscle or bone) the higher its stage and aggression [10, 11].

Perineural invasion, lymphovascular invasion and involved margins are also important prognostic factors that should be assessed in each case to further subcategorize the risk group of the cutaneous malignancy [11, 12]. Apart from the histological patterns of skin cancer, usually all of them share the clinical presentation to an extent. The Most common presentation of these cancers are a pigmented lesion on a sun exposed area (usually the head and neck region) in an elderly patient. Less frequently, these tumor present with either a bleeding ulcer, fungating mass or rapidly growing ulcer/mass [13-18].

In our study, most of the patients presented with the same clinical presentation as these malignancies described above. That was in concordance with what is described in the literature.

Treatment modalities for all types of skin cancers are also mutual. These modalities depend on surgical resection of lesion with safety margins with more or less assessment of the regional lymph nodes either by frozen section (like in cMM cases) or by resection of the regional lymph nodes (in cSCC mainly). Mohs micrographic surgery (MMS) is a frequently used technique that provides total margin visualization for treatment of skin neoplasms [19-21].

Conclusion

Malignant skin tumors were most frequent in the sixth decade (28%) and frequency was more in males than females, with head and neck region (54.05%) being the most common site involved. SCC (56.76%) was the most common malignant tumor followed by BCC. Both SCC and BCC were most commonly seen in the seventh decade. SCC showed male preponderance while BCC was more common in females. The lower extremity (legs) was the most common site for SCC, while the face was the most common site for BCC. The vast diversity of skin tumors produces difficulty in diagnosis. The ability to properly diagnose and treat the tumors is a vital skill for all clinicians. To conclude, any lesion, for which the diagnosis is uncertain, based on the history and clinical examination, should be biopsied for histopathological examination to rule out malignancy.

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Ethical Compliance: All data collection and analysis in the study were in accordance with the ethical standards of the national research committee.

Data Access Statement: Research data supporting this publication are available from I-SEHA system – Governmental hospitals – Salmaniya Medical Complex – Kingdom of Bahrain

Conflict of Interest Declaration: The authors declare that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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