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**Research Article**

# Histologic and Demographic Profile of Nonmelanoma Skin Cancer (NMSC) in Filipinos Seen in a Tertiary Care Clinic: A Retrospective Study from 2018 To 2021

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## Abstract

**Introduction:** Nonmelanoma Skin Cancer (NMSC) is the most frequent type of malignancy in humans. It includes a variety of cutaneous malignancies that are not melanocytic in origin. Demographic and histologic characteristics are helpful in prognosticating patients with NMSC. Available data on the demographic and histologic profile of NMSCs only include Caucasians and data from developed countries. This study provides an updated profile on NMSC prevalence in Filipinos, providing an avenue to further strengthen knowledge, hasten advancement of research, and facilitate creation of better health policies and programs regarding NMSC in Filipino skin. **Study design:** Retrospective study. **Methodology:** Medical records and biopsy logbooks of patients seen at a tertiary care center in the Philippines who were diagnosed with a nonmelanoma skin cancer from 2018-2021 from the available medical records and biopsy logbooks were included in this study. One hundred sixty-five (165) patient records and 189 available slides were reviewed. Data for age were analyzed using means and standard deviation. Data for tumor location, histopathologic diagnosis and histologic characteristics were analyzed using frequencies and proportions. **Results:** The mean age of patients affected with nonmelanoma skin cancer at diagnosis is 62.75 □ 15.12 years old with a range of 21 years old to 97 years old. There is female preponderance, with a sex ratio of 0.53:1. The head and neck area are the most common affected site in the patients included in this study, comprising of 135 out of 188 tumors (71.81%). The most common nonmelanoma skin cancer upon review of slides in this study is basal cell carcinoma accounting for 64.36% (121 out of 188) tumors biopsied, with the nodular type being the most common histopathologic subtype. There was no perineural and lymphovascular invasion seen in the slides reviewed. Squamous cell carcinoma was the second most common NMSC, comprising 22 patients and 22 tumors reviewed, composed mostly of well-differentiated tumors with two exhibiting acantholysis, a poor prognostic feature. Eleven (11) patients had squamous cell carcinoma-in-situ, none exhibiting eccrine gland involvement. Nine (9) patients with actinic keratosis were found on review of records and slides with 3 patients having hypertrophic actinic keratosis, a high-risk feature for progression to overt malignancy. Patients with Paget's disease were

composed of 8 of the Mammary-type and 2 of the extramammary-type. Dermal, perineural and lymphovascular invasion were not seen in the cases of Paget's disease reviewed. Of the 4 cases of porocarcinoma reviewed, all exhibited a pushing border, without necrosis within the tumor, and absence of lymphovascular and perineural invasion, with <14 mitotic figures/ 10 High Power Field (HPF). Only one case each of angiosarcoma, Kaposi sarcoma and dedifferentiated liposarcoma were reviewed in this study. **Conclusion:** Nonmelanoma skin cancer affects a great proportion of the population. Identifying certain histologic features aid in prognosticating patients with NMSC. Further studies on the histopathologic characteristics and their association with patient outcomes may prove to be beneficial.

**Keywords:** Nonmelanoma skin cancer; Filipinos; NMSC

# Introduction

The integumentary system is an intricate and complex organ of the human body that has derivations from both the ectoderm and mesoderm [1]. Because of the multiplicity of origins, it may be a host to a variety of both benign and malignant tumors. Cutaneous malignancies or skin cancers are the most common form of cancer in humans, comprising around 1 million of the new cases of cancers diagnosed yearly in the United States [2] and is continuously increasing in an exponential pattern globally [1,3-5]. Ultraviolet radiation (UVR) is the most significant risk factor for the development of cutaneous malignancies [4-6]. Skin cancer may be broadly divided into two groups, melanoma, which involves all cutaneous malignancies from the aberrant proliferation of melanocytes, and nonmelanoma skin cancer.

Nonmelanoma skin cancer (NMSC) includes a vast array of cutaneous malignancies that are not of melanocytic origin. NMSC is the most frequent type of malignancy in humans, comprising approximately 1/3 of all cancers worldwide [5]. The most common of these NMSCs are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [5]. Together, they comprise more than 90% of all diagnosed NMSCs [5,7]. Other diseases in the NMSC category include Merkel cell carcinoma, dermatofibrosarcoma protuberans, Kaposi sarcoma, angiosarcoma, porocarcinoma, sebaceous carcinoma, etc. [5]. In comparison to melanoma, NMSCs are more common in terms of occurrence but pose a lower risk of mortality. However, NMSCs, being the most common form of cutaneous malignancy, also pose a significantly higher degree of morbidity in patients diagnosed. If treatment is inadequate or not initiated early in the course of the disease, there is a perceived rise in morbidity, and mortality rates rise due to significant disfigurement, local recurrence, or distant metastasis.

Data on the demographic and histologic profile of NMSCs are widely available; however, these researches and reports only include Caucasians and data from developed countries. A handful of research on NMSC in Asian skin are accessible but upon extensive literature search, Filipino data on NMSC is lacking. This study will hopefully provide a new and updated perspective on NMSC prevalence in Filipinos, for which current data is lacking.

Identification of the demographic and histologic profile of Filipino patients diagnosed with NMSC will provide an avenue to further strengthen knowledge, hasten advancement of research, and facilitate creation of better health policies and programs regarding NMSC, particularly in Filipino skin.

## Objectives

**General Objective:** To describe the histologic and demographic profile of patients diagnosed with a nonmelanoma skin cancer and who were biopsied at the UP-PGH Department of Dermatology from 2018-2021.

### Specific Objectives

1.  To describe the demographic profile of patients with nonmelanoma skin cancer in terms of age and sex,

2.  To identify the common sites where lesions arise in patients diagnosed with nonmelanoma skin cancer,

3.  To identify the types of nonmelanoma skin cancer that arose in these patients based on histopathologic diagnosis,

4.  And to identify the histologic characteristics of these nonmelanoma skin cancers.

## Methodology

### Study design

This is a retrospective study of patients who were biopsied at the UP-PGH Department of Dermatology between January 2018 and December 2021 with a final histopathologic diagnosis of a nonmelanoma skin cancer. These patients include cases seen at the out-patient department as well as cases referred to the PGH Department of Dermatology in the emergency room and in-patient facilities (charity service). Only patients with a final histopathologic diagnosis of a nonmelanoma skin cancer were included in this retrospective study. Patients with irretrievable histopathologic slides or block specimens were excluded from this study. This study was submitted for approval to the University of the Philippines Manila Research Ethics Board prior to conduction. Waiver of informed consent process was requested by the researchers under the provisions that the research procedures entail no more than the minimal risk.

## Data Collection, Management and Statistical Analysis

The primary investigator assigned a unique identification number to each patient. The following data were extracted by the primary investigator from the biopsy records: age, sex, location of tumor and final histopathologic diagnosis. Biopsy slides and block specimens were obtained from the archive and was pre-read by the primary investigator. All slides were read and verified by the adviser, a board-certified dermatopathologist. Descriptive analysis using mean, standard deviation, and range were done for age, which is a continuous variable. For sex, location of tumor, final histopathologic diagnosis and tumor characteristics on histopathology, enumeration, and frequencies and proportions were used to analyze the data collected.

## Results and Discussion

From the years 2018 to 2021, a total of 186 patients were diagnosed with a nonmelanoma skin cancer. Out of the 186 patients, with some having multiple tumors, 212 tumors were biopsied and reported to be a NMSC since some patients had multiple tumors. Only 188 slides from 165 patients were available for review. Nine (9) patients had multiple tumors while 156 patients had a solitary tumor. Only the 165 patients with available records and biopsy slides for review were included in the data analysis with regards to age and sex. All 188 slides available for slide review were included in the data analysis with regards to location of tumor, histopathologic diagnosis, and tumor characteristics (Figure 1).
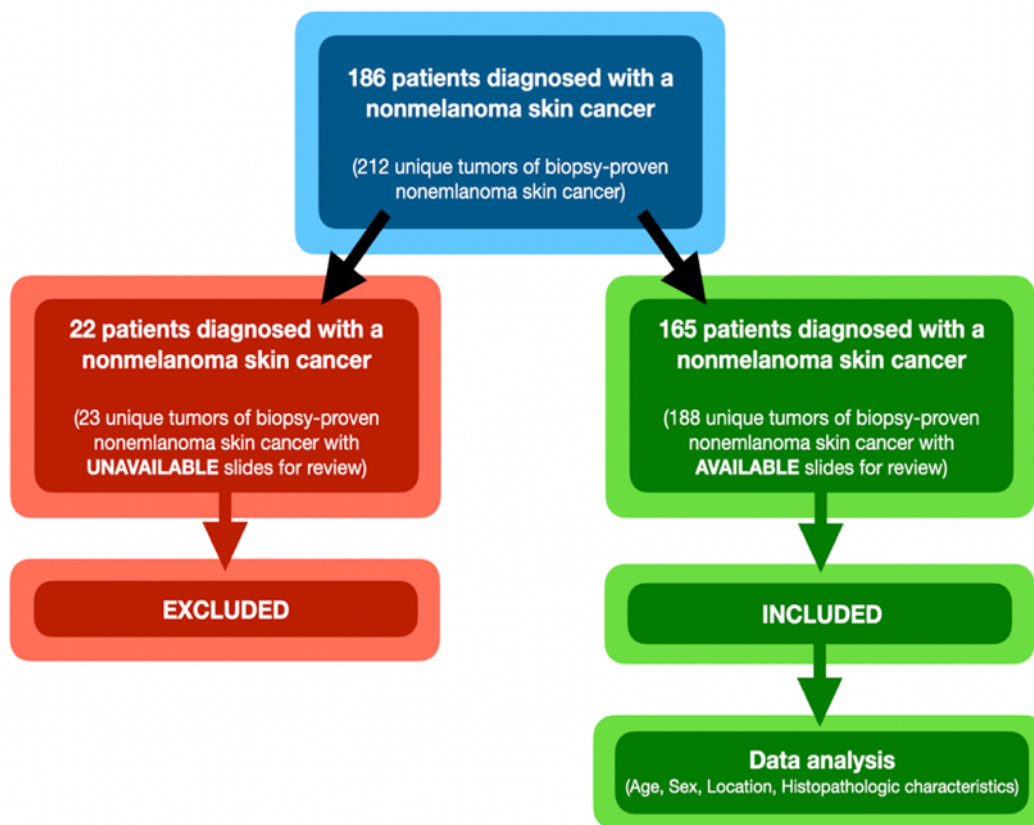


**Figure 1:** Inclusion and exclusion of data reviewed.

## Age and Sex

A total of 165 patients histologically proven to have NMSC were included in the analysis for age and sex. Fifty-seven (57) of the patients are male, which constituted 34.55% of the study population, while 108 patients or 65.45% are females, with a male: female sex ratio of 0.53:1. The mean age of patients with NMSC upon diagnosis is $62.75 \pm 15.12$ years old with a range of 21 years old to 97 years old. Accounting for sex, males have a lower mean age upon diagnosis of a NMSC ($57.95 \pm 16.95$ years old) compared to women ($65.29 \pm 13.47$ years old). In terms of age at initial diagnosis of NMSC, the data gathered in this study is congruent with the available data in the literature [8], particularly in the elderly population. In terms of sex predilection, NMSCs are known to be more common in men that in women [6-9]. A plausible explanation as to the higher percentage of women affected in this study may be attributed to their better health-seeking behavior for suspicious-looking lesions on their body.

## Tumor location

In the 165 patients included in this study, there were 188 unique tumors biopsied. Nine (9) patients had multiple tumors, explaining the difference in the patient number and slide count. Most of the NMSC tumors biopsied and included in this study were located on the head and neck area (135/188 tumors, 71.81%). The succeeding area to have the most tumors was the trunk (31/188 tumors, 16.49%), followed by the upper extremities (13/188 tumors, 6.91%) and the lower extremities (9/188 tumors, 4.79%). As was mentioned earlier, UVR is a potent risk factor for the development of NMSC lesions [4-6]. The head and neck area are considered to have incurred more UVR damage due to its relative exposure to sunlight compared to other parts of the body and may possibly explain the preferential appearance of NMSC lesions in this location. This finding is similar to that of Bas, et al. epidemiologic study on NMSC [8].

## Histologic diagnosis and tumor characteristics

In terms of histopathologic diagnosis of NMSC, basal cell carcinoma is the most common NMSC tumor histologically diagnosed, comparable to available international data [6,8,10,11]. Listed in Table 1 are the number of patients diagnosed with other NMSC in this study.

| Histologic diagnosis | Number patients | Number of tumors |
|---|---|---|
| Basal cell carcinoma | 105 | 121 |
| Squamous cell carcinoma | 22 | 22 |
| Squamous cell carcinoma-in-situ | 11 | 18 |
| Actinic keratosis | 9 | 9 |
| Paget's disease | 11 | 11 |
| Porocarcinoma | 4 | 4 |
| Kaposi sarcoma | 1 | 1 |
| Angiosarcoma | 1 | 1 |
| Dedifferentiated liposarcoma | 1 | 1 |
| *TOTAL* | **165** | **188** |

**Table 1:** Histologic diagnosis of patients with nonmelanoma skin cancer.

## Basal cell carcinoma (BCC)

A total of 105 patients with 121 tumors had basal cell carcinoma. Most patients with BCC were female (75 patients, 71.43%). The mean age at the time of diagnosis of patients with BCC in this study is $64.34 \pm 14.18$ years old. The most common location of a BCC was the head and neck (109/121 tumors, 90.08%) followed by the trunk (7/121 tumors, 5.79%) and upper extremities (4/121 tumors, 3.31%). There was only 1 patient who had a BCC in the lower extremity (0.83%). According to available literature, there is a male predominance in terms of patients afflicted with BCC [8]. This conflicting data in our study may be attributed to the fact that female patients in our country may have a better health-seeking attitude and translates to seeking earlier consultation for suspicious lesions. According to other previous studies done, the head and neck area was also the most common site for a basal cell carcinoma to appear [1,8].

The most common histologic type of BCC seen in these patients was the nodular type (55/121, 45.45%) followed by the

superficial type (6/121 tumors, 4.96%), micronodular (5/121 tumors, 4.13%) and basosquamous carcinoma (1/121, 0.83%). Fifty-four (54) patients (44.63%) had a combination of 2 or more types of BCC. The most common combination of BCC subtypes seen in one biopsy were nodular and micronodular (26/121 tumors, 21.49%) followed by nodular and infiltrative (12/121 tumors, 9.92%), nodular and superficial (9/121 tumors, 7.44%), and nodular, micronodular, and infiltrative types (7/121 tumors, 5.78%). In previous studies done, the nodular type was also considered as the most frequent type of BCC histologically diagnosed [1,7-9].

Perineural and lymphovascular invasion were not seen in any of the slides reviewed. Perineural invasion is an important histologic feature to be identified as it is associated with a higher risk of recurrence [11]. Lymphovascular invasion is not a common finding in patients with BCC, but multiple case reports have linked its presence with metastatic basal cell carcinoma [12] (Figure 2).
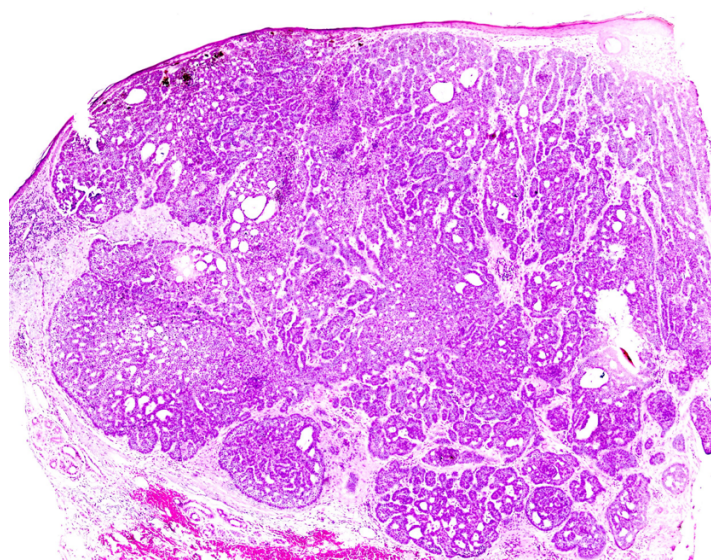


**Figure 2:** Nodular basal cell carcinoma (Hematoxylin and eosin, 20x).
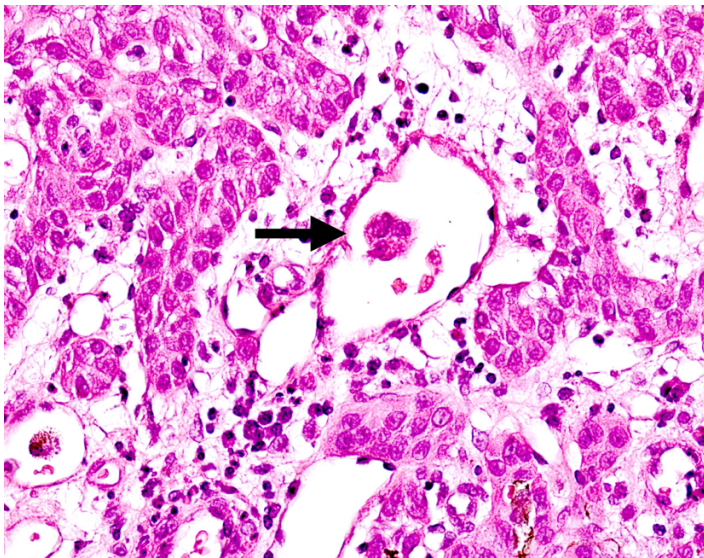
## Squamous cell carcinoma (SCC)

Twenty-two (22) patients were included in this subset, having been diagnosed with a squamous cell carcinoma. All patients had only one SCC lesion; thus, there were also 22 slides that were available for review. The mean age of patients diagnosed with SCC in this study is 61.00 ± 17.90 years old. There were 14 male patients (63.64%) and 8 female patients (36.36%). Most of the lesions were seen in the head and neck area (9/22 tumors, 40.91%), followed by the lower extremity (6/22 tumors, 27.27%), upper extremities (4/22 tumors, 18.18%) and the trunk (3/22 tumors, 13.64%). Out of the 22 SCC tumors reviewed, 4 were of the keratoacanthoma-type, 3 were of the verrucous type, and 2 had acantholysis. Table 2 summarizes the histologic features seen in the SCC tumors reviewed in this study (Figures 3 and 4).

| Histologic characteristics | Frequency |
|---|---|
| **Differentiation** | |
| Well-differentiated | 18 |
| Moderately differentiated | 4 |
| Poorly differentiated | 0 |
| **Depth of invasion** | |
| Papillary dermis | 3 |
| Reticular dermis | 19 |
| **Invasion of other structures** | |
| Lymphovascular invasion | 1 |
| Perineural invasion | 2 |
| **Mitosis (/HPF)** | |
| 0 to 1 | 12 |
| 1 to 2 | 3 |
| 2 to 3 | 4 |
| 3 to 4 | 1 |
| 4 to 5 | 1 |
| 5 to 6 | 0 |
| 6 to 7 | 1 |

**Table 2:** Histologic characteristics of patients with squamous cell carcinoma.
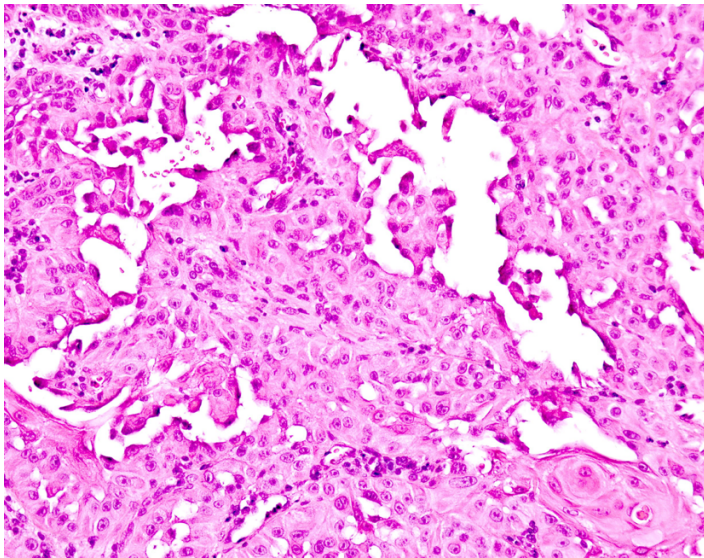
**Figure 3:** Acantholytic squamous cell carcinoma (Hematoxylin and eosin, 400x).



**Figure 4:** Lymphovascular invasion in acantholytic squamous cell carcinoma (black arrow) (Hematoxylin and eosin, 400x).

According to the 8th edition of the AJCC, histopathologic tumor characteristics that portend a higher risk for patients with squamous cell carcinoma include: perineural invasion, poorly differentiated or undifferentiated histology and involvement of structures past the subcutaneous tissue.13 Since most of the biopsies done on these lesions are superficial punch biopsies (4 mm or less), definitive assessment for perineural invasion as well as tumor depth is not available. These high-risk features portend higher risk for recurrence and distant metastasis [13,14]. A fallback of the AJCC 8th edition criteria is that it is only applicable for tumors located in the head and neck area. A definitive prognostication tool for cutaneous SCC, irrespective of the tumor location, has yet to be proposed.

Lymphovascular invasion also bears an increased risk for metastasis and death [15]. Certain histologic subtypes, such as the acantholytic and desmoplastic type, also bear a poorer prognosis for patients with cutaneous SCC [13,14]. Mitotic activity also correlates with the differentiation tumor, as it is frequently high in poorly differentiated tumors, and is low in well-differentiated tumors [13].

### Squamous cell carcinoma-*in-situ* (SCCIS)

A total of 11 patients were histologically diagnosed with squamous cell carcinoma-in-situ, with 18 unique tumors biopsied. The mean age of patients with SCCIS upon diagnosis in this study is 64.27 ± 13.60 years old. Six (6) patients were female (54.55%) while 5 patients were male (45.45%). The most common tumor location of SCCIS in this study is the trunk (9/18 tumors, 50.00%), followed by the upper extremity (4/18 tumors, 22.22%), head and neck (4/18 tumors, 22.22%), and lower extremity (1/18 tumors, 5.56%). Although UVR also plays an important role in the pathogenesis of SCCIS, other contributing factors may increase the risk of acquiring the disease such as in chronic scars and HPV-related tumors and this may explain why the trunk is considered as the most common tumor location in this subset of NMSCs in this study [16].

There was one tumor that had acantholysis and one other tumor that had pagetoid features. Most of the tumors (9/18 tumors, 50.00%) reviewed were accompanied by a dense mixed-cell infiltrate. Less than half (7/18 tumors, 38.89%) had a moderately dense mixed-cell infiltrate, while 11.11% (2/18 tumors) had a sparse mixed-cell accompanying infiltrate. None of the tumors exhibited eccrine gland involvement on review of slides. Eccrine gland involvement in squamous cell carcinoma-*in-situ*, is postulated to arise from the direct extension of tumor cells into the eccrine unit [17]. There have been no definitive studies to date with regards to its contribution to patient prognosis, although it may be surmised that deep involvement of eccrine gland units may contribute to recurrent lesions in superficially treated SCCIS.

Currently, transcriptomic, and proteomic analyses have been initiated to identify certain biomarkers and molecular alterations that may contribute to prediction of progression of SCCIS into invasive SCC [18] (Figure 5).
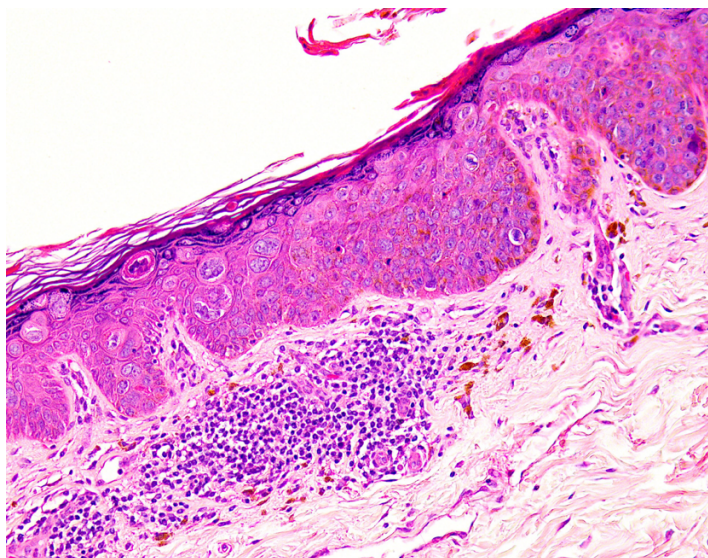
**Figure 5:** Pagetoid squamous cell carcinoma-in-situ (Hematoxylin and eosin, 200x).
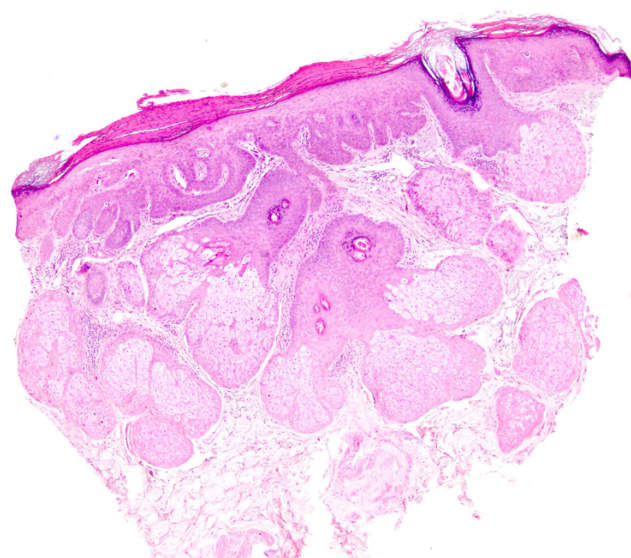


**Figure 6:** Common-type actinic keratosis (Hematoxylin and eosin, 40x).

### Actinic keratosis (AK)

Nine (9) patients in this study underwent biopsy and were found to have AK. The mean age of patients with actinic keratosis in this study is $62.67 \pm 18.82$ years old. Five (5) patients were male (55.56%) while 4 were female (44.44%). The lesions were found on the head and neck area, except for one tumor that was located on the lower extremity (right leg). An accompanying moderately dense mixed cell infiltrate was seen in 6 out of 9 patients on histology, while the remaining 3 had a dense, interstitial accompanying mixed-cell infiltrate. Table 3 shows the different types of AK seen in this study (Figure 6).

| Histologic subtype | Frequency |
|---|---|
| Cheilitis | 2 |
| Common type | 1 |
| Atrophic | 2 |
| Bowenoid | 1 |
| Hypertrophic | 2 |
| Hypertrophic and acantholytic | 1 |

**Table 3:** Histologic subtypes of actinic keratosis.

AKs are premalignant lesions, with a 5-10% risk of developing into cutaneous SCC. Currently, histologic subtype is the only known histopathologic feature that contributes to the prognosis of patients having AK. In particular, the hypertrophic and proliferative variants have been associated with a more aggressive behavior and higher malignant potential [16,19].

**Paget's disease**

Out of the 11 patients reviewed to have Paget's disease, 9 had mammary Paget's disease (MPD), while 2 had extramammary Paget's disease (EMPD). All patients who had MPD were female while the 2 patients who had EMPD were composed of one male and one female. The mean age of patients who have Paget's disease is $57.00 \pm 13.11$ years old. There was no dermal invasion noted in the cases of Paget's disease included and reviewed in this study. Perineural and lymphovascular invasion were also not present. Table 4 summarizes the data collected with regards to the mitotic index of the tumor slides reviewed (Figure 7).
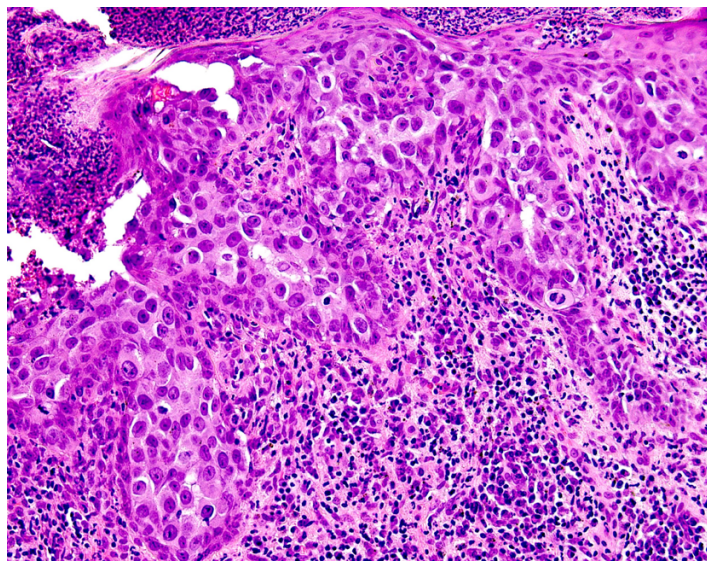


**Figure 7:** Mammary Paget's disease (Hematoxylin and eosin, 200x).

| Mitotic index | Frequency |
|---|---|
| 0 to 1 | 4 |
| 1 to 2 | 3 |
| 2 to 3 | 2 |
| 3 to 4 | 2 |

**Table 4:** Mitotic index of patients with Paget's disease.

In MPD, ulceration was more frequently seen in patients with advanced disease. Male patients tend to have a poorer survival rate (~20-30% 5-year survival rate) compared to females [20]. Poorer prognoses are seen in patients with an accompanying palpable breast mass, palpable lymph nodes as well as a poorer histologic grade of accompanying breast cancer [20].

Although dermal invasion and number of mitotic figures in malignancies would signify a poorer prognosis for patients, studies have shown that there is no significant difference when it comes to the possibility of tumor recurrence, particularly for extramammary Paget's disease. Recurrence was more often seen in patients with a positive surgical margin upon removal [21].

**Porocarcinoma**

Only 4 cases of biopsy-proven porocarcinoma were seen from the years 2018 to 2021. All patients were females with a mean age of $58 \pm 11.63$ years old. Upon review of slides, all four tumors exhibited a pushing border, absence of necrosis, absence of both lymphovascular and perineural invasion, and <14 mitotic figures/ 10 HPF. Two of the four tumors had a benign poroma component seen adjacent to the tumor. In the study by Robson et al, the most common location where porocarcinomas arise are on the lower limb, and only a small number of patients had a tumor on the head and neck [22]. Histologic features may help in prognosticating patients with porocarcinoma. In the literature, it is said that an infiltrating tumor margin indicates a higher probability of distant metastasis, while the presence of >14 mitotic figures/ 10 HPF and lymphovascular invasion indicates a higher chance for the development of nodal metastasis [22] (Figure 8).
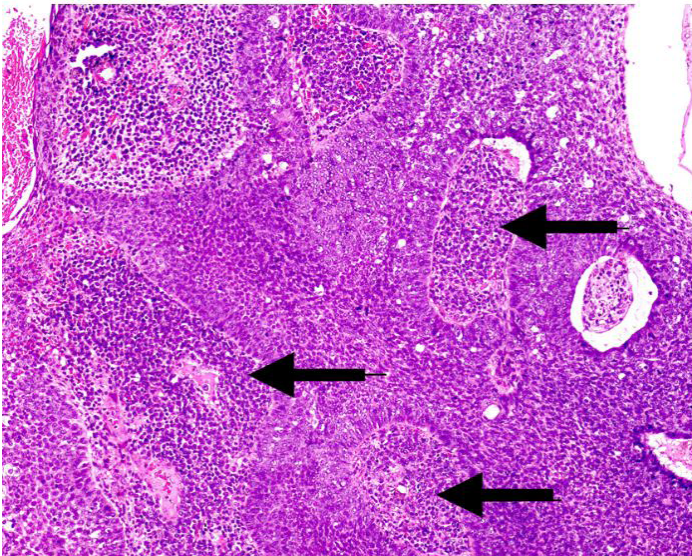
**Figure 8:** Necrosis in porocarcinoma (black arrows) (Hematoxylin and eosin, 100x).

### Kaposi sarcoma (KS)

Out of the 5 patients with Kaposi sarcoma, only 1 slide was available; thus, only 1 patient was included in this study and subsequently reviewed. The patient was a 21/M whose lesion was located on the right arm. Upon review of slide, the lesion was noted to be in the patch stage, without areas of necrosis and ulceration. Proliferating endothelial cells only showed minimal atypia. Promontory sign was also seen in the slide reviewed. The presence of the promontory sign is a clue to identification of Kaposi sarcoma on histology. There are no available studies that have correlated specific histopathologic features and prognosis in patients with Kaposi sarcoma; however, these characteristics are useful in defining the stage of Kaposi sarcoma of the tumor [23]. Promontory sign is most prominent in the patch stage [23]. Hemosiderin deposition and eosinophilic globule formation were seen most in the plaque stage [23]. Ulceration, frank tumor necrosis, atypia and mitosis are features most associated with the tumor or nodular stage of KS [23] (Figure 9).
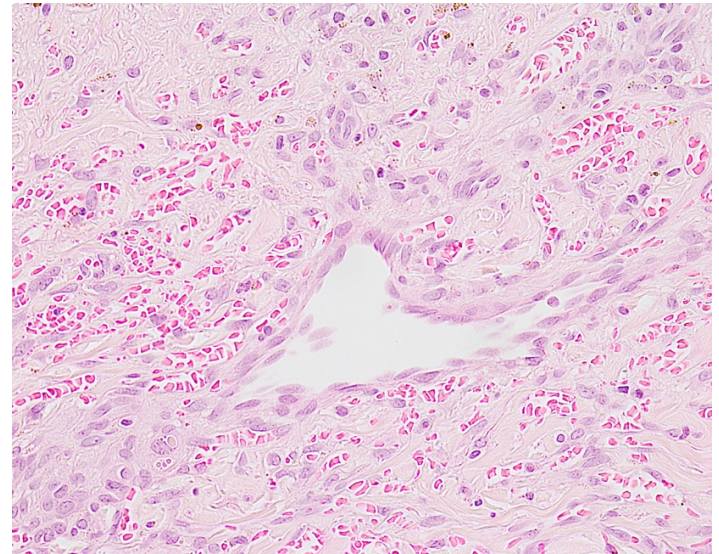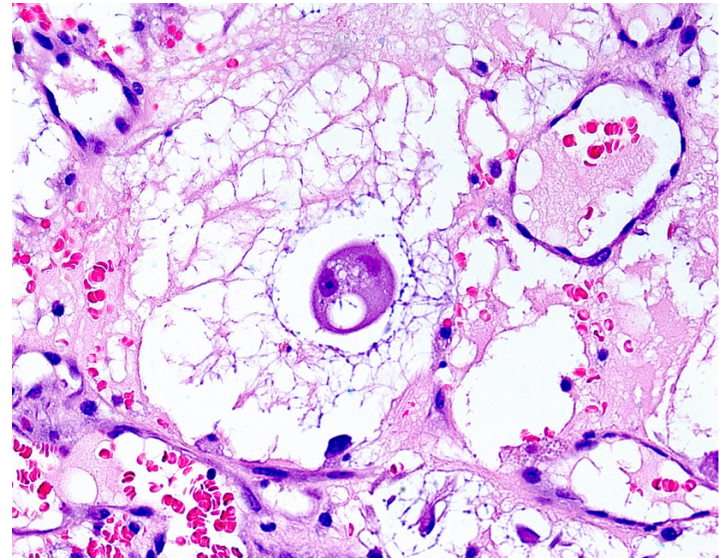


**Figure 9:** Kaposi sarcoma (Hematoxylin and eosin, 400x).

### Angiosarcoma

One (1) patient (54/F) had an angiosarcoma located on the scalp (head and neck area). It was a low-grade tumor with 0-1 mitoses/ HPF and did not have lymphovascular nor perineural invasion. In a study by Wang, et al., angiosarcomas were classified into low-grade and high-grade tumors. Low-grade tumors were characterized by anastomosing irregular, vascular channels lined by atypical endothelium, while high-grade tumors were composed of solid sheets of atypical spindle cells without overt formation of blood vessels. Low-grade angiosarcomas portend a more favorable prognosis compared to high-grade angiosarcomas [24]. Perineural and lymphovascular invasion may herald an imminent distant or nodal metastasis; therefore, surgical management of these patients may not be enough and other adjuvant regimens such as radiotherapy and chemotherapy may be needed [24] (Figure 10).
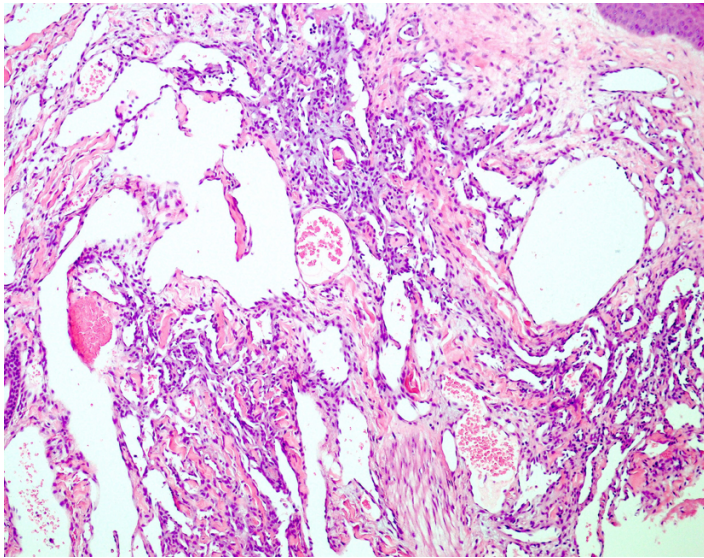
**Figure 10:** Angiosarcoma (Hematoxylin and eosin, 200x).

### Dedifferentiated liposarcoma (DDLS)

A case of dedifferentiated liposarcoma on the left buttock (trunk), in a 51/F was reviewed within the period. The tumor was multilobulated with a biphasic architecture. A prominent myxoid stroma with numerous stellate cells and lipoblasts were seen in one area, while another area was composed of sheets of highly pleomorphic cells, some having epithelioid features. Within the solid sheets of pleomorphic cells, numerous atypical mitotic figures were also seen. An adjacent area of an atypical lipomatous tumor/well-differentiated liposarcoma was not evident. The tumor stained positive for Alcian blue as well as other immunohistochemical stains including vimentin, MDM2, p16. The tumor was negative for the following stains: CK7, CK20, CD34, CEA, EMA, SMA and S-100. Histologic grading is one of the components used in prognosticating DDLS tumors, according to the American Joint Committee on Cancer (AJCC, 8th edition) [25]. Histologic grading includes total differentiation, mitotic count, and areas of necrosis [25]. DDLS are known to be aggressive tumors, garnering a score of 3/3 for tumor aggression. Numerous mitotic figures (>20/ HPF) give an additional score of 3, while multiple areas of necrosis (>50% of the tumor), adds a score of 2. With the total sum of 8, this tumor, based on the AJCC histologic grading, is a high-grade neoplasm (Figure 11).



**Figure 11:** Lipoblast in dedifferentiated liposarcoma (Hematoxylin and eosin, 400x).

### Conclusion

Nonmelanoma skin cancer constitutes a great proportion of malignancies in the population. Proper and timely identification clinically and histologically allows for earlier treatment initiation and prevention of tumor progression. Identification of key histologic features aids in prognosticating patients afflicted with a NMSC; therefore, further studies on the histologic characteristics and their association with patient outcomes may prove beneficial in the long-term.

### Conflicts of Interest

Dr. Villena and Dr. Cubillan declare no conflict of interest.

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