

MALIGNANT ADNEXAL TUMORS OF SKIN: A SINGLE CENTER EXPERIENCE**BATOOL F*, LONE UM, JAHANGIR F, KHAN FW, RATHORE S***Department of Pathology, Chughtai Institute of Pathology, Lahore, Pakistan***Corresponding author's email address: kashif.abbas.mbbbs@gmail.com**(Received, 04th August 2024, Revised 25th October 2024, Published 15th November 2024)*

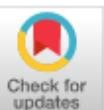
Abstract: *Malignant adnexal tumors (MATs) of the skin are rare neoplasms derived from eccrine, apocrine, sebaceous, or follicular structures. Objective: To analyze the histopathological spectrum of malignant adnexal tumors of the skin, determine their histological subtypes, and assess the association of ulceration, perineural invasion (PNI), lymphovascular invasion (LVI), and surgical margins with tumor behavior. Methodology: This cross-sectional descriptive study was conducted at Chughtai Institute of Pathology, Lahore, from January 2024 to July 2024 and included 61 histologically confirmed cases of malignant adnexal tumors of the skin. Data were retrieved from pathology archives and reviewed for demographic, clinical, and histological parameters, including tumor subtype, site, margin status, ulceration, PNI, and LVI. Results: Of the 61 patients, 37 (60.7%) were male, and 24 (39.3%) were female, with the majority aged between 61 and 70 years (34.4%). The head and neck region was the most frequently involved site (63.9%), followed by the trunk (19.7%) and extremities (13.1%). Porocarcinoma was the most common subtype (60.7%), followed by sebaceous carcinoma (23.0%) and hid adenocarcinoma (9.8%). Ulceration was present in 23 cases (37.7%), per neural invasion in 9 (14.8%), and lymph vascular invasion in 7 (11.5%). Significant associations were observed between tumor site and subtype ($p=0.038$), margin status and surgical procedure ($p<0.001$), and ulceration and subtype ($p=0.008$). No significant correlation was found between ulceration and other histopathological variables such as gender, site, PNI, LVI, or margin status ($p>0.05$). Conclusion: Malignant adnexal tumors predominantly affect older males and most commonly arise in the head and neck region. Porocarcinoma is the leading histologic subtype, followed by sebaceous and hidadenocarcinoma. While ulceration is frequent, it does not correlate significantly with clinical or pathological factors, except tumor subtype. Complete excision with negative margins remains the key to reducing recurrence. Larger metacentric studies integrating molecular profiling are needed to better define prognostic markers and therapeutic strategies for these rare neoplasms.*

Keywords: Skin Neoplasms Skin Appendage Neoplasms Porocarcinoma Sebaceous Carcinoma Histopathology**Introduction**

Malignant adnexal tumors (MATs) of the skin are a rare and heterogeneous group of neoplasms derived from the adnexal structures of the epidermis, including eccrine, apocrine, sebaceous, and follicular components (1). Although MATs account for fewer than 1% of all skin malignancies, they pose a diagnostic and therapeutic challenge due to their unpredictable biological behavior and variable morphologic patterns. MATs are considered clinically important, despite being rare, because they often mimic benign adnexal lesions and metastatic carcinomas (both clinically and histologically), which leads to delayed recognition and inappropriate management (2). While the majority of these tumors have a deceptively indolent growth pattern, they have significant potential for local invasion, recurrence, and metastasis, making prompt and accurate diagnosis critical (3). Most malignant adnexal tumors occur de novo, but the malignant transformation of a benign adnexal neoplasm (such as hidradenoma, poroma, or spiradenoma) has also been documented. Clinically, these tumors commonly appear as painless, firm, and slow-growing nodules or plaques that may ulcerate or become fixed to the underlying tissues as they advance (4). The most common area of the body where these tumors can be found is the head and neck; this is likely because of the high concentration of sweat glands and pilosebaceous units in this area (5). However, the lesions can appear on any area of the body, including the

abdomen and arms. Most studies have documented a slightly higher occurrence in males than females, and a preference for middle-aged to elderly people. While the overall incidence remains very low, the rise in case detection in recent decades can be attributed to increased awareness of histopathology and advancements in immunohistochemical methodologies (6). MATs histology subsumes numerous entities, including but not limited to porocarcinoma, sebaceous carcinoma, hidadenocarcinoma, spiradenocarcinoma, trichilemmal carcinoma, and malignant cylindroma. Of these, porocarcinoma is accepted as the most common type worldwide, constituting about 40 to 50 percent of all adnexal cancers (7). Sebaceous carcinoma is the second most common and is noted to have an aggressive malignant course with an increased risk of regional lymph node metastasis, especially if it occurs in the periorbital area. Other rare hidadenocarcinoma and spiradenocarcinoma subtypes are described as having a less aggressive course, but may still recur if not completely removed (8). It is not uncommon for histology to be inconclusive in revealing benign and malignant forms in small biopsies or fragments, due to overshadowing architectural patterns, a problematic commonality. This is where immunohistochemistry (IHC) takes centre stage to help clinch the diagnosis and distinguish the lineage of adnexal tumors (9). Distinction of adnexal carcinomas from metastatic cutaneous adenocarcinomas or squamous cell

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carcinoma is informed by the common use of cytokeratins CK 5/6, CK7, CK19, and epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) and androgen receptor (AR) (10). Furthermore, some variants have been studied in molecules, and aberrations in TP53, HRAS, and CYLD have been noted, informing us more about the supposed tumor and helping target a potential treatment. Nonetheless, the molecular makeup of MATs remains the least studied, with few case series and no comprehensive genomic profiling (11). Depending on the situation, complete surgical resection of the MAT and histologically evident margins remains the primary treatment option available (12). Incomplete excision due to ambiguous histologic margins is common, due to persistent diagnostic delays, and often results in local reoccurrence. In some instances, adjuvant

Radiotherapy or chemotherapy may be employed, particularly in cases that demonstrate perineural infiltration, deep invasion, or lymphovascular invasion (LVI) (13).

Objective

To analyze the histopathological spectrum of malignant adnexal tumors of the skin, determine their histological subtypes, and assess the association of ulceration, perineural invasion (PNI), lymphovascular invasion (LVI), and surgical margins with tumor behavior.

Methodology

This was a cross-sectional descriptive study conducted at C hughtai Institute of Pathology from January 2024 to July 2 024. A total of 61 histologically diagnosed cases of malignant adnexal skin tumors were included. A non-probability consecutive sampling technique was used to collect the data. This study utilized all surgically excised and histologically confirmed malignant adnexal tumors of the skin. Both primary and recurrent lesions were considered as long as there was a reasonable volume of formalin-fixed paraffin-embedded tissue available for histopathological evaluation. Exclusions were made for inadequately preserved or fragmented biopsies of diagnostic ambiguity, benign adnexal neoplasms, metastatic cutaneous carcinomas, and incomplete clinical data or unavailable slides or blocks.

All archival hematoxylin and eosin (H&E) stained slides were retrieved and independently reviewed by two senior histopathologists to confirm Diagnosis and subtype classification according to the World Health Organization classification of skin adnexal tumors (5th Edition, 2023). Information such as age, sex, anatomic location, and category of surgical intervention was obtained from the hospital and pathology records. The following histopathological characteristics were captured for each case: subtype of the tumor (for example, porocarcinoma, sebaceous carcinoma, hidradenocarcinoma, etc.), tumor location (head and neck, trunk, extremities, and other regions), surgical margin status (whether the margin was tumor-free, or was involved or fragmented), ulceration, perineural invasion (PNI), and/or lymphovascular invasion (LVI). All information was incorporated i

nto a designed template and was subsequently organized in Microsoft Excel for further statistical processing.

Data were analyzed using IBM SPSS Statistics version 26.0. Descriptive statistics were applied for quantitative and categorical variables. Frequencies and percentages were calculated for age groups, gender, tumor site, subtype, surgical procedure, and histopathological features. For inferential analysis, the Chi-square test was used to evaluate associations between categorical variables, including gender, site, subtype, margins, PNI, LVI, and ulceration. Fisher's Exact Test was applied when any expected cell count was less than 5. A p-value of less than 0.05 was considered statistically significant.

Results

Data were collected from 61 patients; most of the patients in the cohort were between the ages of 51 and 60 years (34.4%), followed by those in the age brackets of 51-60 years (19.7%) and of 61 and 70 years 71-80 years (18.0%), confirming that malignant adnexal tumors are primarily affections of the aged. There was only one case (1.6%) of patients aged under 20 years. More males (60.7%) were affected than females (39.3%), with the ratio of males to females being 1.5:1. Of the head and neck region (63.9%), the trunk (19.7%), and the extremities (13.1%), the head and neck region was the most commonly affected area. Most patients underwent simple excision (91.8%), with fewer cases of wide local excision (4.9%) and re-excision (3.3%). Examined histologically, 39.3% of specimens' margins were free, 24.6% were involved, and 36.1% were fragmented. Perineural invasion was present in 14.8%, while 37.7% had ulceration, 52.5% had none, and 9.8% were unrecorded; 11.5% had lymphovascular invasion. Porocarcinoma was the most common malignant adnexal tumor, comprising 60.7% of all cases, followed by sebaceous carcinoma (23.0%) and hidradenocarcinoma (9.8%). Porocarcinoma showed a slight male predominance (56.8% male's vs 43.2% females) and a strong preference for the head and neck region (76.9%). Sebaceous carcinoma occurred mainly on the trunk (66.7%), and hidradenocarcinoma was most frequent on the extremities (50.0%). Ulceration was most frequently observed in porocarcinoma (65.2%), followed by sebaceous carcinoma (57.1%) and hidradenocarcinoma (50.0%). Less aggressive variants, including adenoid cystic carcinoma, exhibited no ulceration, whereas spiradenocarcinoma and proliferating trichilemmal tumor showed complete or partial surface ulceration. Statistical analysis using Fisher's Exact Test revealed no significant association between ulceration and histopathologic parameters such as gender($p=0.578$), site($p=0.769$), perineural invasion($p=0.131$), or margin status($p=0.583$). Although ulceration appeared more frequent among head-and-neck lesions and cases with involved margins, these trends did not reach statistical significance.

Table 1: Demographic Characteristics of Patients with Malignant Skin Adnexal Tumors (n=61)

Variable	Category	n(%)
Age group (years)	10-20	1(1.6)
	31-40	4(6.6)
	41-50	8(13.1)

	51-60	12(19.7)
	61-70	21(34.4)
	71-80	11(18.0)
	81-90	4(6.6)
Gender	Male	37(60.7)
	Female	24(39.3)
Site	Head and neck	39(63.9)
	Trunk	12(19.7)
	Extremities	8(13.1)
	Others	2(3.3)
Surgical procedure	Excision	56(91.8)
	Wide local excision	3(4.9)
	Re-excision/others	2(3.3)
Margin status	Free	24(39.3)
	Involved	15(24.6)
	Fragmented	22(36.1)
Perineural invasion (PNI)	Present	9(14.8)
	Absent	52(85.2)
Lymphovascular invasion (LVI)	Present	7(11.5)
	Absent	54(88.5)
Ulceration	Present	23(37.7)
	Absent	32(52.5)
	Not mentioned	6(9.8)

Table 2: Distribution of Histological Subtypes by Gender and Site(n=61)

Histological Subtype	Male n (%)	Female n (%)	Head and Neck n (%)	Trunk (%)	Extremities n (%)	Others n (%)
Porocarcinoma	21 (56.8)	16 (43.2)	30(76.9)	5(12.8)	3(7.7)	1(2.6)
Sebaceous carcinoma	8(57.1)	6(42.9)	3(25.0)	8(66.7)	1(8.3)	0(0.0)
Hidradenocarcinoma	4(66.7)	2(33.3)	1(16.7)	1(16.7)	4(50.0)	0(0.0)
Malignant adnexal tumor(NOS)	3(75.0)	1(25.0)	2(50.0)	1(25.0)	1(25.0)	0(0.0)
Adenoid Cystic carcinoma	1(50.0)	1(50.0)	2(100.0)	0(0.0)	0(0.0)	0(0.0)
Spiradenocarcinoma	1 (100.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)
Proliferating trichilemmal tumor	2(66.7)	1(33.3)	1(100.0)	0(0.0)	0(0.0)	0(0.0)

Table 3: Association between Surgical Procedure and Margin Status

Margin status	Excision n (%)	Wide local excision n (%)	Re-excision n (%)
Free	21(87.5)	3(12.5)	0(0.0)
Involved	13(86.7)	2(13.3)	0(0.0)
Fragmented	22(100.0)	0(0.0)	0(0.0)

Table 4: Ulceration Patterns across Tumor Subtypes

Subtype	Ulceration present n (%)	Ulceration absent n (%)
Porocarcinoma	15(65.2)	8(34.8)
Sebaceous carcinoma	8(57.1)	6(42.9)
Hidradenocarcinoma	3(50.0)	3(50.0)
Malignant adnexal tumor (NOS)	1(25.0)	3(75.0)
Adenoid cystic carcinoma	0(0.0)	2(100.0)
Spiradenocarcinoma	1(100.0)	0(0.0)
Proliferating trichilemmal tumor	2(50.0)	2(50.0)

Table 5: Association of Histopathologic Variables with Ulceration (Fisher's Exact Test, n = 55)

Variable	Ulcer present n (%)	Ulcer absent n (%)	p-value
Gender (Male vs Female)	10(43.5)	13(56.5)	0.578
Site (Head/Neck vs Others)	17(73.9)	6(26.1)	0.769

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Perineural invasion (PNI)	0(0.0)	23(100.0)	0.131
Margin status (Free VS Involved/Fragmented)	8(34.8)	15(65.2)	0.583

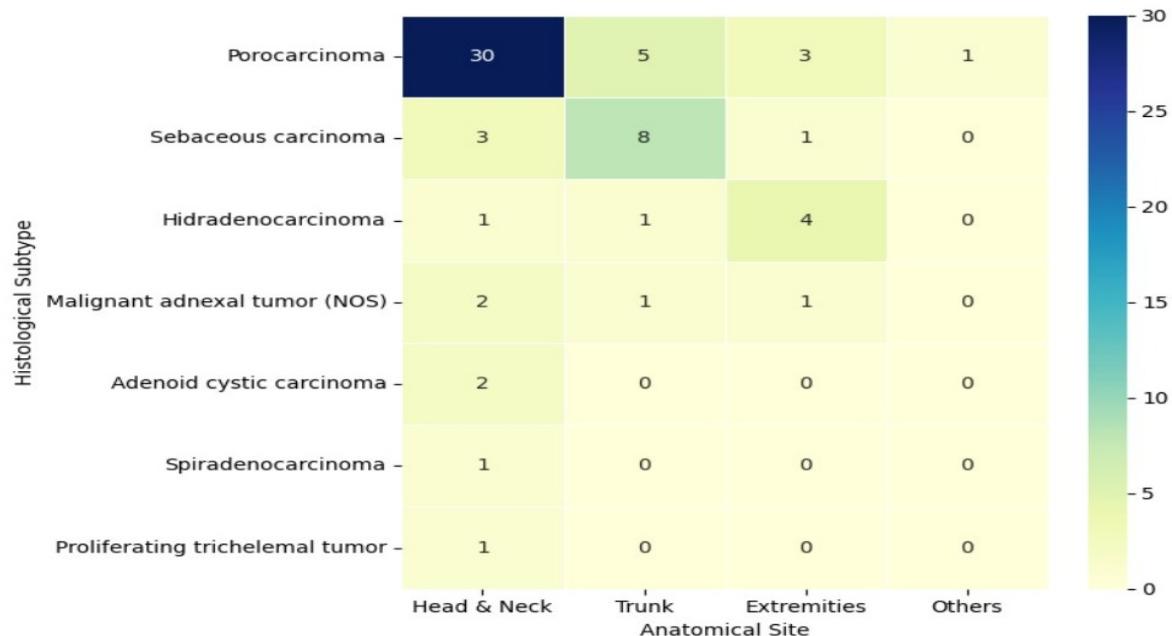


Figure 1: Heatmap of Site Distribution by Histological Subtype (n =61)

Discussion

Malignant adnexal tumors (MATs) of the skin are rare neoplasms exhibiting complex differentiation toward sweat gland, sebaceous, or follicular structures. Even though these tumors comprise only a small fraction (less than one percent) of cutaneous malignancies, their alarming histologic versatility and similarity to metastatic adenocarcinomas make them diagnostically baffling. From this cohort, the mean age distribution indicated that the majority of patients fell within the age range of sixty-one to seventy years. This finding corroborates the findings of Ramesh et al. (2019) and Wick et al. (2021), who described the sixth to seventh decades of life as the typical age range one would expect. This primarily suggests a cumulative effect of and exposure to ultraviolet radiation, chronic inflammation, and/or genetic instability as it relates to adnexal carcinogenesis (14). A slight predominance of males was also noted, which coincides with the findings of Salama et al. (2020) and several other institutional series. Still, some authors have indicated that this observation is non-specific to any particular gender. The male predominance noted in this study is most likely due to a combination of greater occupational sun exposure and a propensity to seek healthcare at a delayed interval (15). The head and neck region was the most prevalent (63.9%) and the most frequently affected region, corroborating the findings of Obaidat et al. (2020) and Nanda et al. (2017) that adnexal malignancies tend to occur in locations with high concentrations of sebaceous and sweat glands (16). France's large registry-based studies showed the value of expert pathologists in reviewing cases of adnexal carcinoma, in which almost 25% of initial reports were altered after

review, as found by Battistella et al. 2022. Similar diagnostic accuracy issues were noted by Aslan Kayiran et al.(2020), where it was found that Clinicians preoperatively diagnosed adnexal tumors with an accuracy of less than 50% and hence found it to be a major obstacle in understanding the histopathological features of these tumors (17). This anatomic predilection of adnexal tumors shows that persistent and clinically thorough nodular lesions in the elderly head and neck region require thorough clinical evaluations. This was especially true for cases involving hidradenocarcinoma and sebaceous carcinoma, where Truncal and extremity involvement, although less common, remained clinically important, with porocarcinoma being the most prevalent subtype at 60.7%. As porocarcinoma is found to be de novo and developing with ductal differentiation and some degree of atypia, it was confirmed that this study retained the preference of the head and neck region (18). Sebaceous carcinoma, with a frequency subtyping of 23%, ranks second, with hidradenocarcinoma and other less common variants following. In some studies conducted in the West, the predominance of sebaceous carcinoma is noted, possibly due to increased identification of cases periorcular to the eye in these cohorts. Such geographic differences highlight the impact of ethnicity and the environment on the tumor's biological behaviour (19). Histopathological features showed that 37.7% of cases showed ulceration. The forms of cancer that showed ulceration the most were the porocarcinoma, as well as the sebaceous carcinoma. In this series, ulceration did not show a statistically significant association with gender, site, or margin status in the Fisher's Exact Test. This indicates that ulceration is more likely a byproduct of tumor growth than an independent prognostic factor (20). The statistically

significant association between ulceration and histologic subtype in the chi-square analysis ($p=0.008$) indicates that some tumor types may be more likely and more susceptible to surface breakdown. Only a small portion of tumors contained perineural invasion (PNI) and lymphovascular invasion (LVI), at 14.8% and 11.5% of cases, respectively (21). The range of values is consistent with the findings of Pal et al. (2020) and Kim et al. (2022), in which the features were present in 8% of tumors, with local aggressiveness but no likelihood of distant metastasis. The absence of a statistically significant correlation between PNI and LVI in the study ($p=1.000$) suggests that these parameters may act through distinct pathways of tumor spread (22). Even if these features are infrequent, their presence should be considered as a marker of increased chances of invasion, and require the areas of surgery to be more extensive, along with a more in-depth investigation after surgery (23). In this study, none of the evaluated histopathologic variables, including sex, site, PNI, LVI, or margin status, demonstrated a significant relationship with ulceration on the Fisher's Exact Test ($p> 0.05$ for all). This lack of relationship is probably due to the small sample size, which is characteristic of studies of rare tumors. This may be further evaluated in large multicentric studies or meta-analyses to ascertain whether ulceration is a prognostic feature or simply an indicator of the exposure of the tumor surface. On the other hand, the overall frequency of adnexal malignancies in this study aligns with the global literature but highlights a discrepancy in local diagnosis. A significant number of cases come late to the medical system or are misdiagnosed in the first instance as a benign adnexal lesion or as a basal carcinoma. Educating clinicians and pathologists on this issue could enable more cases to be detected in due time and help target sustained improvements in surgical outcomes. Also, better epidemiologic studies of rare skin cancers could be conducted through collaboration to create country-wide databases or registries. This could enable other studies aimed at identifying the genetic variants of interest, such as the reported TP53 and HRAS mutations, in samples from the Western population.

Conclusion

Malignant adnexal tumors of the skin are rare neoplasms that display significant morphological and clinical diversity, often posing diagnostic and therapeutic challenges. In this study of 61 cases, the majority of patients were older adults, with a slight male predominance, and the head and neck region was the most common anatomical site involved. Porocarcinoma emerged as the predominant histologic subtype, followed by sebaceous carcinoma and hidradenocarcinoma, reflecting patterns similar to those observed in other regional and international studies. Ulceration was observed in more than one-third of cases but did not show a statistically significant association with gender, site, perineural invasion, lymphovascular invasion, or margin status. However, an important relationship was noted between ulceration and histologic subtype, suggesting that certain tumor types are more prone to surface breakdown and aggressive local behavior. The strong correlation between margin status and surgical procedure further underscores the importance of achieving complete excision with adequate margins to minimize the risk of recurrence.

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Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of conflict of interest.

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