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Management of patients with skin adnexal carcinomas

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ABSTRACT

Adnexal cancers of the skin constitute a heterogeneous group of malignant tumors with specific pathologic and biological differences. This review aims to provide clinicians with a summary of how to manage the diagnosis, staging, and treatment of cutaneous adnexal cancer patients. In clinical practice, the complexity of this clinical and pathological heterogeneity is partially mitigated by adopting standardized universal classification systems. The WHO classification is used for pathologic diagnosis. Among appendageal skin tumors, it includes four groups of cutaneous adnexal malignancies (apocrine/eccrine differentiation, sebaceous differentiation, follicular differentiation, site-specific appendageal tumors) and seven malignant adnexal tumors of the eyelid. Clinical and pathologic staging should follow the latest AJCC/UICC classification, which includes site-specific systems to be used for these cancers: skin carcinoma of the head and neck, skin carcinoma of the eyelid, anal canal and perianal skin, vulva, penis, breast (for Paget disease), and any other skin carcinoma. The diagnostic hypothesis of genetic syndromes should always be considered for patients diagnosed with an adnexal skin neoplasm, especially when cancers arise in unusual or multiple anatomic sites. The pathologic diagnosis should be performed by expert pathologists, and patients should be referred to high-volume centers. In curative treatments, radical surgery, when feasible, should always be considered the first option for local or regional disease. The opportunity to deliver post-operative treatment should always be discussed at a multidisciplinary level. Patients suffering from advanced disease should be included in clinical studies. Outside trials, the seek for potential druggable targets is advised.

1. Introduction

Primary skin cancers include melanocytic tumors and the vast non-melanoma skin cancers (NMSCs) group. The former group is dominated by melanoma, the latter by basal and squamous cell carcinoma, encompassing most primary skin malignancies. Other primary tumors arising from the skin include cutaneous lymphomas, soft tissue, and neural tumors (Table 1). A small fraction of NMSCs comprises appendageal tumors, also known as adnexal tumors [1].

These neoplasms, which may be benign or malignant, usually arise from the subepidermal stratus of the skin. Their histopathologic differentiation resembles the corresponding healthy counterpart of the skin components: sweat glands, sebaceous glands, and hair structures.

The overview presented in this article will address cutaneous adnexal malignant tumors (i.e., carcinomas).

2. Epidemiology

2.1. Methods

Two of the most relevant cancer registries worldwide were queried to study the epidemiology of adnexal carcinomas of the skin: the SEER (Surveillance, Epidemiology, and End Results) for the USA and the RARECARENET database for Europe. The following searches were performed to obtain the incidence and survival data,:

- USA: SEER*Stat software version 8.4.0.1 [2]. Database “Incidence – SEER Research Data, 17 Registries, Nov 2021 Sub (2000–2019) – Linked to County Attributes – Time Dependent (1990–2019) Income/Rurality, 1969–20220 Countries”. Selection: malignant

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Table 1
Skin cancers according to the last IARC/WHO classification (5th edition, 2022), compared to the previous edition.

WHO 4th ed (2018)	WHO 5th ed (2022)	Notes (5th vs. 4th edition)
Keratinocytic/epidermal tumors		Unchanged
Melanocytic tumors		Unchanged
Appendageal tumors		Unchanged
-	Tumors of the nail unit	Added
Tumors of haematopoietic and lymphoid origin		Unchanged
Soft tissue and neural tumors	Soft tissue tumors	Neural tumors moved to *Endocrine and Neuroendocrine Tumors (5th ed.)*
-	Metastases to skin	Added
-	Genetic tumor syndromes associated with skin malignancies	Added

behavior, known age. Site and morphology. Site recode – rare tumors = 40 adnexal carcinomas of skin
  - o Incidence. Age-adjusted rates
  - o Survival. Statistic: Relative survival. Method: Actuarial. Expected survival: US by SES/geography/race 1992–2018, ages 0–99, state-county. Selection: first primary only
- Europe: On line analysis resource of the RARECARENET project [3]. Period of diagnosis 2000–2007. Filters: cancer list = "Rare skin cancer + non cutaneous melanoma - Adnexal carcinoma of skin"
  - o Incidence. Age-adjusted incidence rate overtime in Europe - Age-adjusted incidence rate in Europe by sex. 83 Cancer Registries
  - o Survival. Relative survival - Relative survival (2000–2007). 94 Cancer Registries.

2.2. Results

With the caveat of different years of observation (2000–2019 for the USA, 2000–2007 for Europe) and the potential differences between cancer registries, considering together the various cutaneous adnexal carcinomas independently of their pathologic subtype, the annual incidence rate is lower than 1 × 100,000 subjects/year in Western Countries and is higher in men than in women (Table 2). This incidence makes adnexal cancers of the skin a group of rare tumors (i.e., their incidence is lower than the RARECARE definition of <6/100,000/year [3]). Unfortunately, we lack tumor registry data on each specific adnexal cancer. The whole group of adnexal cancers of the skin accounts for 2.2–7 new cases per million subjects/year (Table 2). Thus, given that appendageal tumors are made of numerous pathologic entities, most of them may be reasonably considered ultra-rare cancers, given the definition of ≤ 1/1,000,000/year [4].

Moreover, we observed that the 5-year relative survival was 86% (95% confidence interval 84–88%) in Europe, 93.8% (standard error 0.6%) in the USA. Although no comparisons can be made between these registry data, the most relevant observation that we emphasize is that the relative cancer survival is high (>85% at 5 years) in cutaneous adnexal cancer patients.

Table 2
Number of observed cases (obs.) and age-adjusted incidence rate (adj. rate) of cutaneous adnexal carcinomas per 100,000 subjects/year.

	All		Males		Females	
	obs.	adj. rate	obs.	adj. rate	obs.	adj. rate
Europe	4684	0.22	2420	0.274	2264	0.185
USA	11,478	0.7	6755	0.9	4723	0.5

3. Pathologic classification

The epidemiological data mentioned a mixed population of patients affected by adnexal tumors of the skin taken from several European and North American cancer registries. However, skin appendageal tumors do not form a single group. In the International Agency for Research on Cancer (IARC) / World Health Organization (WHO) classification of skin tumors, a chapter is dedicated to adnexal neoplasms. This classification defines four overarching groups of malignancies (Table 3, Fig. 1): carcinomas differentiated towards sweat glands (i.e., with eccrine and apocrine differentiation), hair follicles, sebaceous glands, and some site-specific cancers [1]. Given these cancers' frequent involvement of periocular skin structures, the fifth edition of the IARC/WHO classification of eye and orbit tumors includes a section specifically dedicated to malignant adnexal tumors of the eyelid. This list contains seven pathologic entities (Fig. 2), which are also included in the skin cancer classification (sebaceous carcinoma, adenoid cystic carcinoma, signet-ring cell/histiocytoid carcinoma, mucinous carcinoma, endocrine mucin-producing sweat gland carcinoma, microcystic adnexal carcinoma, apocrine carcinoma).

4. Staging

In addition to an unambiguous pathological classification, cutaneous adnexal malignant tumors ought to be staged according to the latest versions of the classifications endorsed by the American Joint Committee on Cancer (AJCC) [5] and the Union for International Cancer Control (UICC) [6]. In the eighth edition, specific staging systems exist for skin carcinoma of the head and neck, carcinoma of the skin of the eyelid, and anal canal and perianal skin (especially for extramammary Paget disease), vulva, penis, breast (for Paget disease), and for skin carcinomas arising from any other anatomic site (Tables 4 and 5, Fig. 3).

In the case of sebaceous carcinoma, recent evidence showed that the eighth edition of the TNM classification led to a T category understaging in up to one-third of patients compared to the seventh edition of the same staging system [7]. Therefore, following the last edition of the currently available staging system, providing complete prognostic

Table 3
Overview of the different cancer entities among cutaneous adnexal cancers (adapted from the IARC/WHO Classification of Skin Tumors, 5th edition).

Overarching group	Specific pathologic entities
Apocrine and eccrine differentiation	• Adnexal adenocarcinoma, NOS • Microcystic adnexal carcinoma • Cribriform tumor (previously carcinoma) • Porocarcinoma • NUT carcinoma • Malignant neoplasms arising from spiradenoma, cylindroma, or spiradenocylindroma • Malignant mixed tumor • Hidradenocarcinoma • Endocrine mucin-producing sweat gland carcinoma • Mucinous carcinoma • Digital papillary adenocarcinoma • Adenoid cystic carcinoma • Apocrine carcinoma • Squamoid ductal eccrine carcinoma • Syringocystadenocarcinoma papilliferum • Secretory carcinoma • Signet-ring cell/histiocytoid carcinoma
Follicular differentiation	• Proliferating trichilemmal tumor • Pilomatrical carcinoma • Trichoblastic carcinoma/carcinosarcoma • Trichilemmal carcinoma
Sebaceous differentiation	• Sebaceous carcinoma
Site-specific appendageal tumors	• Mammary Paget disease • Extramammary Paget disease • Adenocarcinoma of mammary-gland type

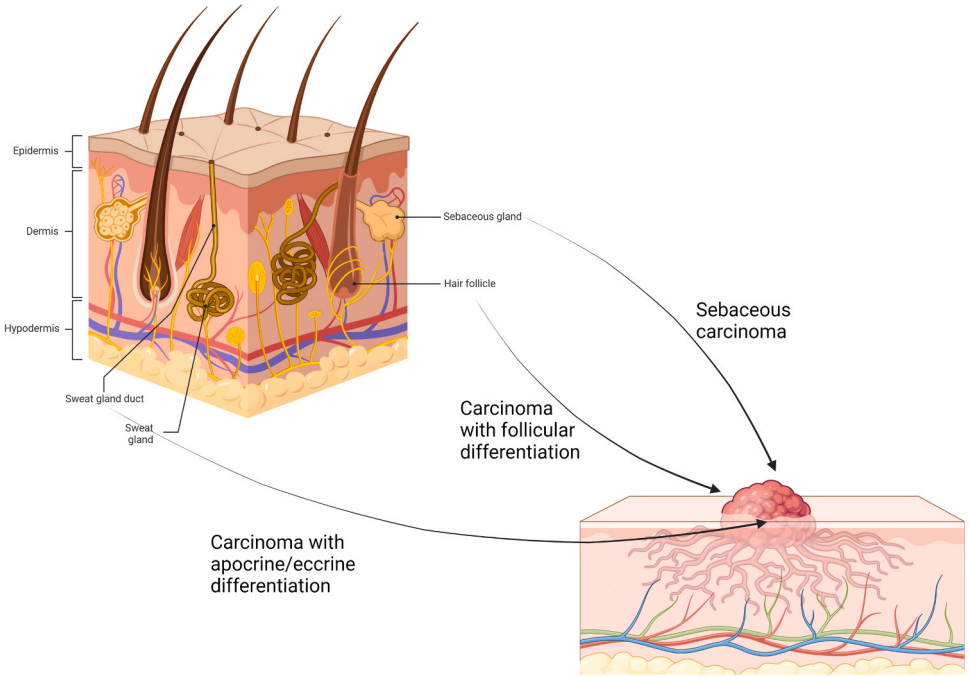

Fig. 1. Schematic representation of adnexal malignancies of the skin based on their differentiation. Created with BioRender.com.

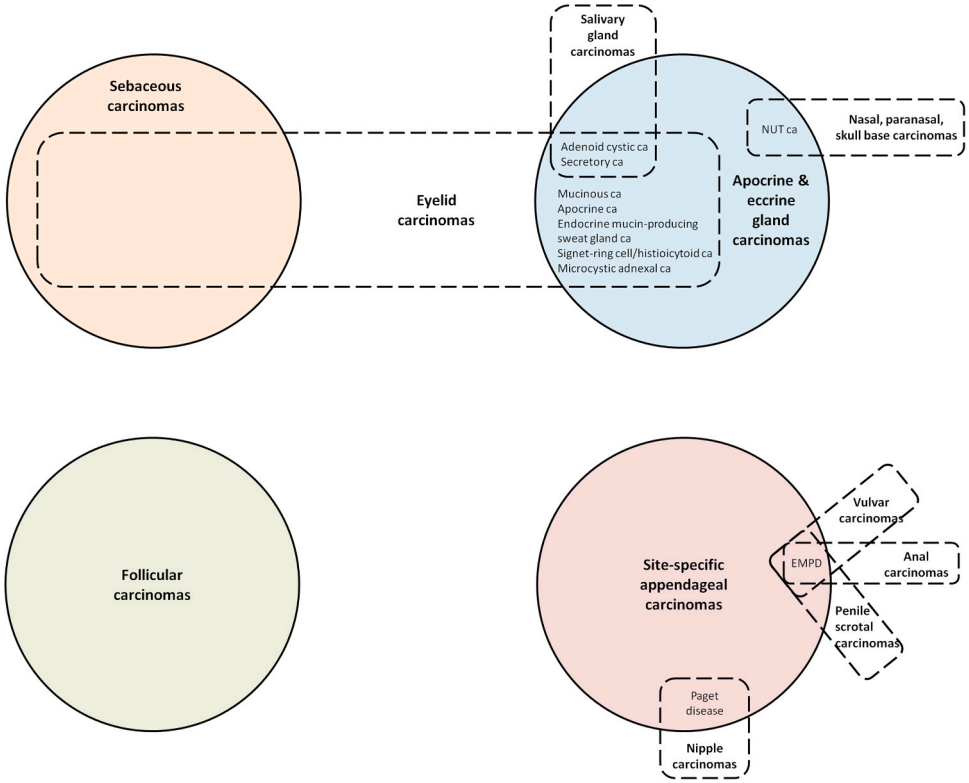

Fig. 2. Graphical representation of the four groups of cutaneous adnexal malignancies (colored circles) based on the WHO 2022 classification and possible overlaps between pathologic entities and anatomic sites (boxes with dotted lines). Note: the dimension of circles and boxes are not proportional to the incidence or the prevalence of the condition. Abbreviations: ca, carcinoma; EMPD, Extramammary Paget disease.

information for the correct treatment choice is advisable.

5. Selected clinical-pathologic entities

Unlike the staging system that fits all adnexal skin malignancies, the WHO pathologic classification defines four main groups of cancers (Table 3). The following paragraphs will cover each of these entities.

Table 4
UICC/AJCC TNM classifications. Abbreviations: ENE-, without extranodal extension; ENE+ , with extranodal extension.

TNM			Skin	Head and neck	Eyelid
T stage (clinical and pathological)		T1	Tumor ≤ 2 cm		Tumor ≤ 10 mm T1a Not invading the tarsal plate or eyelid margin T1b Invades tarsal plate or eyelid margin T1c Involves full thickness of eyelid
		T2	Tumor > 2 cm and ≤ 4 cm		Tumor > 10 mm and ≤ 20 mm T2a Not invading the tarsal plate or eyelid margin T2b Invades the tarsal plate or eyelid margin T2c Involves full thickness of eyelid
		T3	Tumor > 4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion		Tumor > 20 mm T3a Not invading the tarsal plate or eyelid margin T3b Invades tarsal plate or eyelid margin T3c Involves full thickness of eyelid
		T4	T4a Tumor with gross cortical bone/ marrow invasion T4b Tumor with axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space		T4a Tumor invades ocular or intraorbital structures T4b Tumor invades (or erodes through) the bony walls of orbit or extends to paranasal sinuses or invades the lacrimal sac/ nasolacrimal duct or brain
N stage	cN	cN0	No regional lymph node metastasis		
		cN1	Single node ≤ 3 cm	Single ipsilateral ENE- node ≤ 3 cm	Single ipsilateral node ≤ 3 cm
		cN2	Single ipsilateral node > 3 cm and < 6 cm OR multiple ipsilateral nodes < 6 cm	N2a Single ipsilateral ENE- node > 3 cm and < 6 cm N2b Multiple ipsilateral ENE- nodes none < 6 cm N2c Bilateral or contralateral ENE- nodes < 6 cm	Single ipsilateral node > 3 cm OR bilateral or contralateral nodes
		cN3	Single node ≥ 6 cm	N3a Single ENE- node > 6 cm N3b Single or multiple ENE+ nodes	-
	pN	pN0	Same as cN	No regional lymph node metastasis	Same as cN
		pN1		Single ipsilateral ENE- node ≤ 3 cm	
		pN2		pN2a Single ipsilateral ENE+ node ≤ 3 cm OR single ipsilateral ENE- node > 3 cm and < 6 cm pN2b Multiple ipsilateral ENE- nodes < 6 cm pN2c Bilateral or contralateral ENE- nodes < 6 cm	
		pN3		pN3a Single ENE- node ≥ 6 cm pN3b Single ENE+ node ≥ 3 cm OR multiple ipsilateral, or any contralateral or bilateral ENE+ node(s)	
M stage		M0	No distant metastasis		
		M1	Distant metastatic disease		

Table 5
UICC/AJCC staging systems.

Stage	Skin & Head and neck	Eyelid
0	Tis N0 M0	-
I	T1 N0 M0	IA: T1 N0 M0 IB: T2a N0 M0
II	T2 N0 M0	IIA: T2b, T2c, T3 N0 M0 IIB: T4 N0 M0
III	T3 N0 M0 T1, T2, T3 N1 M0	IIIA: Any T N1 M0 IIIB: Any T N2 M0
IV	IVA: T1, T2, T3 N2, N3 M0 OR T4 Any N M0 IVB: Any T Any N M1	Any T Any N M1

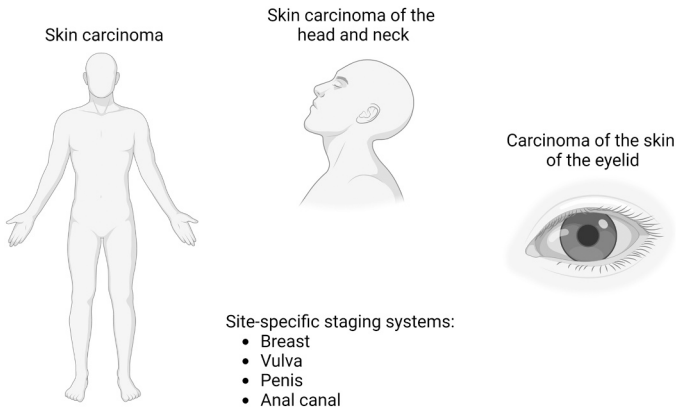

Fig. 3. AJCC/UICC systems used to stage adnexal malignancies of the skin. Created with BioRender.com.

5.1. Tumors with apocrine and eccrine differentiation

Carcinomas with apocrine and eccrine differentiation are malignant epithelial tumors whose phenotype differentiates toward sweat glands. This group includes 17 different pathologic types (Table 3).

Some are entities typically found in other anatomic sites (Figs. 2 and 3). In this context, NUT carcinoma, adenoid cystic carcinoma, and

secretory carcinoma are the same malignancies described in major and minor salivary glands and widely described in the WHO classification of head and neck tumors [1] and in other relevant pathologic handbooks [8].

Other skin-specific adnexal cancers include microcystic adnexal carcinoma, a locally aggressive tumor with frequent perineural infiltration [9]. For this reason, managing microcystic adnexal carcinoma patients arising in the head and neck, the need for contrast-enhanced radiologic scans (notably magnetic resonance imaging) should always be considered to assess intracranial extension [10]. Although this tumor is morphologically similar to basal cell carcinoma, sonic hedgehog alterations are unlikely to play a significant role in microcystic adnexal carcinoma [11].

Another sweat gland malignancy is porocarcinoma. This tumor, which is the malignant counterpart of the poroma, most frequently arises from the head and neck, and lower limbs and might have the propensity for regional spread [12]. In the last years, translocations involving YAP1 have been described in porocarcinoma. YAP1 is a transcriptional mediator of the Hippo signaling pathway that activates gene expression toward tumor proliferation [13]. This gene may be fused with either NUTM1 [14,15], which is the same gene translocated in NUT midline carcinoma, or MAML2 [15], the genetic hallmark of mucoepidermoid carcinoma of salivary glands [8]. At the current stage, this information is a valuable tool for pathologists in the differential diagnosis of cutaneous adnexal cancers. Even though YAP inhibitors are under development in oncology [13], currently, we lack a pharmacologic approach against this molecular target for porocarcinoma. However, it is worth noting that in the context of adnexal cancers of the skin, gene fusions involving YAP1 are almost pathognomonic of poroid tumors [16].

Hidradenocarcinoma is another cutaneous adnexal malignancy differentiated toward eccrine sweat glands [1]. Also this tumor may have MAML2 translocations [17], and sporadic cases may have HER2 amplifications [18], with subsequent potential therapeutic implications for patients with advanced disease. Another molecular marker is NUT, expressed in 80% of poroid hidradenocarcinomas vs. 17% of classic poroma vs. 11% porocarcinoma [19]. Such a different prevalence in the three entities may help in differential diagnosis.

5.2. Tumors with follicular differentiation

These tumors are characterized by a phenotype differentiated toward hair follicles [1]. From a morphological point of view, some of these cancers, such as trichoblastic carcinoma, have several similarities with basal cell carcinoma. In this context, available literature focused on the clinicopathological characteristics specific to each of the two pathologic entities [20], which may help in the differential diagnosis.

Interestingly, the similarity between cutaneous adnexal cancers with follicular differentiation and basal cell carcinomas may be exploited from a therapeutic point of view. Indeed, some trichoblastic carcinoma cases have been reported to respond to hedgehog inhibitors [21], standard of care for basal cell carcinoma. For these biological, pathological, and clinical resemblances, patients with advanced disease should be offered molecular profiling to identify possible targets of hedgehog inhibitors so that off-label vismodegib [22] or sonidegib [23] could be proposed.

5.3. Tumors with sebaceous differentiation

Sebaceous carcinoma most frequently arises from the head and neck, especially in the periocular region. As with most adnexal cancers of the skin, these tumors are usually cured with radical surgery, and regional lymph node involvement is relatively rare. They are prevalent in men and can be part of Muir-Torre syndrome (Section 5.5) [1].

SEER data showed that, compared to a reference population, patients with sebaceous carcinoma are at a slightly higher risk of developing second primary tumors [24]. In particular, literature data showed a higher frequency of second primary tumors (lung, pancreas, salivary gland, skin; breast cancer for women and chronic lymphocytic leukemia). The highest risk was observed in 40/45-year-old Caucasian patients [24].

Some risk factors for sebaceous carcinoma have been identified so far. The main ones are those typically associated with skin tumors, notably ultraviolet radiation, age, genetic susceptibility, and immune suppression. Interestingly, the role of oncogenic viruses in these cancers has been increasing in importance in the last few years [25].

In particular, recent articles showed that 18% of sebaceous carcinoma are associated with high-risk human papillomavirus (HPV). However, differently from oropharyngeal squamous cell cancer, HPV was not found to be prognostic in sebaceous carcinoma, and the immunohistochemical staining of p16 failed to be a surrogate marker for HPV infection [26].

In molecular biology, TERT promoter mutation was observed in approximately one-fourth of sebaceous carcinoma and none of its benign counterparts. Therefore, detecting this molecular alteration may help pathologists distinguish malignant from benign sebaceous tumors [27].

5.4. Site-specific appendageal tumors

Site-specific appendageal malignant tumors include three entities (Table 3): Mammary Paget disease, Extramammary Paget disease, and Adenocarcinoma of mammary-gland type. The first of these diseases is the well-known subtype of breast cancer, and the diagnostic workup and treatments should follow what is standard for breast cancer patients [28].

The most significant entity of this group is extramammary Paget disease (EMPD). The WHO classification defines it as “a rare adenocarcinoma characterized by a predominant intraepithelial growth of neoplastic cells originating in the skin (primary EMPD) or representing the intraepithelial spread of an underlying visceral carcinoma (secondary EMPD)” [1]. The most frequent primary site is the anogenital area. Some authors proposed a specific staging system that might be specific for extramammary disease [29]. Although not currently in use, this may be helpful for the refinement of the subsequent editions of the TNM staging system.

Similar to what is commonly observed in a quota of breast cancers, some extramammary Paget disease cases may bear HER2 overexpression [30]. The HER2-positive disease is associated with more aggressive behavior, with local infiltration and regional involvement [31].

5.5. Hereditary syndromes and cutaneous adnexal cancers

The fifth edition of the IARC/WHO classification of skin tumors dedicated a chapter to genetic tumor syndromes associated with skin malignancies [1]. In this section, seven entities are described: Familial melanoma, BAP1 tumor predisposition syndrome, Xeroderma pigmentosum, Nevoid basal cell carcinoma syndrome (Gorlin syndrome), Carney complex, Muir-Torre syndrome, Brooke-Spiegler and related syndromes. Among them, the ones that may be associated with cutaneous adnexal cancers are the last two. Both are inherited autosomal dominant conditions. Patients affected by the Muir-Torre syndrome develop sebaceous tumors synchronously or sequentially with visceral malignancies, including gastrointestinal and gynecological cancers [32]. Available guidelines recommend that $<$ 50-year-old subjects affected by extraocular sebaceous carcinoma may undergo Muir-Torre screening by assessing tumor tissue mismatch repair proteins [33].

Brooke-Spiegler syndrome is driven by alterations of the tumor suppressor gene CYLD, and is associated with the development of multiple adnexal neoplasms, often benign, with specific phenotypic variants that include multiple familiar trichoepithelioma [34].

6. Treatments

Given the rarity of these malignancies, no universal guidelines exist for adnexal tumors of the skin. Nonetheless, in the last years, histotype-specific guidelines have been published for some entities, notably microcystic adnexal carcinoma [10], sebaceous carcinoma [33], and EMPD [30].

6.1. Curative treatments

Independently of the pathologic differentiation, cutaneous adnexal carcinomas usually follow similar therapeutic approaches. Local disease, with or without regional extension, is usually cured with loco-regional treatments.

6.1.1. Surgery

When feasible, optimal surgery should always be pursued [1,10,30,33]. There is evidence that patients receiving surgery for adnexal cancers of the skin have excellent disease-specific survival [35].

6.1.1.1. Surgical management of primary tumor. Margin-controlled techniques include complete circumferential peripheral and deep margin assessment (CCPDMA) or Mohs micrographic. Guidelines recommend these surgical methods as the best surgical options for sebaceous carcinoma (both extraocular and periocular) [33], EMPD (both intraepidermal and invasive) [30], and microcystic adnexal carcinoma [10].

Wide local excisions are not recommended in periocular sebaceous carcinomas [33] but may be taken into account as alternative approaches for invasive EMPD [30] or with microcystic adnexal carcinomas located in anatomic sites where a 2-cm margin resection is feasible [10].

Indeed, narrow local excisions provide similar outcomes to wide excisions while being burdened by less morbidity [35].

6.1.1.2. Frequency and management of regional lymph node metastases. Registry data showed that the vast majority (89.1%) of subjects diagnosed with adnexal carcinomas had a limited disease (stage I-II) [35]. The prevalence of stage III varied based on primary tumor histology, ranging from a minimum of 4.4% of sebaceous carcinoma up to an average of 12.5% of sweat gland carcinomas (pooling together Sweat gland carcinoma not otherwise specified, Hidradenocarcinoma, Spiradenocarcinoma, Sclerosing sweat duct tumor, Porocarcinoma, and Eccrine adenocarcinoma) [35]. Such variability ought to be considered while planning surgery for locally advanced adnexal cancer patients.

The same article reported that the frequency of positive nodes varied (9.1–50%) based on the primary tumor pathologic type. However, the number of subjects undergoing a nodal biopsy was also heterogeneous and pathology-dependent (e.g., 7.2% in microcystic adnexal carcinoma vs. 26% in hidradenocarcinoma) [35]. Therefore, it is likely that the observed differences have been influenced by the different a priori probability of assessing lymph nodal status rather than an intrinsic disease-dependent different probability of regional involvement.

In this context, the utility of lymph node biopsy remains unclear, given its low sensitivity [35,36]. In a series of 25 patients undergoing sentinel lymph node biopsy (SLNB), a regional involvement was identified only in one case (4%) affected by apocrine carcinoma [36].

Clinical practice guidelines do not recommend the routine use of SLNB in EMPD [30], microcystic adnexal carcinoma [10], and extraocular sebaceous carcinoma [33]. At the same time, this procedure may be considered in patients with stage $\geq$T2c eyelid sebaceous carcinomas [33].

6.1.2. Adjuvant treatments

Although literature data on adjuvant radiotherapy are limited, so there is no robust consensus in its indication, post-operative radiation may be offered in selected cases based on the loco-regional disease burden at diagnosis and on pathologic features [10,30,33].

No clinical studies are available to suggest the use of concomitant chemotherapy. However, borrowing the scientific evidence that is available for head and neck squamous cell carcinoma patients [37–39], in selected cases, the option to deliver concomitant chemotherapy in association with adjuvant radiation may be considered (e.g., non-radical resection where wide excision is not feasible, extracapsular spread, a high number of involved lymph nodes, primary cancer arising in the head and neck, absence of relevant comorbidities, etc.). In this scenario, a multidisciplinary discussion is mandatory for each patient. Moreover, if a subject is treated at a low-volume clinical institution, a referral to a tertiary cancer center should be strongly recommended [40,41].

6.2. Palliative treatments

The goal of achieving radical surgery, with or without postoperative radiation, is also applicable for operable local recurrences. However, in case of unresectable relapse or metastatic disease, palliative radiotherapy or systemic treatments may be necessary to control symptoms.

6.2.1. Chemotherapy

Several chemotherapeutic approaches have been proposed [42]. Although some clinical activity may be seen using cytotoxic drugs [42], these agents are not standard-of-care for adnexal cancers of the skin. However, in case of absence of clinical trial availability and any druggable alterations, chemotherapy should be taken into account in patients suffering from advanced disease, especially in case of rapidly progressing metastatic disease, high tumor burden, or loco-regionally advanced disease deemed unsuitable for surgery or radiation. Given that adnexal skin malignancies are of epithelial origin [1], active drugs that should be considered are platinum salts, gemcitabine, anthracyclines, and taxanes.

6.2.2. Precision medicine

New systemic strategies may be pursued, notably immunotherapy and targeted therapy. In the context of precision oncology, the immune microenvironment and the molecular profile of these rare cancers should be studied before exploring new approaches.

6.2.2.1. Immunotherapy. The PD-L1 expression varies across several cutaneous adnexal malignancies [43]. It is higher in apocrine carcinoma and invasive EMPD on both tumor and immune cells. Other entities, such as sebaceous and trichoblastic carcinomas, may have a PD-L1 positive immune infiltration while being PD-L1 negative on tumor cells, while all the remaining pathologic types are mostly PDL1-negative. All taken together, a minority of adnexal cancers of the skin have a high PD-L1 expression on cancer cells or tumor microenvironment, respectively 11% and 24% [43].

In sebaceous carcinoma, PD-L1 expression showed a prognostic significance based on the expression site: PD-L1 overexpression on cancer cells provides worse survival and, on infiltrating lymphocytes, better outcomes [44]. In the context of PD-L1 expression in the microenvironment, the prevalence of combined positive score (CPS) ≥ 1 in sebaceous carcinoma is 51.4% [45]. Interestingly, this frequency is significantly higher in extraocular than in ocular cases (75.7% vs. 44.4%, respectively, $p < 0.05$) [45].

Apart from PD-L1 expression, it is worth noting that FDA approved the anti-PD1 pembrolizumab agnostically for unresectable or metastatic pre-treated tumors with microsatellite instability-high (MSI-H), mismatch repair (MMR) deficient tumors or tumor mutational burden-high (TMB-H, defined as ≥ 10 mutations/megabase [46,47]. Therefore, advanced cutaneous adnexal cancer patients with these molecular characteristics may benefit from this immune checkpoint inhibitor. However, it is worth noting that in a cohort of 103 patients affected by

adnexal cancers of the skin, the prevalence of MSI-high was 2% only (11% in sebaceous carcinoma). In the same setting, TMB was found to be low (median TMB 3.6 mut/MB, ranging from 3.5 mut/MB in sweat duct to a maximum of 6.1 mut/MB in sebaceous gland carcinomas) [48]. Despite these results, a case report of near complete response to pembrolizumab was published in microsatellite-stable metastatic sebaceous carcinoma [49].

These inconsistent observations underline the complexity of these malignancies and the need for further research in the field.

6.2.2.2. Targeted therapies. Three literature reviews published in 2021 reported a comprehensive overview of the complex biological landscape of this heterogeneous set of malignancies [50–52]. Generally, most of the genetic alterations found in these cancers are observed in sporadic cases [52], and only a few are druggable (Fig. 4). Actionable targets include breast cancer-like molecular alterations in the case of EMPD (e.g., HER2 [30], PI3K [53], TROP2 [54]), PTCH1 mutations, or molecular alterations of the sonic hedgehog pathway in the presence of cancers with follicular differentiation. In this setting, the objective response rate in a cohort of 16 patients treated with vismodegib for inoperable trichoblastic carcinoma was 62.5%, with a median duration of response longer than 6 months [55].

Further potential targets are androgen receptors (AR) and HER2. AR overexpression may mostly be found in sebaceous and mucinous carcinoma [56]. These cases may benefit from an antiandrogen blockade, as it happens in prostate [57], salivary duct carcinoma, and a fraction of salivary adenocarcinoma not otherwise specified [58–61]. In addition to EMPD [31], HER2 amplification may also be observed in poorly differentiated adnexal carcinomas [56]. This observation may have potential therapeutic implications.

7. Conclusions

Adnexal carcinomas of the skin are a vast and heterogeneous group of malignancies with several pathologic and biologic differences (Fig. 5). The understanding of cutaneous adnexal cancer biology is constantly evolving. In clinical practice, the complexity owed to our lack of knowledge is partially mitigated by adopting standardized universal classification systems: the WHO for pathologic diagnosis and the AJCC/UICC for clinical and pathologic staging. Besides, when diagnosing an adnexal skin malignant tumor, especially in unusual anatomic sites or multiple tumors, the diagnostic hypothesis of genetic syndromes should always be considered. In curative treatments, radical surgery, when feasible, should always be regarded as the first option for local or regional diseases. For advanced disease, the seek for potential druggable targets is advised. Last but not least, in the general context of therapeutic management, a multidisciplinary approach in referral centers is strongly recommended to tailor the best therapeutic strategy for each patient.

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Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lisa Licitra declares the following conflicts of interest:

- research funds donated directly to the institute for clinical trials from Astrazeneca, BMS, Boehringer Ingelheim, Celgene International, Eisai, Exelixis, Debiopharm International SA, Hoffmann-La Roche ltd, IRX Therapeutics, Medpace, Merck-Serono, MSD, Novartis, Pfizer, Roche, Buran, Alentis
- occasional fees for participation as a speaker at conferences/congresses or as a scientific consultant for advisory boards from

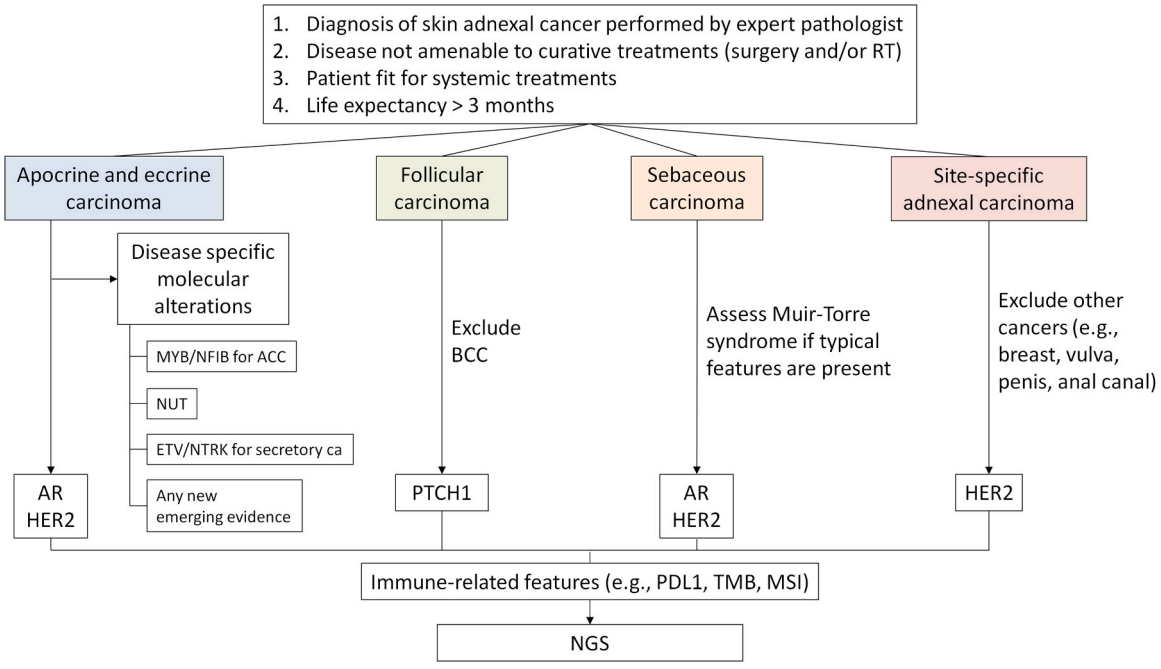

Fig. 4. Algorithm to perform molecular assessments in cutaneous adnexal cancer patients. Abbreviations: ACC, adenoid cystic carcinoma; AR, androgen receptor; BCC, basal cell carcinoma; ca, carcinoma; NGS, next-generation sequencing; TMB, tumor mutation burden.

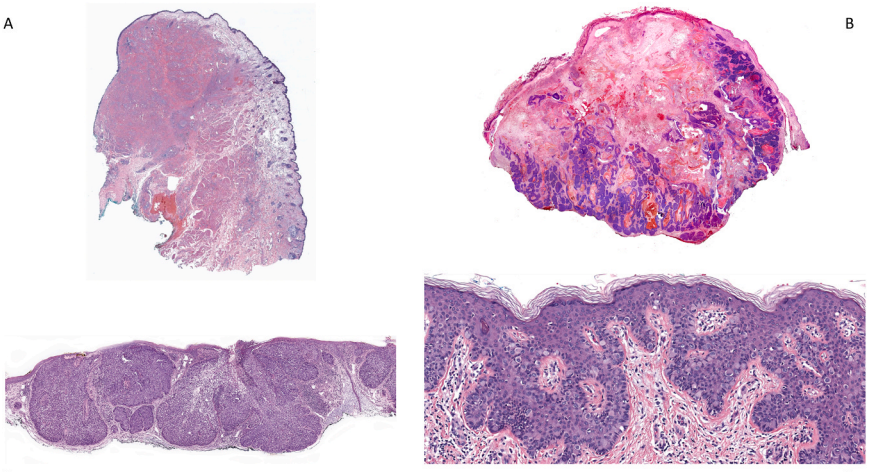

Fig. 5. Examples for each of the four main groups of skin adnexal carcinoma. A. adnexal carcinoma not otherwise specified (sweat gland carcinoma); B. pilomatrical carcinoma (follicular carcinoma); C. sebaceous carcinoma; D. Extramammary Paget disease (site-specific adnexal carcinoma).
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Astrazeneca, Bayer, MSD, Merck-Serono, AccMed, Neutron Therapeutics, Inc.

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The remaining authors have no conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcskn.2023.100006.

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