Impact of expert pathology review in skin adnexal carcinoma diagnosis: Analysis of 2573 patients from the French CARADERM network

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Running head: Impact of expert pathology review for skin adnexal carcinomas

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Abstract

Purpose: To prospectively assess the impact of expert pathological review of skin adnexal carcinoma diagnosis in France

Methods:

From 2014 to 2019, 2,573 samples from patients with newly diagnosed or suspected skin adnexal carcinomas were reviewed prospectively by expert pathologists through the national Caraderm network. Changes in diagnosis between referral and expert review were analyzed regarding their potential impact on patient care or prognosis.

Results:

The samples comprised 2,205 newly diagnosed adnexal carcinomas, 129 benign adnexal tumors, 136 basal cell carcinomas (BCC), 74 squamous cell carcinomas (SCC), 6 cutaneous metastases, 13 other malignancies. There were 930 (42%) sweat gland carcinomas, of which porocarcinoma (261; 11.8%), microcystic adnexal carcinoma (125; 5.7%) and hidradenocarcinoma (109; 4.9%) were the most frequent subtypes; 778 (35%) hair follicle carcinomas, 238 (11%) sebaceous carcinomas, and 212 (10%) extramammary Paget diseases/mammary-like anogenital gland adenocarcinomas. A diagnostic change between referral and expert review occurred in 503 (21.3%) patients, significantly higher for cases sent with a provisional diagnosis seeking expert second opinion (45.7%) than for cases sent with a formal diagnosis (2.8%) ($p<.0001$). Sweat gland carcinomas were more prone to diagnostic discrepancies than other tumors ($p<.0001$), including 1.8% of patients with sweat gland carcinoma subtype misclassification with predicted clinical impact. Changes between benign and malignant conditions occurred in 117 samples (5% of patients).

Conclusion:

The study provides a unique description of the distribution of skin adnexal carcinomas, and highlights the importance of expert review for these rare cancers. Optimal clinical management was impacted in a significant proportion of patients.

Keywords

skin adnexal carcinoma; sweat gland carcinoma; hair follicle carcinoma; sebaceous carcinoma; expert pathological review; misdiagnosis; rare cancer network.

Introduction

Skin adnexal carcinomas are a wide and heterogeneous group of rare malignant skin neoplasms that differentiate towards one or more of the following appendageal structures: sweat gland (either eccrine or apocrine), hair follicle and sebaceous gland. The 2018 WHO classification recognizes 25 subtypes of skin adnexal carcinomas, with 16 subtypes of sweat gland carcinomas.[1] Precise classification of these cancers is based on histopathological examination, potentially requiring specific immunostainings (IHC) or molecular analysis.[1] However, the rarity of skin adnexal carcinomas and the significant changes of their classification over time have prevented healthcare professionals from gaining sufficient clinicopathological experience, and definite diagnosis often requires a specific expertise.[2-5]

The age-standardized incidence rate (ASR) of skin adnexal carcinoma is estimated to be 5.1 per million person-years in the USA and between 2.8 and 5.3 per million person-years in Europe,[5-8] with an incidence increase in recent years as for other skin cancers.[5,7] Data regarding incidence of skin adnexal carcinomas are however limited, being based on cancer registries where diagnoses are not always verified, and in which some 2018 WHO classification subtypes are lacking.[5-8] A call to create global registers dedicated to skin cancers to ascertain more precise knowledge has been made.[5]

The Caraderm network is a national clinico-pathologic Rare Cancer Network established in France in 2014 and funded by the French National Cancer Agency, dedicated to rare skin cancers (www.caraderm.org). Among its objectives, Caraderm aims to provide a systematic expert pathologic review of every newly diagnosed skin adnexal carcinoma and to optimize further care of the patients. Previous studies have supported the impact of expert review on rare cancer diagnoses, and highlighted the importance of dedicated pathologists' networks.[9-

[11] Here we provide data on 2,205 skin adnexal carcinomas. All cases were prospectively included between 2014 and 2019, the diagnoses were based on the WHO 2018 classification criteria for skin tumors and systematically reviewed by the pathologists of the CARADERM network. The data analysis allowed us to present the overall frequency and relative distribution of specific entities of adnexal carcinomas and to demonstrate the importance of an expert pathologic review for the optimal clinical management of patients with adnexal carcinoma, especially for carcinomas with sweat gland differentiation.

Material and methods

The Caraderm Network review process

Since 2014, pathologists in France have been encouraged to submit samples of all newly diagnosed or suspected skin adnexal carcinoma to a reference center of the Caraderm network, in which 22 expert pathologists have specific experience of these rare cancers, work in an academic institution, and have access to dedicated ancillary techniques, such as immunohistochemistry and molecular tests.

Caraderm pathologists aim to provide an expert diagnosis within a reasonable time (mean time 20 days), allowing for therapeutic decision making according to the revised diagnosis. Expert pathologists receive tumor blocks or original stained slides, have access to clinical information, and make their expert diagnosis on the basis of the combination of clinical data, histology, immunophenotype, and molecular data when needed. Four to five national gatherings of all the network pathologists are organized annually, where they discuss the most difficult cases together and validate collegially the revised diagnoses, assuring a homogeneous review process between the different expert sites of the Caraderm network. Final diagnoses rendered in Caraderm network since 2014 follow a subtype classification that parallels the WHO 2018 classification for skin tumors (Table S1).[1]

The Caraderm electronic database prospectively records the clinical and pathological data including the final and submitted (referral) diagnoses, taking into account whether patients had an initial formal diagnosis or were sent with a provisional diagnosis to obtain an expert second opinion. Data are stored anonymously in agreement with the French law (CNIL authorization DR-2015-604; CCTIRS authorization 15-252). Data extraction from the

database was performed in April 2020, for all patients included between January 2014 and December 2019.

Evaluation of diagnostic changes between referral and expert review

Among the 2,976 cases registered in the adnexal carcinoma database in the study period, 2,573 had benefited from an expert pathological review. The 403 patients without pathological review were not considered in this study. Among the 2,573 patients who had their histological sample reviewed, 201 were submitted without a diagnosis proposed by the referral pathologist. A total of 2,372 patients were thus eligible for comparison of referral and expert diagnoses (Fig.1). We calculated the percentage of patients whose diagnosis did not change between referral and expert review (overall concordance).

Diagnostic changes were divided in 5 main categories: change from unclassified adnexal carcinoma to a precise subtype of adnexal carcinoma; misclassification of adnexal carcinoma subtypes; change from malignant to benign adnexal tumor, or vice versa; change from adnexal carcinoma to other non-adnexal related malignancy, or vice versa; change from adnexal carcinoma to other benign condition, or vice versa. We calculated the percentage of diagnostic change of each category among all diagnostic changes, and among all patients eligible for comparison. Regarding the misclassification of sweat gland carcinoma subtypes, we differentiated diagnostic changes between subtypes with the same prognostic profiles, and diagnostic changes between subtypes with different prognostic profiles, based on literature data (Table S2 indicates subtypes of sweat gland carcinoma with high metastatic risk and with low/not reported metastatic risk).[1] We analyzed the molecular analyses performed in cases with diagnostic change, and their impact on diagnosis.

The frequency of diagnostic discrepancy among the main groups of adnexal carcinoma (sweat gland carcinoma, hair follicle carcinoma, sebaceous carcinoma, and others) was compared using chi-square test. We also compared the percentage of diagnostic changes in patients sent with a formal referral diagnosis and in patients sent with a provisional diagnosis for expert second opinion, using chi-square test. P values of .05 or less were considered to be statistically significant. Analyses were performed using GraphPad Prism software.

Potential impact of a change in diagnosis on clinical management

Because therapeutic recommendations or consensus guidelines are lacking for most subtypes of adnexal carcinoma, we have considered that a diagnostic change had a significant impact on clinical management in the following situations: 1) change from a malignant to a benign lesion, or vice versa; 2) misclassification involving a sebaceous carcinoma diagnosis, regarding the potential association of sebaceous carcinoma with Muir-Torre syndrome and the risk of an extra-cutaneous malignancy; 3) misclassification of sweat gland carcinoma subtype with change from high metastatic-risk to low/unreported metastatic risk subtypes, or vice versa.

Results

Distribution of adnexal carcinoma entities from the Caraderm expert review

From January 2014 to December 2019, the samples of 2,573 patients were referred to the Caraderm pathologists for a newly diagnosed or suspected adnexal carcinoma. Of the 2573 cases referred, 2,205 were adnexal carcinomas, 129 benign adnexal tumors, 136 basal cell carcinomas (BCC), 74 squamous cell carcinomas (SCC), 6 cutaneous metastases, and 13 other malignancies.

The adnexal carcinomas comprised 930 sweat gland carcinomas (42%), 778 hair follicle carcinomas (35%), 238 sebaceous carcinomas (11%), 212 site-specific carcinomas (extramammary Paget disease and adenocarcinoma of anogenital mammary-like glands) (10%), 20 myoepithelial carcinomas (1%), and 27 complex or unclassified adnexal carcinomas (1%) (Fig. 2A). Among hair follicle carcinomas, trichoblastic carcinoma/carcinosarcoma was the most frequent (n=571; 73%), followed by proliferating trichilemmal tumor (PTT) (n=135; 17%) (Fig. 2B). Among sweat gland carcinoma, porocarcinoma (n=261; 28%), microcystic adnexal carcinoma (MAC) (n=125; 13%), hidradenocarcinoma (n=109; 12%) and adnexal adenocarcinoma not otherwise specified (NOS) (n=107; 12%) were the most frequent subtypes. At least 2 examples of each WHO 2018 sweat gland carcinoma specific subtype were encountered, the less frequent subtypes being histiocytoid/signet-ring cell carcinoma (n=2), secretory carcinoma (n=3), and endocrine mucin-producing sweat gland carcinoma (n=6) (Fig. 2C). Almost all site-specific tumors were represented by extramammary Paget diseases (n=210 out of 212), while adenocarcinoma of the anogenital mammary-like glands was exceptional (n=2).

Concordance between referral and expert diagnoses

Among the 2,372 patient samples eligible for comparison of referral and expert diagnoses, 9 cases were excluded based on insufficient material provided, precluding any final diagnosis, leaving 2,363 patients with a comparable referral and expert diagnosis (Fig. 1). Among these, 1,860 had concordant diagnoses (78.3% overall concordance) while 503 (21.7%) had discordant diagnoses. Detailed concordance rates for each adnexal carcinoma subtype are presented in Table 1.

Diagnostic concordance rates were high (>80%) for the most frequent subtypes of adnexal carcinoma, i.e. extramammary Paget disease (205/207; 99% concordance rate), PTT (116/124; 93.6%), trichoblastic carcinoma/carcinosarcoma (469/533; 88%), sebaceous carcinoma (185/220; 84.1%), porocarcinoma (210/249; 84.3%) and MAC (101/116; 87.1%). Some rare entities with peculiar and recognizable histology had also a very high concordance rate, i.e. mucinous carcinoma (25/27; 92.6%) and histiocytoid/signet-ring cell carcinoma (1/1; 100%). Other adnexal carcinoma subtypes had low (<60%) to intermediate overall concordance rate (60 to 80%). The tumor subtypes with most discrepancies were malignant neoplasms arising in cylindroma, spiradenoma and spiradenocylindroma (12/25; 48% overall concordance), adenocarcinoma of anogenital mammary-like glands (1/2; 50%), syringocystadenocarcinoma papilliferum (SCACP) (6/11; 54.6%) and cribriform carcinoma (6/11; 54.6%).

Overall, sweat gland carcinomas were significantly more likely to have diagnostic discrepancy (215/847; 25.4% diagnostic discrepancy) than hair follicle carcinoma (99/725; 13.7%), sebaceous carcinoma (35/220; 15.9%), or other subtypes (11/228; 4.8%) (p<.0001; Fig.3A).

Molecular analyses were performed in 27 out of 503 cases with discordant diagnosis (5.4%), adding positive arguments for sebaceous carcinoma diagnosis in 11 cases with microsatellite instability, confirming diagnosis by the presence of gene rearrangement using FISH or RNAseq in 10 sweat gland carcinomas (4 hidradenocarcinomas, 2 adenoid cystic carcinomas, 2 malignant myoepithelioma, 1 porocarcinoma, 1 secretory carcinoma), excluding the presence of gene rearrangement using RNAseq in 2 sweat gland carcinomas NOS, confirming mutational activation of the Sonic Hedgehog pathway in 2 BCC, confirming diagnosis of 1 matrical carcinoma by the presence of *CTNNB1* mutation, detecting *CYLD* mutation in 1 trichoblastic carcinoma patient suspect of Brooke-Spiegler syndrome, and detecting *NRAS* mutation in 1 melanoma.

Categorization of diagnostic changes and their impact on clinical management

We have next analyzed the types of diagnostic change between referral and expert diagnoses in the 503 discordant cases (Table 2). Diagnostic changes were mostly related to misclassification of adnexal carcinoma subtypes in 35% of cases, to a change from adnexal carcinoma to other skin malignancy or vice versa in 32.6% of cases, and to a change from malignant to benign adnexal tumor or vice versa in 21.7% of cases. Regarding diagnostic changes between adnexal carcinoma and other skin malignancies, most discrepancies were related to BCC or SCC diagnoses (69 and 71 out of 164, respectively). The rate of diagnostic change was significantly lower in cases sent with a formal diagnosis (n=38 out of 1,345 patients; 2.8%) than in cases sent with a provisional diagnosis for expert second opinion (n=465 out of 1,018 patients; 45.7%) ($p<.0001$; Table 3).

Most diagnostic changes (304 of 503; 60%) involved a discrepancy in evaluating tumors with sweat gland differentiation (Fig.3B). More in details, these changes corresponded to either a referral diagnosis wrongly classified as sweat gland differentiation, missed sweat gland

differentiation, error in subtyping a sweat gland carcinoma, or error in assessing malignancy of a sweat gland tumor.

Lastly, we assessed the predicted clinical impact of diagnostic changes. Because first-line treatment of localized skin carcinomas (BCC, SCC or adnexal carcinoma) relies mainly on surgery with safe margins, we predicted clinical impact in only specific situations: 1) a change from malignant to benign lesion, or vice versa, occurred in 117/2363 patients (5%); 2) a misclassification involving a sebaceous carcinoma diagnosis, regarding the potential association of sebaceous carcinoma with Muir-Torre syndrome, occurred in 42/2363 patients (1.8%); 3) a misclassification of sweat gland carcinoma subtype with change from high metastatic risk to low/not-reported metastatic risk subtypes, or vice versa, occurred in 42 patients (1.8%). Thus, 201 patients of 2363 with comparable referral and expert diagnoses (8.6%) had a diagnostic change predicted to impact patient management.

Discussion

In this large nationwide prospective study of expert pathologic review of 2,573 patients with newly diagnosed or suspected adnexal skin carcinomas, we have provided a novel insight into the relative frequency of each skin adnexal carcinoma subtype according to the new WHO 2018 classification. We have also demonstrated the importance of a real-time expert pathologic review for these rare cancers, with 21.3% diagnostic changes and 8.6% of predicted clinical impact on patient management.

Out of 2,205 confirmed adnexal carcinomas, the majority had sweat gland differentiation (42%), while 35% had hair follicle differentiation and 11% sebaceous differentiation. According to published ASR estimates varying between 2.8 and 5.3 per million person-years in Europe based on population based cancer registries (CR),[5-8] the expected number of new adnexal carcinomas in France would be estimated between 188 and 355 cases per year (considering a 66.99 million French population in 2019). In 2019, our expert pathologic network validated 498 new adnexal carcinoma cases. This means that published ASR may be clearly underestimated. Comparing to published epidemiological studies in the field, [5-8] we have confirmed the predominance of carcinomas with sweat gland differentiation. However, while other studies reported few hair follicle carcinomas, we have noticed an important number of them. This may be explained by the lack of inclusion of proliferating trichilemmal tumor (PTT) and trichoblastic carcinoma/carcinosarcoma in previous studies. Indeed PTT, often considered of intermediate malignancy and sometimes of higher malignancy (so-called malignant PTT), with ICD-O code 8103/1, was not included in epidemiological CR-based studies. [5-8] In addition, the trichoblastic carcinoma/carcinosarcoma entity has only been recently included in the WHO classification and given a specific ICD-O code (8100/3).[1] This

may explain the lower representation of hair follicle carcinomas in previous epidemiological studies. Because PTT and trichoblastic carcinoma/carcinosarcoma are recently proposed WHO entities, further studies will be needed to confirm their frequency. The distinction between trichoblastic carcinoma/carcinosarcoma and BCC is also challenging, and may need further refinement of their pathological and molecular diagnostic criteria in the future.[12-16]

Among sweat gland carcinomas, the most frequent subtype in our study was porocarcinoma (28%; representing 11.8% of all adnexal carcinomas). Previous epidemiological studies reported a frequency of porocarcinoma among adnexal carcinomas varying between 7% and 55%.[5-7] In accordance with our results, porocarcinoma was the most frequent sweat gland carcinoma subtype in a SEER population-based study in 2018 and in the Tuscany CR study in 2019.[5,17] Two older studies, based on a SEER subset and on the Netherlands CR reported microcystic adnexal carcinoma and hidradenocarcinoma as the most frequent subtype, respectively.[6-7] This difference may be explained by increasing incidence of porocarcinoma,[5] regional population difference, possible reporting bias in CR, or by variations in criteria for sweat gland carcinoma subtype diagnosis.

The interest of expert pathology review in cancers has already been demonstrated, in order to obtain an accurate diagnosis with potential impact on patient management, especially in the field of rare cancers.[9-11,18,19] Importantly, we report here a diagnostic change in about 20% of samples sent for expert pathologic review with diagnosed or suspect adnexal carcinoma. This high discrepancy rate is comparable to the discrepancy rate in lymphoma diagnosis, in a comparable French network for rare cancers.[9] It can be explained by two reasons: the difficulty of adnexal carcinoma classification with respect to synonyms, news entities, and the evolution of definition of some entities;[5] the lack of dedicated knowledge of

general surgical pathologists in this very specialized pathology area. To our knowledge, no comparative data exist in the literature regarding the discrepancy rate in skin adnexal carcinoma diagnosis.

The carcinomas with sweat gland differentiation were significantly more prone to diagnostic discrepancy than hair follicle or sebaceous carcinomas. This may be explained by the important number of carcinoma subtypes with sweat gland differentiation, including recently defined subtypes, such as secretory carcinoma,[20] cribriform carcinoma,[21] histiocytoid/signet-ring cell carcinoma[22] or endocrine mucin-producing sweat gland carcinoma.[23] In the Caraderm network, pathologists also benefited from molecular tools to better assess sweat gland carcinoma subtypes, including fluorescent *in situ* hybridization, DNA and RNA-sequencing using next generation sequencing techniques to detect recurrent molecular alterations: *ASLK1*[24] ir *CYLD*[25] mutation; *ETV6,*[26] *MAML2,*[27] *MYB,*[28] *NUTM1* and *YAP1*[29] rearrangement.

The therapeutic management of adnexal carcinoma is not consensual,[5] although efforts have been recently made to produce recommendations for MAC and sebaceous carcinoma management in the US.[30,31] Thus it is often difficult to assess whether a change in adnexal carcinoma subtype leads to significant clinical impact. Nonetheless, we identified 3 situations where a clinical impact of the diagnostic change was predictable, in 8.6% of patients, mainly due to a change in malignancy assessment of an adnexal tumor (benign *vs* malignant).

Overall, our data demonstrates that expert pathologic review is useful in skin adnexal carcinoma for a better care of patients, and points out the entities with most discrepancies for which this review is of particular interest. The further expansion of our clinico-pathologic

database dedicated to adnexal carcinomas will provide in the future unique follow-up data on a prospectively built national cohort. It will be an opportunity to better assess metastatic rates of rare subtypes, recurrence rates according to first-line treatments, to refine diagnostic and prognostic criteria, and to help build recommendations for these rare cancers.

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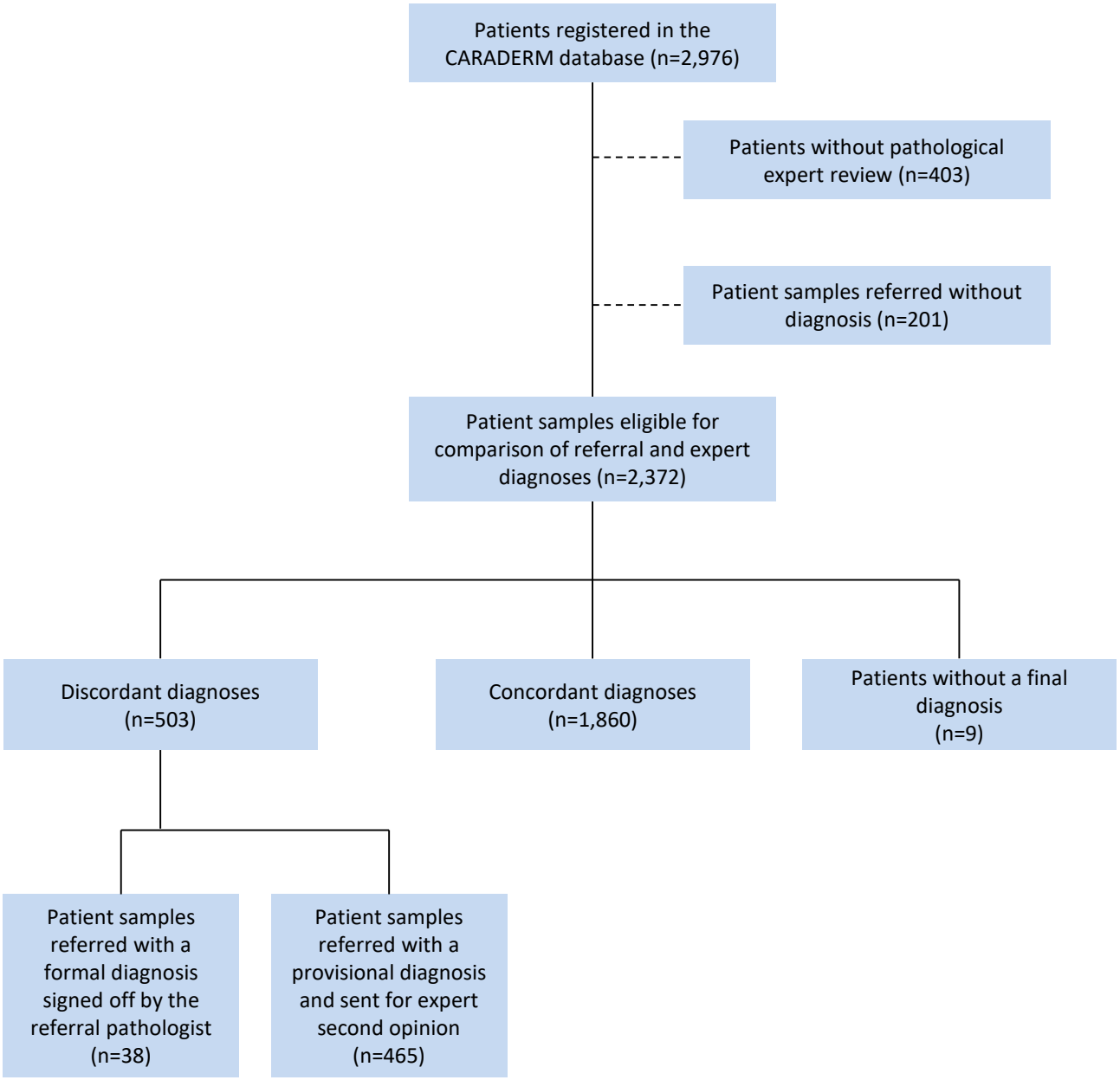
Legend of the figures

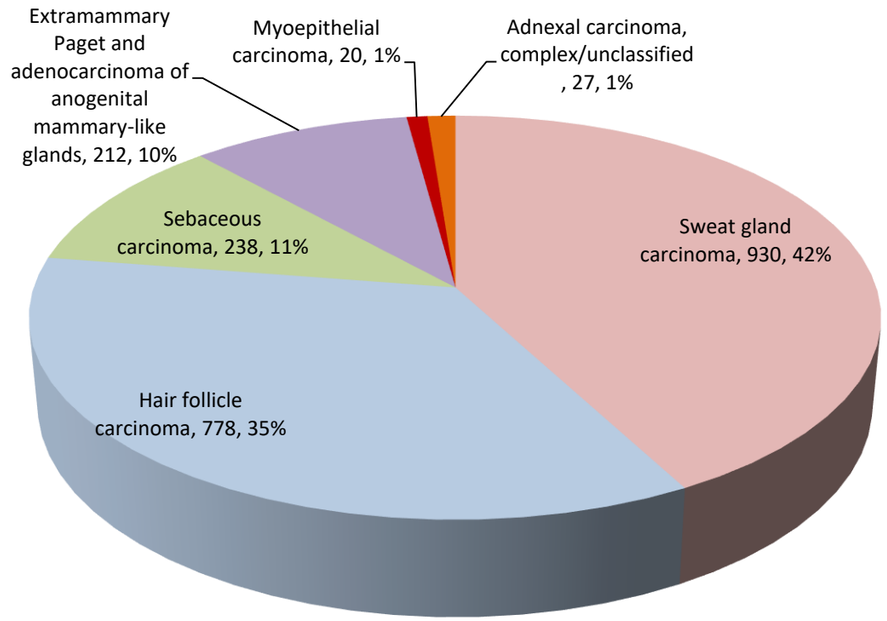
Figure 1: Flowchart of the Caraderm Network study

Figure 2: A) Distribution of the main categories among the 2,205 skin adnexal carcinomas diagnosed through the Caraderm Network over the 2014-2019 period. B) Carcinomas with hair follicle differentiation subtype distribution. C) Carcinomas with sweat gland differentiation subtype distribution.

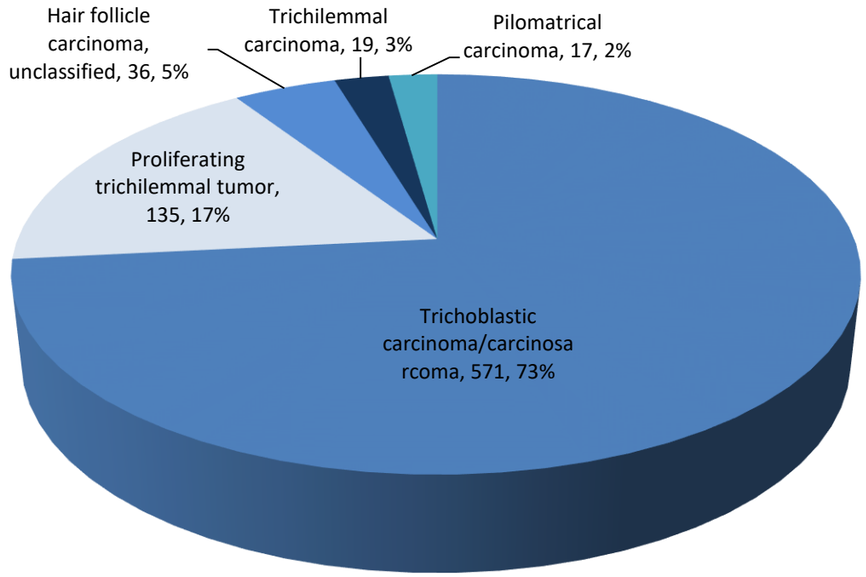
Figure 3: A) Frequency of discrepancies according to the expert-diagnosis' line of differentiation in skin adnexal carcinomas. The population analyzed included the 2,363 patients with comparable referral and expert diagnosis. B) Frequency and subcategories of discrepancies involving sweat gland differentiation, in referral diagnosis, expert diagnosis, or both. The population analyzed included the 2,363 patients with comparable referral and expert diagnosis.


Patients registered in the CARADERM database (n=2,976)
Patients without pathological expert review (n=403)
Patient samples referred without diagnosis (n=201)
Patient samples eligible for comparison of referral and expert diagnoses (n=2,372)
Discordant diagnoses (n=503)
Concordant diagnoses (n=1,860)
Patients without a final diagnosis (n=9)
Patient samples referred with a formal diagnosis signed off by the referral pathologist (n=38)
Patient samples referred with a provisional diagnosis and sent for expert second opinion (n=465)

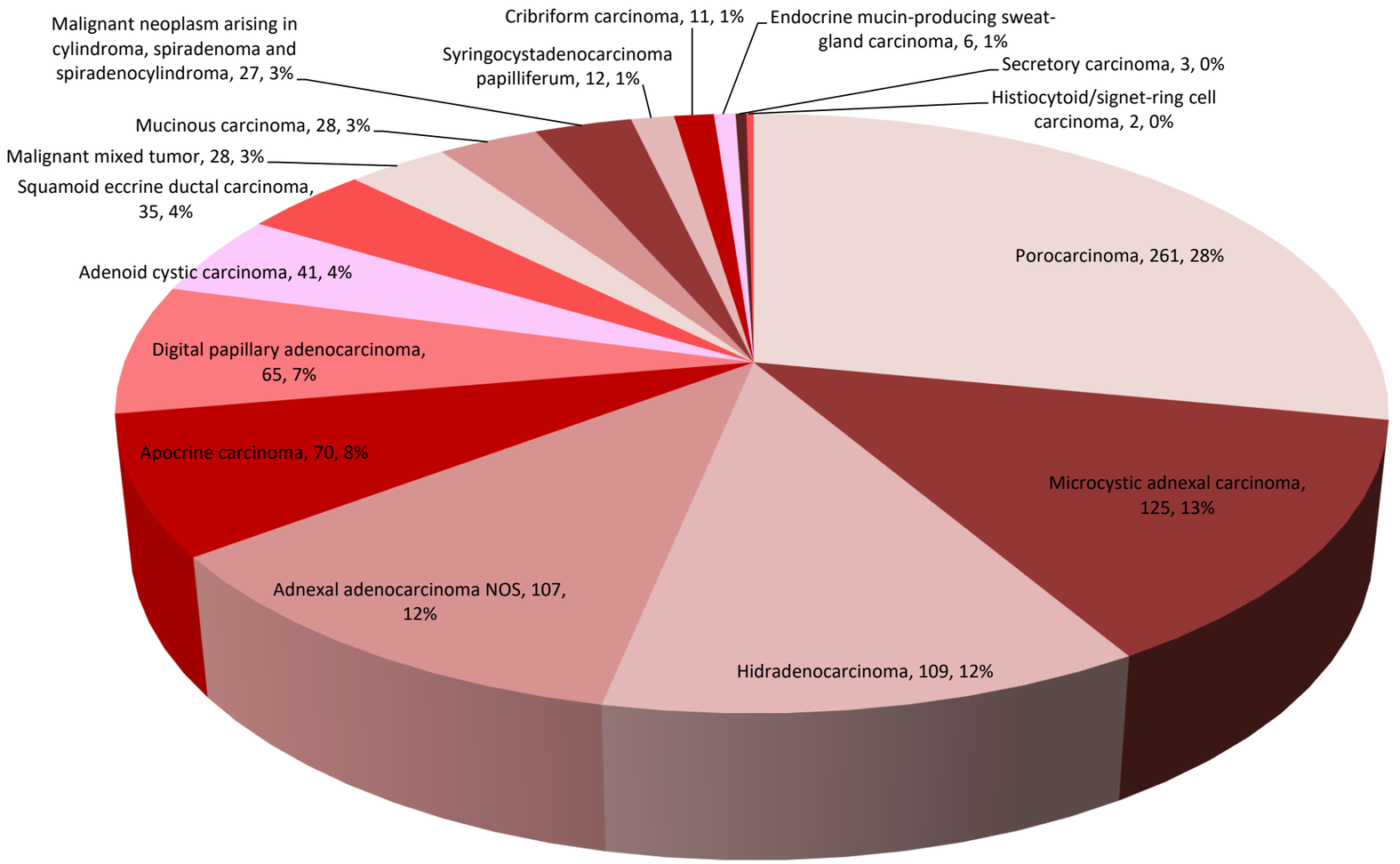
A


Extramammary Paget and adenocarcinoma of anogenital mammary-like glands, 212, 10%
Myoepithelial carcinoma, 20, 1%
Adnexal carcinoma, complex/unclassified, 27, 1%
Sebaceous carcinoma, 238, 11%
Sweat gland carcinoma, 930, 42%
Hair follicle carcinoma, 778, 35%

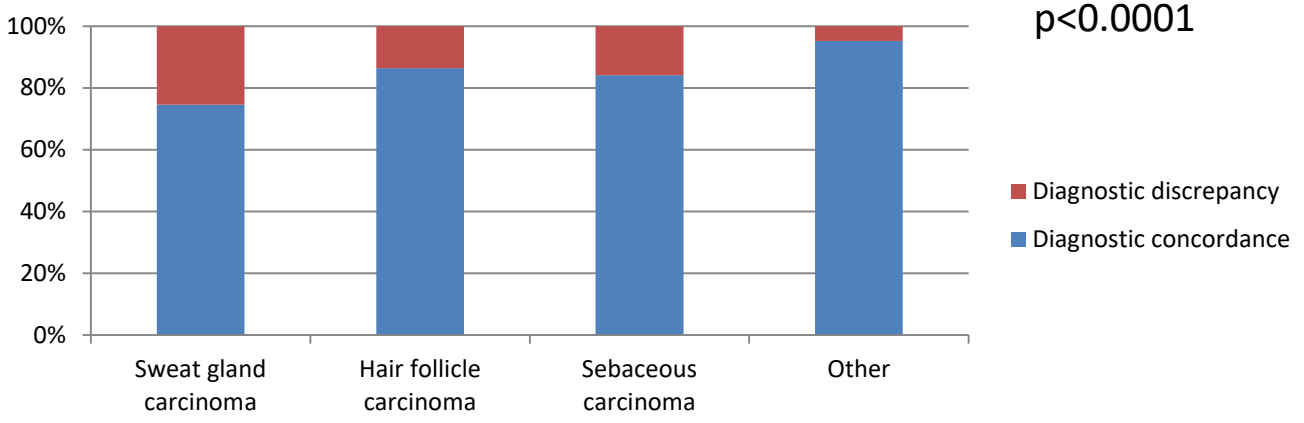
B


Hair follicle carcinoma, unclassified, 36, 5%
Trichilemmal carcinoma, 19, 3%
Pilomatrical carcinoma, 17, 2%
Proliferating trichilemmal tumor, 135, 17%
Trichoblastic carcinoma/carcinosarcoma, 571, 73%

C


Malignant neoplasm arising in cylindroma, spiradenoma and spiradenocylindroma, 27, 3%
Cribriform carcinoma, 11, 1%
Endocrine mucin-producing sweat-gland carcinoma, 6, 1%
Syringocystadenocarcinoma papilliferum, 12, 1%
Secretory carcinoma, 3, 0%
Histiocytoid/signet-ring cell carcinoma, 2, 0%
Mucinous carcinoma, 28, 3%
Malignant mixed tumor, 28, 3%
Squamoid eccrine ductal carcinoma, 35, 4%
Adenoid cystic carcinoma, 41, 4%
Digital papillary adenocarcinoma, 65, 7%
Apocrine carcinoma, 70, 8%
Porocarcinoma, 261, 28%
Microcystic adnexal carcinoma, 125, 13%
Adnexal adenocarcinoma NOS, 107, 12%
Hidradenocarcinoma, 109, 12%

A



B

Diagnostic changes involving sweat gland differentiation (in referral diagnosis, expert diagnosis or both)

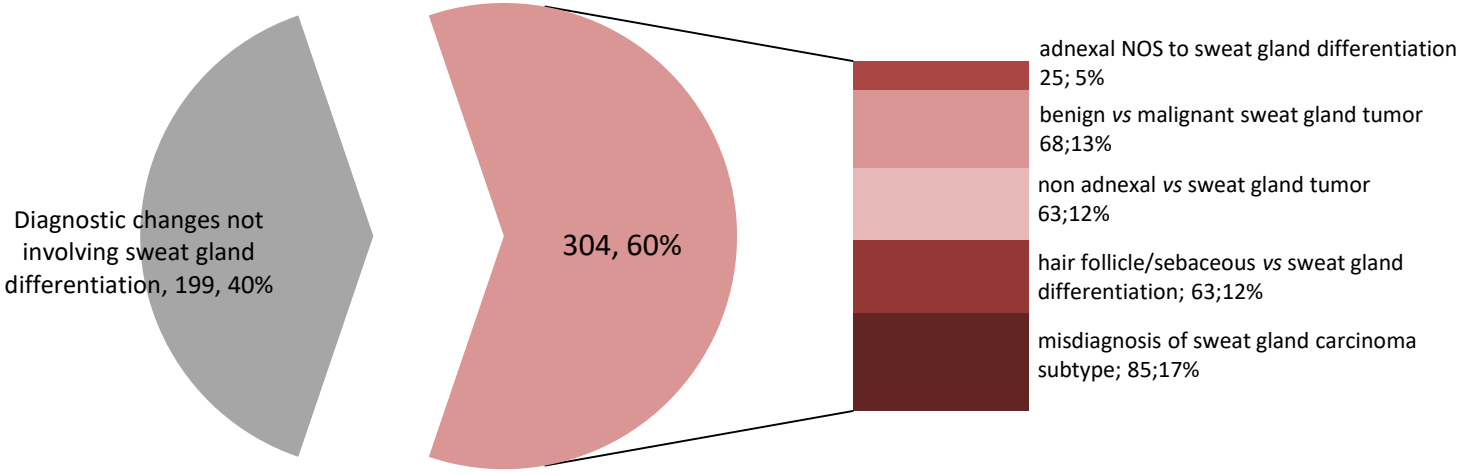


Table 1. Comparison of referral and expert diagnoses among the 2,363 patients with comparable diagnoses.

Main categories of expert diagnosis	**Overall concordance**	
	No.	**%**
Sweat gland carcinomas		
Adnexal adenocarcinoma NOS	57/89	64.0%
MAC	101/116	87.1%
Porocarcinoma	210/249	84.3%
Malignant neoplasm arising in cylindroma, spiradenoma and spiradenocylindroma	12/25	48.0%
Malignant Mixed Tumor	17/23	73.9%
Hidradenocarcinoma	60/89	67.4%
Mucinous carcinoma	25/27	92.6%
Endocrine mucin-producing sweat gland carcinoma	4/6	66.7%
Digital papillary adenocarcinoma	37/57	64.9%
Adenoid cystic carcinoma	24/38	63.2%
Apocrine carcinoma NOS	38/56	67.9%
Squamoid eccrine ductal carcinoma	25/31	80.7%
Syringocystadenocarcinoma papilliferum	6/11	54.6%
Secretory carcinoma	0/3	0.0%
Cribriform carcinoma	6/11	54.6%
Histiocytoid/signet-ring cell carcinoma	1/1	100%
Hair follicle carcinomas		
Pilomatrical carcinoma	11/16	68.8%
Proliferating trichilemmal tumor	116/124	93.6%
Trichoblastic carcinoma/carcinosarcoma	469/533	88.0%
Trichilemmal carcinoma	11/18	61.1%
Hair follicle carcinoma, other/unclassifiable	19/34	55.9%
Sebaceous carcinoma	185/220	84.1%
Site-specific carcinomas		
Extramammary Paget disease	205/207	99.0%
Adenocarcinoma of anogenital mammary-like glands	1/2	50.0%
Myoepithelial carcinoma	9/15	60.0%
Adnexal carcinoma, complex/unclassifiable	11/19	57.9%
Other diagnoses*	190/343	55.4%
Total	1,850/2,363	78.3%

NOTE. The 201 patients sent without referral diagnosis have been excluded. The concordance rate (No. and %) was established as the number of patients of each carcinoma subtype with the same diagnosis from both the referral and expert pathologists among the total number of that subtype according to expert review.

Abbreviations: MAC, microcystic adnexal carcinoma; NOS, not otherwise specified

*This category includes final expert diagnosis of benign adnexal tumors, basal cell carcinomas, squamous cell carcinomas, cutaneous metastases, Merkel cell carcinomas, and melanomas.

Table 2. Analysis of changes between referral and expert diagnoses in the 503 discordant cases.

Type of diagnostic change	**Diagnostic changes among all diagnostic changes**		**Percentage among all patients (n=2,363)**
	No.	**%**	
Unclassified adnexal carcinoma to classified adnexal carcinomas	**46**	**9.1%**	**2.0%**
Misclassification of adnexal carcinoma subtypes	**176**	**35.0%**	**7.5%**
Sweat gland to hair follicle differentiation or vice versa	45	8.9%	1.9%
Sweat gland to sebaceous differentiation or vice versa	18	3.6%	0.8%
Sebaceous to hair follicle differentiation or vice versa	9	1.8%	0.4%
Misclassification in sweat gland carcinoma, with high predicted clinical impact	42	8.4%	1.8%
Misclassification in sweat gland carcinoma, with low predicted clinical impact	43	8.6%	1.8%
Misclassification in hair follicle carcinoma	19	3.8%	0.8%
Malignant to benign adnexal lesions or vice versa	**109**	**21.7%**	**4.6%**
Sweat gland tumors	68	13.5%	2.9%
Sebaceous tumors	18	3.6%	0.8%
Hair follicle tumors	23	4.6%	1.0%
Adnexal carcinomas to other malignancies or vice versa	**164**	**32.6%**	**6.9%**
Adnexal carcinoma to SCC or vice versa	71	14.1%	3.0%
Adnecal carcinoma to BCC or vice versa	69	13.7%	2.9%
Adnexal carcinoma to cutaneous metastasis or vice versa	9	1.8%	0.4%
Adnexal carcinoma to other skin malignancy or vice versa	15	3.0%	0.6%
Adnexal carcinomas to other benign conditions or vice versa	**8**	**1.6%**	**0.3%**
Total changes in diagnosis	503	100%	21.3%

NOTE. The 201 patients submitted without diagnosis have been excluded.

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Table 3. Changes between referral and expert diagnoses for patients sent with a formal diagnosis and patients sent with a provisional diagnosis for expert second opinion.

Type of diagnostic change	**All eligible patients (n=2,363)**			
	Patients sent with a formal diagnosis (n=1,345)		**Patients sent with a provisional diagnosis for expert second opinion (n=1,018)**	
	No.	**%**	**No.**	**%**
Unclassified adnexal carcinoma to classified adnexal carcinomas	**1**	**0.1**	**45**	**4.4**
Misclassification of adnexal carcinoma subtypes	**20**	**1.5**	**156**	**15.3**
Sweat gland to hair follicle differentiation or vice versa	3	0.2	42	4.1
Sweat gland to sebaceous differentiation or vice versa	5	0.4	13	1.3
Sebaceous to hair follicle differentiation or vice versa	0	0	9	0.9
Misclassification in sweat gland carcinoma, with high predicted clinical impact	6	0.5	36	3.5
Misclassification in sweat gland carcinoma, with low predicted clinical impact	3	0.2	40	3.9
Misclassification in hair follicle carcinoma	3	0.2	16	1.6
Malignant to benign adnexal lesions or vice versa	**3**	**0.2**	**106**	**10.4**
Sweat gland tumors	3	0.2	65	6.4
Sebaceous tumors	0	0	18	1.8
Hair follicle tumors	0	0	23	2.3
Adnexal carcinomas to other malignancies or vice versa	**14**	**1.0**	**150**	**14.7**
Adnexal carcinoma to SCC or vice versa	4	0.3	67	6.6
Adnecal carcinoma to BCC or vice versa	10	0.7	59	5.8
Adnexal carcinoma to cutaneous metastasis or vice versa	0	0	9	0.9
Adnexal carcinoma to other skin malignancy or vice versa	0	0	15	1.5
Adnexal carcinomas to other benign conditions or vice versa	**0**	**0**	**8**	**0.8**
Total changes in diagnosis	38	2.8	465	45.7

NOTE. The 201 patients submitted without diagnosis have been excluded.

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.