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## ORIGINAL ARTICLE

# Radiotherapy and prognostic factors in adnexal carcinomas: A retrospective study of 657 patients from the French CARADERM network

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## Abstract

**Background:** Cutaneous adnexal carcinomas are a heterogeneous group of rare neoplasms. Surgical excision is the first-line treatment in localized stage. The use and effectiveness of radiotherapy have not been thoroughly evaluated in these neoplasms.

**Objectives:** The present work analyses prognostic factors on outcomes in skin adnexal carcinomas, based on data from the CARADERM (Cancers Rares DERMatologiques) database.

**Methods:** Data were collected retrospectively including demographic data, tumour types and therapeutic characteristics of all patients included in the CARADERM database, with at least one informative follow-up visit. Analyses were performed on three populations: patients with complete resection of the primary tumour (ADJ/primary population), patients achieving complete remission after complete resection of a recurrent tumour (ADJ/recurrent population) and patients with unresectable locally advanced or metastatic tumours (ADV/MET population). Overall and recurrence/progression-free survivals at 3-year were analysed using Cox regression models.

**Results:** Radiotherapy did not affect overall survival (OS) in the ADJ/primary population. Adjusted recurrence-free survival (RFS) was significantly lower in the radiotherapy group in ADJ/primary group. Older patients had significantly poorer OS and RFS. Tumour size and immunosuppression were significantly associated with poorer RFS only. Radiotherapy had no effect on OS and RFS in the ADJ/recurrent population. Age was the only factor associated with a poorer OS. Radiotherapy was significantly associated with longer progression-free survival (PFS) in age-sex adjusted analysis in the ADV/MET population, without effect on OS.

**Conclusions:** Our study shows that age, tumour size and immunosuppression are significantly associated with survival in localized adnexal carcinomas. Radiotherapy may improve PFS in the ADV/MET population but not in localized and recurrent carcinomas after complete excision.

For affiliations refer to page 7.

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## INTRODUCTION

Cutaneous adnexal carcinomas include many various types and subtypes of rare cutaneous neoplasms. These carcinomas present with differentiation towards the hair follicle, the eccrine and apocrine sweat glands and the sebaceous glands, respectively. This group displays over 20 histological subtypes according with the 2022 OMS classification.<sup>1</sup>

Due to their rarity and diversity, adnexal carcinomas are of difficult diagnosis and their therapeutic management remains unsettled. The absence of established guidelines is due to the lack of strong comparative evidence regarding treatment strategies, though surgery remains the first-line treatment in localized stage.<sup>2</sup>

While surgery for primary tumour and lymph node management for adnexal carcinomas and systemic treatment for trichoblastic carcinomas have been recently evaluated, survival outcomes with radiotherapy have never been analysed.<sup>2,7,8</sup>

The CARADERM (Cancers RAres DERMatologiques) network was created in France in order to obtain a pathological expert review and multidisciplinary clinical guidance for treatment. CARADERM is a two-level expert network with multiple local experts and a national multidisciplinary board, composed each of pathologists and clinicians. Adnexal carcinomas, issued from pathological and clinical centres, constitute the ongoing national CARADERM database, compiling nationwide retrospective and prospective data<sup>9</sup> (granted by the French National Institute for Cancer, INCa).

We performed a retrospective multicentric study to evaluate the impact of radiotherapy and other prognostic factors on cutaneous adnexal carcinomas outcomes.

## MATERIALS AND METHODS

Data were collected from the CARADERM database, including cases from March 2014 to February 2021, sent for referral from 38 clinical centres and 22 pathological centres.<sup>9</sup> Oral consent was obtained from each patient at inclusion in the database. Each case sent by non-expert pathologists or clinicians was systematically reviewed by CARADERM pathologists for pathological diagnosis validation. Each participating clinical centre organizes regular multidisciplinary tumours boards, and all therapeutic managements were validated by either regional or national multidisciplinary tumour boards, involving at least one onco-dermatologist, one surgical expert and one radiotherapy expert.

The present study included all patients presenting with an adnexal carcinoma of any size and stage, with at least one follow-up visit, excluding patients with sebaceous carcinomas and extramammary Paget disease. Indeed, these carcinomas deserve particular management and are associated with particular syndromes or secondary neoplasms. Tumours with uncertain diagnosis were excluded.<sup>10,11</sup> Patients without clear information on radiotherapy management or response after surgical management were excluded.

Each eligible patient was assigned in one of the three following populations according to his disease status. The ADJ/primary population included all patients with primary tumours treated with complete surgical excision (TxN0M0 upon TNM classification). The ADJ/recurrent population included all patients with at least one recurrence locally or to other sites treated with surgery and achieving complete remission. The ADV/MET population included all patients without complete remission, that is, an active disease with local, regional or distant locations.

Demographic data (age, sex and immunosuppression), tumour characteristics (size, histological subtype and TNM classification), treatment data (surgery and/or radiotherapy) and survival outcomes were retrieved from the CARADERM database. Descriptive analyses were performed for overall survival (OS), recurrence-free survival (RFS) in ADJ/primary and ADJ/recurrent populations and progression-free survival (PFS) in ADV/MET population. OS and RFS were defined in the ADJ/primary population from the date of onset of the primary tumour to the date of death, first recurrence or the last follow-up. OS and RFS were defined in the ADJ/recurrent population from the date of first recurrence to the date of death, second recurrence or last follow-up. PFS was defined from the date of inclusion to the date of first progression, death or last follow-up in the ADV/MET population.

Categorical variables were expressed as numbers (percentage) and quantitative variables as median [range]. Median follow-up was estimated using the inverse Kaplan–Meier method. OS, PFS and RFS, according to the use of radiotherapy, were described using the Kaplan–Meier method, considering death, death or progression, and death or relapse as the event of interest, respectively. Due to the low number of radiotherapy-treated patients in ADJ/primary and ADJ/recurrent populations and a low number of deaths, statistical comparisons between patients treated and not treated by radiotherapy could not be performed, whatever the study population regarding OS. In each population separately, the association of radiotherapy with RFS or PFS was analysed using unadjusted and age-sex-adjusted Cox regression models. Hazards ratios (HR) are presented with their 95% confidence interval (95%CI) as effect size, using the group without radiotherapy as the reference group. For each model, proportional hazards assumptions for radiotherapy were performed using Schoenfeld residual plots. All statistical tests were performed at the two-tailed  $\alpha$  level of 0.05 using SAS software, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

Upon the 4181 patients with adnexal carcinoma included in the CARADERM database at the date of analyses, 657 patients fulfilled eligibility criteria and were included in the three populations, with 516 patients in the ADJ/primary, 61 in the ADJ/recurrent and 80 in the ADV/MET populations. Flowchart according to STROBE guidelines is presented in [Figure S1](#). Characteristics of each population

are described in Table 1. Tumour subtype repartition is presented in Table S1.

Median follow-ups were 25 months (interquartile range, IQR, 15–35 months) in the ADJ/primary population, 57 months (IQR 31–109 months) in the ADJ/recurrent population and 36 months (IQR 22–52 months) in the ADV/MET population. During the 3-year follow-up, 31 (6.0%), 4 (6.6%) and 20 (25%) deaths occurred in the ADJ/primary, ADJ/recurrent and ADV/MET populations, respectively.

In the ADJ/primary population, 12 patients were treated with radiotherapy and 502 patients did not. Patients and tumour characteristics according to radiotherapy status are presented in Table 1. Detailed characteristics of patients treated with radiotherapy are presented in Table S2. Tumours treated with radiotherapy had more frequently lymphovascular infiltration (16.7% vs. 3.8%) or perineural invasion (41.7% vs. 7.3%) than tumours that did not receive radiotherapy. The 3-year death rate was 0% in the radiotherapy group and 9.3% in the no radiotherapy group (31 events) (Figure 1a). The 3-year recurrence cumulative incidence was 37.5% in the radiotherapy group (4 events) and 15.7% in the no radiotherapy group (57 events) (Figure 2a). The non-significant association of radiotherapy with shorter RFS in unadjusted analysis reached the significance level after pre-specified adjustment on age and sex (adjusted HR, 3.03; 95% CI, 1.09 to 8.40,  $p = 0.033$ , Table 2).

In the ADJ/recurrent population, 12 patients were treated with radiotherapy and 49 patients did not. Patients and tumour characteristics according to radiotherapy status are presented in Table 1. Detailed characteristics of tumours treated with radiotherapy are presented in Table S3. Recurrence site was local (inside the surgical bed) in four cases, regional (lymph node) in seven cases and both local and regional in one case. No case exhibited in-transit metastasis. The 3-year death rate from all causes was 8.3% in the radiotherapy group (one event) and 7.0% in the no radiotherapy group (three events) (Figure 1b). The 3-year recurrence cumulative incidence was 33.3% in the radiotherapy group (3 events) and 38.5% in the no radiotherapy group (16 events) (Figure 2b). In the unadjusted analysis and in age-sex adjusted analyses, radiotherapy was not associated with RFS (Table 2).

In the ADV/MET population, 24 patients were treated with radiotherapy and 56 patients did not. Patients and tumour characteristics according to radiotherapy status are presented in Table 1. Detailed characteristics of patients treated with radiotherapy are presented in Table S4. Among the 24 patients treated with radiotherapy, 10 had a localized primary tumour, 5 had a localized recurrent tumour and 9 had a metastatic disease among which 4 were exclusively nodal. Among the five patients with extra-nodal involvement, only one patient received radiotherapy on all its tumoral sites (single metastasis). Systemic treatments received are presented in Table S5. Total percentage of patients receiving systemic treatments was similar in the two groups (50% in the radiotherapy group vs. 48.2% in the no radiotherapy group), with conventional chemotherapies being more

frequent in the radiotherapy group, 33.3% vs. 17.8% in the no radiotherapy group. The 3-year death rate was 25.2% in the radiotherapy group (5 events) and 32.6% in the no radiotherapy group (15 events) (Figure 1c). The 3-year progression cumulative incidence was 52.1% in the radiotherapy group (9 events) and 69.2% in the no radiotherapy group (33 events) (Figure 2c). Radiotherapy reached a significant association with better PFS in age-sex adjusted analysis (adjusted HR: 0.45; 95% CI: 0.21–0.95,  $p = 0.036$ , Table 2). To note, in the radiotherapy group, 6 of the 10 progressions occurred outside of irradiated areas, including 1 local, and 5 distant, among which 3 were already present prior radiotherapy.

Univariate analyses were performed to find factors associated with death and relapse in each population. In the ADJ/primary population, OS and RFS at the 3-year endpoint were, respectively, 94.0% and 88.2%. Age at diagnosis was significantly associated with both death and relapse. No other evaluated factor was associated with a significant difference in OS. HR of immunosuppression for OS was 2.334 (95% CI 0.880–6.246,  $p = 0.0885$ ). Tumour size and immunosuppression were significantly associated with reduced RFS, with HR of 1.016 (95% CI 1.007–1.026,  $p = 0.0009$ ) and 2.38 (1.195–4.749,  $p = 0.0137$ ), respectively. Results are presented in Table S6a,b.

In the ADJ/recurrent population, OS and RFS at the 3-year endpoint were 93.4% and 67.8%, respectively. Age at diagnosis was significantly associated with death only. Other evaluated factors (sex and immunosuppression) were not associated with significant differences in OS or RFS. HR of age for RFS was 1.022 (95% CI 0.991–1.055,  $p = 0.1667$ ). Results are presented in Table S7a,b.

In the ADV/MET population, OS and RFS at the 3-year endpoint were, respectively, 75% and 47.5%. Age at diagnosis was significantly associated with both death and progression with HR of 1.050 (95% CI 1.005–1.097,  $p = 0.0308$ ) and 1.031 (95% CI 1.001–1.058,  $p = 0.0191$ ), respectively. HR for metastatic stage (M1) was 2.097 (95% CI 0.803–5.474,  $p = 0.1304$ ) for OS and 2.020 (95% CI 1.028–3.969,  $p = 0.0414$ ) for PFS. The presence of immunosuppression or not was missing for more than 20% of patients in this population (similar in both groups) and was not included in statistical analysis. Results are presented in Table S8a,b.

## DISCUSSION

Skin adnexal carcinomas are commonly treated by surgical excision in a curative intent. Most patients achieved complete remission after the surgical procedure, with very good overall survival, as demonstrated in large retrospective studies<sup>2,12,13</sup> and in the present study. Despite this favourable survival outcome, a few patients, estimated less than 5%, have poorer prognosis associated with locally advanced, nodal or metastatic diseases.<sup>2</sup> International guidelines for the management of skin adnexal neoplasms either in localized, advanced or metastatic stages have not been established to date. Radiotherapy has been proposed as an adjuvant treatment

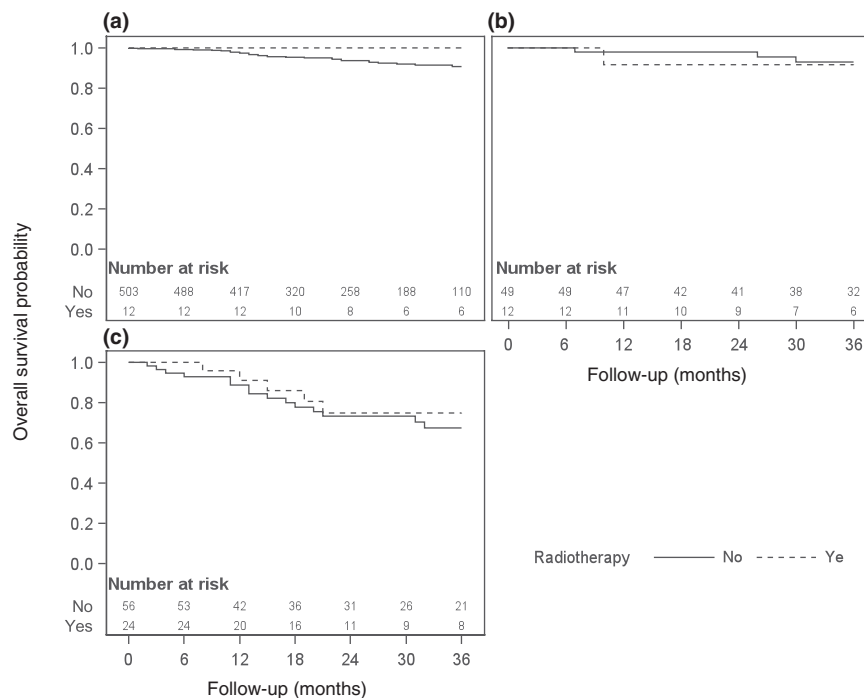
**TABLE 1** Characteristics of patients according to radiotherapy in the three different populations.

	ADJ/primary population		ADJ/recurrent population		ADV/MET population	
	Radiotherapy		Radiotherapy		Radiotherapy	
	No (n = 504)	Yes (n = 12)	No (n = 49)	Yes (n = 12)	No (n = 56)	Yes (n = 24)
Age						
Years	68 [21–100]	66.5 [47–86]	67 [20–94]	63 [44–94]	73 [18–94]	73.5 [33–95]
Sex						
Male	285 (56.5)	7 (58.3)	31 (63.3)	6 (50)	31 (55.4)	16 (66.7)
Female	219 (43.5)	5 (41.7)	18 (36.7)	6 (50)	25 (44.6)	8 (33.3)
Immunosuppression						
No	331 (65.7)	9 (75.0)	35 (71.4)	11 (91.7)	41 (73.2)	16 (66.7)
Yes	33 (6.5)	2 (16.7)	5 (10.2)	1 (8.3)	2 (3.8)	3 (12.5)
Unknown	140 (27.8)	1 (8.3)	9 (18.4)	0 (0)	13 (23.2)	5 (20.8)
Tumour size						
mm	14 [0–155]	17 [5–100]				
Tumour localization						
Head & Neck	247 (49.0)	7 (58.3)	33 (67.3)	3 (25.0)		
Trunk	73 (14.5)	4 (33.3)	7 (14.3)	5 (41.7)		
Upper limb	87 (17.3)	1 (8.3)	5 (10.2)	3 (25.0)		
Lower limb	81 (16.1)	0 (0)	4 (8.2)	0 (0)		
Genitals/Buttocks	16 (3.2)	0 (0)	0 (0)	1 (8.3)		
T stage						
1	247 (49.0)	7 (58.3)				
2	72 (14.3)	0				
3	23 (4.6)	0				
4	38 (7.5)	5 (41.7)				
5	8 (1.6)	0				
Unknown	116 (23.0)	0				
N stage						
0	0	0	1 (2.0)	0 (0)	31 (55.3)	11 (45.8)
1	0	0	8 (16.3)	8 (66.7)	16 (28.6)	8 (33.3)
2	0	0	40 (81.6)	4 (33.3)	9 (16.1)	5 (20.8)
M stage						
0	0	0	47 (95.9)	12 (100)	46 (82.1)	19 (79.2)
1	0	0	2 (4.1)	0 (0)	10 (17.9)	5 (20.8)
Surgery						
Standard technique	436 (86.5)	11 (91.7)				
Micrographic	55 (10.9)	0 (0)				
Unknown	13 (2.6)	1 (8.3)				
Surgical clinical margins						
<1 cm	190 (37.7)	4 (33.3)				
1–2 cm	189 (37.5)	6 (50.0)				
2–3 cm	50 (9.9)	1 (8.3)				
>3 cm	2 (0.4)	0 (0)				
Unknown	72 (14.3)	1 (8.3)				
Infiltration depth						
Superficial/pagetoid	30 (6.0)	0 (0)				

**TABLE 1** (Continued)

	ADJ/primary population		ADJ/recurrent population		ADV/MET population	
	Radiotherapy		Radiotherapy		Radiotherapy	
	No (n=504)	Yes (n=12)	No (n=49)	Yes (n=12)	No (n=56)	Yes (n=24)
Dermis	196 (38.9)	3 (25.0)				
Hypodermis	126 (25.0)	2 (16.7)				
Subfascial	42 (8.3)	5 (41.7)				
Unknown	91 (18.1)	1 (8.3)				
Lymphovascular infiltration						
No	451 (89.5)	9 (75.0)				
Yes	19 (3.8)	2 (16.7)				
Unknown	14 (2.8)	0 (0)				
Perineural invasion						
No	435 (86.3)	6 (50.0)				
Yes	37 (7.3)	5 (41.7)				
Unknown	13 (2.6)	1 (8.3)				

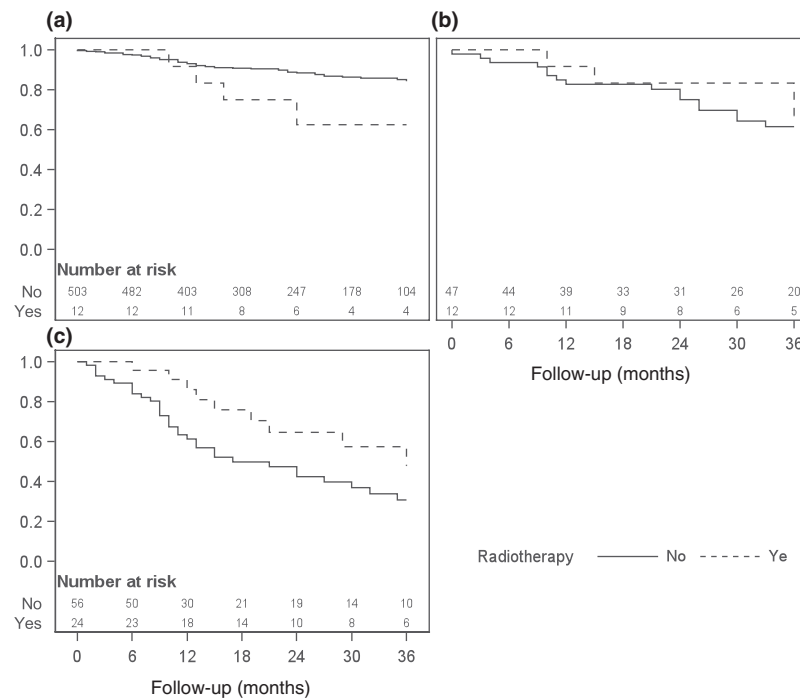
Note: Values are presented as frequency (percentage) or median [range].



**FIGURE 1** Overall survival curves according to radiotherapy groups in the three populations. (a) ADJ/primary population. (b) ADJ/recurrent population. (c) ADV/MET population.

after surgery or as a unique treatment for different tumours such as eccrine porocarcinoma, hidradenocarcinoma or microcystic adnexal carcinoma.<sup>3-5</sup> Its modalities have been detailed upon a recent review of case reports.<sup>6</sup> Yet, the impact of radiotherapy on outcomes of skin adnexal neoplasms has never been evaluated to the best of our knowledge.

Our study suggested that radiotherapy was significantly associated with a longer PFS in incompletely resected locally advanced or oligometastatic skin adnexal neoplasms compared with patients who did not receive radiotherapy. To note, our results might be underestimating radiotherapy impact, since among the 10 patients in progression in the



**FIGURE 2** Relapse-free survival or progression-free survival curves according to radiotherapy groups in the three populations. (a) ADJ/primary population. (b) ADJ/recurrent population. (c) ADV/MET population.

**TABLE 2** Impact of radiotherapy on 3-year relapse-free survival or progression-free survival in the three populations.

Population	No radiotherapy group	Radiotherapy group	Unadjusted HR (95% CI)	<i>p</i>	Adjusted HR (95% CI)	<i>p</i>
ADJ/primary	57 (15.7%)	4 (37.5%)	2.74 (0.99–7.55)	0.052	3.03 (1.09–8.40)	0.033
ADJ/recurrent	16 (38.5%)	3 (33.3%)	0.71 (0.21–2.44)	0.59	0.78 (0.22–2.72)	0.69
ADV/MET	33 (69.2%)	9 (52.1%)	0.50 (0.24–1.05)	0.068	0.45 (0.21–0.95)	0.036

Note: Values are number of events (3-year cumulative incidence, %). Hazard ratios were calculated using no radiotherapy group as reference. Adjusted for age and sex.

radiotherapy group of the ADV/MET population, only 4 involved areas treated with radiotherapy, making progression rate 16.7% including exclusively sites treated with radiotherapy. This favourable outcome on PFS was not confirmed in the adjuvant setting for completely resected primary or recurrent adnexal carcinomas. Radiotherapy in completely resected primary carcinomas was associated with a shorter PFS after pre-specified adjustment on age and sex. This questionable result may be explained by inherent selection bias in our retrospective study and by the hypothesis that radiotherapy is possibly more frequently used for more aggressive skin adnexal neoplasm with higher recurrent risk and poorer prognosis. Indeed, perineural invasion and lymphovascular infiltration were more frequent in the radiotherapy group of the ADJ/local population compared to the no radiotherapy group. This finding is in accordance with a recent observational study on spiradenocarcinoma in which the authors showed similar conclusions.<sup>14</sup>

As radiotherapy is a locoregional treatment, the proper endpoints to evaluate its efficacy are RFS and PFS, contrary

to OS, especially in cases with metastatic diseases. As stated above, progression in the radiotherapy group of the ADV/MET population occurred mostly in sites that were not irradiated, reinforcing the idea that radiotherapy enables a local control in these patients. Improvement of PFS in localized diseases may have an impact on OS in this setting. However, our study failed at demonstrating any impact of radiotherapy on OS in all populations. This failure might be explained by the lack of power of our study. Indeed, the number of patients in radiotherapy sub-groups and the number of deaths were low, with a 94% OS, which is in accordance with previous studies.<sup>2</sup> This might be due to the lack of knowledge of the impact of radiotherapy in adnexal carcinomas, limiting its indication in multidisciplinary discussions. Once again, only case reports are available in the literature. Pejorative factors that could lead to the choice of adjuvant or first-line radiotherapy are tumour size, depth, invaded surgical margins, lymphovascular invasion and perineural involvement, as it is considered in squamous cell carcinomas.<sup>3,4</sup> These factors have only been studied for specific subtypes and seem

variable upon subtypes.<sup>8,15</sup> In the present study, all cases of completely resected tumours treated with adjuvant radiotherapy exhibited at least one of the pejorative prognostic factors discussed upwards.

The efficacy of several systemic treatments has been recently published in skin adnexal carcinomas.<sup>16,17</sup> Sonic hedgehog inhibitor vismodegib has shown promising efficacy in trichoblastic carcinoma.<sup>7</sup> Similarly, anti-PD1 inhibitors have shown favourable results in selected adnexal carcinomas (NCT03012581, Secured Access to Nivolumab for Adult Patients with Selected Rare Cancer Types, results unpublished). Interestingly, these emergent therapies were more frequently used in patients of the ADV/MET group that did not receive radiotherapy, which could even diminish the suggested impact of radiotherapy shown in our study. The efficacy of radiotherapy combined with cytotoxic agents, immunotherapies or targeted therapies warrants evaluation in the present setting.

Regarding prognostic factors, our study showed that age at diagnosis was significantly associated with both death and relapse in patients with skin adnexal carcinomas. Regarding OS, these findings differ from those of Avraham et al. in which age was not associated with 5-years OS after resection of eccrine carcinomas (HR 1.65, 95%CI 0.50–5.40,  $p=0.410$ ).<sup>12</sup> Nevertheless, our results are in accordance with those of Stam et al. upon multivariate analysis for OS in patients with invasive adnexal carcinoma (HR 1.08, 95% CI 1.07–1.09).<sup>13</sup> Our study shows that tumour size (T stage) and immunosuppression were significantly associated with reduced RFS in patients with localized primary adnexal carcinomas.

## CONCLUSION

Based on the present results, radiotherapy could be considered as an alternative treatment option for patients with locally advanced, incompletely resected or oligometastatic skin adnexal carcinomas. Adjuvant radiotherapy did not achieve significant efficacy in localized or recurrent completely resected tumours because of a probable lack of power in our study. The CARADERM group will investigate prognostic factors in particular specific subtypes in a near future in order to explore more precisely outcomes of patients with skin adnexal carcinomas.

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## CONFLICT OF INTEREST STATEMENT

All authors (RZ, SDall, MBB, NM, PS, NK, CL, OZ, MAA, JJG, JPA, EM, FGB, BC, GQ, FBP, SDala, OD, ED, LM, MB and TJ) have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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