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Squamoid eccrine ductal carcinoma: clinical, histological and immunohistochemical features

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Abstract

Squamoid eccrine ductal carcinoma (SEDC) is a cutaneous adnexal malignancy that is histologically challenging to distinguish from squamous cell carcinoma. We report three cases of this rare entity and review the present literature regarding clinical, histological, and immunohistochemical features. Patients presented with a single nodule or plaque lesion on their back and temple. The shave biopsies for Patient A and C were interpreted as SEDC. Patient B's initial shave biopsy was interpreted as probable surface of squamous cell carcinoma, and subsequent excision revealed SEDC. Ductal differentiation was confirmed by positive expression of epithelial membrane antigen and carcinoembryonic antigen immunostains in all three patients. Review of the 67 previously reported cases emphasizes the importance of diagnosing SEDC accurately and promptly given its potential for distant metastasis and mortality. Perineural or lymphatic invasion is associated with higher rate of recurrence or metastasis. There should be high pathologic suspicion for SEDC in an elderly patient presenting with a palpable lesion, even if located outside of the head and neck area, particularly when there is suggestion of ductal differentiation in a sample of a squamous neoplasm.

Keywords: adnexal carcinoma, ductal differentiation, eccrine, squamoid neoplasm

Introduction

Squamoid eccrine ductal carcinoma (SEDC) is a cutaneous adnexal malignancy. It is exceedingly rare, comprising less than 0.1% of the cutaneous tumors, although underreporting may contribute to its rarity. Since 1991, when it was first described [1], a total of 67 cases have been reported in the literature (**Table 1**). Squamoid eccrine ductal carcinoma demonstrates deep ductal and superficial squamous differentiation, which could mimic squamous cell carcinoma (SCC) on histologic evaluation of superficial biopsy specimens. Current data on this rare entity is lacking. We report three cases and review the literature to provide guidance on diagnosis, prognosis, and management.

Case Synopsis

Clinical presentations

Patient A was a 72-year-old man who presented with an irregularly shaped asymptomatic 1.5cm pink nodule on his left upper back with clinical differential diagnosis of a melanocytic nevus, scar, or SCC (**Figure 1A**). Patient B was a 74-year-old man who presented with a 1.5cm irregular and tender pink nodule with white scale on his right suprascapular region with clinical impression of an irritated seborrheic keratosis versus SCC (**Figure 1B**). Patient C was an 88-year-old woman who presented with a 2cm pink scaly plaque on her right temple that was suspicious for SCC (**Figure 1C**).

Histopathologic findings

A shave biopsy was performed for all three patients. Patient A's biopsy showed an infiltrative epithelioid tumor composed of nodules, nests, and cords of atypical cells with squamous and ductal

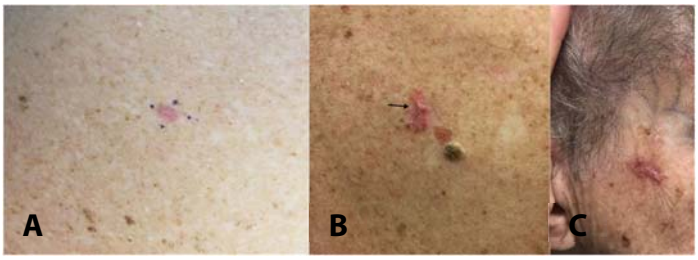

Figure 1. ***A)*** *Patient A presented with an irregularly shaped asymptomatic 1.5cm pink nodule on his left upper back.* ***B)*** *Patient B presented with a 1.5cm irregular and tender pink nodule with white scale on his right suprascapular region.* ***C)*** *Patient C presented with a two cm pink scaly plaque on her right temple.*

differentiation (**Figure 2A-D**). Epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) immunohistochemical (IHC) stains highlighted the intracytoplasmic lumina (**Figure 2E-F**). Patient B's initial sample showed surface of an atypical cystic and endophytic squamous proliferation, suggestive of surface of a well-differentiated SCC (**Figure 3A**). Subsequent excision showed a tumor composed of nests, cords, and strands of atypical cells with squamous and ductal differentiation, deeply infiltrating into the subcutis (**Figure 3B**). Although there was cystic-like growth with squamous differentiation within the superficial aspect of the tumor, the deeply infiltrative component revealed ductal differentiation with positive expression of EMA and CEA (**Figure 3C-F**). Positive expression of p63 and CK5, along with negative expression of CK7 and CK20, were consistent with a primary cutaneous origin. Patient C's biopsy showed an infiltrative tumor in the dermis with squamous and ductal differentiation and positive expression of EMA and CEA (**Figure 4A-F**).

Case outcomes

There was no evidence of vascular or perineural invasion in our three cases. Patients A and B underwent complete excision and no recurrence were noted three months and three years later, respectively. Patient C underwent Mohs micrographic surgery without recurrence within seven months after surgery.

Discussion

It is important to diagnose SEDC accurately and promptly given its potential for metastasis and mortality. Our review finds a mortality rate of 5%, which is likely an underestimate of the true rate given the limited available patient follow-up. Additionally, of the 49 previously reported cases for which follow-up was available, 18% recurred within 5 months to 2.7 years after initial diagnosis, 14% metastasized to lymph nodes, and 6% metastasized to distant sites (Table 1). These rates are greater than for SCC with 3% recurrence rate after Mohs surgery [2,3] and 4-9% metastatic rate [3,4]. Perineural or lymphovascular invasion was present in 20% of the reviewed cases and approximately 20% of cases with perineural invasion and 33% of cases with lymphatic invasion recurred or metastasized (Table 1), [5-35].

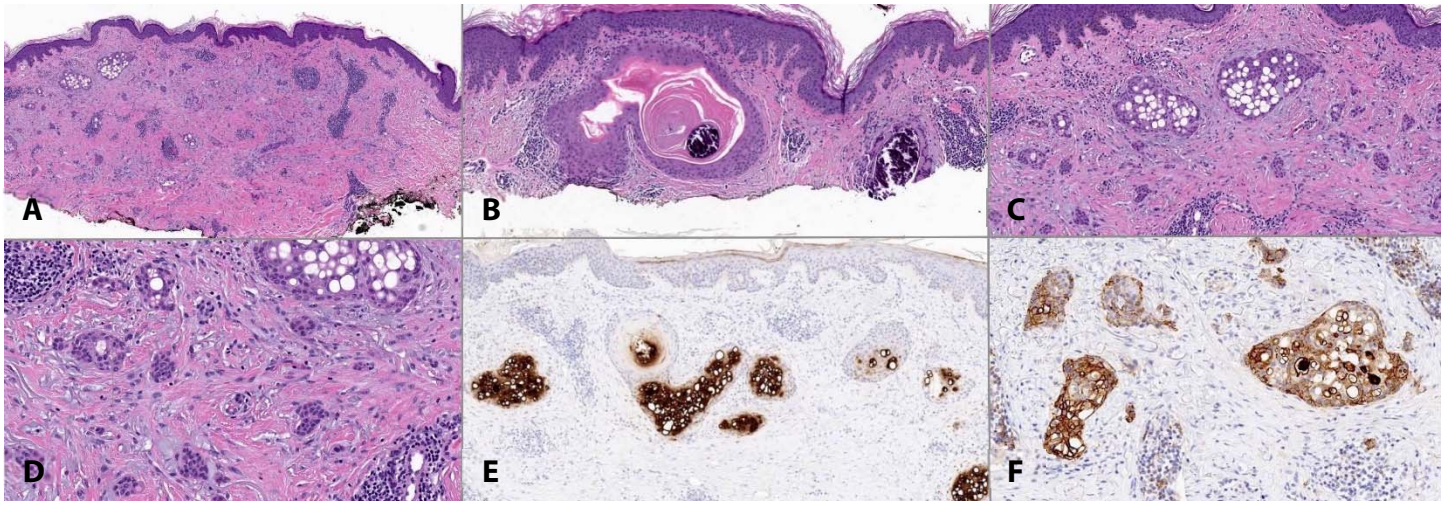

Figure 2. *Patient A.* ***A)*** *H&E section shows an infiltrative carcinoma composed of nests and cords of atypical cells with squamous and ductal differentiation, 40×; and* ***B)*** *superficial aspect of the tumor with cystic component, 200×. C,* ***D)*** *High-power illustrations show ductal differentiation;* ***C)*** *100×,* ***D)*** *400×. Immunostains highlight intracytoplasmic lumina with* ***E)*** *CEA, 100×; and* ***F)*** *EMA, 400×.*

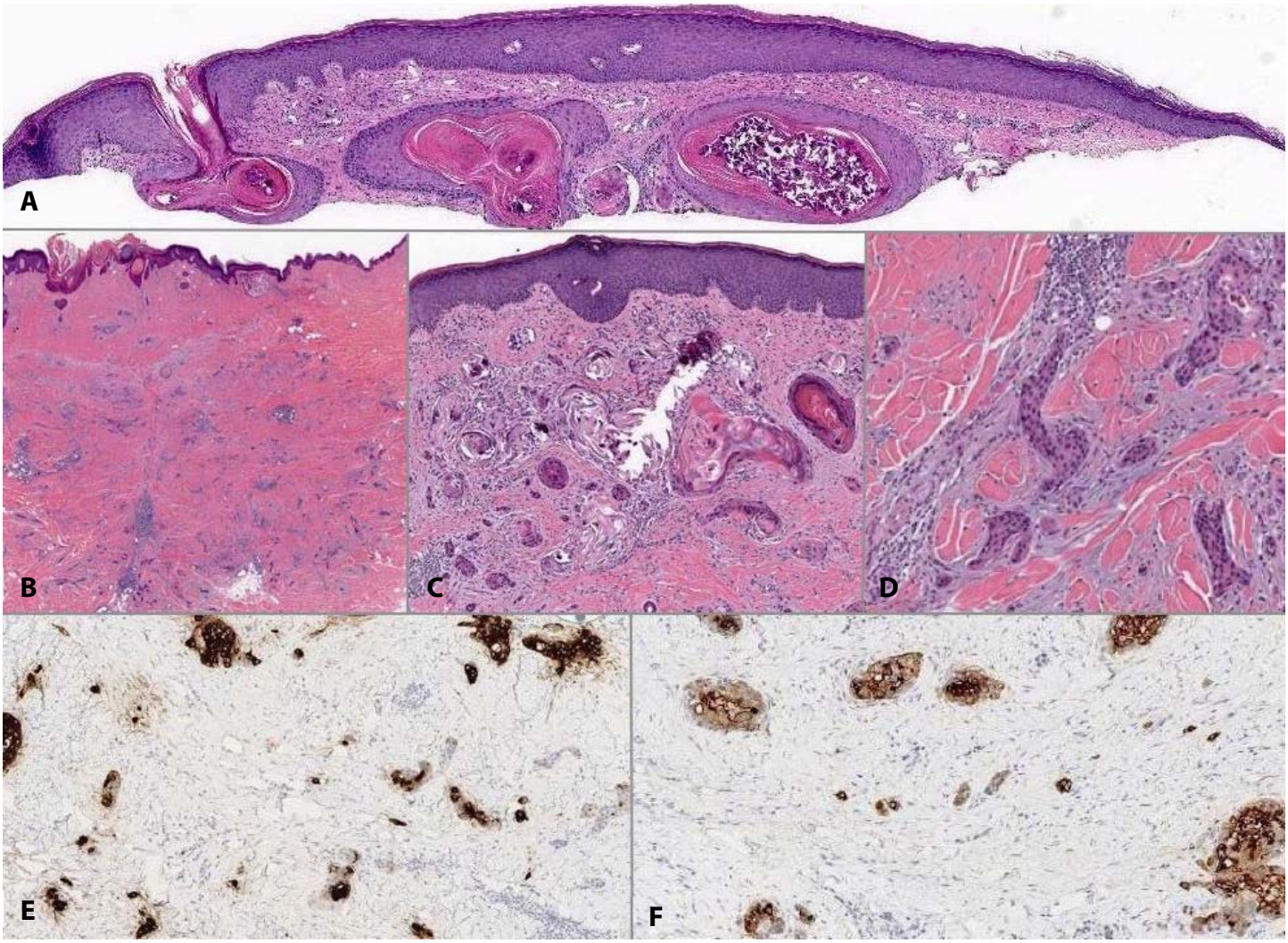

Figure 3. *Patient B.* ***A)*** *H&E section of the initial biopsy shows prominent cystic squamous appearance, 200×.* ***B)*** *The excision shows a tumor composed of nests, cords, and strands of atypical cells with squamous and ductal differentiation, infiltrating into the subcutis, 40×.* ***C)*** *While there is residual cystic-like growth with squamous differentiation within the superficial aspect of the tumor, the deep infiltrative component reveals ductal differentiation, 100×.* ***D)*** *High-power illustrations of ductal differentiation, 400×. Immunostains highlight intracytoplasmic lumina with* ***E)*** *CEA, and* ***F)*** *EMA immunostains. 100×.*

Clinically, SEDC most commonly presents as an asymptomatic irregularly-shaped palpable papule or nodule on the head of an elderly man. There is variation in size, ranging from 0.16cm to 7.8cm at the time of diagnosis. Location ranges from scalp to toe, notably with 36% of cases occurring outside the head and neck area, including 20% on the limbs and 14% on the trunk. The median age at the time of diagnosis is 77 years (range 10-96) and 56.25% of patients are men. Squamoid eccrine ductal carcinoma's low prevalence and non-specific clinical features that overlap with those of more common cutaneous malignancies could result in diagnostic delay. As dermoscopic findings have rarely been reported and vary, their utility in the diagnosis is not yet known [5,6]. There are no established risk factors, although rare cases in the setting of immunosuppression related to organ transplantation or leukemia have been reported [7].

Histologic examination remains the most important diagnostic tool for SEDC. Squamoid eccrine ductal carcinoma often deeply infiltrates within the dermis and, in up to 70% of cases, extends into the subcutaneous tissue. A case series found tumor thickness ranging from 0.15cm to 1.8cm, although it did not comment on any association with tumor behavior [8]. Most cases exhibit epidermal connection, often with no in situ component or one

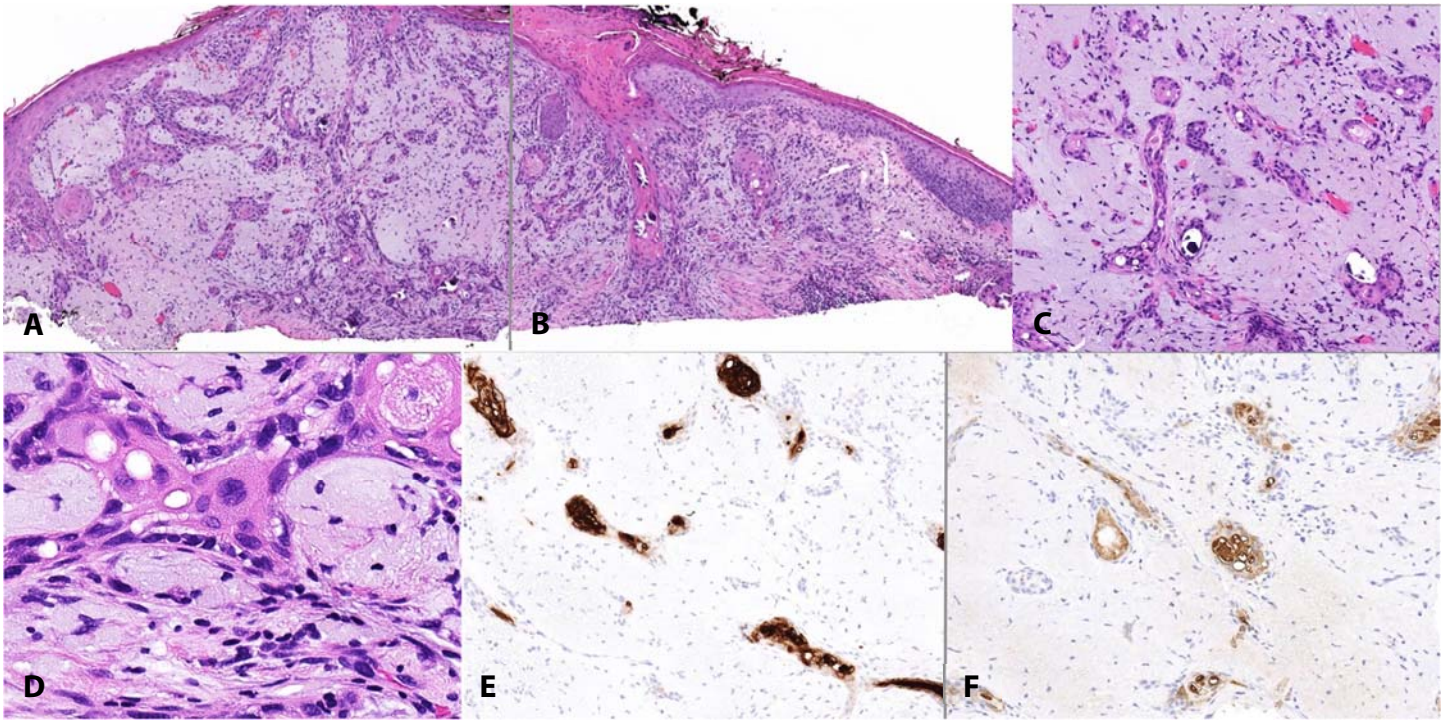

Figure 4. *Patient C.* ***A, B)*** *H&E section shows a tumor with squamous and ductal differentiation,* ***A, B)*** *100×.* ***C, D)*** *High-power illustrations of ductal differentiation;* ***C)*** *200×,* ***D)*** *400×. Intracytoplasmic lumina are highlighted by* ***E)*** *CEA, and* ***F)*** *EMA immunostains. 200×.*

that appears distinct from actinic keratosis or SCC in situ [8-10]. There is usually a biphasic growth pattern of nested and cystic squamous proliferation more superficially and ductal differentiation within the deeper aspects. The superficial squamoid nests may reveal keratinization, horn cysts, intercellular bridges, and squamous eddies [9]. The deeper aspect of the tumor with ductal differentiation is often composed of angulated basaloid cells with tubular structures in a desmoplastic stroma [11]. Thus, a superficial shave or punch biopsy that primarily captures the surface squamoid appearance could be indistinguishable from a well- or moderately-differentiated SCC, as occurred in several previously reported cases [10,12-16]. Although there is more distinction between SEDC and poorly-differentiated SCC, there were two cases of misinterpretation of SEDC as poorly-differentiated SCC [6,17]. In representative specimens, IHC stains can be critical for making the correct diagnosis. CEA and EMA highlight ductal differentiation in SEDC, whereas a similar staining pattern is not expected in SCC [10]. Although there have been no cases with both EMA and CEA stains being negative, negative expression of one of these stains alone does not exclude SEDC, as reported in four cases [13,18-20].

In addition to SCC, the histologic differential diagnosis includes microcystic adnexal carcinoma, porocarcinoma, and cutaneous metastasis [17,21]. Compared to SEDC, microcystic adnexal carcinoma is more common on perioral and periocular areas as well as nasolabial folds. It reveals a lower degree of cytologic atypia with prominent keratocysts in the dermis without epidermal connection and a deeper-seated component of infiltrative cords and ducts without squamoid differentiation [7,9,10,21,22]. Porocarcinoma generally arises in the setting of a poroma with uniform polygonal cells on distal extremities [10,11,21], and cutaneous metastasis could be distinguished according to their immunohistochemical staining pattern. Positive expression of p63 and CK5/6 in SEDC support primary cutaneous origin and negative expression of these markers has not been reported in SEDC [23].

There is no consensus on the management of SEDC, which is usually surgically removed. Of the eight cases treated with Mohs and sixteen cases treated with conventional excision, up to 12.5% and 31.25%, respectively, recurred or metastasized. Radiation has been used for SEDC that invaded into the neurovascular structures, failed multiple excisions, or

recurred. However, lack of sufficient data precludes assessment of potential benefits as recurrence and death related to disease progression in this setting have been also reported [24-25]. Imaging including MRI and CT-scan was utilized in five cases to assess the extent of primary, recurrent, or potentially metastatic SEDC [12,13,16,17,26,27]. With rate of metastasis to the lymph nodes being 14% and to distant sites being 6%, imaging could be beneficial especially in cases with neurovascular invasion. Sentinel lymph node biopsy was used for one case of SEDC with lymphatic invasion [17]. Recurrence occurred in 18% of cases and the shortest time to recurrence was five months.

Conclusion

In conclusion, despite there being over 60 reported cases of SEDC, it remains an under-considered diagnosis. Our literature review provides a detailed assessment of SEDC's clinical course, revealing a mortality rate of at least 5%, a metastasis rate of 16%, and a recurrence rate of 18%. We find that perineural and lymphatic invasion could be associated with higher risk of recurrence and metastasis. We emphasize the importance of biopsy technique to capture a fully representative sample and we highlight histopathologic differences between SEDC and other cutaneous neoplasms. There should be high pathologic suspicion for this neoplasm in an elderly patient presenting with a palpable tumor, even if located outside the head and neck area, particularly when there is suggestion of ductal differentiation in a partial biopsy sample of a squamous neoplasm.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Summary of current cases and the previously reported 67 cases of SEDC.*

Studies	Age/sex	Location	Size (cm)	PNI/LVI	Management and outcome
Patient A	72/M	Back	1.5	NA	Ex → no recurrence at 3mo
Patient B	74/M	Back	1.5	NA	Ex → no recurrence at 30mo
Patient C	88/F	Temple	2	NA	Mohs → FU NA
Yim et al. [12]	80/M	Ear	1.5	NA	CT scan → Ex → no recurrence at 9mo
Mckissack et al. [9]	91/F	Finger	2	NA	MRI → Amputation → PET/CT, met to LN at 3mo → died
Lobo-Jardim et al. [4]	76/F	Nose	NA	NA	Ex → FU NA
Jacob et al. [17]	77/M	Chest	5	PNI	Ex → LN and distant met → radical resection and LN dissection→ no recurrence at 60mo
Rovesti et al. [5]	75/M	Temple	2	PNI	Mohs → no recurrence at 12mo
Sharma et al. [27]	50/M	Scalp	1	NA	No recurrence at 5mo
Graham et al. [24]	80/M	Forehead	NA	NA	Mohs → no recurrence at 24mo
van der Horst et al. [21]	96/M	Forehead	1	NA	No recurrence at 28mo
	92/M	Sternum	2	NA	No recurrence at 8mo
	94/F	Cheek	0.6	NA	Died at 7mo
	89/M	Forehead	NA	NA	Died at 22mo
	42/M	Cheek	1.3	NA	LN met at 8mo → recurrence at 14mo → died at 32mo
	60/F	Cheek	1	NA	No recurrence at 32mo
	82/M	Hand	2.2	NA	No recurrence at 32mo
	82/F	Calf	2.5	NA	No recurrence at 43mo
	85/M	Ear	1.3	NA	No recurrence at 36mo
	74/F	Arm	1	NA	FU NA
	38/M	Forehead	1.2	NA	No recurrence at 51mo
	72/M	Scalp	1.5	NA	Recurred, LN met
	91/M	Neck	1.5	NA	Died at 32mo
	71/F	Cheek	0.8	NA	No recurrence at 30mo
	84/M	Ear	0.7	NA	No recurrence at 40mo
	10/M	Neck	0.5	NA	LN met → no recurrence at 99mo
	80/M	Scalp	2	NA	No recurrence at 24mo
	53/F	Nose	1	NA	Recurred at 20mo → no recurrence at 50mo
	55/M	Nose	NA	NA	Recurred at 24mo
	68/M	Temple	1.1	NA	Recurred at 7mo → no recurrence at 13mo
	19/M	Nose	NA	NA	No recurrence at 11mo
	87/F	Hand	2	NA	Recurred at 12mo
	77/F	Forehead	0.8	NA	No recurrence at 10mo
	80/M	Scalp	0.6	NA	No recurrence at 6mo
	94/F	Cheek	1.7	NA	FU NA
	79/M	Ear	0.6	NA	No recurrence at 30mo

	86/M	Ear	0.7	NA	No recurrence at 17mo
	83/F	Arm	0.8	NA	FU NA
	49/F	Lip	1	NA	FU NA
	62/F	Chest	0.6	NA	FU NA
Saraiva et al. [28]	72/F	Nose	NA	NA	Ex x2 and radiation for recurrence at 5mo → no recurrence at 23mo
Chan et al. [18]	85/M	Scalp	NA	No	Ex → FU NA
Magro et al. [29]	75/F	Wrist	NA	No	FU NA
Segars et al. [13]	89/M	Back	NA	PNI	Ex x2 → FU NA
Limbert et al. [30]	81/M	Chest	NA	NA	FU NA
Wang et al. [11]	91/F	Finger	NA	NA	MRI → amputation → PET/CT with met to arm and LN at 2mo
Frouin et al. [23]	74/F	Nose	1.5	PNI and LVI in 4 patients	Ex x5 with enucleation, amputation, radiation → died from SEDC at 42mo
	81/F	Forehead	NA		Ex x 2 → no recurrence at 156mo
	91/F	Nose	NA		Ex → no recurrence at 68mo
	71/F	Canthus	0.5		Ex → no recurrence at 92mo
	80/M	Cheek	7.8		Ex x 2 → no recurrence at 44mo
	76/F	Cheek	NA		Ex → no recurrence at 54mo
	96/F	Cheek	4		Mohs → recurred at 32mo
Ranasinghe et al. [19]	65/M	Nose	0.7	PNI	Mohs → FU NA
Clark et al. [31]	75/M	Clavicle	0.16	NA	Mohs → no recurrence at 12mo
Jung et al. [25] and Kim et al. [26]	53/M	Scalp	2.6	NA	CT → Ex → FNA with met to LN at 5mo → Ex and LN dissection
Perkins et al. [10]	72/M	Ear	NA	LVI	Mohs → FU NA
Pusiol et al. [32]	54/F	Tibial	1.2	NA	Ex → no recurrence at 18mo
Terushkin et al. [6]	63/M	Cheek	2.7	No	Mohs → no recurrence at 10mo
Kavand et al. [20]	61/F	Toe	NA	No	Amputation → no recurrence at 8mo
Chhibber et al. [14]	90/M	Forearm	NA	LVI and PNI	Ex → no recurrence at 5mo
Wasserman et al. [16]	68/M	Chest	0.9	LVI	Ex → negative CT and SLNB → no recurrence at 12mo
Kim et al. [15]	30/F	Neck	2.5	NA	Negative CT→ Mohs → no recurrence at 14mo
Herrero et al. [33]	41/M	Knee	2	NA	FU NA
Wong et al. [34]	81/M	Ear	≤2.5	PNI	Ex with 3 recurrences within 36mo
	85/F	Hand	≤2.5	NA	Ex → FU NA
	86/F	Axilla	≤2.5	PNI	Ex → FU NA

CEA, carcinoembryonic antigen; cm, centimeter(s); CT, computerized tomography; EMA, epithelial membrane antigen; Ex, excision; F, female; FDG, F-labeled fluoro-2-deoxyglucose; FU, follow up; IHC, immunohistochemistry; LN, lymph node; LVI, lymphovascular invasion; M, male; met, metastasis; mo, month(s); NA, not available; PET, positron emission tomography; PNI, perineural invasion; SLNB, sentinel lymph node biopsy;