HHS Public Access

Author manuscript

J Am Acad Dermatol. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

J Am Acad Dermatol. 2017 February ; 76(2): 327–333. doi:10.1016/j.jaad.2016.09.024.

Acantholytic squamous cell carcinoma is usually associated with hair follicles, not acantholytic actinic keratosis, and is not "high risk": Diagnosis, management, and clinical outcomes in a series of 115 cases

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Abstract

Background—Acantholytic squamous cell carcinoma (aSCC) is regarded as a high-risk variant of cutaneous squamous cell carcinoma (SCC). Acantholytic actinic keratosis (aAK) has been regarded as a precursor risk factor for aSCC. However, supporting evidence is limited.

Objective—We sought to document clinical features, histologic features, management, and outcomes in a series of aSCC cases.

Methods—Definitions of aSCC, aAK, and aSCC arising in association with aAK were applied to a consecutive series of aSCC cases. Clinical characteristics and outcomes were obtained from electronic medical records.

Results—Of 115 aSCC cases (103 patients, mean age 71.8 years), actinic keratosis was present in 23% (27/115) but only 7.8% (9/115) exhibited associated aAK. Ten cases (10/115, 9%) fulfilled strict histologic criteria for follicular SCC as previously defined, but 50 of 115 (43%) of our aSCC cases exhibited predominant involvement of follicular epithelium rather than epidermis. Clinical outcome (median follow-up, 36 months) was available in 106 of 115 (92%). One patient experienced regional extension (parotid), and 1 patient experienced a local recurrence (nose). No disease-related metastases or deaths were documented.

Limitations—This was a single-institution retrospective study from the United States.

Conclusions—The presence of acantholysis in cutaneous SCC does not specifically confer aggressive behavior, a finding that may inform clinical practice guidelines.

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Conflicts of interest: None declared.

A portion of this work was presented at the 52nd Annual Meeting of the American Society of Dermatopathology, San Francisco, CA, October 11, 2015.

Keywords

acantholysis; acantholytic actinic keratosis; cutaneous oncology; dermatopathology; follicular squamous cell carcinoma; nonmelanoma skin cancer; outcomes; prognosis; squamous cell carcinoma

Squamous cell carcinoma (SCC) is the second most common form of skin cancer and most common cause of death from nonmelanoma skin cancer.[1-3] Acantholytic SCC (aSCC) is a distinctive histologic subtype of SCC first described by Lever[4] in 1947 as a form of sweat gland carcinoma. Synonyms in the literature include adenoid SCC (adenoacanthoma of Lever) or pseudoglandular SCC. aSCC also encompasses the rare histologic subsets of pseudovascular SCC, pseudoangiosarcomatous SCC, and small-cell SCC.[1,5-10] aSCC has long been regarded as an intermediate- to high-risk form of SCC.[1,11] A frequently cited reference in support of the high-risk nature of aSCC is the case series published in 1989 by Nappi and coworkers,[11] who reported that 19% of their 49 patients developed fatal metastases. Case reports and small case series have also documented aggressive behavior.[12-15] However, comparatively lower mortality was reported by other institutions, with the largest published series of 155 patients by Johnson and Helwig[16] reporting only 3% mortality.[17] Garcia and Crowson[18] recently questioned whether aSCC is truly an aggressive tumor. However, aSCC remains classified as a high-risk form of SCC in the 2016 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for cutaneous SCC (v1.2016)[19] and current clinical practice guidelines from the European Organization for Research and Treatment of Cancer (EORTC).[20] The emerging role for sentinel lymph node biopsy for high-risk SCC magnifies the importance of accurate risk stratification for cutaneous SCC.[3]

As a histologic variant of SCC, the diagnosis of aSCC is necessarily a histologic diagnosis. aSCC is regarded as a rare variant of cutaneous SCC. Although diagnosing aSCC has not historically been controversial, there are no validated or standardized minimal criteria for the diagnosis of aSCC. Similarly, a definition of aSCC arising in association with acantholytic actinic keratosis (aAK) (or SCC arising in association with actinic keratosis [AK] generally) has not been proposed. Moreover, acantholysis has been documented in other variants of SCC, including follicular SCC,[21] spindle-cell SCC,[22,23] and even rarely as an incidental finding in keratoacanthoma (KA),[24] despite the fact that some investigators definitionally exclude KA if acantholysis is present.[25] Cassarino and colleagues,[1] in their comprehensive review of the histopathology of cutaneous SCC, characterized aSCC as exhibiting intratumoral acantholysis “At least focally, but often extensively....” In the largest series to date, Johnson and Helwig[16] noted that aSCC tumors typically arose from the upper portion of follicular outer root sheath, but characteristic involvement of follicular epithelium was not mentioned in subsequent descriptions of aSCC[11,26] or follicular variants of SCC.[21,27,28] Of note, Carr and coworkers[29] identified a central acantho lytic mucin pool in over half of their series of 30 cases of follicular SCC and contrasted this finding with the characteristic suprabasilar acantholysis that typifies aAK and aSCC. Multiple authorities state that aSCC is often present in association with aAK.[30-32] AK is a widely accepted precursor to, and risk factor for, cutaneous SCC,[33] with aAK representing the presumptive precursor of aSCC.[16]

However, a formal evaluation of the degree of association between aAK and aSCC has not been reported. Similar to aSCC, aAK is a rare variant of AK, representing less than 5% of 402 AKs in the series of Carapeto and Garcia-Perez[34] and 10% in the series of 300 AKs by Pensley and Sims.[35]

In this study, we developed and uniformly applied definitions of aSCC, aAK, and aSCC arising in association with AK/aAK to facilitate review of the associated clinical features, management, and clinical outcomes in aSCC.

METHODS

A natural language search for “acantholytic squamous cell carcinoma” and “squamous cell carcinoma, acantholytic” was performed on the database of an academic medical center's dermatopathology laboratory to identify a consecutive sampling of tissue specimens with a diagnosis of aSCC (2006-2011). Study material was fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin-eosin for histologic diagnosis. All cases were originally interpreted by a board-certified dermatopathologist.

Study definitions were developed to be compatible with existing descriptions in published studies and reviews.[1,5,11,16,17] The study definitions were as follows.

Acantholytic SCC

This was defined as SCC containing atypical keratinocytes associated with loss of cohesion between epidermal or adnexal epithelial cells with formation of intraepithelial clefts (most commonly suprabasilar). Acantholytic keratinocytes exhibit a round shape with a central round uniformly staining basophilic nucleus, eosinophilic cytoplasm, and absence of desmosomal attachments on hematoxylin-eosin stain affecting at least half of the cell circumference. A pseudoglandular appearance may result when acantholysis is prominent. Associated spongiosis and dyskeratotic keratinocytes may also be present.

aSCC, follicular type

aSCC (Fig 1) appears centered upon 1 or more hair follicles, with or without infundibulocystic differentiation/features, but *lacking* features of KA (ie, verrucous crateriform profile composed mostly of large keratinocytes with pale eosinophilic glassy cytoplasm) (Fig 2), and lacking involvement of epidermis; ulcerated tumors do not qualify.

aSCC, follicular pattern

We define this as aSCC predominantly involving and/or predominantly arising from involved follicular epithelium (Fig 3).

Actinic keratosis

We define this as epidermis (interadnexal) with parakeratosis and atypia/crowding of underlying basilar keratinocytes, involving adjacent epidermis, without directly underlying SCC.

Acantholytic AK

This is defined as AK exhibiting acantholysis (defined above) or intraepidermal clefts (usually suprabasilar).

aSCC arising in association with AK

This is defined as aSCC with basilar epidermal atypia and parakeratosis of the epidermis peripheral to the main tumor (same or adjacent section), with any degree of sparing of at least 1 adnexal structure, *without* directly underlying invasive tumor (Fig 4).

Solar elastosis

Mild solar elastosis was defined as discrete individual gray solar elastotic fibers separated by collagen fibers. Severe solar elastosis was defined as solid or nodular accumulations of elastotic material displacing the background collagen.

After establishing the study definitions, all cases were reviewed with concurrence at the time of the study by at least 3 investigators, including the first and corresponding authors plus 1 or 2 additional board-certified dermatopathologists. Inclusion criteria included the fulfillment of minimal histologic criteria as described in the study definition of aSCC. Exclusion criteria included cases that did not fulfill minimal histologic criteria or did not clearly demonstrate invasive carcinoma as a result of superficial sampling.

Histologic attributes included AK (present, absent, indeterminate/insufficient tissue); aAK (present, absent, indeterminate/insufficient tissue); solar elastosis (mild, severe, indeterminate); follicular SCC (yes, no, indeterminate); and follicular pattern in SCC (yes, no, indeterminate).

Clinical attributes were obtained by review of the patient's electronic medical record: age at time of biopsy, gender, ethnicity/race (Caucasian, Hispanic, African American, Asian, other), anatomic site, tumor size, immune status (organ transplantation, radiation exposure, other, not known), treatment (Mohs, standard excision, electrodessication and curettage, radiation, other), follow-up duration, and outcome (alive with no evidence of disease, local recurrence, distant metastasis, death from disease, death from unrelated causes) at most recent follow-up.

Data was recorded in Excel 2010 (Microsoft Corp, Redmond, WA). Institutional review board approval was obtained.

RESULTS

A total of 115 specimens from 103 patients were identified and studied (Table I). The average tumor size among those listed (69% of tumors) was 1.2 cm (range 0.1-5.0 cm). Most patients were treated with Mohs micrographic surgery. No disease-related deaths were recorded. Associated AK was identified in 23% (27/116) of the aSCC tumors, but less than 8% of these (9/116) were aAK (Table II). Most of the specimens were shave biopsies, but acantholysis comprised less than 25% of the aSCC tumor in the tissue sections in nearly all cases. Clinical features of aSCC with a follicular pattern are summarized in Table III. Nearly

half of aSCC cases predominantly, if not exclusively, appeared to involve follicular epithelium.

DISCUSSION

Evidence-based standardization of clinical practice guidelines is a defining feature of 21st century medical practice. In the realm of high-risk SCC, the recent trend toward consideration of sentinel lymph node biopsy magnifies the importance of accurate risk stratification among SCC subtypes.[3] Moreover, although acantholysis is a readily and universally recognized histopathologic feature, minimal criteria for the diagnosis of aSCC, or the relationship of aSCC with other SCC subtypes such as follicular SCC, is uncertain. Yet, a pathologic diagnosis of aSCC is widely accepted among practicing dermatopathologists. Despite multiple reports of aggressive behavior associated with aSCC, the largest aSCC series do not support aSCC as a high-risk subtype of SCC.

Although deductive reasoning supports the assumption that aAK is a common precursor to aSCC, less than 8% were associated with aAK in our series (23% AK overall). Similarly, in the largest aSCC series, only 6.4% (10/155) of aSCC were associated with aAK.[16] Given the lack of an explicit or uniformly applied definition of AK-associated SCC, variable prevalence rates may be attributed to variable definitions in addition to presumed true differences in prevalence between populations. For example, the aAK depicted in Fig 8 by Johnson and Helwig[16] might not be regarded as classic for AK by some observers (and excluded using the definitions in our study) because there is no epidermal involvement at all. As another example, in a recent case report by Ruini and colleagues[36] documenting the progression of AK to SCC, the example of AK provided in their Fig 4, *B*, shows a lesion entirely lacking parakeratosis but involving follicular epithelium. However, studies have consistently demonstrated that aAK comprises only a minority of AK, whatever the absolute value of the AK “denominator.” The concomitant observation that nearly half of our cases of aSCC predominantly, if not exclusively, appeared to involve follicular epithelium suggests that aAK may not be a required or typical antecedent to aSCC, ie, despite the shared attribute of acantholysis, aAK and aSCC may develop via parallel signaling pathways, rather than in series. The possibility that aAK might be obscured or replaced by aSCC cannot be excluded; however, nearly half of aSCC in our series predominantly involved follicular epithelium, whereas AK (all variants) classically exhibits a reciprocal pattern, primarily involving interadnexal epidermis and sparing adnexal epithelium (hair follicle, eccrine duct), at least initially. The observation by Carr and colleagues[29] that a central acantholytic mucin pool characterizes follicular SCC (vs suprabasilar acantholysis, without mucin, in aAK and aSCC) also warrants further study. We did not perform mucin stains in our cases, as ancillary histochemical staining was not required in our routine practice.

The concept of follicular SCC was introduced by Diaz-Cascajo et al[21] in 2004 as a variant of cutaneous SCC originating from follicular epithelium; in this series, a few foci of acantholysis were documented in 5 of 16 cases. Kossard[28] introduced well-differentiated, moderately differentiated, and infiltrative variants of infundibulocystic SCC in 2012 as histologic subtypes of follicular SCC distinct from KA; in this series, acantholysis was not mentioned at all. In 2011, Misago et al[27] reported 8 cases of follicular/infundibular SCC and

infundibulocystic SCC, the latter exhibiting an infiltrative pattern of growth and merging histologically with microcystic adnexal carcinoma; in this series, acantholysis was not mentioned at all. However, acantholysis was a relatively common feature in a review that referenced a series of 30 follicular SCC cases.[29]

Regarding metastatic potential, Cassarino et al[1] stratified SCC into categories of low (≤2% metastatic rate), intermediate (3%-10%), and high (>10%), and aSCC was classified as intermediate risk. Thus, “aggressive behavior” in cutaneous SCC can be defined as encompassing intermediate risk (3%-10% metastatic rate) and high risk (>10% metastatic rate) subgroups. NCCN regards aSCC as high risk,[19] as does the EORTC and Working Group of the French Dermatology Recommendations Association.[20,37] However, in a recent series of 110 cases of SCC, acantholysis was not a significant prognostic factor.[38] The 2010 Union for International Cancer Control and 2010 American Joint Committee on Cancer TNM classifications confer elevated risk for cutaneous carcinomas larger than 2 cm and exhibiting deep infiltration (bone and soft tissue), without specifying histologic subtypes, although a recent review of these classifications suggested that histology should be considered, with emphasis on microscopic tumor thickness and perineural invasion (not acantholysis).[39]

The average clinical tumor size in our series is similar to those previously reported. Specifically, the tumor size in our series (1.2 cm; range 0.5-5.0 cm) is slightly larger than that in the largest series by Johnson and Helwig[16] and appears comparable with that of Nappi and coworkers.[11] Thus, clinical tumor size alone does not appear to account for the variation in reported mortality. Tumor depth of extension remains a likely relevant prognostic variable in aSCC that bears investigation, because existing case series of aSCC have not recorded tumor thickness (Table IV). The anecdotal recollection of memorably aggressive aSCC cases may correlate with thicker tumors and/or involvement of anatomically high-risk sites such as the ear, where involvement of subcutis or underlying fascia occurs with a relatively smaller depth of extension compared with other sites.

In conclusion, we applied uniform, detailed definitions of aSCC, aAK, and aSCC arising in association with AK/aAK to report, to our knowledge, the largest case series of aSCC in a half century. We confirmed a common association of aSCC with follicular epithelium, and only infrequent association of aSCC with aAK, and no evidence of increased morbidity or mortality. The presence of acantholysis in SCC per se does not specifically confer aggressive behavior by cutaneous SCC and may inform clinical practice guidelines.

Acknowledgments

Dr Kiuru's involvement in this research was in part supported by the National Cancer Institute, National Institutes of Health, through grant K12CA138464.

Abbreviations used

aAK	acantholytic actinic keratosis
AK	actinic keratosis

aSCC	acantholytic squamous cell carcinoma
EORTC	European Organization for Research and Treatment of Cancer
KA	keratoacanthoma
NCCN	National Comprehensive Cancer Network
SCC	squamous cell carcinoma

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CAPSULE SUMMARY

- Acantholytic actinic keratosis has been regarded as a precursor of acantholytic squamous cell carcinoma (SCC), a reportedly aggressive high-risk form of SCC.
- In this series of 115 cases, acantholytic SCC was more commonly associated with follicular epithelium than acantholytic actinic keratosis and did not display aggressive behavior.
- The presence of acantholysis, per se, in cutaneous acantholytic SCC does not confer aggressive clinical behavior.

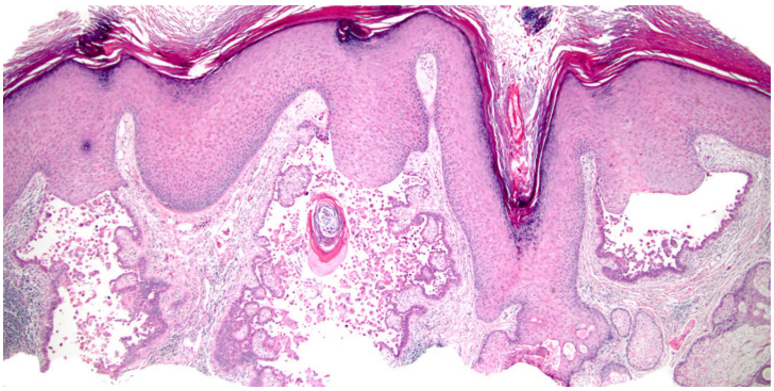

Fig 1.

Acantholytic squamous cell carcinoma, follicular type. The tumor involves follicular epithelium but not epidermis. (Hematoxylin-eosin stain; original magnification: ×20; inset, ×100.)

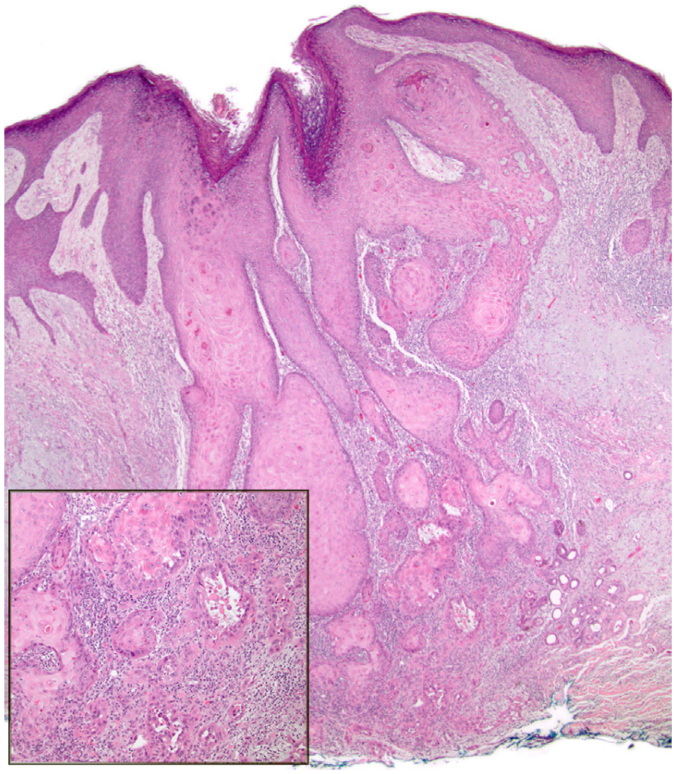

Fig 2.

Acantholytic squamous cell carcinoma with features of keratoacanthoma. The tumor is mostly composed of large keratinocytes with abundant pale eosinophilic (glassy) cytoplasm. Acantholysis is present. (Hematoxylin-eosin stain; original magnification: ×20; inset, ×100.)

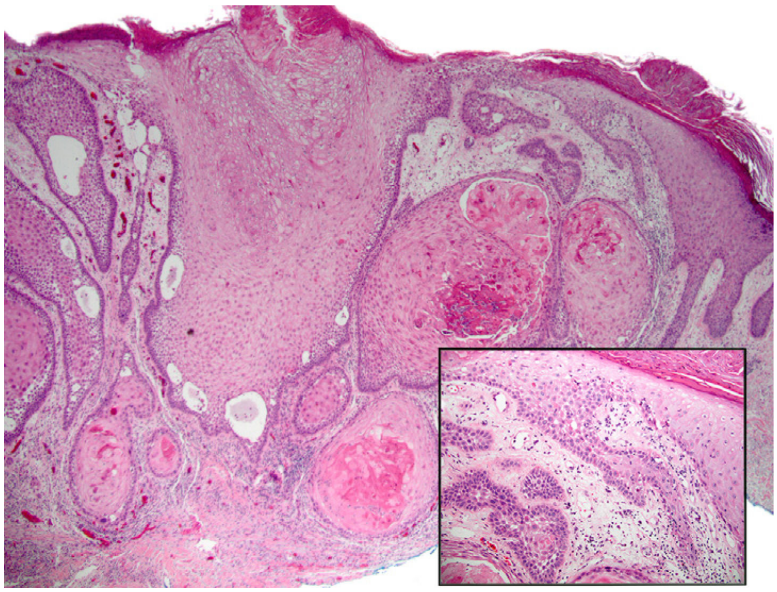

Fig 3.

Acantholytic squamous cell carcinoma (aSCC), follicular pattern. The tumor is centered upon follicular epithelium but also involves epidermis. Some features of actinic keratosis (parakeratosis, basilar epidermal atypia) are present; by our definition, this example did *not* qualify for aSCC arising in association with actinic keratosis because there is invasive carcinoma in the directly underlying dermis. (Hematoxylin-eosin stain; original magnification: ×20; inset, ×100.)

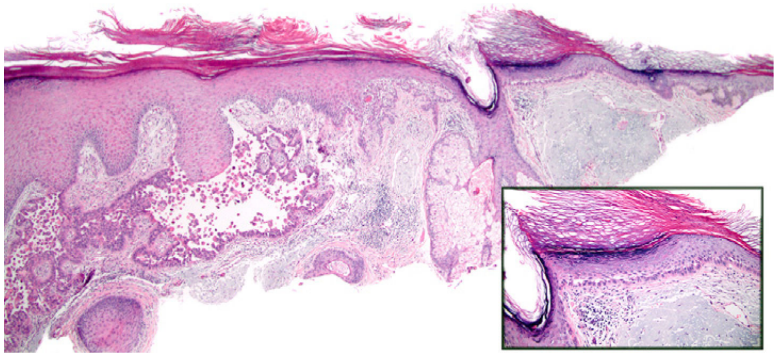

Fig 4.

Acantholytic squamous cell carcinoma (SCC) with associated acantholytic actinic keratosis (aAK). aAK exhibiting parakeratosis, atypical basilar keratinocytes with suprabasilar acantholytic clefting, sparing of adnexal epithelium, severe solar elastosis, and absence of directly underlying SCC. (Hematoxylin-eosin stain; original magnification: ×20; inset, ×100).

Table I

Clinical and histologic features of acantholytic squamous cell carcinoma

Patient gender and mean age	72 y
	Male (79%)
	Female (21%)
Ethnicity/race	Caucasian (83%)
	Other/declined to state (17%)
Tumor sites	Face (42%)
	Ear (14%)
	Scalp (13%)
	Arm (12%)
	Other (19%)
Immune status	Organ transplantation (10%)
	HIV (3%)
	Corticosteroid therapy (6%)
	Other (1%)
Treatment	Mohs micrographic surgery (58 cases)
	Standard excision (17)
	Electrodessication and curettage (1)
	Mohs + standard excision (1)
	Mohs + standard excision + radiation (1)
	Other (7)
	Unknown (29)
Outcome	NED (90)
	Dead, unrelated cause (7)
	Dead, unknown cause (1)
	Recurrence (2 local, 2 distant)
	Unknown (7)
Follow-up: mean, median	34 mo, 29 mo
Associated actinic keratosis	24%
Associated acantholytic actinic keratosis	8%
Solar elastosis	Severe (78%)
	Mild (11%)
	Present (mild vs severe) (4%)
	Indeterminate (7%)

NED, Alive, no evidence of disease.

Table II

Clinical and histologic features of acantholytic squamous cell carcinoma arising in association with acantholytic actinic keratosis

Age, y/gender	Site	Clinical	Size, cm	Solar elastosis	Immunosuppression	Outcome
90/F	Forehead	Unknown	Unknown	Severe	No	Dead, unknown cause
83/M	Back	Rough spot	3.8	Mild	No	NED
78/M	Scalp	Painful papule	0.5	Severe	Chronic lymphocytic leukemia	NED
78/M	Forearm	Papule	1.7	Mild	No	NED
77/M	Cheek	Patch	Unknown	Severe	No	NED
73/M	Ear, helix	Unknown	0.7	Severe	No	NED
70/M	Ear, rim	Unknown	Unknown	Severe	No	Dead, unrelated cause
68/M	Scalp	Depressed patch	0.8	Severe	No	NED
64/M	Forehead	Mobile mass	3.0	Severe	No	NED

F, Female; *M*, male; *NED*, alive, no evidence of disease.

Table III

Selected clinical features of acantholytic squamous cell carcinoma exhibiting a follicular pattern

Patient gender and mean age	70 y
	Male (82%)
	Female (18%)
Tumor sites	Face (64%)
	Other (36%)
Treatment	Mohs micrographic surgery: 30 cases (60%)
Outcome	NED: 40 (80%)
	Dead, unrelated cause: 4 (8%)
	Dead, unknown cause: 3 (6%)
	Local recurrence: 1 (2%)
	Unknown: 2 (4%)
Solar elastosis	Severe (78%)
	Mild (12%)
Follicular SCC*	Yes (20%)
	No (80%)

NED, Alive, no evidence of disease; *SCC*, squamous cell carcinoma.

*See "Methods" section for definition.

Table IV

Summary of published acantholytic squamous cell carcinoma case series

Study	No. of tumors/patients	Clinical tumor size, cm	Tumor thickness	Mortality	Follow-up
Johnson and Helwig,[11] 1966	213/155	0.4-12	Unknown	5/155 (3%)	1 mo-30 y (median, 6.7 y)
Nappi et al,[6] 1989	55/49	0.4-6 (mean 0.8)	Unknown	7/36 (19%), all >1.5 cm	6 mo-10 y
Current study	115/103	0.1-5.0 (mean 1.2)	Unknown	0/88	(median, 29 mo)