CUTANEOUS SQUAMOUS CELL CARCINOMA: A COMPREHENSIVE CLINICOPATHOLOGIC CLASSIFICATION

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ACKNOWLEDGMENT

I. INTRODUCTION
- Most clinicians and pathologists do not adequately subtype invasive SCC, despite varying aggressiveness (akin to superficial vs. infiltrative and micronod BCC)
- Distinct histologic subtypes of SCC exist, most are well-accepted, but their malignant potential is often not well-recognized or controversial
- Other parameters clearly influence biological behavior, including tumor size, depth of invasion, degree of differentiation, perineural invasion, and host immunological status

BACKGROUND:
- Previous classifications not comprehensive, and not based on malignant potential, although most authors comment on variants with more aggressive behavior
- Ackerman initially proposed categorizing all SCCs as "one entity with many faces", where he described SCC arising from solar keratoses and carcinoma in situ, as well as keratotic, pseudoglandular (adenoid), pale-cell (clear cell), necroizing, verrucous, spindle cell, and keratoacanthoma (KA)-like variants of SCC
  - Not subdivided based on malignant potential

II. SUBTYPES OF SCC
- We divide invasive SCC into categories of low, intermediate, and high risk based upon rates of recurrence and metastasis

<table>
<thead>
<tr>
<th>Risk of metastasis</th>
<th>Low (&lt;3%)</th>
<th>Intermediate (3-10%)</th>
<th>High (&gt;10%)</th>
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<td>SCC arising in</td>
<td>Acantholytic SCC, Desmoplastic SCC, Invasive Bowen's, Adenosquamous CA, de novo SCC, rad &amp; scar-assoc</td>
<td>ILE, invasive</td>
<td>ILE</td>
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<td>AK, HPV-related</td>
<td>Lesion SID, spindle cell CA</td>
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<td>SCC, T.L.C.</td>
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<td>spindle cell CA</td>
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A. LOW RISK INVASIVE SCCs

Most SCCs are relatively indolent, vast majority arise within AKs in sun-damaged skin of elderly, other low grade variants include:
- Verrucous carcinoma, other HPV-related SCCs, spindle cell SCC (unassociated with radiation), and tricholemmal carcinoma (TLC)

1. SCC ARISING IN AKs

- Accounts for the vast majority of invasive SCC
- up to 95% of invasive SCC assoc w/AKs
- rate of AKs leading to invasive SCC estimated at 0.2 - 10% per year
- These tumors are often superficially invasive, well-differentiated, and cured by excision
- Invasive SCC arising in AK only rarely metastasizes, estimated risk ≤ 1%

2. SCC ASSOCIATED WITH HPV INFECTION

VERRUOUS CARCINOMA

Clinical:
Indolent, slow-growing tumors with exophytic appearance
Several variants described, including:
- Oral (oral florid papillomatosis), anogenital (Buschke-Lowenstein tumor) or plantar (epithelioma curucatum), Epidermodysplasia verruciformis (EDV) – genetic (AR), sporadic and HIV-related forms
HPV association:
- VG: HPV 6 & 11
- EDV: HPV 3 & 10 (benign); 5, 8, 9, 14, 20 (malignant)

Histology:
- Verrucous carcinoma (all variants): proliferation of enlarged, bland eosinophilic keratinocytes with bulbous downgrowths and “pushing invasion”
- EDV: epidermal acanthosis with enlarged, mildly atypical, bluish-gray keratinocytes, some perinuclear halos
VERRUCOUS CARCINOMA

Prognosis:
• Low-grade tumors with very rare metastases (less than 2%)
• So-called “warty carcinomas” are different and more aggressive along with other genital skin associated mucosal HPV subtypes (basaloid, warty basaloid, etc).
• Radiation therapy not recommended, as reported to lead to dedifferentiation to high grade SCC
  - Virtually all metastatic cases had been irradiated

3. SPINDLE CELL SQUAMOUS CELL CARCINOMA

Clinical:
- Uncommon variant of SCC, usually arising in sun-damaged skin, head and neck; more aggressive tumors a/w radiation or scars (high risk SCC)

Histology:
- Usually large, dermal-based tumors composed of proliferation of poorly-differentiated, oval to elongated spindle cells; may see overlying epidermal atypia or connections to invasive tumor

IPON:
- HMWCK (CK5/6 or 34BE12) or p63 to distinguish from AFX, spindle cell melanoma, leiomyosarcoma

Prognosis for spindle cell and sarcomatoid SCC:
- Most cases are actinic related, superficial and have low risk of metastasis (analogous to AFX). However, some cases may be more aggressive, especially arising in scars or post-radiation
4. TRICHOLEMMAL CARCINOMA

Clinical:
- Only rare cases reported, usu. sun-exposed skin of elderly patients, usually rapidly growing keratotic papule/nodule, may be ulcerated
- Clinical dx usu. BCC or SCC
- No assoc w/Cowden's syndrome

Prognosis:
- Excellent, rare recurrences, no clearly documented metastases (unlike clear cell SCC)

Histology:
- Multilobular, infiltrative proliferation of atypical, pale keratinocytes with peripheral palisading and hyalinized BM, no keratohyaline granules; shows a high mitotic rate
- Pagetoid spread may be present
- Diff'nt dx: desmo tricholemma, clear cell SCC, clear cell BCC, less likely: clear cell hidradenoma and metastatic RCC

B. INTERMEDIATE RISK SCCs

These are less common tumors, and their malignant potential is more controversial, may reflect the lack of large studies and reporting bias:
- Acantholytic SCC, lymphoepithelioma-like carcinoma of the skin (LELCS), intraepidermal epithelioma (IEE)/Borst-Jadassohn tumor with invasion
1. ACANTHOLYTIC (ADENOID) SCC

Clinical:
- Sun-exposed skin of elderly, male > female
- Nonspecific presentation, usually nodular, pink/red lesion, often clinical dx is BCC, SCC, or KA

Prognosis:
- Tumor of reported intermediate risk based on metastatic rate, wide range reported (5 – 19%), likely the lower end of range

2. LYMPHOEPITHELIOMA-LIKE CARCINOMA (LELCS)

Clinical:
- Rare tumor, usually elderly on head and neck, sun-damaged skin
- Not EBV-related (as are nasopharyngeal LELC)
- Differential diagnosis: rare LCNEC with LH

Prognosis:
- Initially thought to be aggressive, but so far only 2 metastases and 1 documented death from this tumor (out of 40 cases)

Histology: large epithelioid cells intermixed with lymphocytes and plasma cells
3. INTRAEPIDERMAL EPITHELIOMA (IEE)/JADASSOHN TUMOR WITH INVASION

Controversial whether IEE is a true entity or not, many may represent clonal SKs, hideroacanthoma simplex, or clonal Bowen's. However, invasive tumors arising in these lesions appear to be SCC, and have been reported to be more aggressive lesions (6 - 10% mets)

Clinical:
Few series, but most described as plaques with flat or verrucoid features

C. HIGH RISK SCCs

Similar to intermediate group, many of these are rare tumors with few large studies to determine malignant potential:
- Invasive Bowen's disease, desmoplastic SCC, malignant proliferating pilor tumor (PPT)/cyst, de novo SCC, adenocarcinoma cell carcinoma, and SCC arising in association with radiation, burn scars, chronic conditions and immunosuppression

Histology:
- Classic Bowen's disease overlying an invasive tumor composed of islands of squamoid to basoid cells, often with central areas of necrosis
- May show adnexal differentiation (eccrine, apocrine, or sebaceous)

1. BOWEN'S DISEASE WITH INVASION

Clinical:
- Often not well-recognized clinically due to non-specific features, but usually rapidly growing, ulcerated tumor occurring in a scaly or erythematous patch

Prognosis:
- 5 - 8% of Bowen's disease may become invasive, and up to 13% - 20% of those patients develop metastases.
- Putative assoc w/ internal malignancies disproven
2. DESMOPLASTIC SCC

Clinical:
- Aggressive variant, often on sun-damaged skin, ears, cheeks, and nose, of elderly males

Prognosis:
- High rates of recurrence and metastasis (22 – 77%, later reported on lip)

Histology:
- Cords and trabeculae of oval to spindled squamoid cells infiltrating a dense, desmoplastic stroma (> 30% stroma), frequent keratinization and perineural invasion

3. MALIGNANT PROLIFERATING PILAR TUMOR (PPT)/CYST, or SCC ARISING IN PPT

Clinical:
- Rare, usually scalp tumors, older adults, present as multinodular cystic masses, may ulcerate

Prognosis:
- PPTs are benign tumors with recurrent potential; malignant PPTs/SCC arising in PPT are highly aggressive, frequently metastatic carcinomas (up to 30% metastases)

Histology:
- PPT: well-circumscribed dermal tumor consisting of multiple haphazard, interconnecting cystic lobules lined by a stratified squamous epithelium exhibiting tricholemmal keratinization, and cystic spaces filled with keratin and debris
- Malignant PPT/SCC arising in PPT: areas of severe cytological atypia, abundant mitoses, and stromal invasion are required for diagnosis
4. DE NOVO SCC

Clinical:
- Poorly recognized, uncommon variant, presents on either sun damaged or protected skin as nodule or indurated, erythematous area with crusting, ± ulceration

Prognosis:
- 8-14% incidence of regional or distant metastases

Histology:
- Infiltrative, dermal-based tumor with no epidermal or adnexal connections

5. ADENOSQUAMOUS CARCINOMA

Clinical:
- Rare but highly aggressive tumors, elderly patients, head and neck and genitalia

Prognosis:
- Frequent recurrences and metastases leading to tumor-related death (up to 50%)

Histology:
- Nests and lobules of squamous cells with keratocytes, foci of glandular diff'nt lined by cuboidal to columnar cells with secretions (mucin & CEA+)

Differential diagnoses: mucoepidermoid carcinoma, adenoid cystic carcinoma, squamous eccrine ductal adenocarcinoma
6. SCC 2° TO CHRONIC CONDITIONS & RADIATION

SCC develops more frequently in chronically injured or immunosuppressed skin, including:
- Long standing ulcers, burns, sinus tracts, organ transplant patients
Also, skin affected by chronic inflammatory disorders such as:
- Discoid lupus (DLE), lichen sclerosis, lichen planus, dystrophic EB, and lupus vulgaris
These are aggressive tumors, with higher rates of invasion, recurrence, and metastatic potential

1. Burn scar SCC (Marjolin’s ulcer):
   - Male predominance (3:1), LEs, latency period 4 mos (acute) to 35 yrs (chronic), high metastatic rate (36% - 52%)
2. SCC arising in lupus (DLE):
   - Rare, more common in African-Americans, high metastatic rate (31%)

3. Radiation-induced SCC:
   - Increases risk of SCC by 3X, earlier age leads to greater risk, tumors are aggressive and frequently metastatic
   - Any histologic subtype, but spindle cell common
4. Immunosuppression-related SCC:
   - Cancer, HIV+, transplant, increased risk for SCC on sun-exposed sites (＞BCC), risk related to degree and duration of immunosuppression
**C. SCC OF INDETERMINATE MALIGNANT POTENTIAL**

Rare tumors which have only been the subject of very few studies with small number of cases, therefore, their malignant potential is unclear.

- Signet ring and clear cell SCC, pigmented SCC, papillary SCC, follicular SCC, SCC arising in adnexal cysts, myxoid squamous cell carcinoma
  - keratoacanthoma??

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**III. ADDITIONAL PROGNOSTIC FACTORS IN CUTANEOUS SCC**

- Despite the generally good prognosis of cutaneous SCC, the behavior of metastatic SCC is very poor, with less than 35% of patients surviving for 5 years.
- The metastatic potential of SCC is clearly related to depth of tumor invasion:
  - < 2 mm in thickness never metastasized
  - 2 - 6 mm metastasized at rate of 4.5%
  - > 6 mm metastasized at rate of 15%

(Brunneringer et al., Microstaging of squamous cell carcinoma, Am J Clin Pathol 1990;94:62)

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**ADDITIONAL PROGNOSTIC FACTORS**

Grade of differentiation has also been shown to be of prognostic significance:

- Rowe et al. showed that poorly differentiated SCC (Broders' grades III-IV) has a much higher rate of metastasis than well and moderately-differentiated (grades I-II) (33% versus 9%, res.)

Also, perineural invasion is clearly an adverse prognostic finding, which portends higher rates of recurrence and metastasis (up to 47% and 35-80%, res.)

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**IV. CONCLUSIONS**

- Cutaneous SCC includes multiple subtypes of varying malignant potential
- It is recommended that the following features be reported in routine pathology reports:
  1. Histologic subtype
  2. Degree of differentiation (well, mod, or poorly)
  3. Approximate depth of invasion
  4. Perineural invasion
  5. Hematolymphatic invasion