

Question 1

A 55-year-old gentleman is referred for Mohs surgery of a biopsy positive metatypical basal cell carcinoma of the R lateral forehead.

Based on the findings on this slide what additional tests would you consider?

- A. Send tissue for CK 20 staining.
- B. Order a CT to look for pulmonary changes/renal oncocytoma.
- C. Send tissue for MLH-1, and MSH-2 and 6 staining.
- D. Check thyroid function tests.

Discussion

Question 1

Correct Answer:

C. Send tissue for MLH-1, and MSH-2 and 6 staining.

Main Histologic Features:

- Dermal neoplasm with sebaceous differentiation throughout the tumor
- Significant mitotic activity with atypical mitoses
- No peripheral palisading or peritumoral mucin
- Incidental overlying squamous cell carcinoma in situ

Differential Diagnosis:

- Basal cell carcinoma with sebaceous differentiation
- Sebaceoma
- Trichilemmal carcinoma
- Granular cell tumor

Clinical Concerns:

- Facial neoplasms can be associated with systemic syndromes:
 - Fibrofolliculomas/trichodiscomas seen in Birt-Hogg-Dubé syndrome
 - 80-90% risk of pulmonary cysts
 - 15-20% risk of renal cancer, particularly oncocytoma
 - Trichilemmomas seen in Cowden syndrome
 - Thyroid involved in 66% of cases
 - Malignancy develops in at least 40% of patients.
- Sebaceous neoplasms can be seen in Muir-Torre syndrome (MTS) which carries an increased risk of colon, genitourinary, breast and hematologic malignancies.
- MTS is more commonly associated with extraocular sebaceous carcinomas.
- MTS can be screened for by using immunohistochemical tissue stains for MLH-1, MSH-2 and MSH-6 proteins (Muir-Torre panel). Absence of staining identifies tumors with mismatch repair deficiency and suggests MTS, which can then be confirmed by genetic testing.

References:

- Ansai S, Takeichi H, Arase S, Kawana S, Kimura T. Sebaceous carcinoma: an immunohistochemical reappraisal. *Am J Dermatopathol.* 2011; 33:579-587.
- Shalin SC, Lytle S, Calojne E, Lazar AJF. Sebaceous neoplasia and the Muir-Torre syndrome: important connections with clinical implications. *Histopathology.* 2010; 56(1): 133-147.
- McCalmont TH. The company you keep. *J Cutan Pathol.* 2013;40:863-864.

Question 2

A 71-year-old woman is referred for Mohs surgery of a large (5.2x3.2cm) biopsy positive squamous cell carcinoma in situ with follicular involvement and extensive acantholysis of the scalp vertex.

Based on the findings on this slide what would you do?

- A. Stop the margin is clear of cancer.
- B. Stop and send tissue for direct immunofluorescence.
- C. The peripheral margin is positive for cancer, take an additional layer.
- D. The peripheral and deep margins are positive for cancer, take an additional layer.



Discussion

Question 2

Correct Answer:

B. Stop and send tissue for direct immunofluorescence.

Main Histologic Features:

- Intraepidermal split with hyperkeratosis and papillomatosis
- Significant acantholysis with dyskeratosis
- No significant cellular atypia or mitoses

Differential Diagnosis:

- Acantholytic squamous cell carcinoma
- Inverted follicular keratosis
- Keratosis follicularis (Darier disease)
- Familial benign pemphigus (Hailey-Hailey disease)

Clinical Concerns:

- Pemphigus vegetans can mimic acantholytic squamous cell carcinoma both clinically and histologically.
- Acantholysis without significant atypia or mitoses should prompt consideration of other differential diagnoses to avoid unnecessary surgery and morbidity to the patient and cost to the medical system.

References:

- Howard JC, Russell KJ, Vickers JL, Weiss E. Acantholysis: Worth a Second Look? *Dermatol Surg.* 2014;40(11):1268-70.
- Butler ST, Youker SR, Mandrell J, Flanagan KH, Fosko SW. The importance of reviewing pathology specimens before Mohs surgery. *Dermatol Surg.* 2009;35(3):407-412.
- Duick MG, Zaks B, Moy RL, Kaplan RP. Mohs micrographic surgery-induced pemphigus. *Dermatol Surg.* 2001; 27(10):895-7.
- Ahmed AR, Blouse DA. Pemphigus vegetans. Neumann type and Hallopeau type. *Int J Dermatol.* 1984;23:135-41.
- Mori M, Mariotti G, Grandi V, Gunnella S, Maio V. "Pemphigus vegetans of the scalp." *J Euro Acad Dermatol Venereol.* 2014;Oct 22 doi: 10.1111/jdv.12793.
- Downie J, Dicostanzo D, Cohen S. Pemphigus vegetans-Neumann variant associated with intranasal heroin abuse. *J Am Acad Dermatol.* 1998; 39:872-5.

Question 3

A 64-year-old Caucasian male with no significant prior medical history was sent for treatment of a basal cell carcinoma on the neck. A representative section from the first stage of Mohs surgery is shown.

What is most appropriate next step?

- A. Residual BCC is present. Take another stage and move on.
- B. Patient has residual basal cell carcinoma and likely chronic lymphocytic leukemia/small cell lymphocytic lymphoma. Send the remaining tissue for further work up and take a second layer.
- C. Case is complete. Only inflammation is present.
- D. Patient has residual basal cell carcinoma and likely a concomitant neuroendocrine tumor. Send the remaining tissue for further work up and take a second layer.

Discussion

Question 3

Correct Answer:

- B. Patient has residual basal cell carcinoma and likely chronic lymphocytic leukemia/small cell lymphocytic lymphoma. Send the remaining tissue for further work up and take a second layer.

Main Histologic and Immunohistochemical Features of Chronic Lymphocytic Leukemia/Small Cell Lymphocytic Lymphoma:

- Patterns of dermal infiltration: Perivascular, periappendageal, nodular, and band-like
- Monomorphous population of small, dark, round lymphocytes
- Grenz zone is often present
- Proliferation centers are not seen as commonly as lymph nodes
- Other reactive cells including eosinophils, neutrophils, histiocytes, and plasma cells may be present
- Leukemic infiltrate may surround epithelial neoplasm, e.g. basal cell carcinoma, squamous cell carcinoma
- CD19+, CD20+ (usually weak), CD5+, CD23+, CD43+, CD10-, cyclin D1-

Histologic Differential Diagnosis:

- Metastatic small (oat) cell carcinoma of lung – sheets of uniform round blue small and intermediate-sized cells with scant cytoplasm. Nuclear molding, a feature of small cell carcinomas can be useful for differentiation of small cell and non-small cell carcinomas. IHC: TTF-1+.
- Merkel cell carcinoma – small blue cells with minimal cytoplasm and tightly packed nuclei in sheets or trabecular array. IHC: CK20+ in a paranuclear dot pattern, synaptophysin+, chromogranin+, and neuron-specific enolase+.
- Melanoma (small cell (neuroendocrine-like) variant) - Occurs more commonly within the nasal cavity and paranasal sinuses. Melanoma with small cell morphology often lacks melanin pigment. IHC: S100+.
- Neuroblastoma – elongated small blue cells with hyperchromatic nuclei and rosette formation. IHC: Neuron-specific enolase+.
- Ewing's sarcoma/ Primitive Neuroectodermal Tumor - Small blue cells that tend to have a high nucleocytoplasmic ratio. The cytoplasm is pale blue, abundant cytoplasmic glycogen can be demonstrated by PAS staining. IHC: CD99+.

Clinical Concerns:

- Chronic lymphocytic leukemia/small cell lymphocytic lymphoma – same process. CLL: presence of tumor in blood/bone marrow, small lymphocytic lymphoma: malignant cells in other tissues/organs without evidence of leukemia
- Low-grade clonal B-cell lymphoproliferative disorder that accounts for 25% of all cases of leukemia in Western countries
- Recurrence rates of BCC are significantly higher after Mohs surgery in patients with CLL

References:

Bahrami A1, Truong LD, Ro JY. Arch Pathol Lab Med. 2008 Mar;132(3):326-48.

Elston, D, Ferringer, Y, Peckham, S, High, WA, DiCaudo, DJ, Ko, C. (2014)
Dermatopathology, (2nd Edition). China: Elsevier.

Mehrany K1, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. Arch Dermatol. 2004
Aug;140(8):985-8.

Question 4

A 37-year-old Caucasian female was referred for treatment of a lesion on the right nasal sidewall. A representative section from the first stage of Mohs surgery is shown.

What is the most likely diagnosis?

- A. Trichoepithelioma
- B. Basal cell carcinoma
- C. Trichoblastoma
- D. Basaloid follicular hamartoma
- E. Trichoadenoma

Discussion

Question 4

Correct Answer:

C. Trichoblastoma

Main Histologic Features of Trichoblastoma:

- Tumors composed of irregular nests of basaloid cells, with no epidermal connection, that resemble basal cell carcinoma
- No retraction artifact
- Stroma resembles normal fibrous sheath of hair follicle, with concentric collagen and many fibroblasts
- Papillary mesenchymal bodies may be present with the stroma
- Mucin within tumor islands, but not in the stroma
- Pigmented variant reported

Histologic Differential Diagnosis:

- Basal cell carcinoma – basaloid cells, peripheral palisading, clefts between epithelium and stroma, myxoid stroma, mucin within stroma.
- Trichoepithelioma – basaloid cells, peripheral palisading, clefts between collagen fibers, fibroblast rich stroma, horn cysts, calcifications, mucin within tumor islands.

Clinical Concerns:

- Rare benign follicular neoplasm
- Usually greater than 1 cm in diameter and involves the deep dermis and subcutis
- Head, particularly scalp is the most common location
- Common tumor within organoid nevi

References:

Elston, D, Ferringer, Y, Peckham, S, High, WA, DiCaudo, DJ, Ko, C. (2014) Dermatopathology, (2nd Edition). China: Elsevier.

Weedon, D. (2002) *Skin Pathology* (second edition). China: Elsevier.

Question 5

A 91-year-old white female presented with a 2-week history of an ill-defined, depressed, slightly tender, violaceous plaque on the vertex, which was biopsy proven to be a well-differentiated angiosarcoma. Mohs surgery was attempted and the slides from the first Mohs layer (frozen sections and permanent sections from the same tissue) are submitted for your review. Which of the following statement is correct?

In this subsection,

- A. The margin is clear of angiosarcoma.
- B. There are focally positive angiosarcoma cells.
- C. There are diffusely positive angiosarcoma cells.
- D. Margin status cannot be determined.

Discussion

Question 5

Correct answer:

- C. There are diffusely positive angiosarcoma cells

Main Histopathologic Features:

- Angiosarcoma is often poorly circumscribed and infiltrative, with varied differentiation within a single lesion. Histological features of angiosarcoma can be subtle. The pathognomonic findings are abnormal, pleomorphic, hyperchromatic malignant endothelial cells that can be rounded, polygonal, or fusiform and can have an epithelioid appearance.
- The well differentiated, angiomatous pattern is characterized by irregular anastomosing vascular channels dissecting between collagen bundles. The vessels are lined by atypical endothelial cells, which can range from a nearly normal, single endothelial-cell lining to more aggressive, multilayered, papillary-like projections into irregular vascular lumens.
- The poorly differentiated tumors contain the malignant endothelial cells that are arranged in solid sheets or cords, with areas of hemorrhage and necrosis, and invading the dermis and underlying tissue.
- Immunohistochemical stains are helpful in diagnosis of angiosarcoma. Angiosarcoma typically expresses endothelial markers including von Willebrand factor, CD34, CD31, *Ulex europaeus* agglutinin 1, and vascular endothelial growth factor (VEGF).

Differential Diagnosis:

- Benign lymphangioendothelioma
- Kaposi sarcoma
- Carcinoma
- Amelanotic melanoma

Clinical Concerns:

- Angiosarcoma is a rare, extremely malignant tumor originating from endothelial cells of vascular or lymphatic differentiation. In some series, 5-year survival rates are only 10–20%.
- There are three main clinical variants: (1) idiopathic angiosarcoma of the scalp and face in the elderly, (2) angiosarcoma associated with chronic lymphedema (Stewart-Treves syndrome), and (3) postradiation angiosarcoma, which is the least common variant.
- Angiosarcoma of the scalp and face usually presents as a painless, rapidly proliferating, ill-defined plaque of dusky to violaceous erythema resembling a bruise and various benign lesions. Long-standing angiosarcoma may develop superimposed tumors and nodules, with ulceration and bleeding.
- Angiosarcoma is managed by wide local excision and adjuvant radiotherapy. Radical surgery attempting for complete resection is considered the primary treatment of choice, which is often difficult to achieve because of diffuse tissue

infiltration and tumor location. Mohs Micrographic Surgery with adjuvant radiation has been shown to produce a favorable outcome in several case reports but frozen sections especially without immunohistochemistry are often inferior to permanent paraffin sections in evaluating margin status of angiosarcoma.

References:

- Lever's Histopathology of the skin. 11th Ed. Edited by Elder DE, 2014; Wolters Kluwer
- Mentzel, T. Sarcomas of the skin in the elderly. *Clin Dermatol* **29**, 80-90 (2011).
- Patton, K.T., Deyrup, A.T. & Weiss, S.W. Atypical vascular lesions after surgery and radiation of the breast: a clinicopathologic study of 32 cases analyzing histologic heterogeneity and association with angiosarcoma. *Am J Surg Pathol* **32**, 943-50 (2008).
- Requena, L. & Sanguenza, O.P. Cutaneous vascular proliferations. Part III. Malignant neoplasms, other cutaneous neoplasms with significant vascular component, and disorders erroneously considered as vascular neoplasms. *J Am Acad Dermatol* **38**, 143-75 (1998).
- Bullen, R. *et al.* Angiosarcoma of the head and neck managed by a combination of multiple biopsies to determine tumor margin and radiation therapy. Report of three cases and review of the literature. *Dermatol Surg* **24**, 1105-10 (1998).



Question 6

An otherwise healthy 62-year-old white male is referred for Mohs surgery for a 5 mm, slightly erythematous papule on the frontal scalp. The slide from the first Mohs layer is submitted for your review.

What are your differential diagnoses?

- A. Vacuolated Bowen's disease/squamous cell carcinoma (SCC) in situ
- B. Melanoma in situ (MIS)
- C. Extramammary Paget's disease (EMPD)
- D. B and C
- E. All of the above

Discussion

Question 6

Correct Answer:

E. All of the above

Main Histologic Features:

- In Bowen's disease/SCC in situ, there are full thickness keratinocyte atypia and maturation disarray, resulting in a "windblown" appearance of the epidermis. Many cells are highly atypical with large, hyperchromatic nuclei. Often there are individual dyskeratotic cells which contain a bright eosinophilic cytoplasm and a hyperchromatic nucleus. There are hyperkeratosis and parakeratosis.
- An occasional finding in Bowen's disease/SCC in situ is vacuolization of the keratinocytes. Single atypical vacuolated keratinocytes scatter among benign keratinocytes, showing a pattern of "Pagetoid Bowen's disease."

Differential Diagnosis:

- Vacuolated Bowen's disease/SCC in situ
- Vacuolated actinic keratosis
- MIS
- EMPD

Clinical Concerns:

- Pagetoid variant of Bowen's disease does not carry a prognostic significance. However, it must be differentiated from MIS and EMPD. Clinical history and presentation are helpful and the final diagnosis can often be made on routine permanent paraffin sections without utilizing immunohistochemistry (IHC) staining.
- Several features help confirm the diagnosis of Pagetoid Bowen's disease and differentiate it from MIS and/or EMPD: lack of maturation of keratinocytes, intercellular desmosomal connections between keratinocytes creating "spiny" appearance, and frequent presence of dyskeratosis.
- In MIS, usually there are associated melanin pigment and possibly nesting of cells.
- In EMPD, there may be some areas showing glandular formation and aggregates, the Pagetoid cell cytoplasm has a subtle mucinous appearance, and tumor cells are predominantly located in the basal layer arranged as single cells or clusters. There may be hyperkeratosis and parakeratosis but usually no dyskeratosis. In contrast, in Pagetoid Bowen's disease, the keratinocytes are atypical and may have a dense/smooth bubble gum pink appearance. Paget cells are often PAS positive and diastase resistant, while vacuolated cells in Bowen's disease may be PAS positive but are usually diastase labile. In addition to PAS, EMPD often stains positive for mucicarmine and Alcian Blue.
- If indicated, IHC staining can be employed to aid in differential diagnoses, as illustrated in the table below.

	Keratin Markers (i.e. HMWK)	Melanocytic Markers (i.e. MART-1, S-100)	CK7
Pagetoid Bowen's disease	+	-	-
MIS	-	+	-
EMPD	-	-	+

References:

- Lever's Histopathology of the skin. 11th Ed. Edited by Elder DE, 2014; Wolters Kluwer
- Raiten K, Paniago-Pereira C, Ackerman AB. Pagetoid Bowen's disease vs. extramammary Paget's disease. J Dermatol Surg.1976;2(1):24-5.
- Strayer DS, Santa Cruz DJ. Carcinoma in situ of the skin: a review of histopathology. J Cutan Pathol.1980;7(4):244-59.

Du X et al. Extramammary Paget's disease mimicking acantholytic squamous cell carcinoma in situ: a case report. J Cutan Pathol. 2010;37(6):683-6.

Question 7

A 43-year-old female with a history of a recurrent basal cell carcinoma of the right shoulder is referred for Mohs surgery.

The correct diagnosis is:

- A. Infiltrative basal cell carcinoma with peritumoral inflammation
- B. Infiltrative basal cell carcinoma with reactive lymph node
- C. Basal cell carcinoma with lymph node metastasis
- D. No evidence of persistent basal cell carcinoma

Discussion

Question 7

Correct Answer:

C. Basal cell carcinoma with lymph node metastasis.

Main Histologic Features:

- Deep dermis reveals infiltrative strands of poorly differentiated basaloid carcinoma.
- Deeper sections reveal tumor infiltrating subcutis and fascia.
- Close inspection of lymph nodes reveals tumor present.

Differential Diagnosis:

- No evidence of persistent tumor with reactive lymph node
- Tumor present with surrounding inflammation
- Secondary lymphoproliferative process

Clinical Concerns:

- Metastatic BCC is incredibly rare (.0028-.55%) but there are increasing reports over the last several decades. May be due to publication bias versus paralleling ongoing epidemic of skin cancer.
- The average age of patients with metastatic BCC is 50 yrs, and average survival is 10 months.
- Lymph nodes are most common sites of metastasis (53%), followed by lung (33%) and bone (20%).
- If there is concern of tumor involvement, immunoperoxidase stains may be useful, particularly Ber-EP4.

References:

- Wysong A, Aasi SZ, Tang JY. Update on Metastatic Basal Cell Carcinoma: A Summary of Published Cases from 1981 Through 2011. *JAMA Dermatol* 2013;149(5):615-6.
- Kist D, Perkins W, Christ S, et al. Anti-human epithelial antigen (Ber-EP4) helps define basal cell carcinoma masked by inflammation. *Dermatol Surg* 1997;23:1067-70.
- Saladi RN, Singh F, Wei H, Lebwohl MG, Phelps RG. Use of Ber-EP4 protein in recurrent metastatic basal cell carcinoma: a case report and review of the literature. *Int J Dermatol*. 2004;43(8):600-3.

Question 8

A 74-year-old male with a 4-centimeter squamous cell carcinoma on the right temple is referred for Mohs surgery.

The correct diagnosis is:

- A. No evidence of persistent squamous cell carcinoma.
- B. Squamous cell carcinoma with extensive peritumoral inflammation but no evidence of neural or lymphovascular invasion.
- C. Squamous cell carcinoma whose most prominent feature is extensive perineural invasion.
- D. Squamous cell carcinoma whose most prominent feature is extensive lymphovascular invasion.

Discussion

Question 8

Correct Answer:

- D. Squamous cell carcinoma whose most prominent feature is extensive lymphovascular invasion.

Main Histologic Features:

- Invasive poorly-differentiated squamous cell carcinoma infiltrates the subcutaneous and fascial tissues in close proximity to nerves multifocally, and while robust perineural inflammation is evident, true perineural invasion is somewhat challenging to appreciate.
- Extensive lymphovascular invasion is present.

Differential Diagnosis:

- Squamous cell carcinoma with perineural invasion
- Tumor present with surrounding inflammation

Clinical Concerns:

- In comparing frozen to paraffin-embedded histology slides for high-risk cutaneous SCC, the false-negative rate (i.e., missed on frozen sections but identified on permanents) of lymphovascular invasion has been reported to be 36%.
- Lymphovascular invasion can typically be differentiated from perineural invasion on Mohs sections, although IHC may be helpful in settings of extensive inflammation or other histologically complicating factor.
- Lymphovascular invasion has been associated with worse clinical outcomes, as has temple location and other factors in this case.

References:

- Chambers KJ, Kraft S, Emerick K. Evaluation of Frozen Section Margins in High-Risk Cutaneous Squamous Cell Carcinomas of the Head and Neck. *Laryngoscope* 2014 Sep 17 (epub ahead of print).
- Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors Predictive of Recurrence and Death From Cutaneous Squamous Cell Carcinoma: A 10-Year, Single-Institution Cohort Study. *JAMA Dermatol.* 2013;149(5):541-7.

Question 9

A 58-year-old white male underwent Mohs surgery for a nodular and adenoid basal cell carcinoma of the right temple. The first Mohs stage demonstrated the following histologic finding:

The correct diagnosis is:

- A. Intravascular basal cell carcinoma
- B. Peritumoral fibrosis
- C. In-transit basal cell carcinoma metastasis
- D. Mucinous eccrine carcinoma

Discussion

Question 9

Correct Answer:

B. Peritumoral fibrosis

Main Histologic Features:

- Peritumoral fibrosis refers to concentric layers of fibrous tissue surrounding or surrounded by tumor formations and may mimic perineural invasion
- Peritumoral fibrosis may also mimic intravascular invasion as retraction artifact with significant tumor stromal fibrosis may simulate a vascular lumen
- Immunohistochemistry using Movat pentachrome stain may differentiate peritumoral fibrosis from intravascular invasion by distinguishing the smooth muscle of the vascular tunica media from the collagen of peritumoral fibrosis. Movat pentachrome stain exhibits the following characteristics: nuclei and elastic fibers stain black; collagen and reticular fibers stain yellow; ground substance and mucin stain blue; fibrin stains bright red, and muscle stains dull red.

Differential Diagnosis:

- Intravascular tumor invasion

Clinical Concerns:

- Intravascular spread of basal cell carcinoma is uncommon but must be considered during examination of Mohs sections as its identification significantly alters work-up, management and prognosis.
- Although peritumoral fibrosis has been described as a mimic of perineural invasion, the present case illustrates that peritumoral fibrosis may also mimic intravascular basal cell carcinoma

References:

- Hassanein AM, Proper SA, Depcik-Smith ND, Flowers FP. Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: potential pitfall in Mohs micrographic surgery. *Dermatol Surg.* 2005 Sep;31:1101-6.
- Bancroft JD and Gamble M. *Theory and Practice of Histological Techniques.* Philadelphia: Churchill Livingstone Elsevier; 2008.

Question 10

An 83-year-old white male underwent Mohs surgery for 2.5cm poorly differentiated squamous cell carcinoma involving the frontal scalp, recurrent after electrodesiccation and curettage. The first Mohs stage demonstrated the following histologic finding at the deep margin:

The correct diagnosis is:

- A. Intranearal squamous cell carcinoma
- B. Squamous cell carcinoma with stromal changes mimicking intraneural invasion
- C. Perineural squamous cell carcinoma
- D. Clear surgical margin

Discussion

Question 10

Correct Answer:

- B. Squamous cell carcinoma with stromal changes mimicking intraneural invasion

Main Histologic Features:

- Longitudinal sectioning of tumor stroma may yield well-circumscribed bundles of cellular, slightly myxoid, stroma that simulate the longitudinal section of a peripheral nerve. Tumor islands within this stroma may mimic intraneural SCC
- Histologic features differentiating longitudinal stroma section from true peripheral nerve: true nerve has perineurium and characteristically 'wavy' fibers and nuclei
- Immunohistochemistry with cytokeratin, S-100 and Movat's pentachrome stain may be helpful in determining the relationship between tumor, nerve and stroma in such difficult cases

Differential Diagnosis:

- Intraneural or perineural squamous cell carcinoma

Clinical Concerns:

- The presence of intraneural or perineural invasion on Mohs sections may alter management and be associated with higher risk of tumor, recurrence, metastasis and poor clinical outcome, particularly in nerves ≥ 0.1 mm.
- Complex interactions between the epidermal cancer cells and their surrounding stroma, consisting of extra-cellular matrix, cancer-associated fibroblasts (CAFs), immune cells and vasculature mediate tumor invasion
- By definition, CAFs are fibroblasts residing in the tumor stroma, either in direct contact with or in the vicinity of epithelial cancer cells. They support tumor progression by inducing ECM remodeling, basement membrane breakdown, and neo-vascularization (via stromal cell-derived factor 1)
- CAFs have myofibroblastic properties and express alpha smooth muscle actin (α -SMA), important in cell adhesion, tension and contractility. Increased stromal α -SMA is clinically associated with increased invasiveness of oral, cervical, colorectal and breast carcinoma
- Morphologically, CAFs in primary cutaneous SCC are long, spindle shaped, and do not exhibit contact inhibition, in contrast to normal dermal fibroblasts, which are short, star shaped, and exhibit contact inhibition.

References:

Commandeur S, Ho SH, de Gruijl FR, et al. Functional characterization of cancer-associated fibroblasts of human cutaneous squamous cell carcinoma. *Exper Dermatol* 2011;20:737–742

Ross AS, Whalen FM, Elenitsas R, et al. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. *Dermatol Surg*. 2009;35:1859–1866.