ASSOCIATION OF COMMUNITY CANCER CENTERS

High Risk Cutaneous Squamous Cell Carcinoma: Recognition and Management

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ACCC
Association of Community Cancer Centers

Disclosures

- Advisory Board, Regeneron-Sanofi
- Speaker Bureau, Genentech

Objectives

- Following this session, attendees should be able to:
- 1) identify lesions suspicious for cutaneous squamous cell carcinoma (cSCC)
- 2) understand the clinical and histologic features of high risk cSCC
- 3) understand the management options for low risk and high risk cSCC, including new treatment approaches for advanced disease

Epidemiology of cSCC

- More than 1 million new cases diagnosed in US each year with annual increase of 2%-4%
- Significant risk of metastasis (4%)
- Case-fatality rate approx. 1.5% at 15,000 cases/year

cSCC - Classification

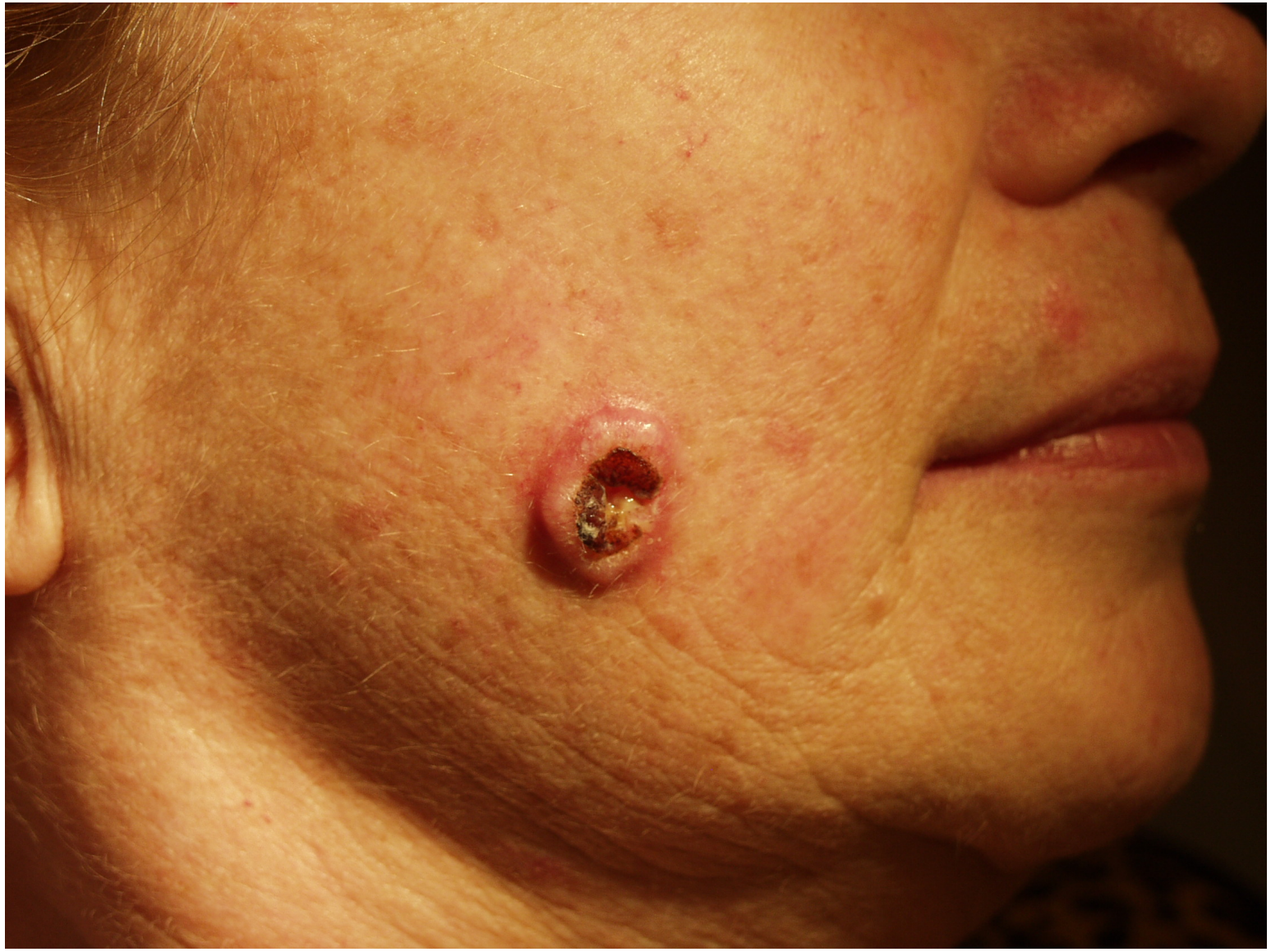
- Low risk tumors
- High risk tumors

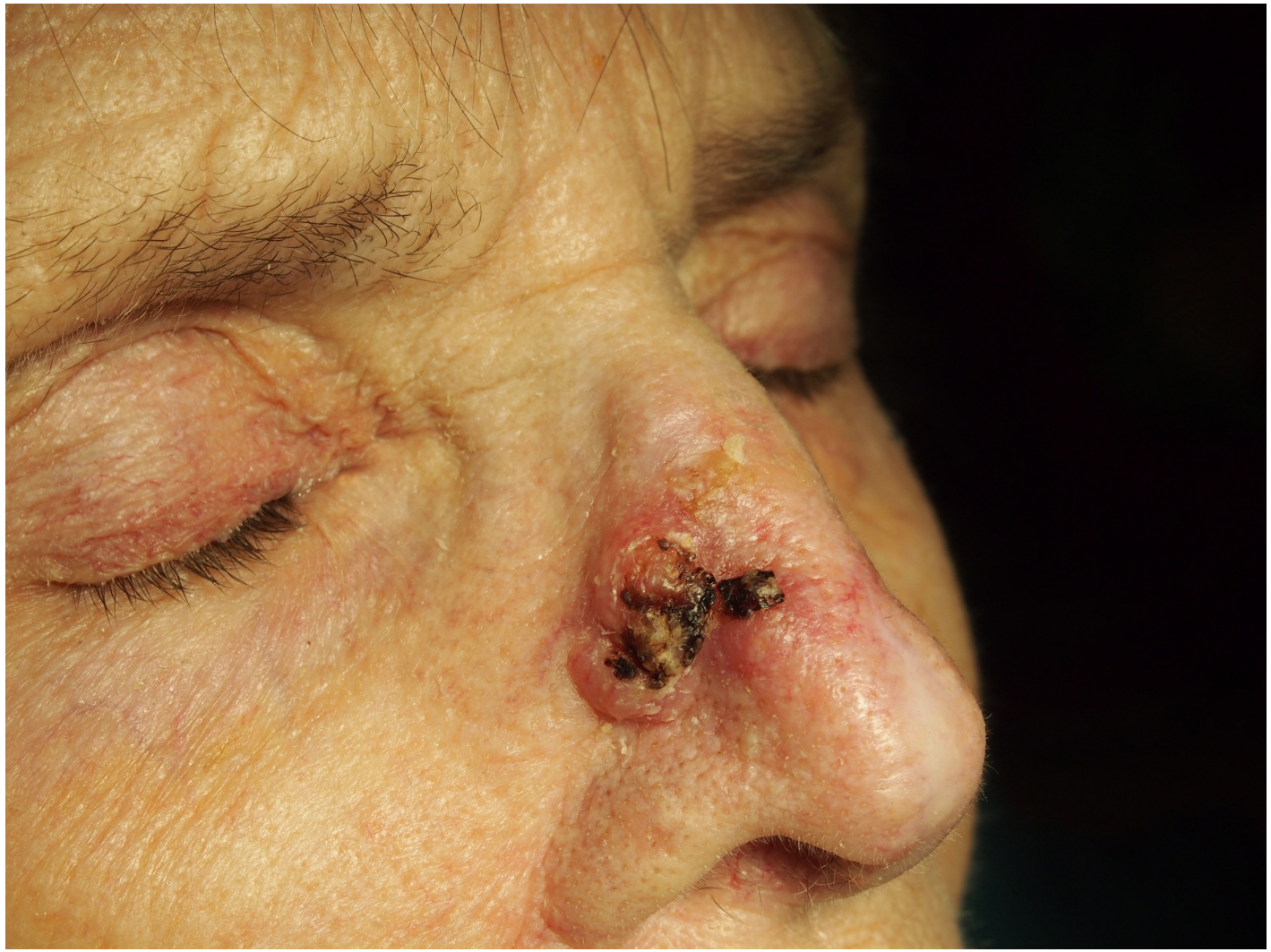
Low risk cSCC

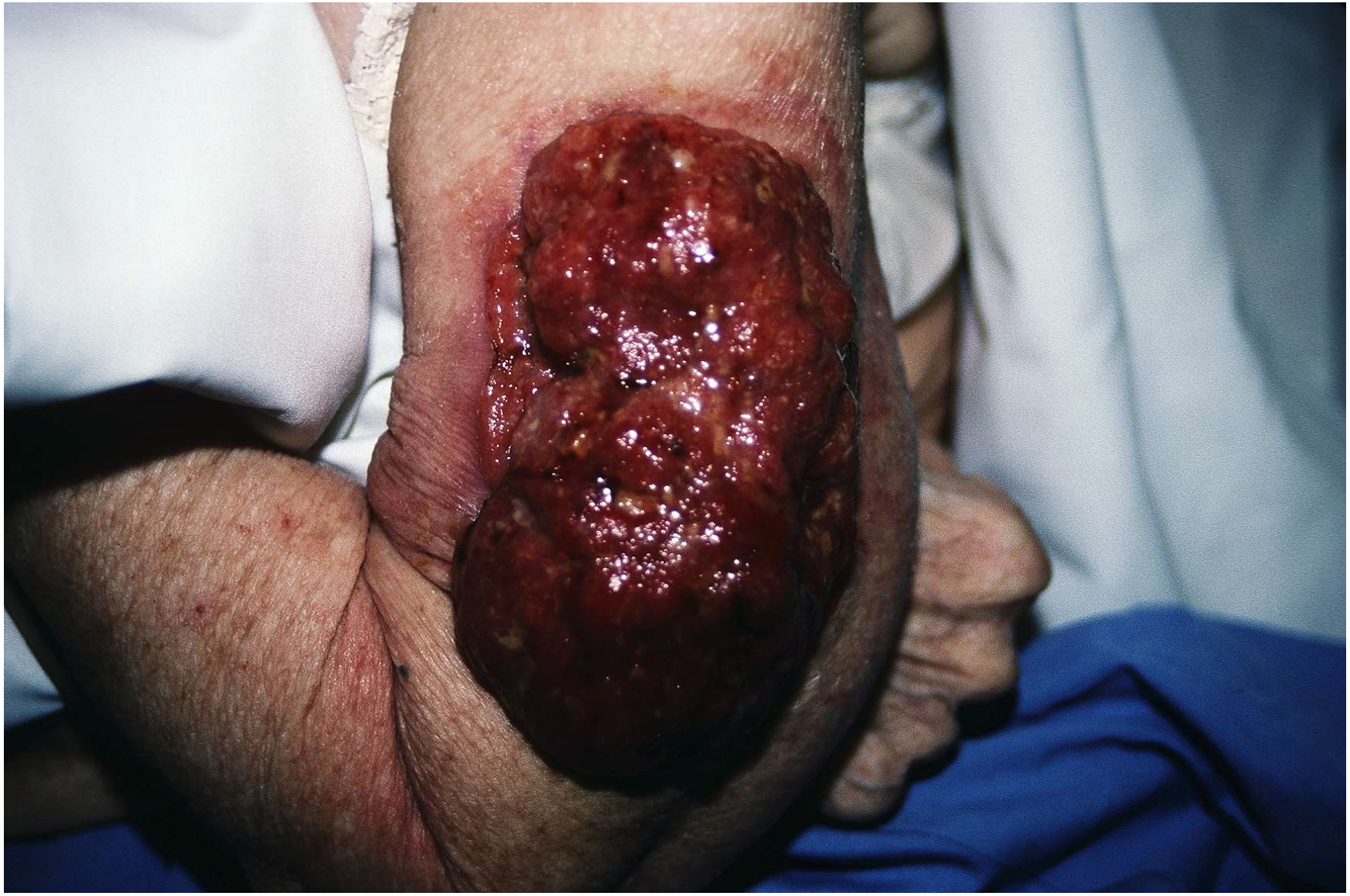
- 5-year recurrence rate is 5-8%
- 5-year rate of metastasis is 5%

High Risk cSCC

- SCC at greater risk for recurrence and metastasis than low risk cSCC

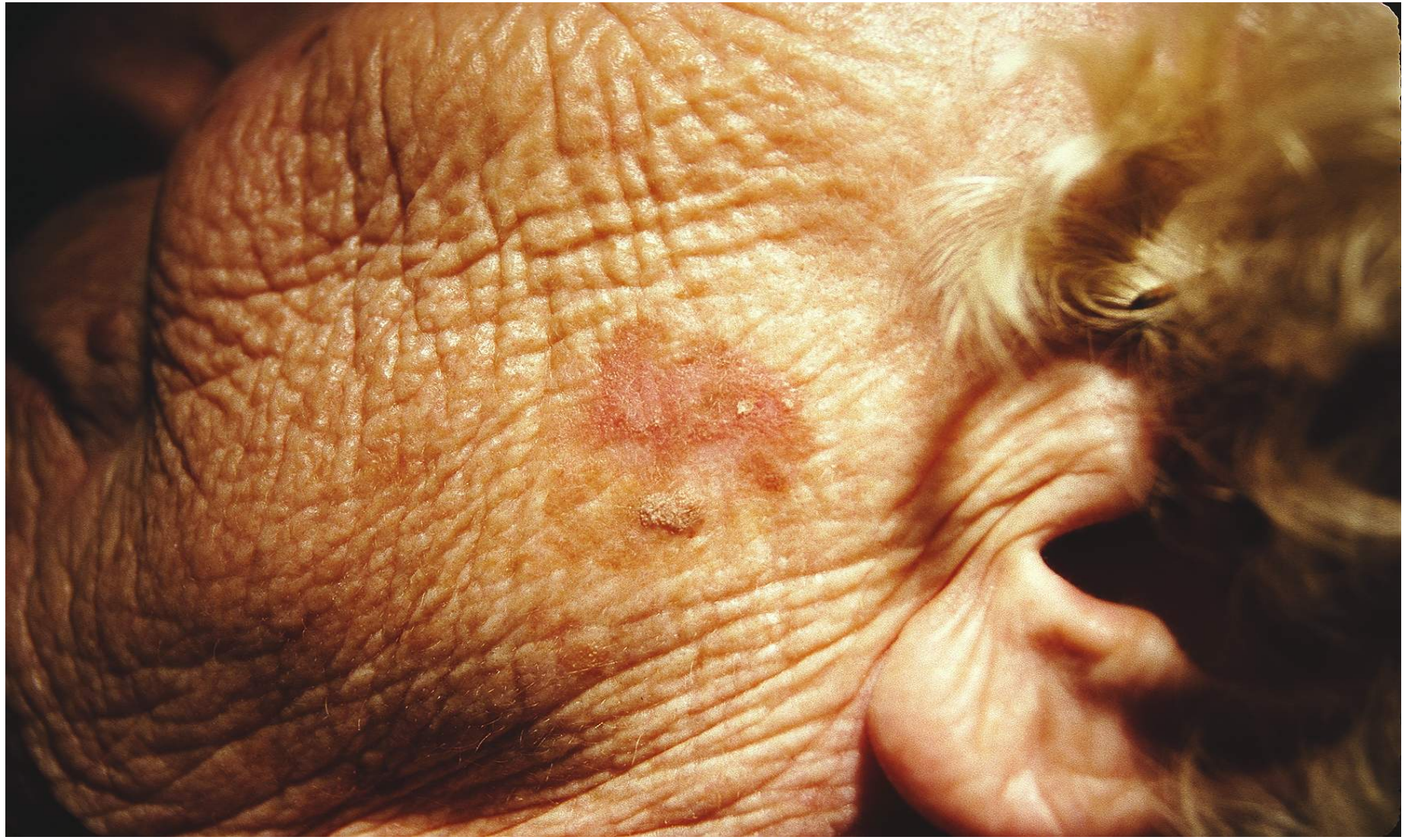


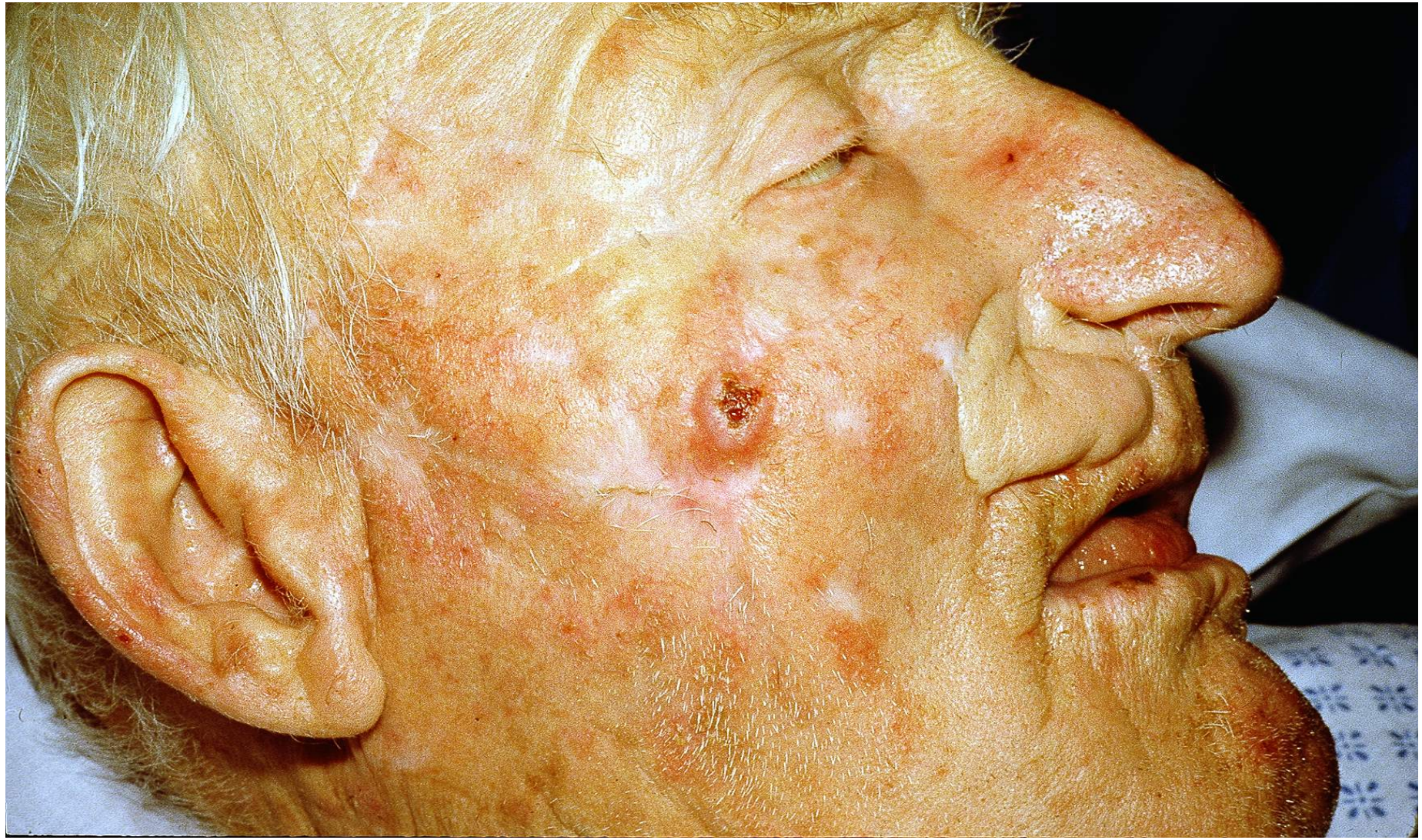




cSCC - Risk Factors

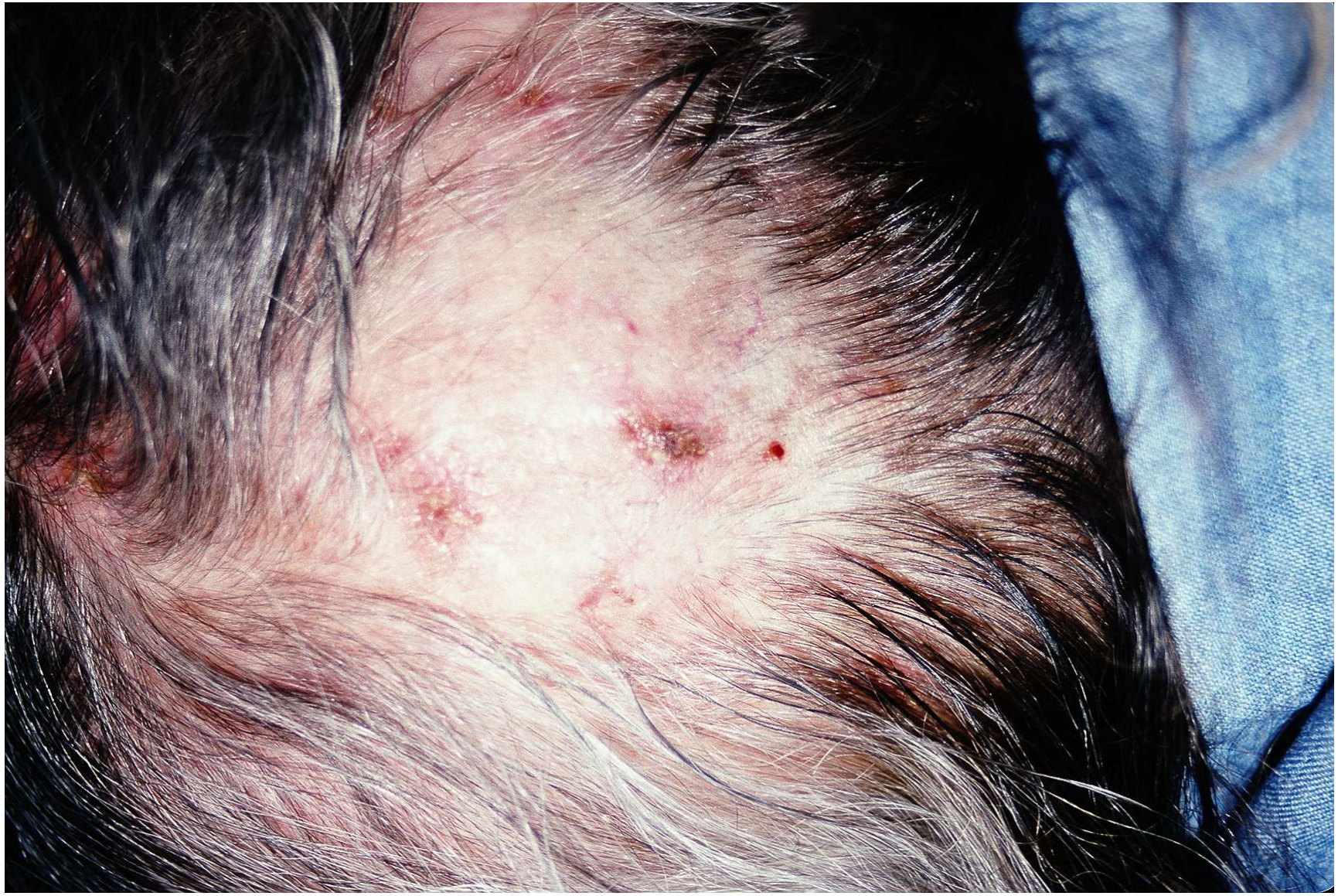
- Ultraviolet radiation
- Ionizing radiation
- Genodermatoses
- Human papillomavirus (HPV)
- Chemical carcinogens
- Immunosuppression
- Chronically injured/diseased skin

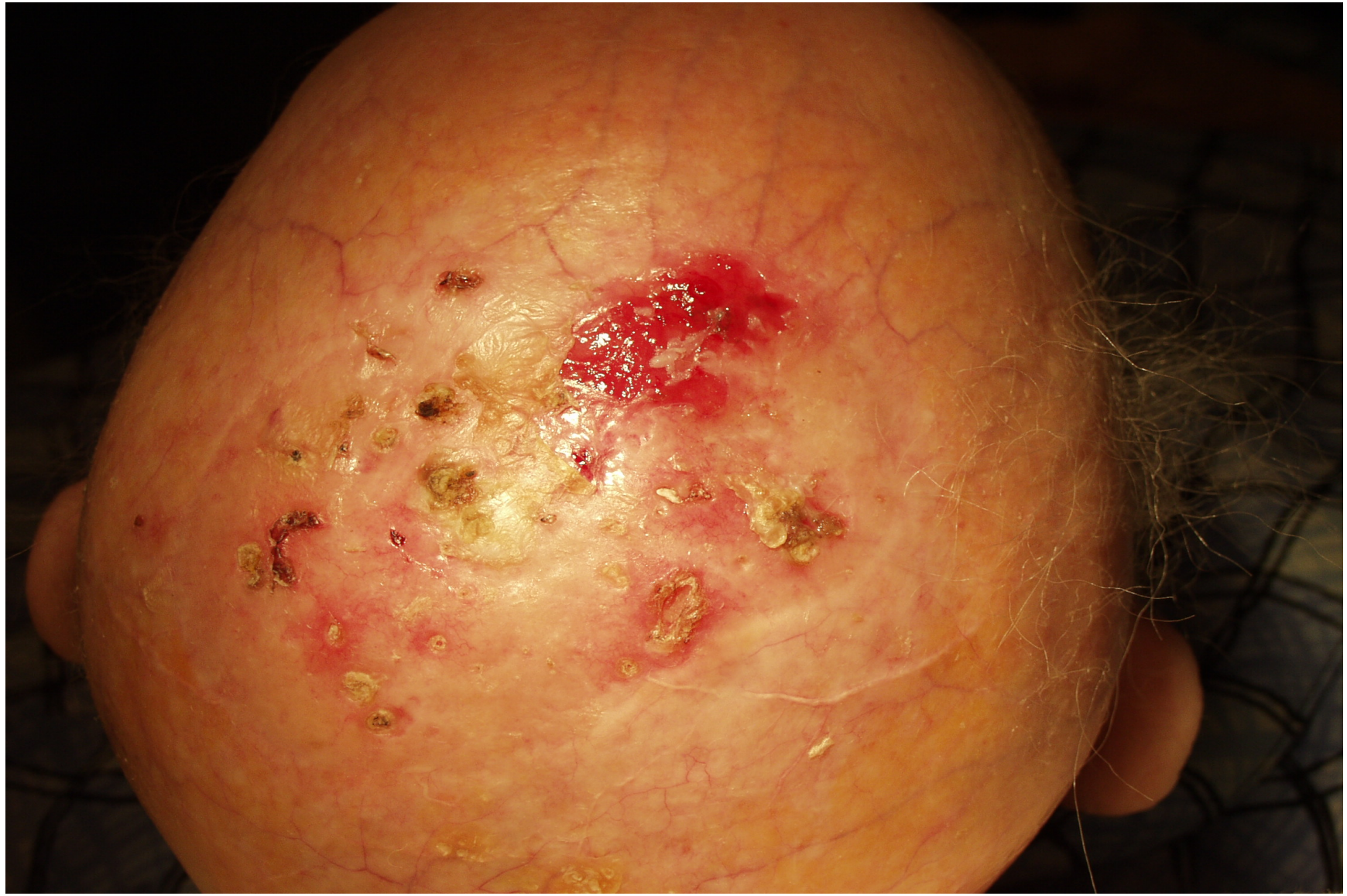




cSCC - Ionizing radiation

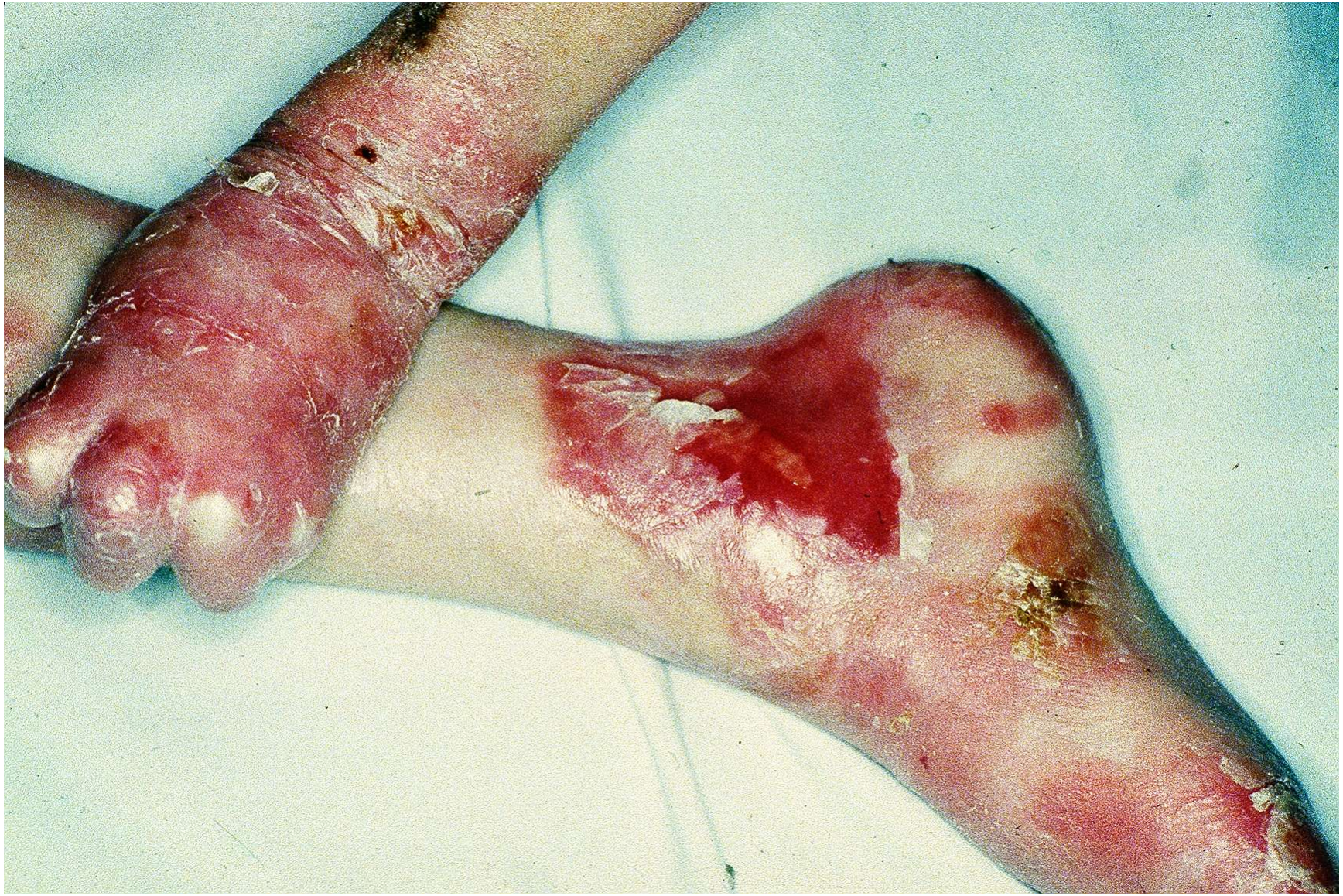
- Used commonly in 1940's-50's to treat benign dermatoses
- SCC risk directly related to total accumulated dose
- Latent period before tumor development varies inversely with total dose
- Tumor development typically related to x-radiation, but gamma and grenz rays further augment risk





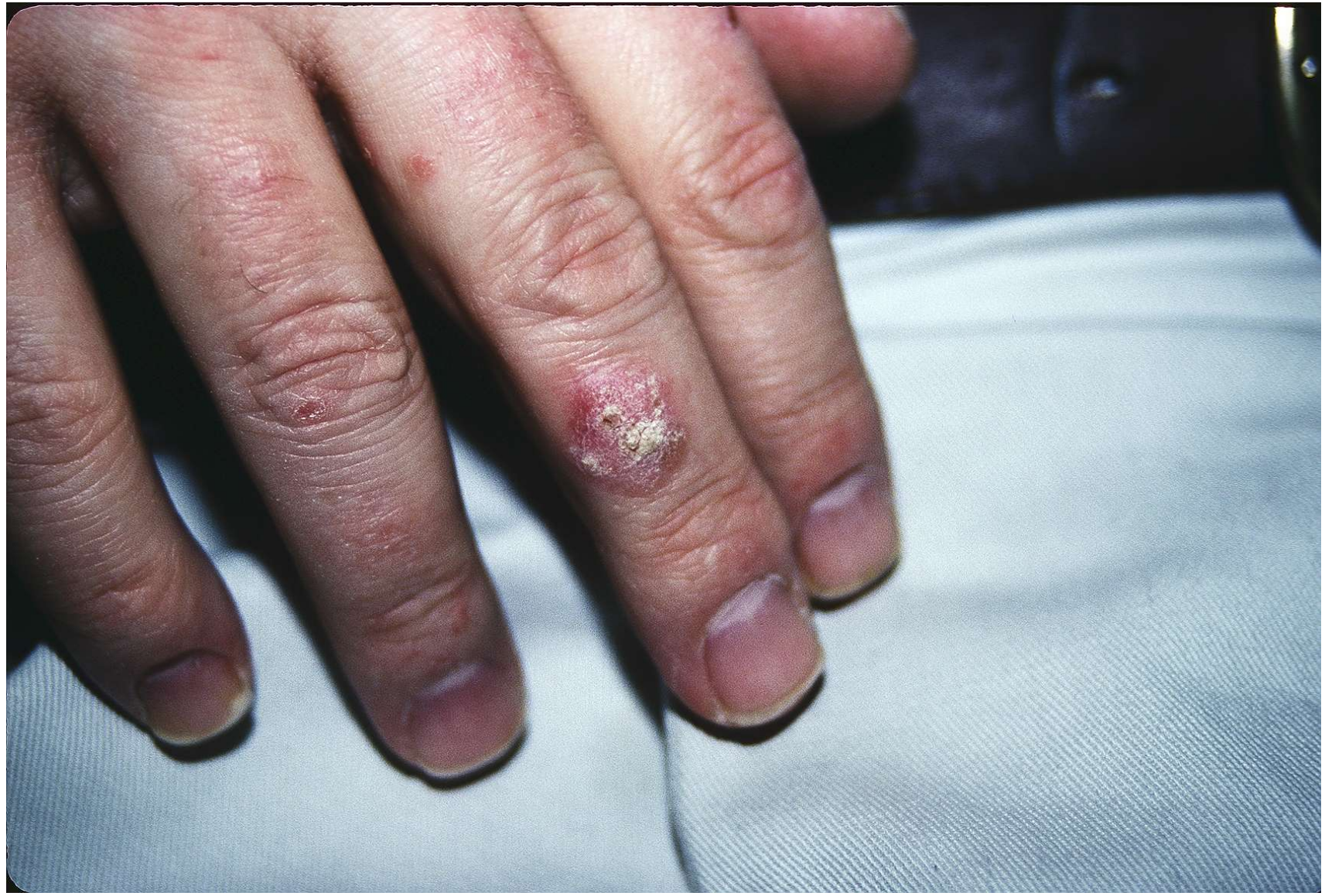
cSCC - Genodermatoses

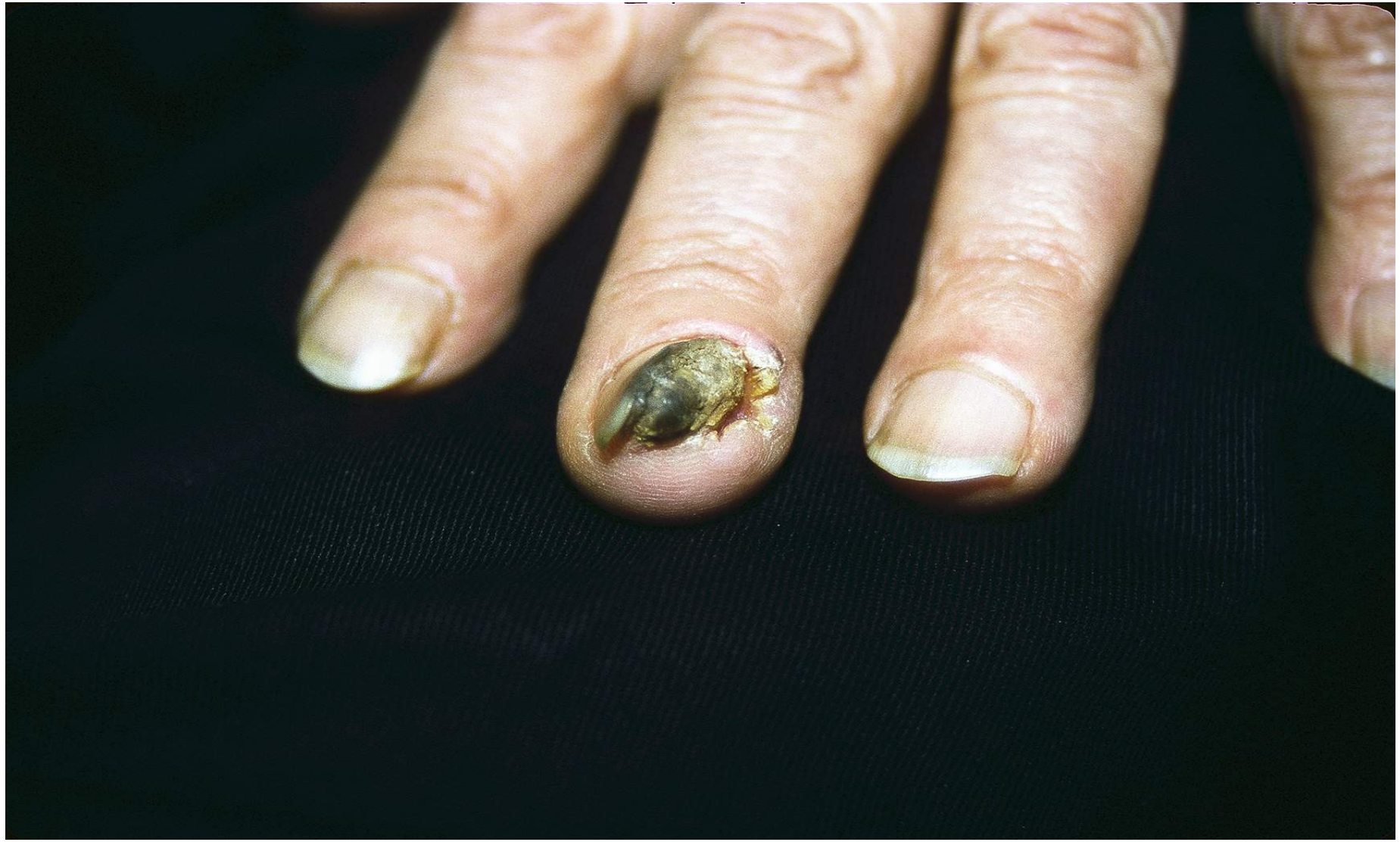
- Oculocutaneous albinism
- Xeroderma pigmentosum
- Dystrophic epidermolysis bullosa
- Epidermodysplasia verruciformis



cSCC - Human papillomavirus (HPV)

- HPV types 6 and 11 common in genital tumors
- HPV type 16 common in periungual tumors



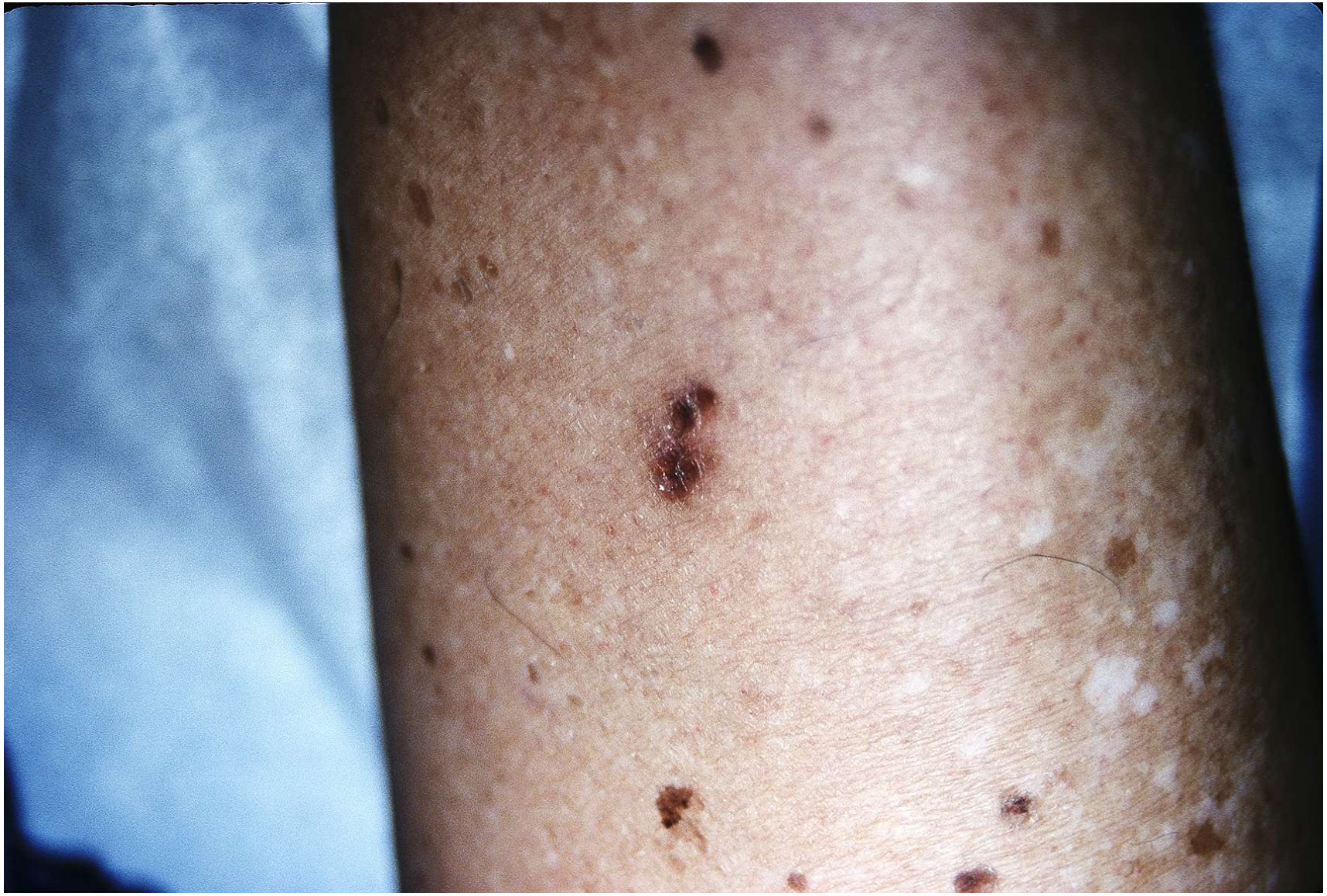


cSCC - Chemical agents

- Arsenic
  - Patent medicines- Fowler's solution, Asiatic pills
  - Tainted wine and unprocessed well water in developing countries
  - Metal ore workers and insecticide handlers

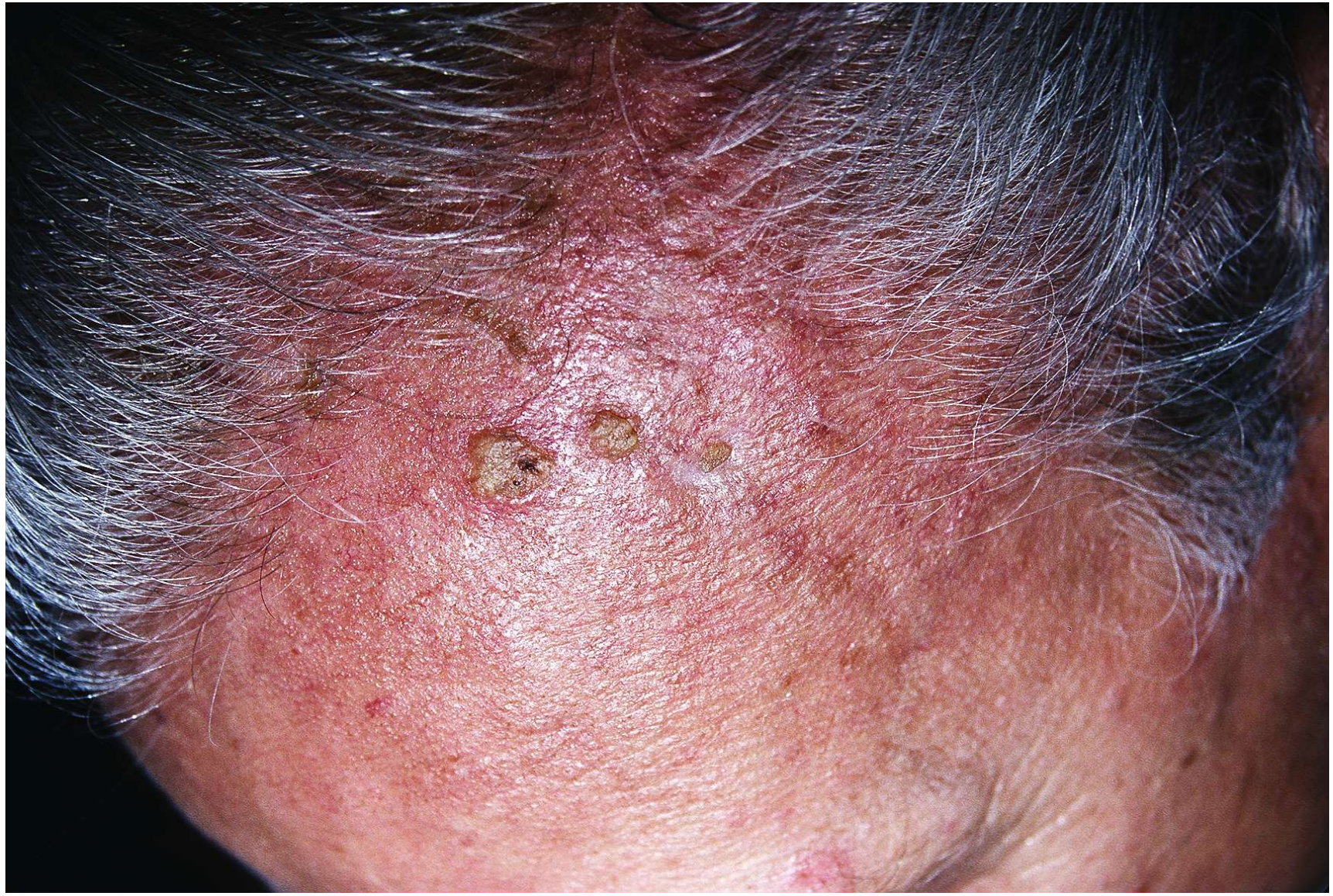
cSCC - Chemical agents

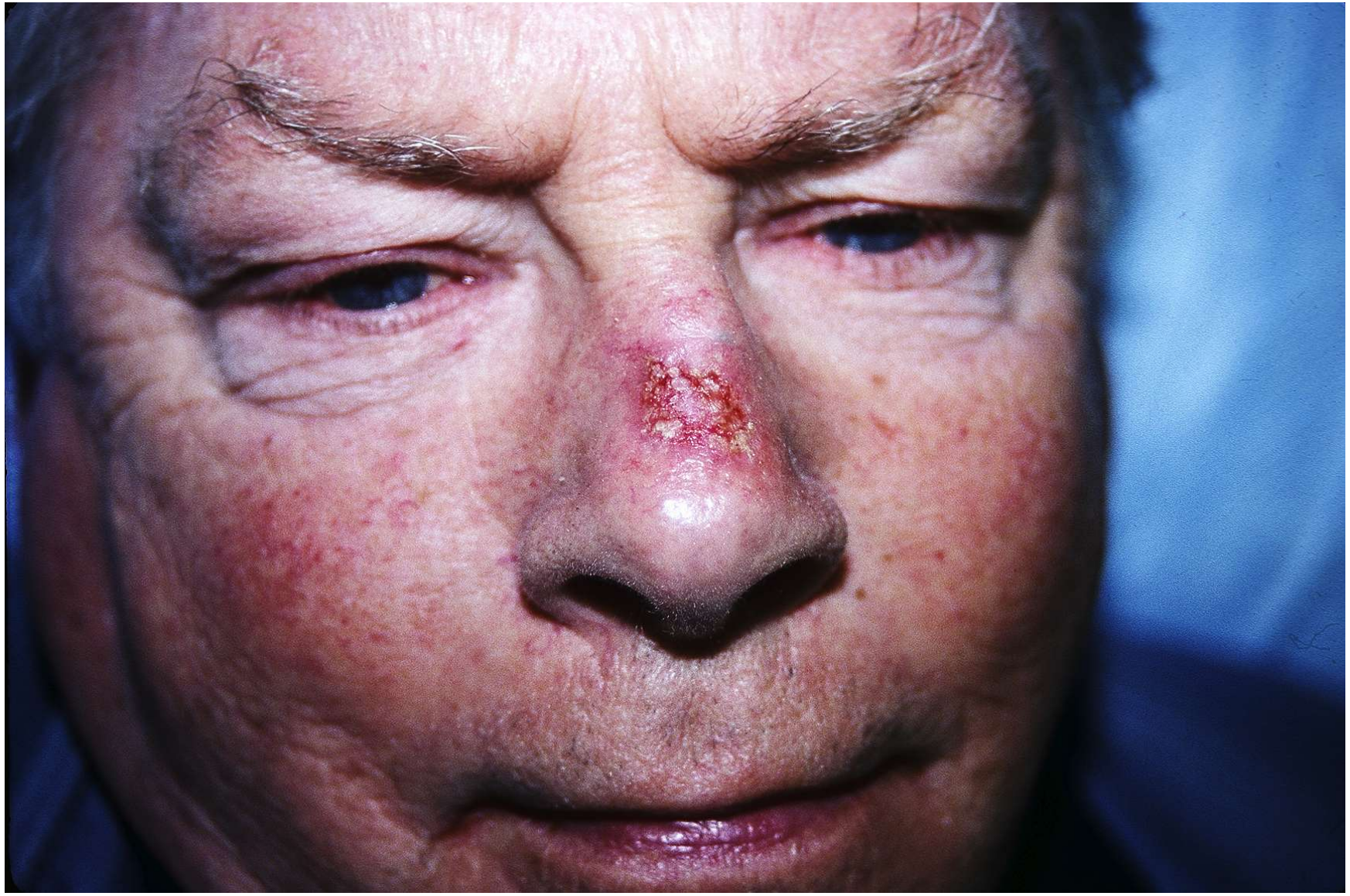
- Arsenic
  - Produces invasive and in situ tumors on exposed and covered skin
  - Arsenical keratoses and/or pits on palms and soles
  - Circular areas of hypopigmentation on trunk
  - Carcinogenicity is dose-dependent, with an associated risk of internal malignancy



cSCC - Immunosuppression

- Organ transplant patients at increased risk
- Higher SCC:BCC ratio
- Transplant patients 65x more likely to develop cSCC
  - Lesions appear 2-4 years after transplant
  - Lesions increase in number over time
  - Lesions more aggressive than in normal hosts
- Tumor formation may be potentiated by immunosuppressive medications, leukemia, lymphoma





cSCC – Injured or chronically diseased skin

Longstanding ulcers

Sinus tracts

Osteomyelitis

Radiation Dermatitis

Vaccination scars

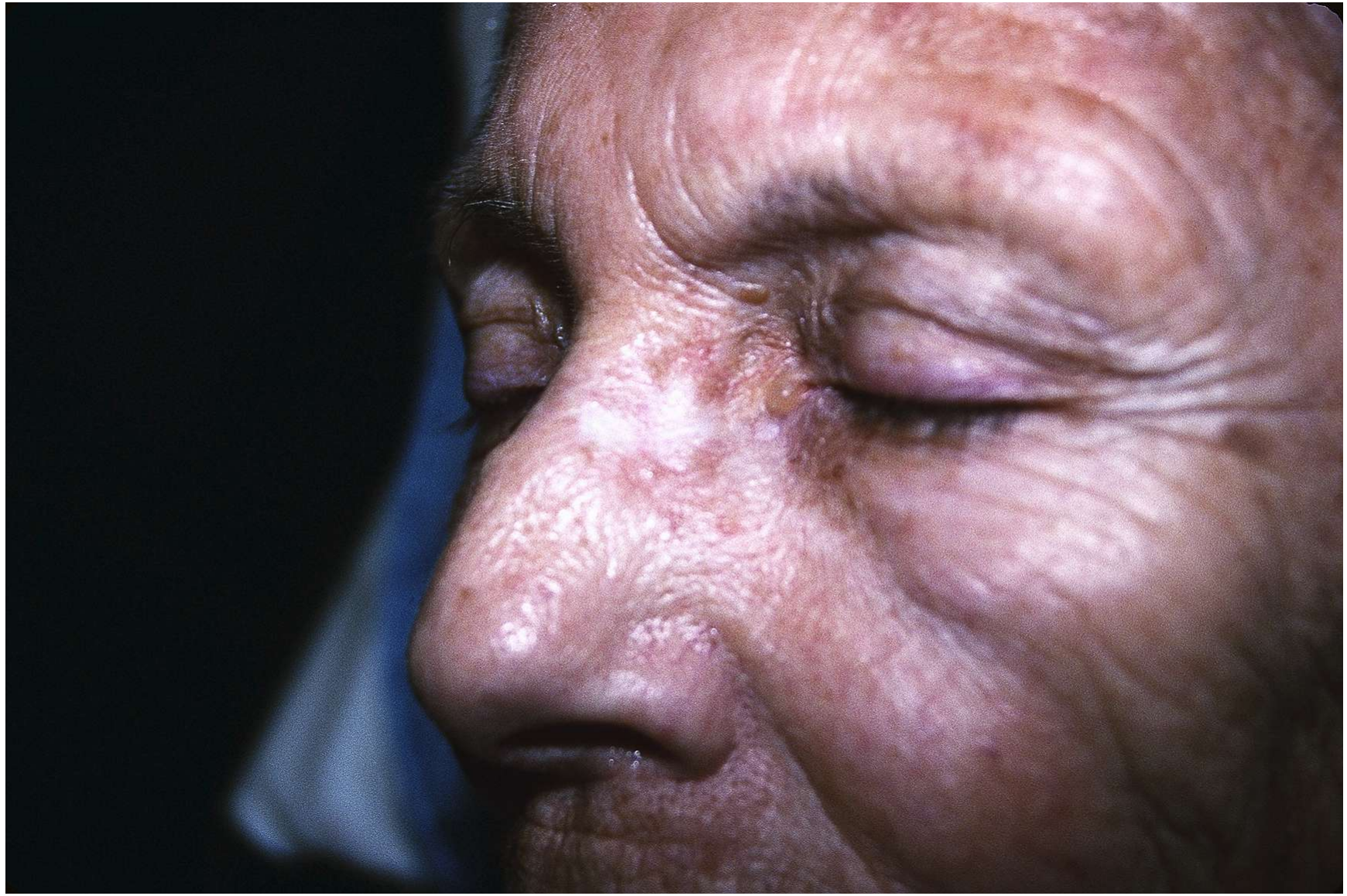
Discoid lupus erythematosus

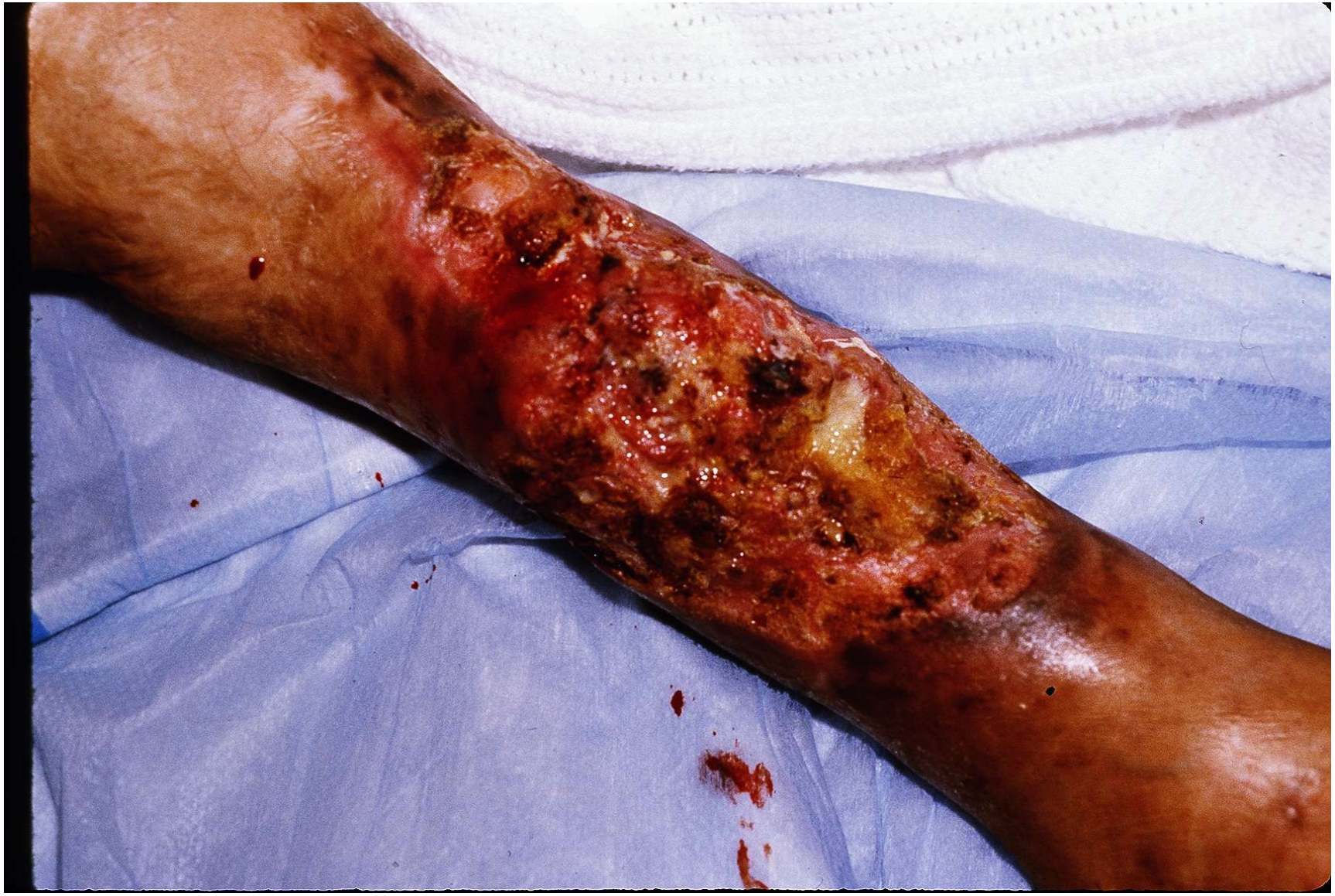
Lichen sclerosus et atrophicus

Lichen planus

Dystrophic epidermolysis bullosa

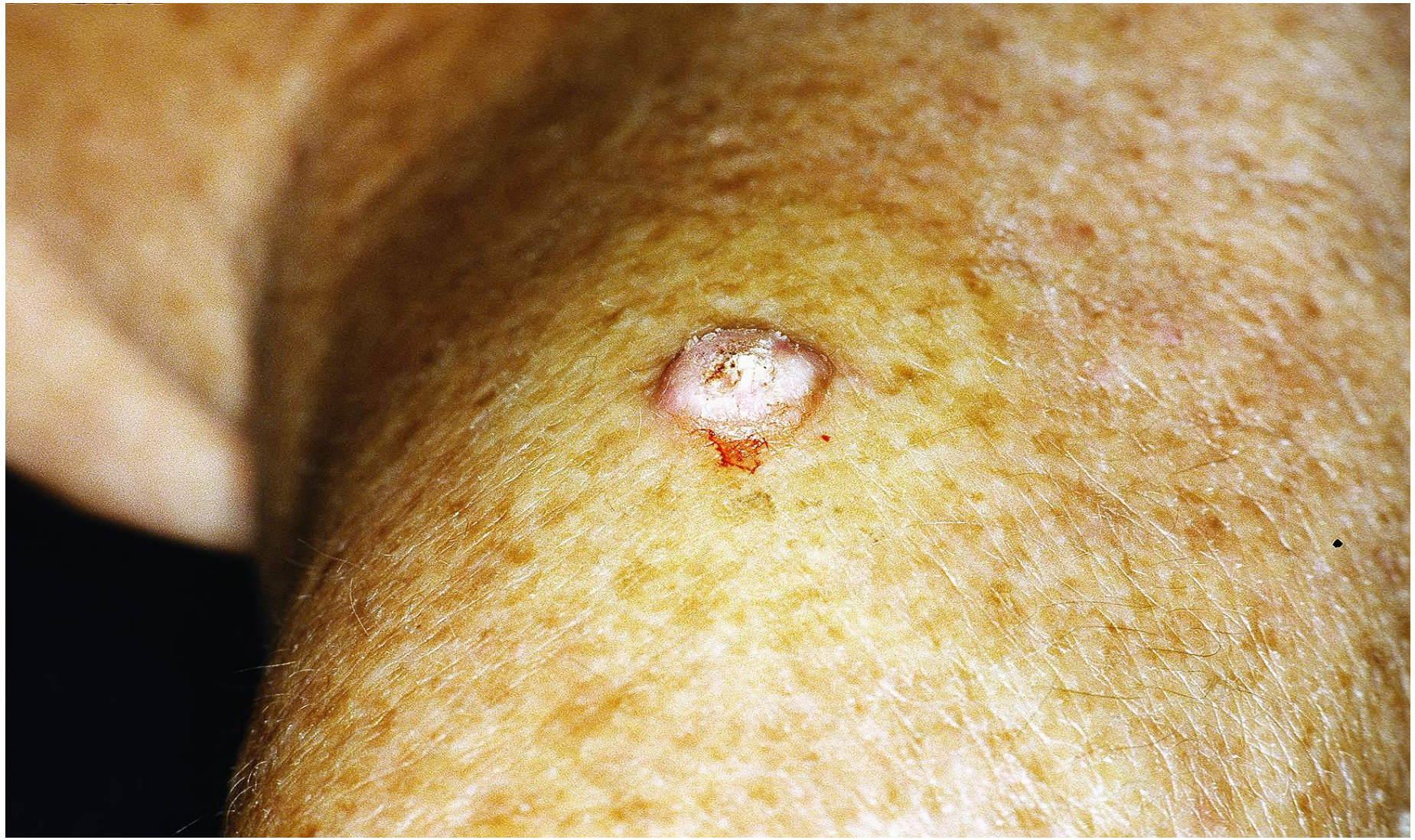
Lupus vulgaris





cSCC - Classification

- Low risk tumors
- High risk tumors



Low risk cSCC

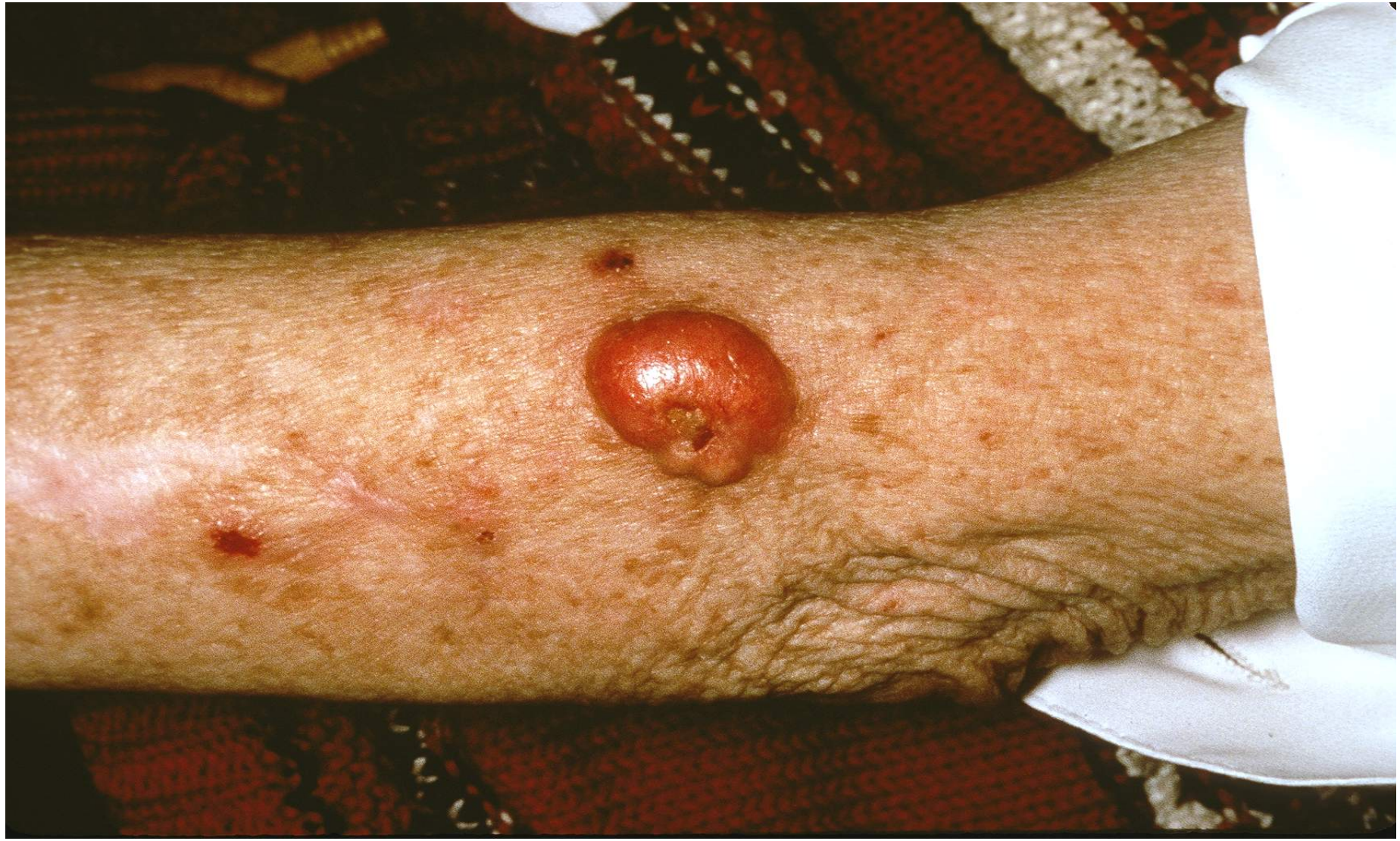
- Size <1 cm
- Well defined
- Primary
- Located on neck, trunk, extremities

Low risk cSCC- Treatment

- Electrodesiccation and curettage (ED&C)
- Excision
- Cryosurgery
- Radiation therapy
- Photodynamic therapy

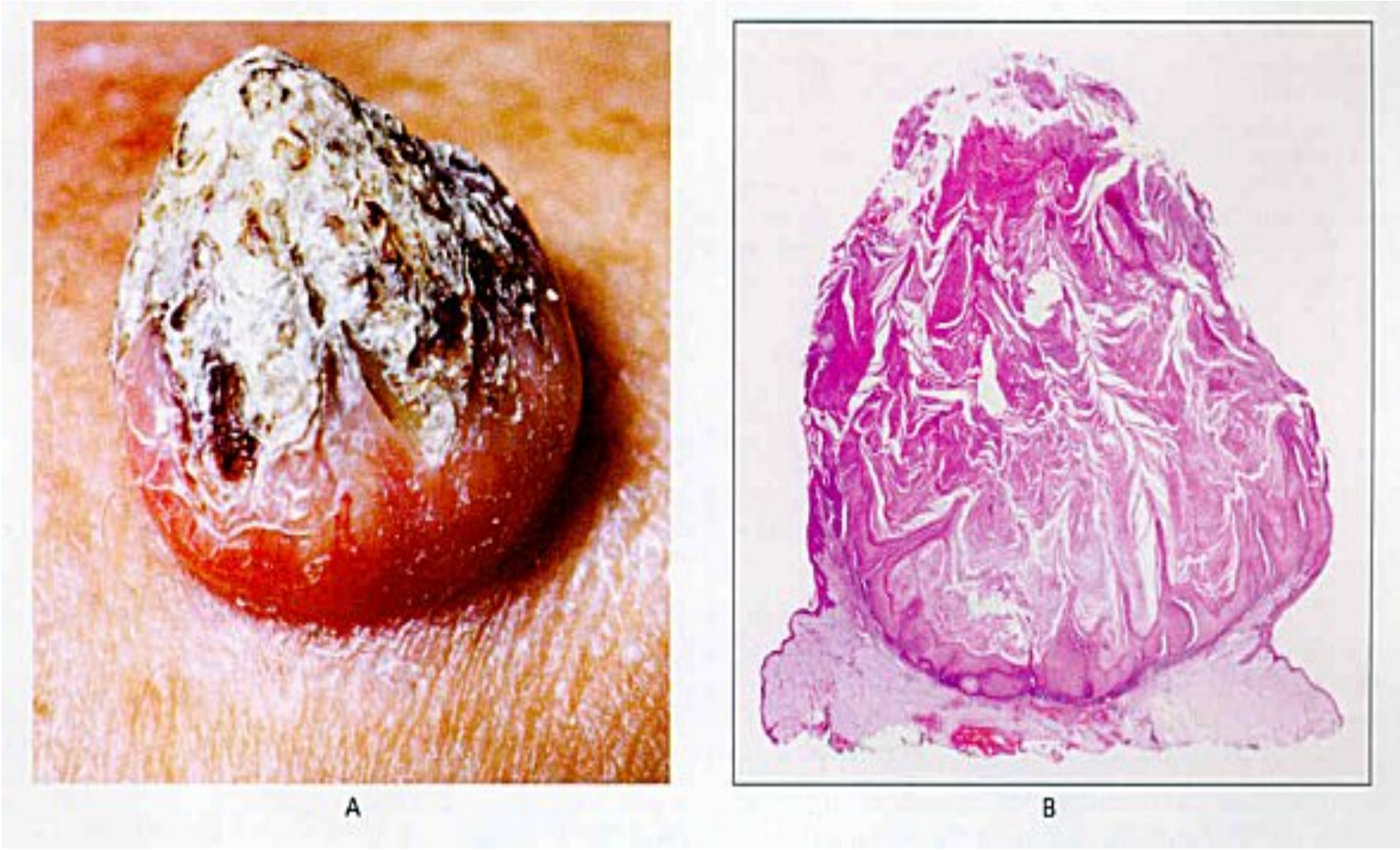
Low risk cSCC –post-treatment recurrence

	< 5 yr follow-up	> 5 yr follow-up
Cryotherapy	3.2%	N/A
ED+C	1.3%	3.7%
Excision	5.7%	8.1%
Radiation	6.7%	10.0%
Non-Mohs modalities	4.0%	7.0%
Mohs surgery	N/A	3.1%



Keratoacanthoma (KA)

- Low-grade keratinocyte malignancy originating in pilosebaceous units
- Rapid growth over weeks to months, followed by resolution over 4-6 months in most cases
- Infrequently presents as multiple tumors or giant lesions (5-15 cm)
- Rarely progresses to invasive or metastatic disease

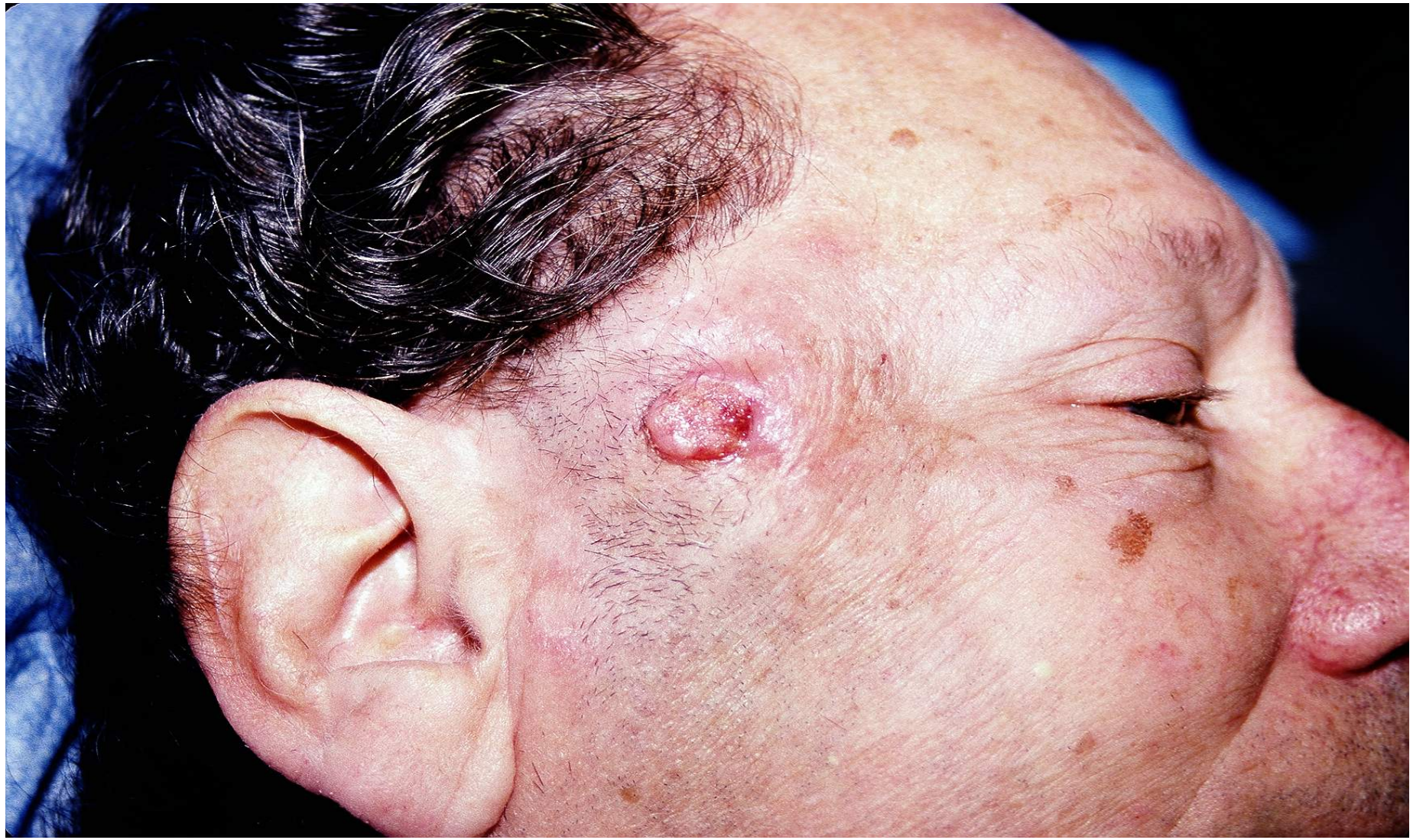


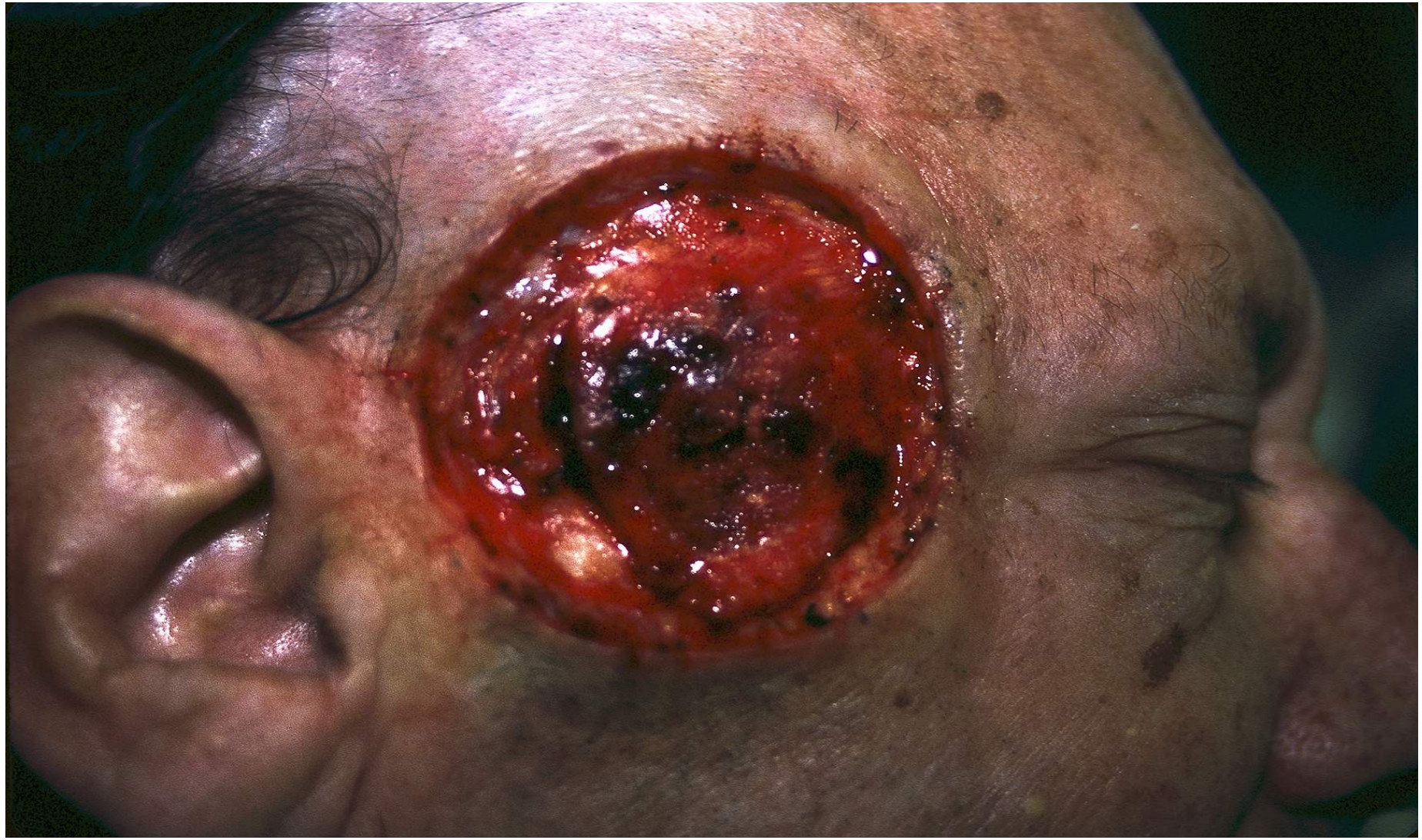
A

B

Keratoacanthoma

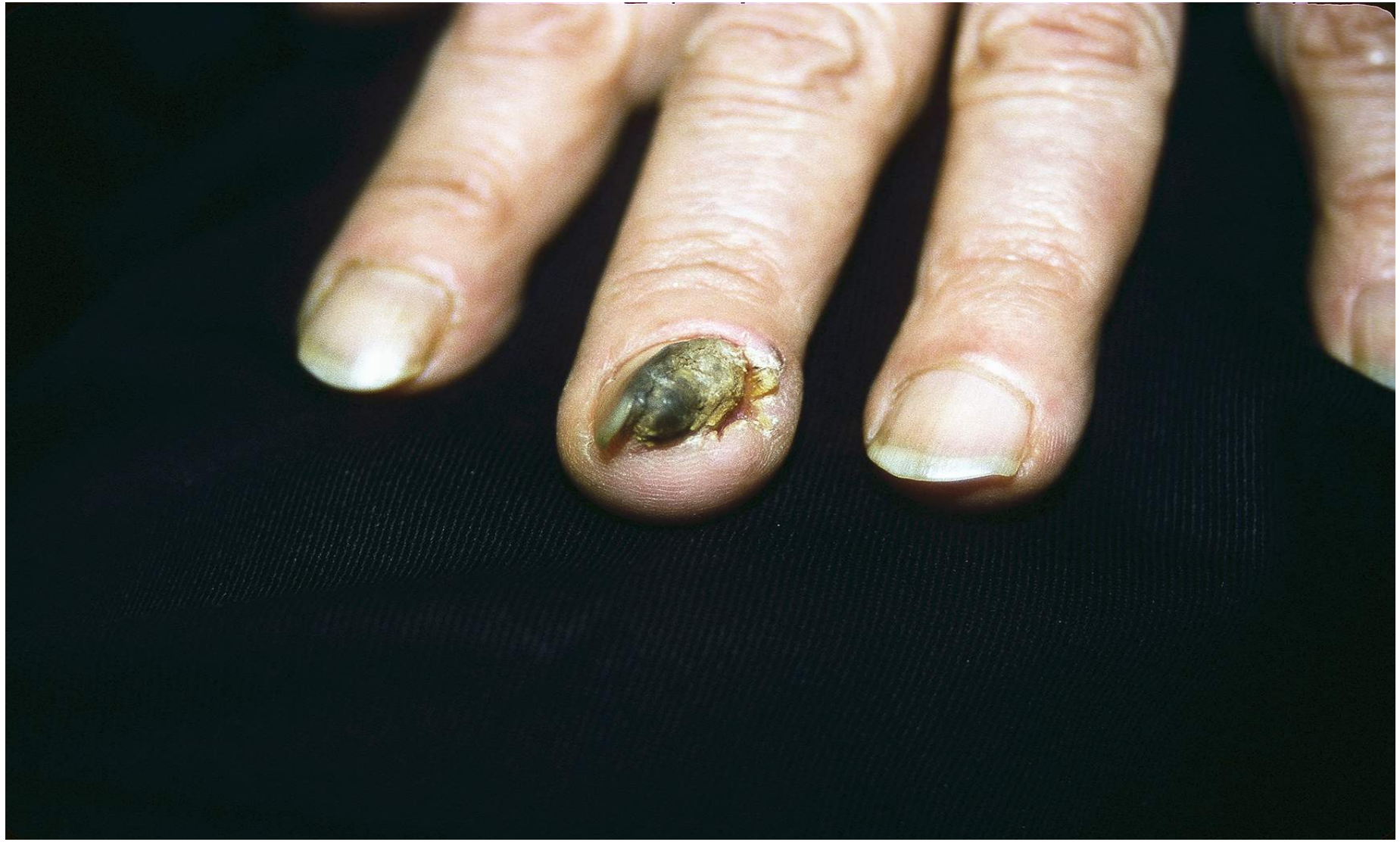
- May have invasive growth pattern on deep margin
- Histologic and clinical differentiation from cSCC can be difficult
- Can be distinguished histologically in 85% of cases
- Should be treated as cSCC if not readily classifiable

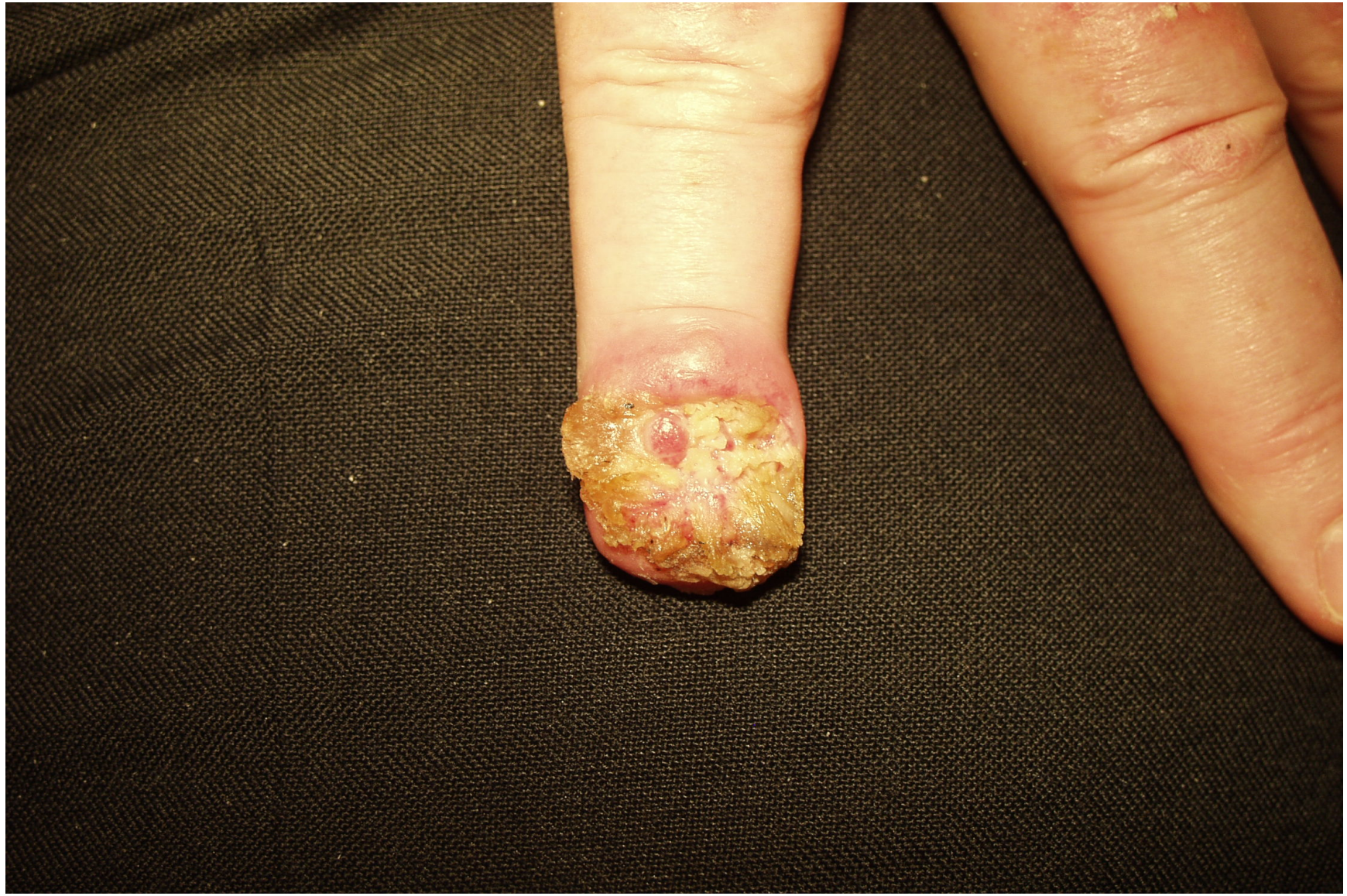




Verrucous carcinoma

- May resemble large warts
- Locally aggressive but rarely metastasizes
- Adequate excision generally results in complete cure
- Reports of malignant transformation after XRT





Clinical Profile of the High Risk cSCC

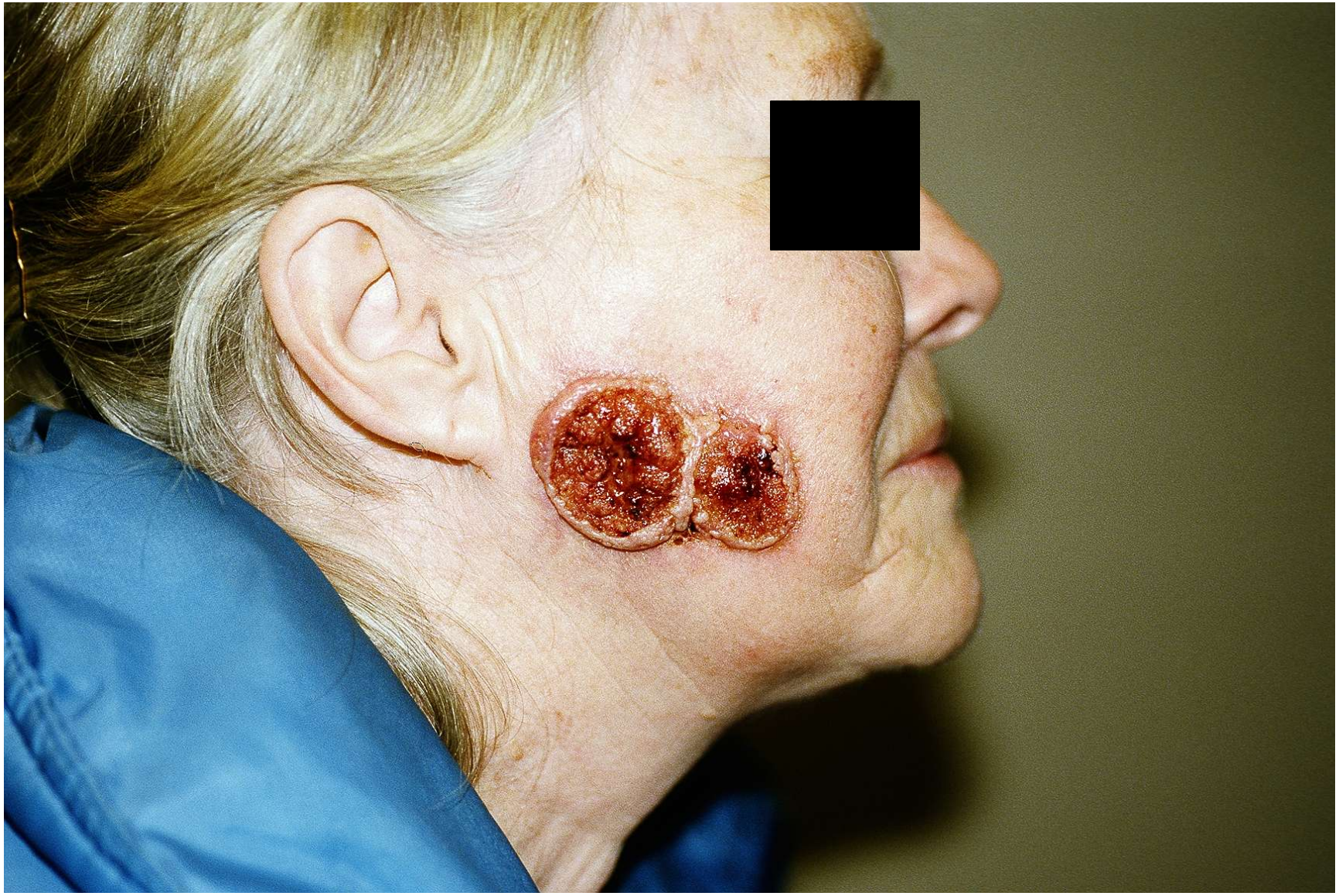
- Size (>2 cm diameter)
- Anatomic site (ear, lip, central face)
- Rapid growth
- Recurrence
- Immunosuppression
- Arising within scar, sinus tract, radiated site

Histologic Profile of the High Risk cSCC

- Depth of invasion to or below deep dermis
- Poorly differentiated
- Perineural invasion
- Recurrence
- Immunosuppression

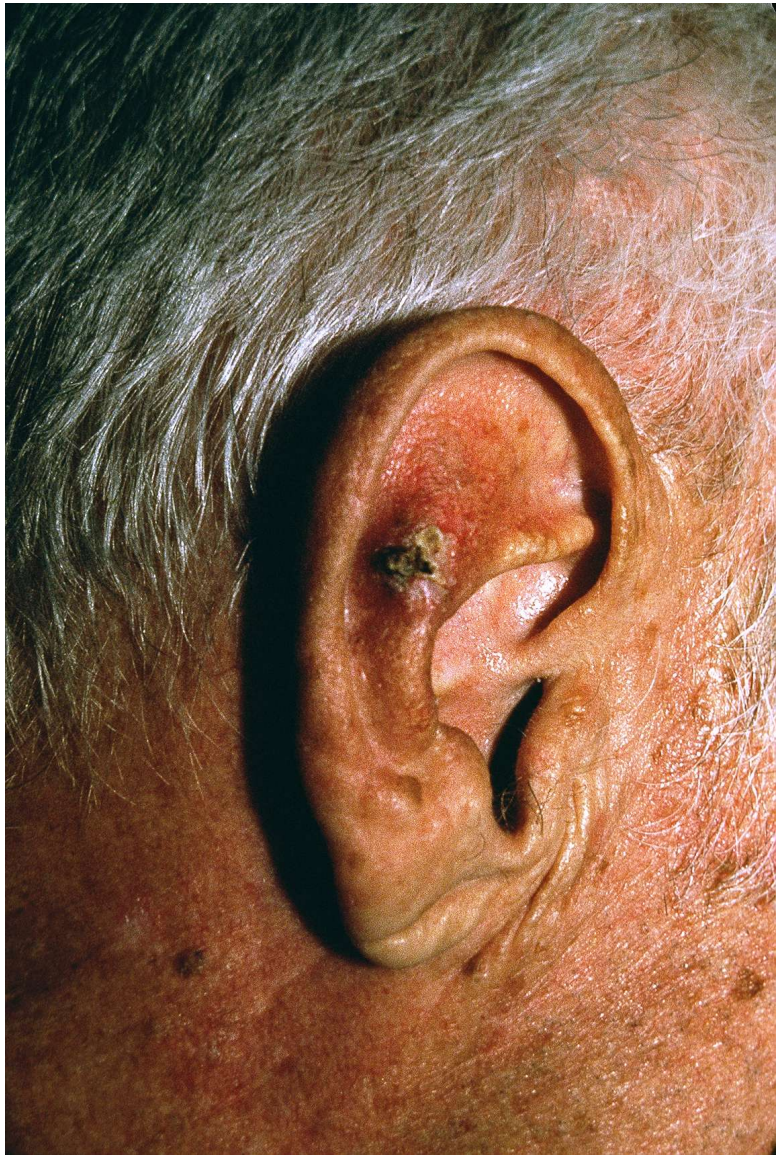
High risk cSCC - Size > 2 cm

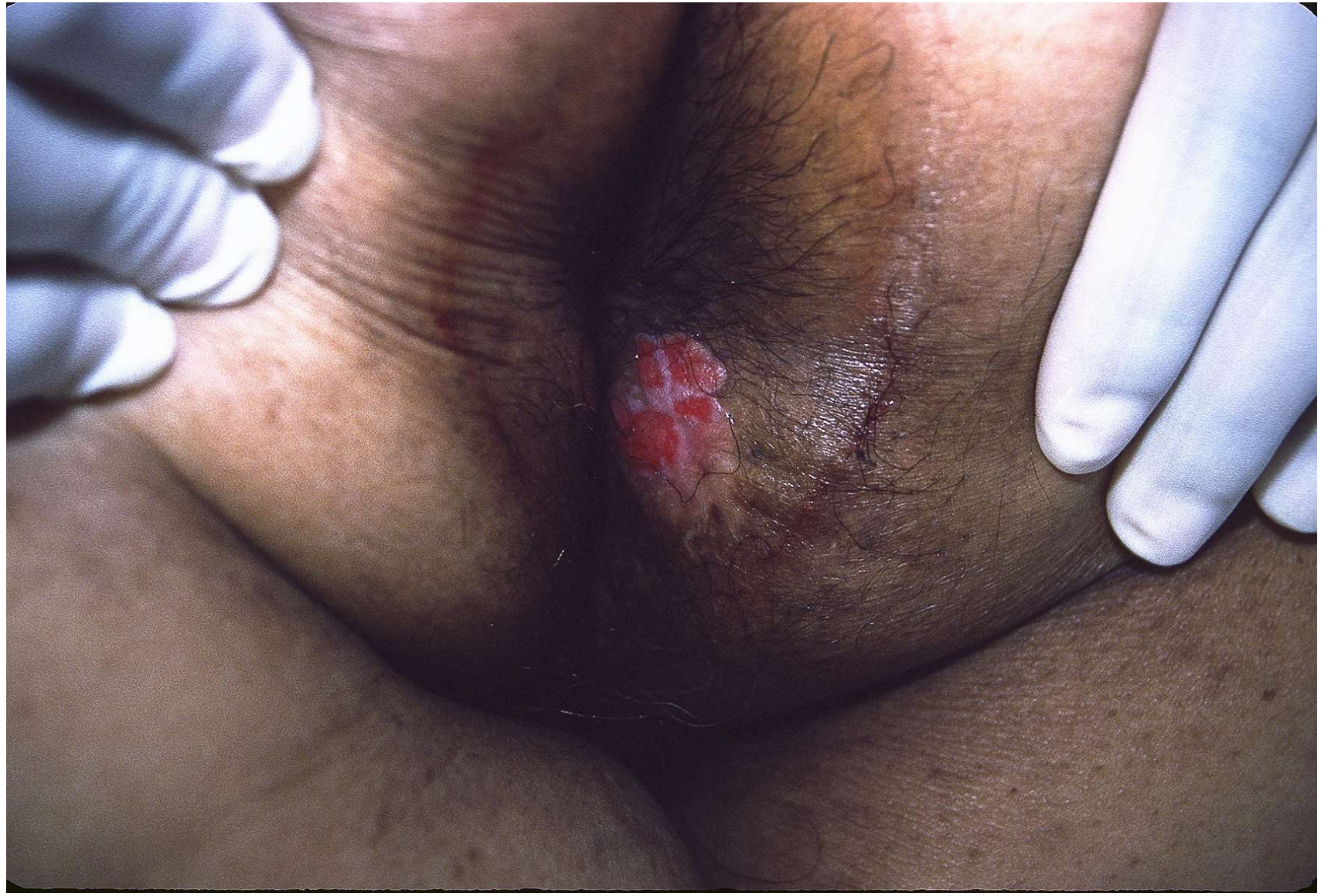
- Recur in 15% of cases
  - twice the rate of lesions < 2 cm
- Metastasize in 30% of cases
  - three times the rate of lesions < 2 cm
- Five year cure rate is 70% with standard treatments



High risk cSCC - Anatomic site

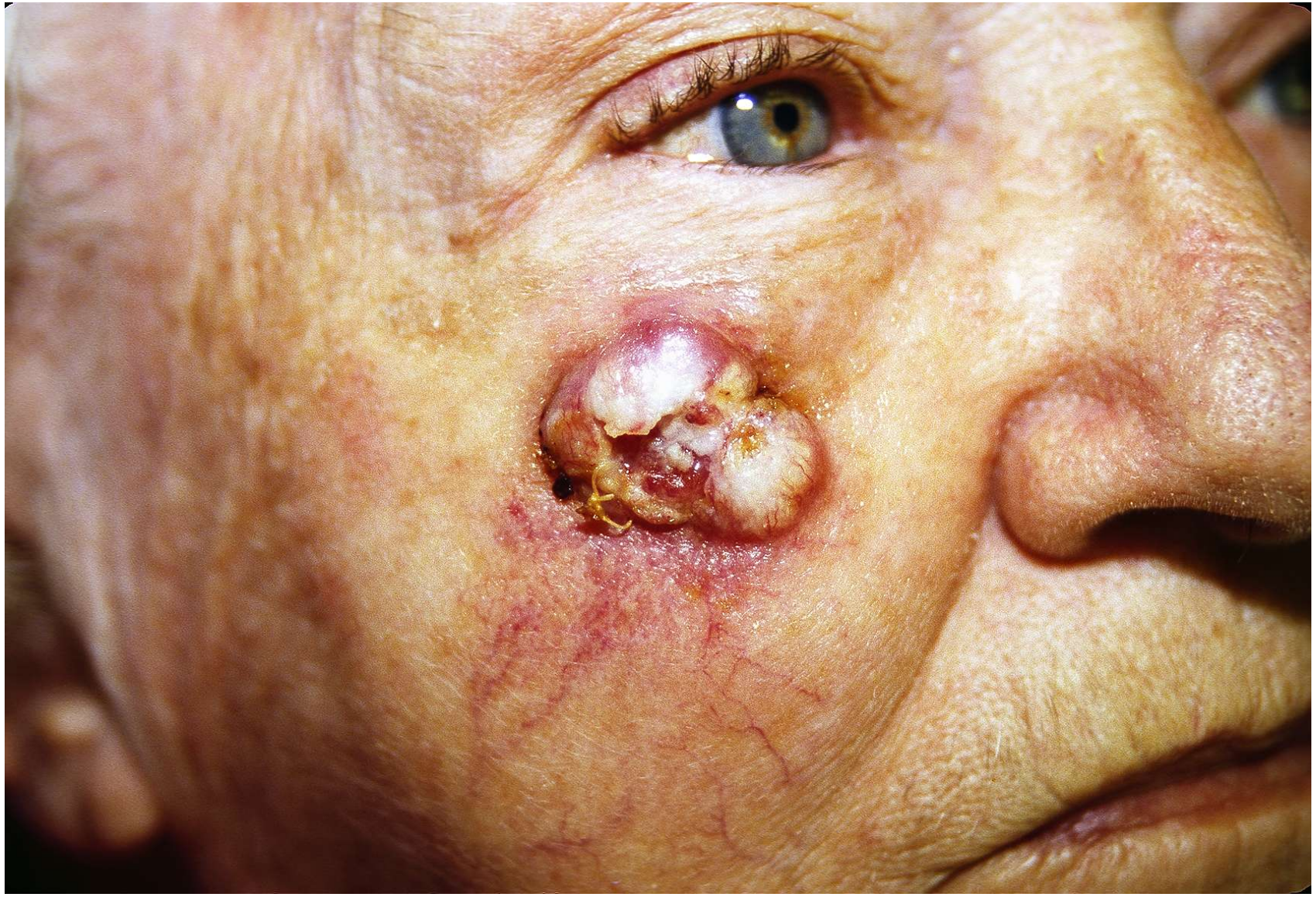
- Rates of recurrence and metastasis range from 10-25% for cSCCs of lip and ear
- Other high risk sites include:
  - Scalp, forehead, temple
  - Eyelids, nose, mucous membranes
  - Dorsal hands
  - Genitalia, perianal region





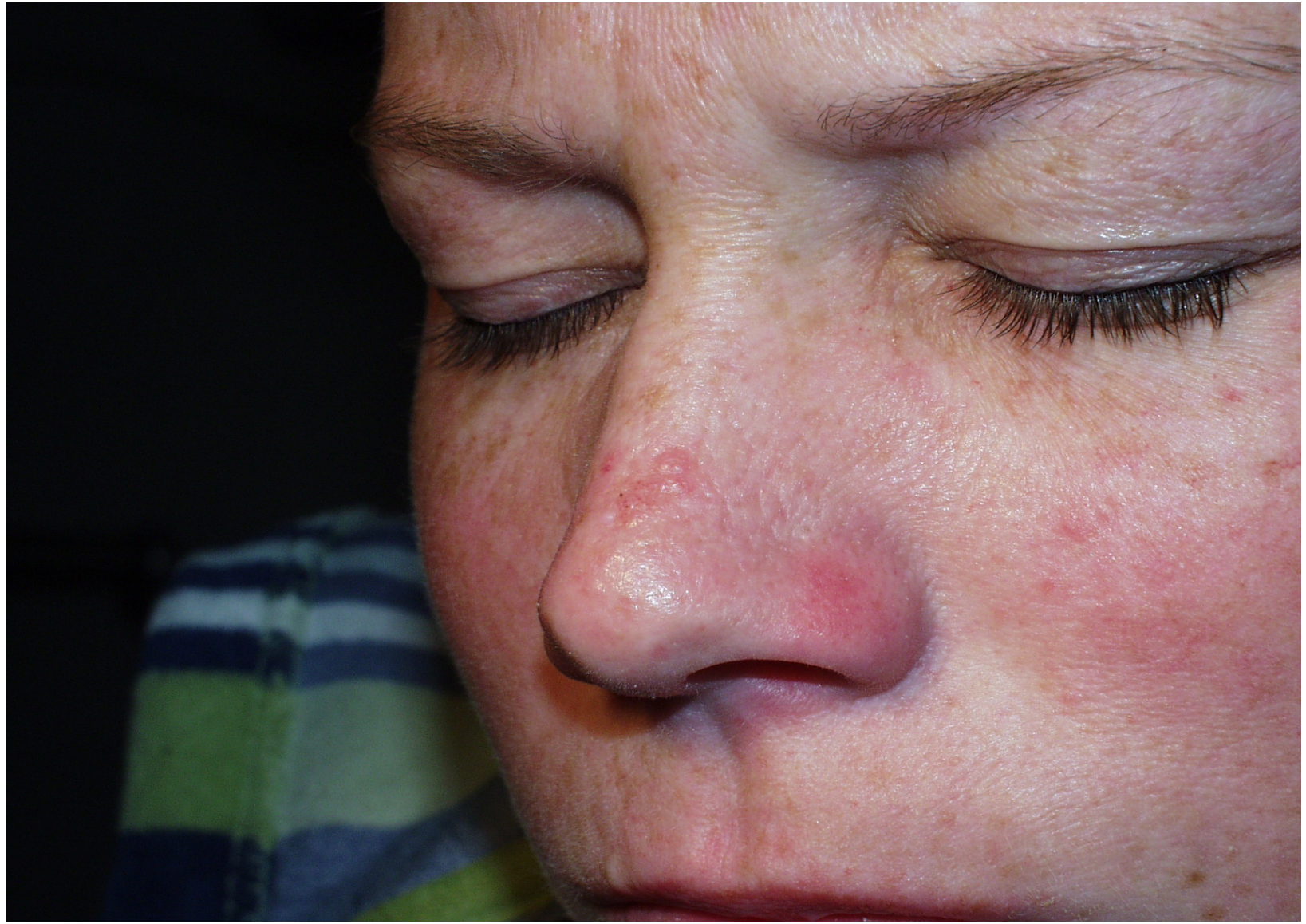
High risk cSCC - Clinical features

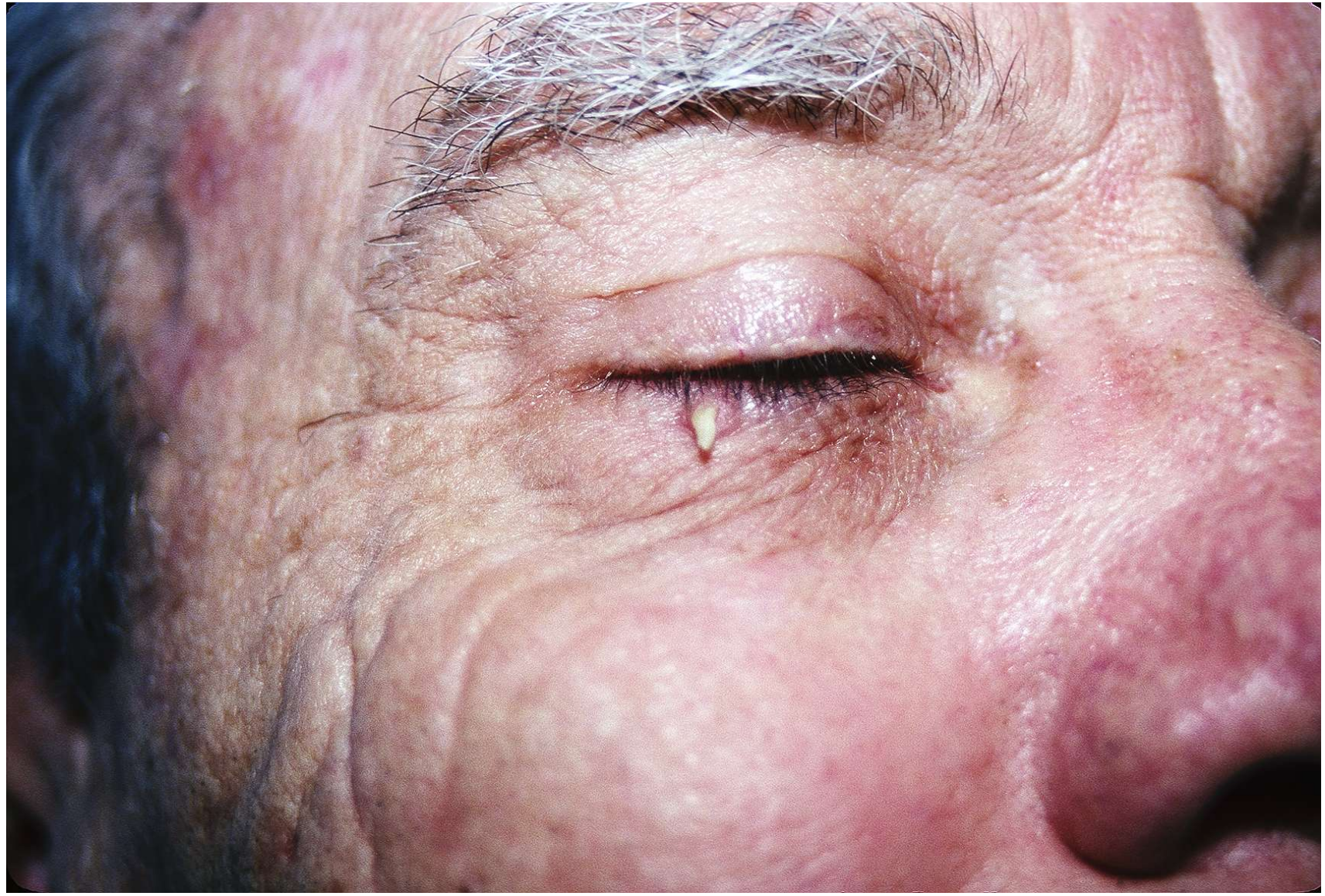
- Rapid growth
  - Tumors may metastasize in up to 33% of cases
- Tumors arising in injured or chronically diseased skin
  - Risk of metastasis approaches 40%



High risk cSCC - Clinical features

- Immunosuppression
  - Risk of metastasis >12%
- History of previous treatment
  - Risk of metastasis 25% for most cutaneous lesions
  - Risk of metastasis 30-45% for ear and lip tumors
- History of irradiation



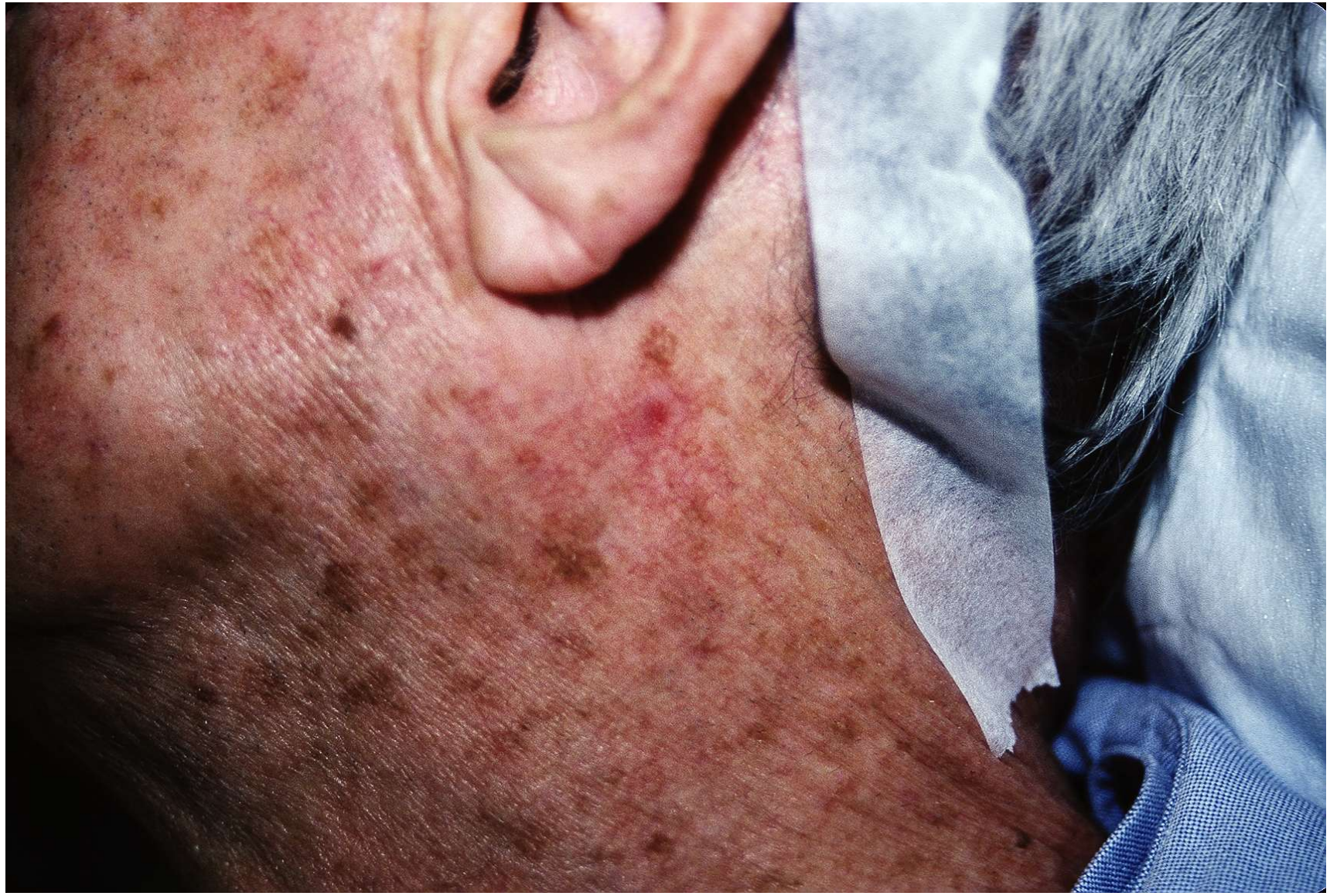


High risk cSCC - Histologic features

- Well differentiated cSCC
  - Local recurrence rate 13.6%
  - Metastatic rate 9.2%
  - 5 year cure rate 94.6%
- Poorly differentiated cSCC
  - Local recurrence rate 28.6%
  - Metastatic rate 32.8%
  - 5 year cure rate 61.5%

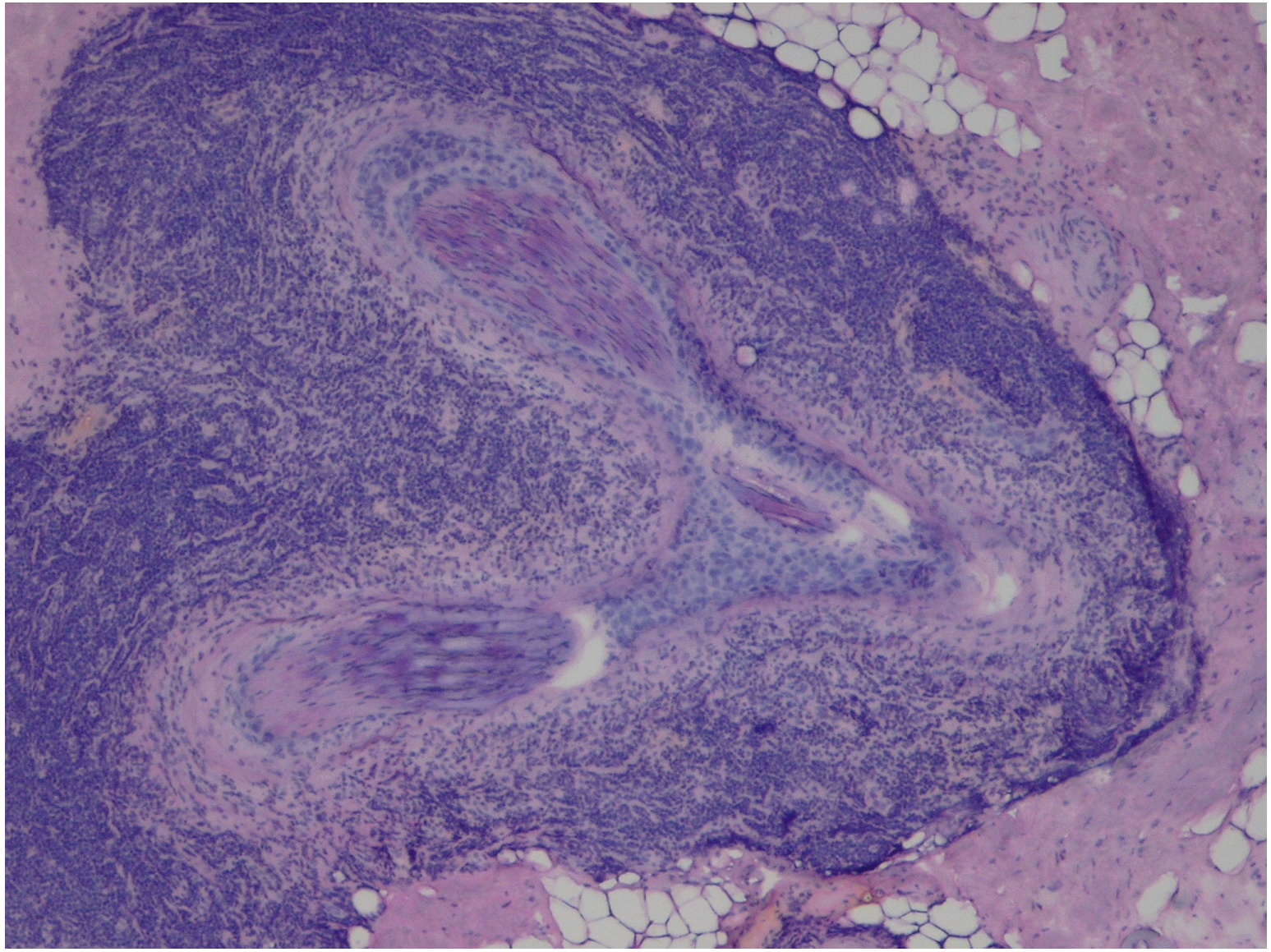
High risk cSCC - Histologic features

- Depth > 4 mm or extension into reticular dermis or subcutaneous fat
  - Local recurrence rate 17.2%
  - Metastatic rate 45.7%



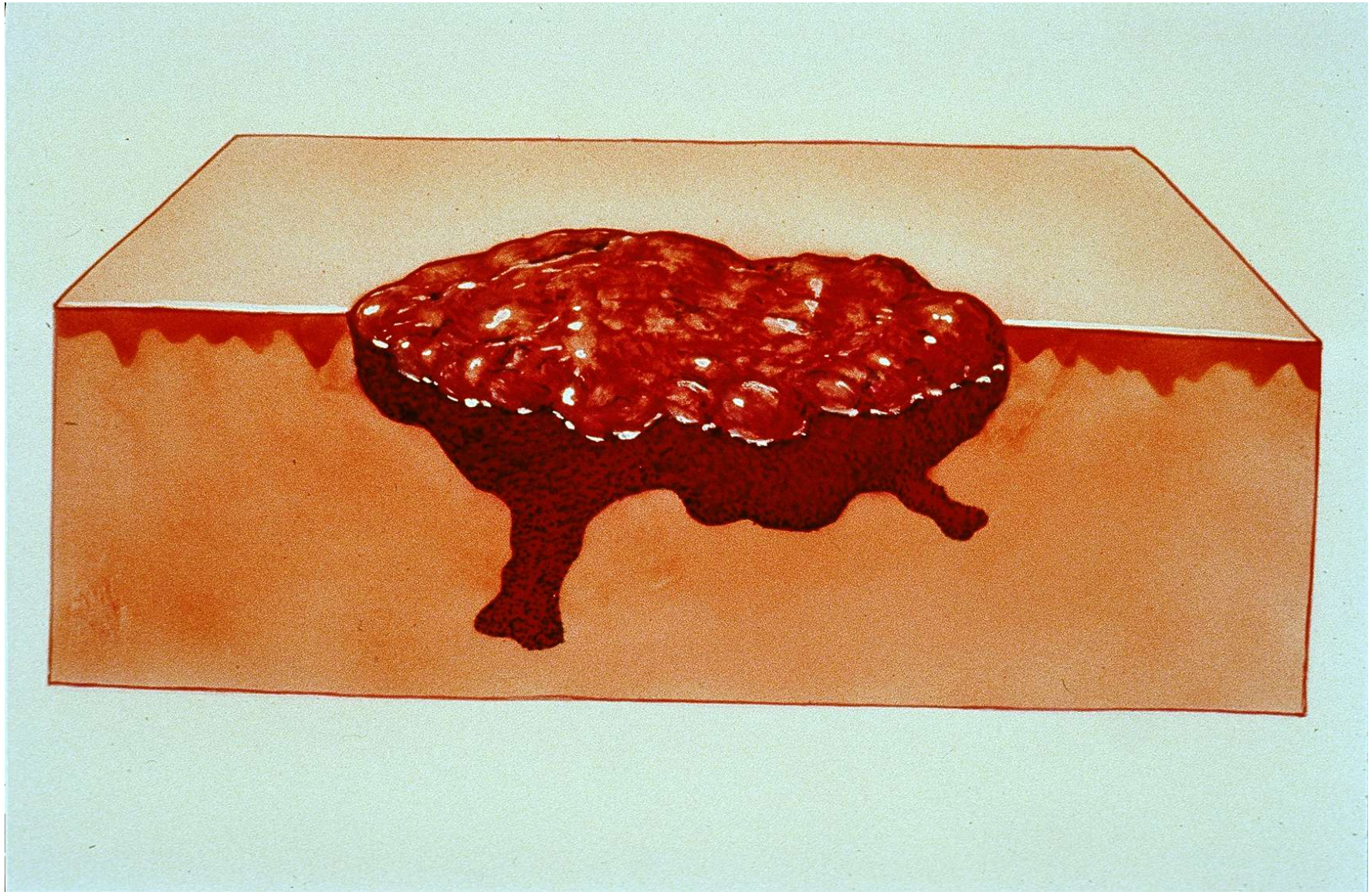
High risk cSCC - Perineural invasion

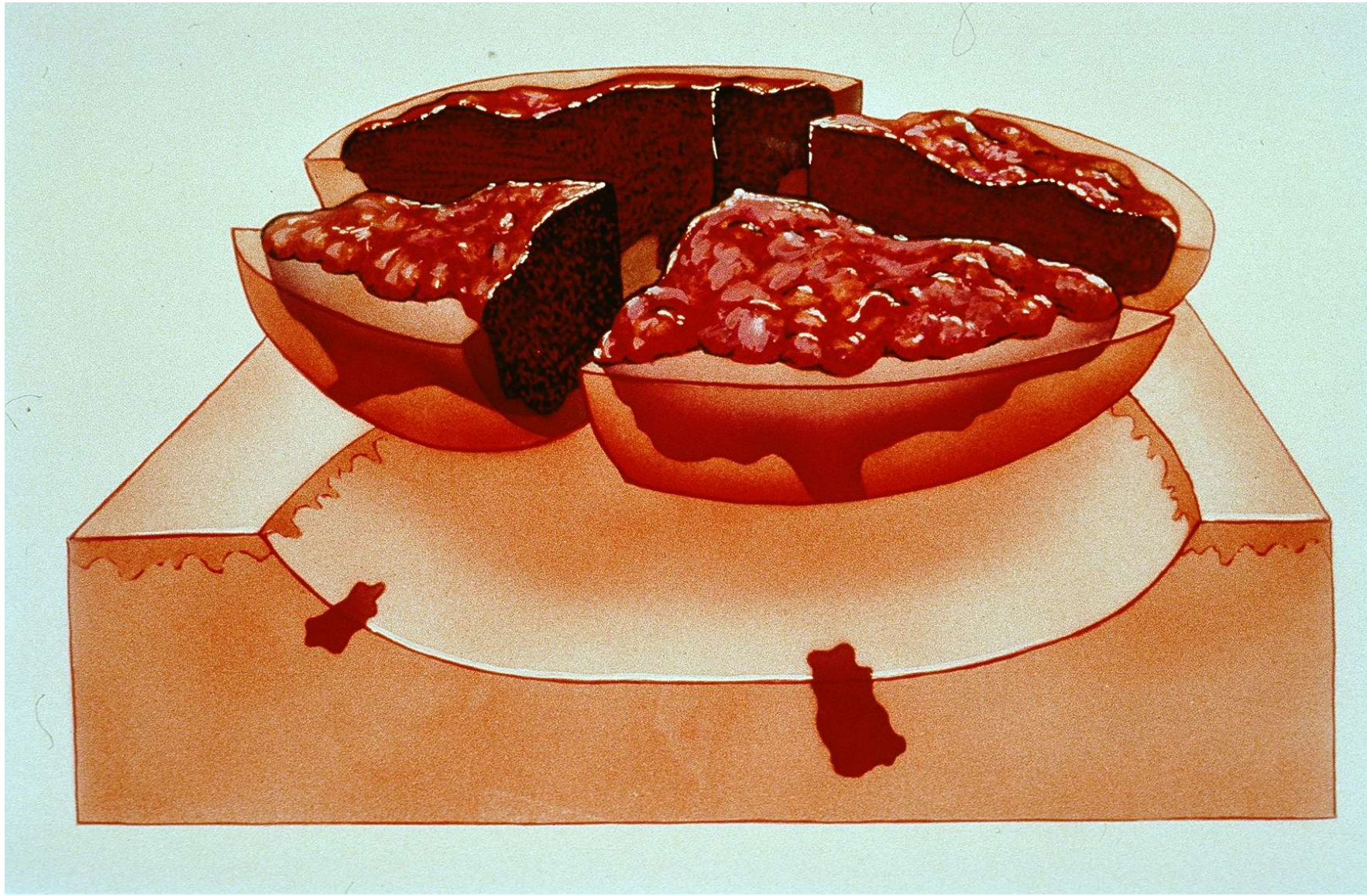
- Occurs in only 5% of cSCCs
- Contiguous movement of tumor cells along nerve fibers (neurotropic spread)
- Not clinically or histologically apparent until significant tumor extension has occurred
- Local recurrence rate: 47.2%
- Metastatic rate: 47.3%
- Most patients with perineural invasion die within 5 years of presentation

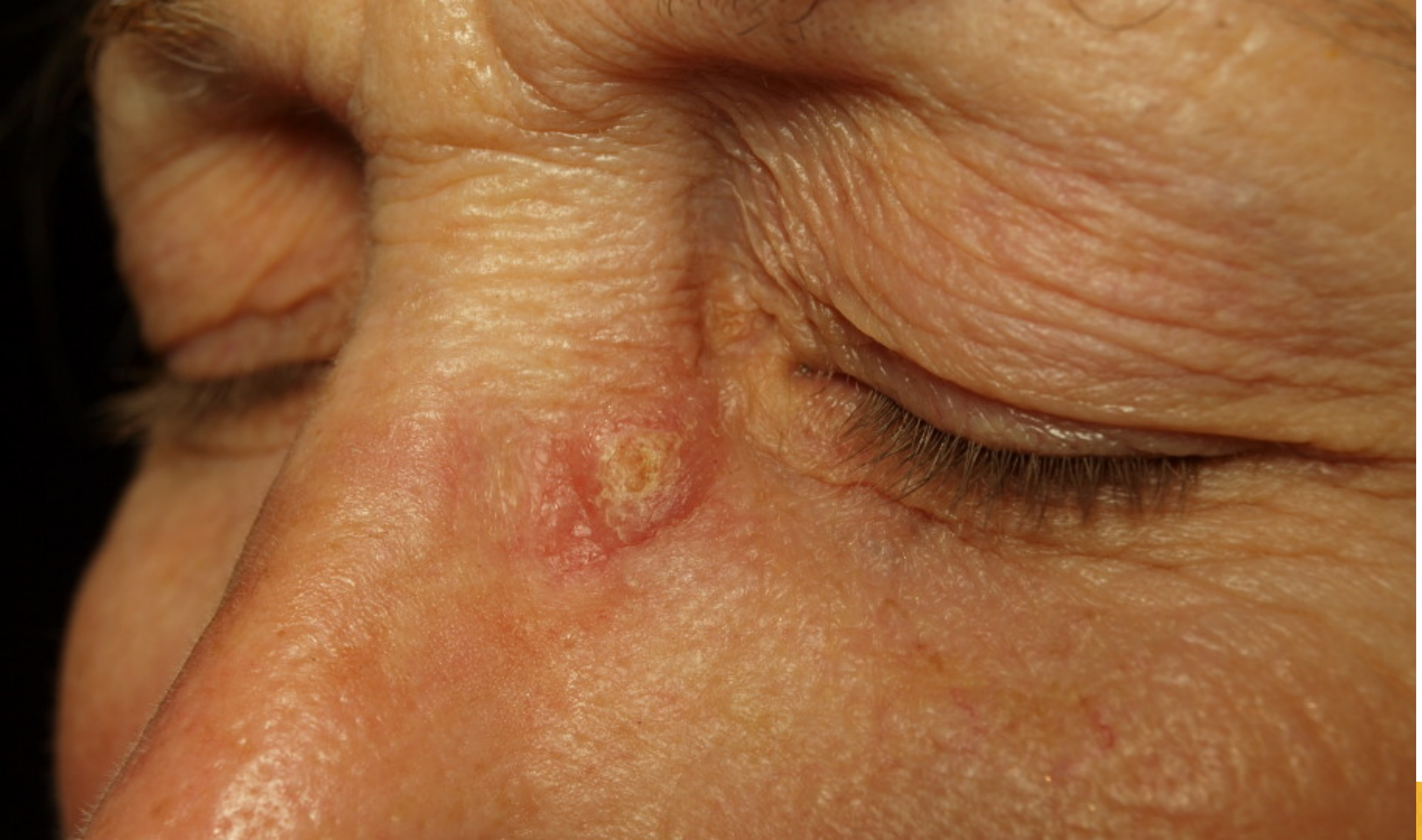


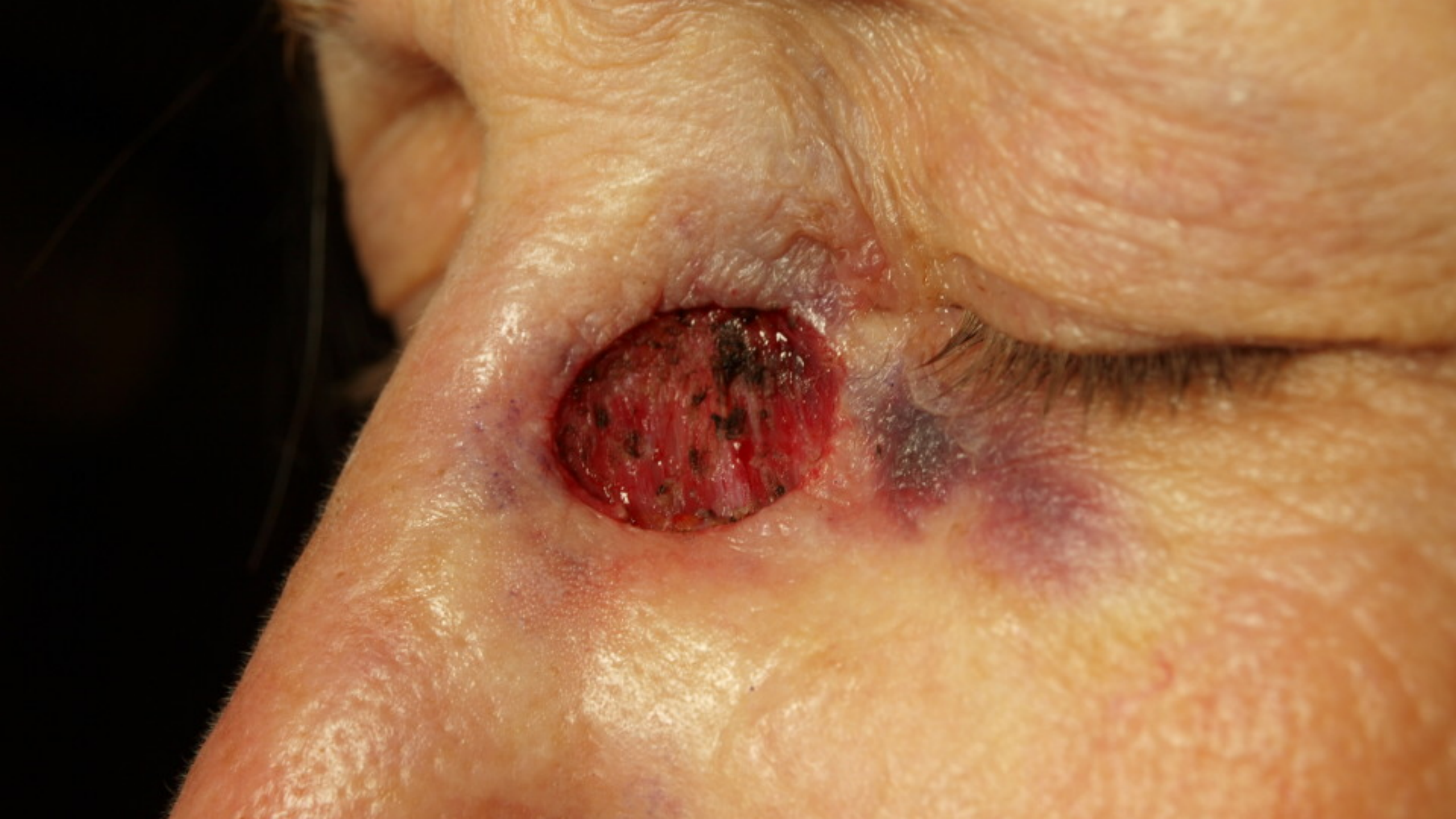
High risk cSCC - Treatment

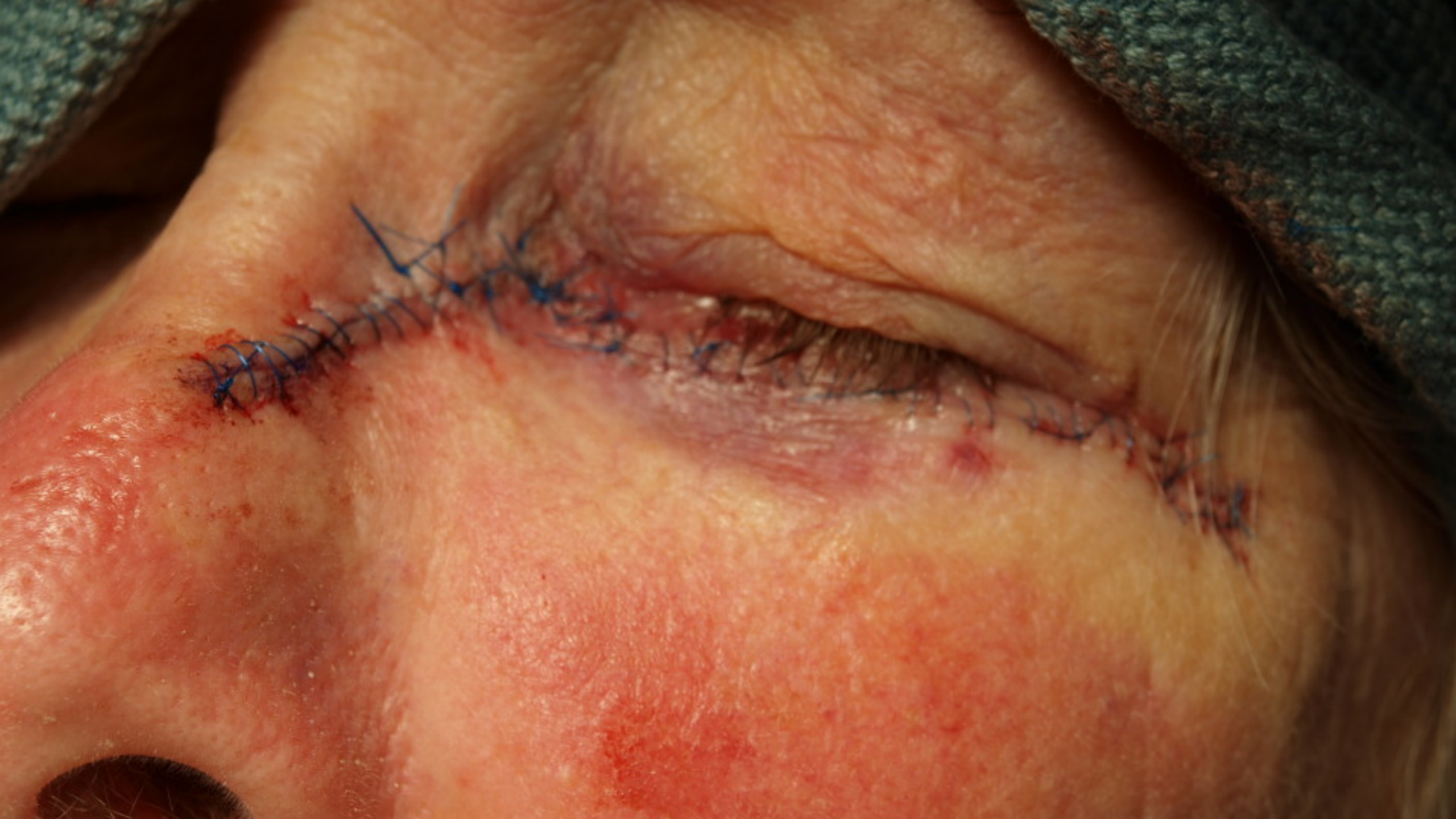
- Mohs micrographic surgery
- Excision with 6-10 mm margins to appropriate anatomic depth
- Consideration of adjunctive treatment for very high risk lesions





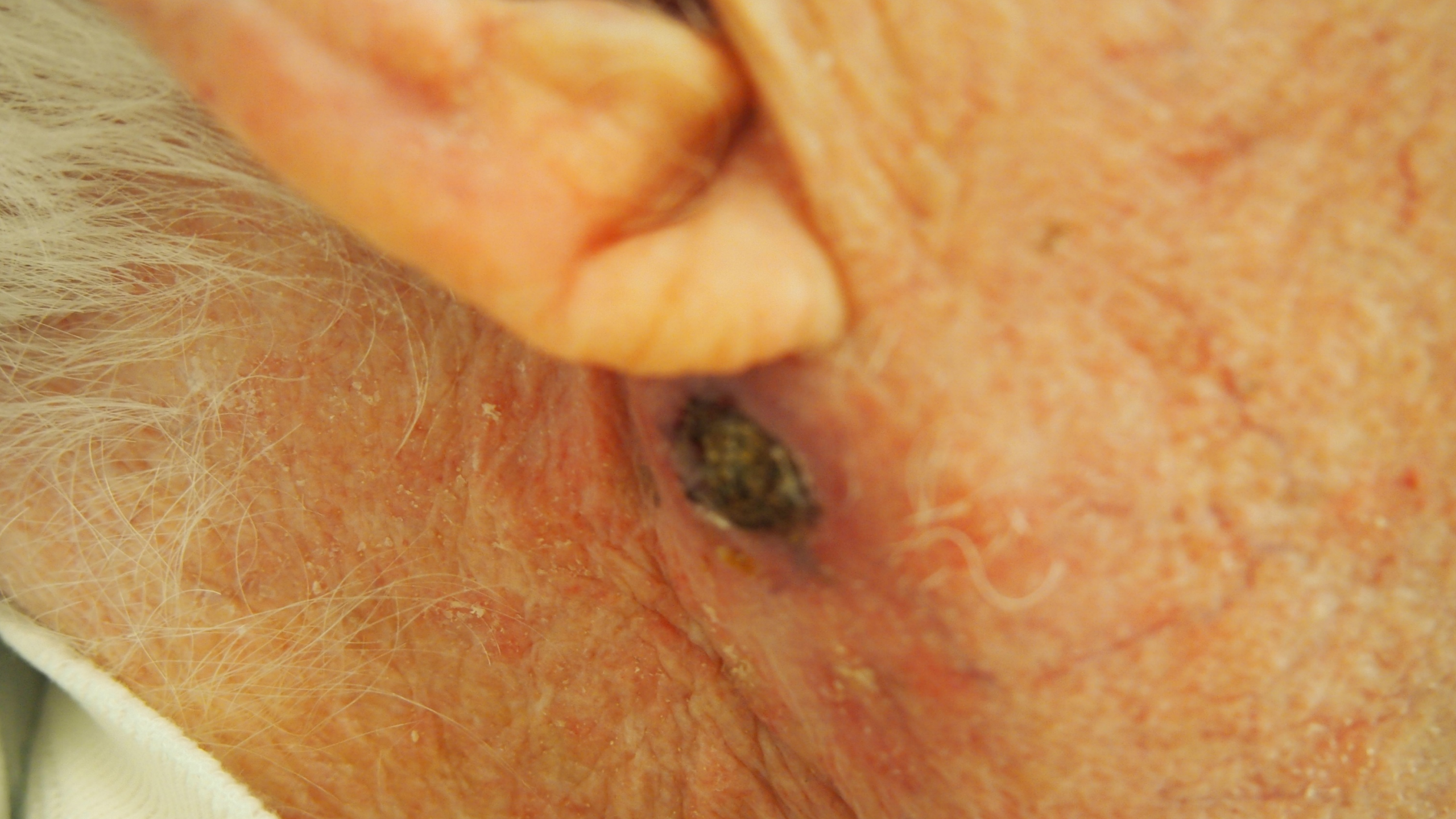


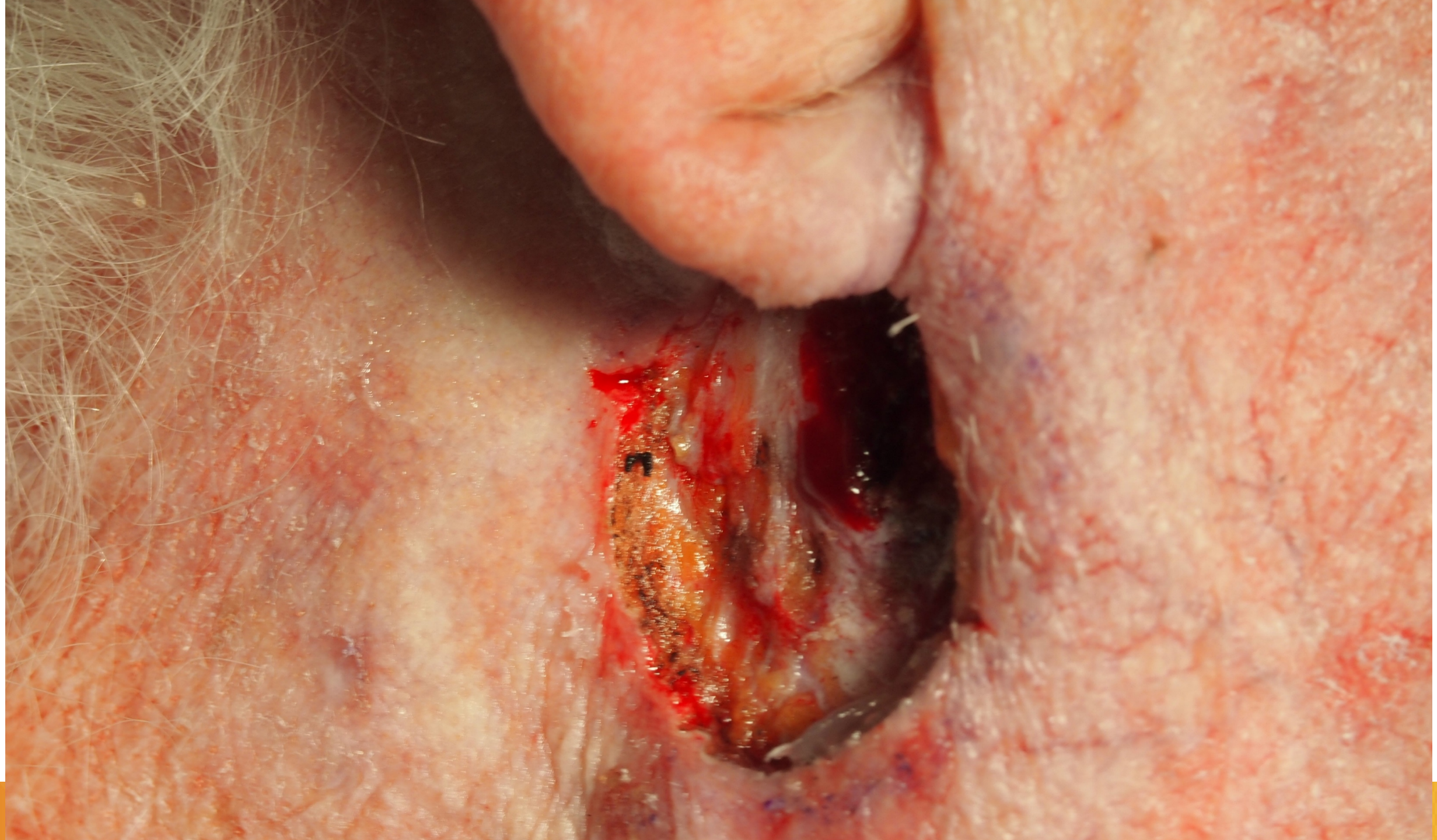


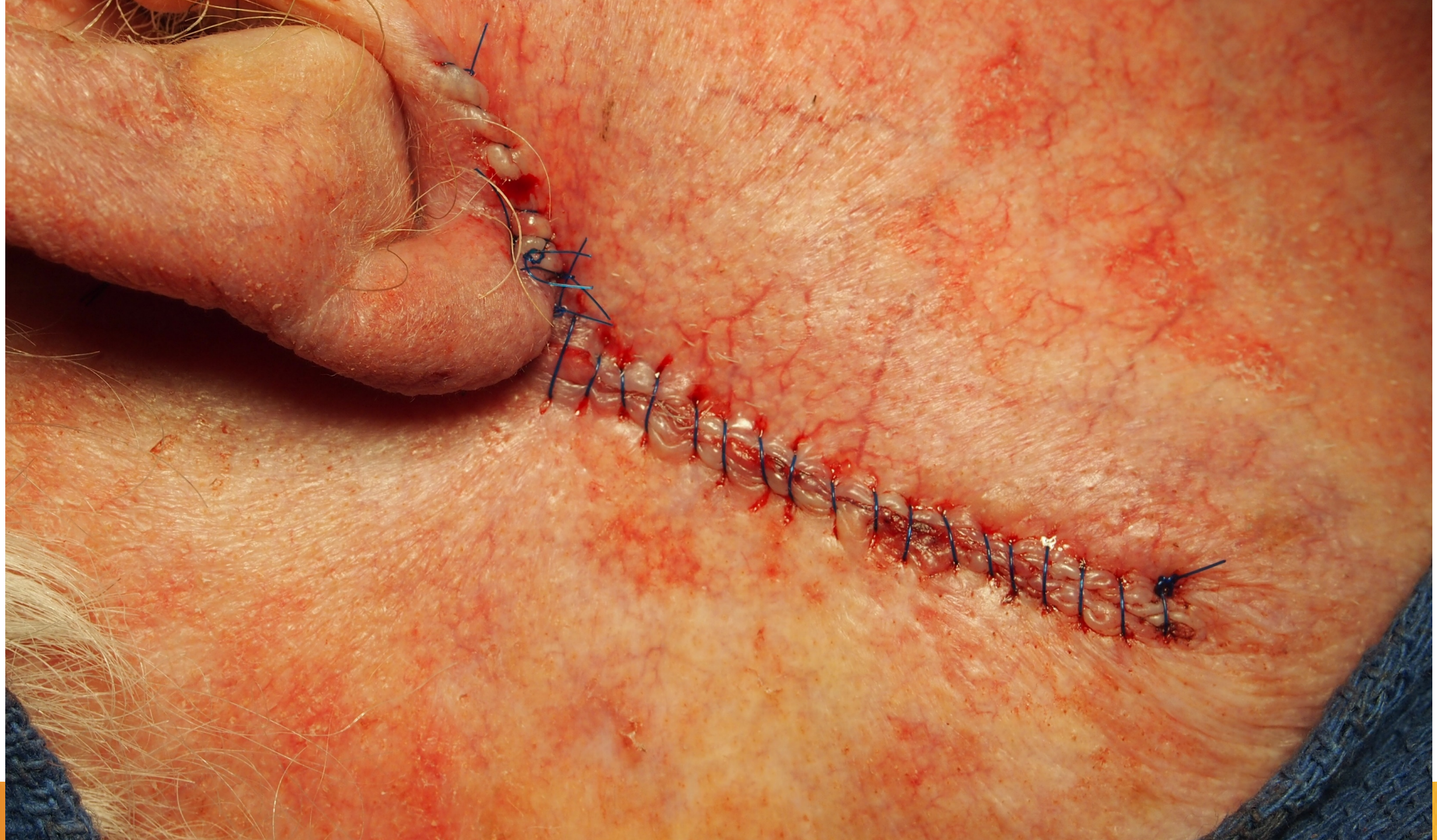


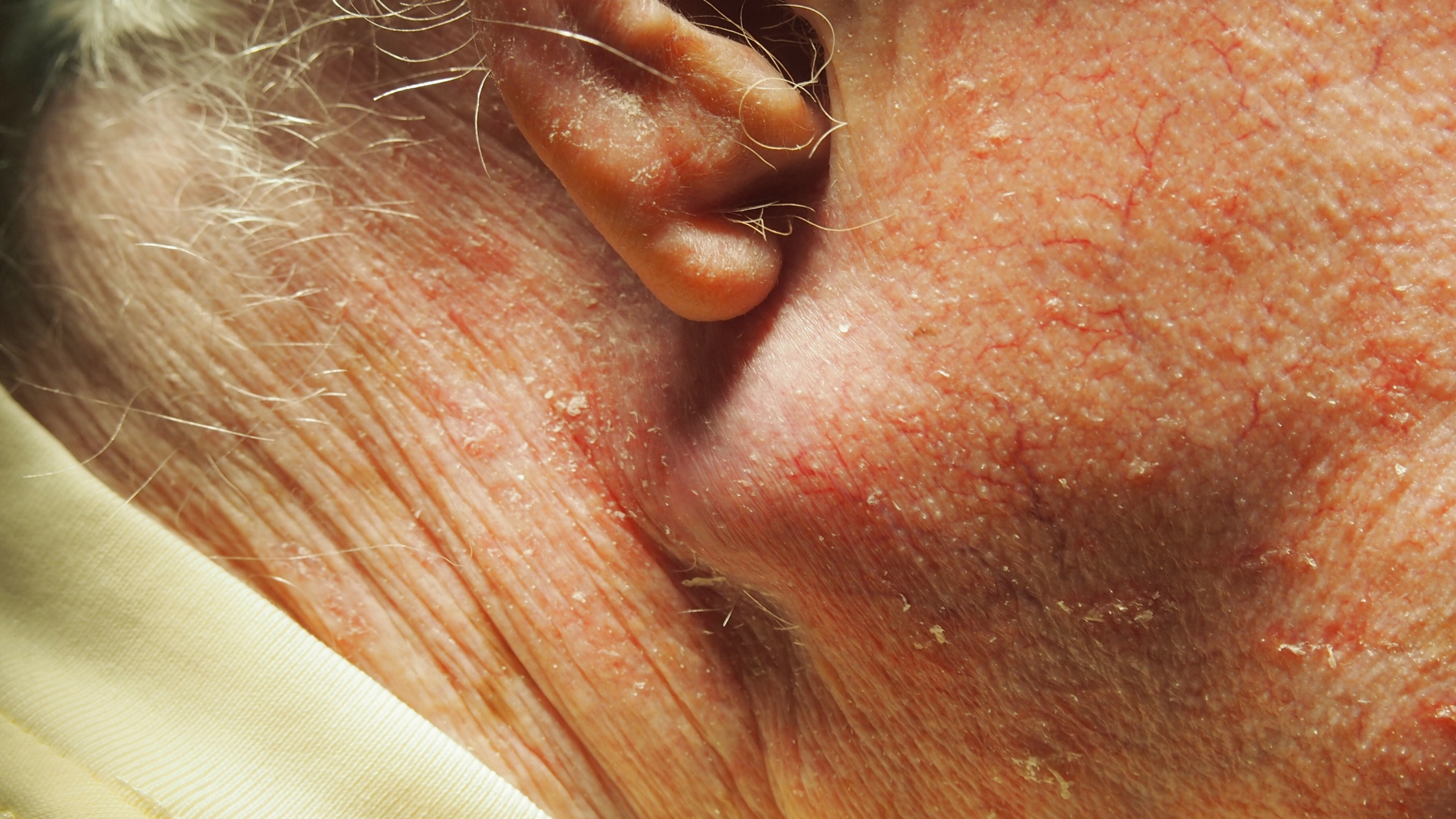
cSCC - Prognosis

- Patients with primary cSCC have excellent prognosis
  - Mohs surgery cure rates: 95-97%
- Patients with metastatic disease have dismal prognosis
    - Regional LN involved in ≈ 80% of cases; 10 year survival rate < 20%
    - Distant metastases present in ≈15% of cases; 10 year survival rate < 10%









BWH cSCC staging system

- 4 tumor risk factors predicted poor outcomes:
  - Poorly differentiated histology
  - Diameter of 2 cm or greater
  - Perineural invasion of any caliber
  - Invasion beyond SQ fat (excluding bone invasion)

Evaluation of AJCC Tumor Staging for cSCC and a proposed alternative staging system. A Jambusaria-Pahlajani et al. JAMA Dermatol 2013 (149): 402-10

BWH T staging system

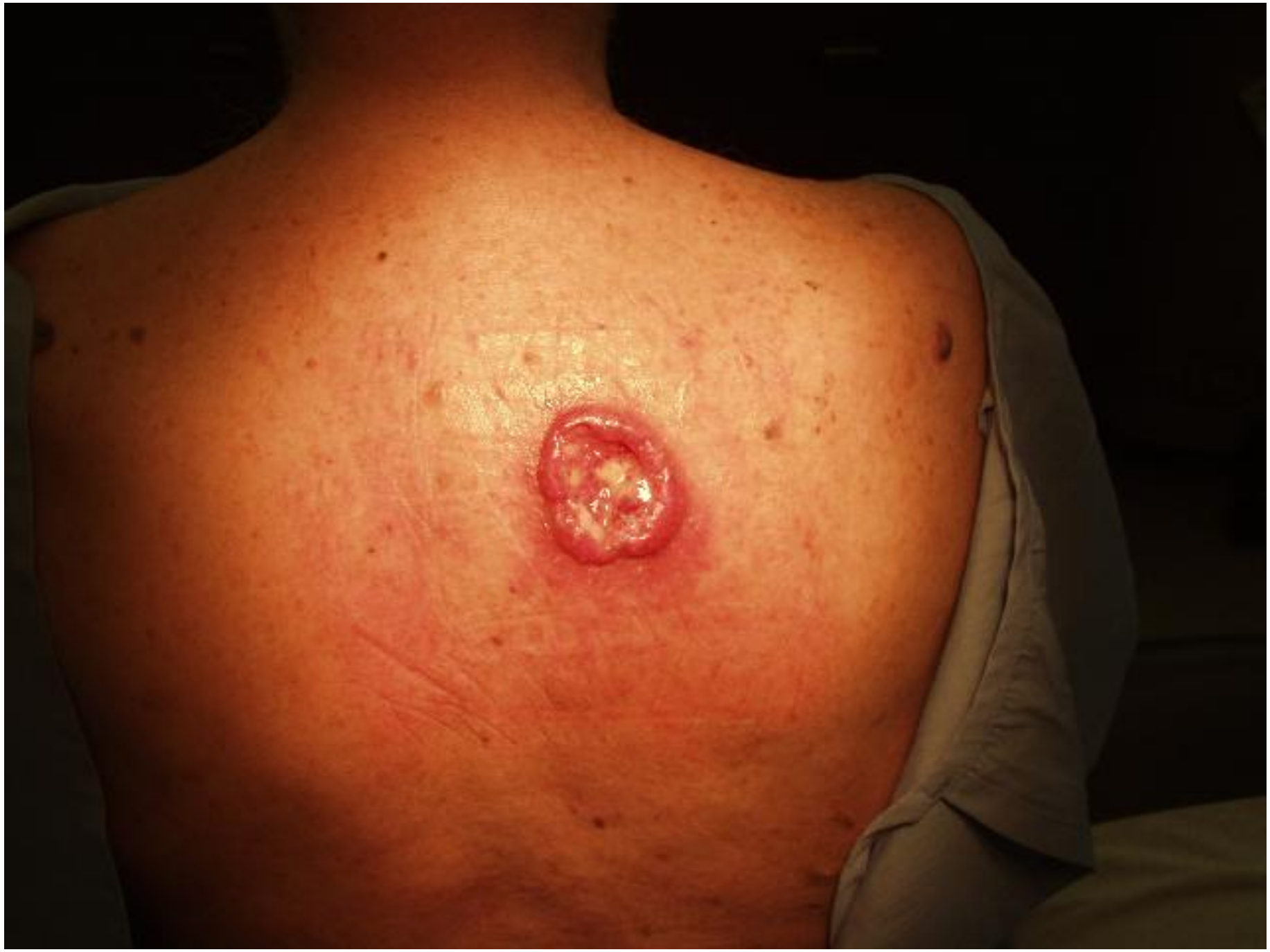
Alternative T stage	Definition	Risk of poor outcome
T0	In situ SCC	N/A
T1	0 risk factors	1.8%
T2a	1 risk factor	9.9%
T2b	2-3 risk factors	33.3%
T3	4 risk factors or bone invasion	100%

BWH T2b and T3 patients

- Subset of high risk cSCC patients
- Tumors with greater propensity for local invasion and regional and distant metastasis
- Not well controlled with conservative treatment
- Require more aggressive management
- High rates of morbidity and mortality

BWH T2b and T3 = Very High Risk cSCC

- Multidisciplinary management
- Dermatologists
- Surgical oncologists
- Medical oncologists
- Pathologists
- Transplant physicians
- Radiation oncologists
- ENT, plastics, oculoplastics

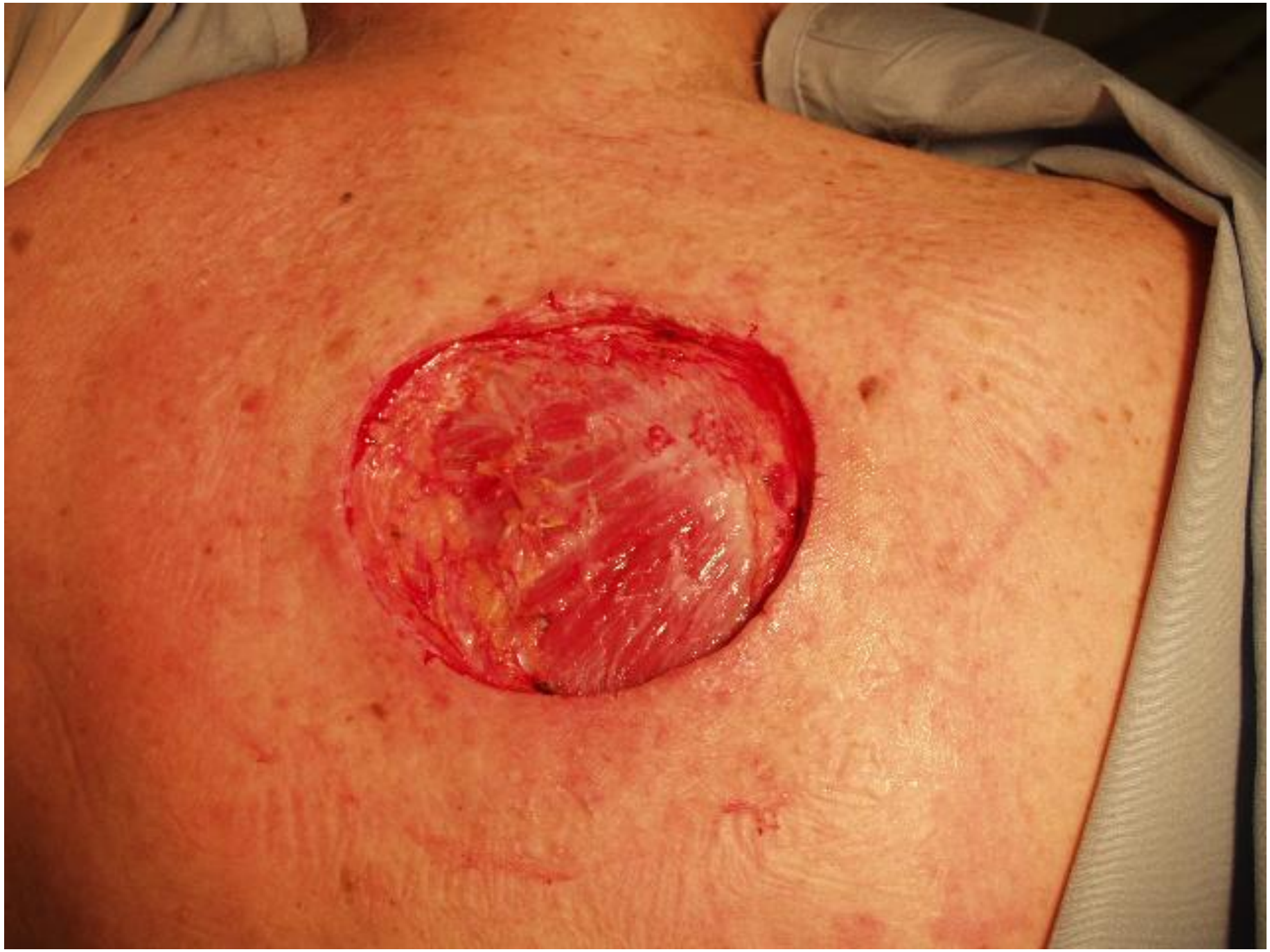


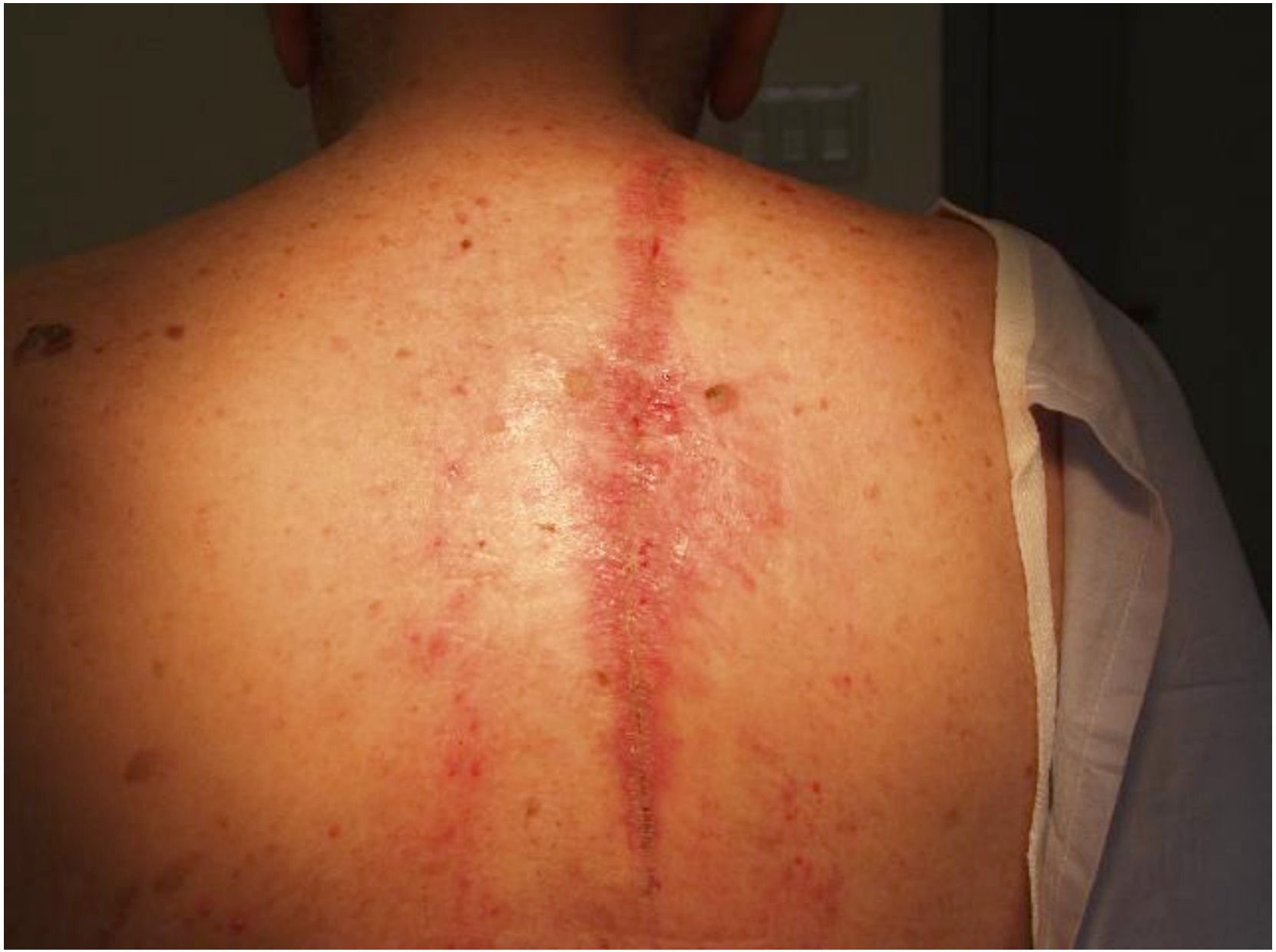
Systemic agents for cSCC

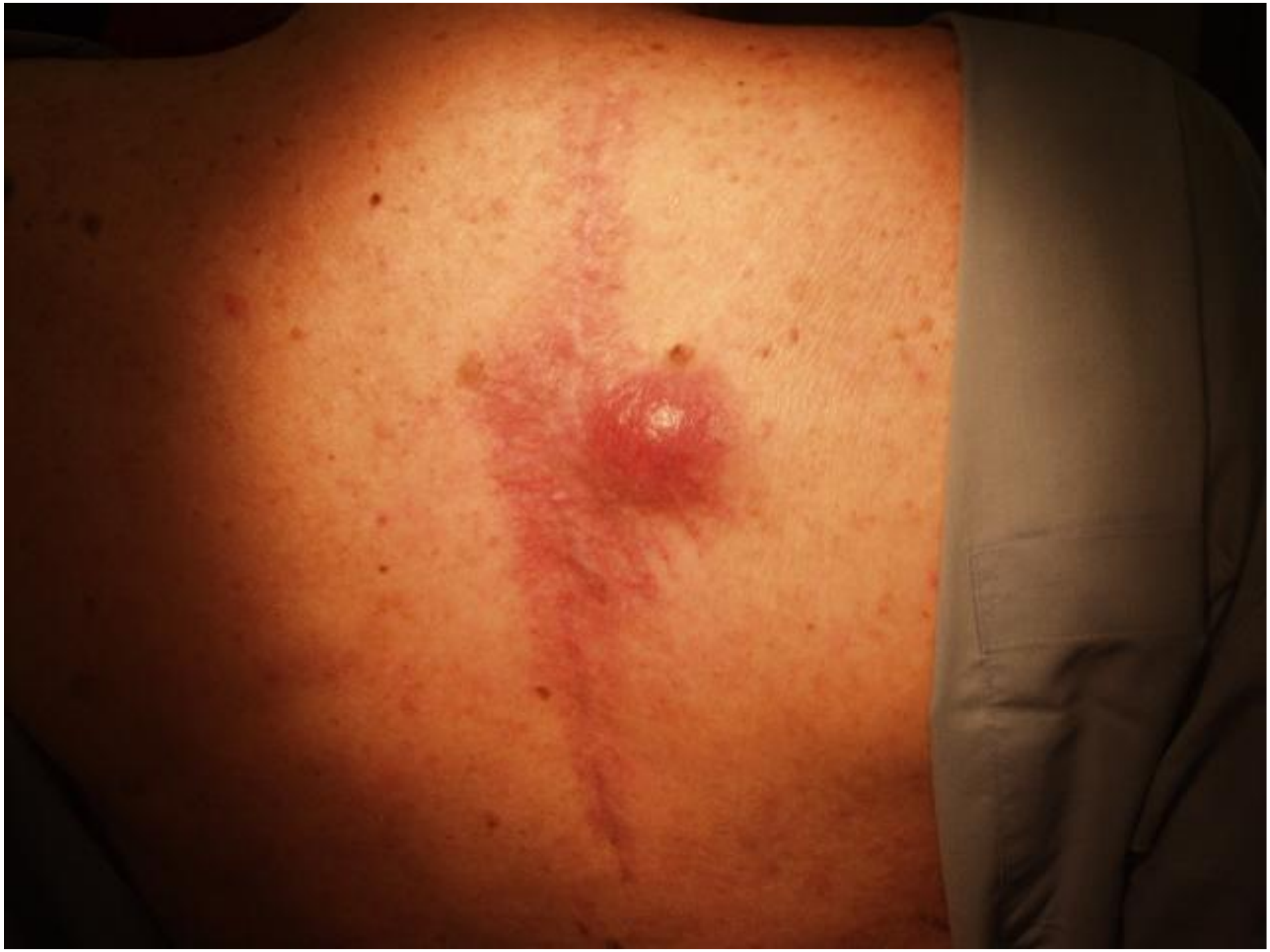
- Cis-platin based combination chemotherapy most commonly used
  - Response rates high
- Toxic effects common: myelosuppression (25%-30%), dose-cumulative peripheral neuropathy (30%-100%), severe emesis (100%)
- Targeted molecular therapy (EGFR inhibitors)
- Immunotherapy/checkpoint inhibition (pembrolizumab, cemiplimab)

EGFR inhibitor: Cetuximab

- Recombinant human-mouse chimeric Ab which competitively inhibits EGFR
- Works well in head and neck SCC, even in cis-platin or XRT-refractory disease
- <18% response rate for locally advanced/metastastic cSCC

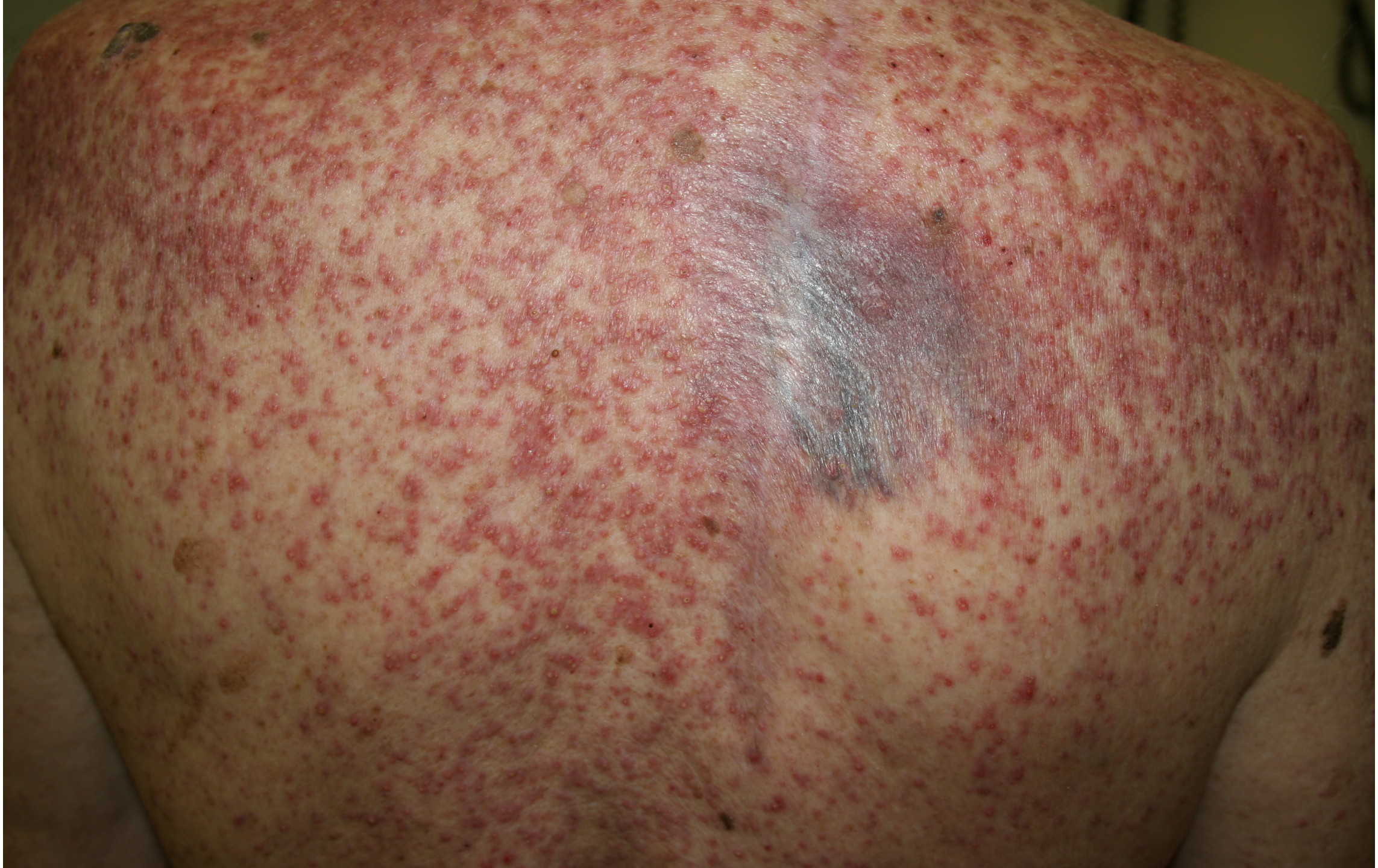


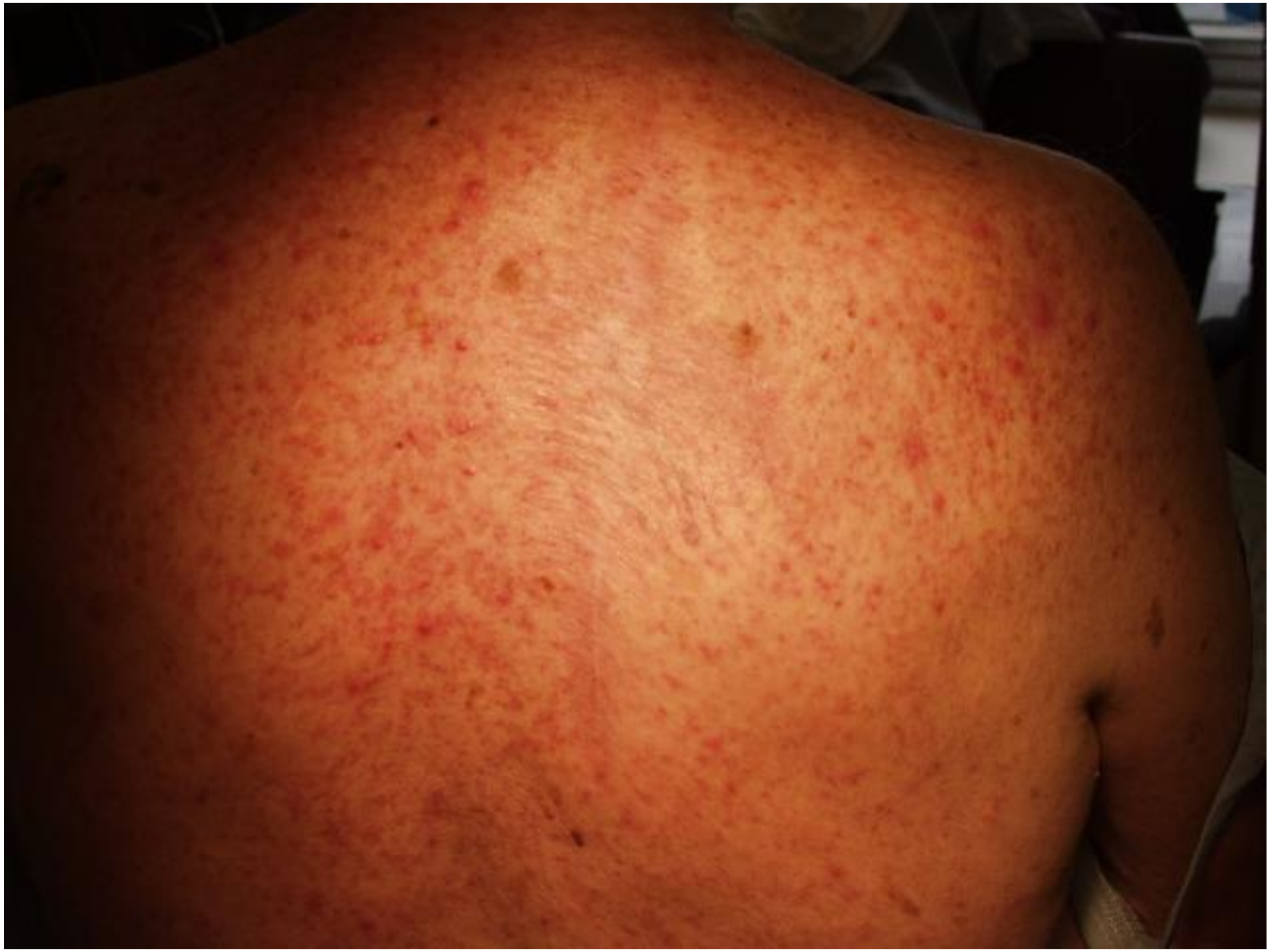




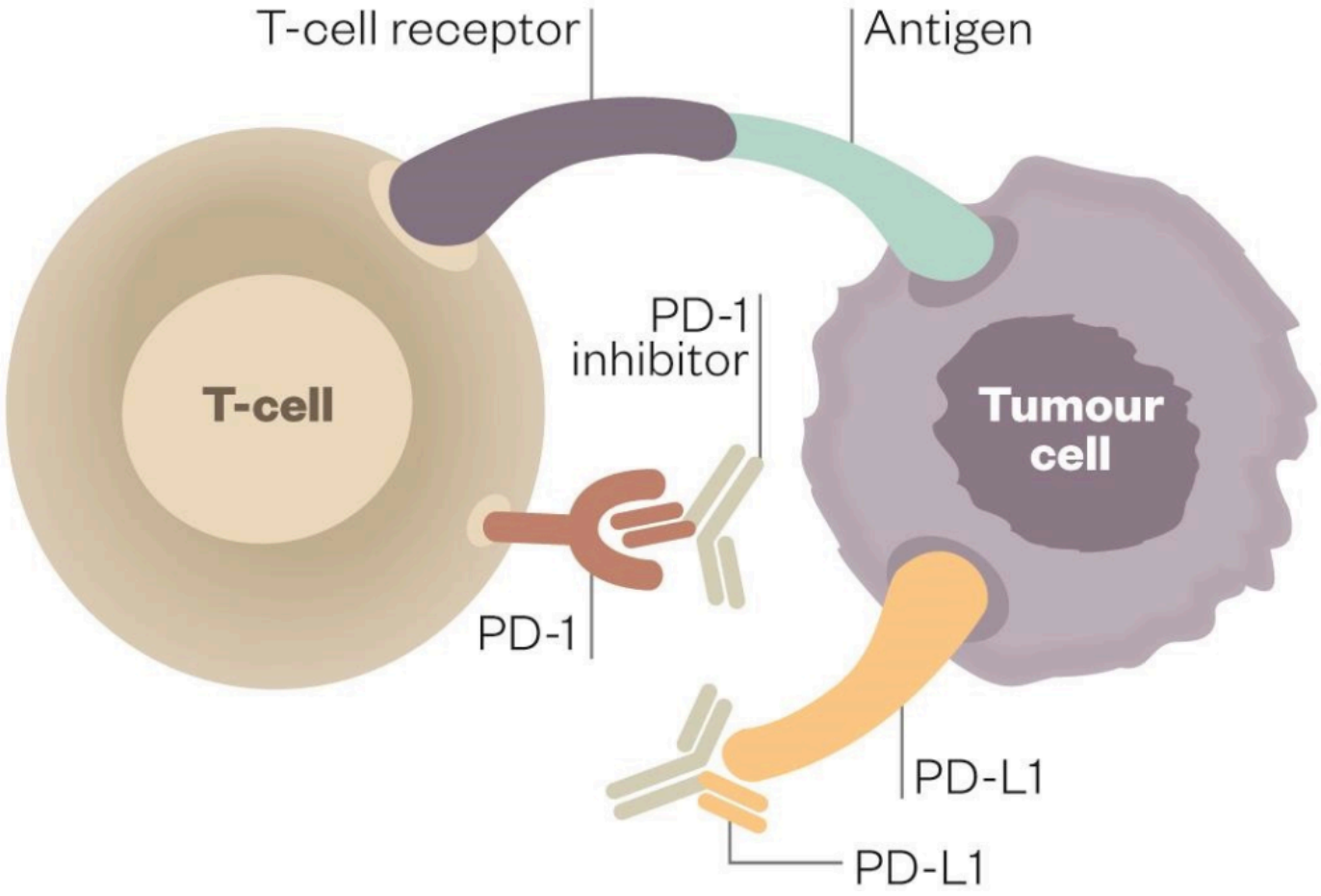
Cetuximab for VHSCC

- Recommended by medical oncology over cis-platinum because of its relative lack of side effects and ease of administration
- Pt started on 4 week cycle of 400 mg/m^2 on day 1, followed by 250 mg/m^2 weekly for 3 weeks





PD-1 and PD-L1 inhibitors

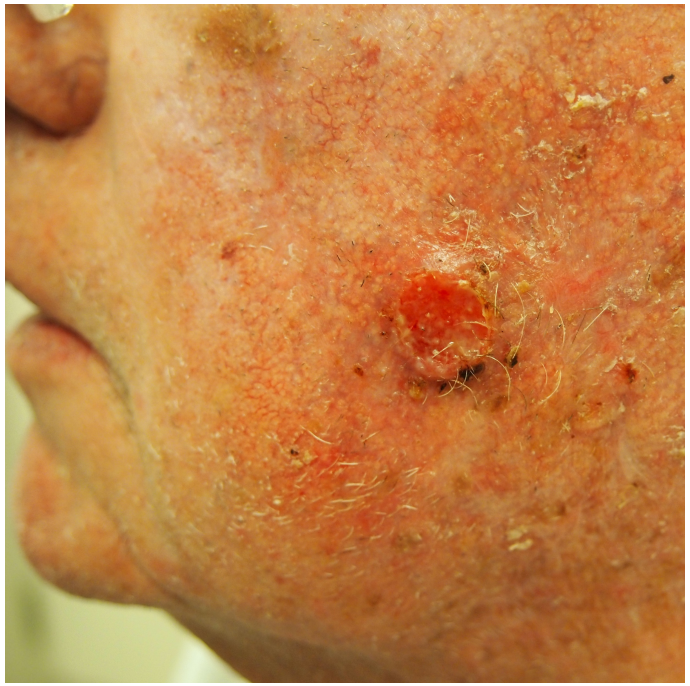


Pembrolizumab

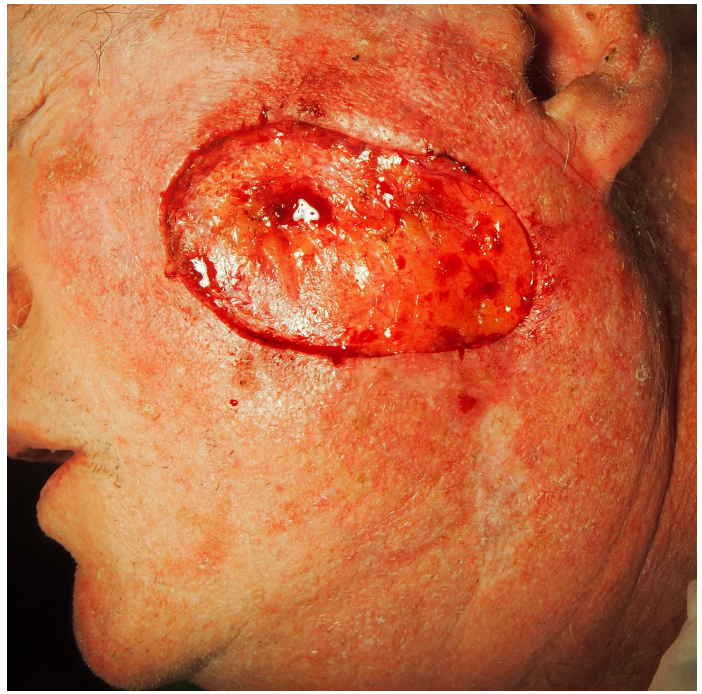
- Programmed cell death protein 1 (PD-1) inhibitor
- First-in-class drug approved by FDA for unresectable melanoma
- Cancer cells upregulate PD-L1 on tumor cells and TILS to escape immune system
- Checkpoint blockade of immune inhibitory pathways using antibodies (PD-1) to PD-L1

Advanced cSCC

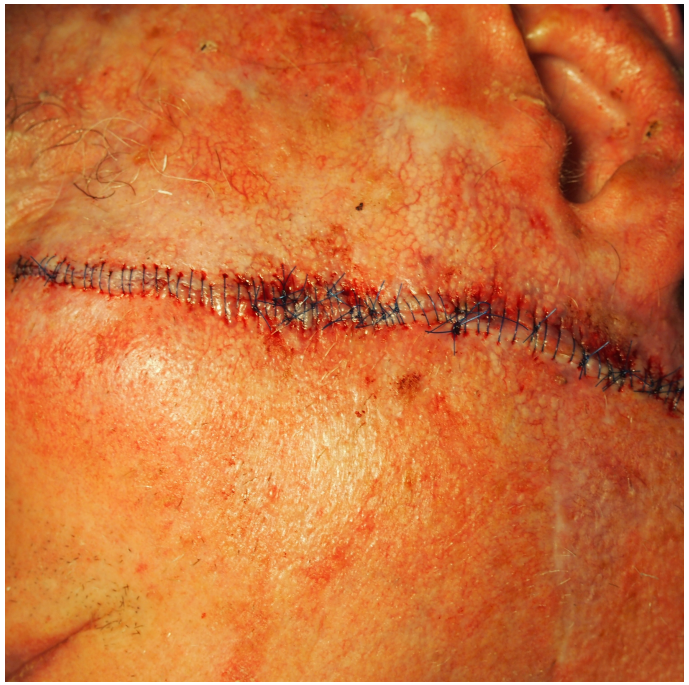
- 79 y/o man with myeloproliferative disorder who underwent Mohs surgery for SCC on left cheek



Pre-op

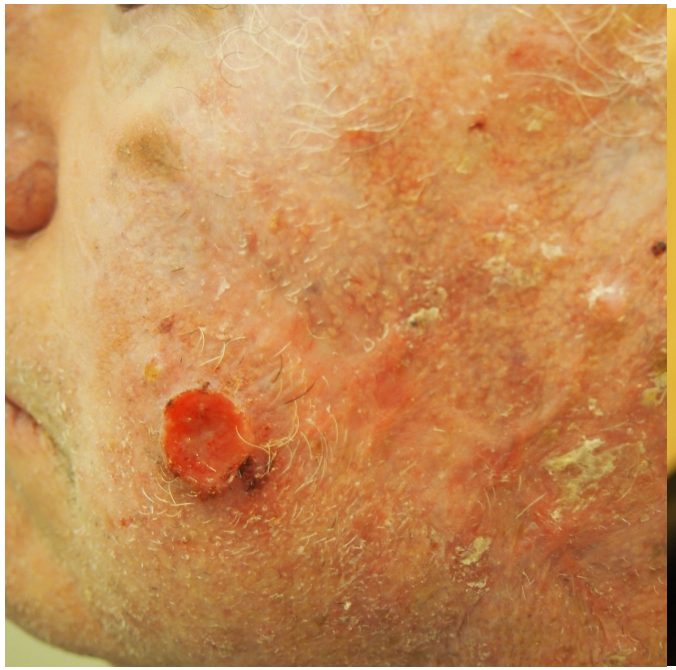


Final defect

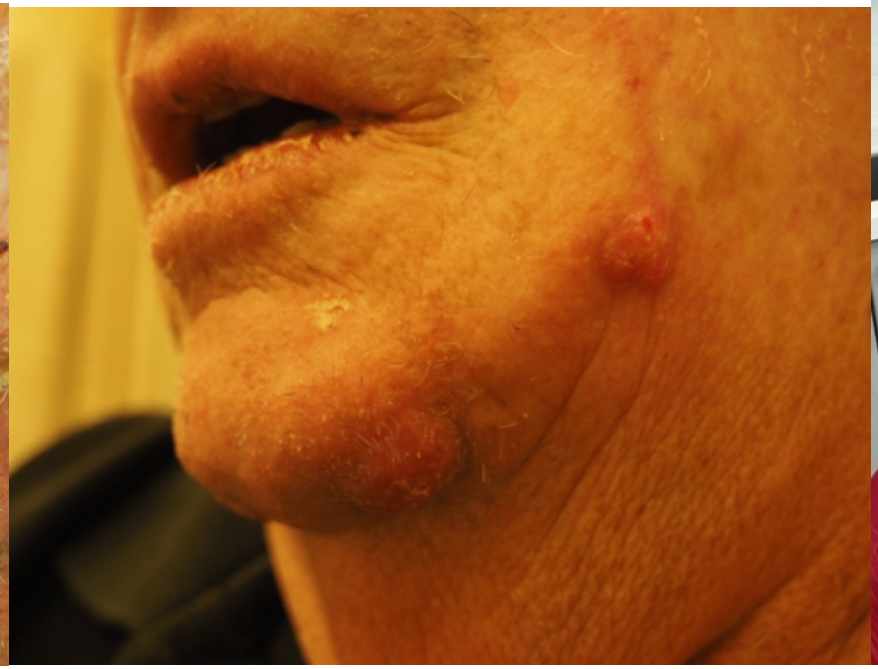


Final repair

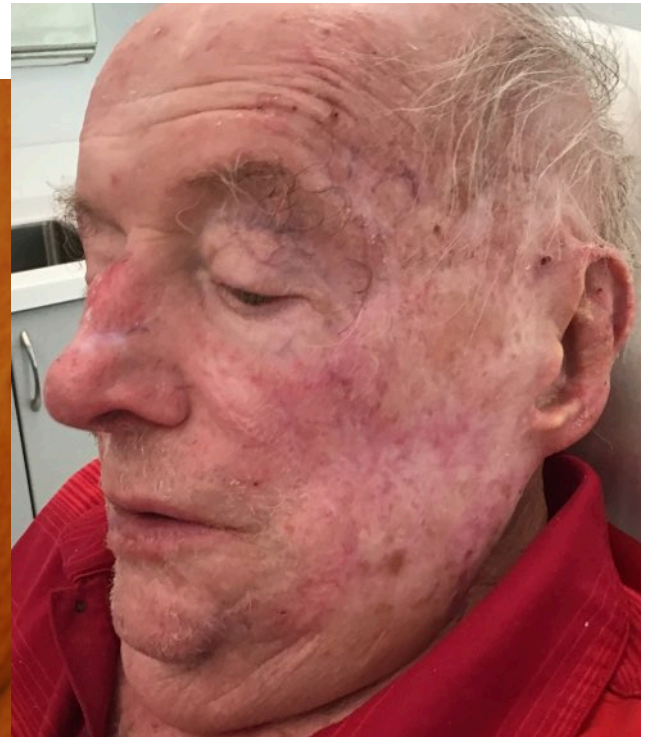
cSCC in-transit mets pre- and post pembrolizumab



One year later



Two years later



Three years post initiation of PD-1 inhibitor

Cemiplimab

- Anti PD-1 human monoclonal antibody
- FDA approved for metastatic or locally advanced cSCC not suitable for curative treatment with surgery or radiation on 9/28/18
- Administered IV, 350 mg over 30 minutes, q2 weeks until disease progression or unacceptable toxicity

FDA approval of cemiplimab

- Based on analysis of data from open label, multicenter, nonrandomized phase 2 trial (EMPOWER-CSCC-1) and two advanced cSCC expansion cohorts from a multicenter open label non-randomized phase 1 trial
- Largest prospective data set in advanced cSCC

Migden MR et al. NEJM 2018: 379: 341-5

Cemiplimab for cSCC

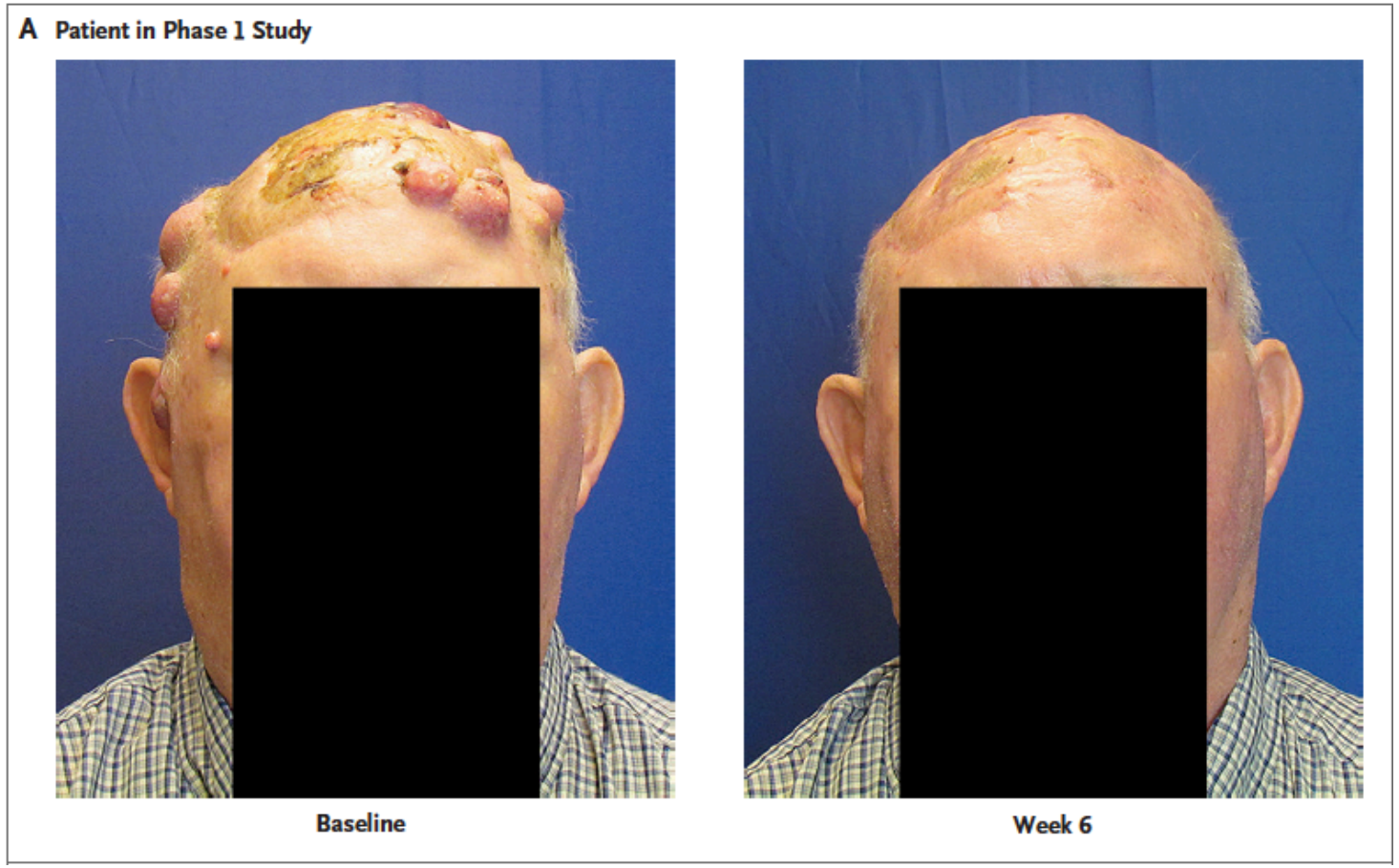
Efficacy endpoints	Metastatic (n=75)	Locally advanced (n=26)
	Phase 1 and 2	Phase 1 expansion cohort
Confirmed ORR	47% (35/75)	50% (13/26)
Complete RR	5% (4/75)	0%
Partial RR	41%(31/75)	50% (13/26)
Median time to response	1.9 months	2.3 months
Durable disease control (>6 months)	61.3%	65%

Migden MR et al. NEJM 2018: 379: 341-51

Safety of cemiplimab

- Most common adverse reactions
  - Fatigue (29%)
  - Rash (25%)
  - Diarrhea (22%)
- Serious adverse events (28%)
  - Cellulitis, sepsis, pneumonia, hypercalcemia

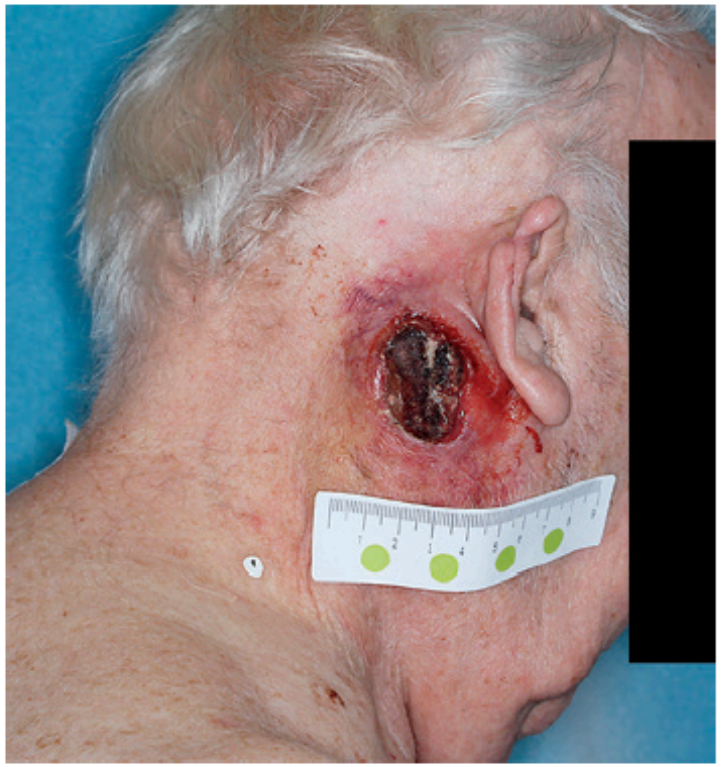
Pre- and post 6 weeks of cemiplimab



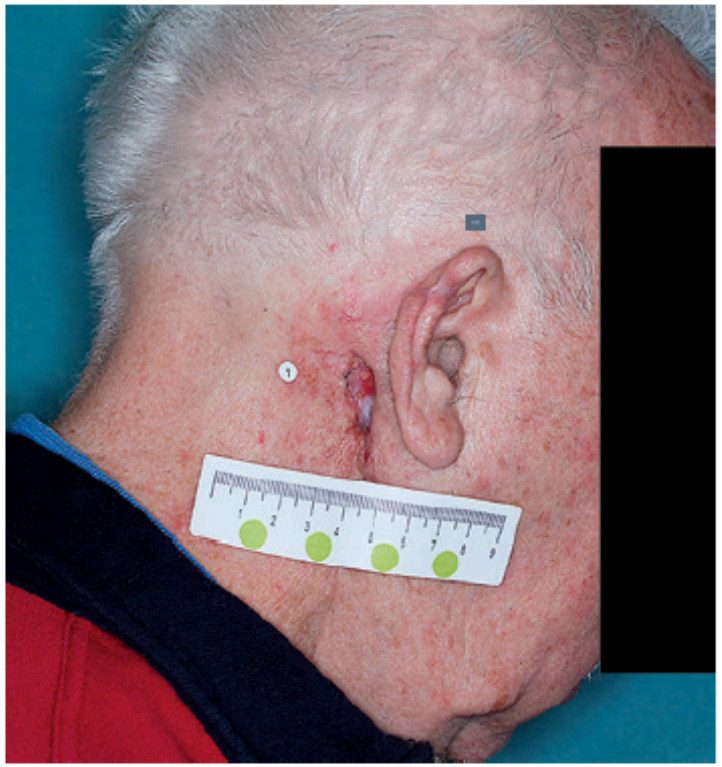
Migden MR et al. NEJM 2018; 379: 341-51

Pre- and post 8 weeks of cemiplimab

B Patient in Phase 2 Study

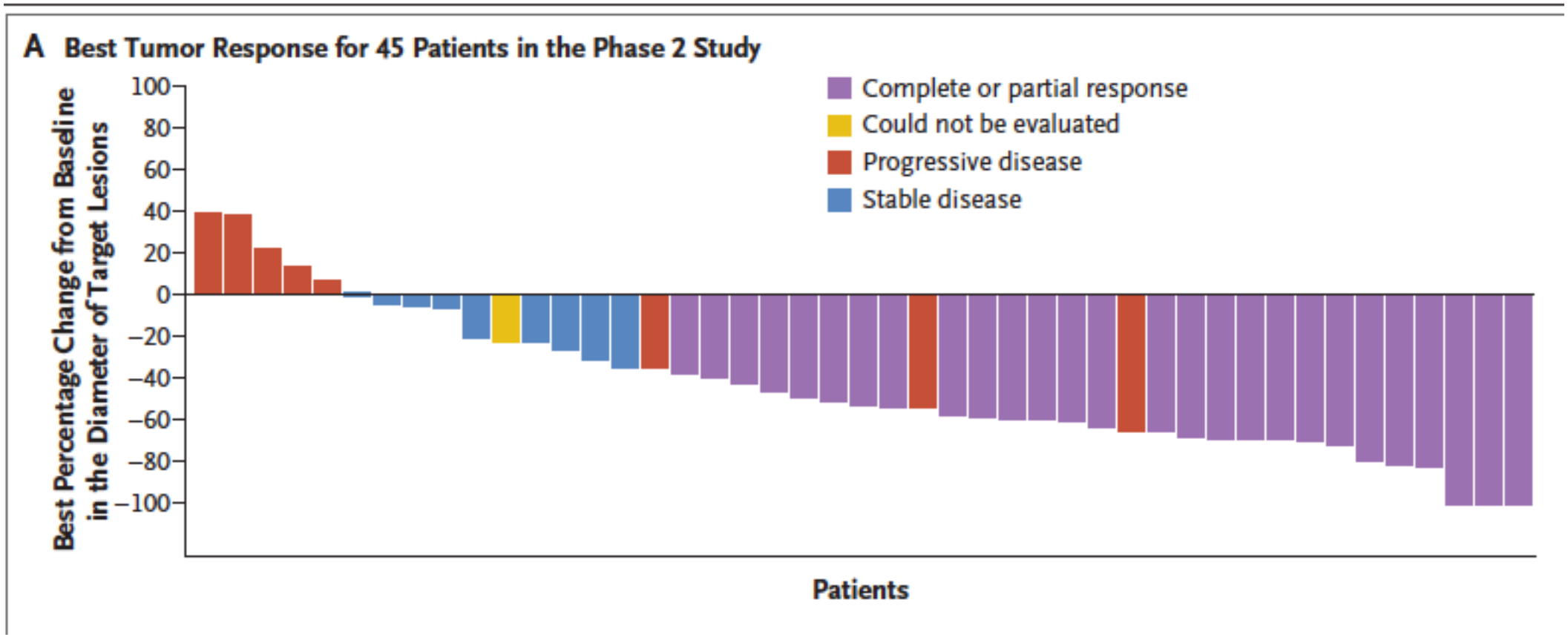


Baseline

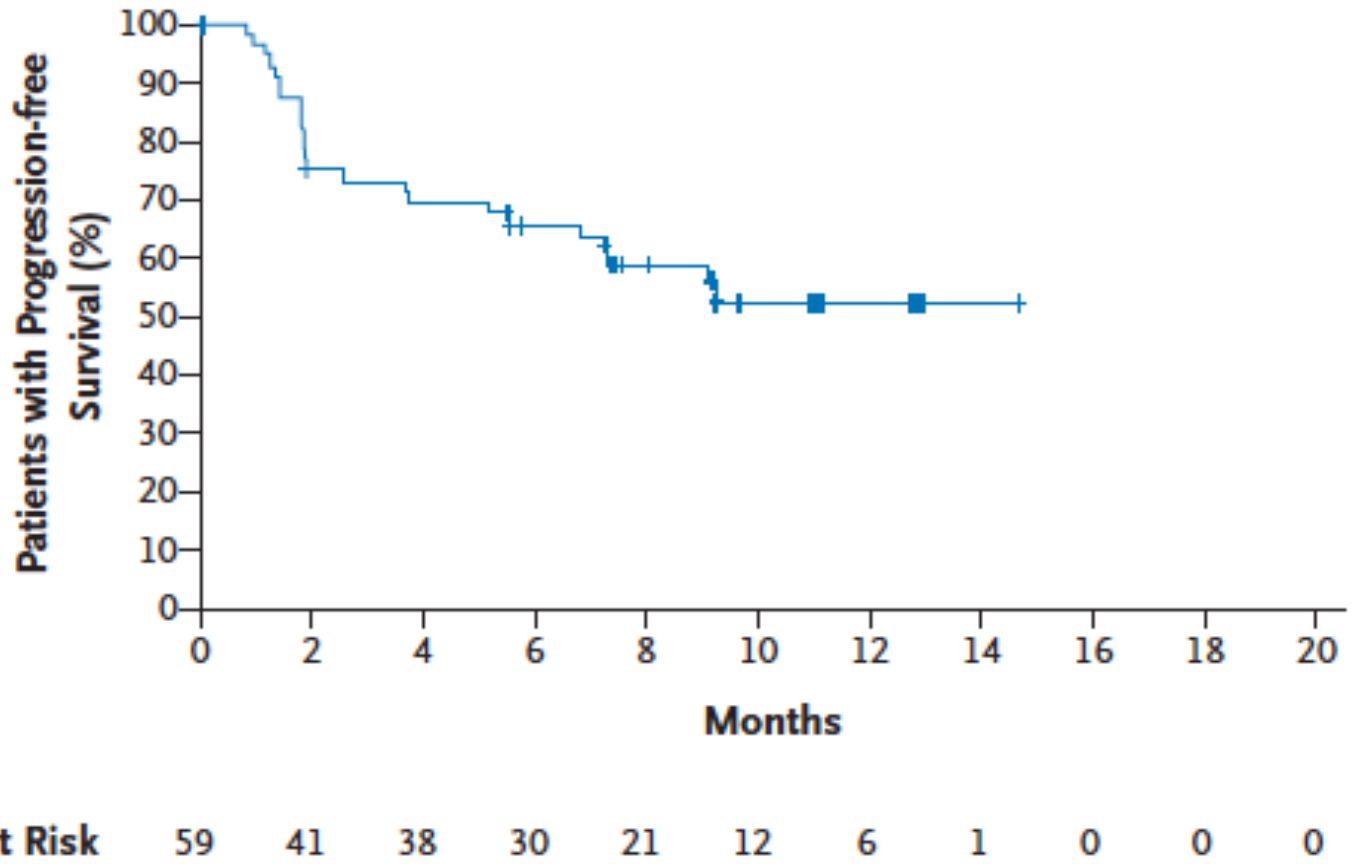


Week 8

Metastatic disease patients: best response



Progression-free survival in metastatic disease treated with cemiplimab



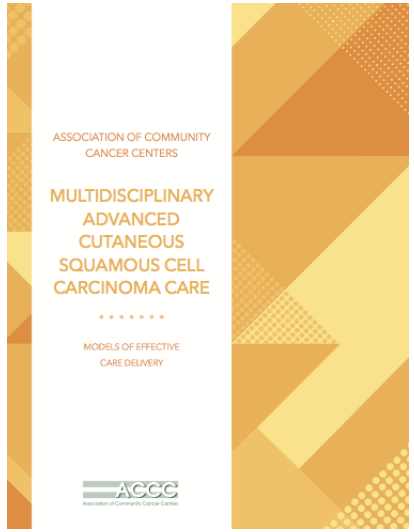
Migden MR et al. NEJM 2018: 379: 341-51

New and emerging cSCC treatments

- Targeted agents and immune checkpoint inhibitors
- Mostly well tolerated with few treatment-limiting side effects
- Have potential to revolutionize management of patients with locally advanced or metastatic cSCC

Importance of Multidisciplinary Care

- Emerging multidisciplinary care models across the country.
- Association of Community Cancer Centers education project on *Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care*.

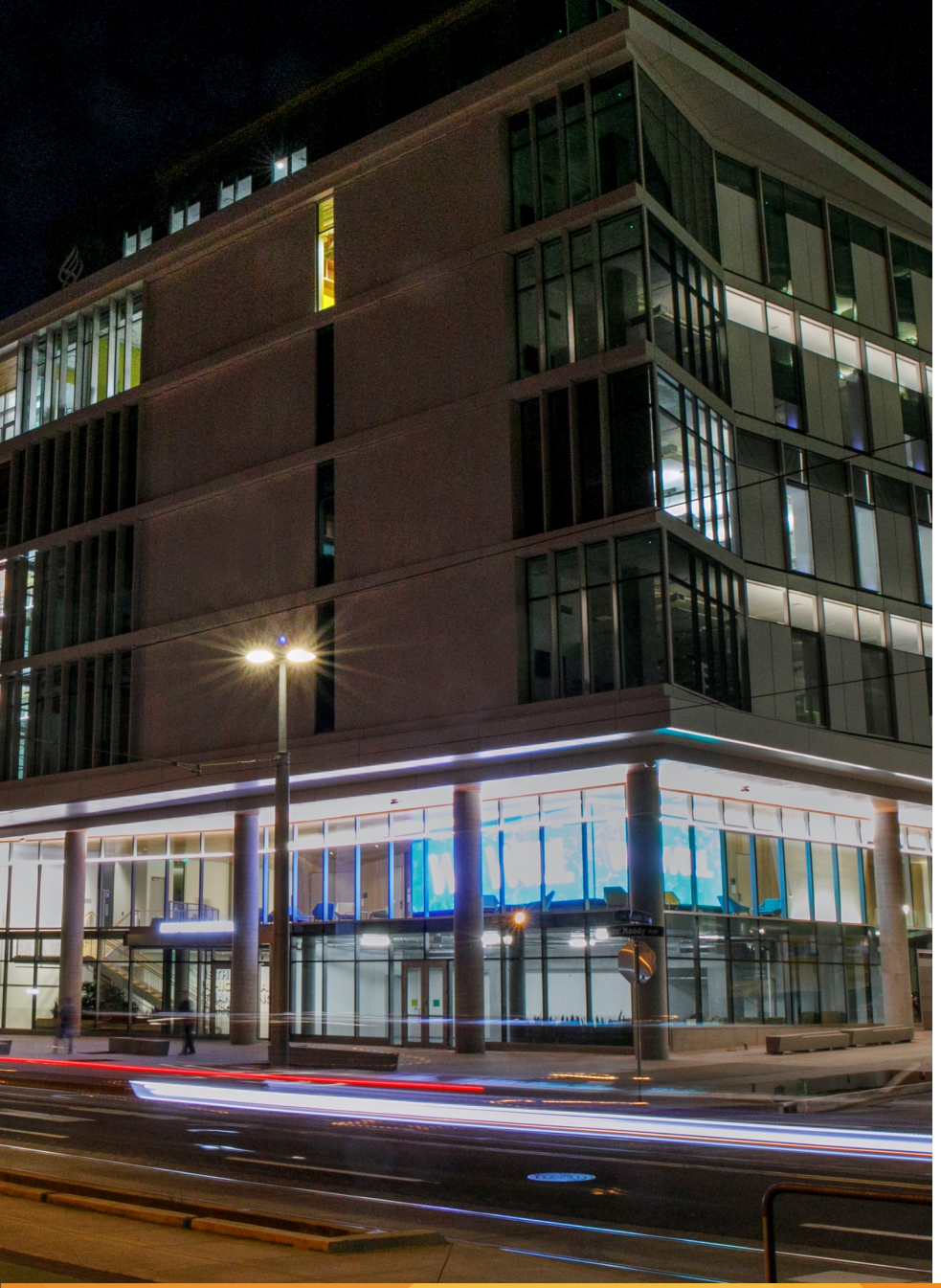


ACCC
Association of Community Cancer Centers

Publication available in print and online!

George Washington Cancer Center

- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- **Newly developed** cutaneous oncology program.
- Multidisciplinary team **led by dermatologic surgeons**.
- Focus on **personalized care**.
- **Ongoing clinical trials** in adjuvant therapy.

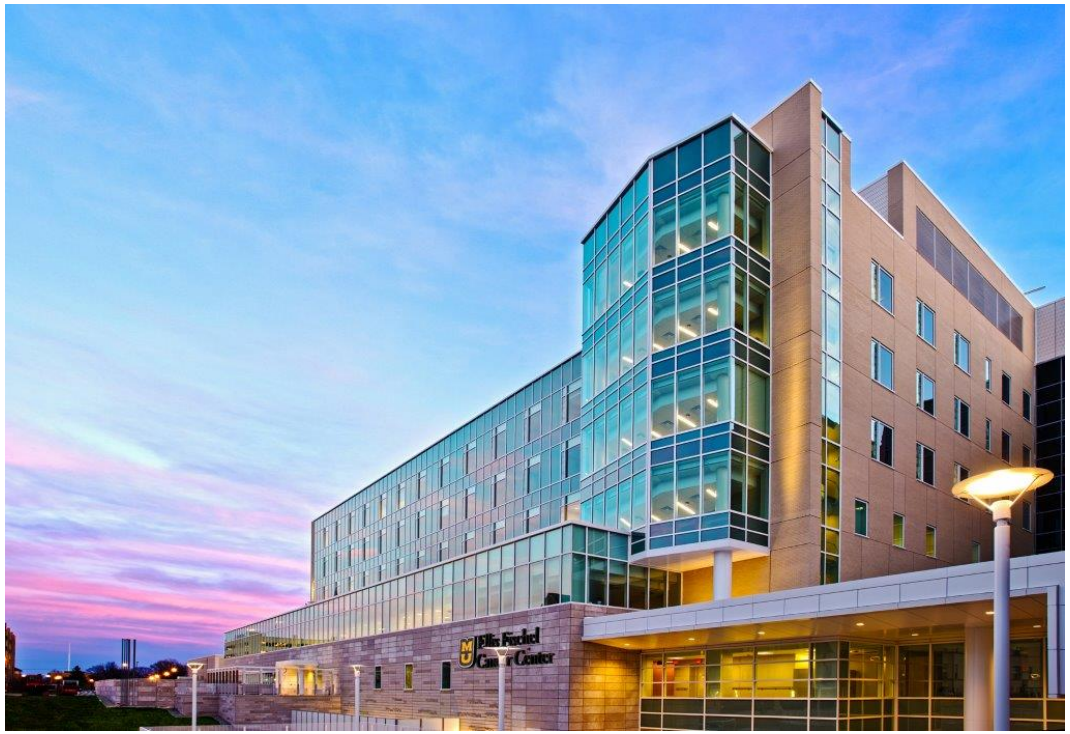


Oregon Health Services University Knight Cancer Institute

- NCI-designated Comprehensive Cancer Center.
- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- Sees a **large volume** of high-risk cSCC patients.
- cSCC program **modeled after well-established melanoma program**.
- Expanding provider access via **virtual tumor boards**.
- Goal to increase access to clinical trials.

University of Missouri-Ellis Fischel Cancer Center

- Certified member of MD Anderson Cancer Care Network.
- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- **Emerging multidisciplinary cutaneous oncology team** with a dedicated cutaneous oncology tumor board and board-certified dermatopathologists.
- Team involves social work, pharmacy, patient, and nurse navigators.
- **Teledermatology** and the **ECHO platform**.
- **Ongoing clinical trials** in biomarker assessment.



References

- Blechman AB, Carucci JA, Stevenson ML. Stratification of poor outcomes for cutaneous squamous cell carcinoma in immunosuppressed patients using the American Joint Commission on Cancer 8th Edition and Brigham and Women's Hospital Staging Systems. Dermatol Surg 2019; 45(9): 1117-1124.
- Cribier et al. Differentiating squamous cell carcinoma from keratoacanthoma using histopathological criteria. Is it possible? Dermatology 1999; 199:208-12.
- Jambusaria-Pahlajani et al. Evaluation of AJCC Tumor Staging for cSCC and a proposed alternative staging system. JAMA Dermatol 2013 (149): 402-10
- Kwon S et al. SLNB for high-risk cSCC. World J Surg Oncol. 2011 Jul 19;9:80.
- Mansouri B, Housewright C. The treatment of actinic keratoses: the rule rather than the exception. J Am Acad Dermatol 2017; 153(11):1200. doi: 10.1001/jamadermatol.2017.3395.
- Migden MR et al. PD-1 Blockade with **Cemiplimab** in Advanced Cutaneous Squamous-Cell Carcinoma. NEJM 2018: 379: 341-5.
- O'Bryan K et al. An evolving paradigm for the work-up and management of high-risk cSCC. JAAD 2013; 69: 595-602
- Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012. *JAMA Dermatol* 2015; 151(10):1081-1086.
- Schmitt AR et al. cSCC as a Predictor of SLNB Results. JAMA Dermatol. 2014 Jan 1;150(1):19-24.
- What are basal and squamous cell skin cancers? American Cancer Society. http://www.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-basal-and-squamous-cell-what-is-basal-and-squamous-cell. Accessed December 29, 2019.

Questions?

Thank You

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This lecture will be made available as an on-demand webinar.

For more information about this project:

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