Cutaneous Squamous Cell Carcinoma (CSCC)

OPTIMIZING RECOGNITION AND REFERRAL PATHWAYS FOR SKIN CANCERS IN LONG-TERM CARE

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Disclosures:

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Agenda

Epidemiology

Risk Factors

Clinical Presentation

Diagnosis

Treatment

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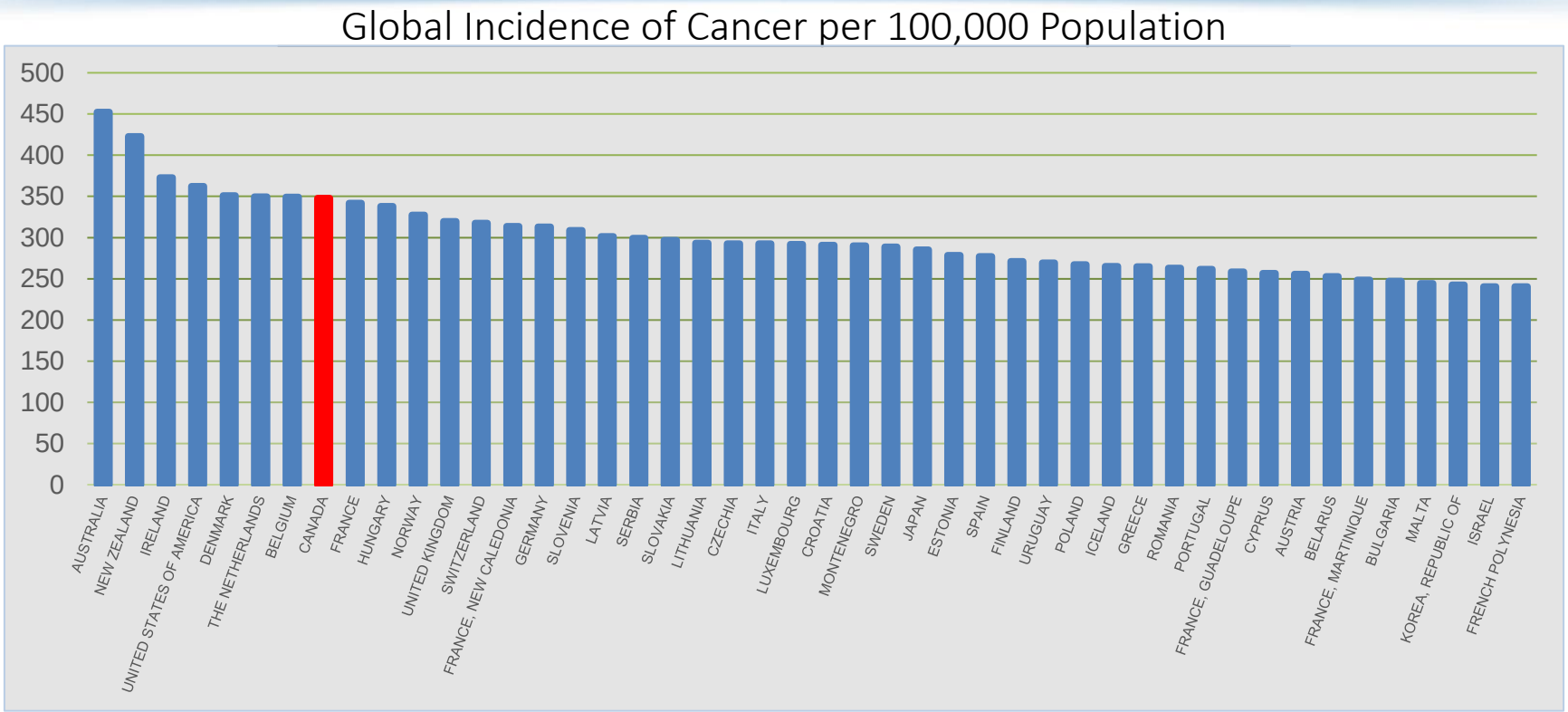
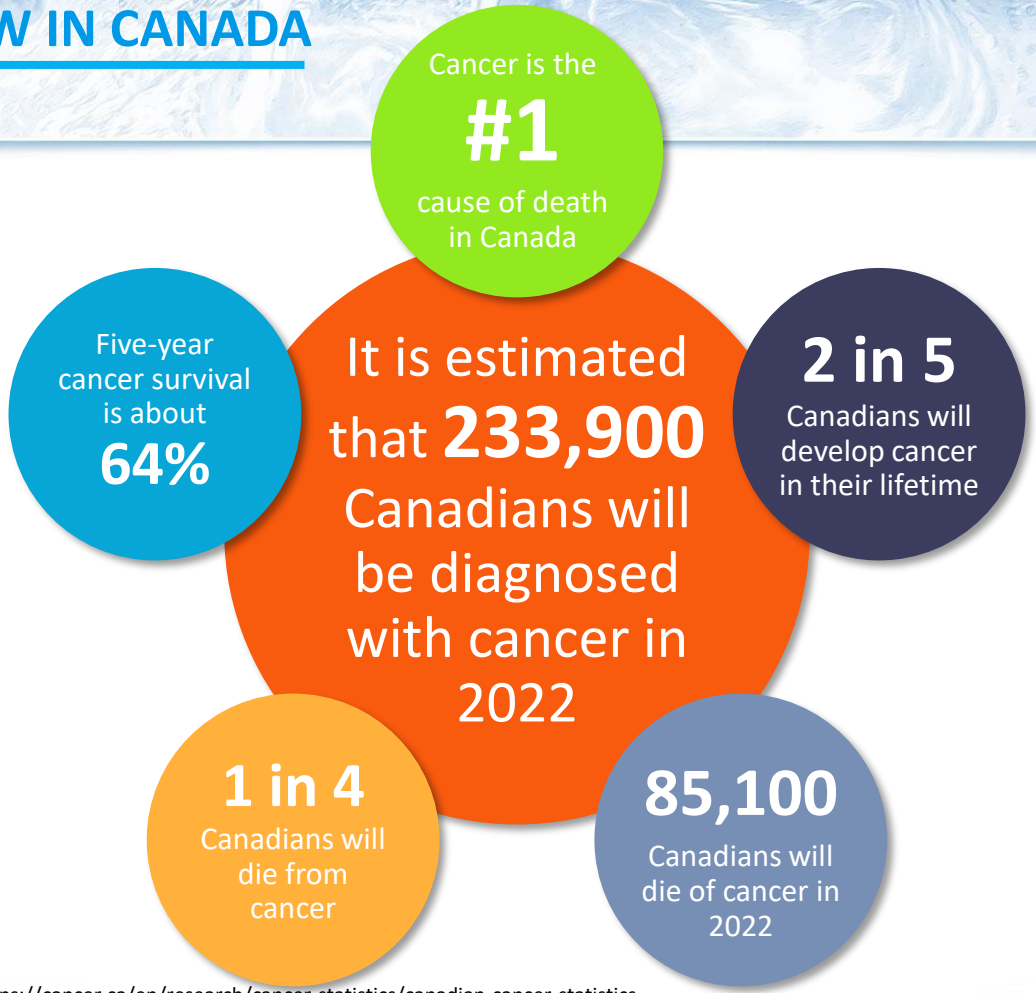
CANCER OVERVIEW IN CANADA



Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A & Bray F (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.

CANCER OVERVIEW IN CANADA



Canadian Cancer Society; 2022. Available at: https://cancer.ca/en/research/cancer-statistics/canadian-cancer-statistics

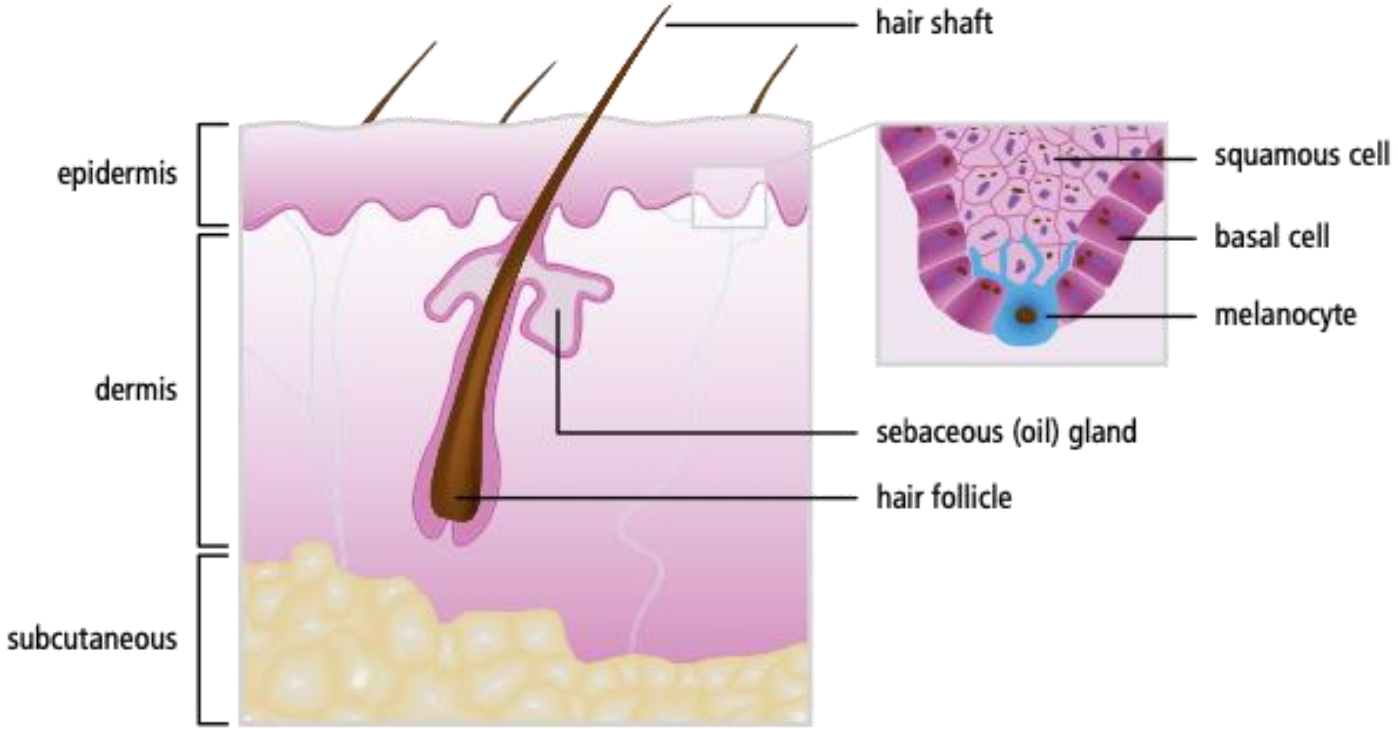
Skin cancer is the **most common cancer** in Canada.

In 2014, an estimated 6,500 new cases of melanoma and **76,100 cases of NMSC** will occur in Canada.

An estimated **440 deaths** due to NMSC

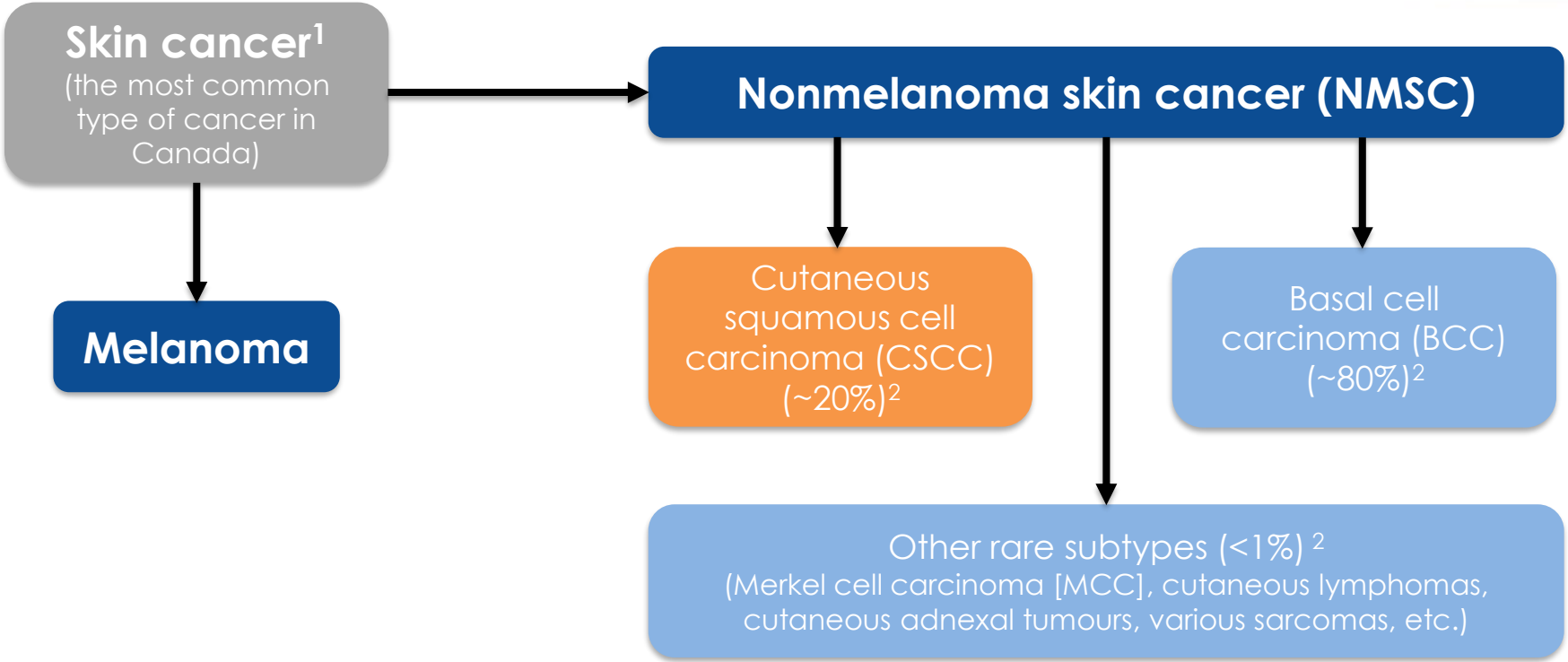
Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014. Available at: cancer.ca

Skin Basic Anatomy



Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014. Available at: cancer.ca

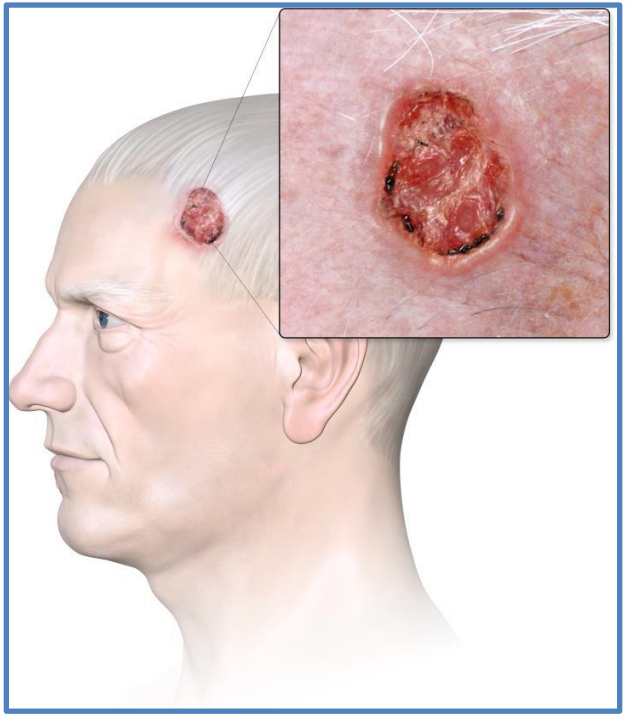
CSCC IS A FORM OF NONMELANOMA SKIN CANCER



1. Canadian Cancer Society. Melanoma: deadliest type of skin cancer is on the rise. Available from: http://www.cancer.ca/en/about-us/for-media/media-releases/national/2014/2014-canadian-cancer-statistics/?region=on; 2. American Cancer Society. What are basal and squamous cell skin cancers? Available from: https://www.cancer.org/cancer/basal-and-squamous-cell-skin-cancer/about/what-is-basal-and-squamous-cell.html.

CSCC SURVIVAL

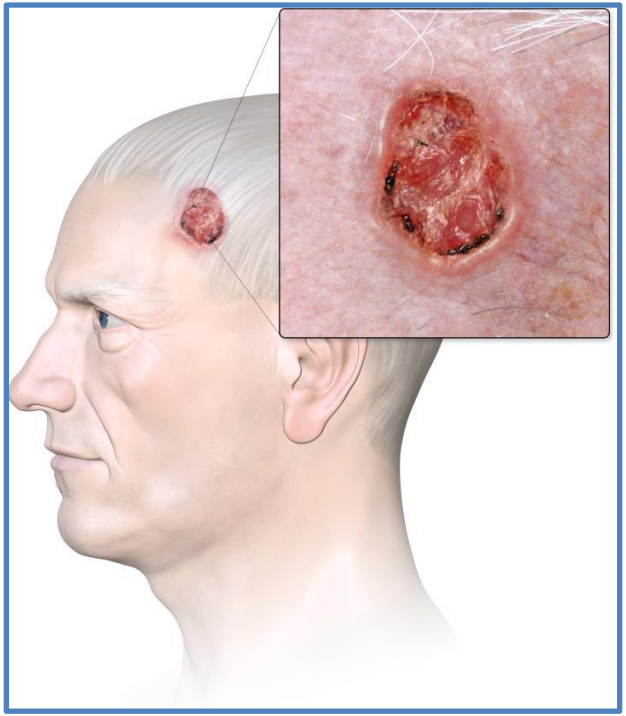
- Generally good prognosis with early detection in 95-98% of patients; curable with surgery
- Cases with tumour progression may lead to incurable metastatic or locally advanced disease that is no longer responsive to surgery or radiation
- The annual incidence of metastasis of CSCC is approximately 4%[3]
- With metastatic disease, estimated 5-year survival is less than 50%



1. Najjar. Cutaneous squamous cell carcinoma clinical presentation. Available from: http://emedicine.medscape.com/article/1965430-clinical;
2. Cancer.Net. Skin cancer (non-melanoma) - introduction. Available from: https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/introduction;
3. Burton et al. Am J Clin Dermatol. 2016;17:491-508.

CSCC IS THE SECOND DEADLIEST SKIN CANCER AFTER MELANOMA

- Mortality rates approximate that of renal cell carcinoma
- Mortality rates approximate that of oropharyngeal carcinomas
- Mortality rates may be double that of melanoma
- < 50 years old – 90% of skin cancer deaths from melanoma
- > 85 years old – majority of skin cancer deaths from cSCC



Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, & deaths from disease in the U.S., 2012. J Am Acad Dermatol. 2013;68:957-966.
Weinstock MA : Death from skin cancer among the elderly: epidemiological patterns. Arch Dermatol. 133:1207-1209 1997

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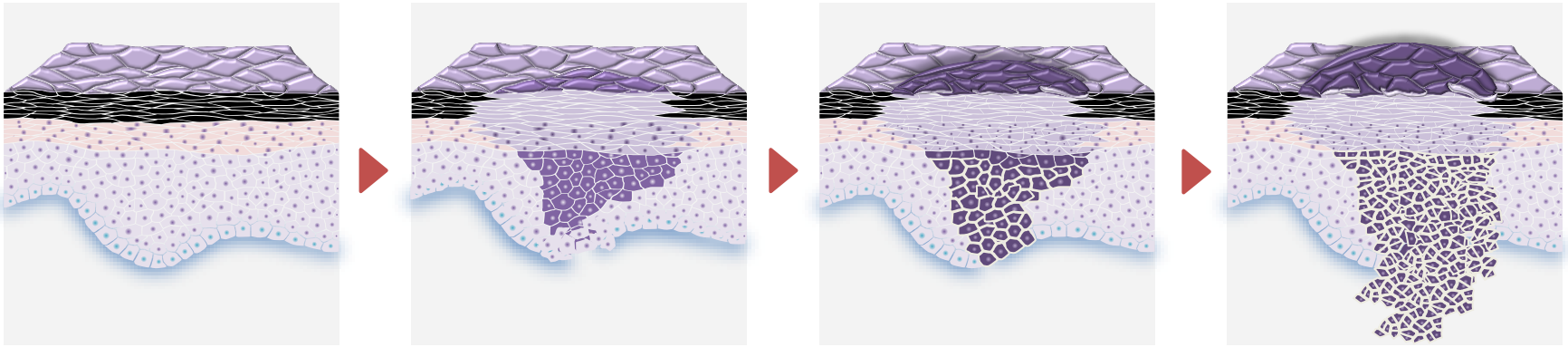
THE CLINICAL PROGRESSION OF CSCC IS CHARACTERIZED BY THE PRESENTATION OF SKIN LESIONS

- The probability of AK progression to CSCC ranges from 0.025-16% for an individual lesion per year[1]
- The annual incidence of metastasis of CSCC is approximately 4%[2]



AK: actinic keratosis.
1. Ratushny et al. J Clin Invest. 2012;122:464-72; 2. Burton et al. Am J Clin Dermatol. 2016;17:491-508.

INCIDENCE OF CSCC IS ASSOCIATED WITH SEVERAL RISK FACTORS

Direct Exposure to Sunlight

UV exposure leads to genetic and protein mutations associated with poor keratinocyte differentiation and invasion into the dermis

Male Gender

A retrospective, multicenter analysis found incidence to be higher in male patients (87%)

Advanced Age

Median age of CSCC patients is 70 years

Immunodeficient Status

Immunosuppression in organ transplant recipients and immunocompromised status related to certain diseases (e.g. CLL, HIV) can increase incidence of CSCC due to impairment of cancer cell recognition

CLL: chronic lymphocytic leukemia; HIV: human immunodeficiency virus; UV: ultraviolet.
Burton et al. Am J Clin Dermatol. 2016;17:491-508.

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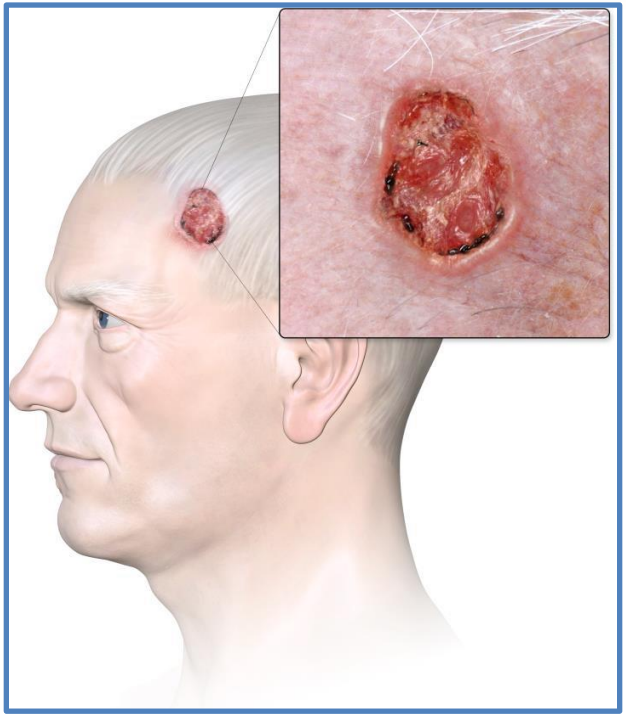
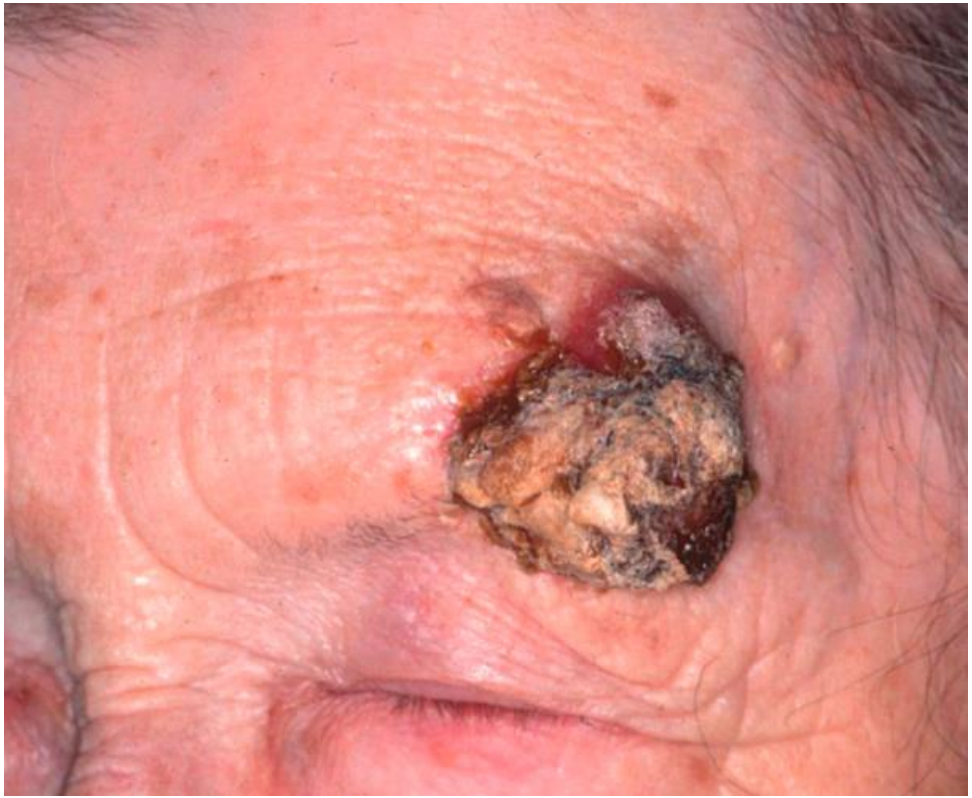
CSCC APPEARANCE: NONHEALING ULCER OR GROWTH IN A SUN-EXPOSED AREA

- Typical signs and symptoms[1]
  - Nonhealing ulcer or abnormal growth in the sun-exposed skin area (~70% in the head and neck)
  - A shallow ulcer with heaped-up edges, often covered by a plaque
- Tumour may grow into deep structures, including connective tissues, cartilage, muscle, and bone[2]
- Numbness, local pain, twitching, and muscle weakness may be signs of perineural invasion[2]
- Most common sites of metastasis are local and regional lymph nodes, manifesting into enlarged nodes[3]



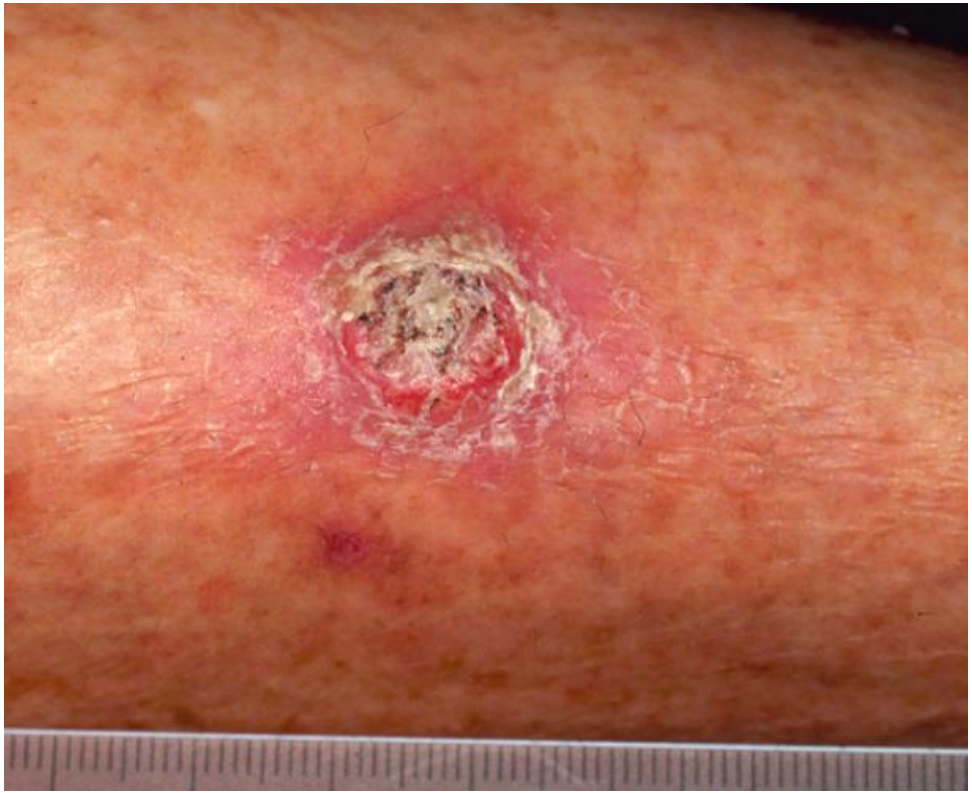
1. Najjar. Cutaneous squamous cell carcinoma clinical presentation. Available from: http://emedicine.medscape.com/article/1965430-clinical; 2. Cancer.Net. Skin cancer (non-melanoma) - introduction. Available from: https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/introduction; 3. Burton et al. Am J Clin Dermatol. 2016;17:491-508.

CSCC CLINICAL PRESENTATION: KERATOTIC NODULE



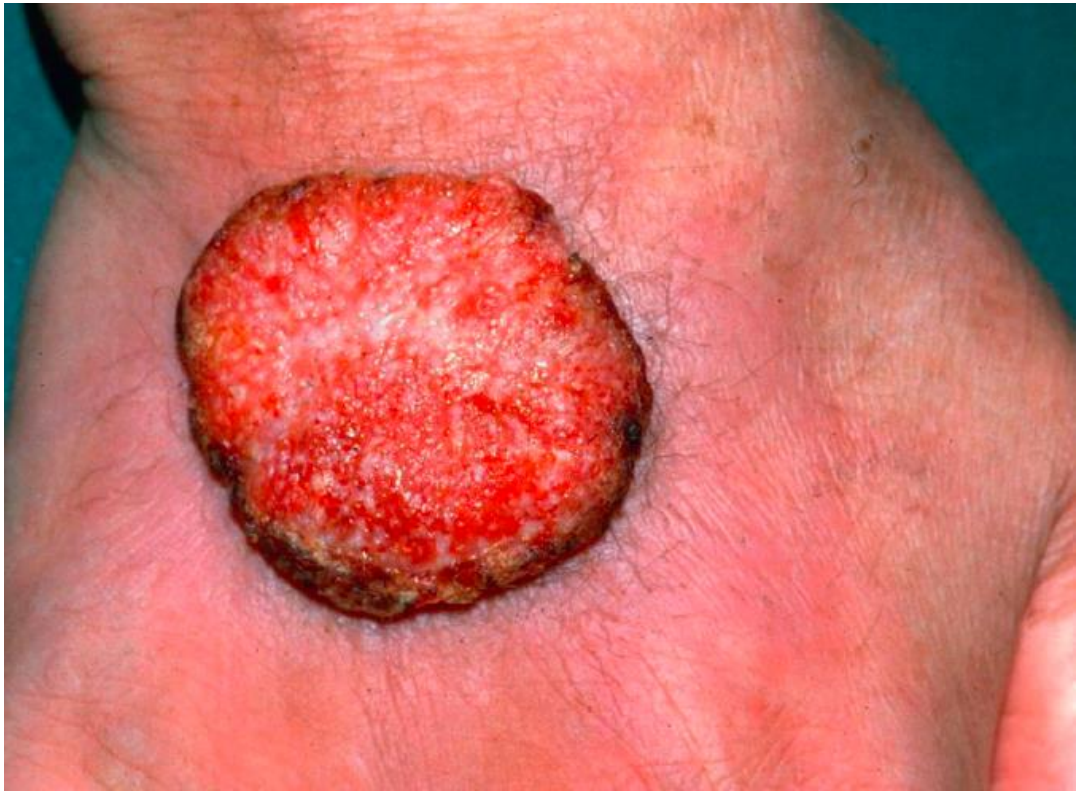
Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

CSCC CLINICAL PRESENTATION: ERODED NODULE AT SITE OF TRAUMA



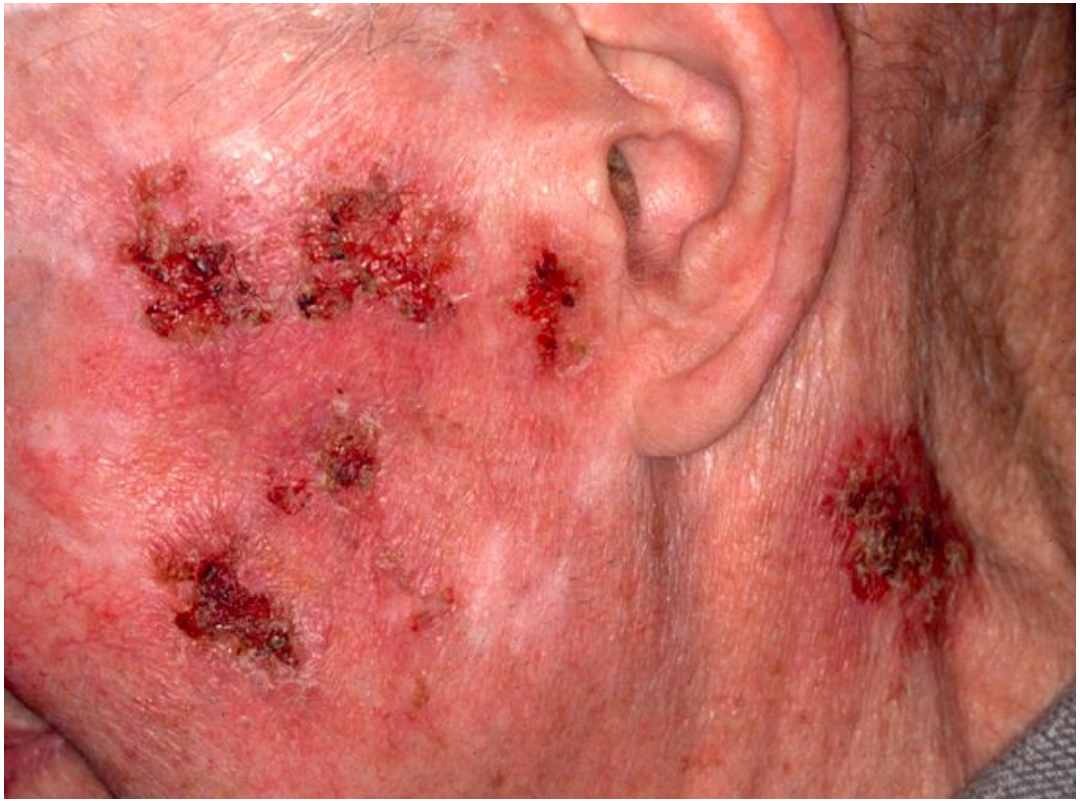
Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

CSCC CLINICAL PRESENTATION: FUNGATING NODULE



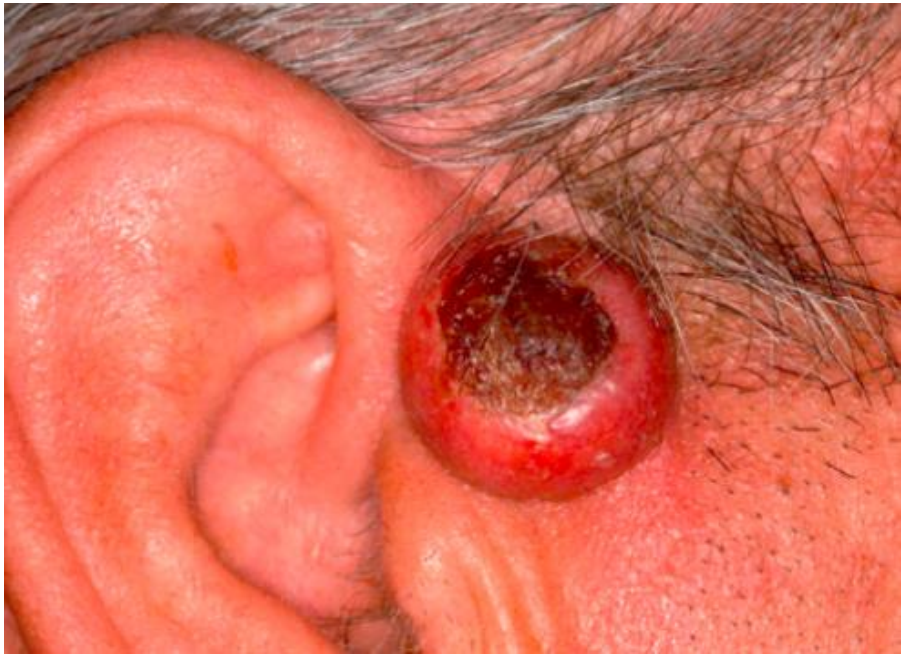
Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

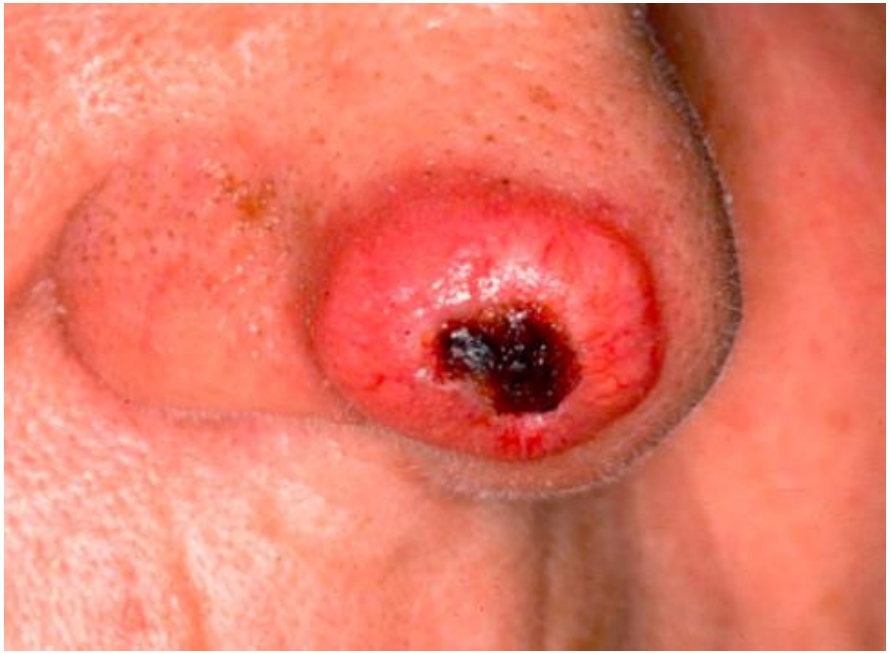
CSCC CLINICAL PRESENTATION: MULTIPLE ERODED SUPERFICIAL



Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

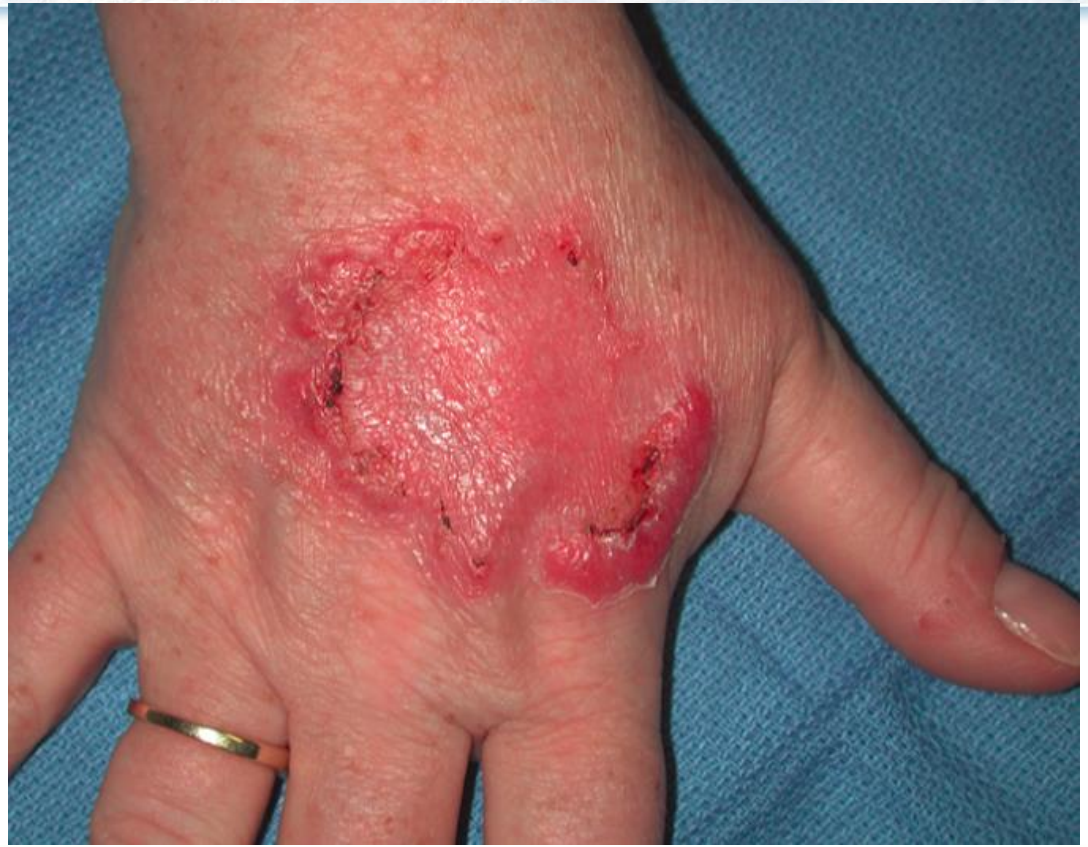
CSCC CLINICAL PRESENTATION: CRATERIFORM NODULES





Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

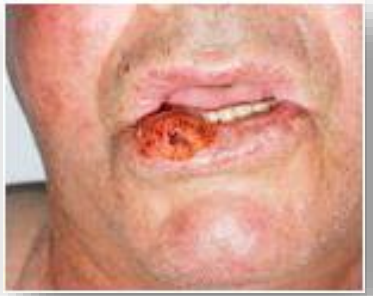
CSCC CLINICAL PRESENTATION: KERATOACANTHOMA CENTRIFUGUM MARGINATUM



Bolognia JL, Schaffer JV. dermatology. 4th ed. Philadelphia , PA: Elsevier; 2018.

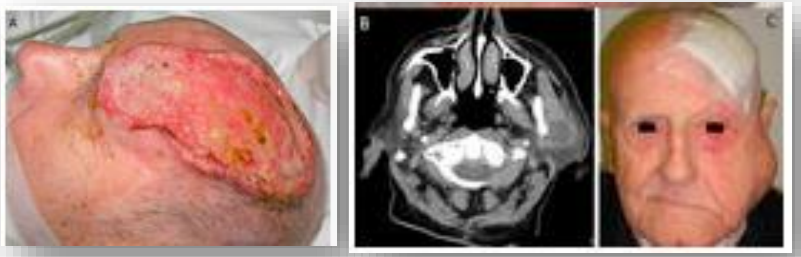
HIGH-RISK FACTORS FOR MCSCC:[1,2] DISEASE CHARACTERISTICS AND PATIENT CLINICAL STATUS

CSCC on the lower lip



High-risk feature: location[1]

Large CSCC located in the left frontoparietal region



High-risk features: size, depth, a Clark level of IV (periosteal invasion), poor differentiation[1]

mCSCC: metastatic cutaneous squamous cell carcinoma.

1. Farasat et al. *J Am Acad Dermatol*. 2011;64:1051-9; 2. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017. [Photos from Nuño-González A, et al. 2011 *Actas Dermosifiliogr* – journal permissions needed].

HIGH-RISK FACTORS FOR MCSCC:[1,2] DISEASE CHARACTERISTICS AND PATIENT CLINICAL STATUS

	Low risk	High risk
CLINICAL RISK FACTORS		
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm	Area M ≥10 mm
	Area H <6 mm	Area H ≥6 mm
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Tumor at site of prior radiation therapy	Negative	Positive
Tumor at site of chronic inflammatory process (SCC only)	Negative	Positive
Rapidly growing tumor (SCC only)	Negative	Positive
Neurologic symptoms: pain, paresthesia, paralysis (SCC only)	Negative	Positive
Immunosuppression	Negative	Positive

PATHOLOGIC RISK FACTORS		
Perineural involvement	Negative	Positive
Subtype (BCC only)	Nodular, superficial	Micronodular, infiltrating, sclerosing
Degree of differentiation (SCC only)	Well differentiated	Moderately or poorly differentiated
Desmoplasia (SCC only)	Negative	Positive
Adenoid, adenosquamous or desmoplastic (SCC only)	Negative	Positive
Tumor thickness (SCC only)	<2 mm	≥ 2 mm (see text)

Area L: low risk for recurrence: trunk, extremities.
Area M: middle risk for recurrence: cheeks, forehead, neck, scalp.
Area H: high risk for recurrence: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, ear,

Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 108; Table 108.10. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

RECURRENCE AND METASTASIS

5-year rates:

Standard Risk[1]		High Risk*[1,2]	
Recurrence	Metastasis	Recurrence	Metastasis
8%	5%	15%	30%

*For example, for large lesions (>2 cm in diameter).

- Numerous risk factors are associated with CSCC progression and metastasis[3,4]
- Recurrence rates can be higher for certain locations, such as the head and neck, and for tumors >2 cm in size[5]

1. Alam and Ratner. N Engl J Med. 2001;344:975-83; 2. Stratigos et al. Am J Clin Dermatol. 2015;51:1989-2007; 3. Karia et al. J AM Acad Dermatol. 2013;68:957-66; 4. Schmults et al. JAMA Dermatol. 2013;149:541-47; 5. Alam and Ratner. N Engl J Med. 2001;344:975-83.

CURRENT CSCC STAGING SYSTEMS DO NOT CONSISTENTLY PROVIDE A SATISFACTORY PROGNOSTIC EVALUATION

- Current staging systems lack external validation[1-3]
- Challenges in discrimination of stages results in significant variation of outcomes[1-3]
  - Tumour size often correlated with outcomes
  - Lymph node involvement has been observed in CSCC patients with both good and poor outcomes

There is no consensus on what staging system to use in clinical practice

Staging System	Tumour Size	Lymph Node Involvement	Risk Factors
American Joint Committee on Cancer[1]	●	●	●
Union for International Cancer Control[2]	●	●	●
Brigham and Women's Hospital[3]			●

1. Amin et al. 8th ed. Springer; New York; 2017; 2. Sobin et al. TMN Classification of Malignant Tumours. 7th ed. John Wiley & Sons; New York; 2009; 3. Jambusaria-Pahlanjani et al. JAMA Dermatol. 2013;149:402-10.

AS DISEASE STAGING IN CSCC CAN OVERLAP, THERE ARE CHALLENGES IN DEFINING AND SEGMENTING PATIENTS, PARTICULARLY IN THE LA POPULATION

One option for CSCC disease staging[1]

	Localized		Locally Advanced		Metastatic
Width	<2 cm	2 cm	>2 cm	>2 cm	2 cm
Depth	<5 mm	5 mm	>5 mm	>5 mm	5 mm
Invasion of critical structures	None	None	Muscle, bone, skull space or perineural	Perineural	Perineural
Spread of disease	Primary site only	Primary site only	Primary site only	Regional lymph nodes	Distant nodes or organs
Histology	Well differentiated	Well differentiated	Poorly differentiated	Poorly differentiated	Poorly differentiated
Location	Trunk, head or extremities	Ears, nose, lips or scalp	Trunk, head or extremities	Trunk, head or extremities	Trunk, head or extremities

- Metastatic and patients at the far end of the LA spectrum are often referred to as "advanced CSCC"; however, clinical criteria for advanced disease are not fixed[1]
- This ambiguity leads to a lack of alignment between different clinical specialties (e.g. dermatologists, oncologists) and can impact treatment choice[2]

LA: locally advanced.
1. Client internal resources; 2. Stratigos et al. Eur J Cancer. 2015;51(14):1989-2007.

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DIAGNOSIS

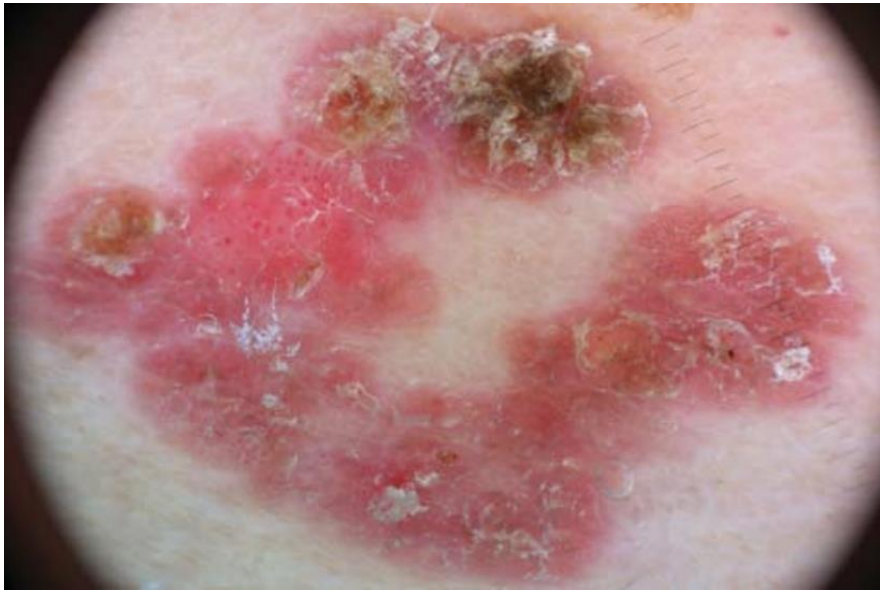
Standard of Care
- Dermoscopy
- Pathology

Novel noninvasive modalities
- Reflectance confocal microscopy
- Optical coherence tomography

DERMOSCOPY

- Handheld device
- 10x magnification
- Peripheral polarized light

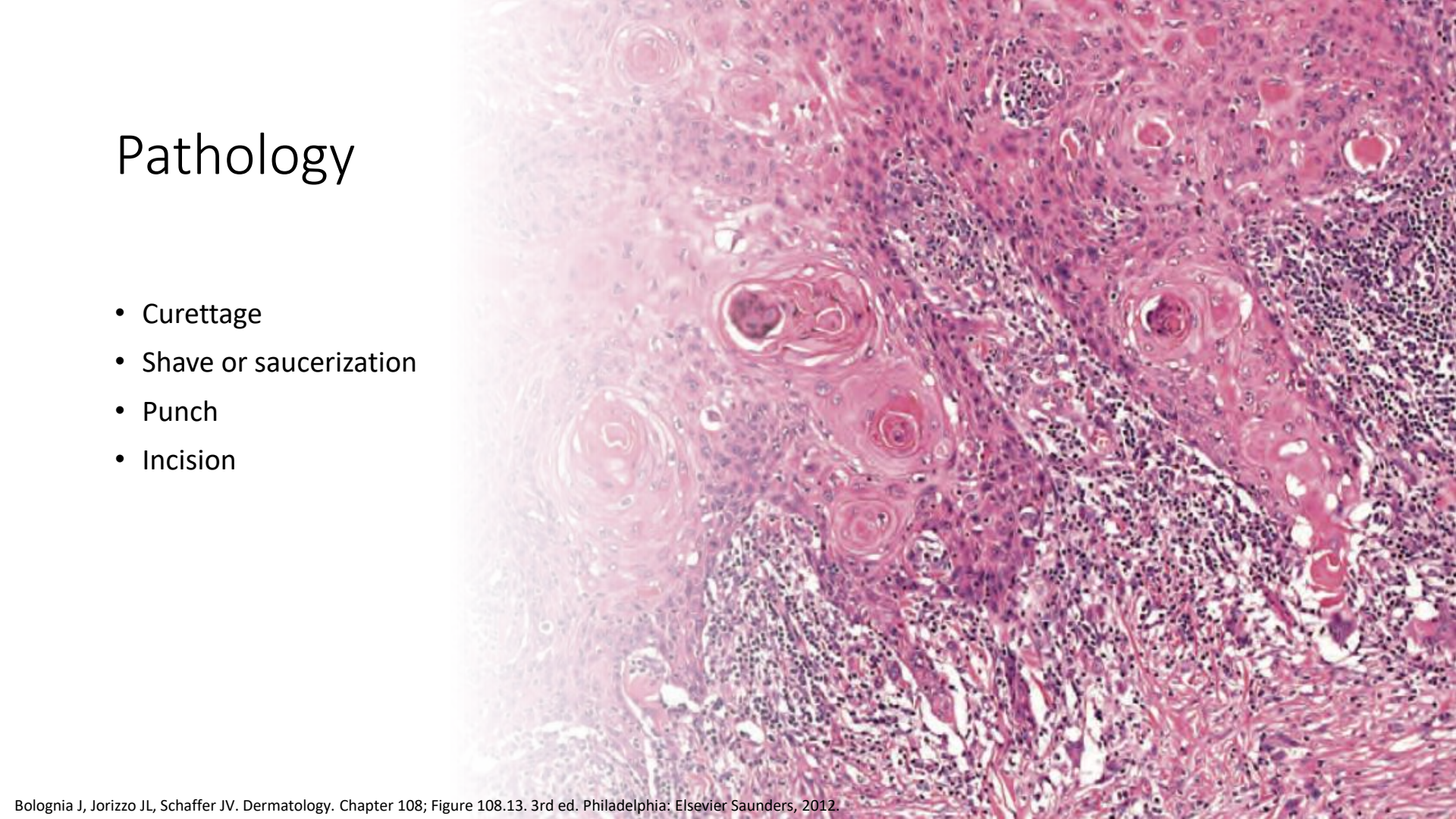
- Specific patterns can be diagnostic of benign or malignant lesions



Marghoob AA, Malvehy J, Braun RP. Atlas of Dermoscopy. 2E . Chapter 5B: Actinic keratosis, Bowen's disease, keratoacanthoma, and squamous cell carcinoma (Zalaudek I, Cameron A, and Rosendahl C) . New York: Informa Healthcare, 2012.

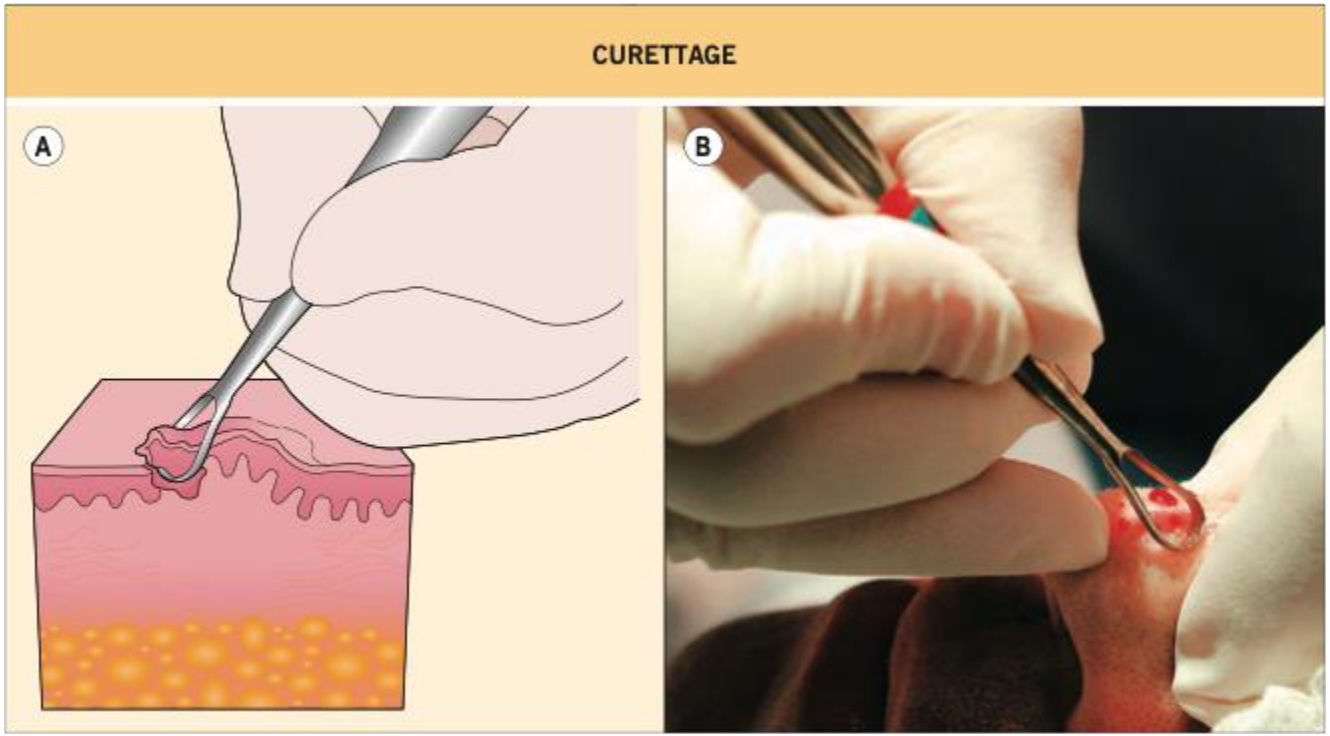
Pathology

- Curettage
- Shave or saucerization
- Punch
- Incision



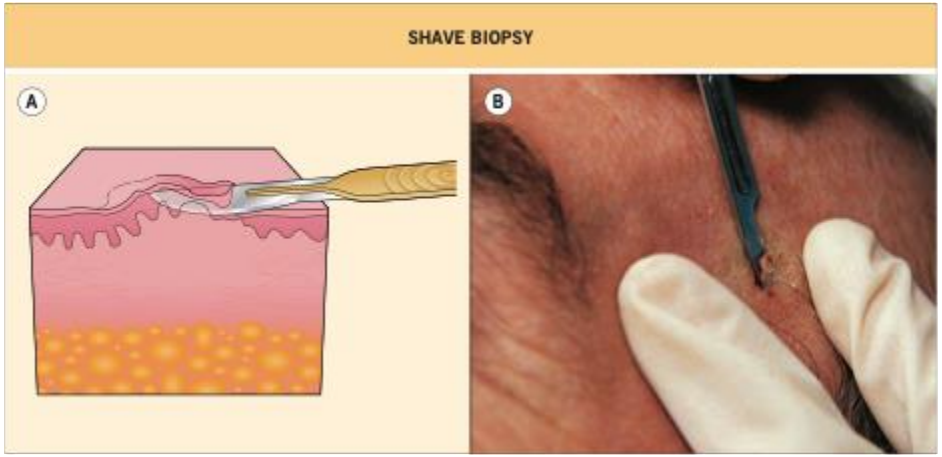
Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 108; Figure 108.13. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

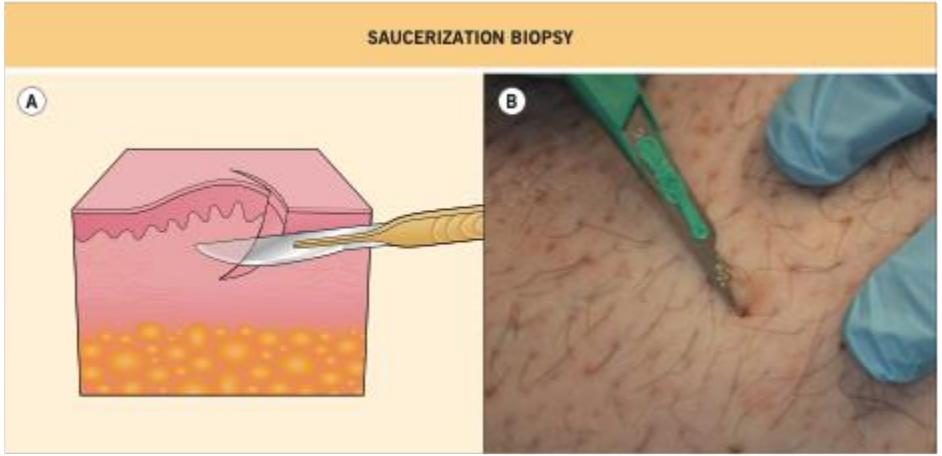
Pathology: Curettage



Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 146; Figure 146.5. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

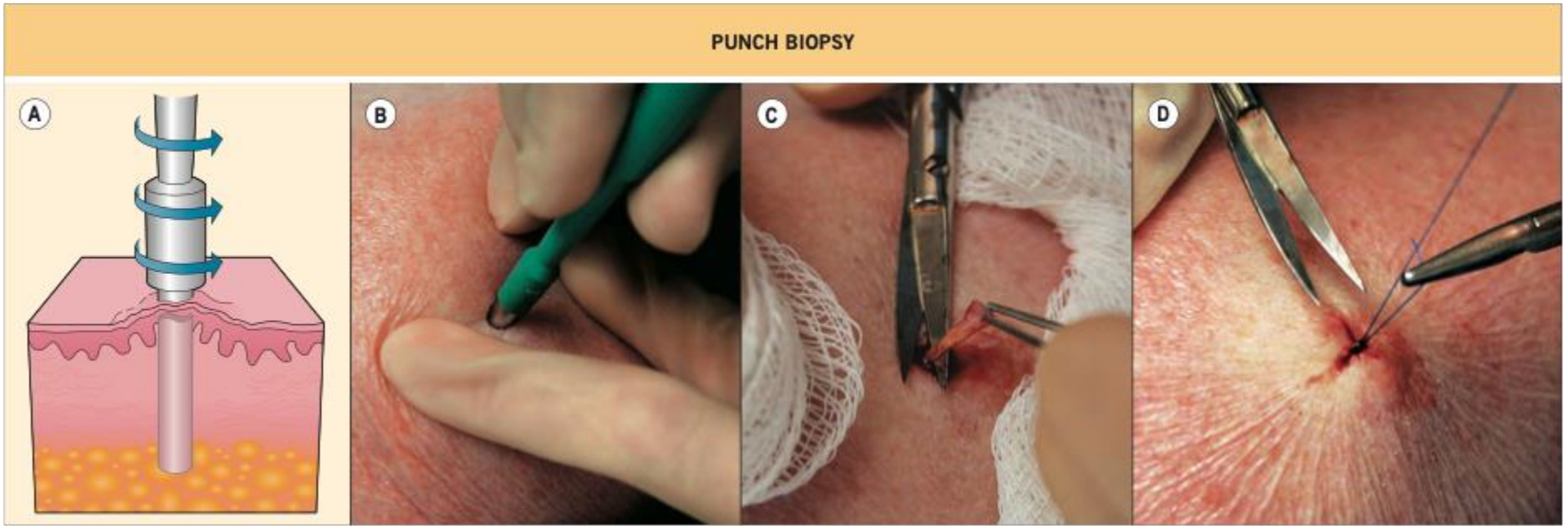
Pathology: Shave/Saucerization





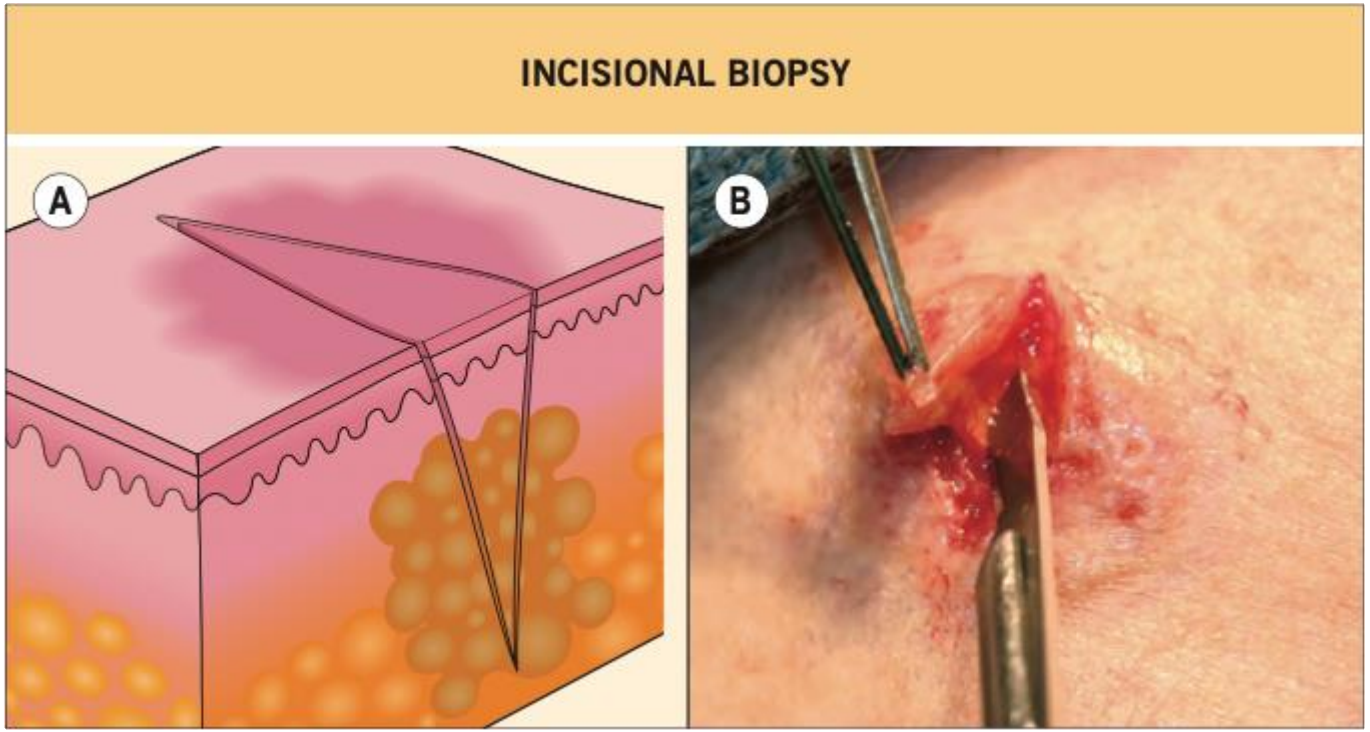
Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 146; Figure 146.7 and 146.8. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

Pathology: Punch



Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 146; Figure 146.9. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

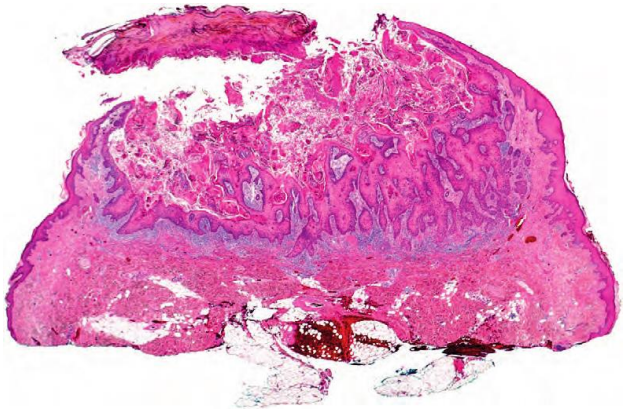
Pathology: Incision

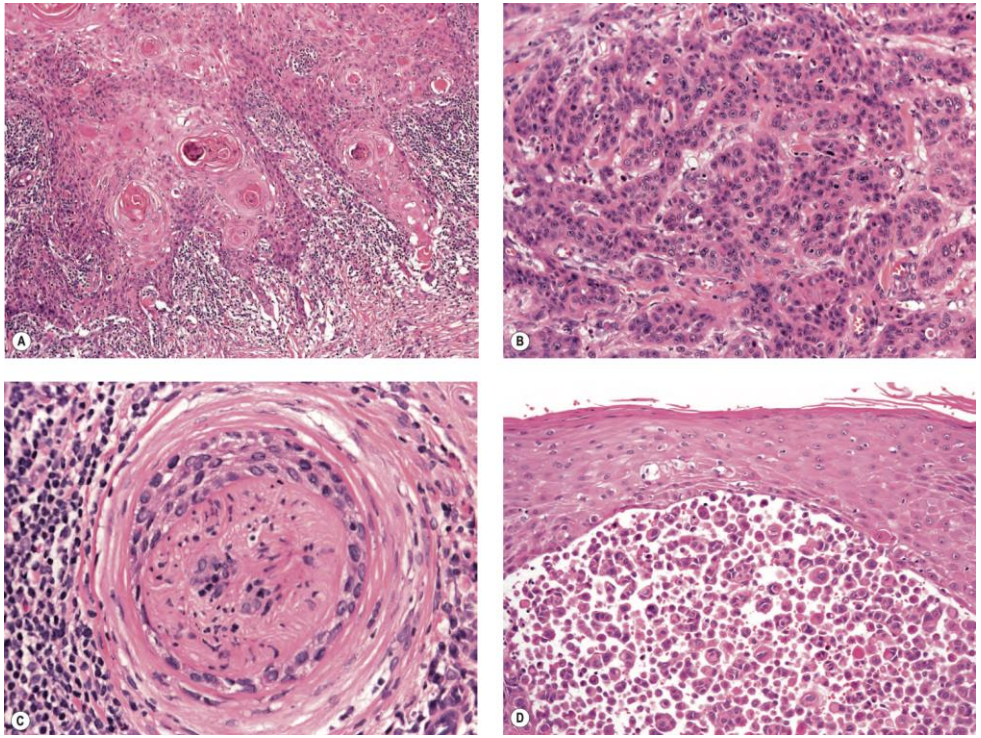


Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 146; Figure 146.10. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

PATHOLOGY

- Pink glassy keratincoytes
- Invasion of dermis by atypical keratinocytes
- Keratin horn pearls = parakeratosis within epidermis





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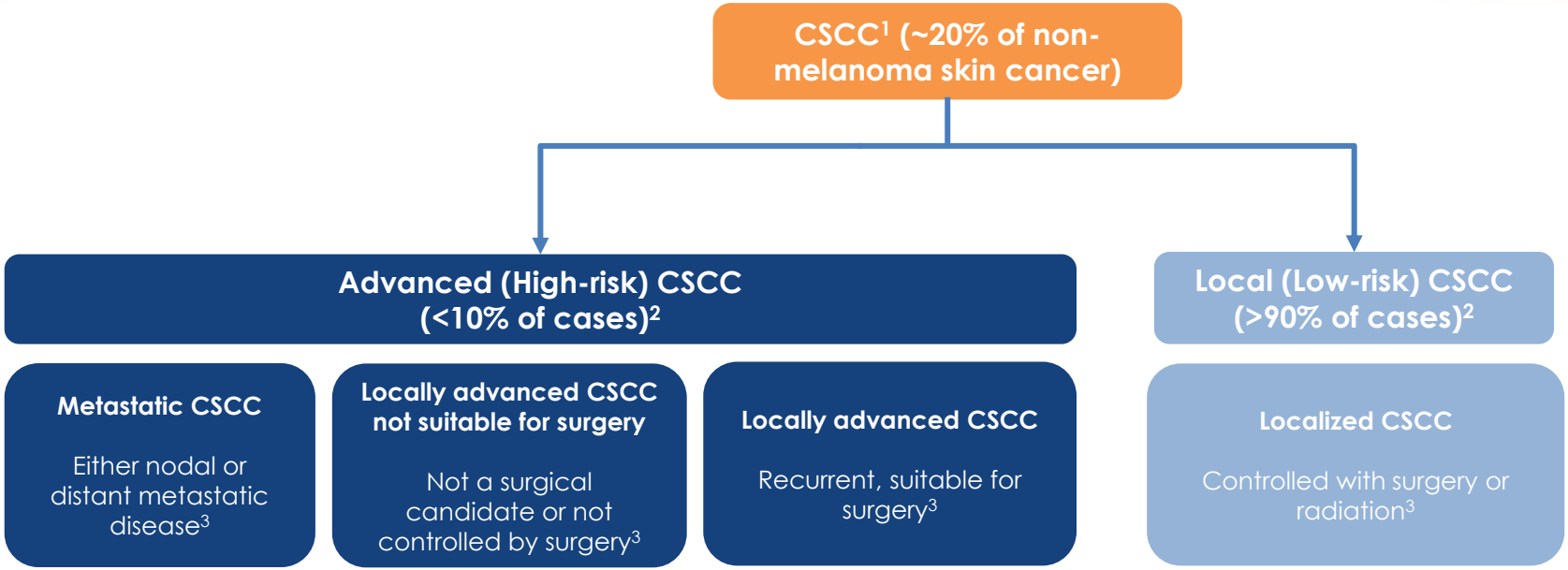
ADVANCED CSCC INCLUDES LOCALLY ADVANCED NOT SUITABLE FOR SURGERY, RECURRENT, OR METASTATIC DISEASE



1. Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/skin-non-melanoma/risks/?region=on. Accessed January 19, 2018;
2. Cranmer et al. Oncologist. 2010;15:1320-28; 3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer (Version 2.2019).

Squamous Cell Carcinoma Treatment

SURGERY

CRYOSURGEY

PHOTODYNAMIC

TOPICAL

INTRALESIONAL

RADIATION

CHEMO

IMMUNOTHERAPY

Surgery

- Excision
- Curettage and Electrodessication
- Curettage alone
- Mohs

Table IX. Level of evidence and strength of recommendations for the surgical treatment of cSCC

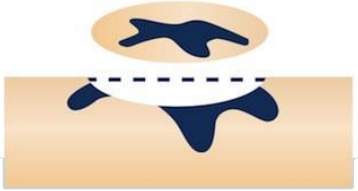
Recommendation	Strength of recommendation	Level of evidence	References
Treatment plan	A	II	55
Standard excision with 4- to 6-mm margins for low-risk primary SCC*	B	II	54
Standard excision for high-risk SCC	B	II	54
C&E for low-risk primary SCC*	B	II, III	54
MMS for high-risk SCC*	B	II, III	41,54,57,58

C&E, Curettage and electrodessication; *cSCC*, cutaneous squamous cell carcinoma; *MMS*, Mohs micrographic surgery; *SCC*, cutaneous squamous cell carcinoma.
*As defined by the National Comprehensive Cancer Network.

Work Group; Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P. Guidelines of care for the management of cSCC. J Am Acad Dermatol. 2018 Mar;78(3):560-578

Mohs Surgery

Skin cancers often have roots that extend beyond the visible tumor.



STEP 1: The Mohs surgeon anesthetizes the area and surgically removes the visible tumor.

STEP 2: The skin specimen is divided into sections and mapped to the surgical site.

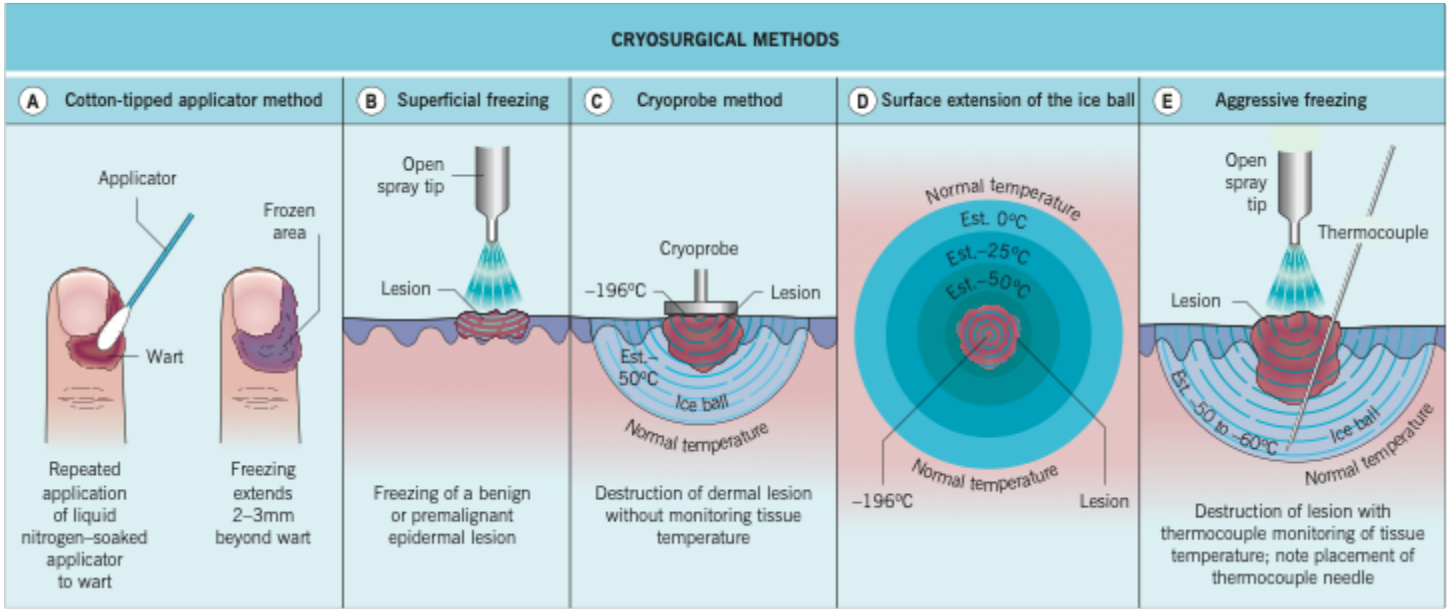
STEP 3: After the lab processes the tissue, the Mohs surgeon microscopically examines its entire undersurface and edges.

STEP 4: If cancer cells remain, the affected tissue will be precisely removed from the surgical site. Multiple stages may be required to remove the cancer roots completely.

The process stops when there is no evidence of residual cancer. The Mohs surgeon will then discuss options for reconstruction of the surgical defect.

Vanguard Skin Specialists website: https://wp02-media.cdn.ihealthspot.com/wp-content/uploads/sites/110/2018/01/02212224/Mohs_Illustration.jpg

Cryosurgery



Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 138; figure 138.2. 3rd ed. Philadelphia: Elsevier Saunders, 2012. 1770.

Photodynamic Therapy

c-PDT

GALDERMA

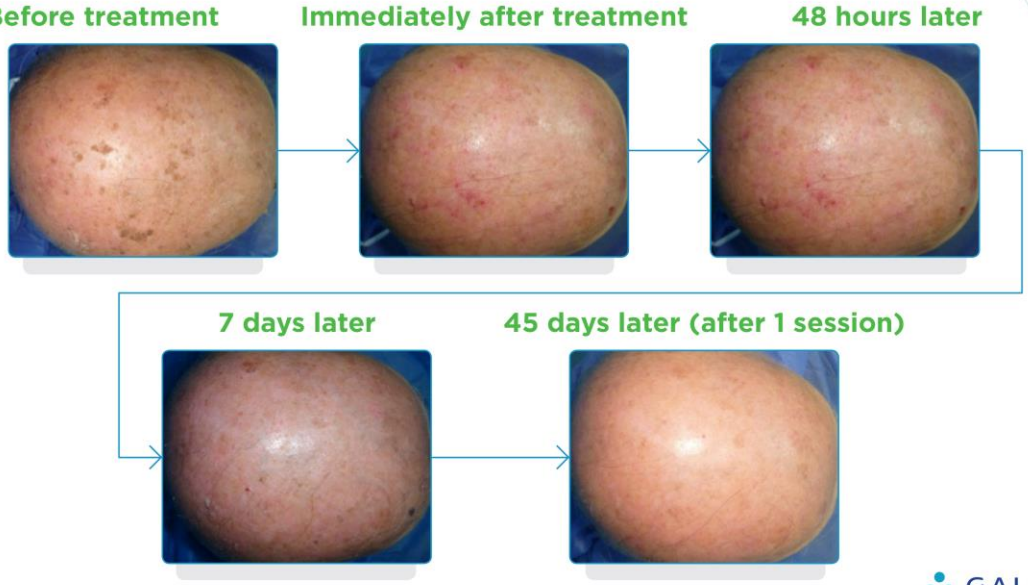
c-PDT

Skin preparation → Application of Metvix® → Occlusion for 3 hours → Removal of Metvix® → Illumination with red light

Metvix® = methyl aminolevulinate

Photodynamic Therapy

PATIENT 1



GALDERMA

1. Boudewijn A genetic explanation of Slaughter's concept of field cancerisation: evidence and clinical implications Cancer Res. 2003 Apr 15;63(8):1727-30
2. D. P, Slaughter *et al.*, Cancer (Phila.), 6: 963-968, 1953

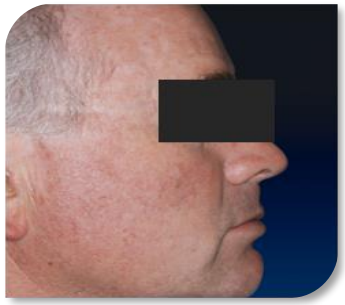
Topical Treatments

Table II. Topical therapies for cutaneous squamous cell carcinoma chemoprevention and treatment

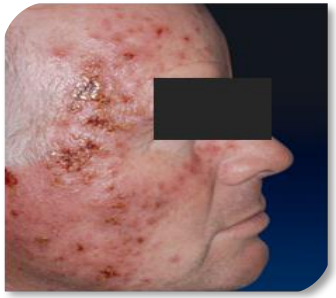
Therapy	Indications	Frequency of application	Mechanism of action	Adverse effects	Level of evidence*
Topical retinoids[47-50]	Ineffective at preventing cSCC according to VA randomized chemoprevention trial,[50] but other studies show decrease in AK count	N/A	Induces apoptosis of tumor cells; downregulate proliferative keratins K6 and K16	Burning, irritation, erythema, and dermatitis	IB
5-fluorouracil[80,81]	Approved by the FDA in 1970 for treatment of AKs; off-label use: treatment of cSCC in situ	AK: 0.5% cream: apply once daily for up to 4 weeks; 5% cream: apply twice daily for 2-4 weeks cSCC in situ: 5% cream: apply twice daily for 3 to 6 weeks; treatment can be continued for ≤10-12 weeks	Pyrimidine analogue: cytotoxic metabolites are incorporated into DNA and RNA, inducing cell cycle arrest and apoptosis	Erythema, shallow erosions, pruritus, dermatitis, burning sensation, and photosensitivity	AK: IA; cSCC in situ: IB
Imiquimod[82,83]	Approved by the FDA for the treatment of AKs; not practical for treatment of field disease because can have significant side effects when applied to large surface areas	AK: Aldara†—apply 2 times/week × 16 weeks Zyclara†—treatment consists of 2 cycles (14 days each) separated by 1 rest period (14 days) with no treatment	Induces, synthesizes, and releases cytokines, thereby inducing secretion of interferon-gamma by naïve T cells	Local reactions: erythema, discomfort, erosion, and dyschromia Systemic symptoms: flu-like symptoms, dizziness, headache, and, rarely, urinary retention	AK: IA; cSCC in situ: IB
Ingenol mebutate[84]	Treatment of AKs	Face or scalp: apply 0.015% gel once daily to affected area for 3 consecutive days Trunk or extremities: apply 0.05% gel once daily to affected area for 2 consecutive days	Multiple mechanisms of action, including direct cell death and protein kinase C–mediated inflammatory response	Severe allergic reactions; herpes zoster; eye pain; periorbital edema; headache; mild to moderate erythema, scaling, and dryness	AK: IB
Diclofenac[85]	Treatment of AKs	Apply 3% gel to lesion area twice daily for 60-90 days	Nonsteroidal antiinflammatory drug that reduces the production of prostaglandins by inhibiting inducible cyclooxygenase-2	Pruritus, rash, desquamation, elevated liver function tests, flu-like symptoms, and headache	IB
Photodynamic therapy[53-56]	Treatment of AKs	Various protocols	Exogenous photosensitizer and light source induces a porphyria; neoplastic cells accumulate more porphyrins than normal cells	Erythema, blistering, desquamation, and discomfort	IB

Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Management of advanced and high-stage tumors. J Am Acad Dermatol. 2018 Feb;78(2):249-261. doi: 10.1016/j.jaad.2017.08.058

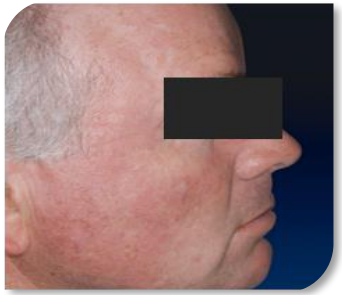
Topical Treatments



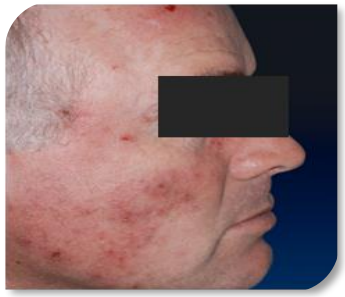
Baseline



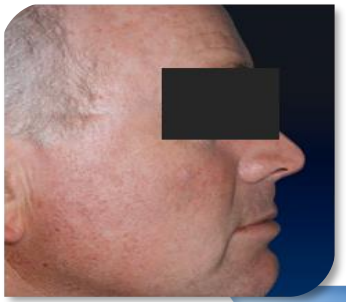
Week 2



Week 4



Week 6



Week 14

Swanson N, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses. J Am Acad Dermatol 10.1016/j.jaad.2009.07004.

Intralesional Treatments

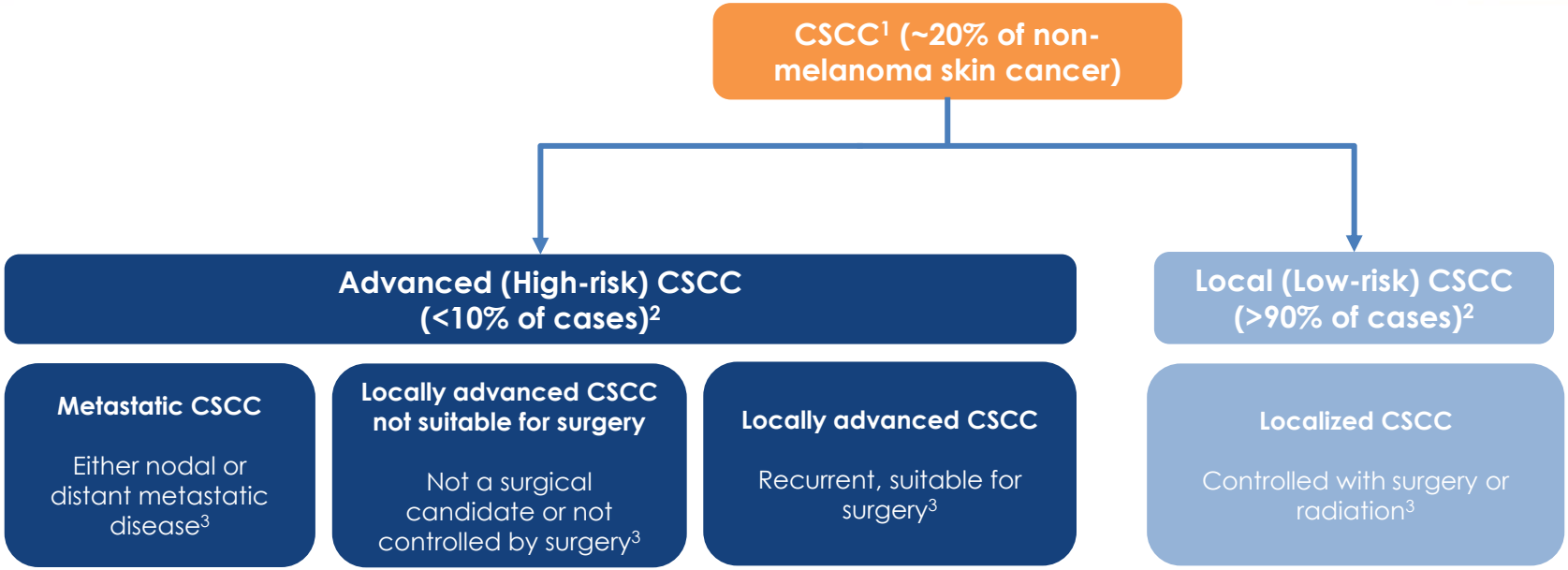
Table V. Intralesional chemotherapies in basal cell carcinoma, efficacy, and levels of evidence

	Superficial BCC		Nodular BCC	
Intralesional chemotherapy	**Evidence***	**Efficacy**	**Evidence***	**Efficacy**
5-fluorouracil†	III	91% HC[141]	IV	91% HC[141]
Interferons‡	II	67-86% HC[142-145]	II	67-86% HC[142-145]
Interleukin-2§	IV	66% HC[146]	IV	66% HC[146]
Bleomycin with electrochemotherapy§	IV	94% 18-month PT CC[147]	IV	94% 18-month CC[147]

BCC, Basal cell carcinoma; *CC*, clinical clearance; *HC*, histologic clearance; *PT*, post-treatment.
Adapted from Micali et al.[121]
*Levels of evidence based on Oxford Centre for Evidence Based Medicine (Table III).[103]
†Commercially unavailable proprietary gel (5-fluorouracil, epinephrine, and bovine collagen).
‡Interferon α or recombinant interferon-β-1α.
§BCC subtype not specified.

Cameron MC, Lee E, Hibler BP et al. Basal cell carcinoma: Contemporary approaches to diagnosis, treatment, and prevention. J Am Acad Dermatol. 2019 Feb;80(2):321-339

ADVANCED CSCC INCLUDES LOCALLY ADVANCED NOT SUITABLE FOR SURGERY, RECURRENT, OR METASTATIC DISEASE



1. Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/skin-non-melanoma/risks/?region=on. Accessed January 19, 2018;
2. Cranmer et al. Oncologist. 2010;15:1320-28; 3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer (Version 2.2019).

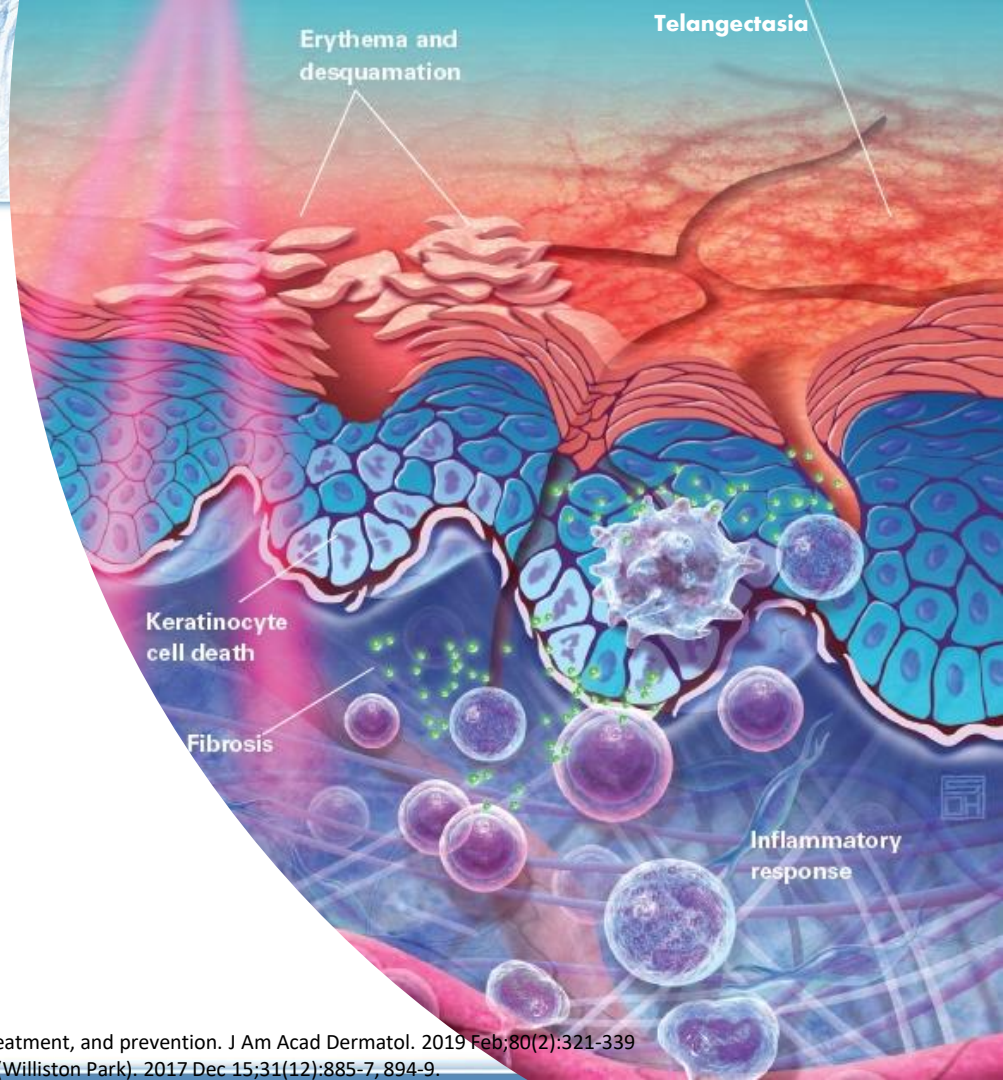
Radiation

MOA: Non-specific DNA damage

Table VI. Physical qualities of radiotherapy sources used in basal cell carcinoma

Radiation quality	Energy, kV	D50,* mm
Superficial x-ray (low voltage x-ray therapy)	60-150	7-10
Orthovoltage x-rays (deep x-ray therapy, conventional x-ray therapy)	150-400	50-80
Megavoltage x-rays, electrons and protons (betatron, linear accelerator, cyclotron, and particle therapy)	>1000	10-200

kV, Kilovolt.
*Depth from the skin's surface at which 50% of the total radiation is absorbed.

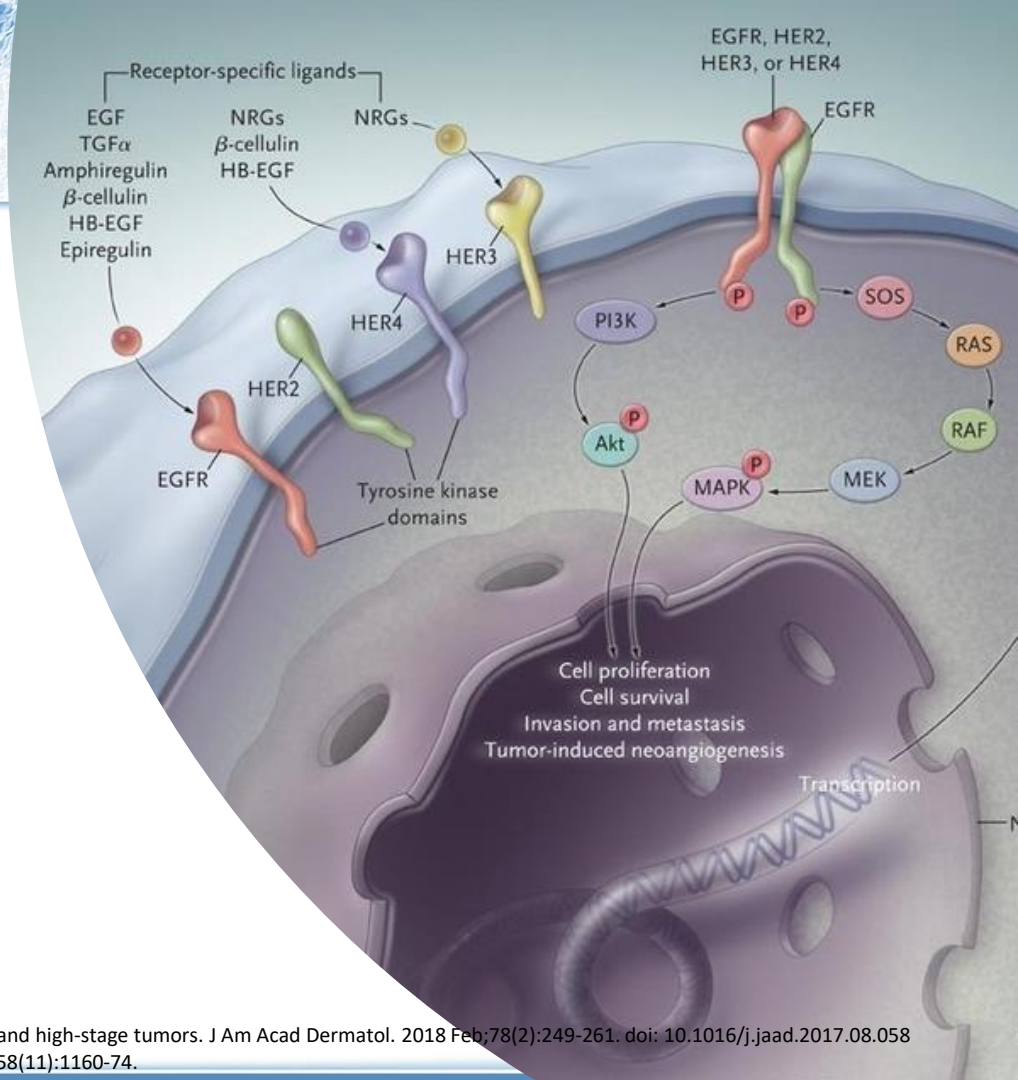


Cameron MC, Lee E, Hibler BP et al. Basal cell carcinoma: Contemporary approaches to diagnosis, treatment, and prevention. J Am Acad Dermatol. 2019 Feb;80(2):321-339
Leventhal J, Young MR. Radiation Dermatitis: Recognition, Prevention, and Management. Oncology (Williston Park). 2017 Dec 15;31(12):885-7, 894-9.

Targeted Therapies

MOA: Inhibits specific molecules involving tumor pathogenesis

- Epidermal growth factor receptor (EGFR) is expressed at the cell surface by [90% of cSCCs and is responsible for cell cycle progression, proliferation, survival, angiogenesis, and metastasis via the Ras-Raf-mitogen-activated protein kinase pathway
- **Cetuximab** may be used for the treatment of locally advanced, unresectable or metastatic squamous cell carcinoma of the skin.
- Note: Recommendation based on a single arm phase II study in 36 patients with a response rate of 28%

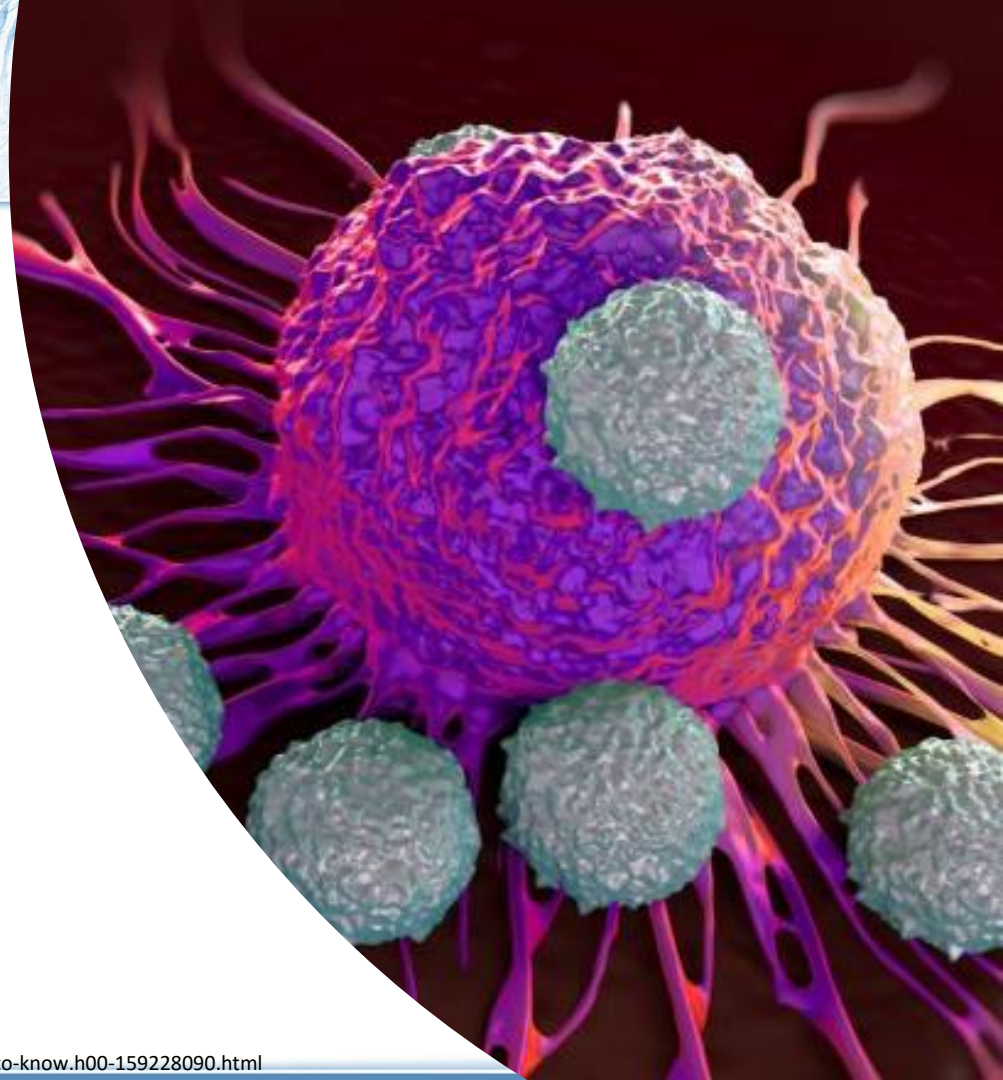


Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Management of advanced and high-stage tumors. J Am Acad Dermatol. 2018 Feb;78(2):249-261. doi: 10.1016/j.jaad.2017.08.058
Image: Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med. 2008 Mar 13;358(11):1160-74.

Immunotherapy

MOA: Activation of host immune mechanisms

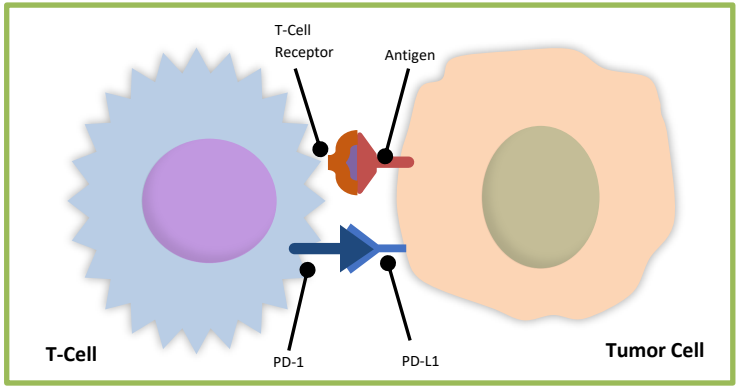
- Paradigm shift in fighting cancer
- Durable, significant response rate in other skin cancers: melanoma and squamous cell carcinoma
- **Cemiplimab**: the first and only Health Canada approved therapy for patients with advanced cutaneous squamous cell carcinoma (CSCC)[1]



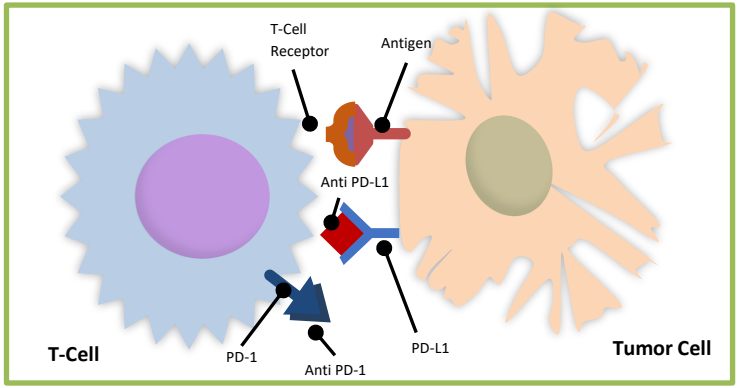
1. LIBTAYO (cemiplimab) Product Monograph. sanofi-aventis Canada Inc. and Sanofi-Genzyme.
Image: https://www.mdanderson.org/publications/cancerwise/immunotherapy-side-effects--what-to-know.h00-159228090.html

Function of PD-1/PD-L1 Axis in Immunosurveillance

Activation of PD-1/PD-L1 Pathway Suppresses T-cell-mediated Tumor Destruction[1,2]



Binding of PD-1 to PD-L1 leads to downregulation of T cell mediated tumor destruction[3]



Blocking the interaction with anti-PD-1/PD-L1 agents helps to restore T-cell function for an anti-tumor response

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Chen DS, Mellman I. *Immunity*. 2013;39:1–10; 2. Gong J et al. *J Immunother Cancer*. 2018;6:8; 3. Caldwell Jr C et al. *Sci Rep*. 2017;7:13682.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

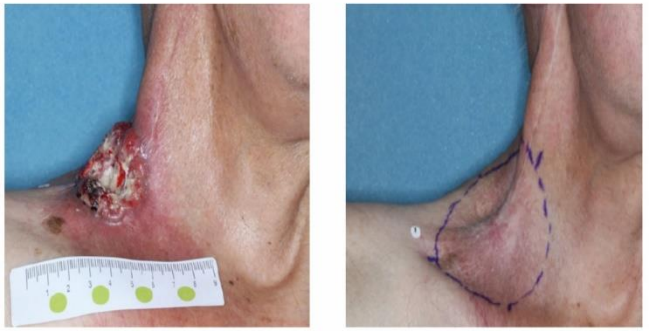
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

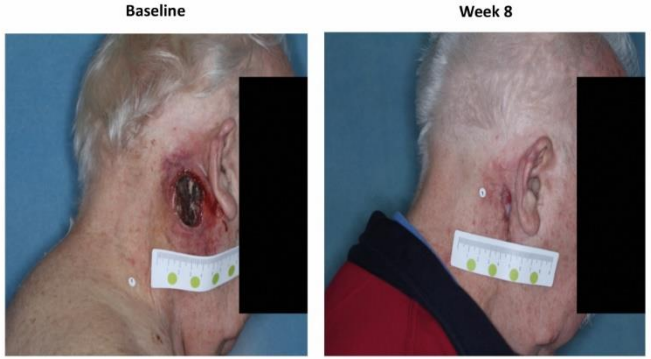
N ENGL J MED 379;4 NEJM.ORG JULY 26, 2018

Examples of Reductions in Visible CSCC Lesions Following Treatment with cemiplimab

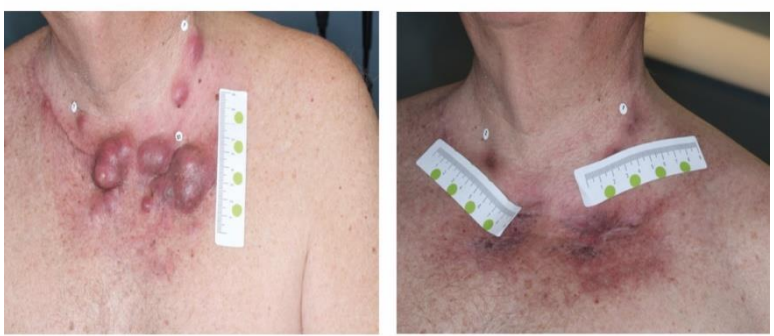
A



B



C



A: This patient is an 85-year-old man with supraclavicular lesion who had received prior radiotherapy.

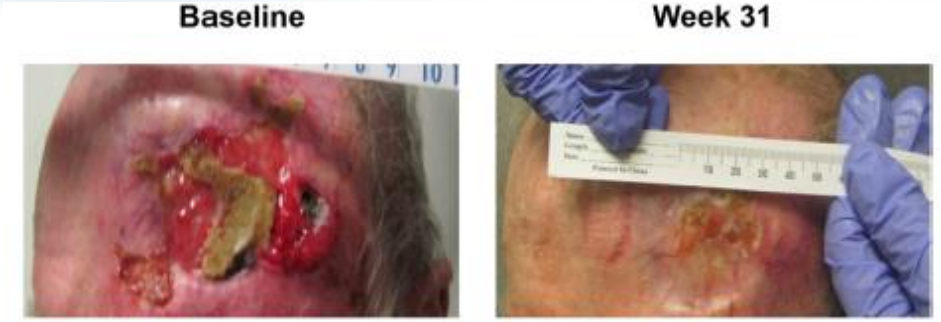
B: This patient is an 83-year-old-man with multiple prior surgeries for CSCC.

C: This patient is a 66-year-old man with anterior chest wall CSCC lesions who had received prior cisplatin.

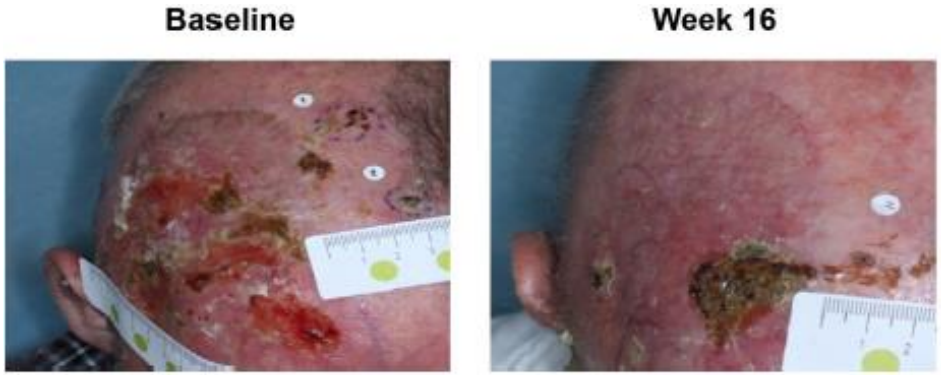
Midgen MR and Rischin D et al. *N Engl J Med*. 2018;379:341-351.

Examples of Reductions in Visible CSCC Lesions Following Treatment with cemiplimab (continued)

D



E



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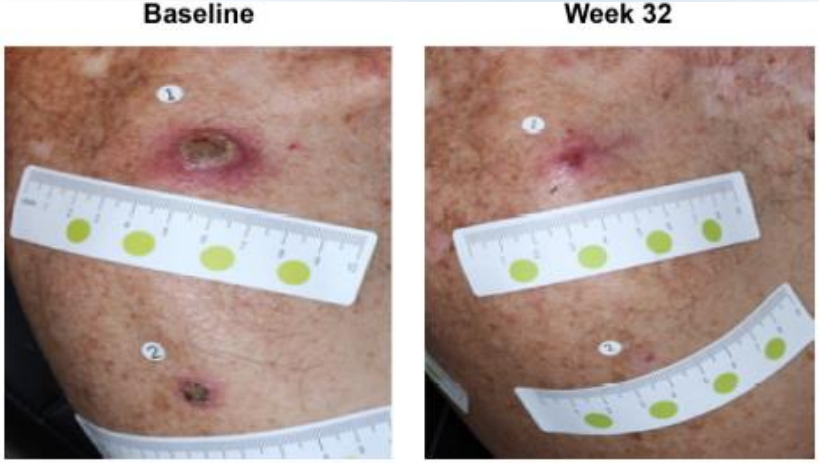


D: This patient is an 80-year-old man with a locally advanced CSCC forehead lesion.

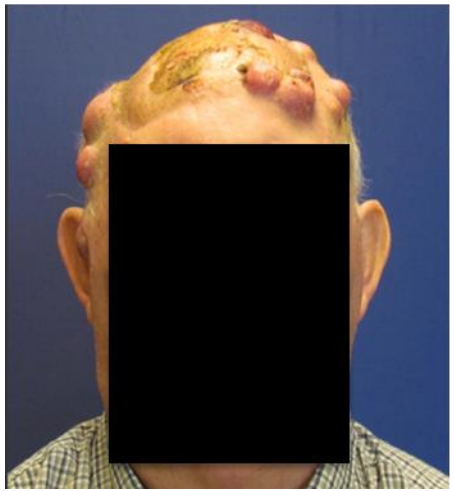
E: This patient is an 74-year-old-man with scalp CSCC.

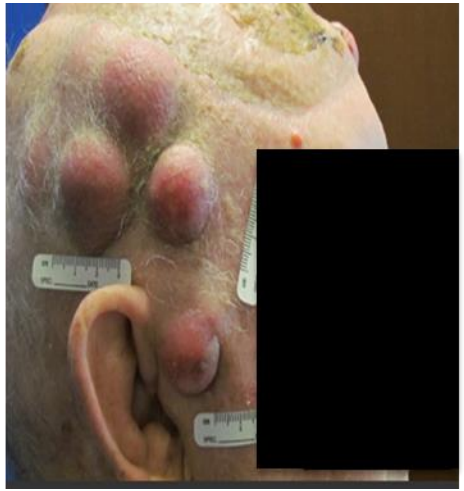
F: This patient is a 56-year-old man with anterior shoulder lesions

Midgen MR and Rischin D et al. *N Engl J Med*. 2018;379:341-351.

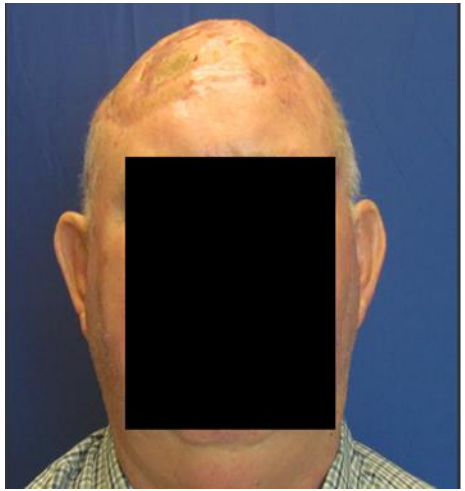
Examples of Reductions in Visible CSCC Lesions Following Treatment with cemiplimab (continued)

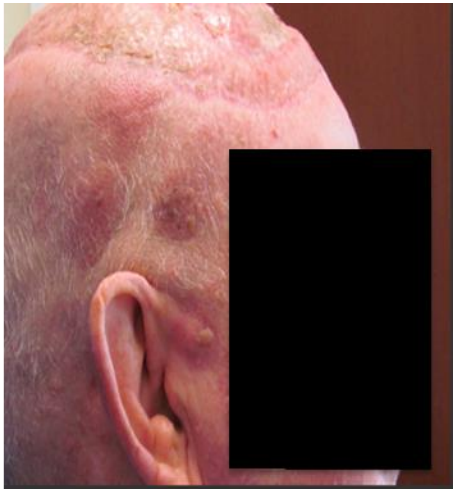
Screening





Response at 6 weeks

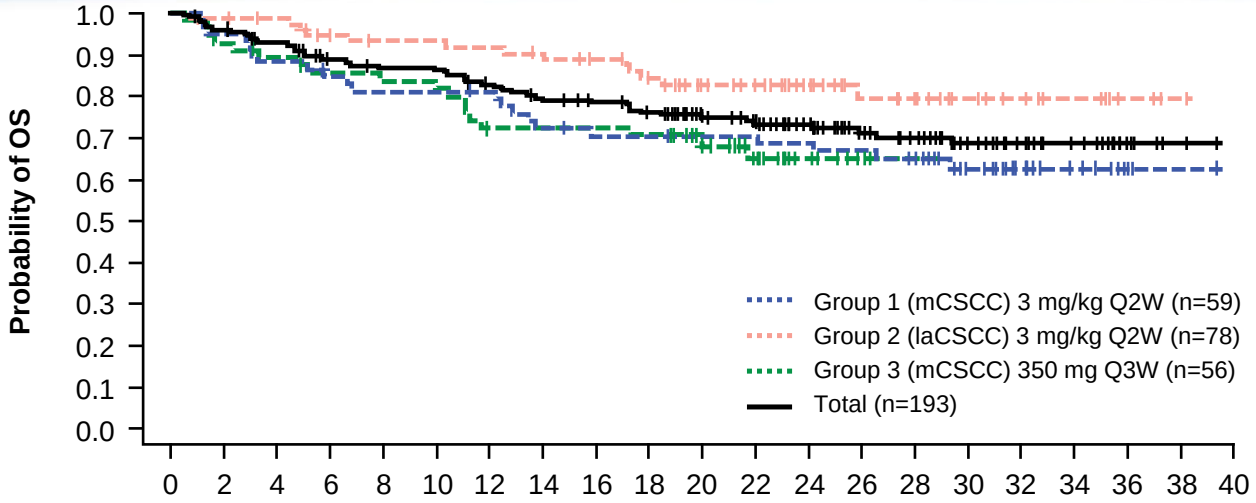




CSCC, cutaneous squamous cell carcinoma.

Papadopoulos KP, et al. *J Clin Oncol*. 2017:35 (suppl; abstr 9503) [podium presentation].

Kaplan–Meier curves for OS



Number of patients at risk																					
Group 1 (n=59)	59	56	52	49	47	47	46	41	39	39	38	38	37	35	33	24	16	11	4	1	0
Group 2 (n=78)	78	76	73	67	65	65	64	62	59	54	44	41	33	25	22	15	12	8	3	1	0
Group 3 (n=56)	56	52	49	46	45	44	38	38	38	37	29	20	9	2	0	0	0	0	0	0	0
Total (n=193)	193	184	174	162	157	156	148	141	136	130	111	99	79	62	55	39	28	19	7	2	0

- Median OS has not been reached. The Kaplan–Meier estimated probability of OS at 24 months was 73.3% (95% CI: 66.1–79.2)

CSCC, cutaneous squamous cell carcinoma; CI, confidence interval; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

Data cut-off date: October 11, 2019. Median duration of follow-up among all patients: 15.7 months (range: 0.6–36.1).

NCT04154943

STUDY DESIGN

Phase II non-randomized, multicentre study (Australia, Germany, United States)

Primary endpoint:

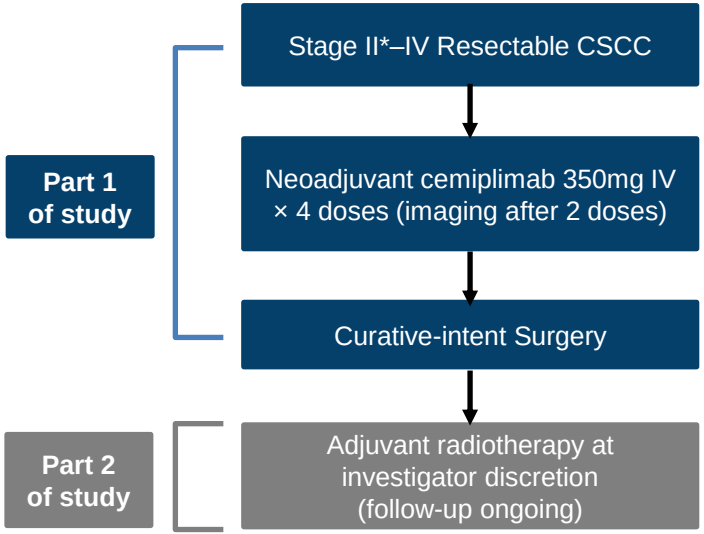
- pCR (0% viable tumor) rate per ICPR
  - The null hypothesis was set for a pCR rate of 25%
  - A sample size of 72 patients was required to provide ≥90% power to reject the null hypothesis at a two-sided significance level of 5%, if the true pCR rate was 44%†

Secondary endpoints:

- MPR (>0% but ≤10% viable tumor) rate per ICPR
- pCR and MPR rates per local pathology review
- Radiological ORR per RECIST 1.1
- Safety and tolerability

Correlative analyses:

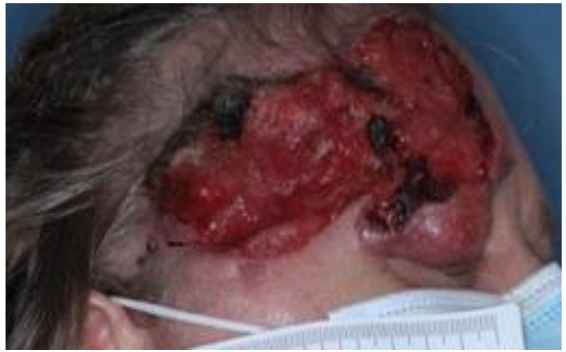
- Exploration of TMB and PD-L1 expression with treatment response



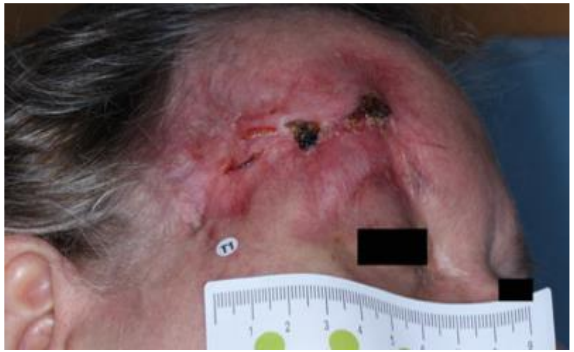
*Stage II required to have primary tumor ≥3 cm in an aesthetically-sensitive region. †Required sample size was increased to 76 patients to account for premature withdrawal from the study.
CSCC, cutaneous squamous cell carcinoma; ICPR, independent central pathology review; MPR, major pathologic response; ORR, objective response rate; PD-L1, programmed cell death-ligand 1; RECIST 1.1., Response Evaluation Criteria in Solid Tumors version 1.1; TMB, tumor mutational burden.

EXAMPLE

- 59-year-old T3N0 CSCC involving the right supraorbital area
- Imaging PR by RECIST 1.1 and pCR by ICPR after neoadjuvant cemiplimab
- Definitive surgery sparing the orbit



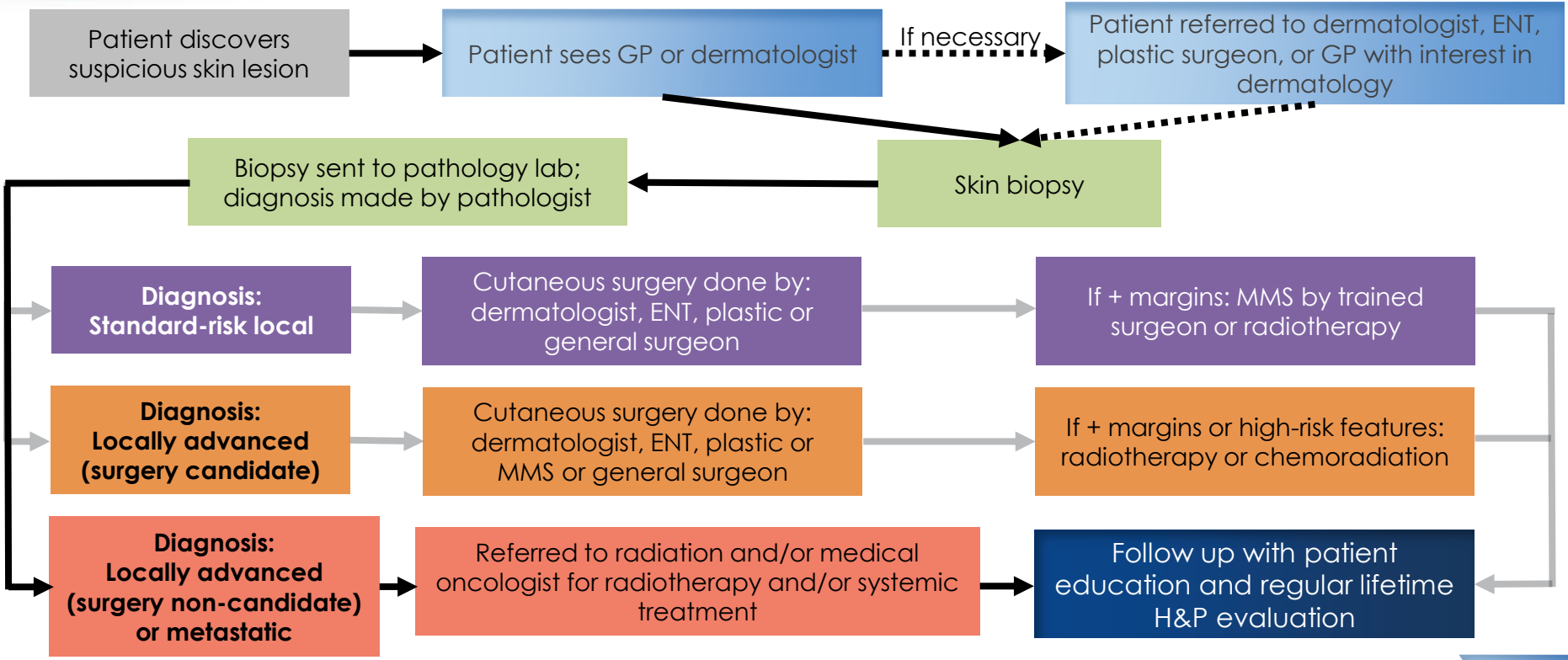
Baseline



Post Neoadjuvant Cemiplimab

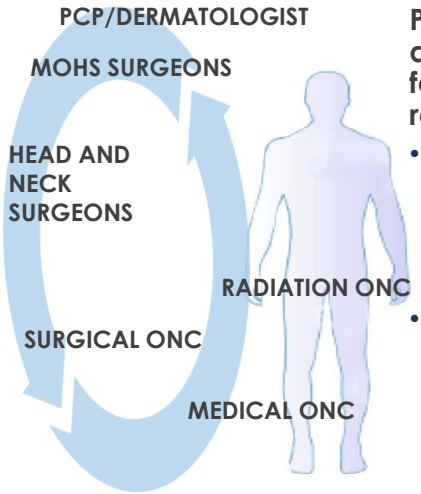
CSCC, cutaneous squamous cell carcinoma; RECIST 1.1., Response Evaluation Criteria in Solid Tumors version 1.1; ICPR, independent central pathology review; pCR, pathologic complete response; PR, partial response.

CHALLENGE IN COORDINATING CARE[1,2]



CSCC: cutaneous squamous cell carcinoma; ENT: Ears nose throat; GP: general practitioner; H&P: history and physical; MMS: Mohs micrographic surgery.
1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer (Version 2.2019); 2. Client internal resources.

PATIENTS WITH ADVANCED CSCC FACE DAUNTING CHALLENGES



Patients with locally advanced CSCC not suitable for surgery or with recurrence[1,2]

- Are often cycled through different therapies and providers who are challenged to coordinate care
- Often involve multidisciplinary tumour board consultations to discuss radiotherapy or systemic treatment

Chemotherapy • Radiation
Medical Oncology • Surgery

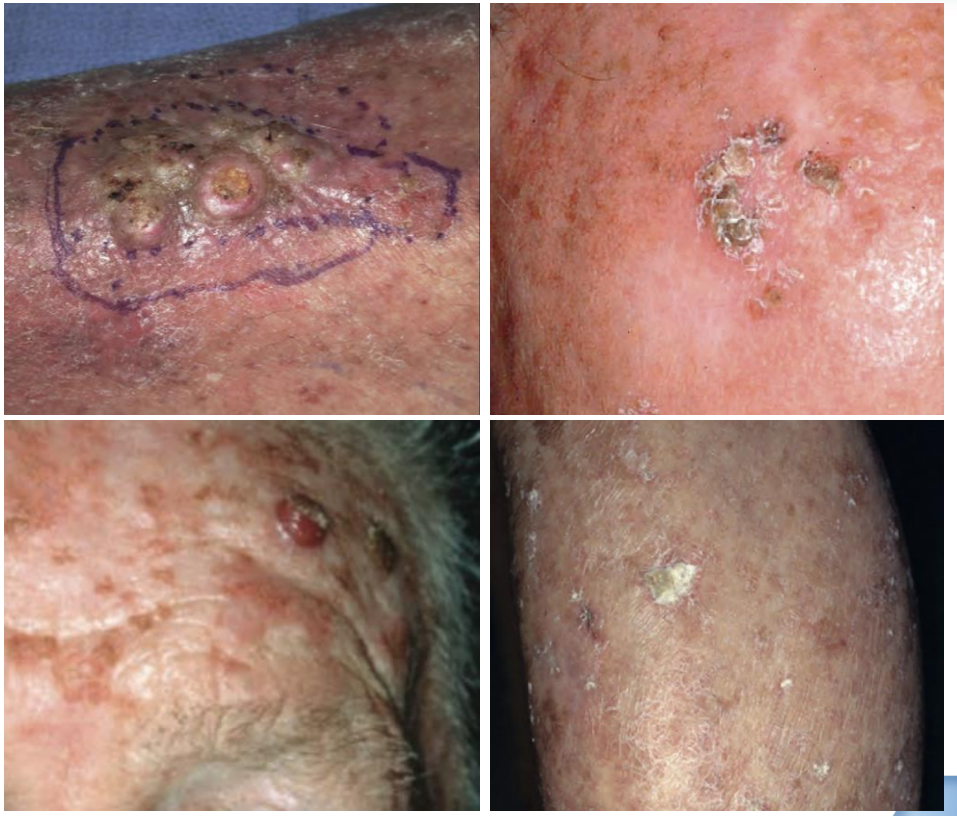
Patients with metastatic CSCC[1,3]

- Are typically treated with systemic therapies but face a high annual mortality rate
- Are often managed by multidisciplinary care but have few treatment options

ONC: oncologist; PCP: primary care physician.
1.Parikh et al. F1000Prime Reports. 2014;6:1-8; 2. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer (Version 2.2019); 3. Cranmer et al. Oncologist. 2010;15:1320-8.

Summary

- cSCC mortality rates may be equal to melanoma
- Generally good prognosis with early detection; curable with surgery
- Life saving treatments now available for metastatic and non-resectable cSCC
- Consider biopsy or referral for any:
  - Nonhealing ulcer
  - Abnormal growth in the sun-exposed skin area
  - Shallow ulcer with heaped-up edges, often covered by a plaque
  - Pink bump that keeps growing (BCC)



Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Chapter 108; Figure 108.1 and 108.3. 3rd ed. Philadelphia: Elsevier Saunders, 2012.

QUESTIONS

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