GIOTI: I tumori della pelle

Fisiologia della pelle e tumori cutanei non melanoma

Centro Eventi Cadempino, 17 novembre 2022

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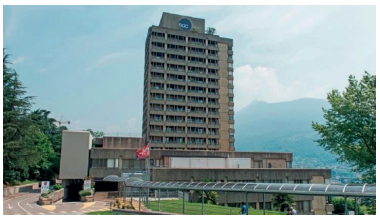

Ente Ospedaliero Cantonale

Sommario

- **Cenni sulla fisiologia della pelle e sull'invecchiamento cutaneo**
- **Non Melanoma Skin Cancers (NMSC) di tipo epiteliale:**
  - *Cheratosi attiniche (precancerosi) (AK)*
  - Carcinoma squamocellulare (SCC)
  - Carcinoma basocellulare (BCC)

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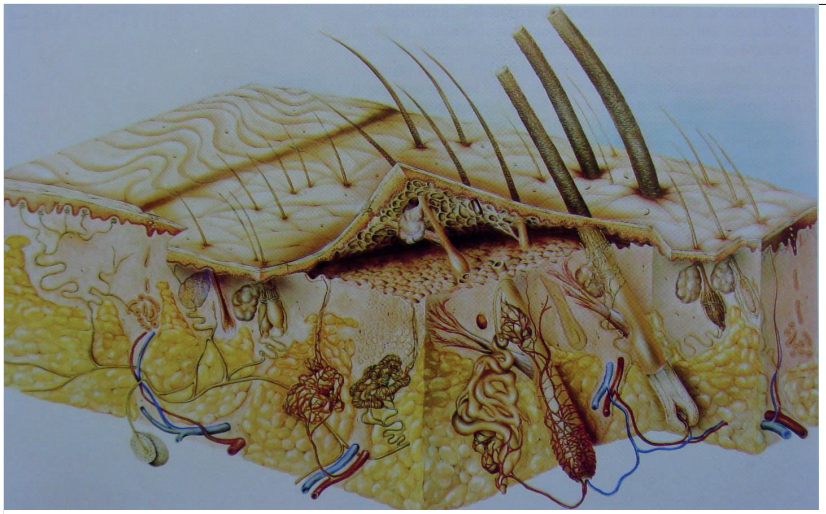
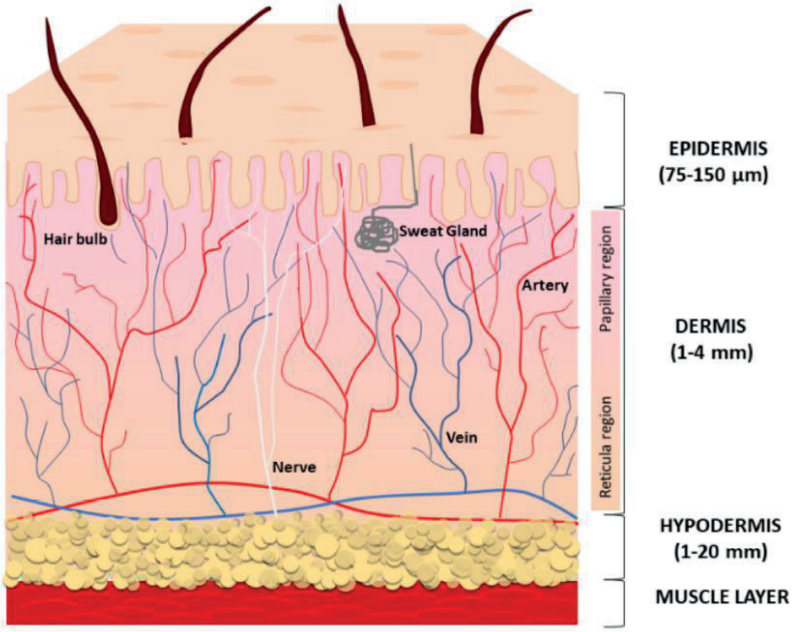


PELLE

- È l'organo più grande ed esteso: **≈ 1.7 m²**
- Composto da 3 strati:
  - **Epidermide**
  - **Derma**
  - **Ipoderma** o **sottocute**
- **Funzioni** della pelle:

- **Protezione** (meccanica, UV, difesa immunologica)
- **Organo sensoriale** (terminali e recettori nervosi)
- **Organo di riserva energetica** (ipoderma)
- **Secrezione** (sebo, sudore, richiamo,…)
- **Sintesi della Vitamina D**
- **Assorbimento**
- **Controllo della Temperatura**
- **Organo di "comunicazione"**

PELLE: le sue dimensioni e il mantenimento della sua integrità



Antioxidants **2022**, 11, 1121. https://doi.org/10.3390/antiox11061121

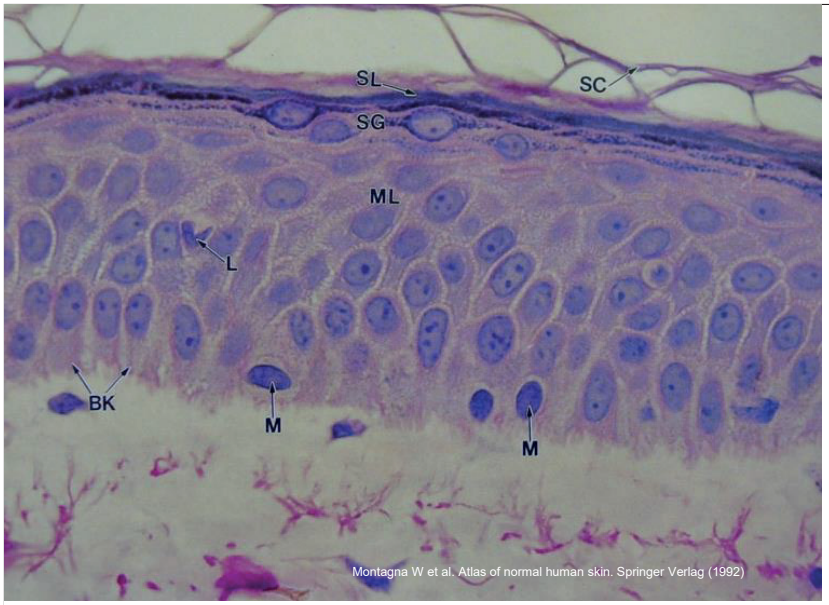
Meccanismi di riparazione:

- Danno fisico
- Penetrazione UV
- Danno termico
- Cicatrizzazione

Mancata riparazione efficace:

- Cicatrizzazione ritardata
- Cicatrici ipertrofiche/cheloidi
- Xeroderma pigmentosum

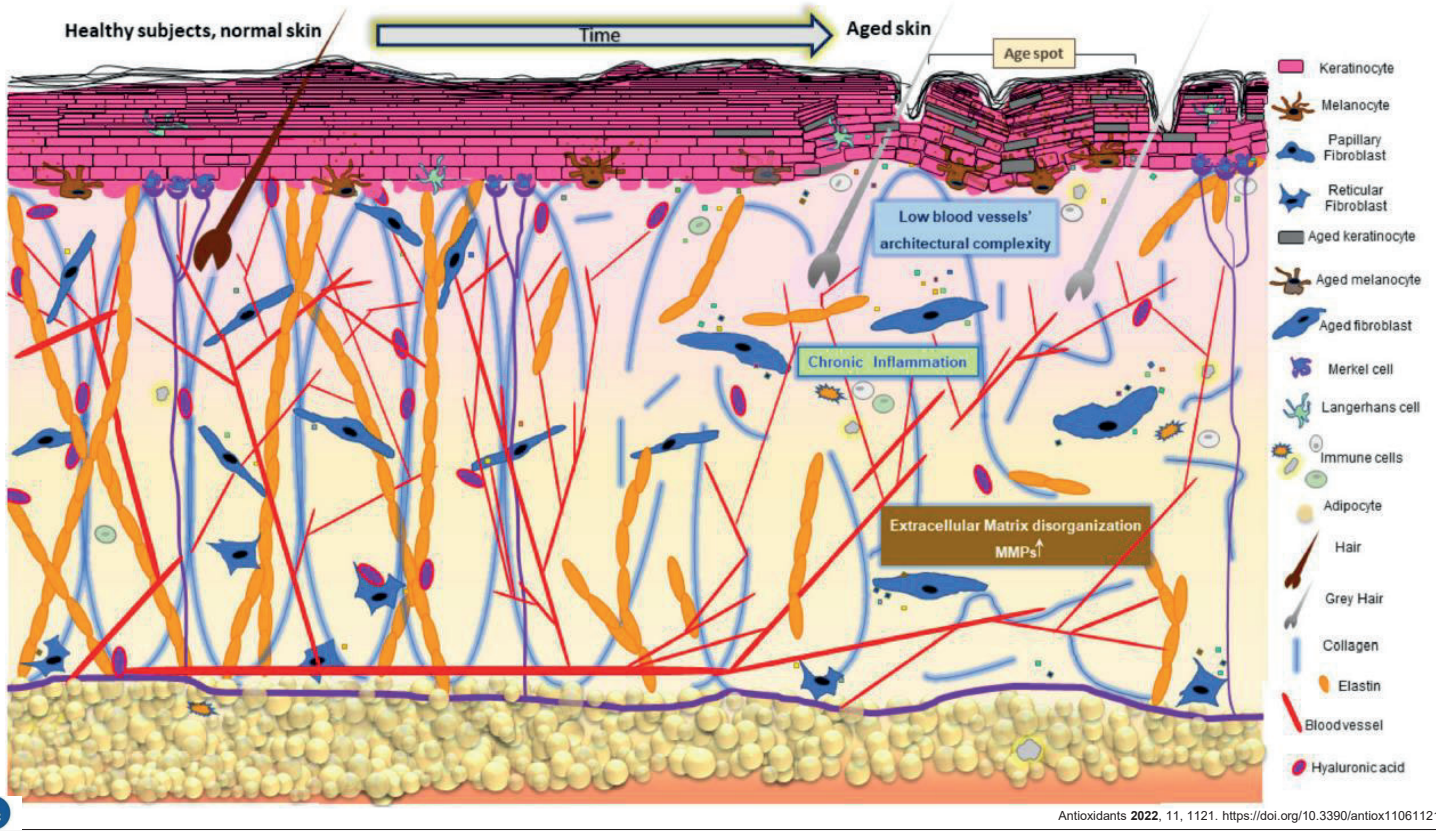
Epidermide: i suoi strati e le sue cellule



Montagna W et al. Atlas of normal human skin. Springer Verlag (1992)

- BK: **Strato basale**
- ML: **Strato spinoso**
- SG: **Strato granuloso**
- SL: **Strato lucido**
- SC: **Strato corneo**

- **Cheratinocita**:
  > 90% dell'epidermide, producono proteine molto solide: le cheratine, che costituiscono l'involucro resistente
- **Melanocita**:
  cellule dendritiche che migrano dalla cresta neurale e si localizzano nell'epidermide. Sintetizzano e secernono la melanina. Rapporto col cheratinocita: 1 : 36
- **Cellula di Langerhans**:
  cellule dendritiche d'origine monocitica; guardiani del sistema immunitario
- **Cellula di Merkel**:
  meccanorecettori che contengono vescicole neuroendocrine e accoppiate a terminali nervosi sensoriali liberi intraepiteliali



Antioxidants **2022**, 11, 1121. https://doi.org/10.3390/antiox11061121

Invecchiamento cutaneo: cause e meccanismi

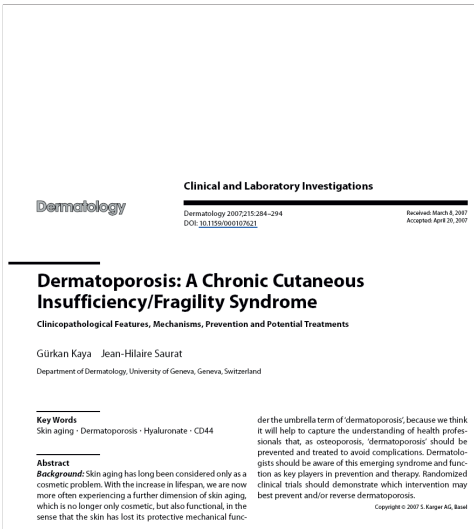
Cause:

- Genetica
- Biochimica: metabolismo ossidativo
- Ormoni
- Fototipo
- UV
- Tabagismo
- Agenti nocivi esogeni (es. diossina)
- …

Meccanismi:

- ***"Intrinsic":***
- Genetica
- Metabolismo
- Apoptosi
- Ormoni

- ***Extrinsic":***
- UV
- Clima
- Fumo (passivo)
- Fattori esogeni
- Igiene di vita
- Alimentazione
- Stress "ossidativo"



Dermatology

Clinical and Laboratory Investigations

Dermatology 2007;215:284–294
DOI: 10.1159/000107621

Received: March 8, 2007
Accepted: April 20, 2007

Dermatoporosis: A Chronic Cutaneous Insufficiency/Fragility Syndrome

Clinicopathological Features, Mechanisms, Prevention and Potential Treatments

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Key Words
Skin aging · Dermatoporosis · Hyaluronate · CD44

Abstract
Background: Skin aging has long been considered only as a cosmetic problem. With the increase in lifespan, we are now more often experiencing a further dimension of skin aging, which is no longer only cosmetic, but also functional, in the sense that the skin has lost its protective mechanical function the umbrella term of 'dermatoporosis', because we think it will help to capture the understanding of health professionals that, as osteoporosis, 'dermatoporosis' should be prevented and treated to avoid complications. Dermatologists should be aware of this emerging syndrome and function as key players in prevention and therapy. Randomized clinical trials should demonstrate which intervention may best prevent and/or reverse dermatoporosis.

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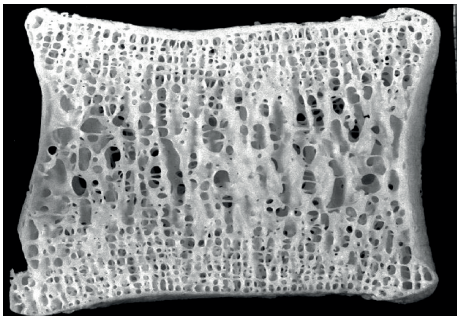
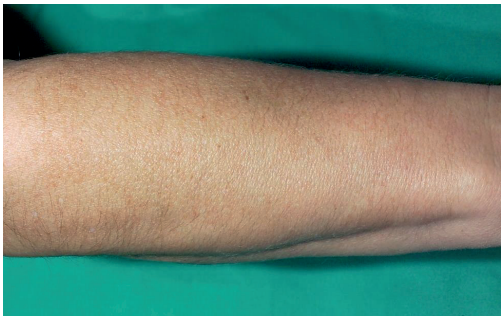
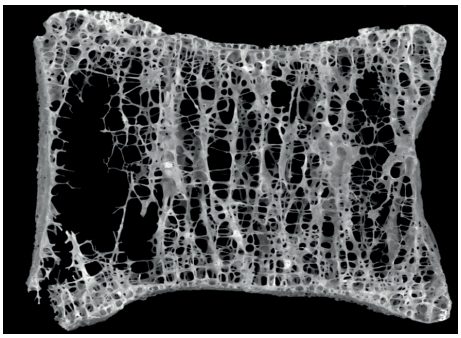
Normal bone



Normal skin



Osteoporosis



Dermatoporosis

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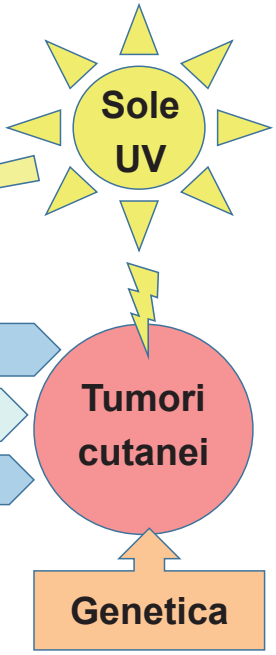
Cancri cutanei: il sole, ma non solo ...

Danno **acuto**:
Colpo di sole

Danno **cronico**:
Sun freckles, …

Krebsliga CH: Illustration: Arbeitsgemeinschaft Dermatologische Prävention e.V.



Genes:
CDKN2A, CDK4,
BAP1, MITF, POT1
...

Fattori di rischio sviluppo NMSC e MM

Rapporto numerico relativo a ciascun tumore	BCC	SCC	MM
• **Fototipo 1 vs 4**	x1	**x2**	x2
• **Anamnesi famigliare**	x1	**x2**	x2
• **Anamnesi personale**	**x4**	**x10**	x7
• **Immunosoppressione**	**x3**	**x18**	x6
• **> 100 nei (sindrome del neo displastico)**	-	-	**x11**
• **Xeroderma pigmentosum**	**x20**	**x5000**	**x2000**

Adapted from Gaide O. Clinical diversity of the SCC: diagnostic tools and critical risk factors, SSDV, Bern 2022

Dati epidemiologici BCC e SCC

	BCC	SCC
• **Prevalenza**	1.5%	0.4%
• **Incidenza** (persone - anno)	**150/100'000** Fototipo 1-4: **≈ 30% rischio** sviluppo **nel corso della vita**	**40/100'000** Fototipo 1-4: 2-4%/anno
• **Sopravvivenza a 5 anni**	≈ 100%	**90%**
• **Rischio Metastasi**	0.0028-0.55%	-
• **Aggressività locale**	< 1%	-
•	**80%** di tutti i NMSC	20% muoiono di cancro

Adapted from Gaide O. Clinical diversity of the SCC: diagnostic tools and critical risk factors, SSDV, Bern 2022

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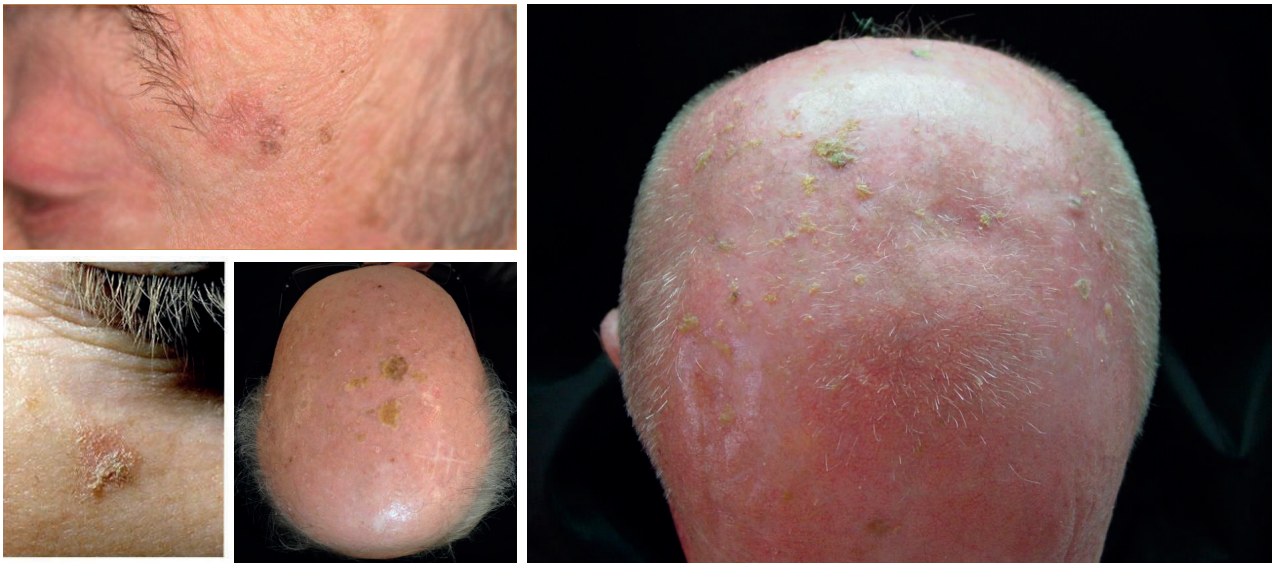
Cheratosi attiniche (AK): Aspetto clinico



Cheratosi attiniche (AK): Quando? Chi? (Epidemiologia)

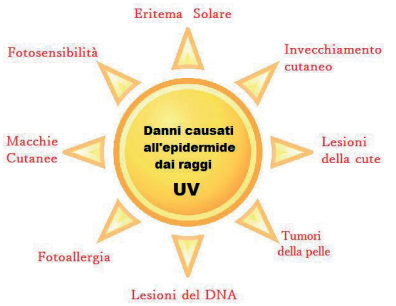
- **Frequentissime**. Secondarie all'esposizione cronica al sole
- **Alto rischio**: Occhi blu, capelli biondi e efelidi **Medio**: **4**

(**fototipo celtico**)

- Praticamente **inesistenti** fototipo **6** e **rare** fototipo **5**

- **Precursori** dei **Carcinomi Squamocellulari** (rischio progressione < 5%).
  Anche **marcatori di rischio** per Carcinomi **Basocellulari**.
  Ma possono anche **regredire** spontaneamente o **restare invariate**

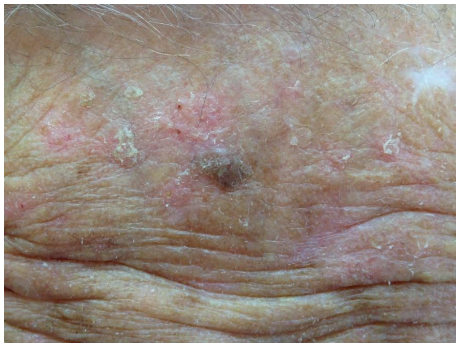
AK: Come si formano? (Eziologia)



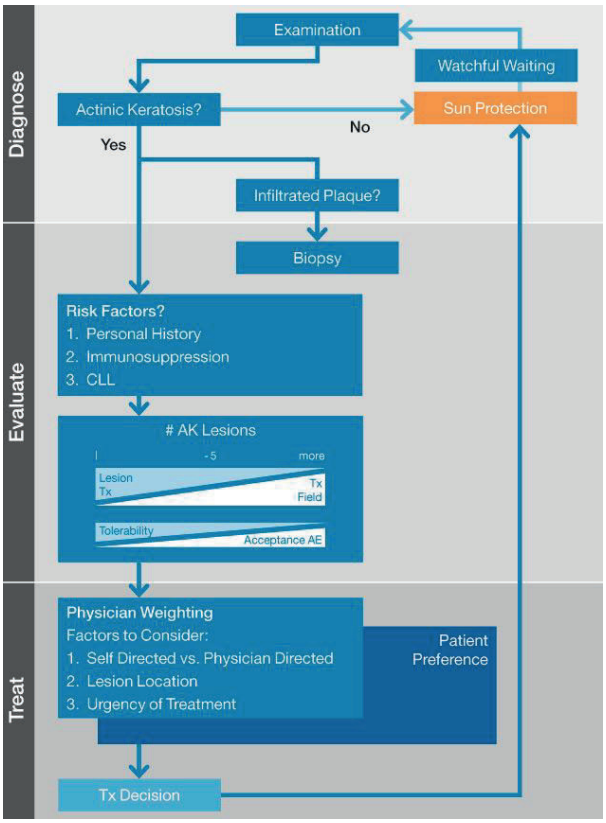
- **Raggi solari UV** responsabili nell'induzione e progressione delle cheratosi attiniche
- Tra iniziazione (cheratosi attiniche) e **insorgenza** di un **carcinoma squamocellulare** possono passare **20-50 anni**
- **Genetica**: gene oncogeno *ras;* gene soppressore tumorale *p53*
- **Sistema immunitario**: → risposta immunitaria con età ↓
  → immunosoppressione
- **Prevalenza:**
  - Australia (caucasici) ≥ 40 anni: 40-60%
  - Europa: Austria ≥ 30 anni: 31%
    Olanda ≥ 30 anni: 37%
    Italia presso studi medici Dermatologia: 27.4%
    Spagna presso studi medici Dermatologia: 28.4%

Del Regno L et al. American Journal of Clinical Dermatology 2022;23:339–352.

Algoritmo per la cura della AK e *Field Cancerization*



The algorithm is intended to aid in the treatment decision process for actinic keratosis and field cancerization and is not intended to replace a physician's best judgement on the most appropriate treatment path for each individual patient



Hofbauer G et al. Swiss clinical practice guidelines on field cancerization of the skin. Swiss Med Wkly 2014 Dec 24;144:w14026.

Management delle AK e *Field Cancerization*

Table 1: Management recommendations for actinic keratosis and field cancerization.

Patient presentation	Recommended management	Suggested timing	Additional information
Photodamage; no other risk factors	Clinical skin examination	If new lesions occur	
	Patient-directed self-examination	Every 3 months	
Fewer than five lesions; no other risk factors	Clinical skin examination	Every 12 months	
	Patient-directed self-examination	Every 3 months	
Recurrent lesions and recalcitrant lesions	Clinical skin examination	Every 3, 6, and 12 months following treatment At least every 6 months thereafter	Recalcitrant lesion requires biopsy by dermatologist
	Patient-directed self-examination	Every 3 months	
History of skin cancer	Clinical skin examination	Every 3, 6, and 12 months following treatment At least every 12 months thereafter	Lymph node exam by dermatology specialist in high-risk patients
	Patient-directed self-examination	Every 3 months	
CLL/OTR	Clinical skin examination by dermatology specialist	For CLL: Every 12 months For OTR: One screening exam pretransplantation Clinical exam at least every 12 months following transplantation	Invasiveness of skin lesions can be clinically underestimated in CLL/OTR.
	Patient-directed self-examination	Every month	

Hofbauer G et al. Swiss clinical practice guidelines on field cancerization of the skin. Swiss Med Wkly 2014 Dec 24;144:w14026.

Fattori che influenzano le decisioni terapeutiche per curare le AK e *Field Cancerization*

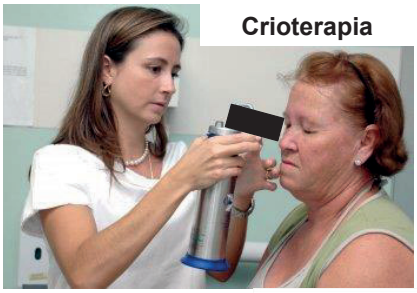
Table 2: Factors that influence treatment decisions for actinic keratosis and field cancerization.
Disease-specific factors
Progression/development of disease
Number of lesions
Localisation and severity of disease
Location of lesions
Recurrence
Patient-specific factors
Age
Mental condition
Ability and willingness to adhere to therapy
History of skin cancer
Risk factors, especially immunosuppression

Hofbauer G et al. Swiss clinical practice guidelines on field cancerization of the skin. Swiss Med Wkly 2014 Dec 24;144:w14026.

Terapie AK

Radioterapia

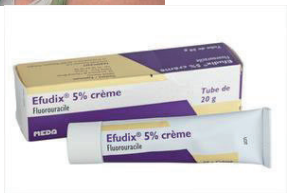
PDT: Photodynamic therapy



Crioterapia

Peeling all'acido tri-cloro-acetico

LASER CO_2



AK: Evidence Base Medicine Treatments

First-line	**Sun protection creams**	**A**
	Cryotherapy	**B**
	Topical 5-Fluoro-Uracil	**A**
	Topical Imiquimod	**A**
	PDT (Photodynamic Therapy)	**A**
	Topical Tirbanibulin	**A**
Second-line	**Topical Retinoids**	**A**
	Topical Diclofenac in hyaluronic acid	**A**
Third-line	**Curettage**	**E**
	Surgical excision	**E**
	Abrasive LASER (CO_2)	**B**
	Chemical Peeling (Trichloroacetic acid)	**D**
	Dermabrasion	**D**

Evidence Levels: A: Double-blind study **B:** Clinical trials ≥ 20 subjects **C:** Clinical trials < 20 subjects **D:** Series ≥ 5 subjects **E:** Anecdotal case reports

Ibrahim SF & Brown MD. Actinic keratoses. in: Lebwohl MG et al. Treatment of skin disease. 4th eds (2014), Elsevier Saunders: pp. 14-7.

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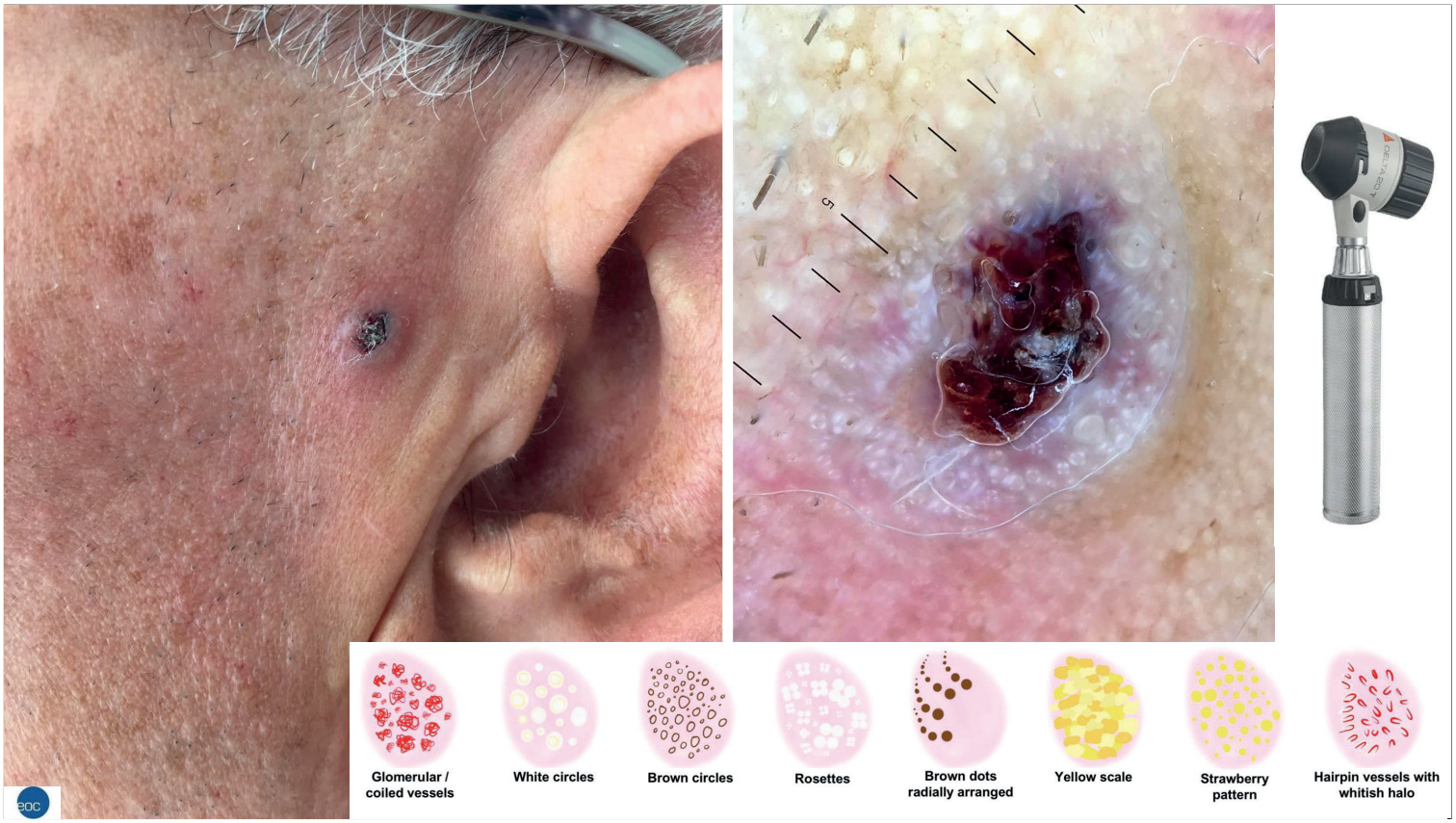
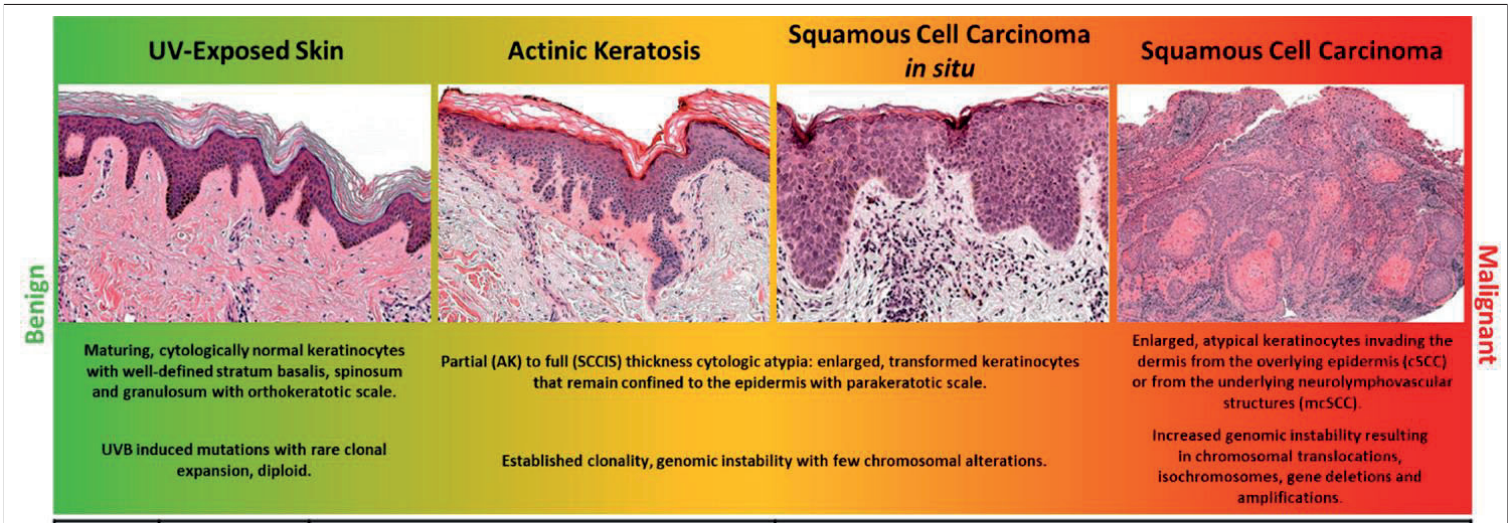
Carcinoma Squamocellulare cutaneo (cSCC): aspetti clinici

Diagnosi clinica di Carcinoma Squamocellulare cutaneo (cSCC)

***Red Flags* cSCC**	
Pazienti ad alto rischio	1) Età avanzata
	2) Pelle chiara
	3) Danno attinico cutaneo evidente di solito con cheratosi attiniche
	4) Professione o ex-prof. e/o tempo libero con esposizione solare
	5) Trapiantati d'organo / CLL
	6) Anamnesi di molteplici cancri della pelle e/o cheratosi attiniche
Storia clinica della lesione cutanea	1) Nuova apparizione (**crescita rapida**)
	2) Mutazione (cambiamento)
	3) **Ulcerazione crateriforme – Tumore cheratinizzante**
	4) **Dolore alla palpazione e/o pressione**
	5) Prossimità a cure di pregressi cancri e/o cheratosi attiniche
	6) Prossimità a escissione incomplete o a cure non chirurgiche di cancri della pelle





	UV-exposed Epidermis	Actinic Keratoses (Aks) ↓ Squamous Cell Carcinoma in Situ (SCCIS)	Invasive Cutaneous Squamous Cell Carcinoma (cSCC) ↓ Metastatic Cutaneous Squamous Cell Carcinoma (mcSCC)
"Driver" Genomic Changes	*NOTCH 1, 2, 3* *KNSTRN*	*NOTCH 1, 2, 3* *KNSTRN* *TP53* *FAT1* *KMT2C* *PIK3CA* *CDKN2A*	*NOTCH 1, 2, 3* *KNSTRN* *TP53* *FAT1* *KMT2C* *PIK3CA* *CDKN2A* *ABI3BP* *IMPA1* *HRAS*

Hedberg ML et al. Int. J. Mol. Sci. **2022**, 23, 3478. https://doi.org/10.3390/ijms23073478.

cSCC: Quando? Chi? (Epidemiologia)

- **Incidenza in Europa**: ♂: 10-20 / 100'000
  ♀: 5-10 /100'000 (Australia: 250 / 100'000)
- **Alto rischio**: Occhi blu, capelli biondi e efelidi Medio: **4**

  (**fototipo celtico**)

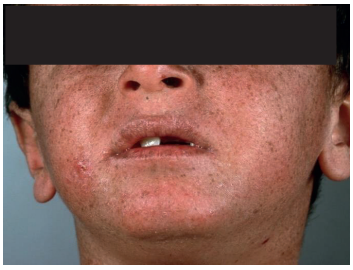
- **Raro** fototipo 6 e 5

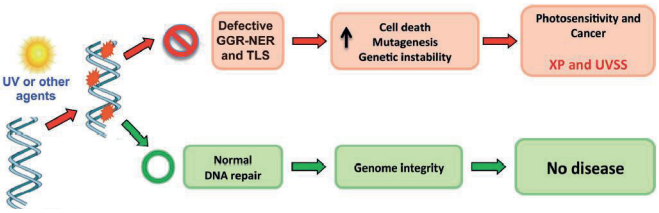
- **Rischio dovuto a 2 fattori**:
  → dose cumulativa di esposizione al sole
  → fototipo

- Esiste una correlazione lineare tra incidenza di cSCC e quantità subita di irradiazione agli UV

cSCC: Come si forma? (Eziologia, Fattori di rischio)

- **Cause** o **fattori favorevoli** allo sviluppo di cSCC:
  → UV
  → Albinismo
  → Genodermatosi (*Xeroderma pigmentosum*)
  → HPV (*Human Papilloma Virus*)
  → As, Catrame, Tabagismo
  → Immunosoppressione



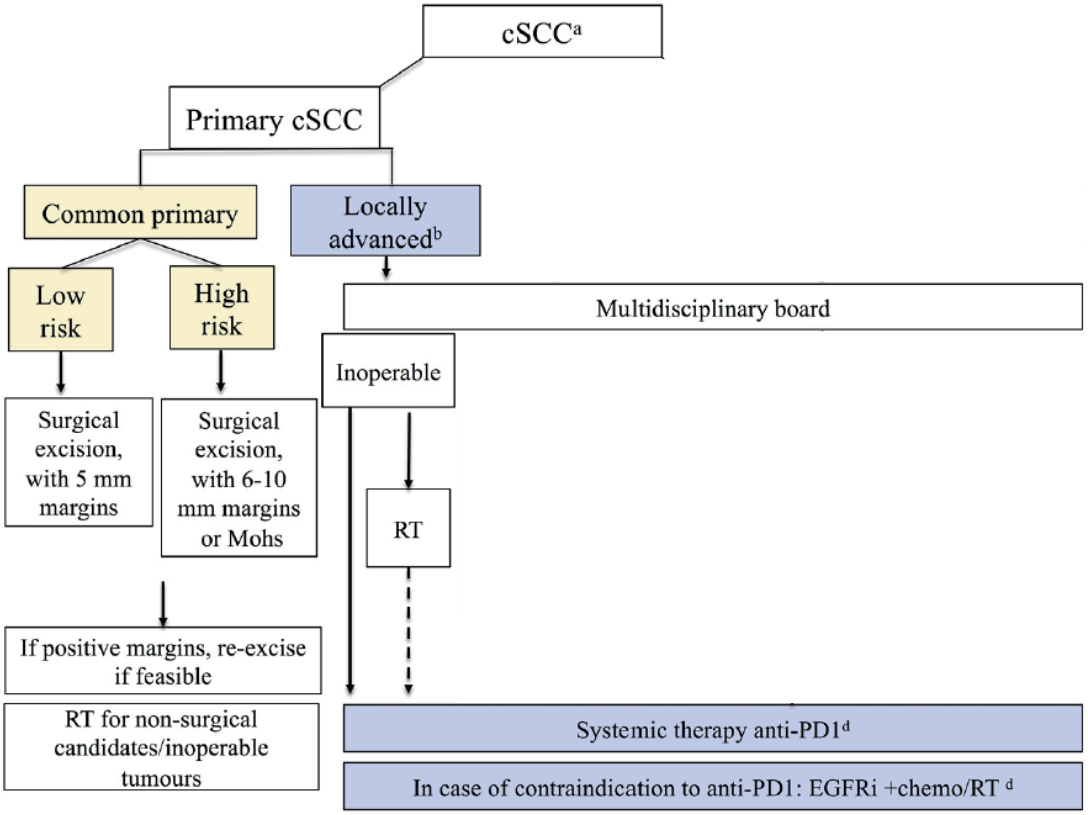


GGR-NER: Global Genome Repair Nucleotide Excision Repair
TLS: Translesion Synthesis

Genet Mol Biol 2014;37(1 Suppl):220-33.

- **"Ruolo doppio"** degli **UV**:
  → Mutazione del DNA (difetti di riparazione)
  → Sistema immunitario
  (Immunosoppressione locale: impedisce eliminazione cloni tumorali)

cSCC: Management



Dessinioti C and Stratigos AJ.Cancers 2022, 14, 3556. https://doi.org/10.3390/cancers14143556.

cSCC: 4 Sistemi di Staging

Staging System	Stage	Risk Factors	High-Risk Factors (If Applicable)
AJCC7	T1	Tumor diameter ≤ 2 cm with <2 high-risk factors	>2 mm thickness Clark level ≥ 4 PNI Primary site ear or lip Poorly differentiated
	T2	Tumor diameter > 2 cm, or any size with ≥2 high-risk factors	
	T3	Tumor with invasion of orbit, maxilla, mandible, or temporal bone	
	T4	Tumor with invasion of other bone, or direct PNI of skull base	
AJCC8	T1	Tumor diameter < 2 cm	
	T2	Tumor diameter ≥ 2 cm and <4 cm	
	T3	Tumor diameter ≥ 4 cm, or minor bone erosion, or PNI, or deep invasion	
	T4	Tumor with gross cortical bone/marrow invasion	
BWH	T1	No high-risk factors	Tumor diameter ≥ 2 cm PNI ≥ 0.1 mm Poorly differentiated Tumor invasion beyond fat
	T2a	1 high-risk factor	
	T2b	2–3 high-risk factors	
	T3	≥4 high-risk factors, or bone invasion	
Brueninger et al.	Clinical stage (cT)	Low risk: Tumor diameter ≤ 2 cm High risk: Tumor diameter > 2 cm	
	Pathological stage (pT)	No risk: Tumor thickness ≤ 2 mm Low risk: Tumor thickness > 2 mm and ≤6 mm High risk: Tumor thickness > 6 mm	
	Co-risk factors	Immunosuppression Desmoplastic type or poor differentiation Primary site ear	

Burns C et al. Cancers 2022, 14, 3556. https://doi.org/10.3390/cancers14153653

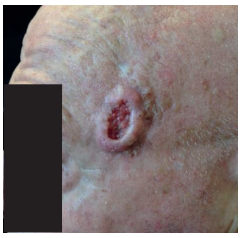
cSCC:

Fattori di rischio per i cSCC ad alto rischio nelle line guida

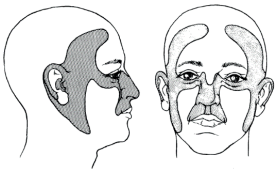
High-Risk Factors	European 2020 [1]	US NCCN 2022 [12]		UK BAD 2020 [13]	
	High Risk for Recurrence (Local or Metastatic)	High-Risk Factor for Local Recurrence, Metastasis, or Disease-Specific Death	Very High Risk for Local Recurrence, Metastasis, or Disease-Specific Death	High Risk for Local Recurrence, Nodal Metastasis, Or Disease-Specific Death	Very High Risk for Local Recurrence, Nodal Metastasis, Or Disease-Specific Death
Tumor-Related High-Risk Factors					
Tumor diameter	>20 mm	Trunk, extremities >2 cm −≤4 cm	>4 cm any location	>20–40 mm	>40 mm
Localization	On temple/ear/lip	Head, neck, hands, feet, pretibial, and anogenital (any size)		On ear/lip	-
Thickness	Thickness > 6 mm or Invasion beyond subcutaneous fat	-	>6 mm or Invasion beyond subcutaneous fat	Thickness > 4–6 mm	Thickness > 6 mm
Invasion				Invasion into subcutaneous fat	Invasion beyond subcutaneous fat
Differentiation	Poor grade differentiation	-	Poor grade differentiation	Poor grade differentiation	-
Histological feature	Desmoplasia	Acandtholytic (adenoid), adenosquamous, or metaplastic (carcinosarcomatous)	Desmoplasia	Lymphovascular invasion	High-grade histological subtype —adenosquamous, desmoplastic, spindle/sarcomatoid/metaplastic
Perineural invasion (PNI)	Histological/symptomatic/radiological PNI	Yes	PNI of a nerve lying deeper than the dermis or measuring ≥ 0.1 mm	Perineural invasion—dermal only; nerve diameter < 0.1 mm	Perineural invasion present in named nerve; nerve ≥0.1 mm; or nerve beyond dermis
Lymphatic or vascular involvement	-	-	Yes	-	-
Bone erosion/invasion	Bone erosion	-	-	-	Any bone invasion
Tumor on scar/chronic inflammation/RT	-	Site of prior RT or chronic inflammation	-	Tumor arising within scar or area of chronic inflammation	-
In-transit metastasis	-	-	-	-	In-transit metastasis
Borders	-	Poorly defined	-	-	-
Primary vs recurrent	-	Recurrent	-	-	-
Rapidly growing tumor	-	Yes	-	-	-
Neurologic symptoms	-	Yes	-	-	-

Dessinioti C and Stratigos AJ.Cancers 2022, 14, 3556. https://doi.org/10.3390/cancers14143556.

cSCC: Fattori Prognosi di Alto Rischio (recidiva/metastasi)



- **Criteri di rischio:** 1 solo criterio di "alto" rischio è sufficiente
- **Dimensione:**
  - **Diametro:** **> 2 cm**
  - **Spessore:** ≤ 2 mm — metastasi rarissime
    > 2 mm - ≤ 6 mm — rischio metastasi modesto (4%)
    > 6 mm (high risk) — rischio metastasi presente (16%)
  - **Infiltrazione:** Aderenza ai **piani profondi**: fascia muscolare, cartilagine, osso
- **Topografia:** a rischio più elevato:
  - Zone H del viso
  - Labbra e mucosa (lingua, vulva, pene)
  - Zona cicatriziale (ustione, RT,…)



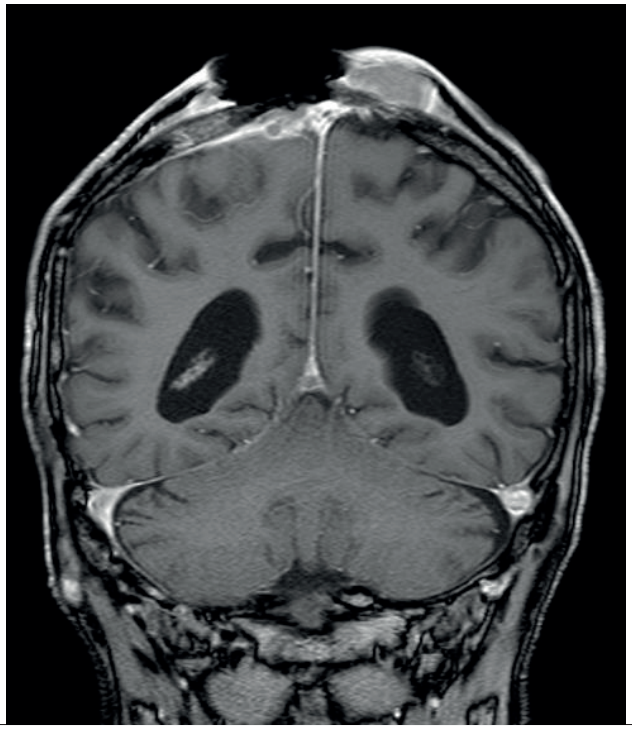
- **Istologia:** ***Differenziazione***:
  - ben differenziato
  - moderatamente differenziato
  - **poco differenziato**
  - **non differenziato**

  rischio di metastasi ▲

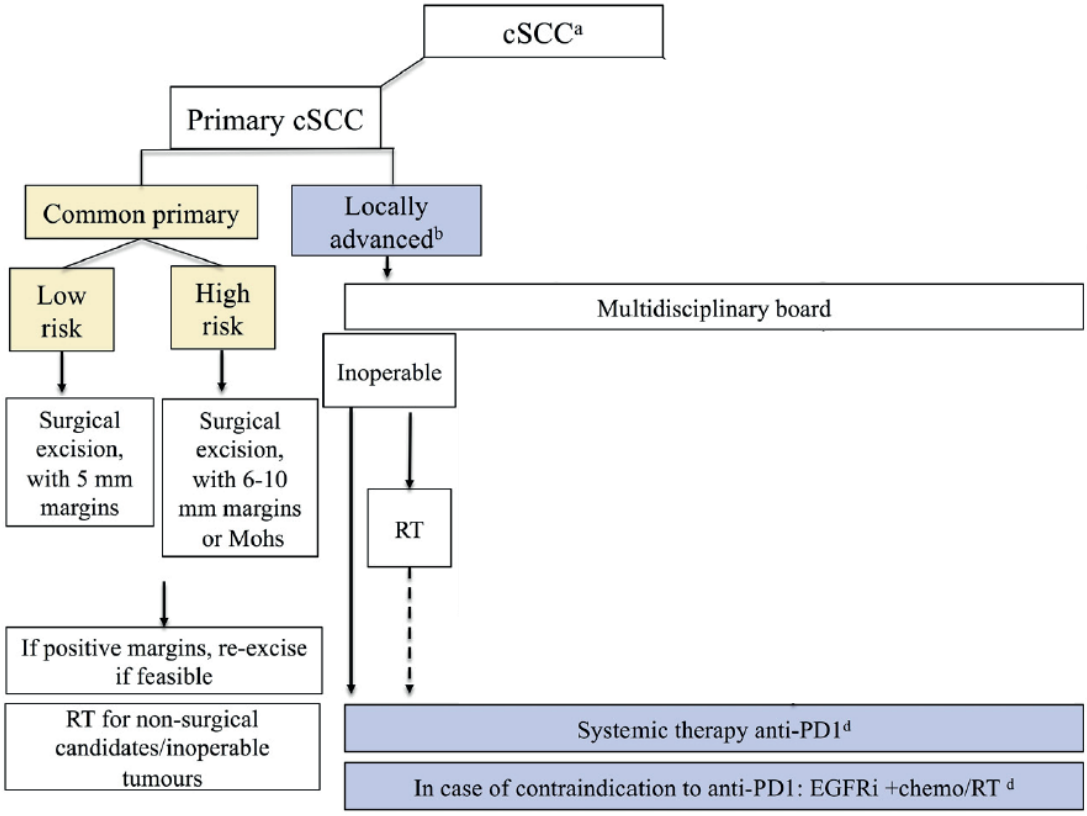
  Caratteristiche:
  Desmoplasia
  Sarcomatoide
  PIN
- **Immunosoppressione:** **Trapiantati d'organo** (rischio di SCC a 5 anni: x70)
  Malattie immunosoppressive: CLL, NHL

Skaria AM et al. Derm Helv 2014;26(7):28-30.

cSCC: Potenziale d'invasione in profondità

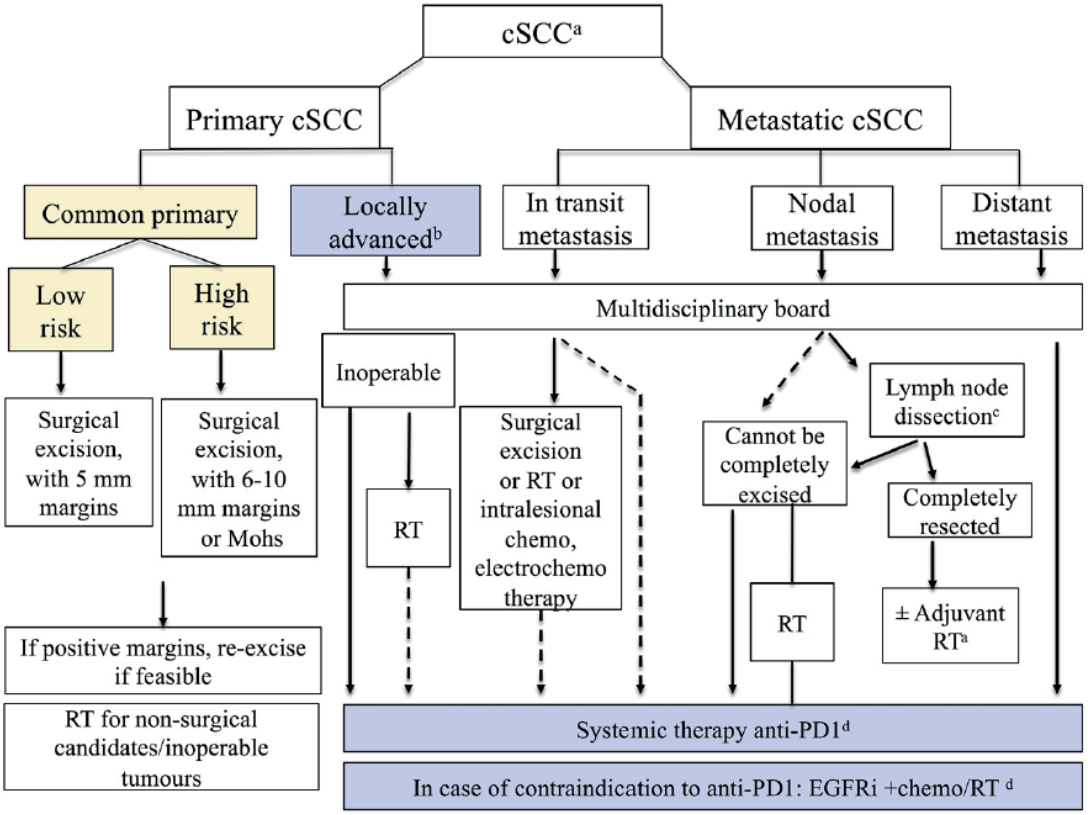


cSCC: Management



Dessinioti C and Stratigos AJ.Cancers 2022, 14, 3556.
https://doi.org/10.3390/cancers14143556.

cSCC: Management



Dessinioti C and Stratigos AJ.Cancers 2022, 14, 3556. https://doi.org/10.3390/cancers14143556.

cSCC: Terapia

Metodo	Procedura / Agente terapeutico	Level
Chemioterapia topica	Imiquimod 5-Fluoro-Uracile	**A** **B**
Distruzione senza controllo dei margini	Crioterapia Curettage e crioterapia Curettage e diatermia LASER CO_2 ablativo PDT IFNγ intralesionale Bleomicina intralesionale Radioterapia	**B** **B** **B** **-** **B** **B** **E** **B**
Resezione con controllo dei margini	**Escissione** **Chirurgia micrografica** (Mohs)	**B** **B**
In caso di **metastasi / «inoperabile»**	*Anti-PD1*: **Cemiplimab**, Pembrolizumab, Nivolumab, Ipilimumab *Chemioterapia*: Cisplatino, 5-FU, Tassani, Capecitabina *Anti-EGFR*: Cetuximab, Erlotinib, Gefitinib, Panitumumab	**A** **-** **B**

Evidence Levels: A: Double-blind study **B:** Clinical trials ≥ 20 subjects **C:** Clinical trials < 20 subjects **D:** Series ≥ 5 subjects **E:** Anecdotal case reports

Lansbury L et al. Treatment of squamous cell carcinoma in: Williams HC et al. Evidence-based Dermatology, 3th eds (2014), Blackwell: pp. 241-9. García-Foncillas J et al. Cancers 2022, 14, 629. https://doi.org/10.3390/cancers14030629. Villani A et al. Adv Ther 2022;39:1164–1178. https://doi.org/10.1007/s12325-022-02044-1.

Sommario

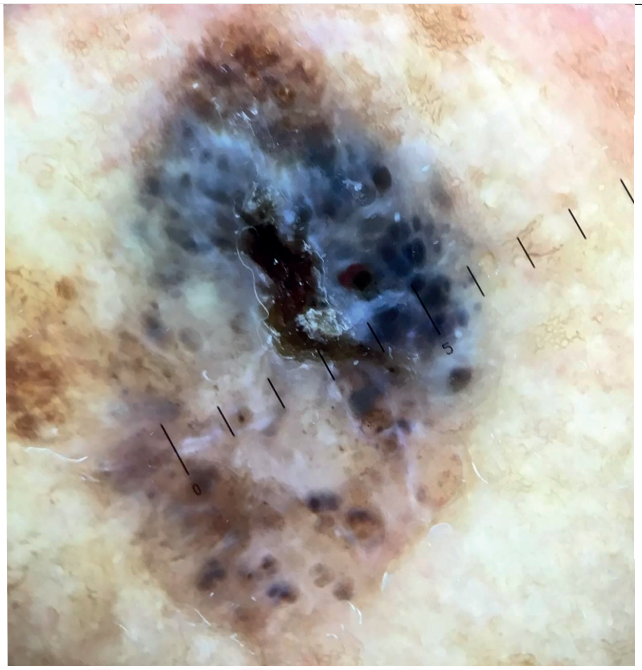
- **Cenni sulla fisiologia della pelle e sull'invecchiamento cutaneo**
- **Non Melanoma Skin Cancers (NMSC) di tipo epiteliale:**
  - *Cheratosi attiniche (precancerosi) (AK)*
  - Carcinoma squamocellulare (SCC)
  - **Carcinoma basocellulare (BCC)**

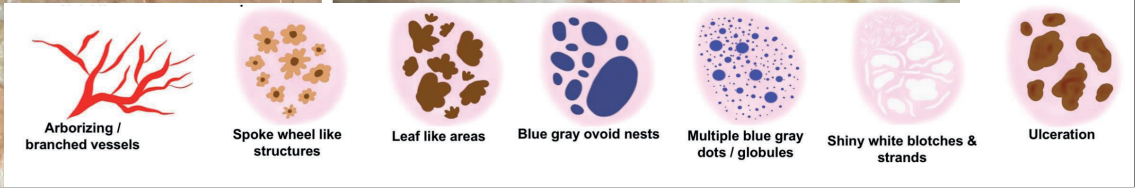
Carcinoma Basocellulare (BCC): aspetti clinici

Diagnosi clinica di Carcinoma basocellulare (BCC)

Red Flags BCC	
Pazienti ad alto rischio	1) Età avanzata
	2) Pelle chiara
	3) Danno attinico cutaneo evidente
	4) Professione o ex-prof. e/o tempo libero con esposizione solare
	5) Trapiantati d'organo
	6) Anamnesi di molteplici cancri della pelle e/o cheratosi attiniche
Storia clinica della lesione cutanea	1) Nuova apparizione
	2) Mutazione (cambiamento)
	3) **Erosione o ulcerazione ricorrente che non tende a guarire**
	4) Prossimità a cure di pregressi cancri della pelle
	5) Prossimità a escissione incomplete o a cure non chirurgiche di cancri della pelle

Tomas S. The 'ultra slow' BCC - two case studies. Aust Fam Physician 2010;39:227-8.





BCC: Quando? Chi? (Epidemiologia)

- **Incidenza in Europa**: → **il più frequente tumore maligno**
  → ≈ **1/3 persone** può svilupparlo nel corso della vita
- **Alto rischio**: Occhi blu, capelli biondi e efelidi Medio: **4**

(**fototipo celtico**)

- **Raro** fototipo 6 e 5

- **Rischio dovuto a 2 fattori**:
  → esposizione al sole / fototipo
  → perturbazione processo di cancerogenesi

- **Non** esiste una **correlazione lineare** tra incidenza di BCC e **quantità** subita di **irradiazione agli UV**
- Non è **mai preceduto** da una **precancerosi**, ma possono coesistere

BCC: Come si forma? (Eziologia)

- **Cause** o **fattori favorevoli** allo sviluppo di BCC:
  → UV (ma rispetto cSCC, assenza di modello sperimentale!)
  → Albinismo
  → *Xeroderma pigmentosum*
  → *Epidermodysplasia verruciforme* (HPV)
  → Sindrome di Muir-Torre
  → Sindrome di Gorlin
  → Raggi X
  → Immunosoppressione

- **Perturbazione processi di "cancerogenesi"**:
  → Attivazione oncogeni *ras*
  → Perturbazione della via di segnalizzazione *sonic hedghog*
  → Disattivazione gene soppressore tumorale *p53*
  → Inibizione dei meccanismi immunitari

Evoluzione «naturale» locale

IMAGES

Evolution of Basal Cell Carcinoma

Giovanni Zoccali, MD, Reza Pajand, MD, Roberto Matteo Crisci, MD, and Maurizio Giuliani, MD*

T0 6 mesi 1 anno

EADO Staging System for BCC

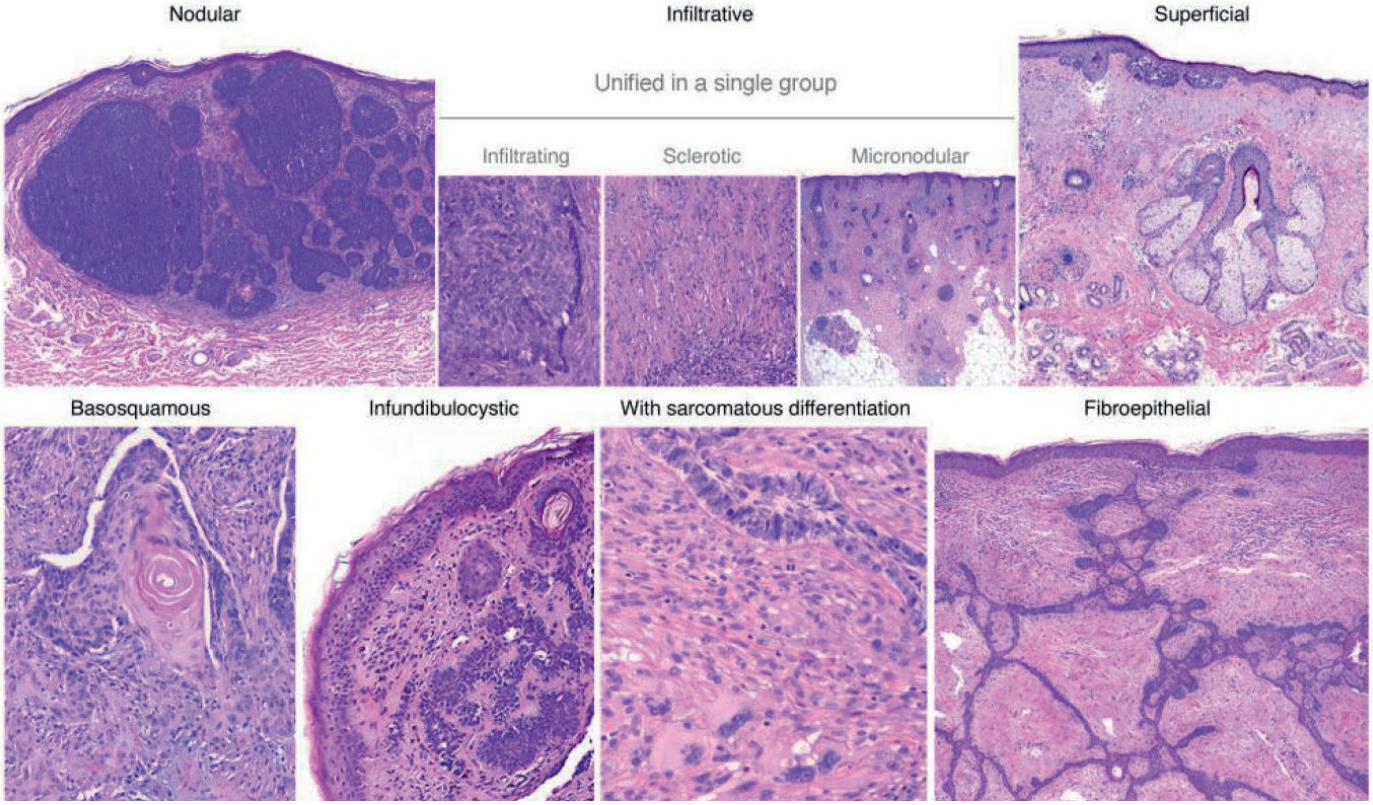
Risk	Stage		Characteristics		Illustrative pictures	DTT-BCC Group (part 1)
Easy To Treat and low risk of recurrence	Common BCC	I	Low-risk common BCC	**None of the other stages characteristics.** *Recurrences only come from blind treatments, or insufficient surgical margins.*		*Not included*
Increasingly Difficult To Treat and increasing risk of recurrence	Common BCC	IIA	Common BCC but somewhat DTT	Common BCC but management is more complex than usual for any reason linked to the tumor (location requiring technical skill, poorly defined tumor borders, prior recurrence) and/or to the patient (poor general status, comorbidities, or unwillingness to cooperate ...). *Good results and low rate of recurrence expected with surgery even if technically complicate, when the patient cooperates.*		*1*
	Common BCC	IIB	DTT-BCC mainly due to multiplicity of common BCC	Very high number of common BCC (>10) or multiple complex BCC (> 5) in the setting of apparently sporadic cases or in Gorlin syndrome*. *When at least 1 of the multiple BCC can be classified III or IV, the patient will be classified accordingly, and not IIB		*2*
	Advanced BCC	IIIA	Locally advanced DTT-BCC out of critical areas	Large and/or destructive tumors in non-critical or functionally significant areas. *Deemed curable without expected functional mutilations.*		*3*
	Advanced BCC	IIIB	Locally advanced DTT-BCC in critical areas	Large and/or or destructive tumors in critical or functionally important areas (periorificial, nose, ...). *Deemed curable by surgery, but functional impairment and/or mutilation are inevitable.*		*4*
	Advanced BCC	IIIC	Extremely advanced DTT- BCC	Giant and/or deeply invasive tumors involving extracutaneous tissue (bone, muscles, vital or sensorial structures) responsible for an extreme clinical situation. *Cure cannot be expected by surgery whatever its extent.*		*5*
	Metastatic BCC	IV		Distant metastases*. *Whatever the initial BCC staging, patient must be classified IV when metastatic.		*Not included*

Legenda: **DTT-BCC:** difficult-to-treat BCCs

Grob JJ et al. JEADV 2021;35:2149–2153.

ISTO:

Classificazione semplificata che riduce i sottotipi rilevanti



Fernandez-Figueras MT et al. JEADV 2022, 36, 351–359.

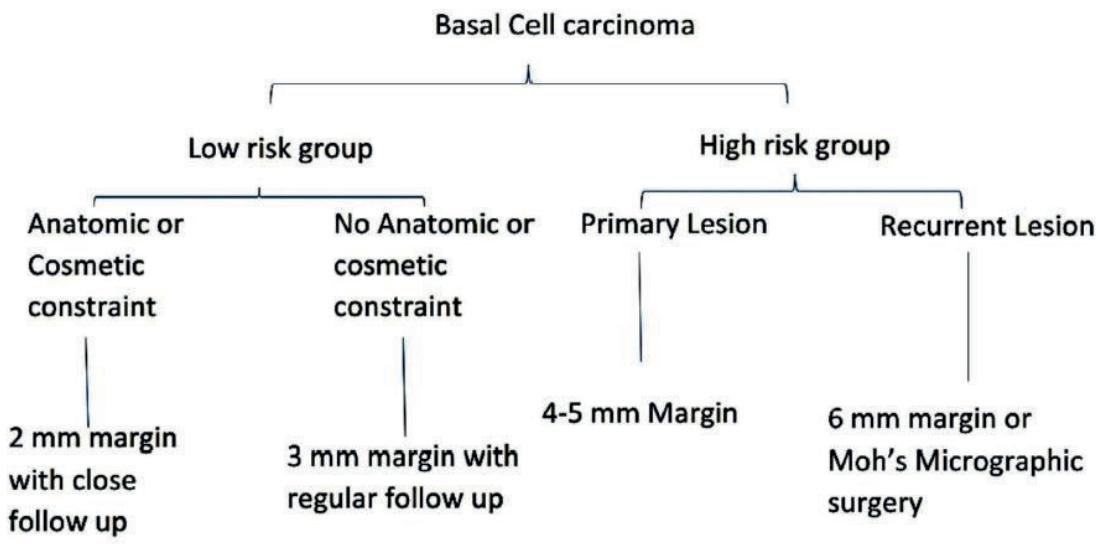
BCC: classificazione dei rischi di recidiva locale

Recurrence-risk group	High-/moderate-risk (H and M zones) [23]	Low-risk (L zone) [23]
History and physical		
Location and size	Trunk, extremities ≥2 cm Cheeks, forehead, scalp, neck, and pretibial any size "Mask areas"[b] of the face, genitalia, hands, and feet	Trunk, extremities <2 cm
Borders	Poorly defined	Well-defined
Primary versus recurrent	Recurrent	Primary
Immunosuppression	(+)	(–)
Site of prior RT	(+)	(–)
Histology		
Subtype	Aggressive growth pattern: infiltrative, micronodular, morpheaform, sclerosing, and further[d]	Nonaggressive growth pattern: nodular, superficial, and other[e]
Perineural involvement	(+)	(–)

Adapted from the NCCN 2021 guidelines [28]. CCPDMA, Complete Circumferential Peripheral and Deep Margin Assessment; H zone, high-risk zone; L zone, low-risk zone; M zone, moderate-risk zone; RT, radiotherapy. [a] Any high-risk factor places the patient in the high-risk category. [b] "Mask areas" of the face: central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular, and postauricular skin/sulci, temple, and ear. [c] This area is a high-risk location, independent of size. [d] Having (mixed) infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or carcinosarcomatous differentiation features in any portion of the tumor. In some cases, basosquamous tumors may be prognostically similar to SCC; clinicopathologic correlation is recommended in these cases. [e] Low-risk histologic subtypes include nodular, superficial, and other nonaggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.

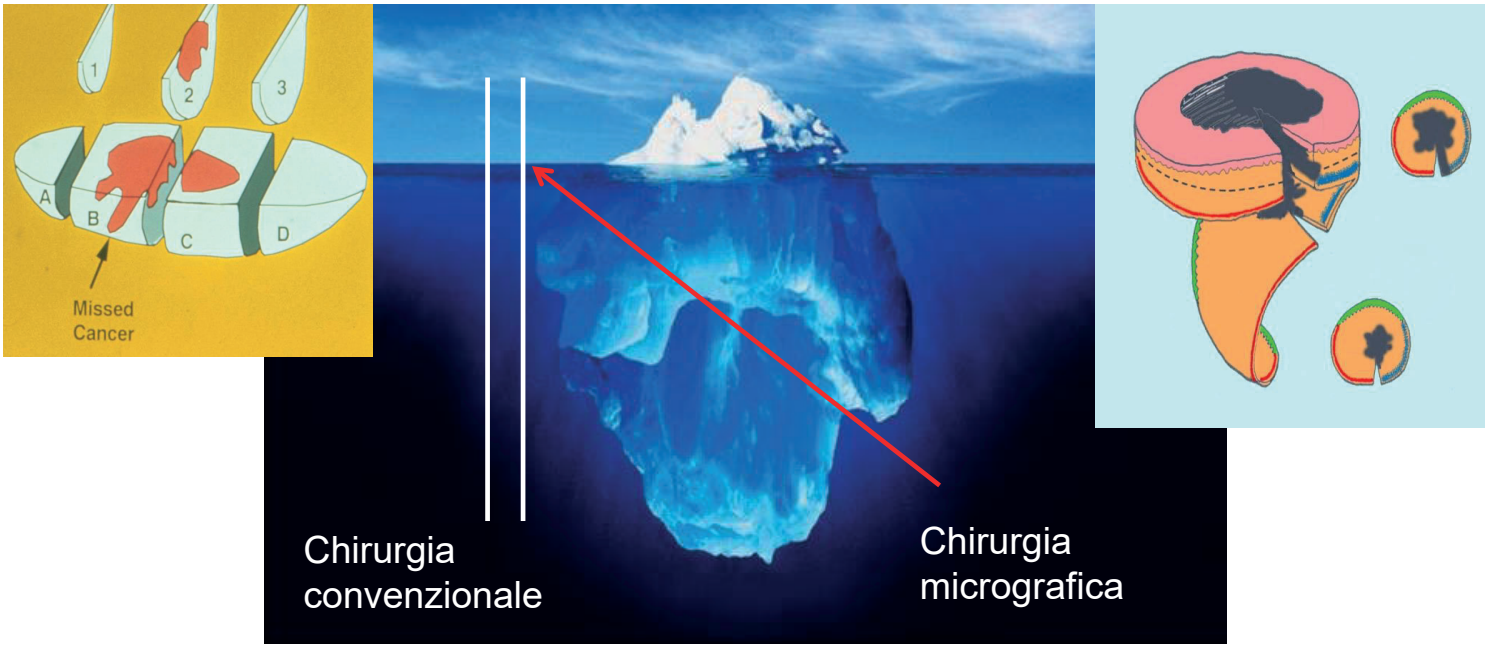
Ramelyte E et al. Dermatology 2022 DOI: 10.1159/000526478

Algoritmo per i margini di escissione nei differenti tipi di BCC



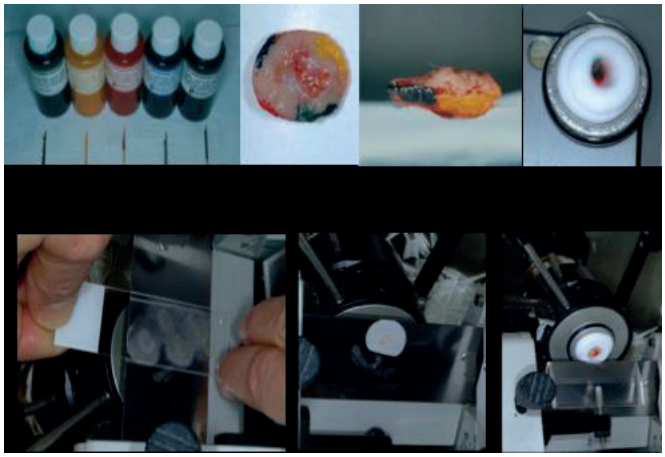
Quazi S J et al. Surgical Margin of Excision in Basal Cell Carcinoma: A Systematic Review of Literature. Cureus 2020;12(7): e9211. DOI 10.7759/cureus.9211

Chirurgia convenzionale o micrografica? Margini di sicurezza?



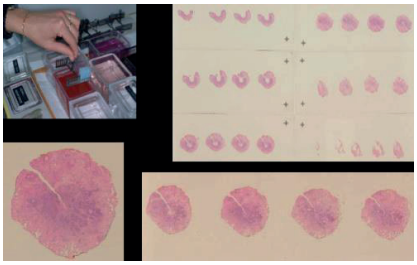
Courtesy of Dr. med. G. Marazza

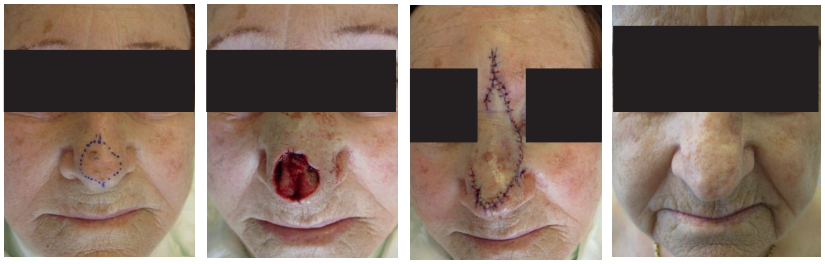
Chirurgia micrografica: svolgimento in breve



Courtesy of Dr. med. G. Marazza

- Escissione della lesione tumorale con margine minimo ragionevole, in anestesia locale
- Analisi isto-patologica
- Eventuali riprese chirurgiche
- Ricostruzione/Chiusura chirurgica





BCC: Terapia

Metodo	Procedura / Agente terapeutico	Level
Chemioterapia topica	Imiquimod 5-Fluoro-Uracile	**A** **A**
Distruzione senza controllo dei margini	Crioterapia Curettage e crioterapia Curettage e diatermia LASER CO_2 ablativo PDT IFN intralesionale (PEG)-IL-2 intralesionale **Radioterapia**	**B** **B** **B** **D** **A** **B** **D** **B**
Resezione con controllo dei margini	**Escissione** **Chirurgia micrografica** (Mohs)	**B** **B**
In caso d'**infiltrazione inoperabile** o **irradiabile** e/o **metastasi**	*Segnalazione di Hedgedog:* **Vismodegib**, **Sonidegib**, Patidegib (Saridegib), Taladegib *Anti-PD1*: Cemiplimab	**A** **-**

Evidence Levels: A: Double-blind study **B:** Clinical trials ≥ 20 subjects **C:** Clinical trials < 20 subjects **D:** Series ≥ 5 subjects **E:** Anecdotal case reports

Lansbury L et al. Treatment of squamous cell carcinoma in: Williams HC et al. Evidence-based Dermatology, 3th eds (2014), Blackwell: pp. 241-9.
Villani A et al. Adv Ther 2022;39:1164–1178. https://doi.org/10.1007/s12325-022-02044-1
Peris K et al. BCC guidelines. European Journal of Cancer 2019;118:10-34.

Conclusioni: Fisiologia della pelle e tumori cutanei non melanoma

- Fisiologia: **Pelle organo di protezione e difesa** (immunologica)
- Invecchiamento cutaneo: **UV e genetica** (fototipo) giocano il ruolo maggiore

- Cancri cutanei: **UV, Genetica e Sistema immunitario**
- **AK:** indizio di invecchiamento cutaneo (fototipo 1-4) e predisposizione a sviluppare NMSC (cSCC)

- **NMSC:**
  - **BCC:**
    - ≈ **1/3 persone** (fototipo 1-4) può svilupparlo nel corso della vita
    - Erosione o ulcerazione ricorrente che non tende a guarire (fragilità cutanea)
    - **Escissione chirurgica** con margini liberi vs chirurgia di Mohs
    - **Radioterapia** per le forme non infiltrative – Farmaci pathway **segnalazione di Hedgedog** - (anti-PD1)
  - **cSCC:**
    - Esiste una correlazione lineare tra incidenza di cSCC e quantità subita di irradiazione agli UV
    - **Ulcerazione crateriforme** – **Tumore cheratinizzante**
    - **Dolore** alla palpazione e/o pressione
    - **Escissione chirurgica** con margini liberi vs chirurgia di Mohs
    - Casi inoperabili / Metastasi: **Radioterapia** – Farmaci anti-PD1; alternativa: Anti-EGFR + chemioterapia

- **Dermatoscopia:** oggi come ieri, grande aiuto per la diagnosi clinica

eoc

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Dr. Med. Carlo Mainetti
Primario Dermatologia EOC, Past-President SGDV / SSDV, Ospedale Regionale Bellinzona e Valli, Ospedale Beata Vergine Mendrisio, Ticino

Si ringraziano i seguenti sponsor:

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Giovedì 17 novembre 2022
Centro Eventi Cadempino

I tumori della pelle

GIOTi
Gruppo Interesse Oncologia Ticino

Onkologiepflege Schweiz
Soins en Oncologie Suisse
Cure Oncologiche Svizzera

Grazie
per l'attenzione

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