

# Disclaimer

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# Basal Cell Carcinoma

# Basal Cell Carcinoma

<http://www.cancer.org.au/File/HealthProfessionals/BasalCellCarcinoma,SquamousCellCarcinomaandRelatedKeratinocyteDysplasias-AGuidetoClinicalManagementinAustralia.pdf>

## Definition :

- BCC is a malignant tumour of *keratinocytes*
- Thought to originate from *keratinocyte* stem cells or transit amplifying cells of the **basal** layer of the epidermis or follicle

➤ INTRO

➤ **CLASSIFICATION**

➤ Diffuse

➤ Circumscribed

➤ Infiltrating

➤ BIOLOGY

➤ CLINICAL ASPECTS

➤ DEMOGRAPHICS

➤ TREATMENT

➤ Surgical

➤ Aldara (Toll Receptors)

➤ PDT, Cx, C&C, Diclofenac

➤ XRT

➤ Incomplete / RECURRENT

➤ Congenital – GORLIN'S Syndrome

# classification

## ➤ **Circumscribed**

- Solid (Nodular), Cystic, Adenoid
- Micronodular / Mixed
- Pigmented

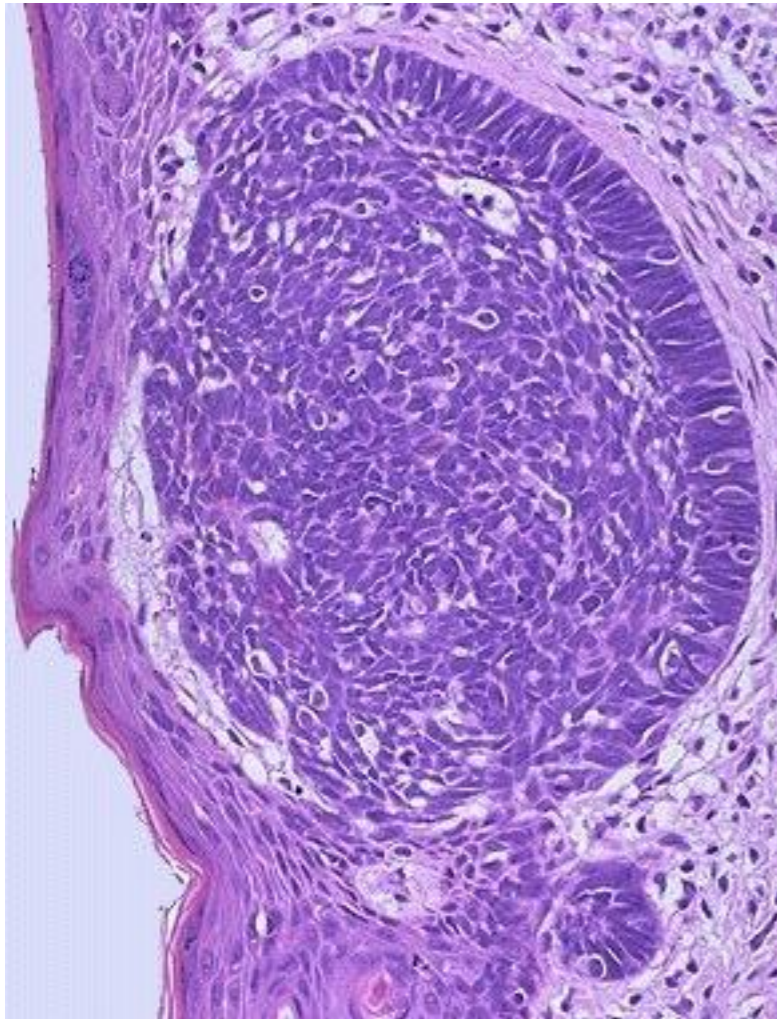
## ➤ **Diffuse**

- *Multifocal* Superficial

## ➤ **Infiltrative**

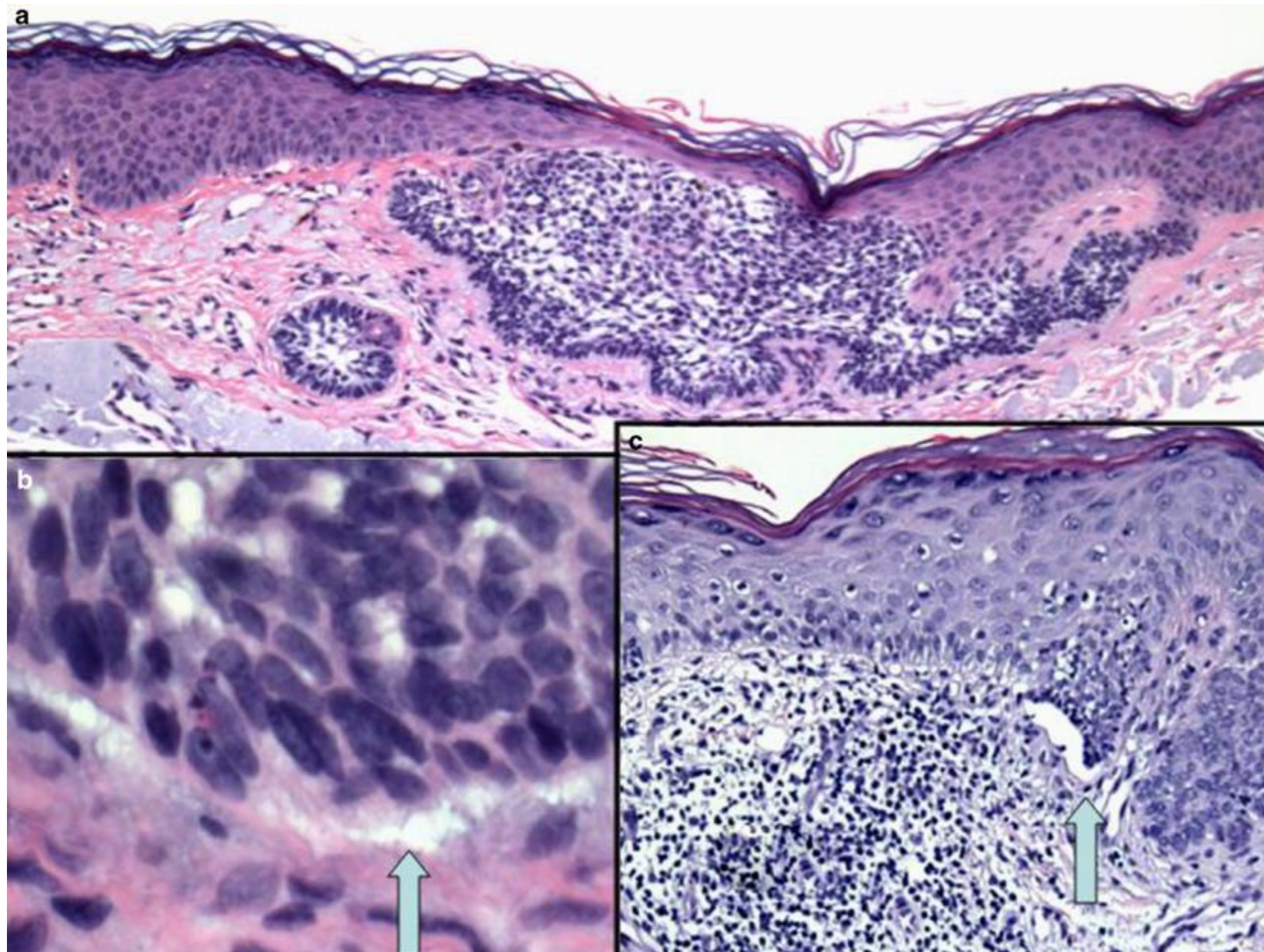
- Infiltrative
- Fibrosing
- Sclerosing, Morphoeic

# histology



- islands of basaloid cells
- peripheral palisading, central chaos
- hyperchromatic nucleus, scant cytoplasm, absent intercellular bridges,
- numerous mitoses + apoptotic tumour cells
- attachment to epidermal undersurface
- adjacent stoma, different to dermis
- expression of mmp ---- metallo-matrix proteases
- solar elastosis in adjacent dermis >90% cases
- variable inflammatory cell infiltrate

# Superficial BCC



## Superficial BCC morphology.

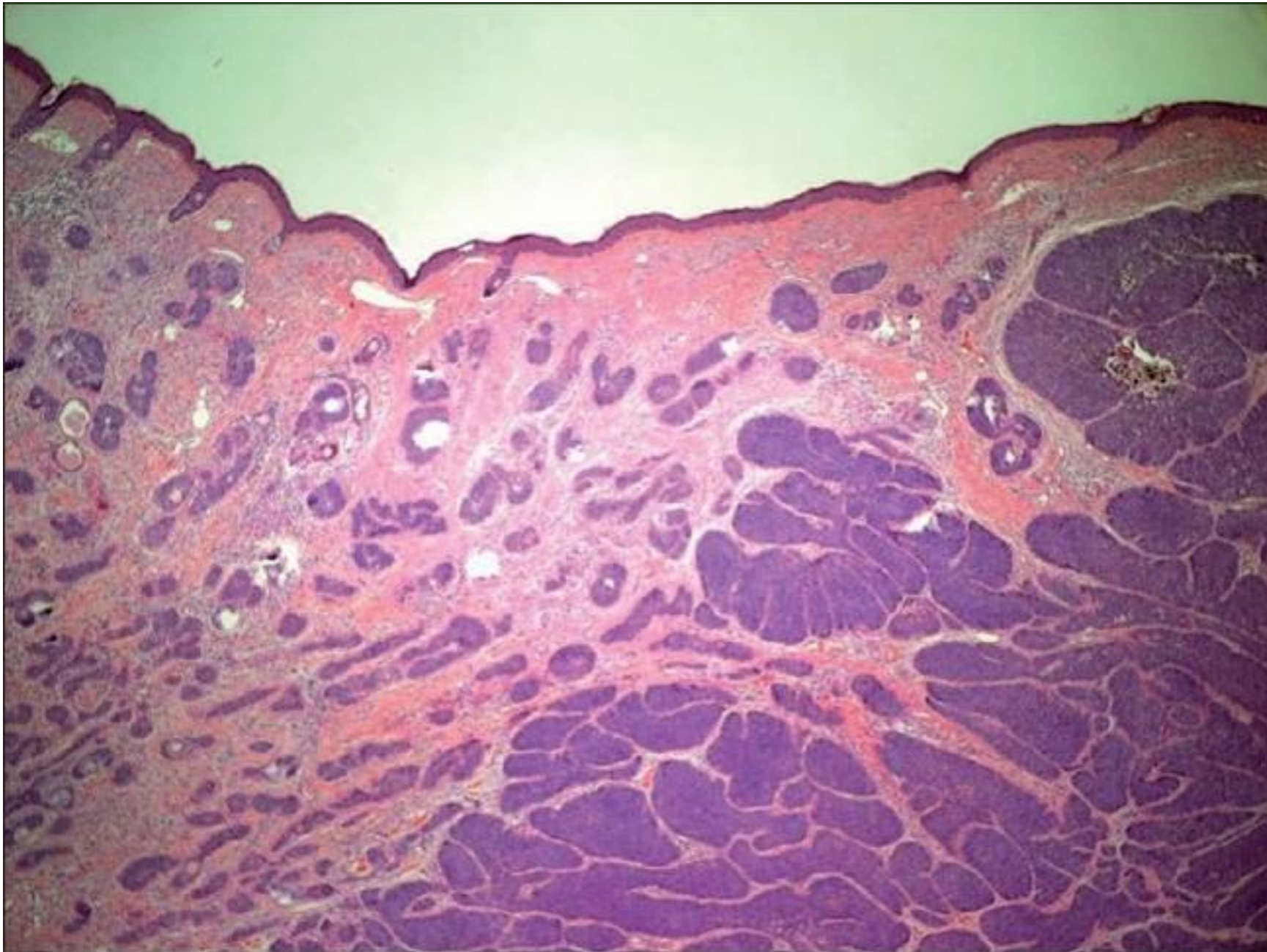
(a) A proliferation of basaloid cell islands attached to the undersurface of the epidermis. Uniclonal. Rarely beyond the papillary dermis.

(b) Slit-like narrow stromal band (arrow) with mucin deposition in the papillary dermis.

(c) Minimal lymphoid infiltrate in apposition to the basaloid nests (arrow) and the undersurface of the epidermis.

(d) Local angiogenesis

# Micronodular BCC



**Small nests of neoplastic basal cells with rounded peripheral contours extending widely throughout the dermis.**

**Minimal palisading.  
Minimal Fibro-inflammatory response**

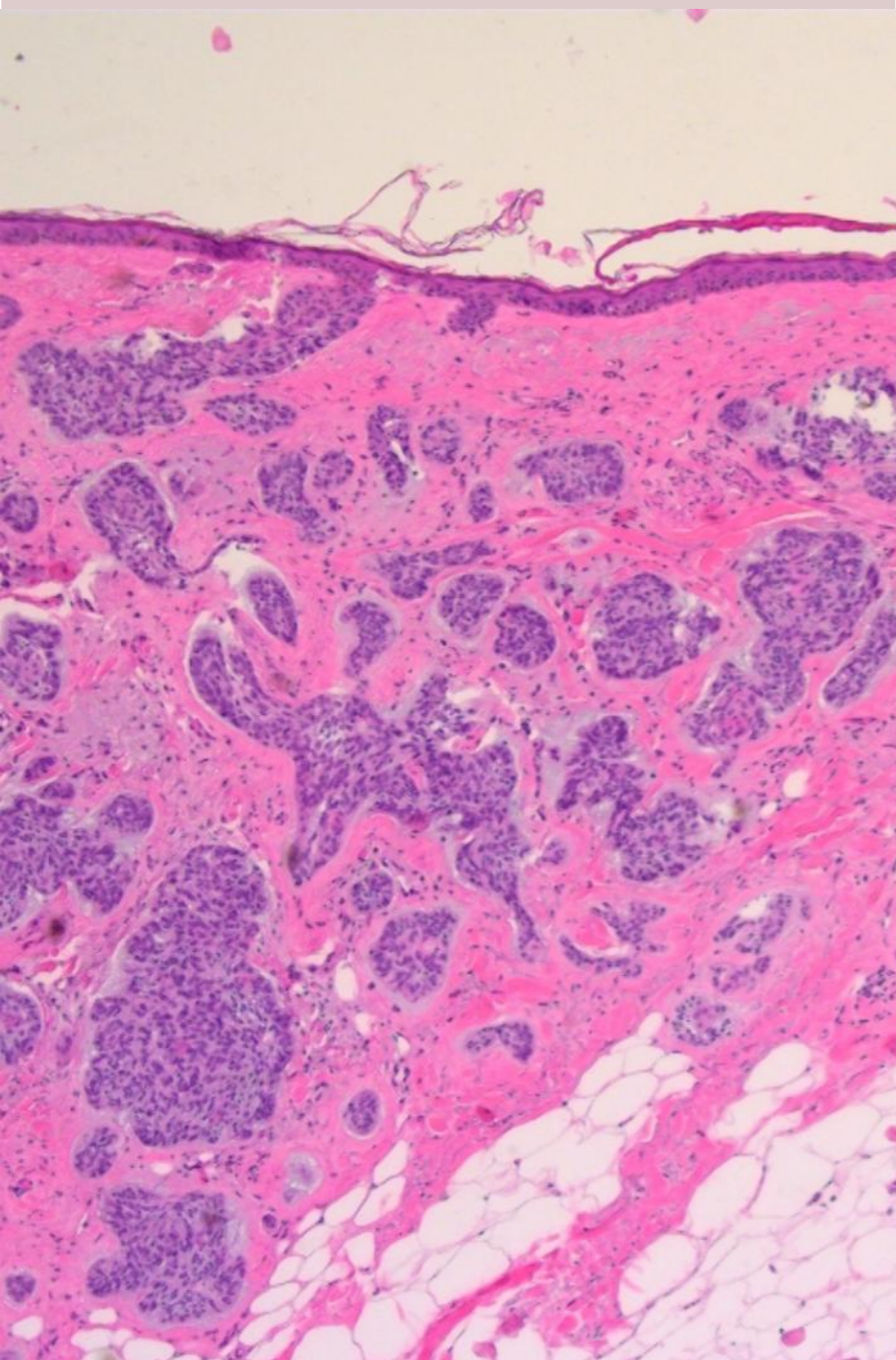
**Transition step in evolution from nodular to aggressive growth BCC.**



## Infiltrative

Basal Cells - +++

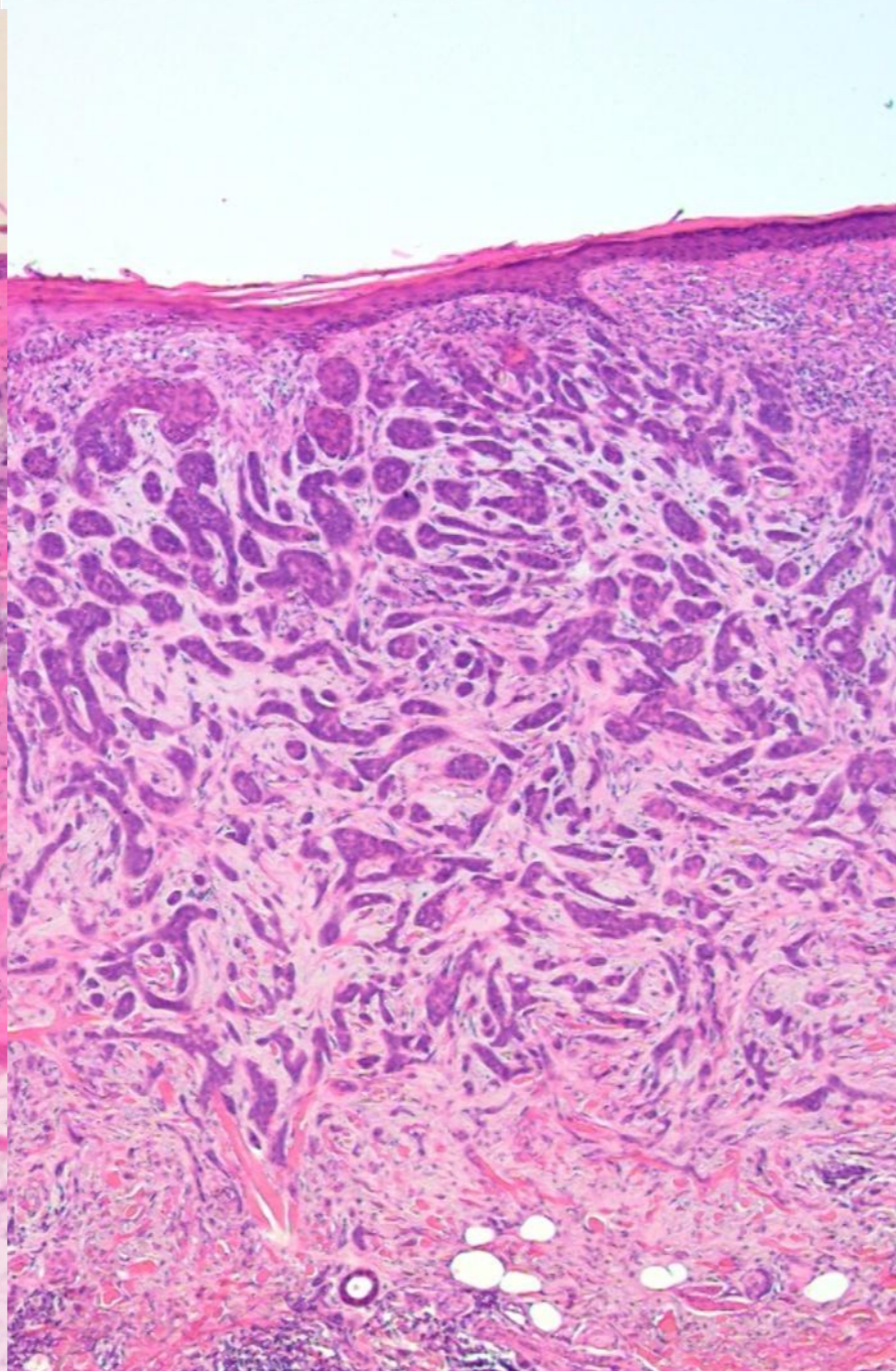
Fibrocytes - +



## Fibrosing

Basal Cells - ++

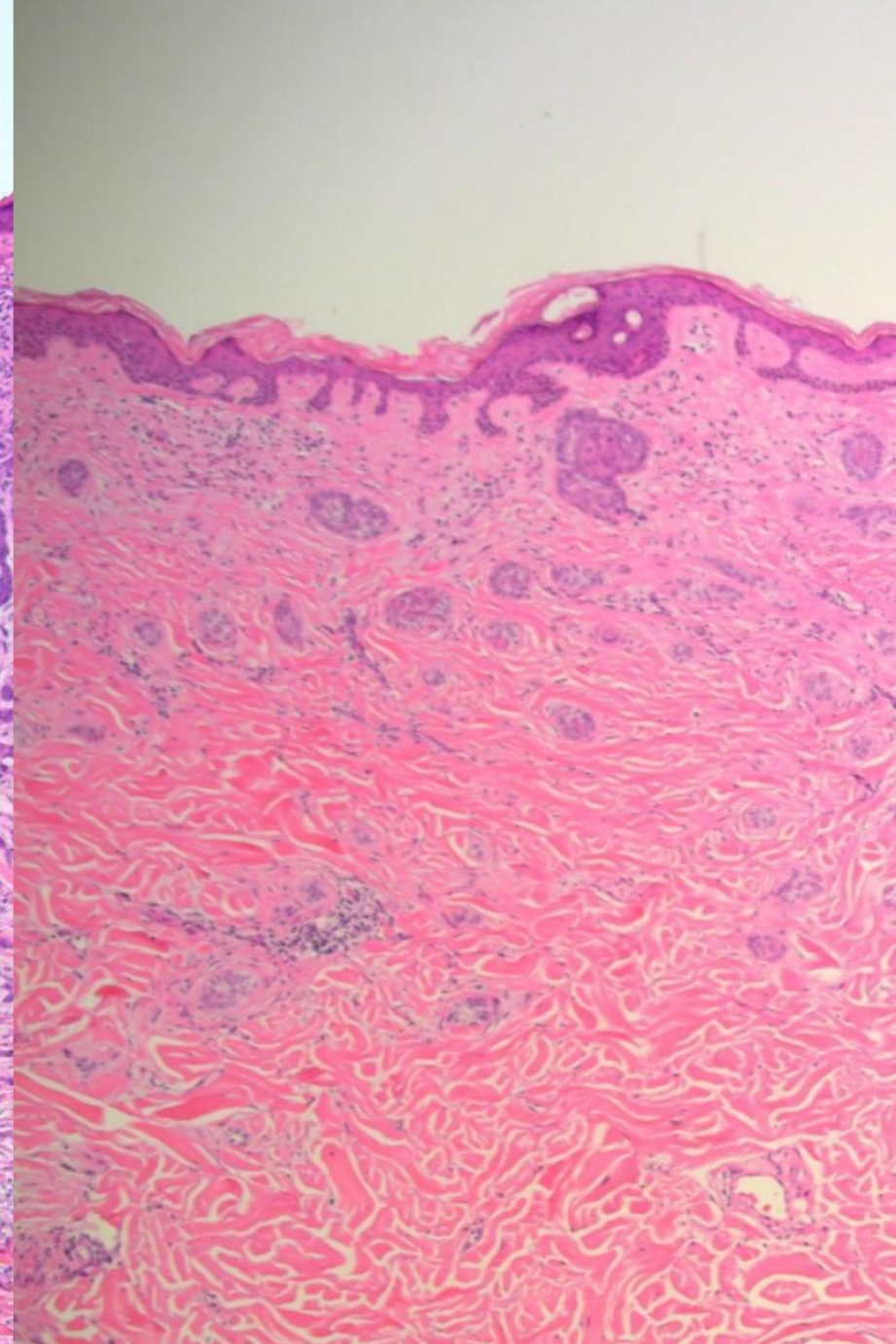
Fibrocytes - ++



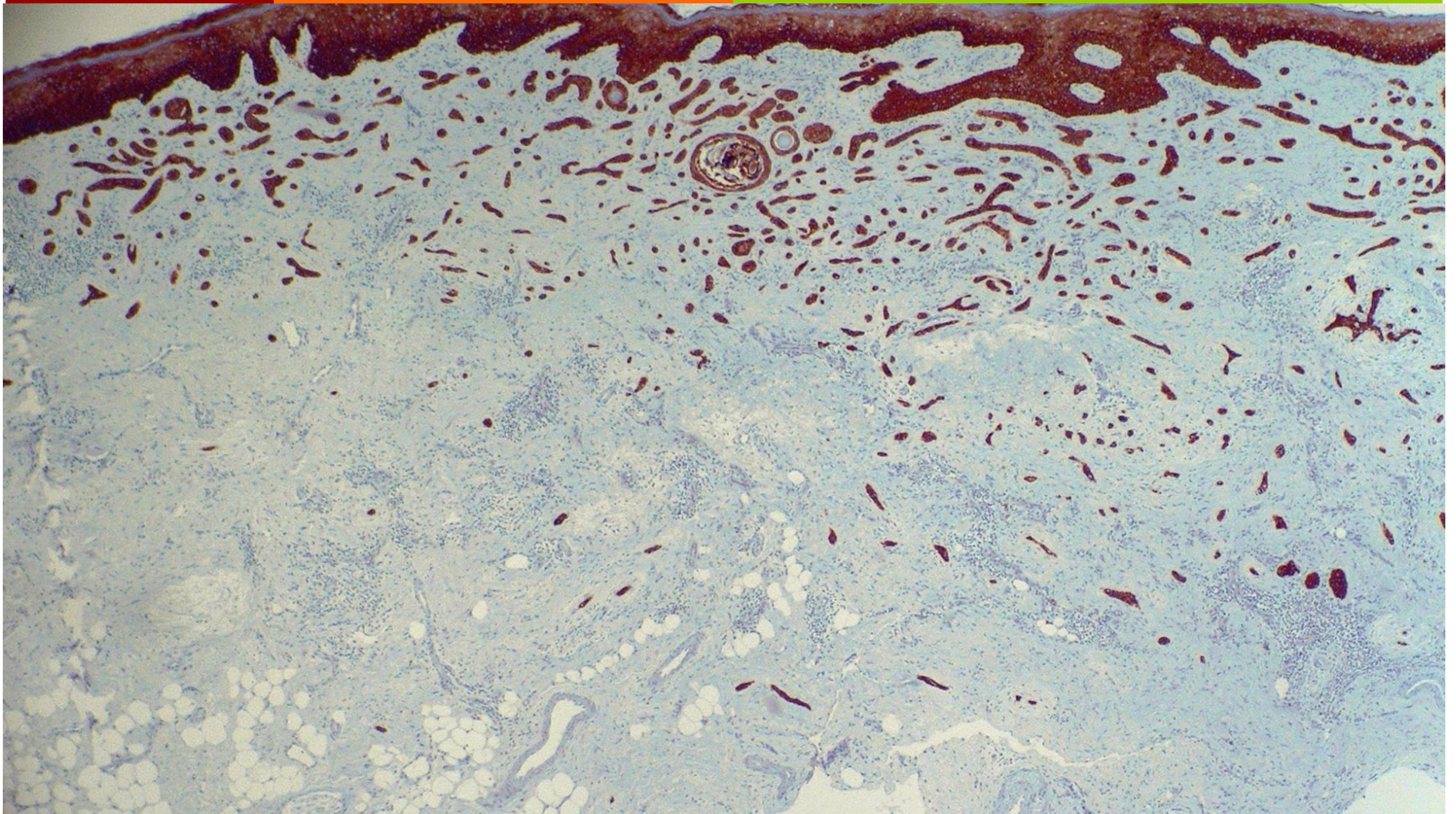
## Sclerosing

Basal Cells - +

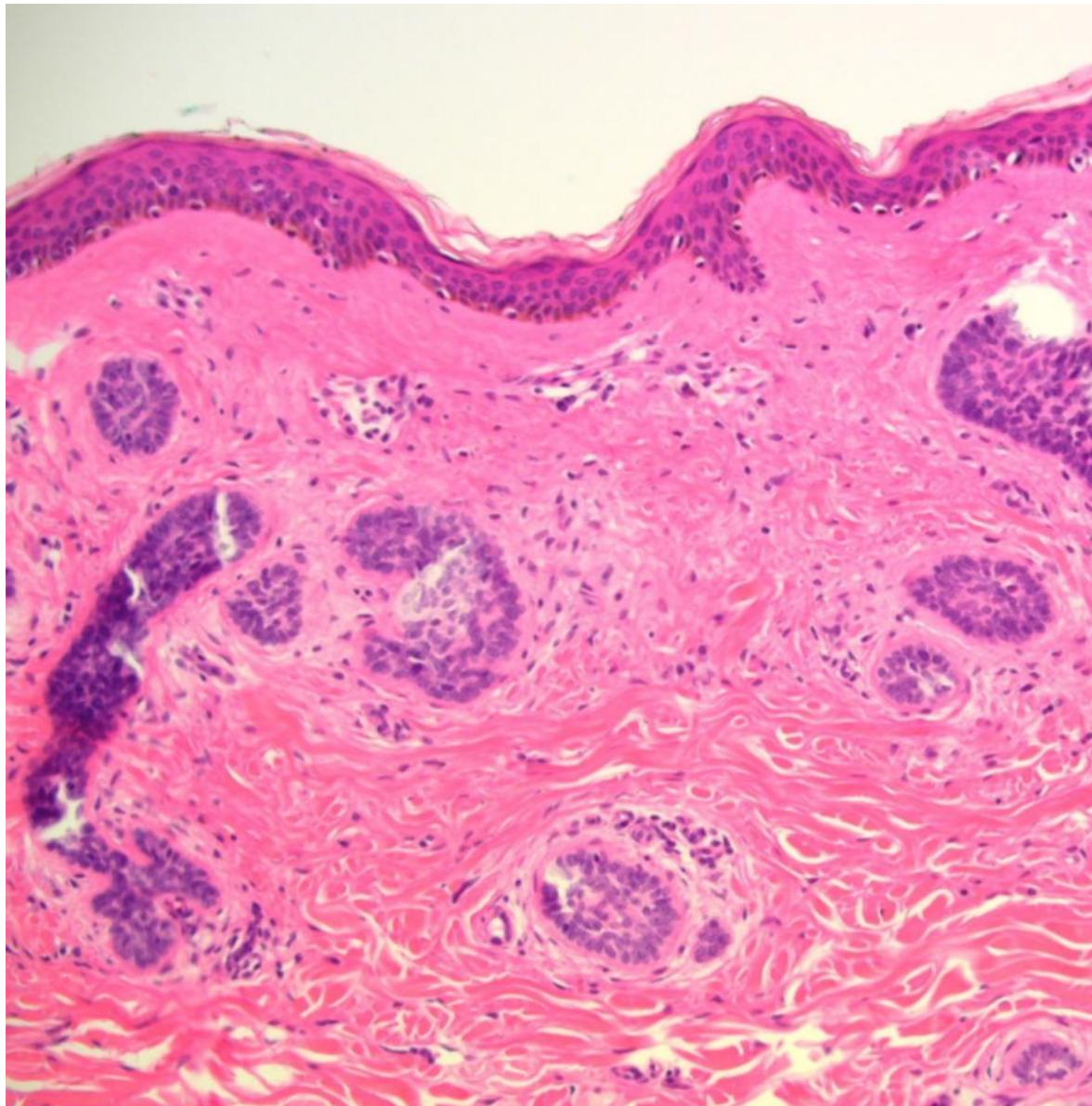
Fibrocytes - +++



# sclerosing BCC

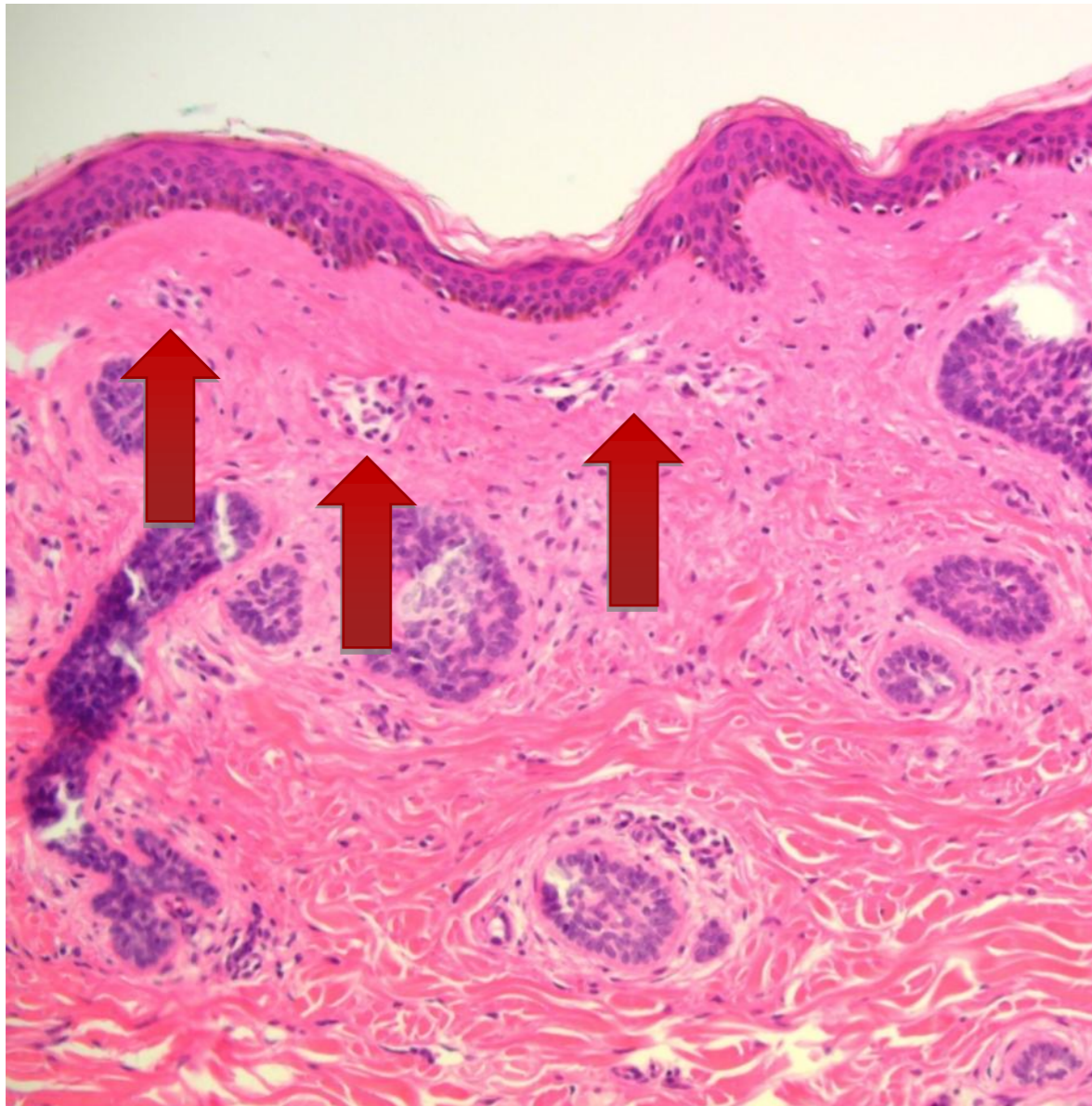


# Clarke Levels



- I – Intra-epidermal
- II – Dermal Invasion
- III – Papillary Dermis only
- IV – Reticular Dermis
- V – Sub-cutaneous

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➤ TREATMENT

➤ Surgical

➤ Aldara (Toll Receptors)

➤ PDT, Cx

➤ XRT

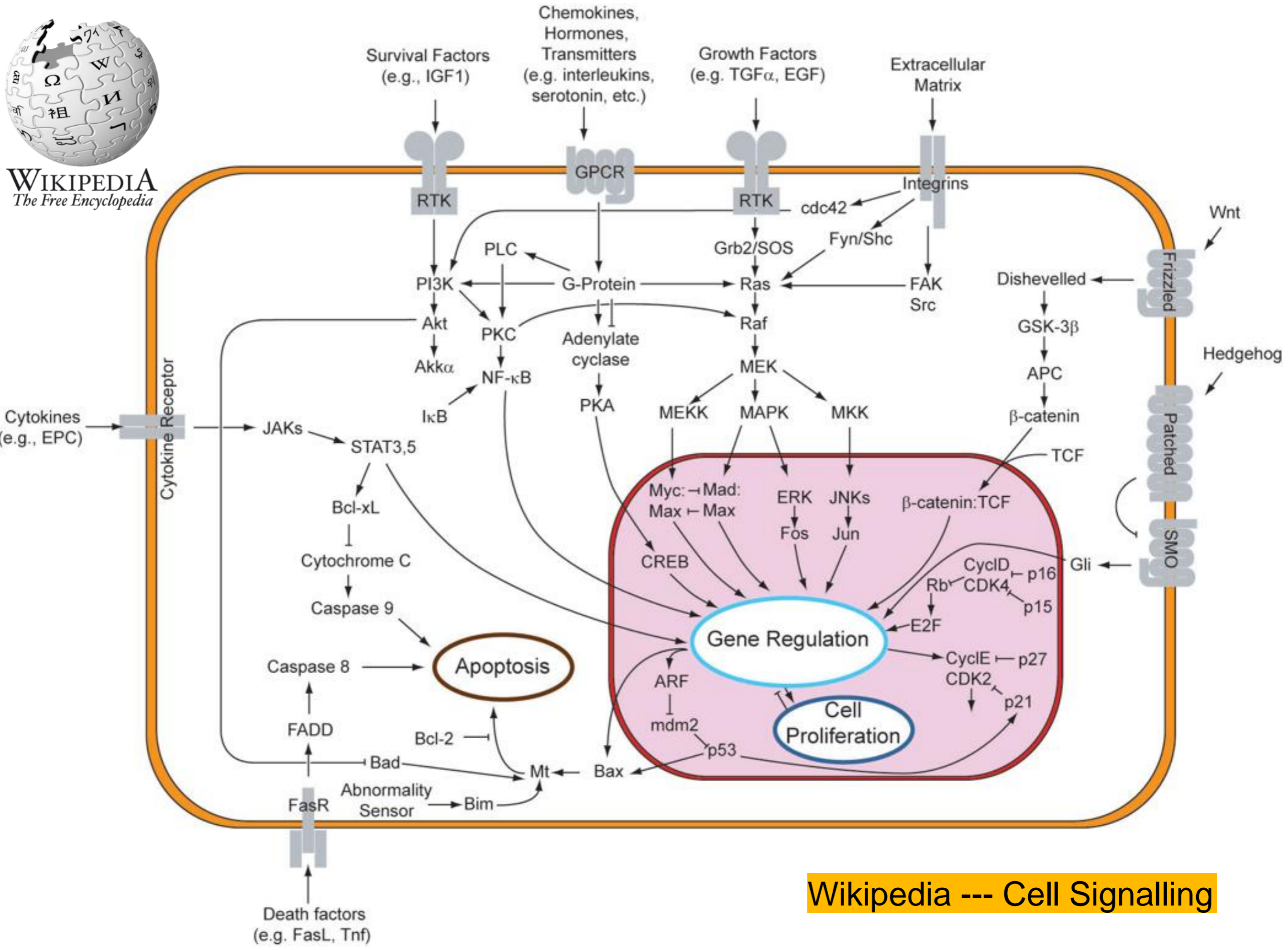
➤ Incomplete / RECURRENT

➤ Congenital – GORLIN'S Syndrome

- Keratin profile similar to the lower hair follicle
- ~50% of bcc's have p53 mutations
- telomerase activity important in pathogenesis of BCC
- PTCH1 gene mutations, codes for **Hedgehog Receptor**, plasma membrane sterol pump, **SMO Smoothened**, GLI
- SOX9 expressed in all BCC's, adnexal ca's
- BMI-1 epigenetic silencer upregulated by Sonic Hedgehog pathway
- DNA mismatch repair (MMR) proteins



WIKIPEDIA  
The Free Encyclopedia



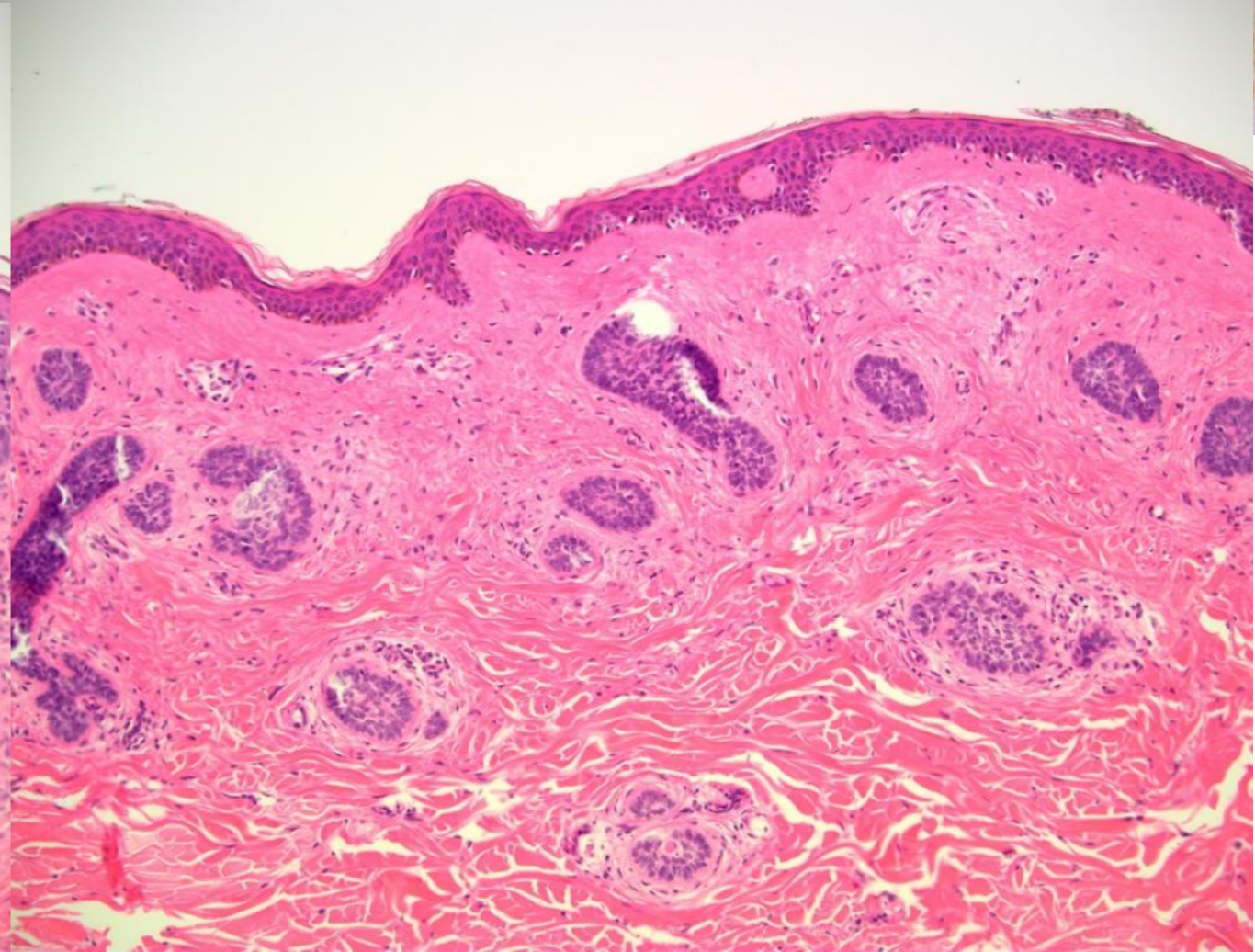
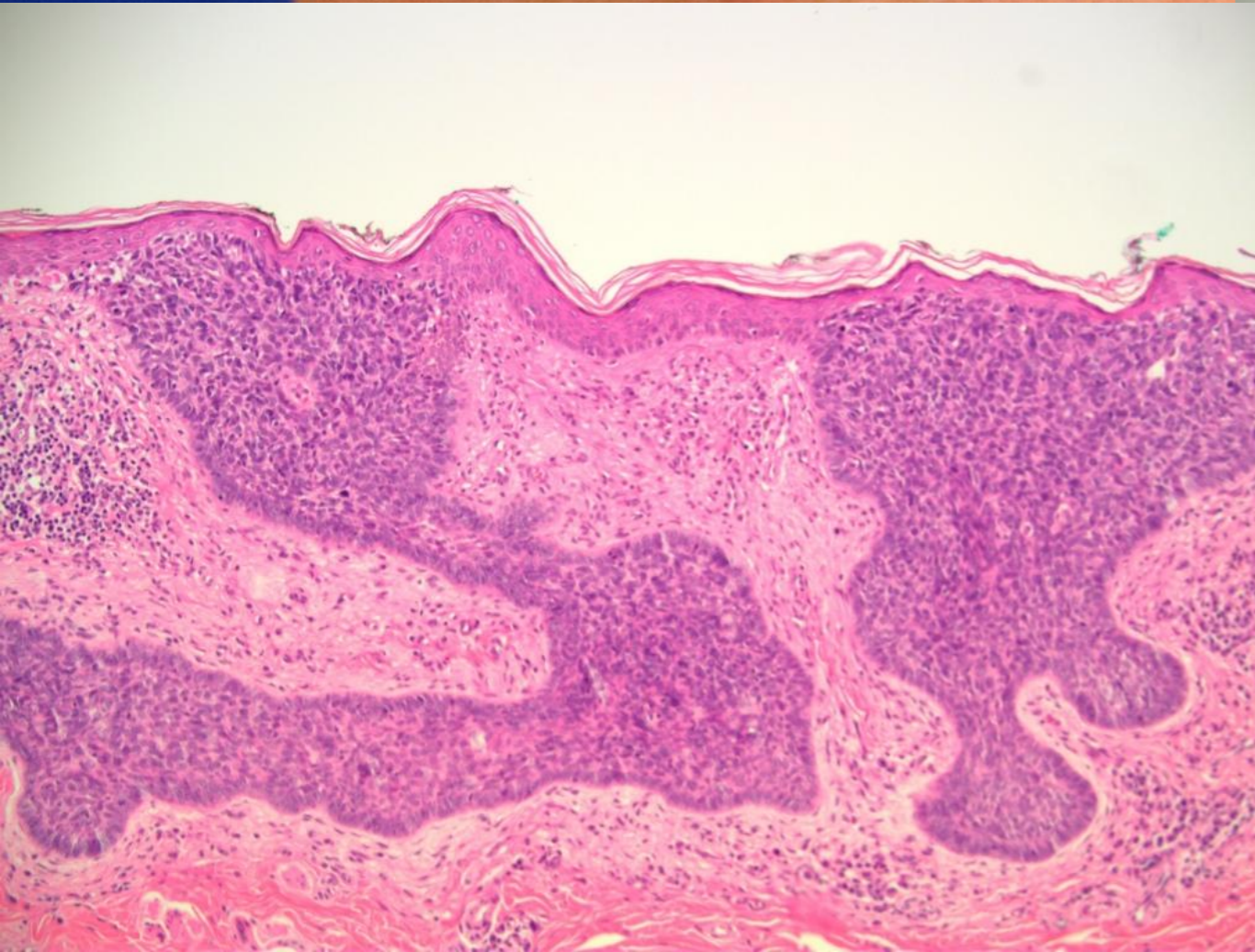


# Clinical aspects

- Pearly pink papule with telangiectasia, rolled border
- Irregular red scaly plaque, ? skin line loss
  - Depressed scariform plaque
  - Ulceration / crusting
- Sun exposed areas in fair skin individuals
- 80% on the head & neck – women 75% central nasal pyramid
- [Aetiology](#): intermittent UVB, age, radiotherapy, trauma-scar, immunosuppression, HPV infection, isolated limb perfusion (mm), arsenic



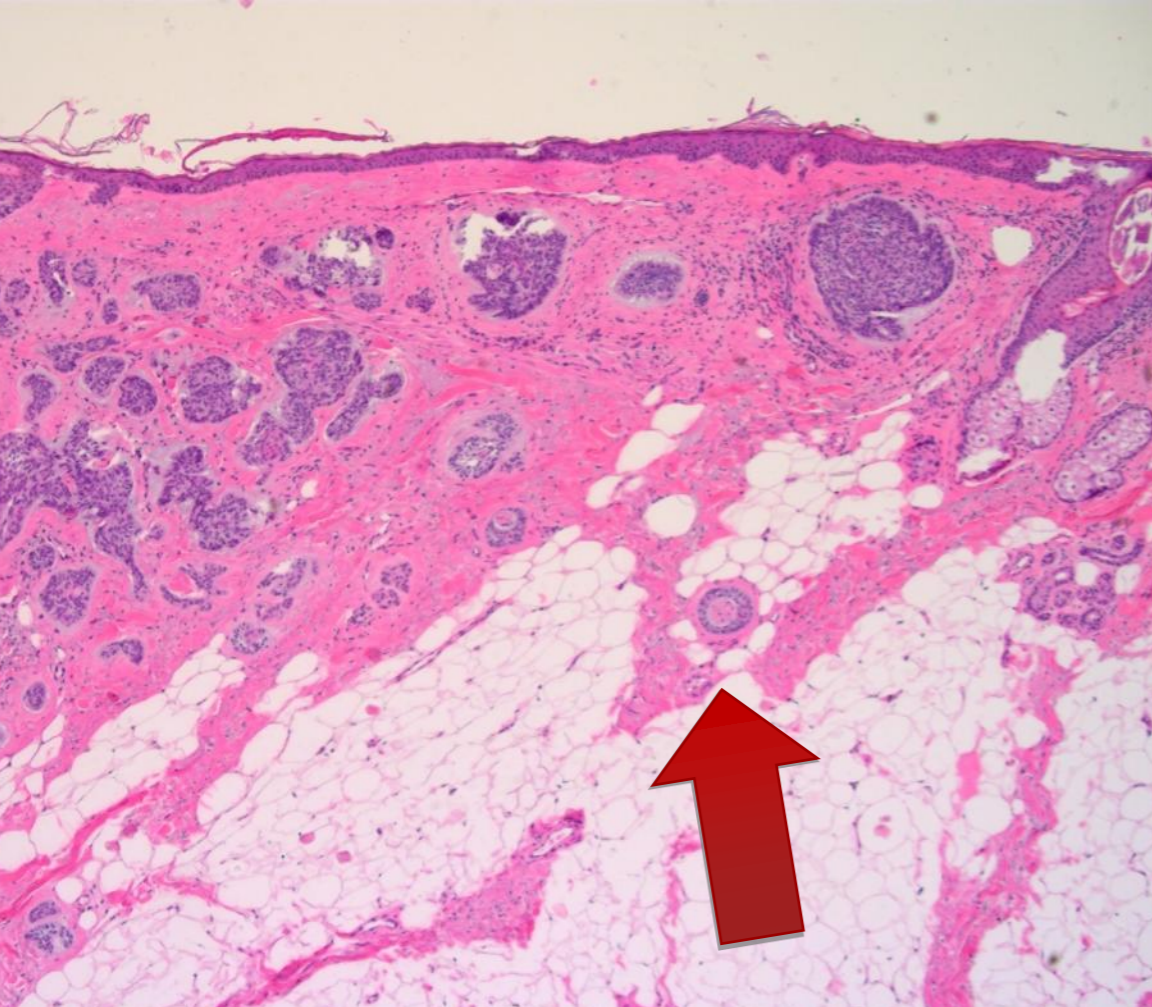




# giant BCC

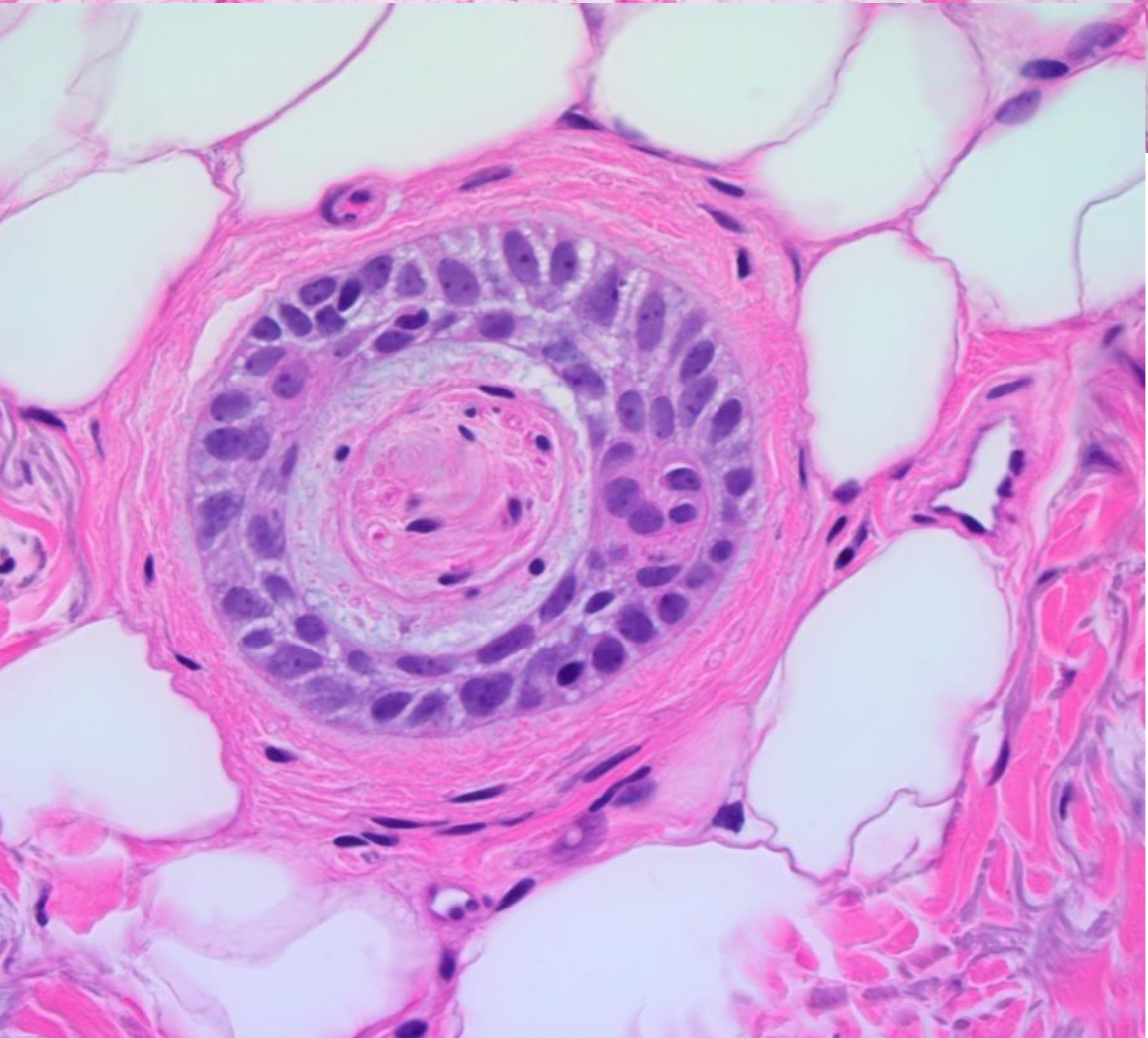


- > 5cm diameter
- micronodular or morphoeic
- deeply invasive
- non-sun exposed areas internationally
- “neglected” BCC’s ?
- higher incidence mets



# perineural infiltration

- **DEFINITION** : presence of tumour adjacent to or along a nerve in the extra-tumour tissue
- Associated with invasive / advanced BCC's
  - 1% of BCC's, <10% of infiltrating, sclerosing types
- There are no therapeutic trials for **management** of Perineural Infiltration
- **Radiation Therapy** +/- surgery is the treatment of choice
- Disregard small **intra-tumoural** foci of perineural Infiltration if good tumour clearance



# differential diagnosis

- Solar keratosis, solar elastosis
- Bowen's, SCC in-situ, IEC – intra-epidermal carcinoma
- SCC, Amelanotic Melanoma
- Trichoepithelioma
- Chronic inflammation + scar
- Solar elastosis
- Sebaceous [glandular] hyperplasia
- Naevus

- Merkel Cell Carcinoma
- Granuloma [pyogenic]
- Fungal / Dermatological
- Scleroderma
- Neurofibromatosis
- Lymphoma
- Pilomatrixoma

# trichoepithelioma

- DEFINITION : benign adnexal neoplasm mostly on the face. The tumour cells form rudimentary hair follicles but not actual hair shafts. PD hamartomas of hair germ
- Single, multiple, desmoplastic
- Small firm rounded shiny nodules



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➤ **TREATMENT**

➤ **Surgery**

➤ Aldara (Toll Receptors)

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➤ XRT

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➤ Mark out under magnification

➤ Margins :

➤ 2mm solid

➤ 4mm superficial

➤ 4-6mm infiltrating

➤ 8-10cm scleroderma

➤ Recurrent – wider again

➤ Care – extra depth in lateral nasal & post-auricular creases

➤ **TREATMENT**

➤ Surgical

➤ Aldara ( Toll Receptors )

➤ PDT, Cx, C&C, Diclofenac

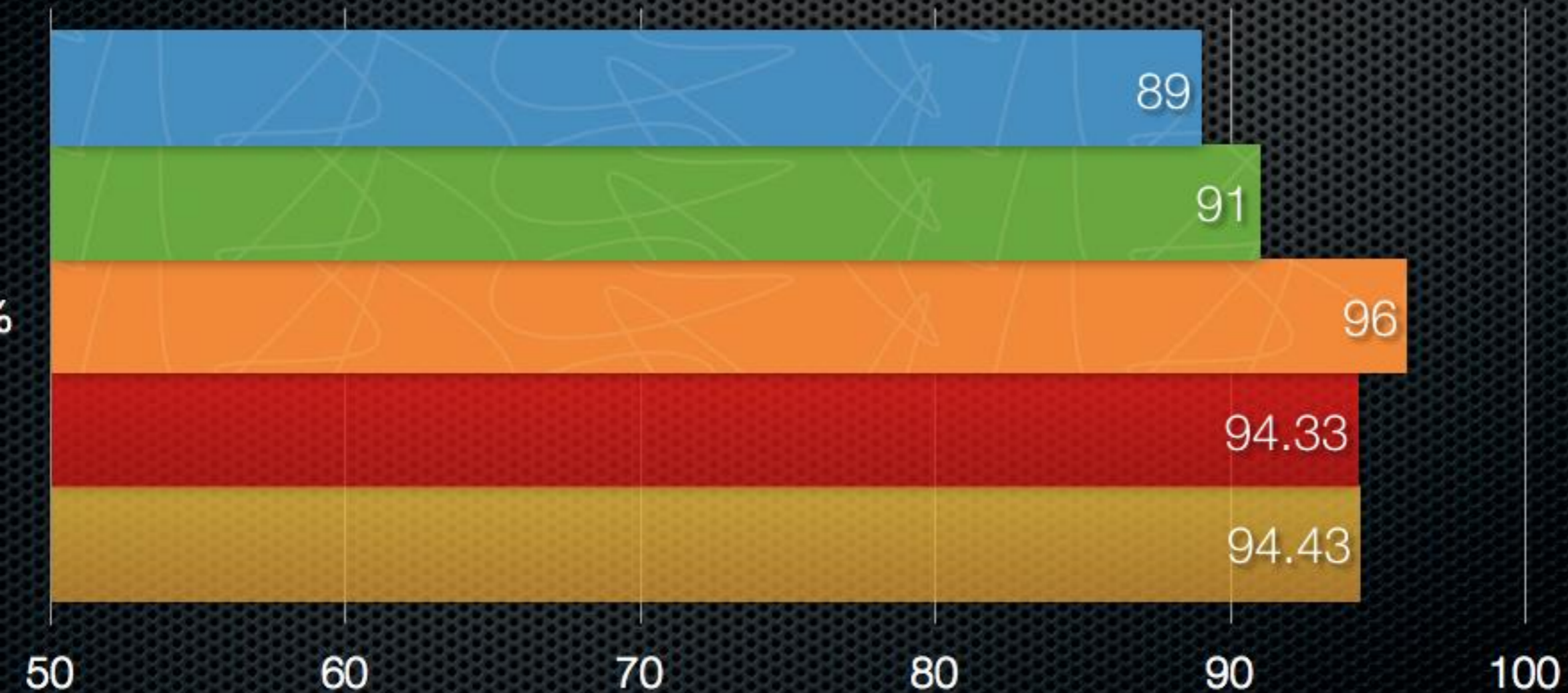
➤ XRT

➤ **Incomplete / RECURRENT**

➤ Congenital – GORLIN'S Syndrome

# BCC % clearance - plastics unit

Jul 2009   Jan 2010   Jul 2010   Jan 2011   Jul 2011

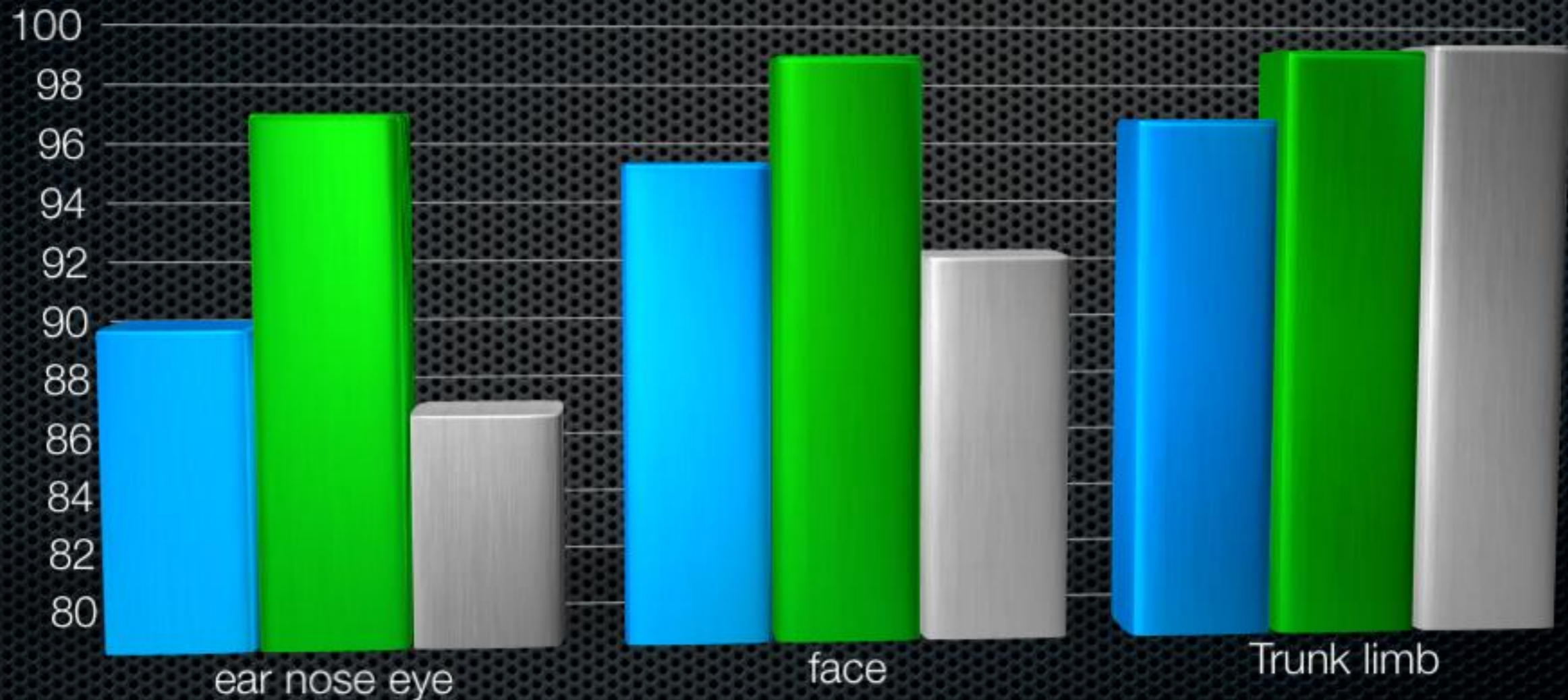




# Regional clearance rates

July - December 2011

BCC SCC IEC



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# Incomplete excision

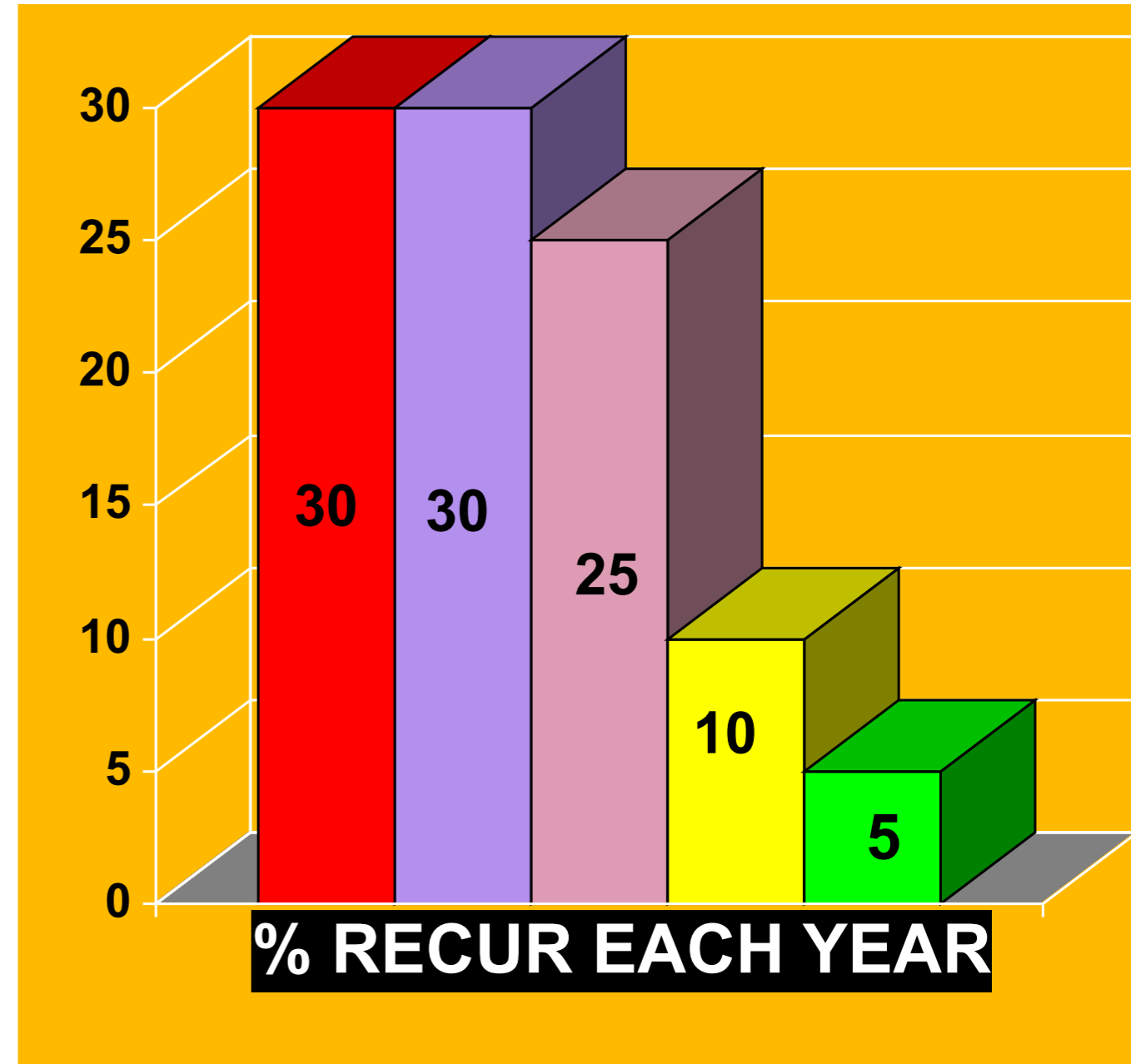
## 2008 Australian Cancer Network – NMSC management :

➤ Incompletely resected BCC's are defined as histologically incompletely or inadequately excised BCC

➤? re-excision / xrt / observation

➤ Recurrence rate after excision with involved margin averages 38% ( deep margins recur x2 lateral margin )

➤ "it is *prudent* to recommend that patients with persistent disease should undergo histologically complete re-excision"



# *(surgically)* .. Recurrent BCC

- Item 31295 – 30% Head & Neck BCC's removed in Qld
  - *1 in 30 BCC's excised in Medicare are classified recurrent*
  - *Dermatological studies on recurrence exclude M/F superficial BCC*
- Decreased Cure Rate with *(surgically)* recurrent BCC
- Recurrences :
  - ***Simple***
  - ***Complex***
  - ***Catastrophic***
- Prevention



# Complex Recurrent BCC

## ➤ **COMPLEX** Recurrent BCC

- 2<sup>nd</sup> or more infiltrative tumour recurrences
- Prior XRT
- Nose/ canthus / eyelid / lip

## ➤ TOOLS :

- Magnified examination
- Wide inked margins
- Pre-op biopsies
- Margin controlled frozen section



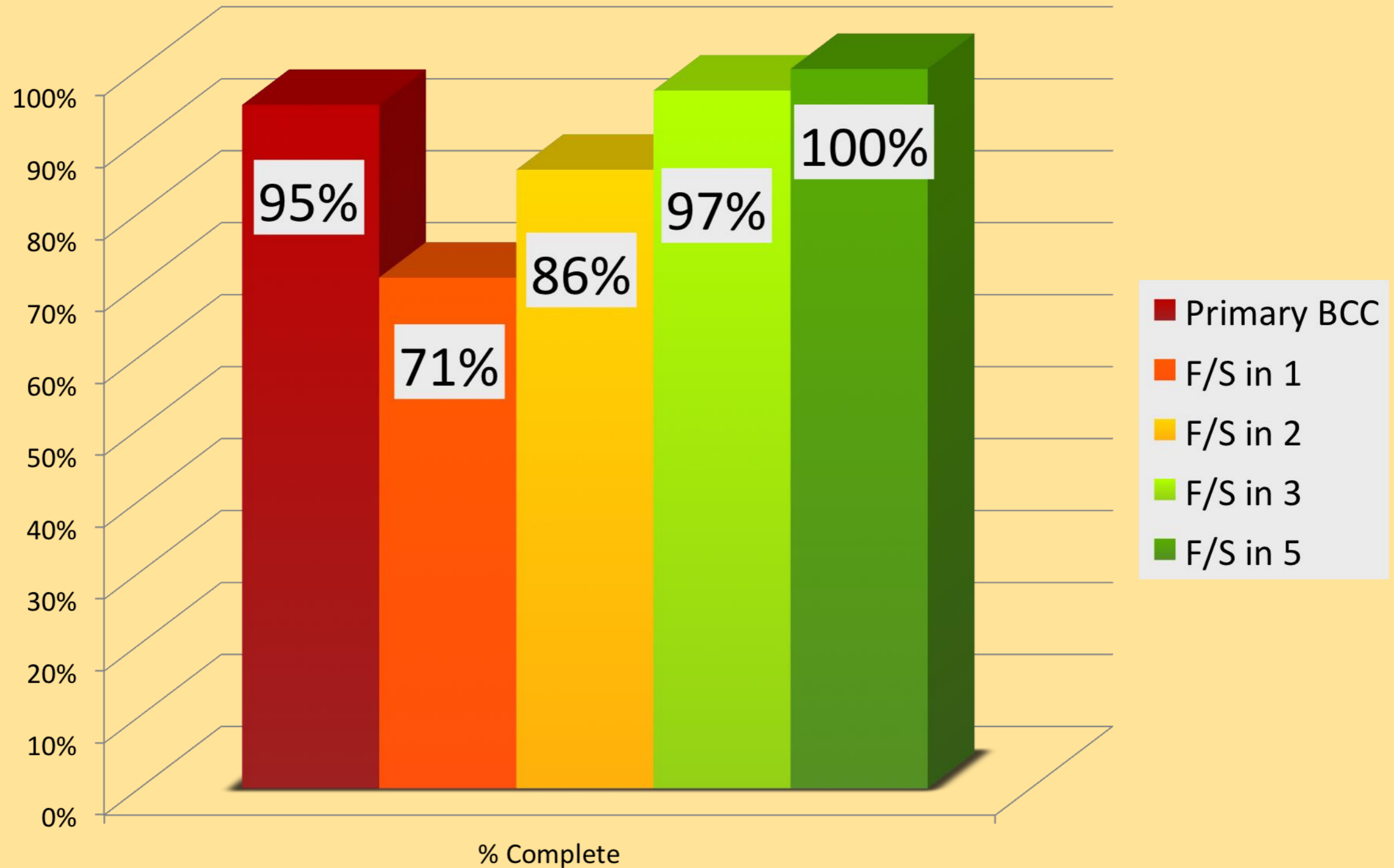
# *surgically* .. Recurrent BCC

## Peripheral In-Continuity Tissue Examination

Hagerty, Richard C.; Worsham, G. Frederick Jr.; Rutland, Eugene D. Jr.; Hagerty, Robert F.

**Plastic & Reconstructive Surgery.** 83(3):539-545, March 1989.

# F/S in recurrent / difficult BCC



# Catastrophic Recurrent BCC

## ➤ **CATASTROPHIC** Recurrent BCC

- Multiply recurrent
- Extreme size, depth, or invasion
- Vital site

## ➤ TOOLS :

- Radical approach
- Time and thoroughness
- Multiple Frozen Section
- Adjuvant Radiotherapy

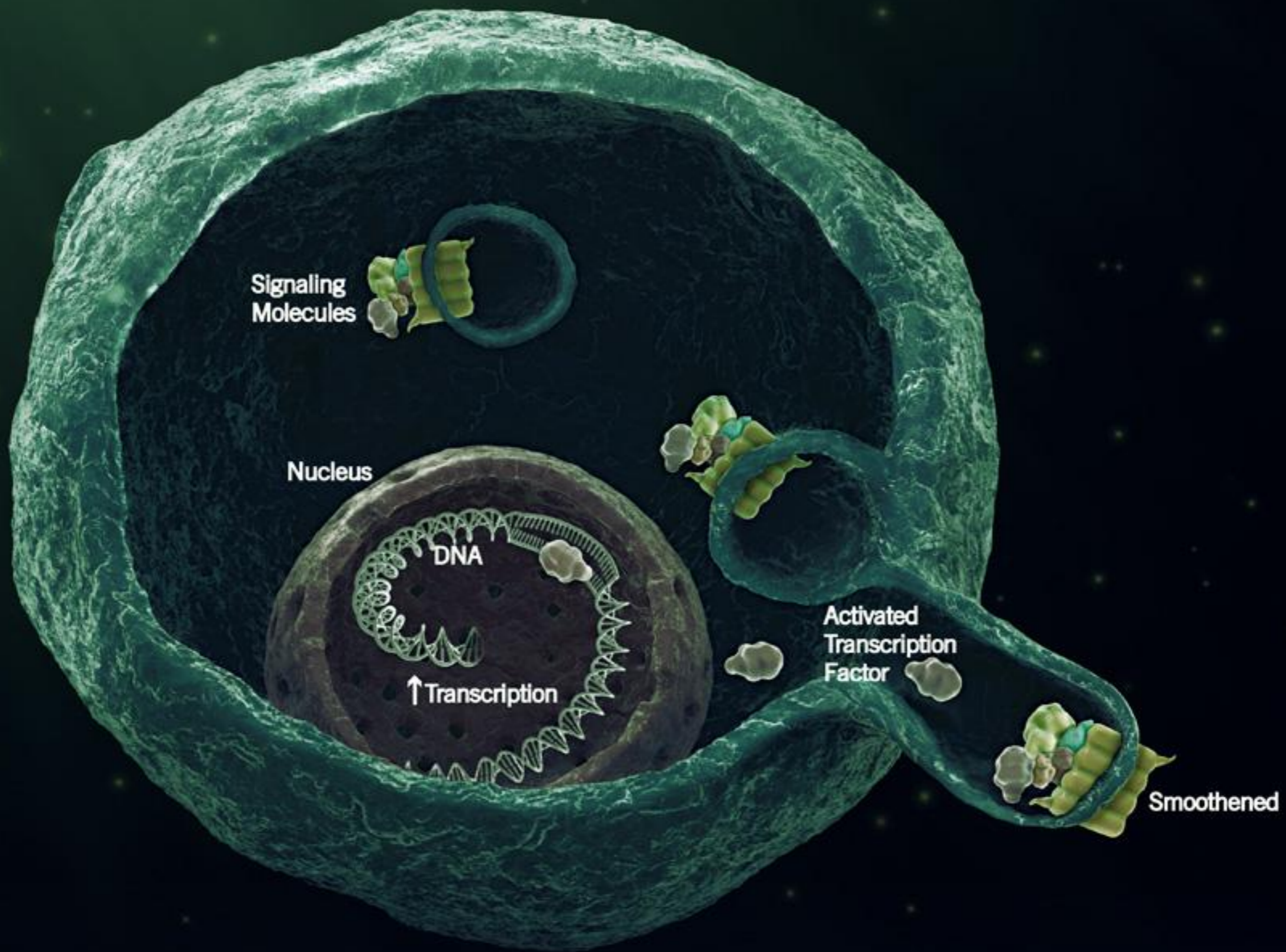


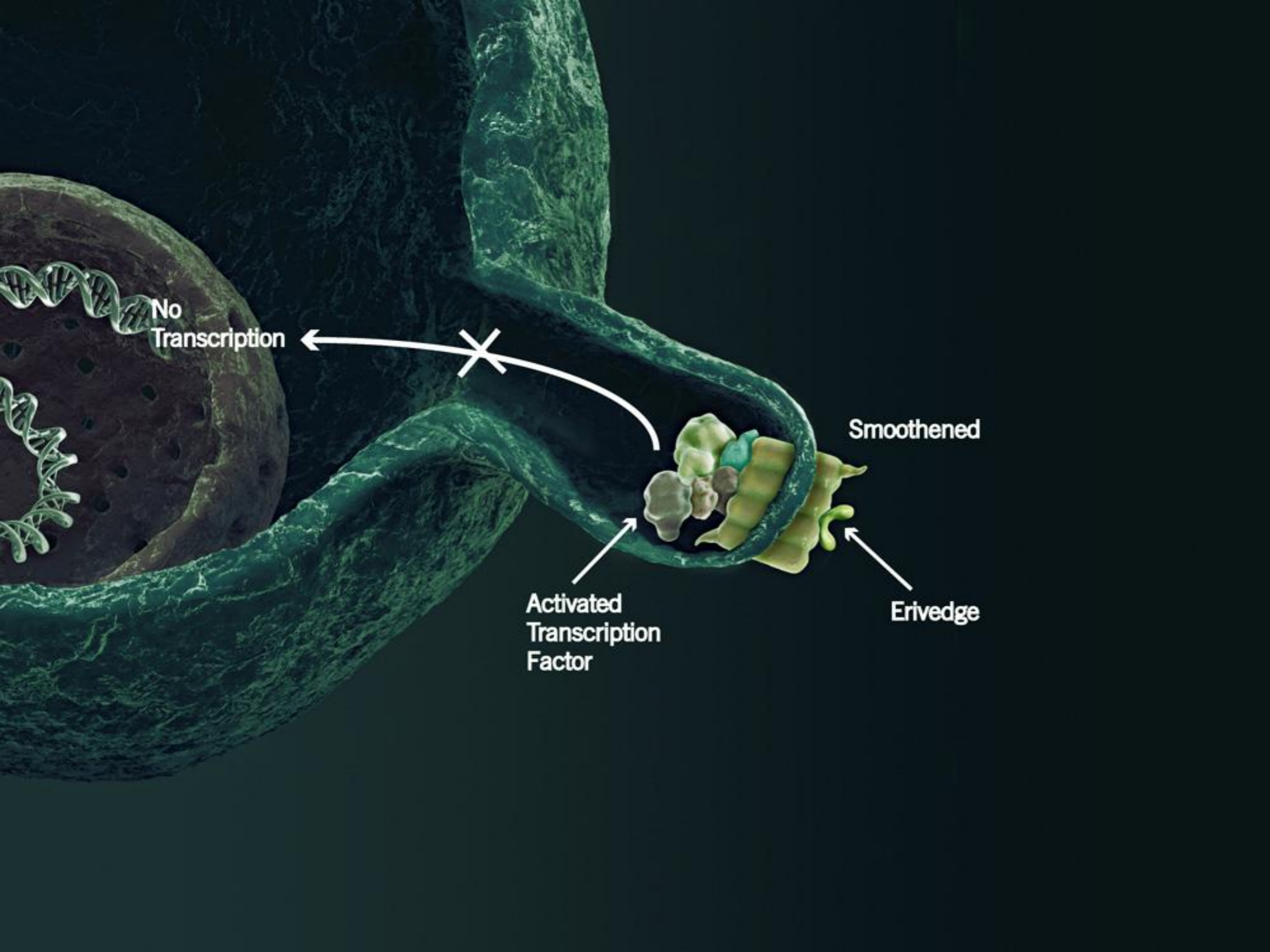




# Erivedge ~ Vismodegib

- Hedgehog pathway inhibitor - Genentech, Roche
- Jan 2012 FDA approval - 150 mgs daily
- competitive inhibition of **SMO receptor**, downstream of PTCH1, >90%. BCC's pathway
- Takes the place of a working PTCH1 protein
- local advanced or metastatic BCC
- Phase III with 104 patients, 43% objective response rate in **locally advanced BCC**, 30% in **BCC metastases**. Median duration effect of **7.6 months**
- Phase II currently in people with operable BCC
- **ETRACONAZOLE** – Second current trial drug – *antifungal which inhibits the synthesis of ERGOSTEROL - the intermediate molecule between PTCH1 and SMO pathway - can cause skin SCC*





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# Gorlin's syndrome – Naevoid Basal Cell Carcinoma Syndrome

- autosomal dominant, high penetrance genetic mutation
- PTCH1 --- chromosome 9q22.3
- PTCH2 --- chromosome 1
- 90% Gorlin's syndrome patients have bcc's by 40
- predilection for sun exposed skin
- Defective response to xrt, bcc's at xrt sites
- odontogenic keratocysts, palmar /sole pits, cutaneous cysts, enlarged calvaria, hypertelorism, (*lipomas, renal agenesis, ovarian cysts, medulloblastomas, salivary gland ACC,*)

# Gorlins





# Aldara

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# Aldara in Superficial BCC

Quirk, Gebauer, De Ambrosis, Owens, Hawkinson --- 2003 **Australia**

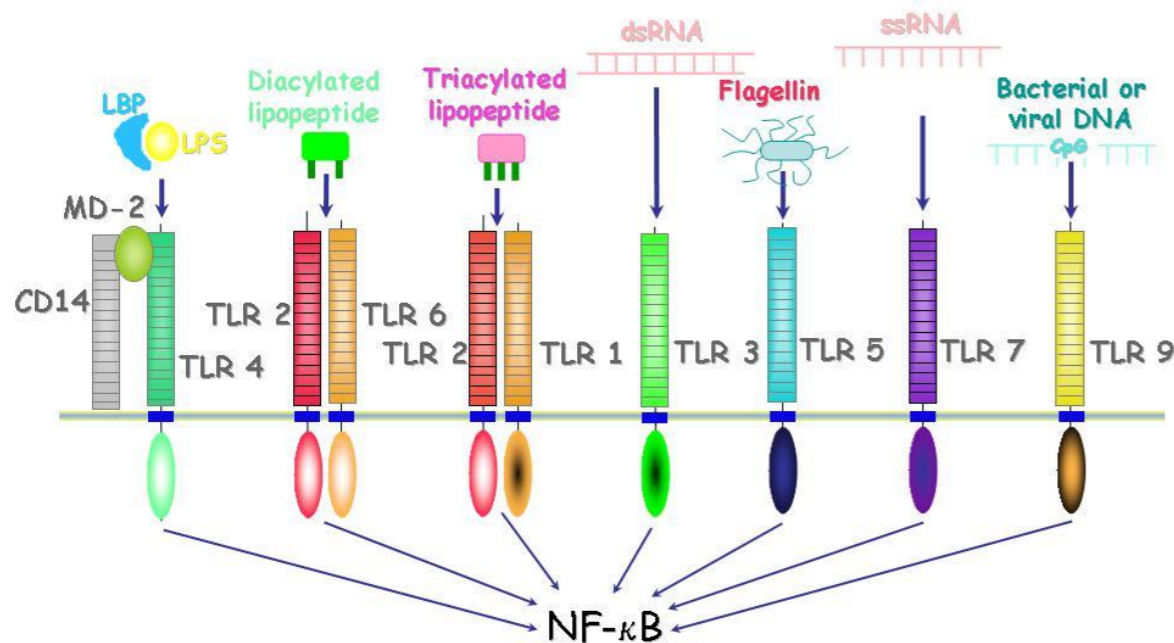


- ➔ 159 / 169 ( **94%** ) of subjects had no **clinical** evidence of sBCC at the target site at the **12-week** post-treatment assessment.
- ➔ **50%** of patients had treatment interrupted for a week to allow skin reactions to settle.



# TLR's ..... Toll Like Receptors

## Activation of TLRs by microbial molecules



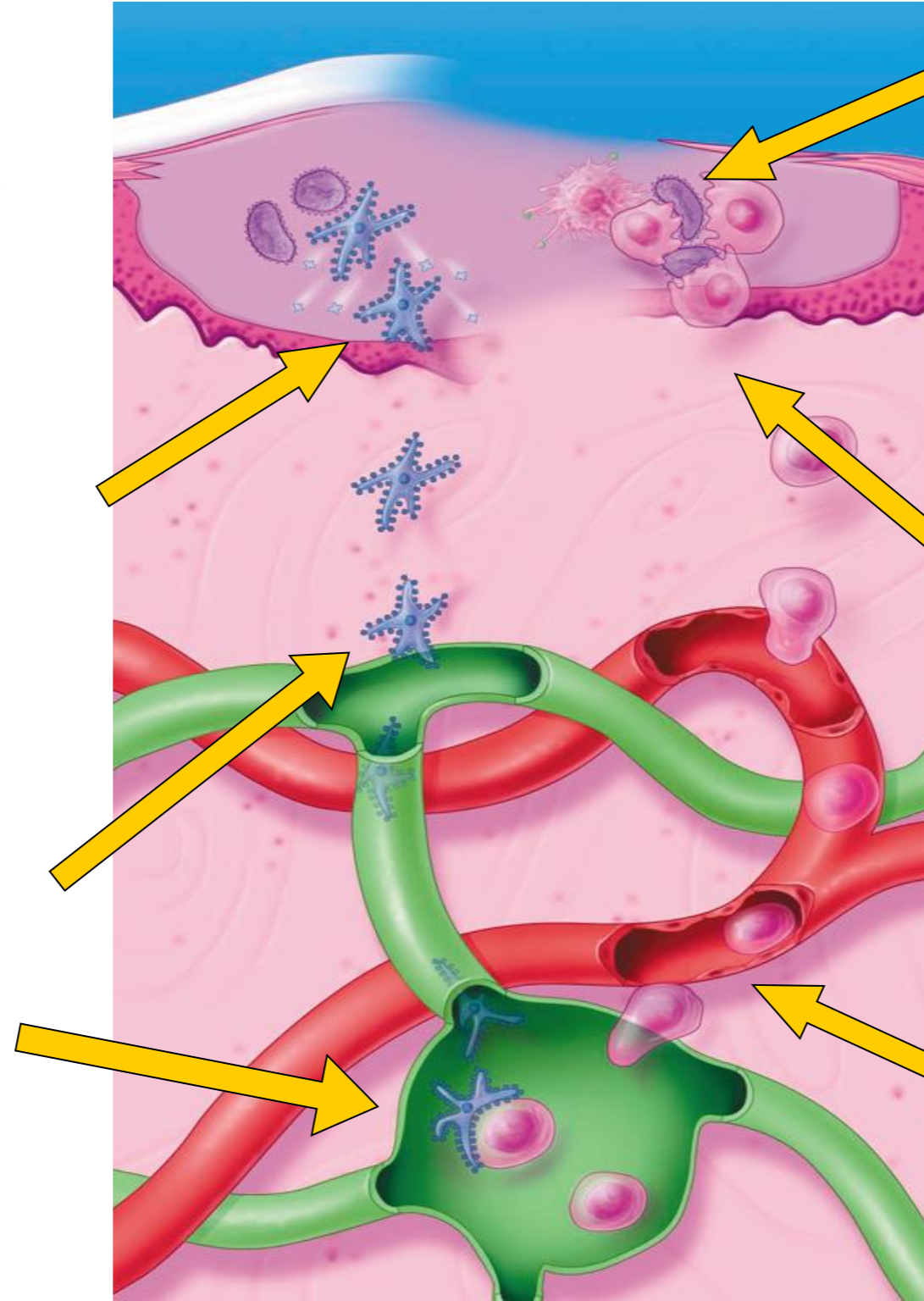
- Aldara binds to **TLR 7 & 8**
- TLR's are a family of 10 transmembrane proteins receptors named **TLR 1-10**
- TLR's recognize common molecule patterns produced by invading pathogens ... *pattern recognition*
- TLR's are found in abundance on **dendritic cells**
- TLR binding **activates** a dendritic cell's immune action
- also found scattered on keratinocytes

# mechanism of action of Aldara

1. Aldara cream applied to tumour area

2. Immature Dendritic Cells **activated** through Toll Like Receptors TLR-7

3. Dendritic Cells mature as they travel to the lymph node and **present** tumour antigen to T-cells



6. T-cells **activated** at site by residual activated Dendritic Cells

5. Cytotoxic T-cells travel to the tumour to kill cancer cells

4. Tumour – specific T-cells enter the blood stream



# Aldara in sBCC Rx

To help you and your doctor monitor your treatment, place a tick for each night you apply Aldara. If you have any concerns about redness of the treatment area, see your doctor who may advise you stop treatment for a few days.

*Daily (Mon to Friday)*

Monitoring your treatment

	M	T	W	T	F	S	S
13/4 Week 1	✓	✓	✓	✓	✓		
25/4 Week 2	✓	✓	✓	✓	✓		
2/5 Week 3	✓	✓	✓	✓	✓		
9/5 Week 4	✓	✓	—				
16/5 Week 5	✓	—	✓	—	✓		
23/5 Week 6	✓	—	✓	—	✓		

It is important to visit your doctor for skin checks as they recommend.

*WASH YOUR HANDS CARE OF BUBBLES \* STOP CREAM & BUBBLES IF SEVERE CRUSTING*

This brochure is for patients who have been prescribed Aldara Cream for the treatment of superficial basal cell carcinoma.

**Aldara**  
(IMIQUMOD)

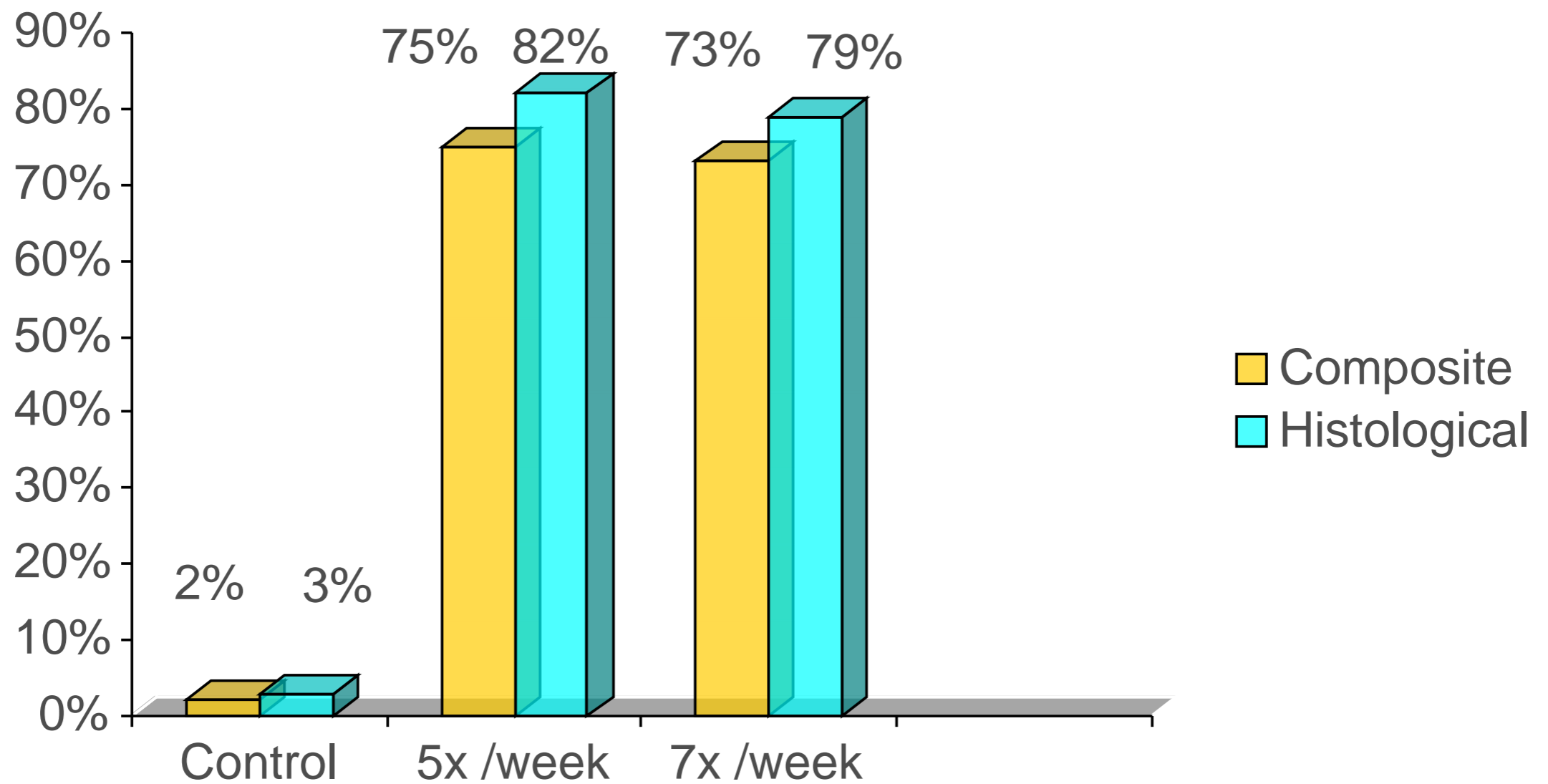
3:05 pm REFERRAL ON FILE

- Biopsy to confirm M/F **superficial BCC**
- Apply ALDARA Imiquimod once daily 5 days a week
- Review at 2 weeks
  - Marked Inflamm'n – rest period for 1 week
  - Flu-like reaction – rest period 1 week
  - No inflammation – increase to 7 days / week
- Continue treatment for 6 weeks from starting date
- Review 12 weeks post treatment

# Aldara in superficial BCC

Geisse et al; 2003 : Harvard USA

Response rate at 12 weeks



# Areas I have found useful

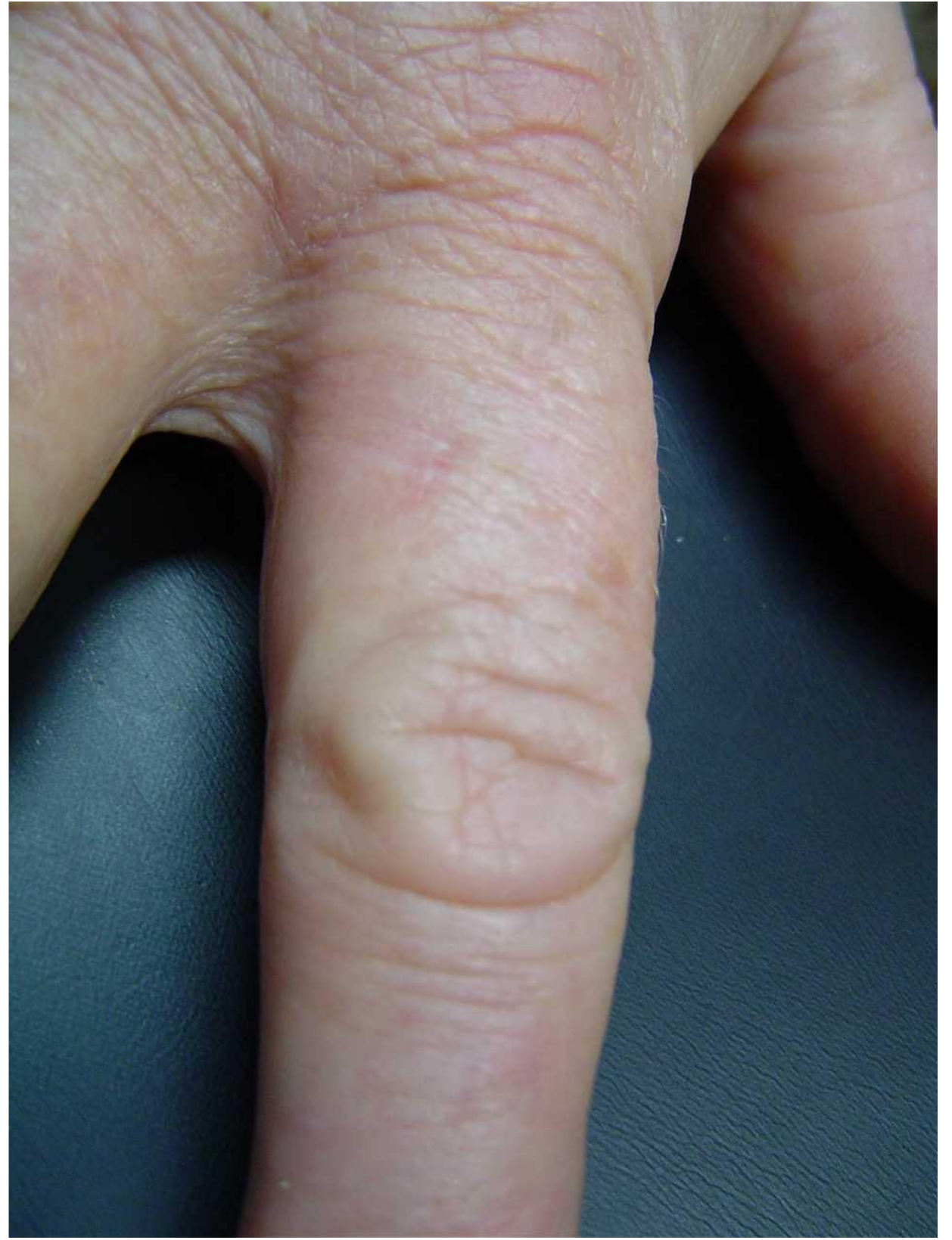
- “ Australian scarf ” area – chest
- IEC on fingers
- Lower legs on elderly
- Face
  - Multicentric multifocal BCC
    - Nose
    - Upper Lip ..... *caution !! ... contraindicated on mucosa*
    - Forehead
  - IEC on face
  - Actinic Keratoses
- Superficial BCC at edge of solid BCC excision
- Back --- multifocal BCC recurrence
- Scalp ( WEAK )



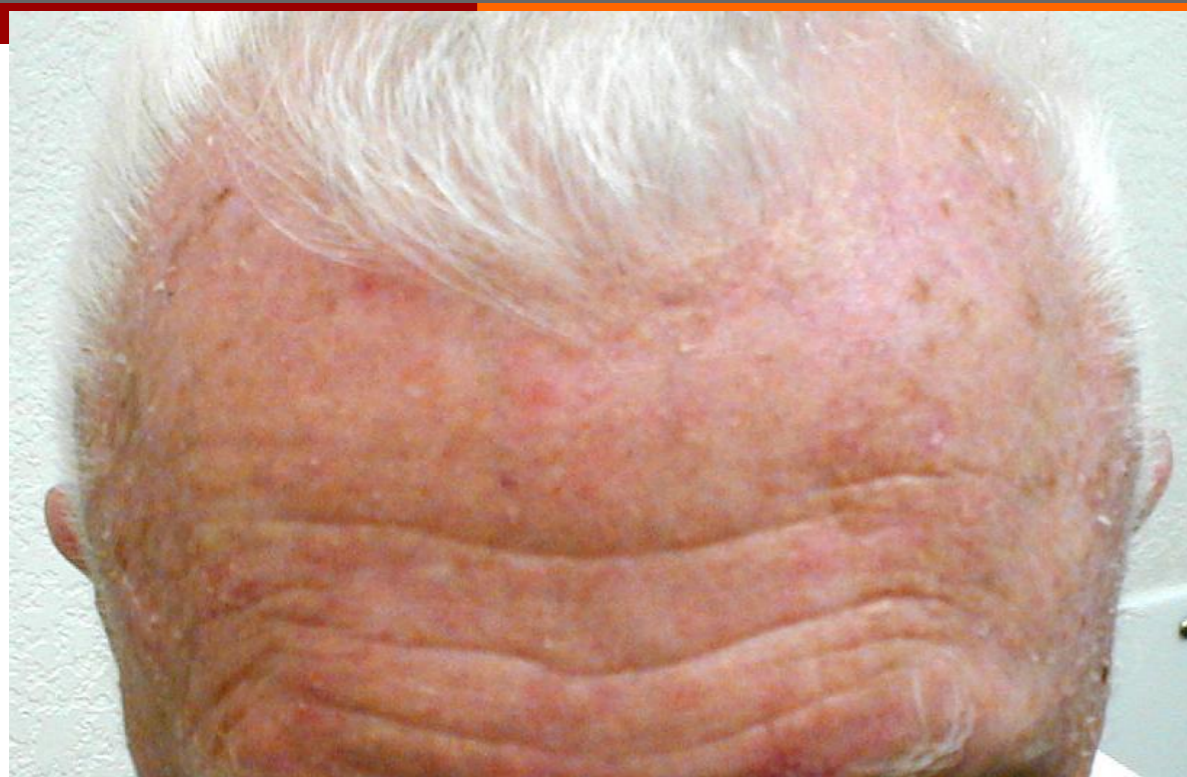








# Brisk Response



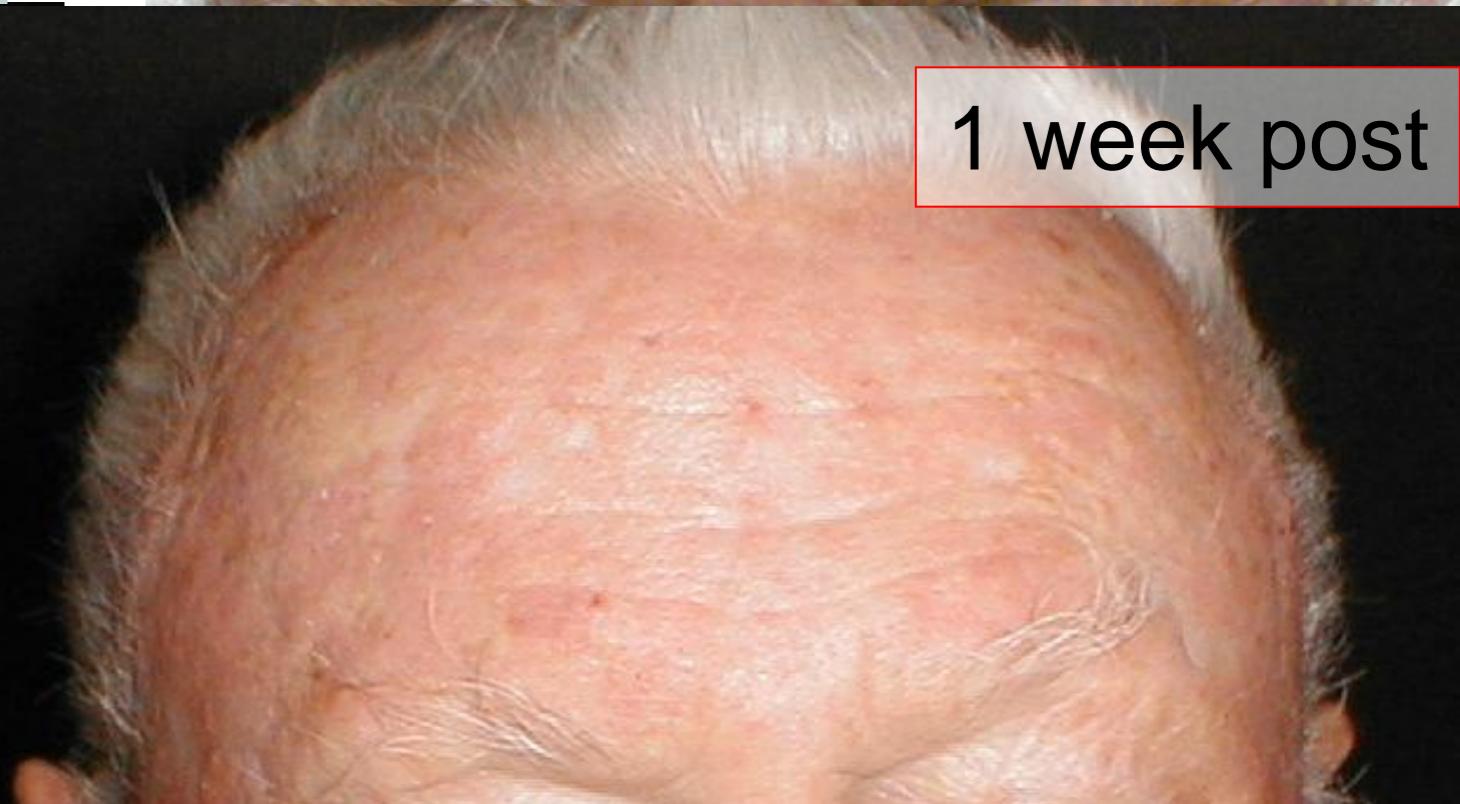
Week 2 – brisk reaction



Week 3 – therapy discontinued



1 week post



Normal inflammation at 2 weeks,  
Rest periods if severely inflamed,  
Avoid mucosal surfaces

# Shortcomings / problems experienced

- **Cost** \$ 150 / packet of 12
- **Time**
- **Follow up**
  - Necessary ..... May need Bx
- **Variable skin reaction**
  - Takes 2 weeks to come on
  - Can be **severe** in the elderly
  - Contraindicated on mucosa –  
**lips** eyelids
  - Skin Reaction in non-treated areas
- **“ Flu ” like symptoms**
- Cure **not proportional** to immune reaction
- **Poor efficacy in the multiple AK / SCC patient**  
or recent sun exposure

# XRT of BCC's

## ➤ Adjuvant local XRT

- Perineural
- Multicentric disease
- Large BCC
- Recurrent disease

## ➤ PRIMARY modality

- Lips / Eyelids ... electron beam
- Multicentric disease
- Elderly / frail
- Poor cure rate in Recurrent BCC

## ➤ TREATMENT

- Surgical
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