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Non surgical management of skin cancer

Dr Alex Chamberlain

Plastic and Reconstructive Surgery Registrars' Conference, March 2009

Non-surgical therapies

Cryotherapy

Aldara (5% Imiquimod) cream

Efudix (5-Fluorouracil) cream

Solaraze (3% Diclofenac) gel

Intralesional MTX

Photodynamic therapy

Superficial radiotherapy

Treatment selection

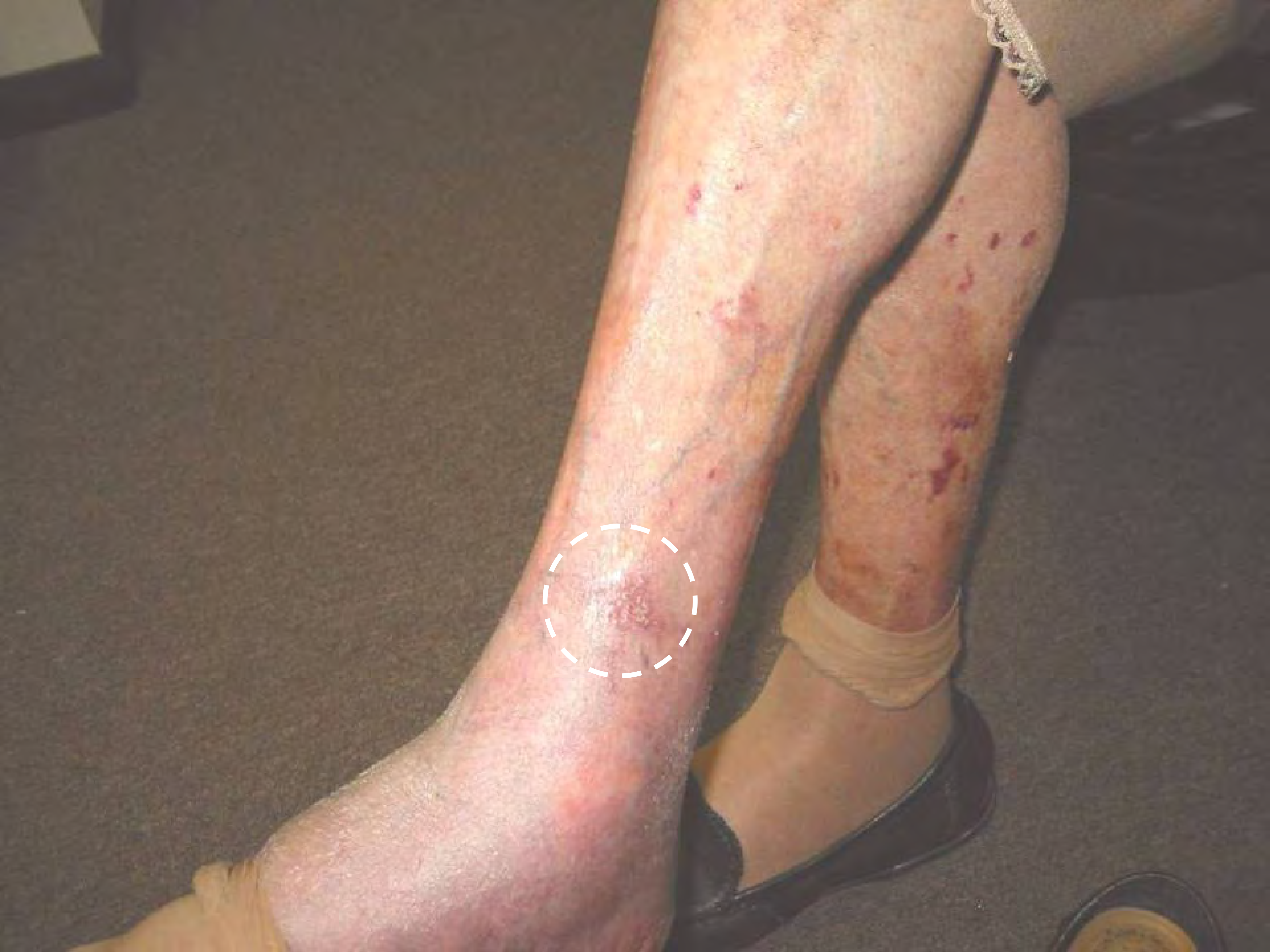
- Tumour factors
  - type, size, depth, site, behaviour
- Patient factors
  - compliance, dexterity, preference
- Toxicity
- Efficacy
- Cost
- Accessibility

Cryotherapy

- Local tissue destruction – cryogen
- Liquid Nitrogen most popular
- Widely used, inexpensive & quick
- Solar keratoses
- Selected tumours only

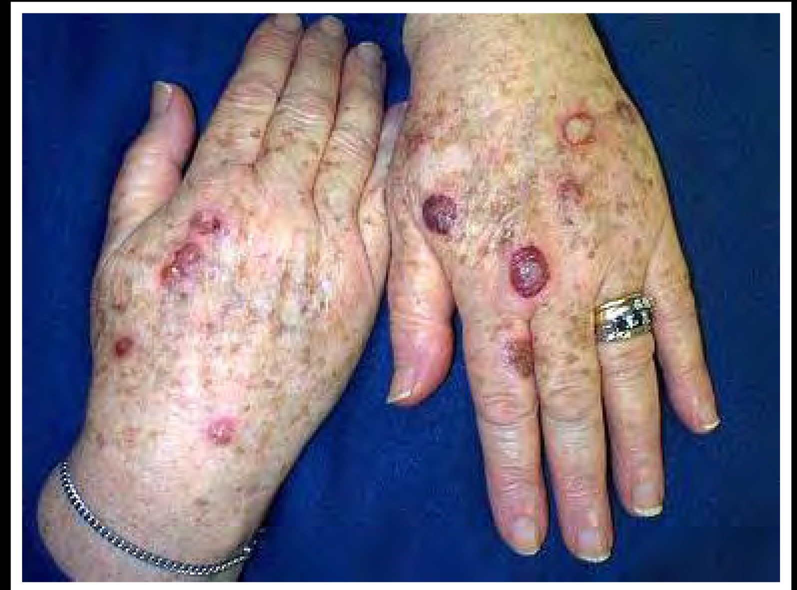
Cryotherapy

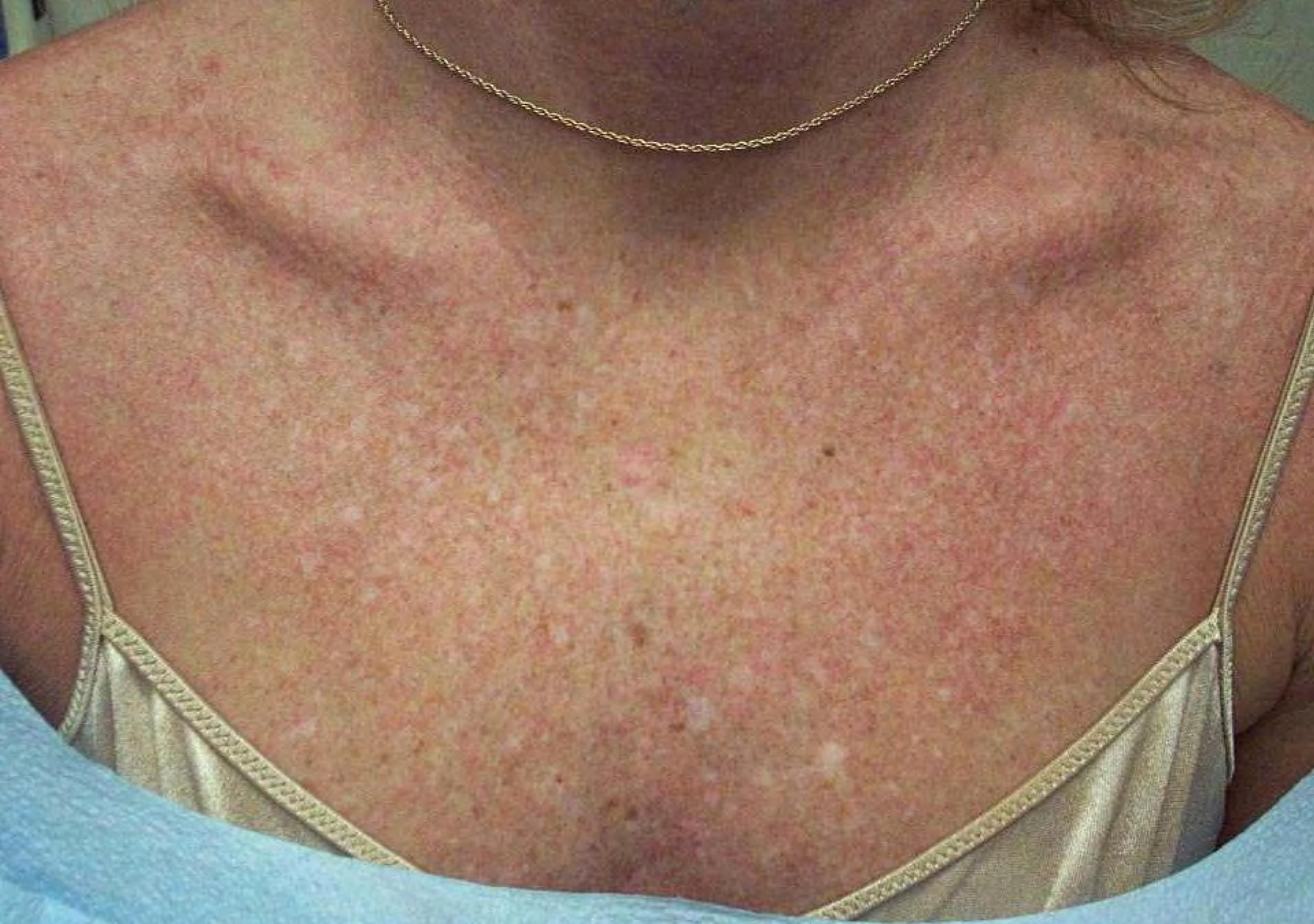
- Low risk, well defined, small tumours
- Trunk & limbs
- SCCIS, sBCC, small nBCC or well diff SCC
- Elderly with surgical contraindications
- Biopsy mandatory
- Can be combined with curettage
- Tumoricidal doses → hypopigmentation



Adverse Effects

- Pain
- Inflammation
- Bleeding
- Infection
- Neuropraxia
- Dyspigmentation
- Hypertrophic or contractile scar
- Hair loss





Slide courtesy of CSL Biotherapies

Aldara™

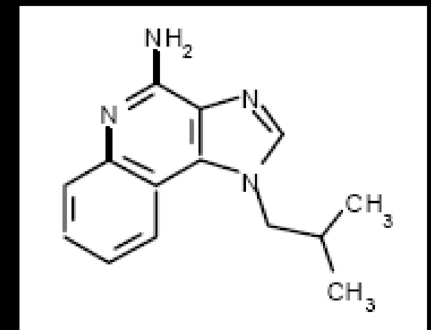
5% Imiquimod cream

Topical immune response modifier

Anti-viral & anti-tumour effects

Mechanism of action

Imidazoquiniline amine
Activates innate & acquired immunity
Toll-like receptor-7 agonist
Activate dendritic cells
Initiation of Th-1 mediated immunity
Induce cytokine release
IFN-α, IFN-γ, IL-6, IL-12, TNF-α



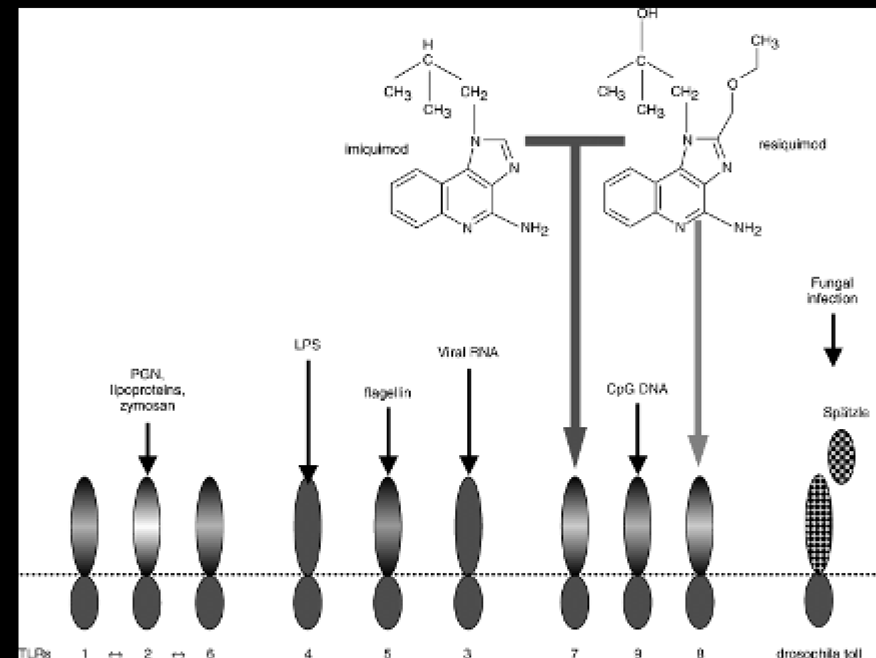
Toll-like receptors

Cell surface proteins

Recognise ‘microbial danger’

At least 11 TLRs in man

Each pathogen specific



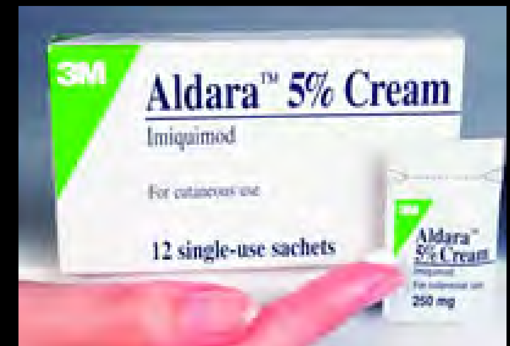
Medzhltov R Nature 1997;388:394

Rhodes Clin Exp Immunol 2002:130:360-9

Aldara™ indications

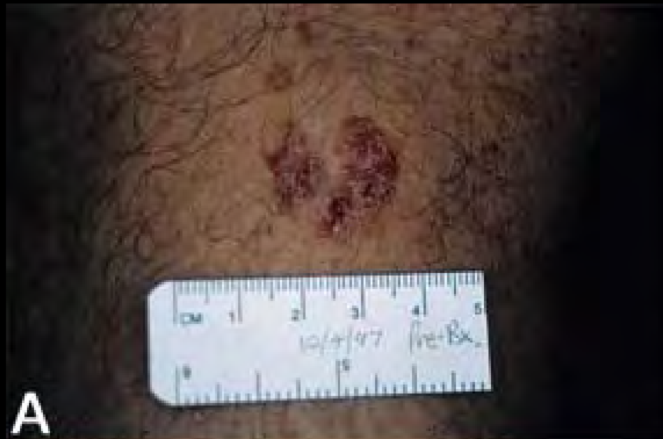
FDA & TGA approved:

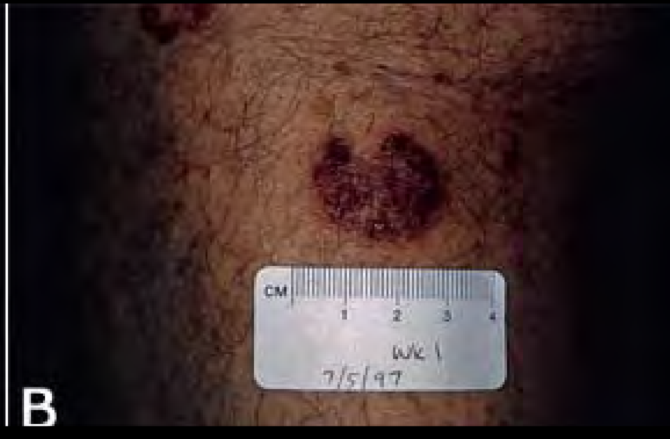
External anogenital warts
Superficial BCC
Solar keratoses (face/scalp)

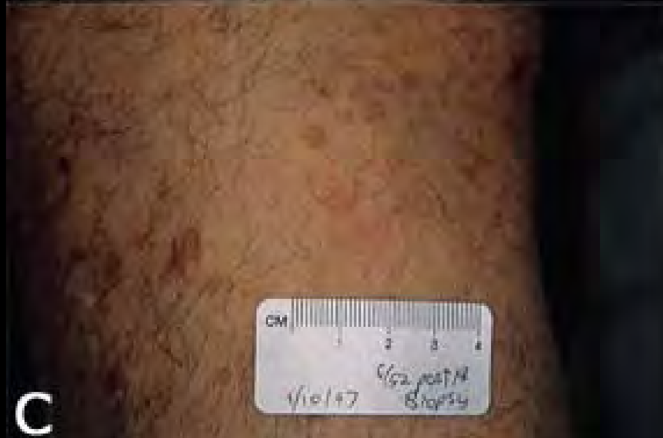


Published off-label uses

Bowen’s disease*
Lentigo maligna*
Actinic cheilitis
Porokeratosis
Mycosis fungoides/CTCL
Extramammary Paget's disease
Local cutaneous metastatic melanoma
Vulval intraepithelial neoplasia

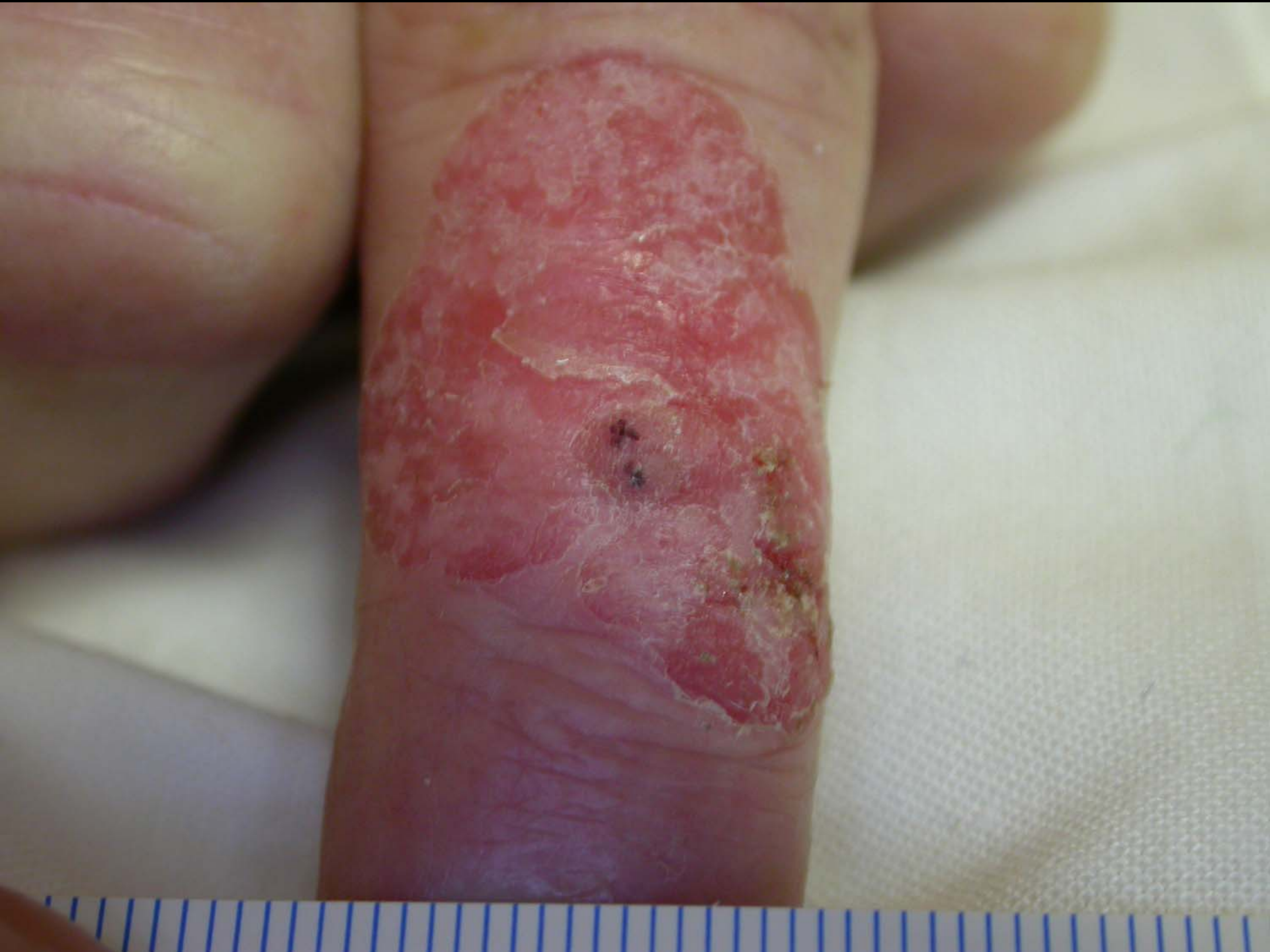


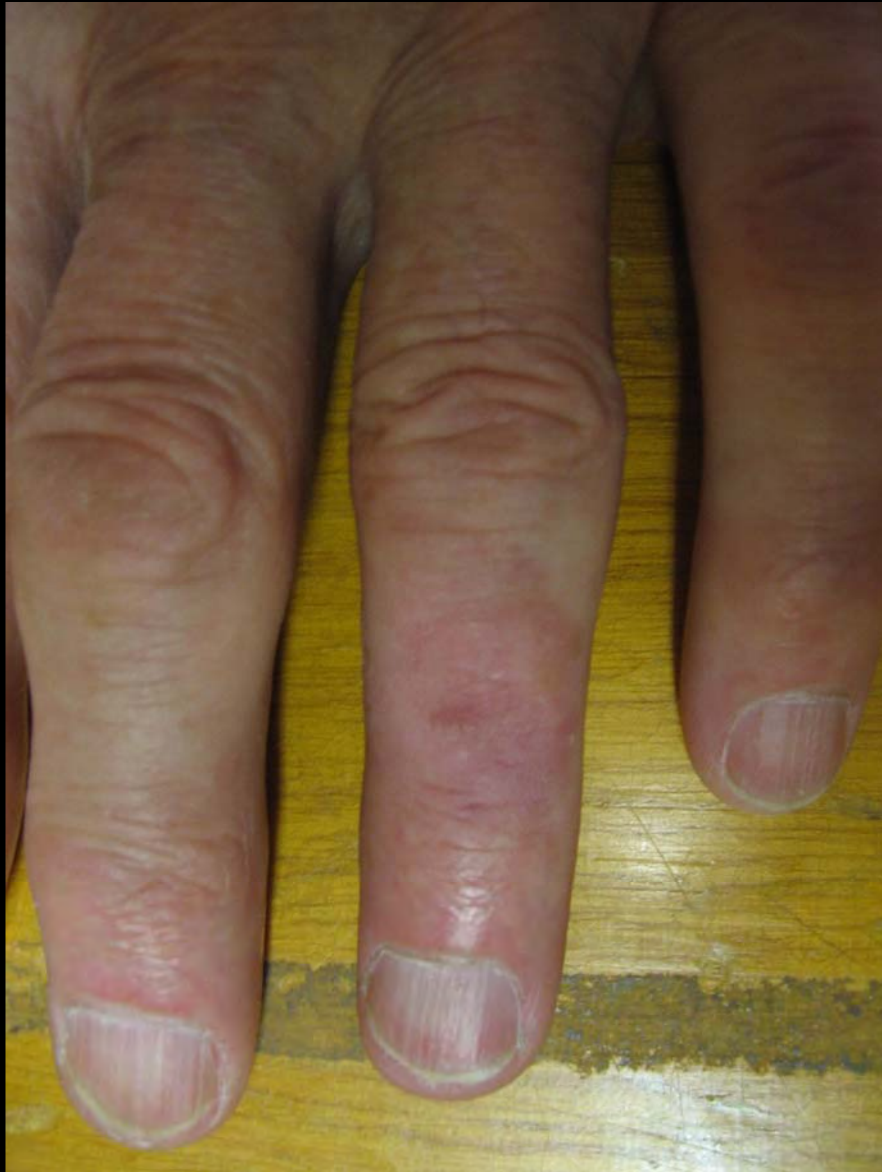


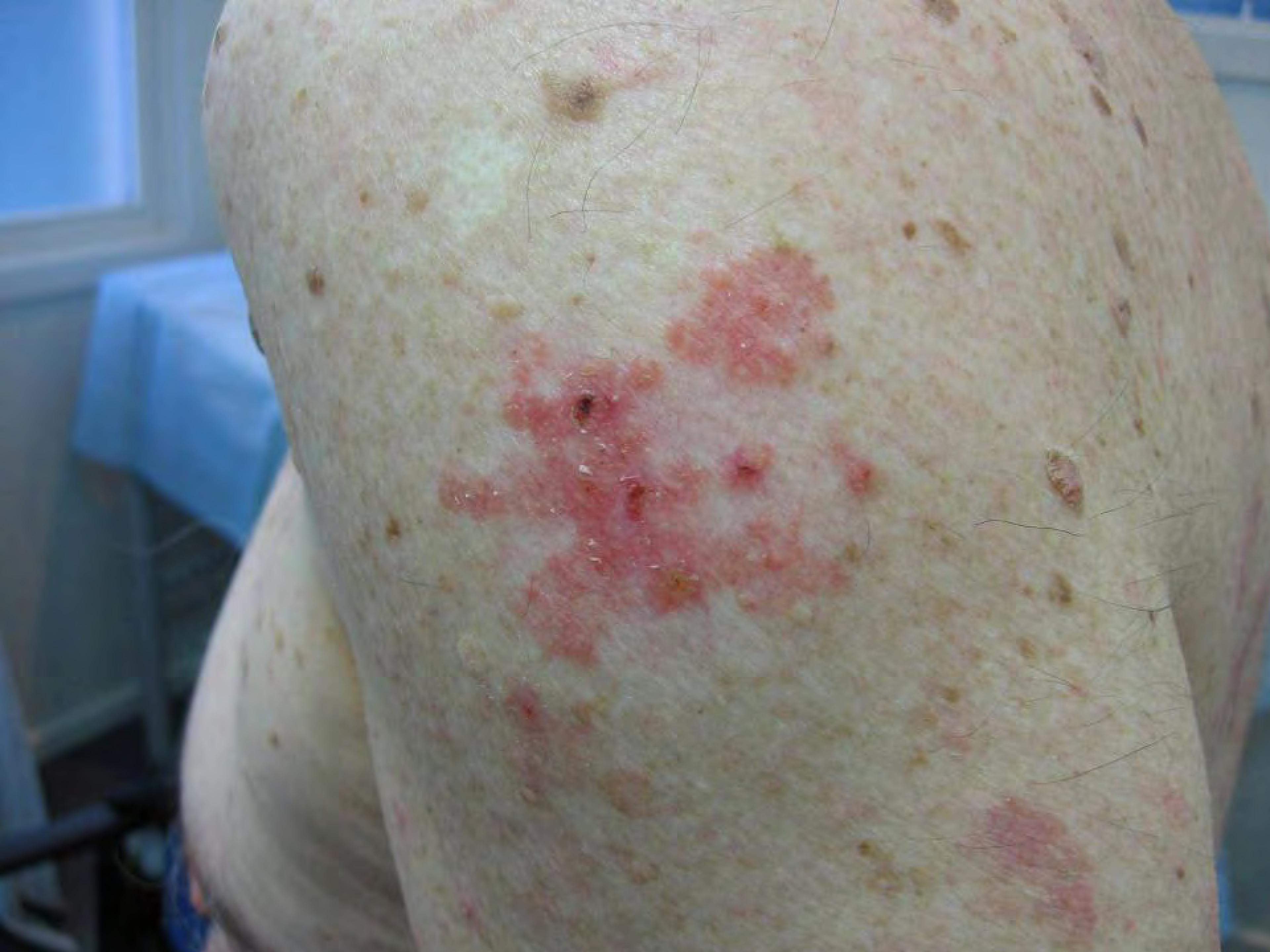


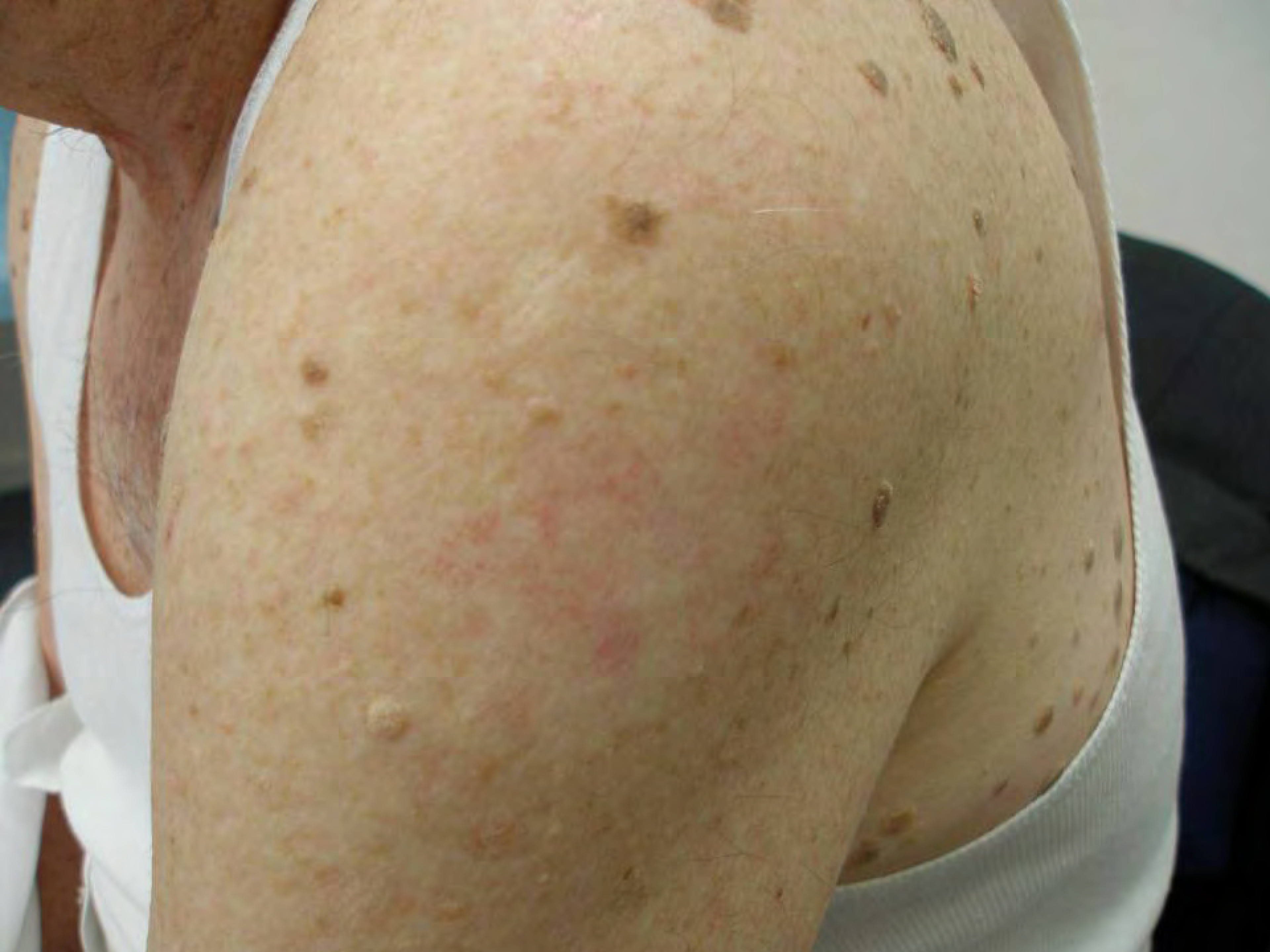
Aldara 5% cream
once daily application
93% clearance rate
4/12 course

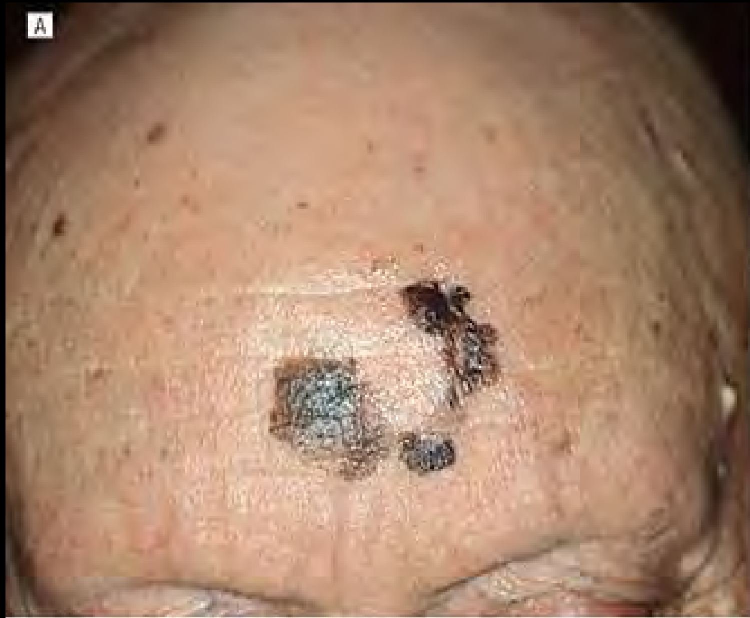
McKenzie-Wood A, Kossard S, de Launey J et al Imiquimod 5% cream in the treatment of Bowen's disease. J Am Acad Dermatol 2001;44(3):462-70

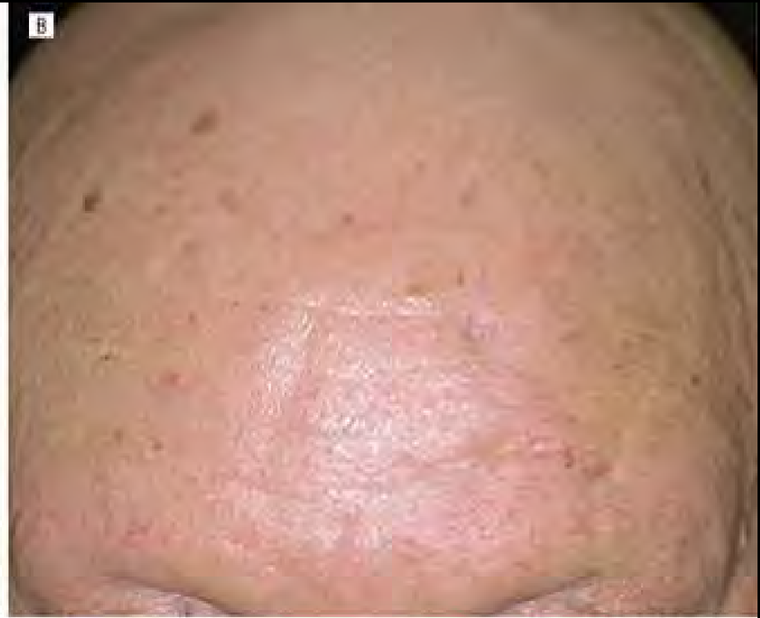


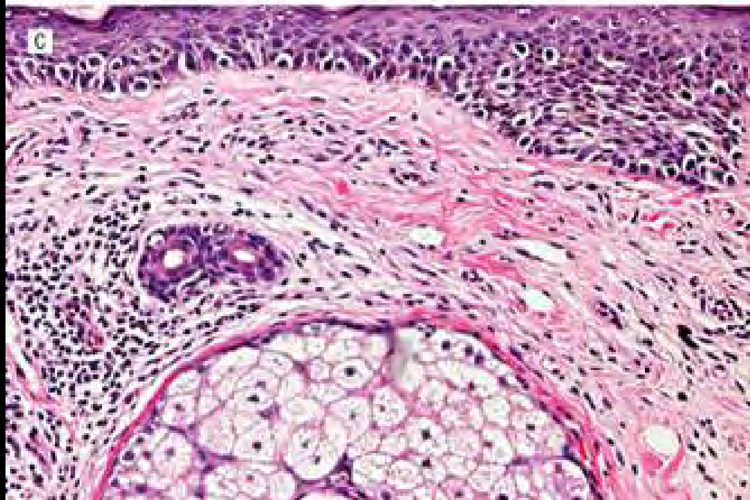


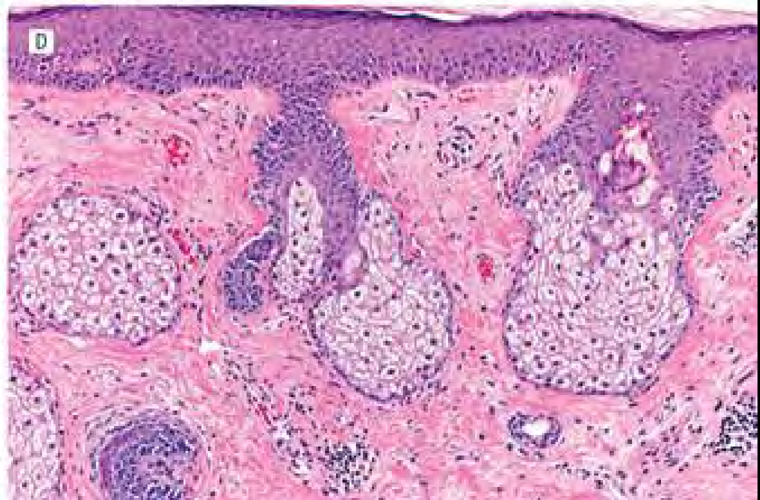












Wolf et al Arch Dermatol 2005;141:510-14

Additional Aldara™ uses

Molluscum contagiosum
Leishmaniasis

Haemangiomas of infancy
Keloid scars
Granuloma annulare
Tattoos
Silicon granuloma
Skin rejuvenation

Solar keratoses

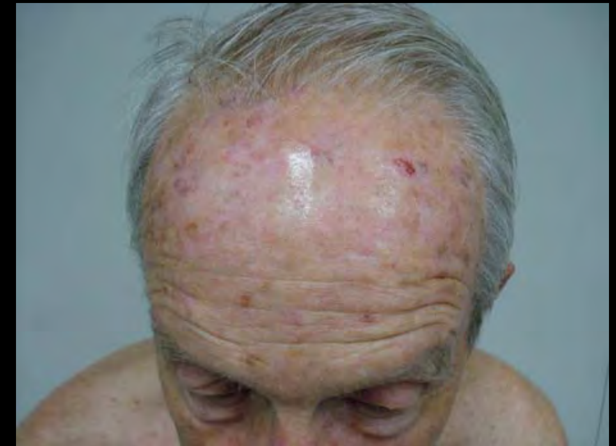
Aldara 3x/wk x 4/52

vs.

LN2 20-40s FTC x 1-2 Rxs

vs.

5-FU bd x 4/52

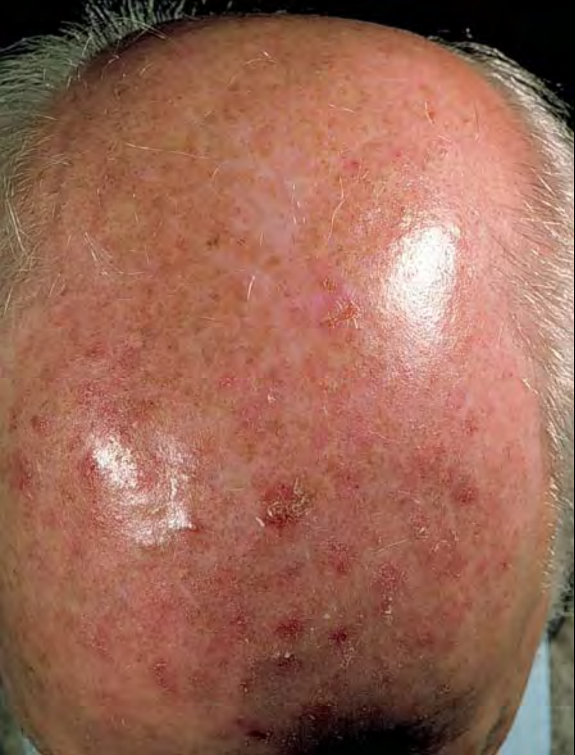


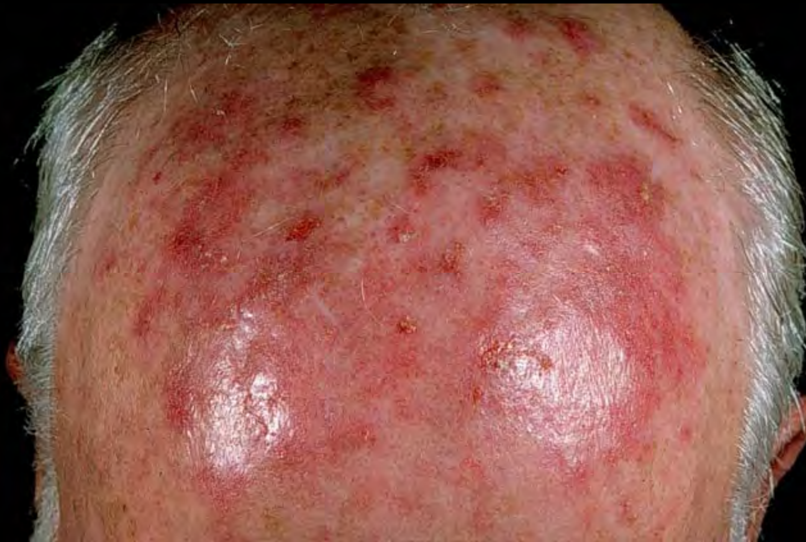
- 75 Caucasian patients
- Head, neck or décolletage

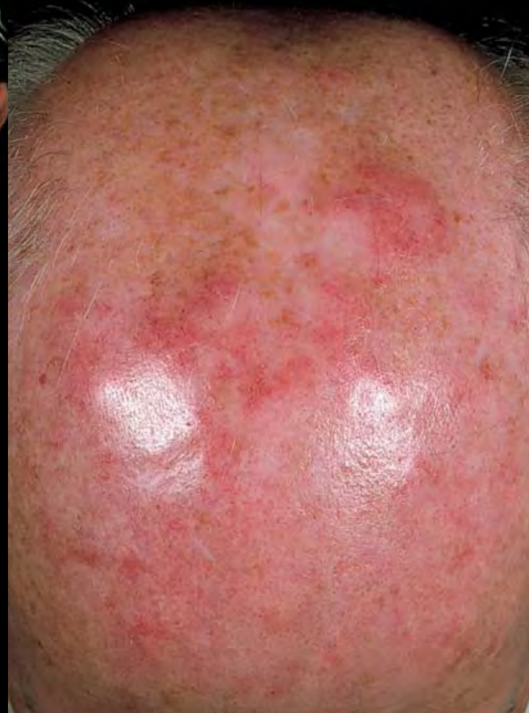
Krawtchenko N et al Br J Dermatol 2007

	Aldara	LN2	5-FU
Initial clearance	85%	68%	96%
Histological clearance	73%	32%	67%
1 year field clearance	73%	4%	33%

Krawtchenko N et al Br J Dermatol 2007







Slide courtesy of CSL Biotherapies

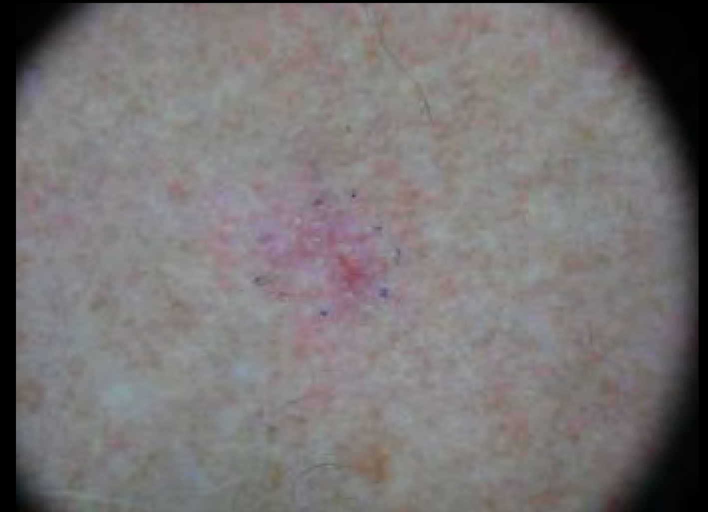
RPBS Authority

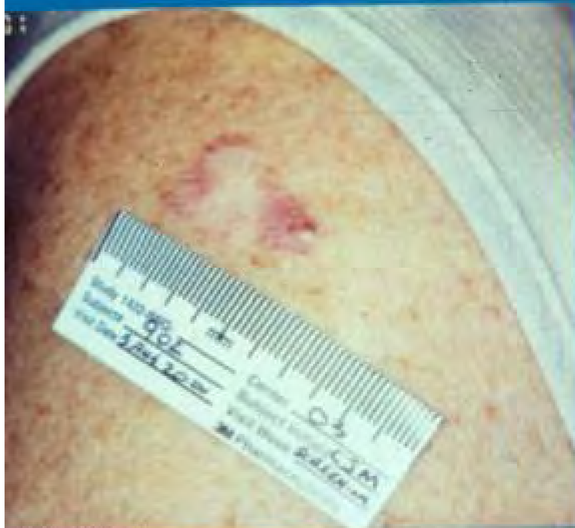
- Solar keratoses of the face and scalp where topical field treatment is desired or other treatments deemed inappropriate

- 12 sachets and 1 repeat

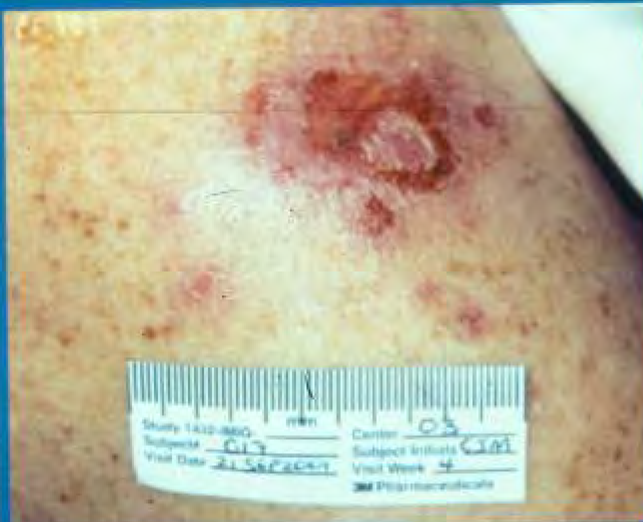
Superficial BCC

- 80-90% histological clearance at 3/12
- 78% 5-year clearance
- Good efficacy in large tumours also
- Better efficacy with more severe local reactions

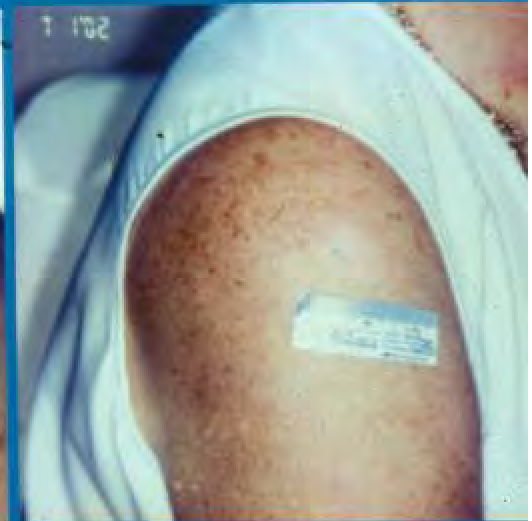




03/08/2001

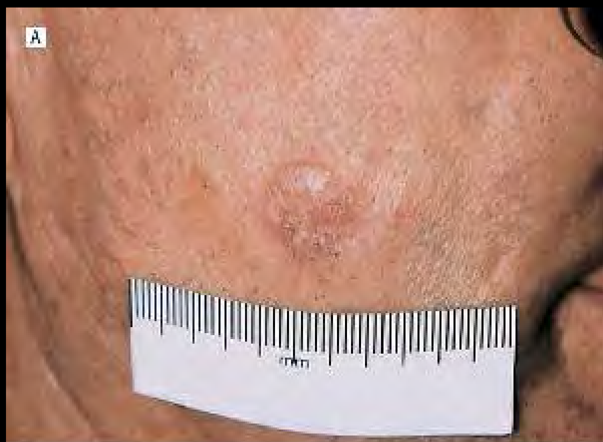


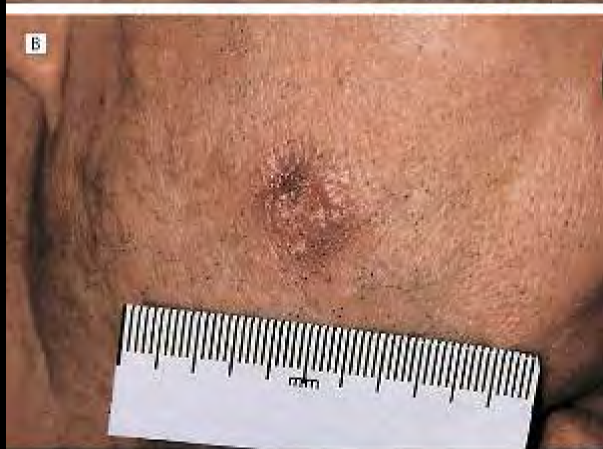
21/09/2001

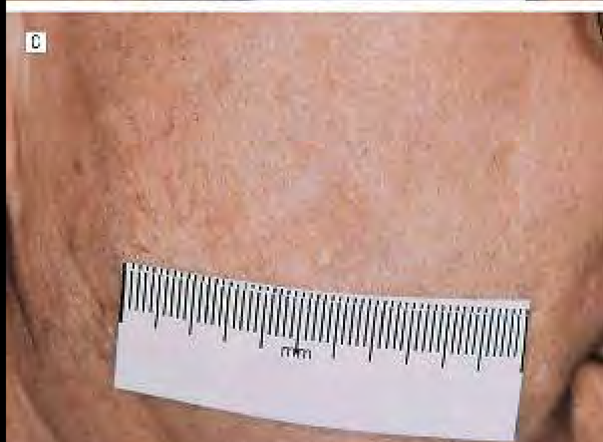


07/01/2002

Aldara™ for sBCC







Lesser efficacy with small low risk nBCC

71% histological clearance at 3/12

Shumack S et al. Arch Dermatol 2002

Presentation

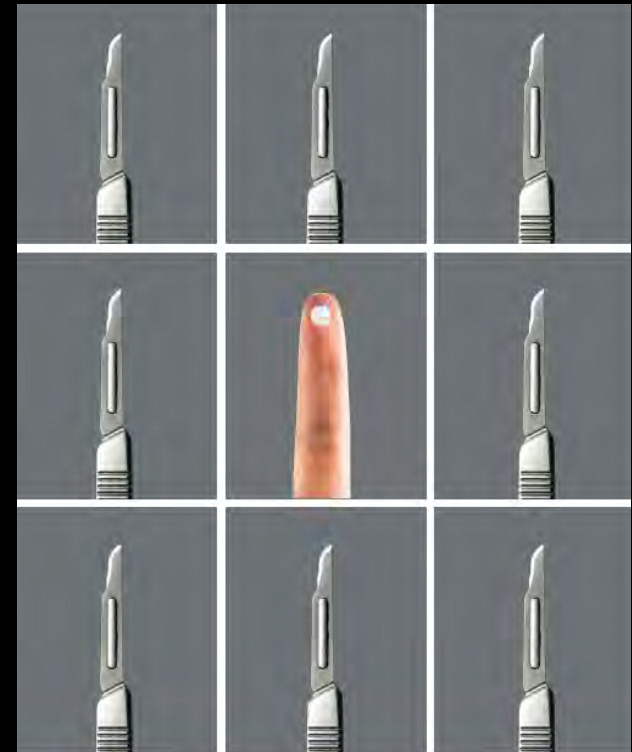
12 x 250mg sachets

$160 per box (private script)

Sparing use of sachets

Multiple not single use/sachet

Keep refrigerated

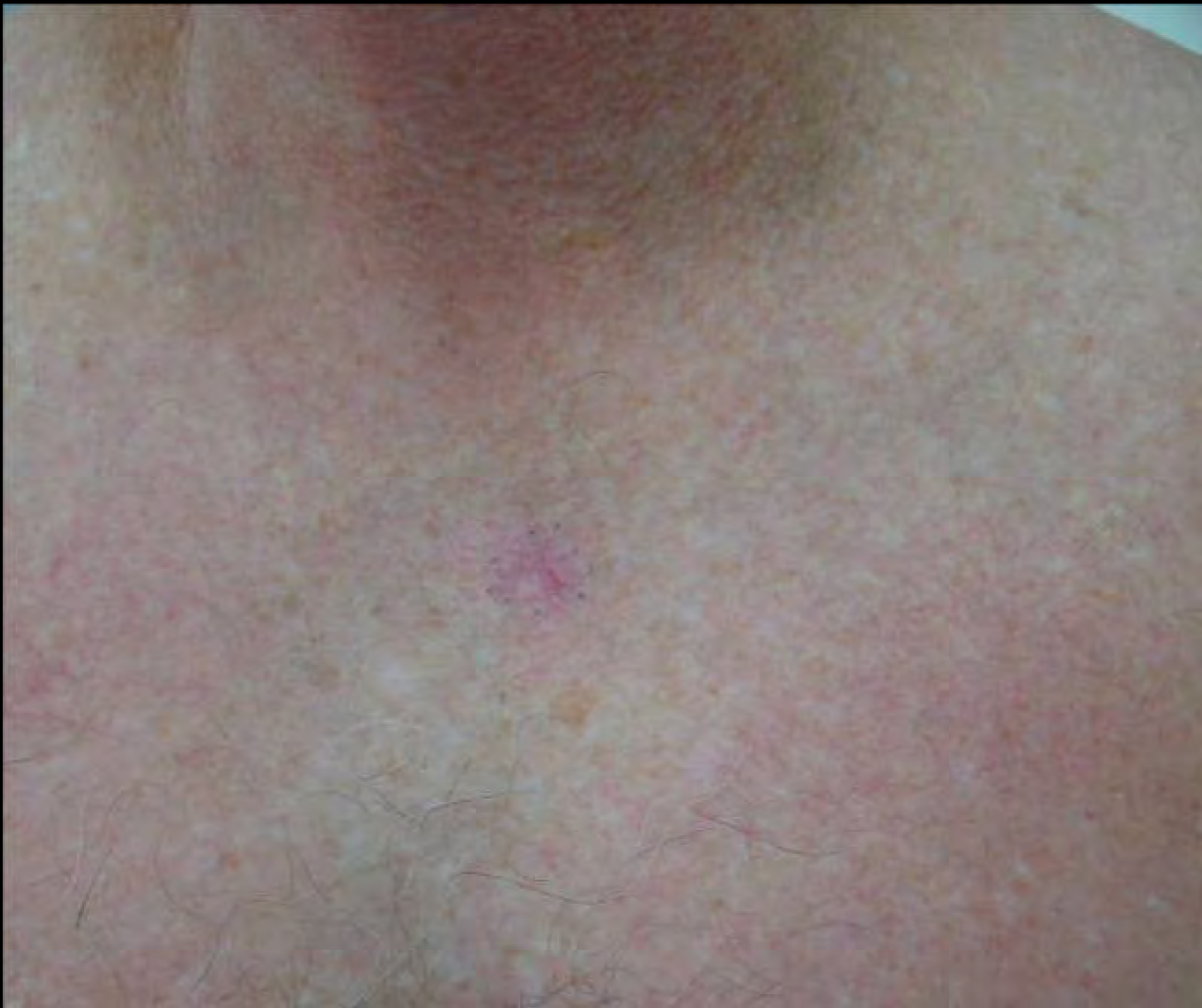


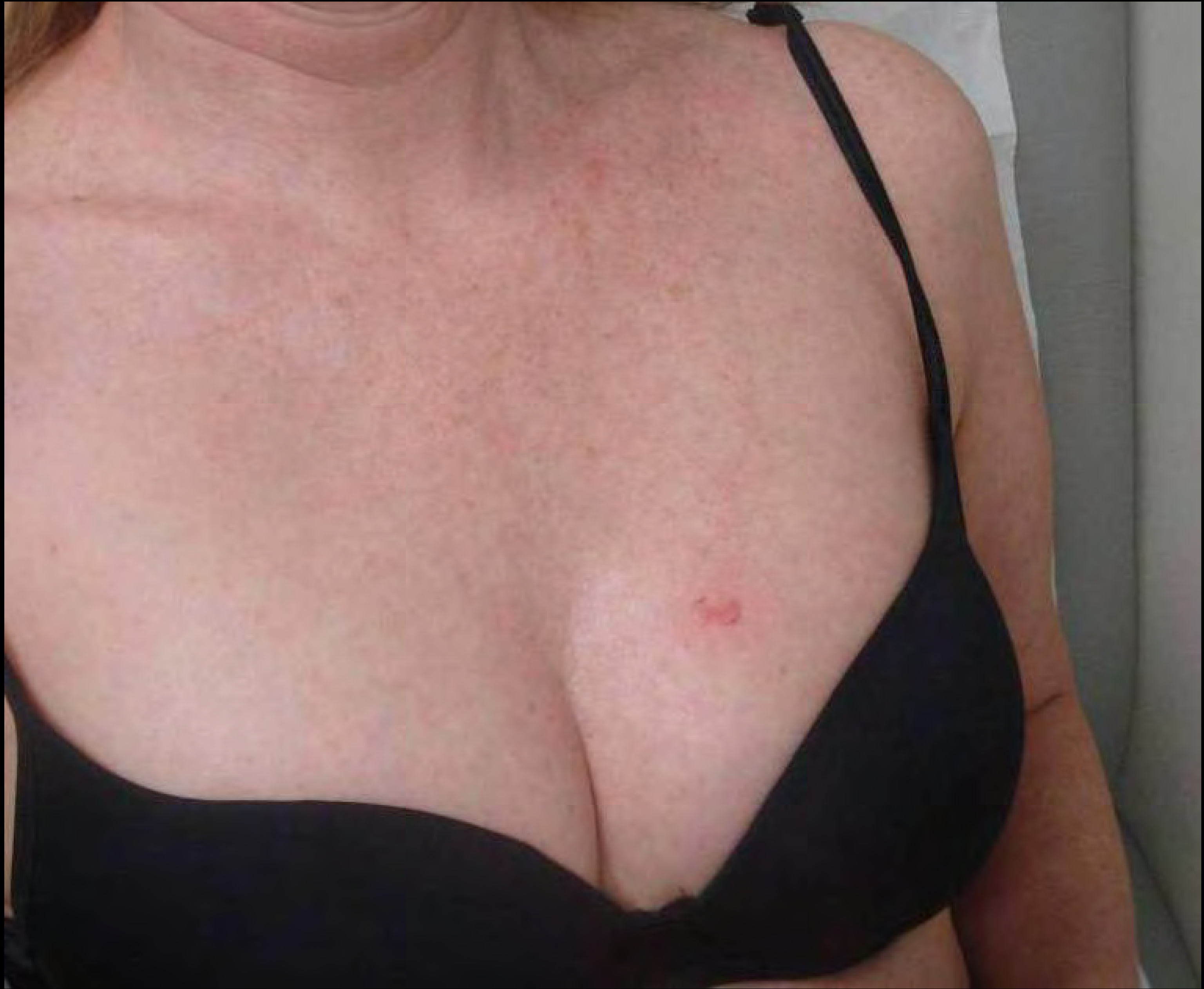
PBS/RPBS Authority

- Biopsy proven previously untreated superficial BCC, normal immune function where topical therapy is desired or other treatments inappropriate (e.g. excision, cryotherapy, curettage and diathermy).
- Must provide date of histopathology and name or approved pathology provider
- 12 sachets and 1 repeat

Patient selection

- Hypertrophic or keloid scar prone
- Multiple or large lesions
- Surgery impractical or undesirable
- Areas of poor healing e.g. below knee with venous disease
- Where cosmesis critical





Regimens

Apply nocte for 8 hrs then wash off

5-10mm margin

If reaction too severe rest period for 1 week

Baseline photographs

BCC	5 X per wk 6/52 (Marks)
AKs	3 X per wk 4/52 (Salasche)
	1/12 on 1/12 off (1-3 cycles)
Bowens	5-7 X per wk 12-24/52 (Kossard)

Expected reaction

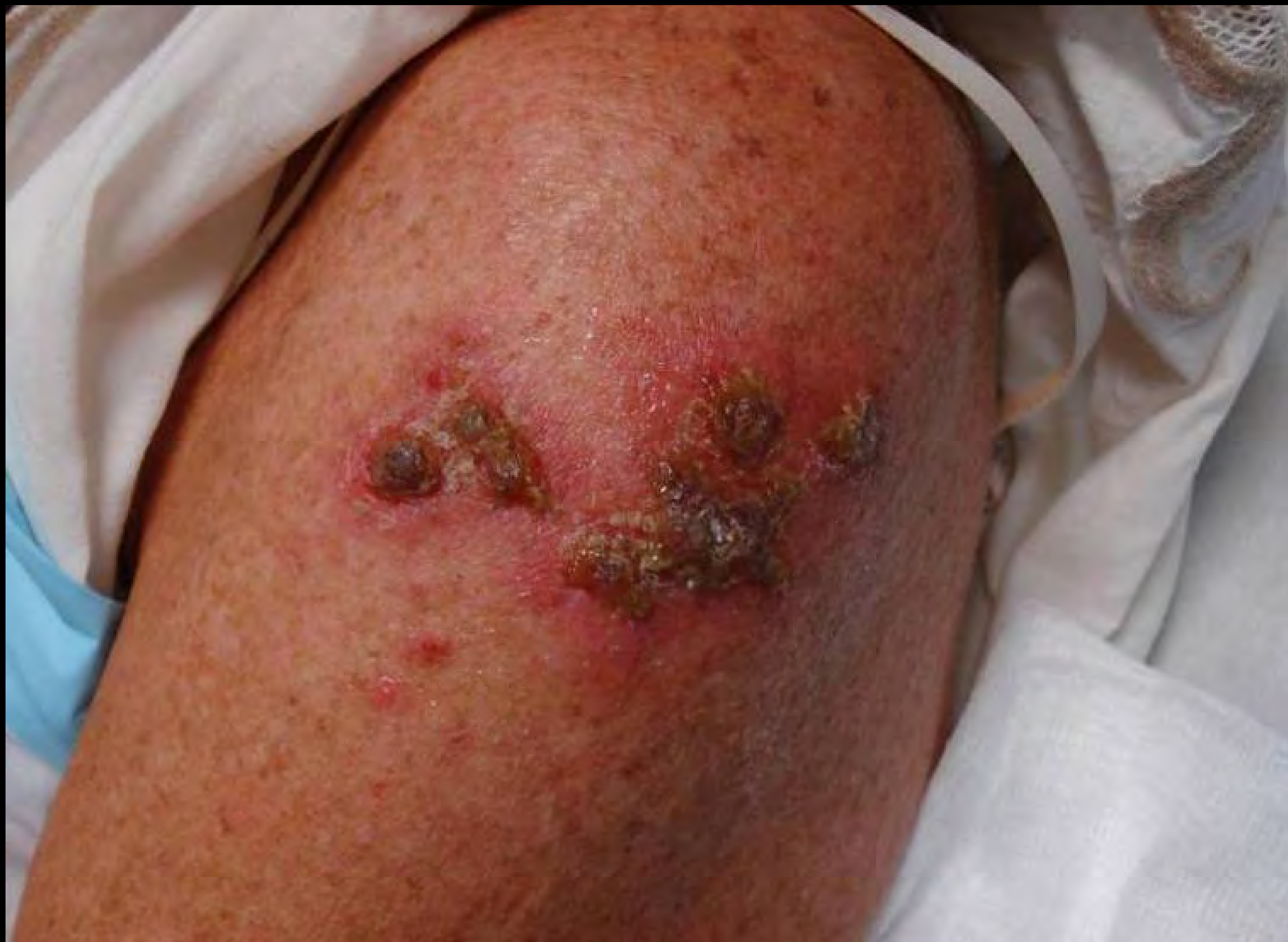
LOCAL

Itch, burning & irritation
Erythema & crusting (30%)
Erosion & ulceration (10%)
Rarely - hypopigmentation, neuropathic pain

SYSTEMIC

Flu-like SEs in 1%
Rarely - flare psoriasis or pemphigus

Safe in HIV & transplant patients
4% pts discontinue Rx due to adverse events



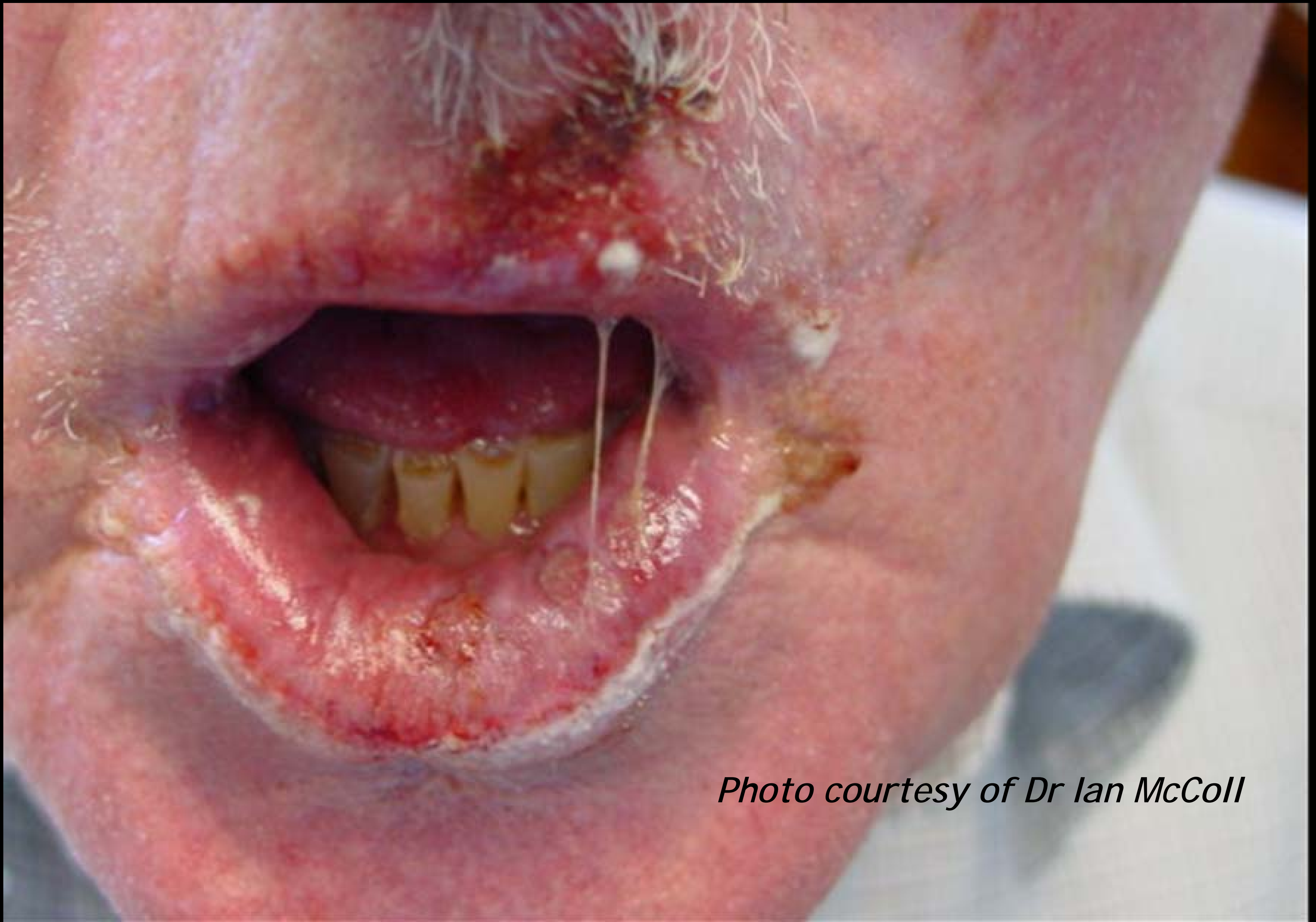
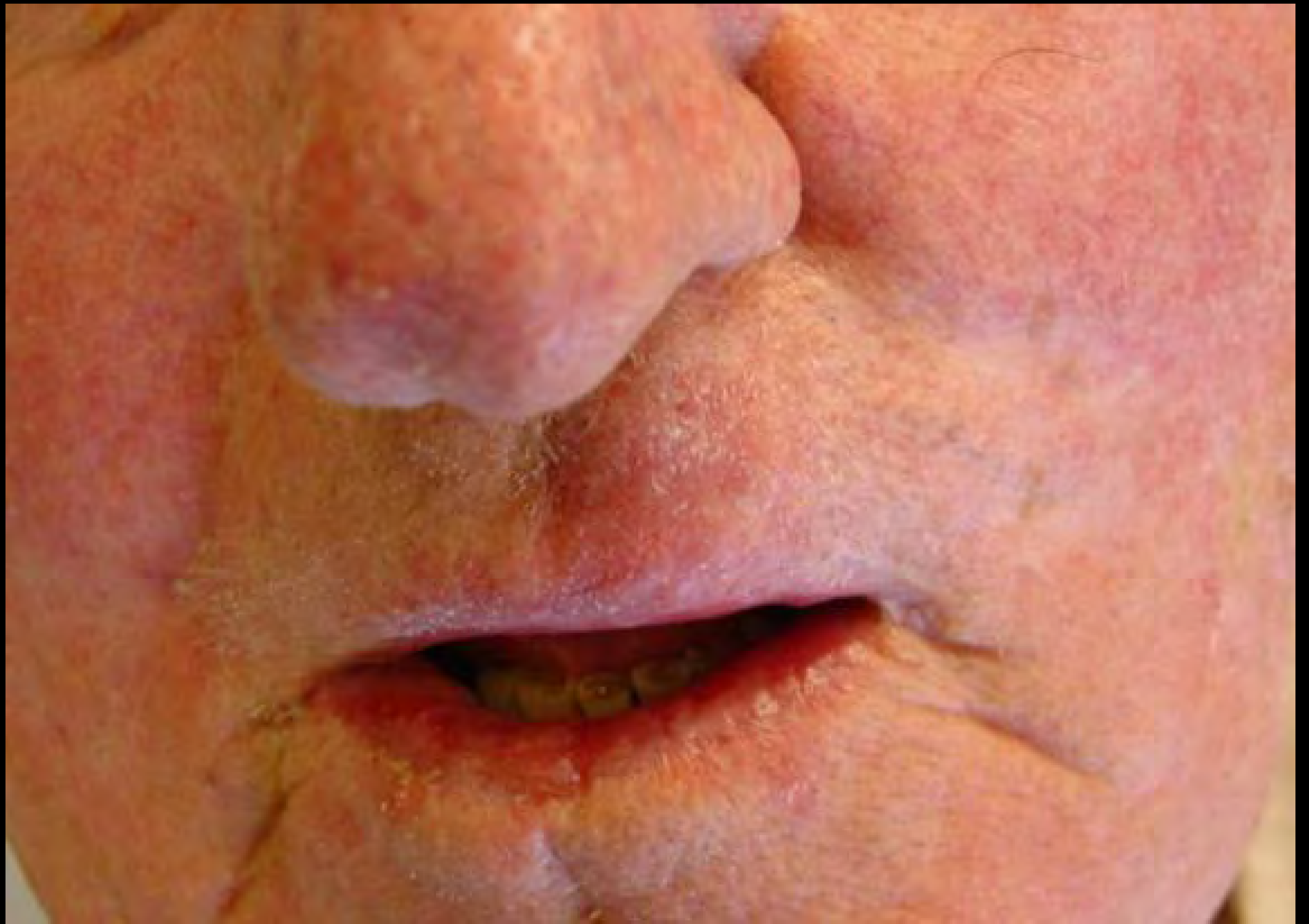
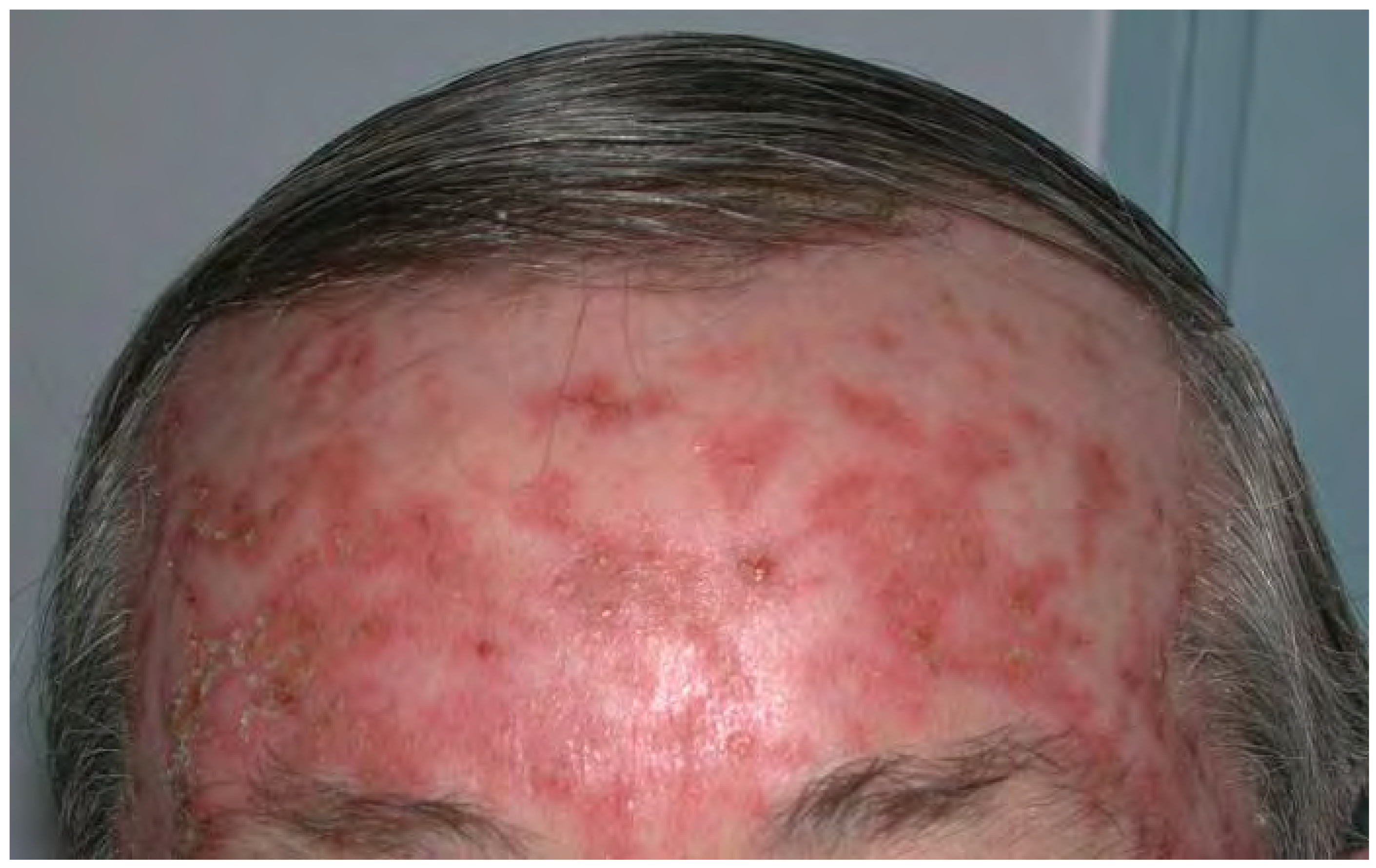


Photo courtesy of Dr Ian McColl

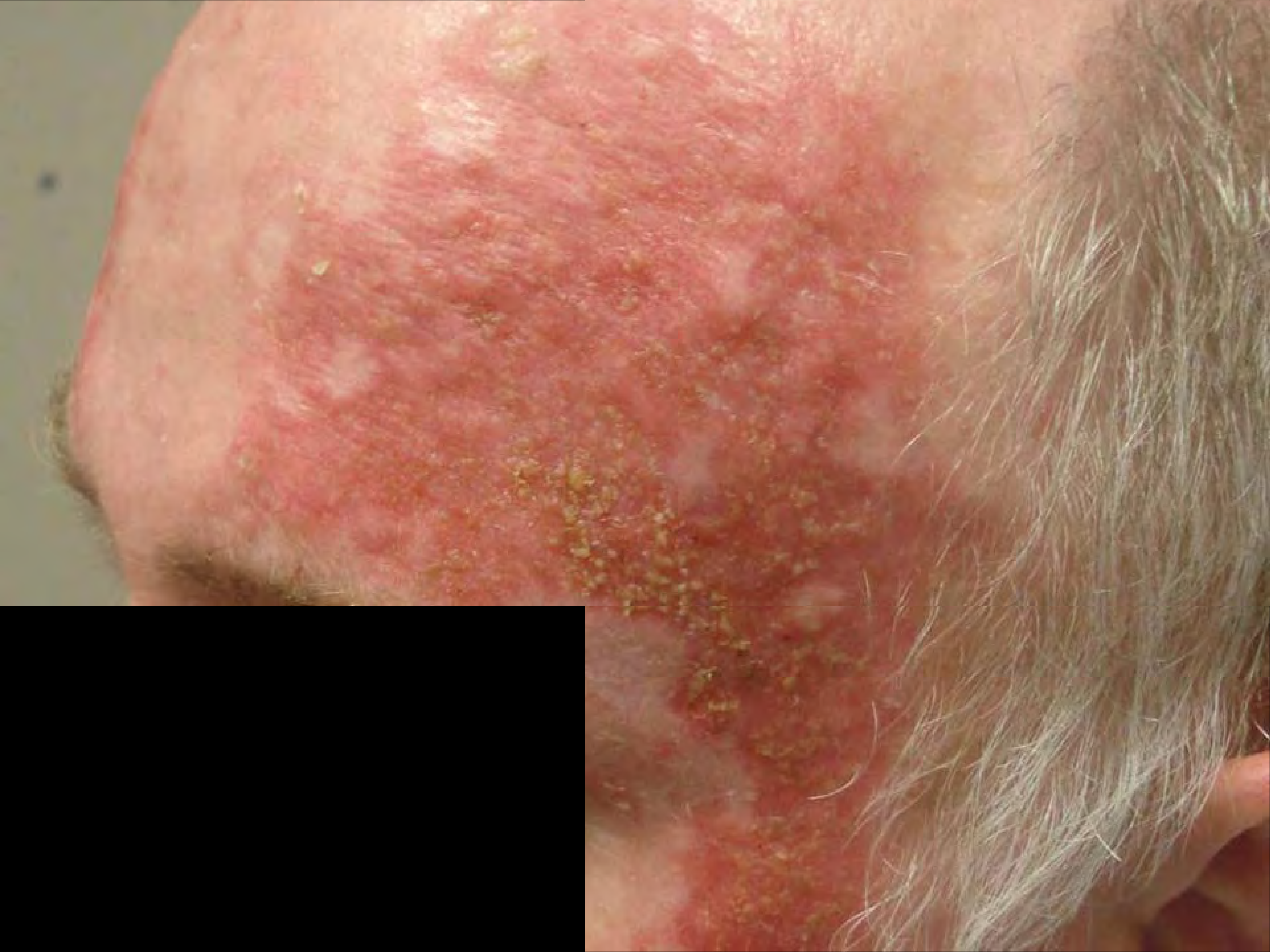


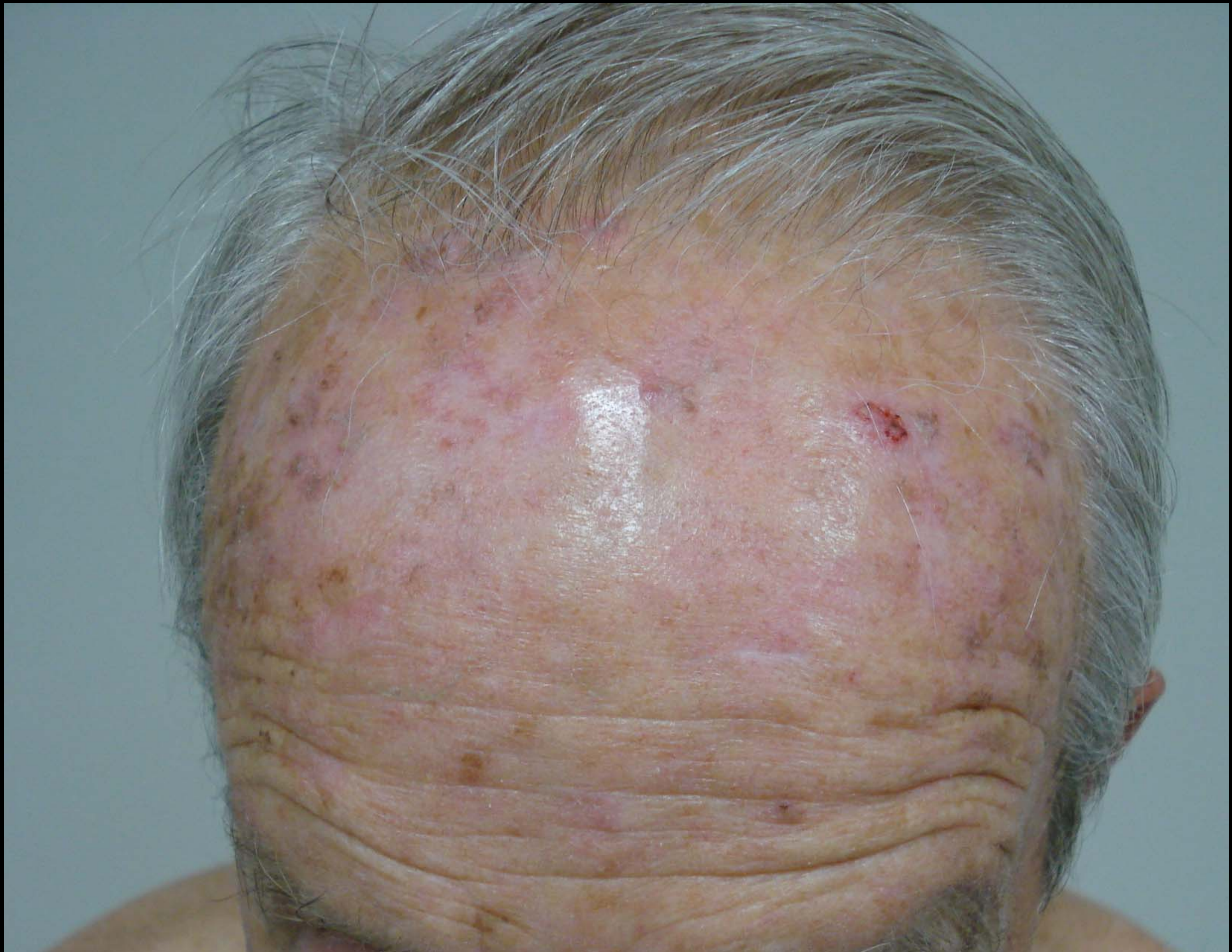
5-Fluorouracil

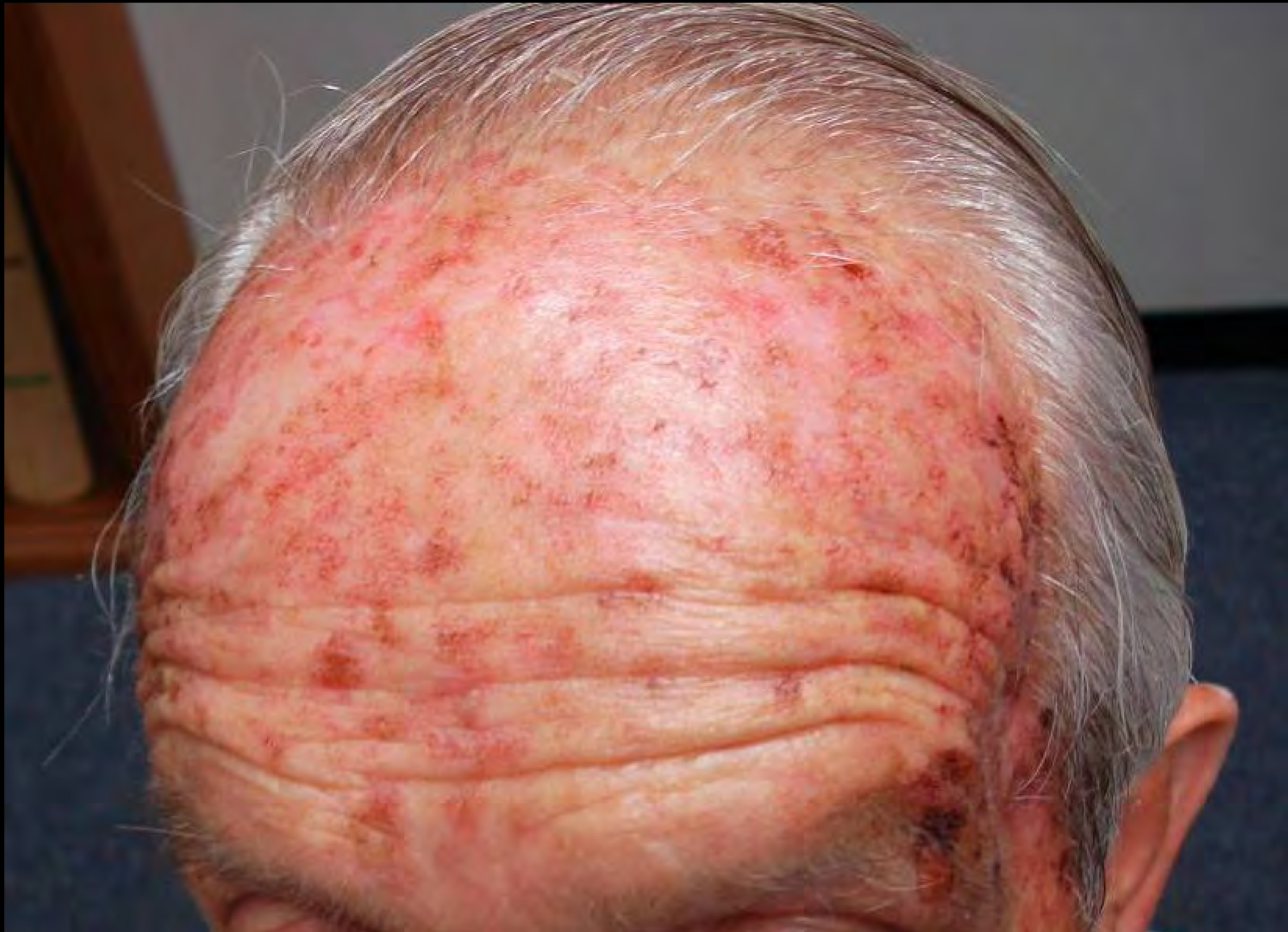
- Fluorinated pyrimidine analogue
- Anti-metabolite
- Cell cycle arrest and apoptosis
- bd for 2-4 wks (Solar keratoses)
- bd for 4-8 wks (Bowen's disease)
- concomitant topical steroid?
- Break when 'red, raw or sore'
- Photosensitising
- benefits = superficial chemical peel

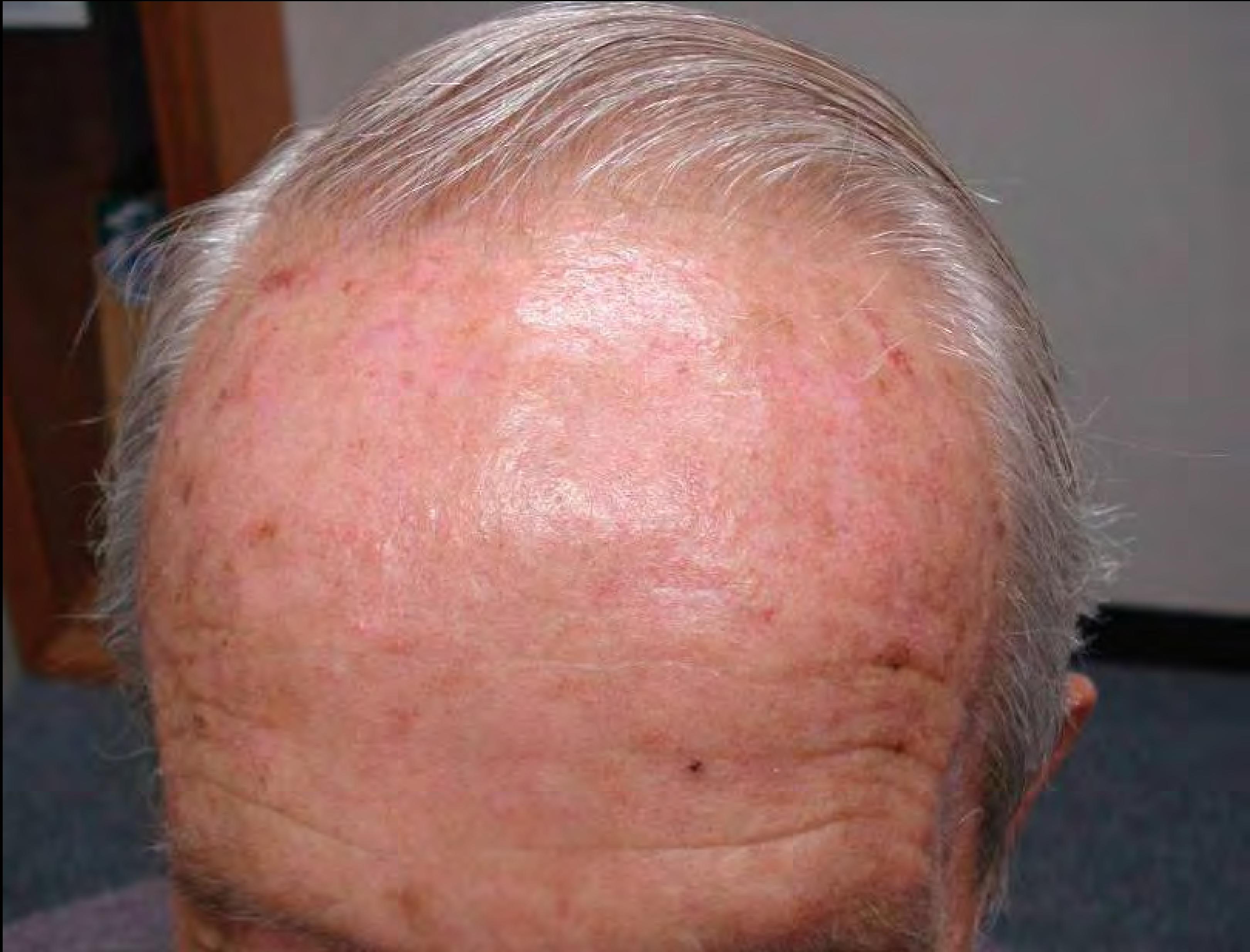


Inflammed actinic keratoses with Efudix™





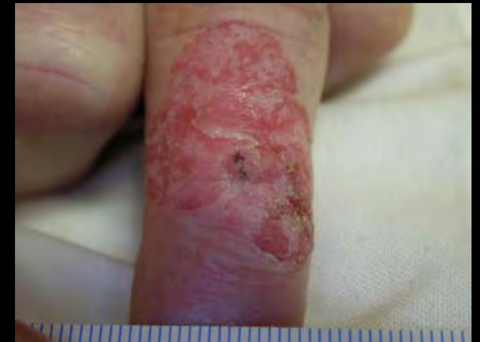




Aldara & Efudix

Case series of 4 patients
Bx proven Bowen's disease of the digit
4/4 failed monotherapy with Aldara
2/4 failed monotherapy with Efudix also

4-8/52 combination therapy
Aldara & Efudix each daily



Ondo AI et al. Topical combination therapy for squamous cell carcinoma in situ with 5-flurouracil and imiquimod cream in patients who have failed topical monotherapy. J Am Acad Dermatol 2006;55:1092-4.

Aldara & Efudix

Mild and tolerable inflammation
Eroded by 4-8 weeks
Clear after another 8 weeks
Clinical end points only
Clear at 12-24 months

Enhanced Efudix effect with IFN & IL-12
Good synergism

Efu-dara®
Imiqui-dix®

Photodynamic therapy

Induced localised cutaneous porphyria

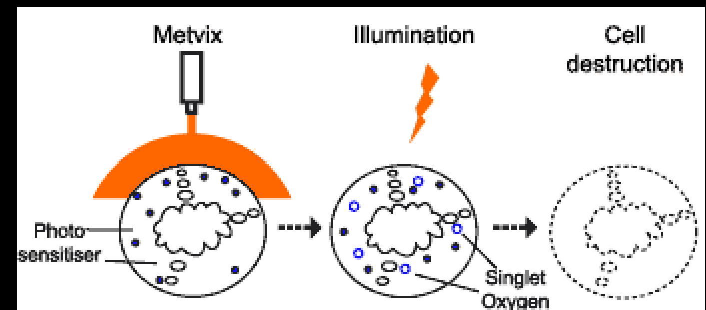
Preferential accumulation dysplastic tissue

Light activation of photosensitiser

Visible light & presence of oxygen

Generation of oxygen intermediates

Target cell cytotoxicity



Photosensitiser

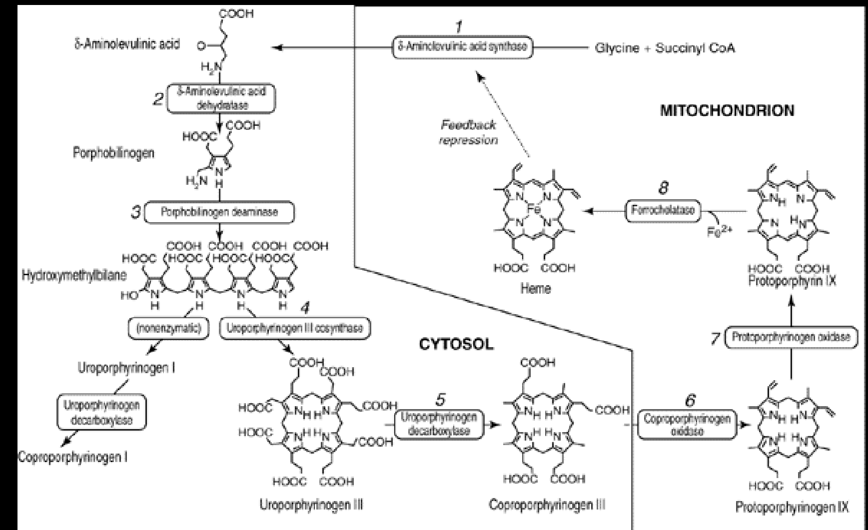
Topical methyl-ALA or ALA

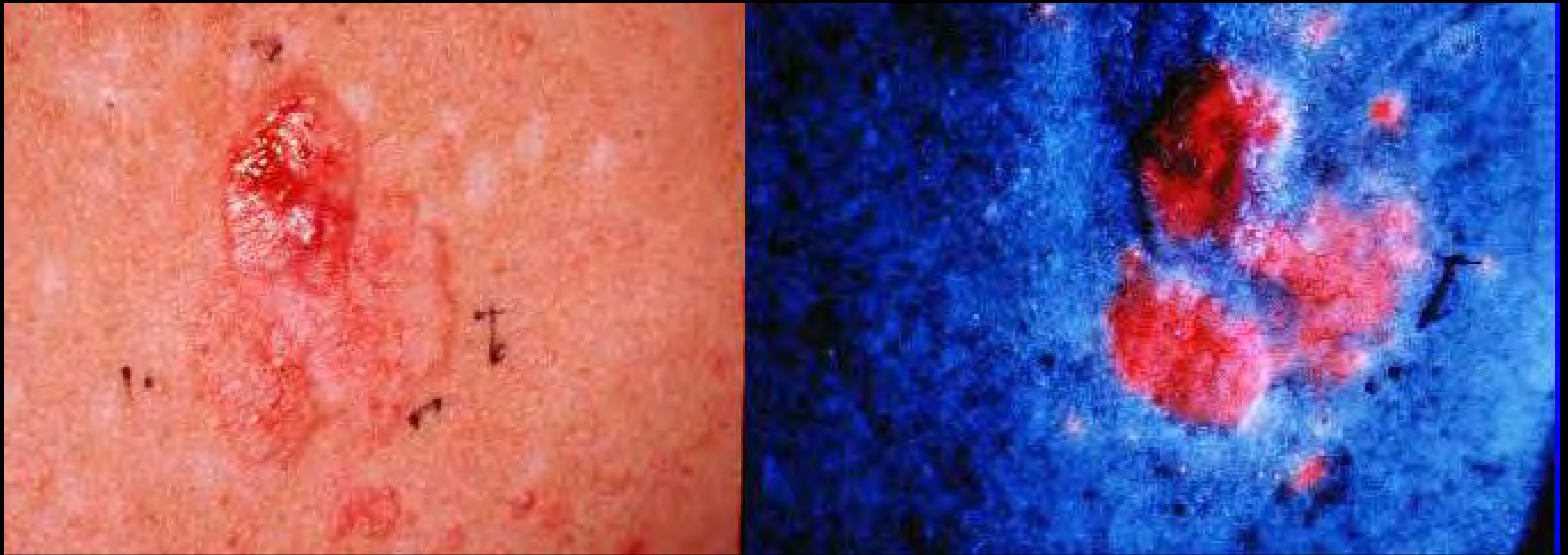
Major endogenous porphyrin = PPIX

Potent photosensitiser

Accumulates in dysplastic tissue

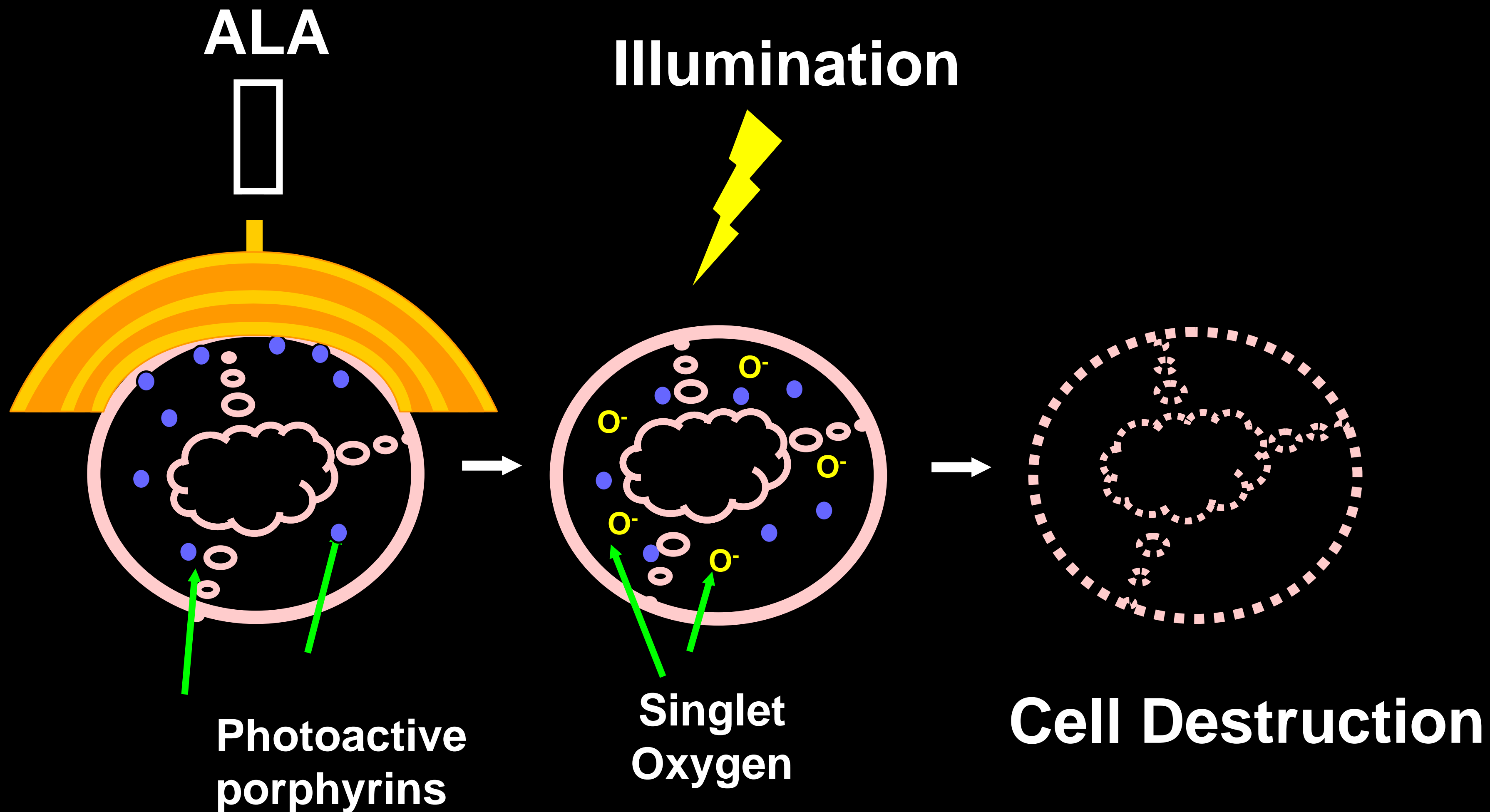
Peak absorption 410-620nm





Accumulation of photoactive porphyrins showing fluorescence under Woods light

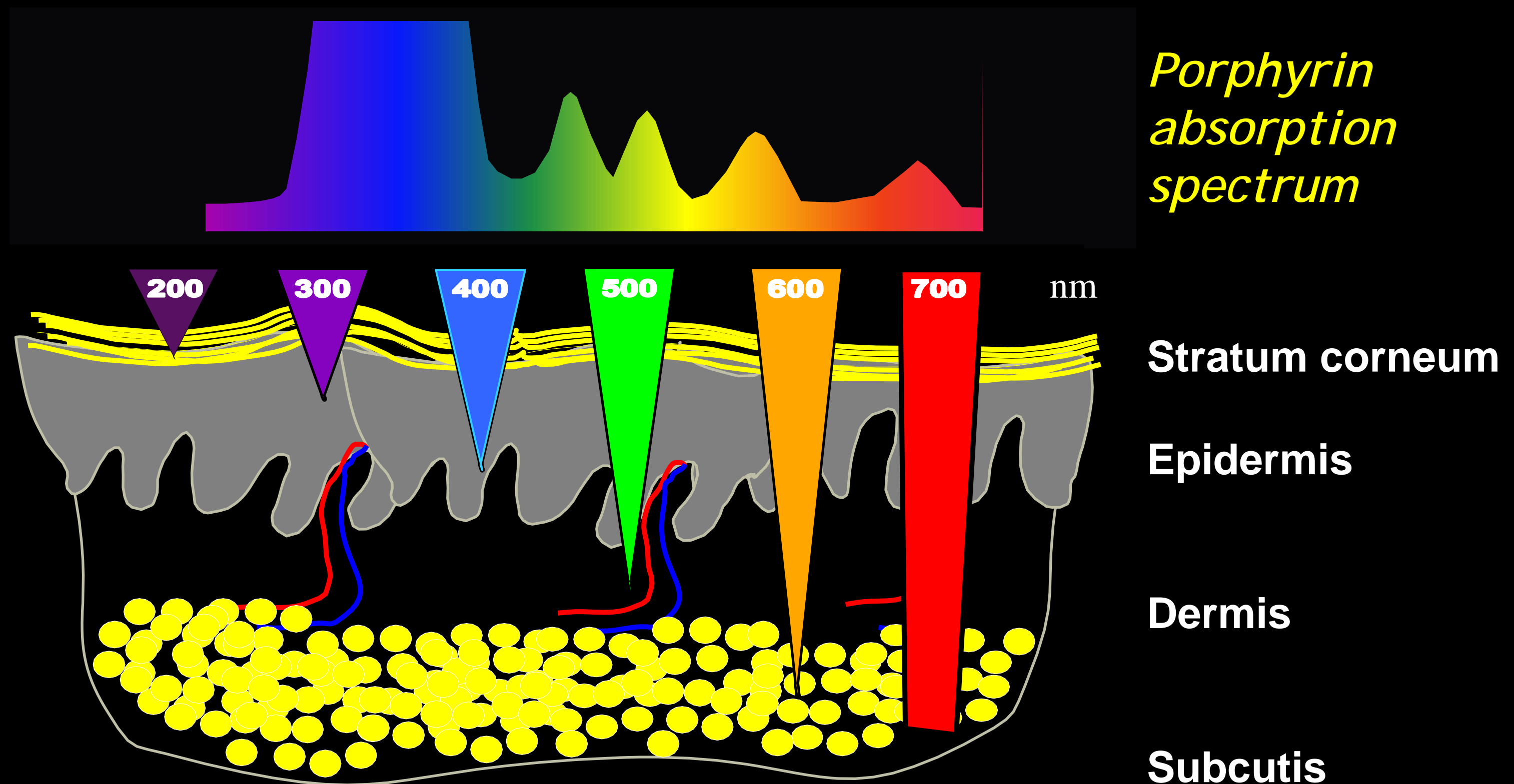
Mechanism of Action



Principles of photoactivation

- Use wavelength corresponding to absorption maxima of photosensitiser
- Penetration appropriate to pathological process
- Longer wavelengths = greater penetration
- Wide variety light sources may be used

The relationship of light wavelength and skin penetration



Light sources

Vascular Laser (Candela V-beam)
Intense Pulsed Light (IPL)
Incandescent lamps
Light emitting diodes (LEDs)
Xenon arc discharge lamps

Indications & efficacy

Solar keratoses (field change)
Bowen's disease
sBCC or nBCC < 2 mm thick
…where surgery inappropriate

Tumours require 2 Rxs 2 weeks apart
Well tolerated & short downtime
Excellent cosmetic result

Treatment protocol

Baseline biopsy & photograph
Remove crust with light curettage
Topical ALA to lesion + margin
Under occlusion and photoprotected
Remove cream 3 hrs later
Woods lamp for surface fluorescence

Treatment protocol

Pre-treatment local anaesthetic optional

Avoid adrenaline

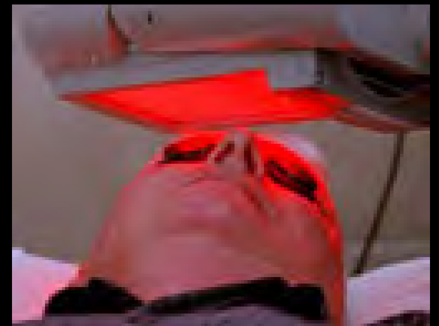
Illuminate field + margin 5mm

Fan & cool water during illumination

Protect treatment site for 48 hrs

Vaseline or antibiotic ointment

2-3 weeks to fully heal



Efficacy

- **Solar Keratoses**

  90% CRR at 6/12 with 2 Rxs (6 RCTs)

- **Bowen's Disease**

  85% CRR at 12/12
  82% CRR at 24/12

Efficacy

- sBCC

  97% CRR at 3/12 with 2 Rxs
  80% CRR at 60/12

- nBCC < 2mm

  91% CRR at 3/12 with 2 Rxs
  86% CRR at 60/12

Efficacy

- **Difficult to treat BCCs**

89% CRR at 3/12

82% CRR at 12/12

80% CRR at 48/12

**large diameter, ear/central face, recurrent, sites of poor healing, surgical contraindications (excluded morphoeic or infiltrating tumours)*

Vinciullo C et al. Br J Dermatol 2005;152:765-772

Cosmetic Result

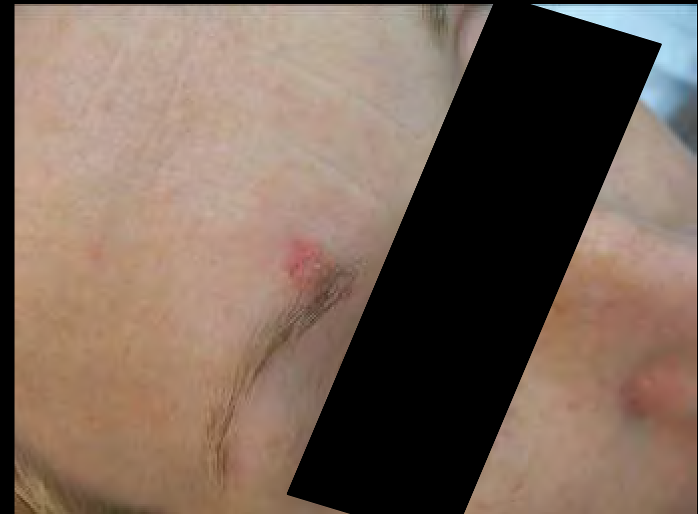
- Rated as good – excellent
- 80-90%
- Patients and investigators
- Across multiple studies

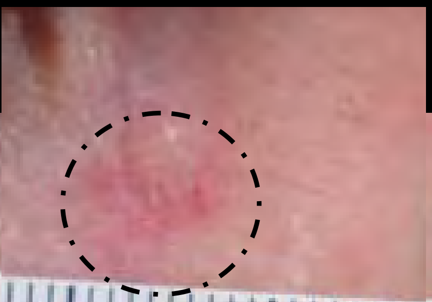
Suitable lesions

- Cosmetically sensitive sites
- Keloid-prone sites
- Healing issues (lower limbs, venous disease, Diabetes etc)
- Large, extensive or multiple lesions

Unsuitable lesions

- Pigmented tumours
- Tumours > 2 mm depth
- Hair bearing skin
- Flexures
- High risk BCC subtypes

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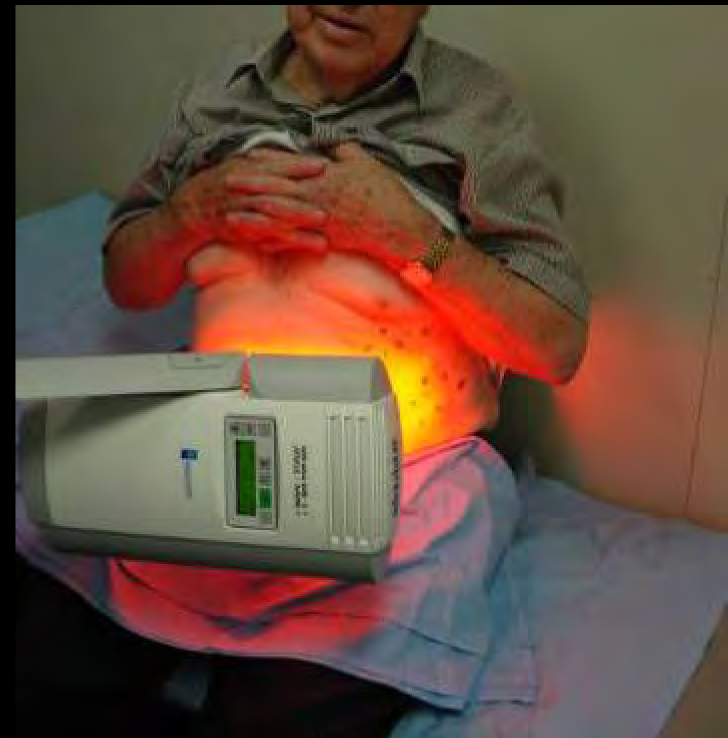
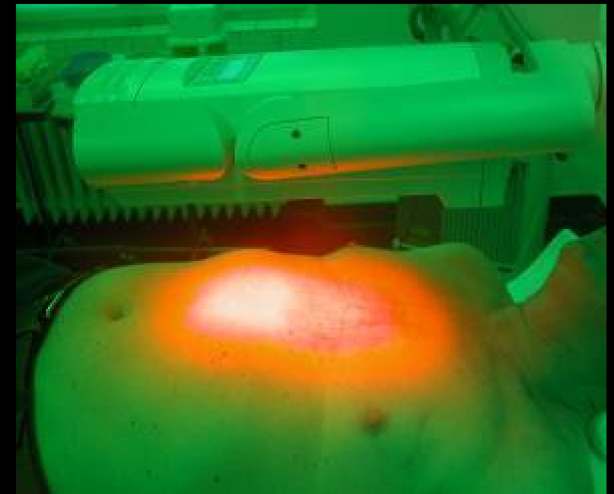
Advantages

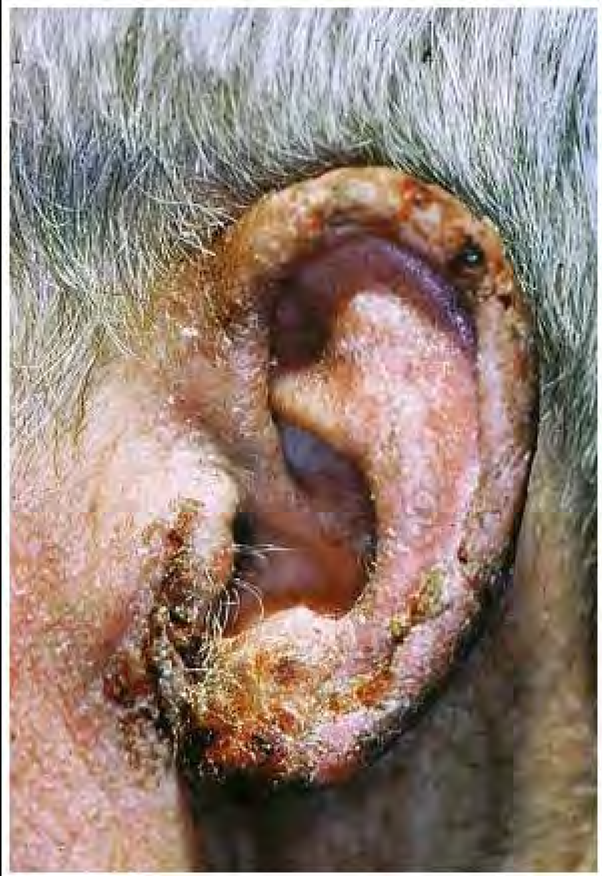
- Cosmesis
- Short down time
- Nurse led procedure
- High patient satisfaction

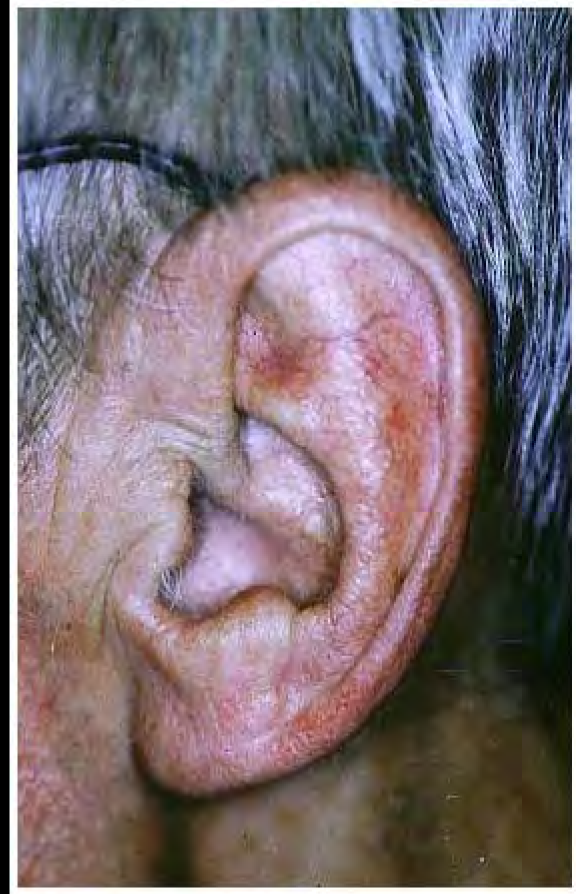


Costs

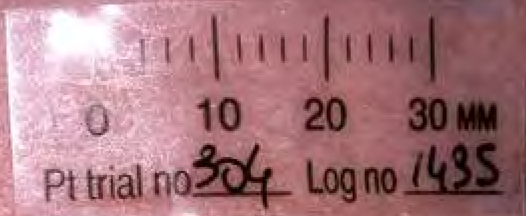
Lamps	$15,000
Cream	$450 for 3g tube Metvix
Treatment	$250/episode

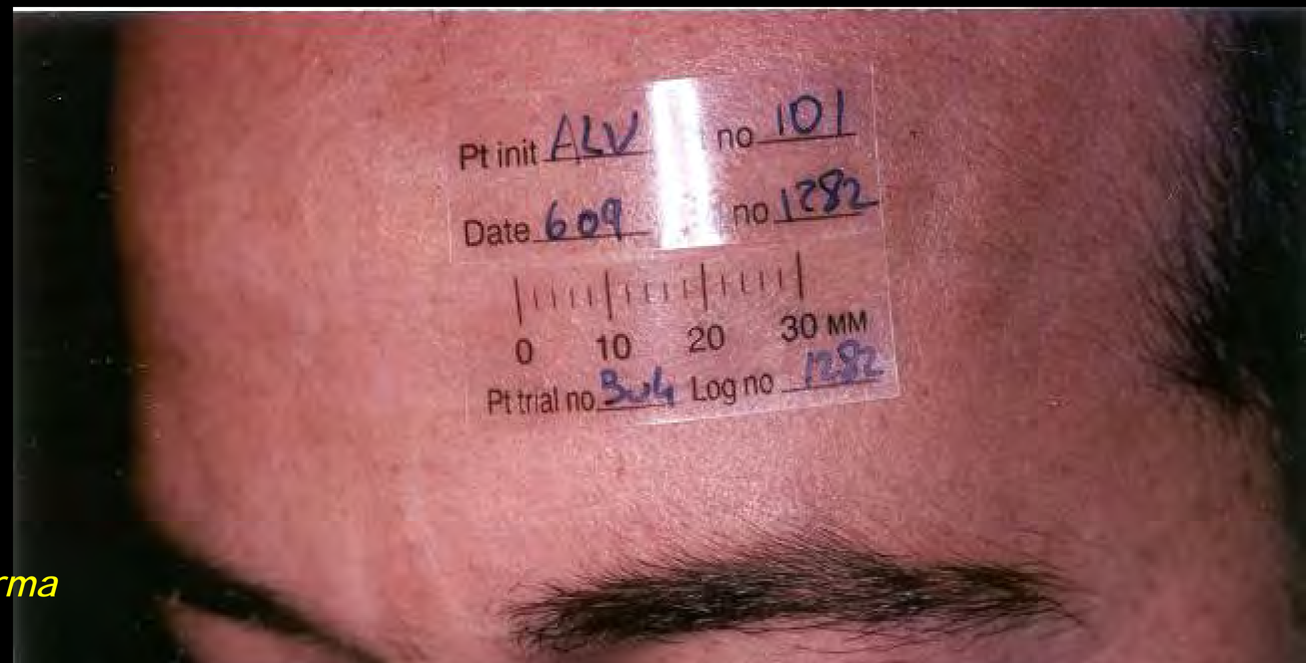


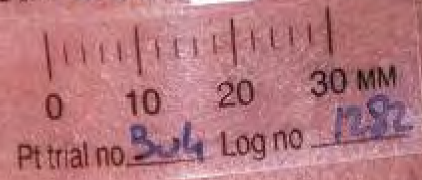




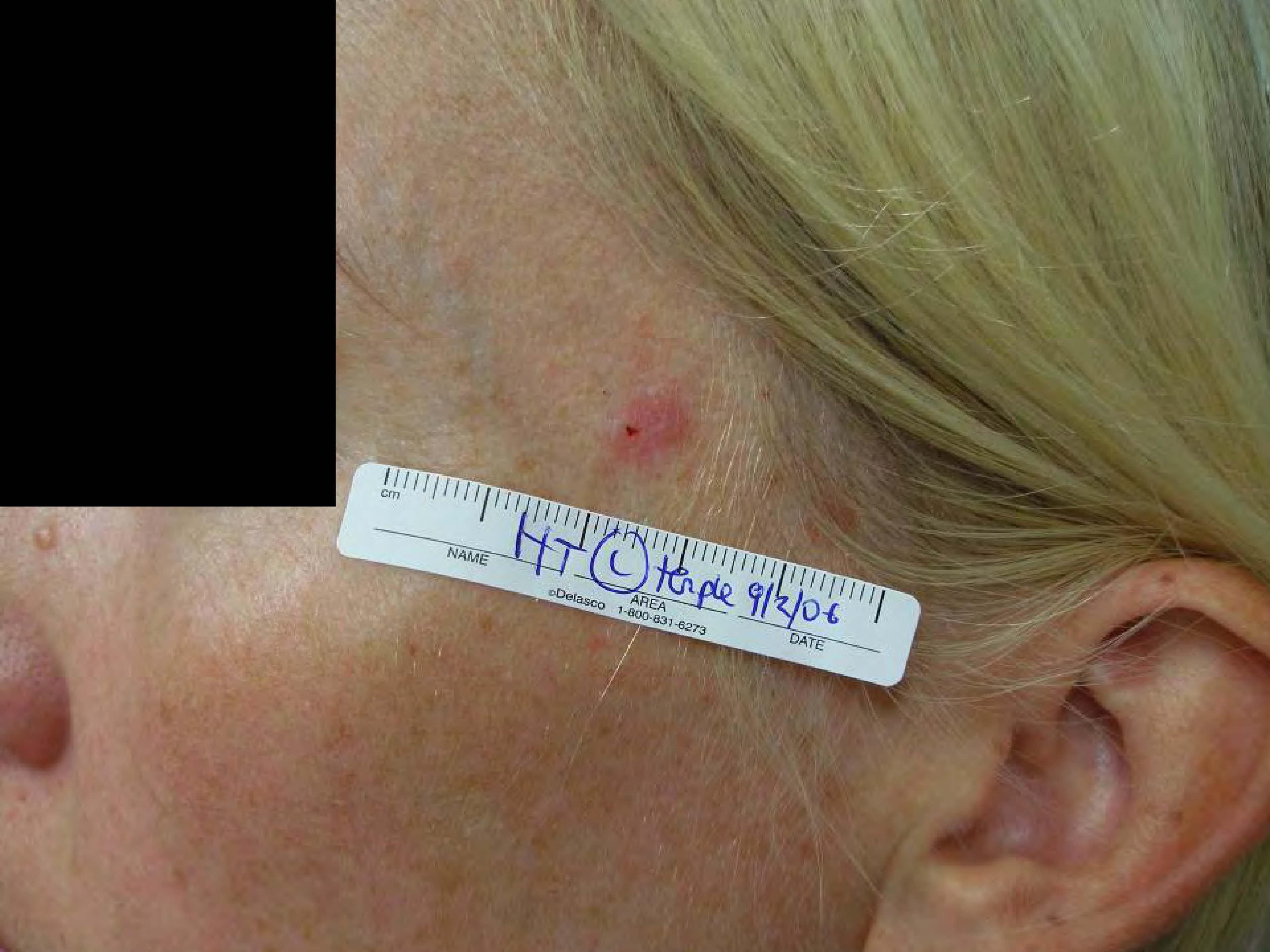
Clinical images courtesy of Galderma







Clinical images courtesy of Galderma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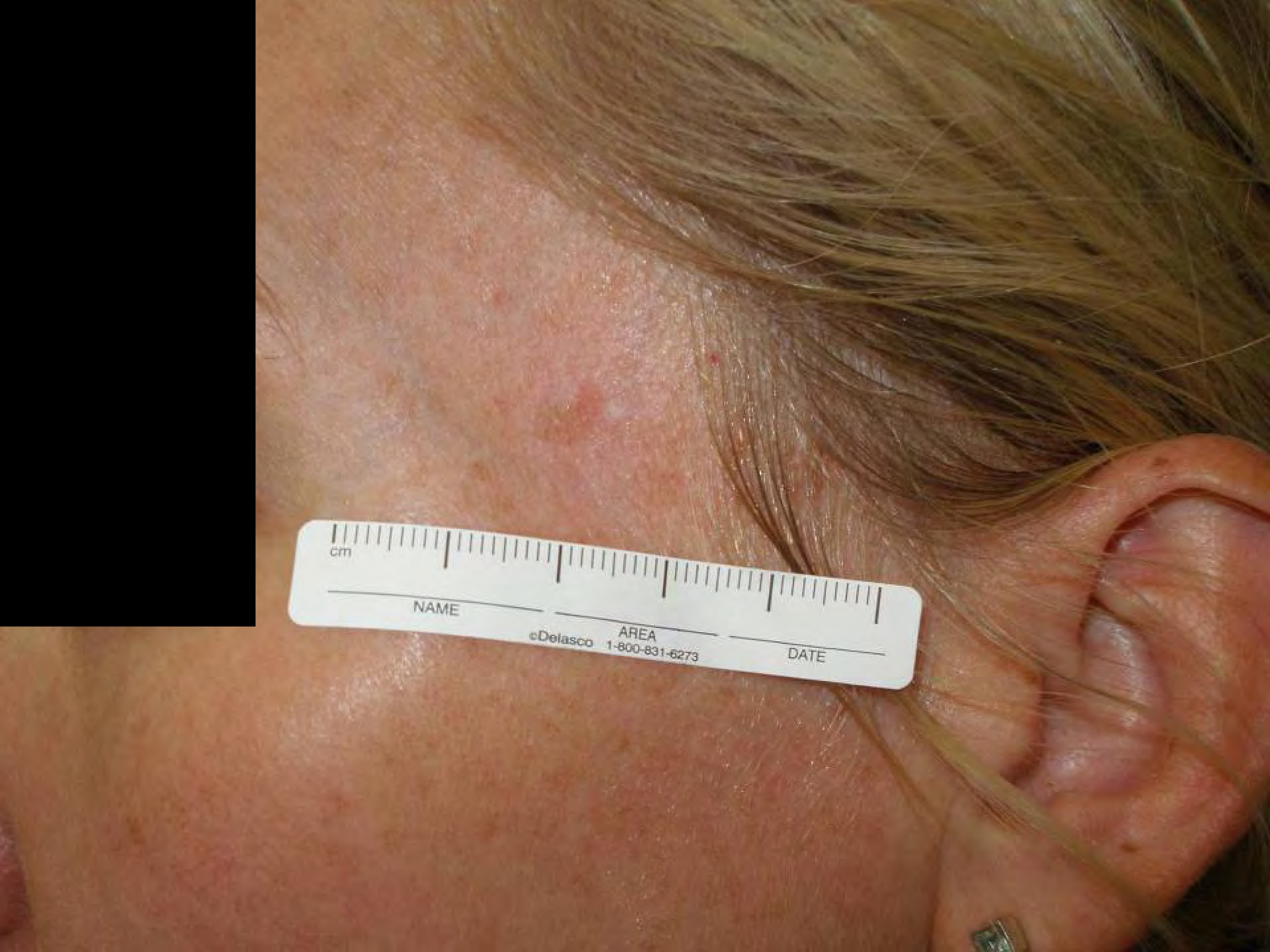

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CSL Biotherapies

3% w/w diclofenac sodium
solaraze™

Solaraze gel

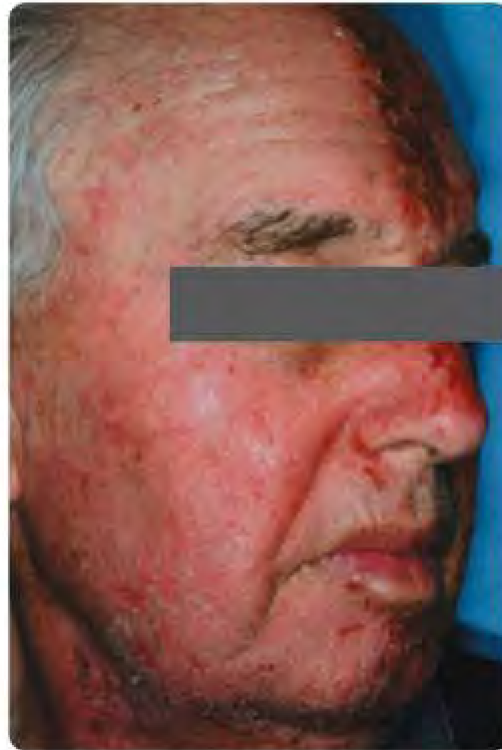
- 3% Diclofenac in Hyaluronic acid gel
- Potent COX-2 inhibitor
- MOA in Rx of solar damage is unknown!
- Field treatment for solar keratoses
- No hypopigmentation
- No photosensitivity
- Good tolerability
- Minimal systemic absorption

Solaraze gel

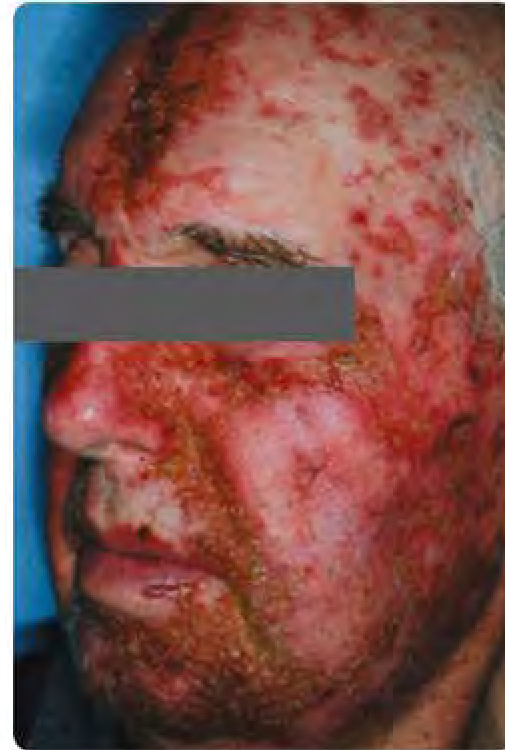
- bd x 90 days
- $90/tube
- Primarily for treatment on H & N
- Limited studies of efficacy
- 30-40% complete response
- 30-40% partial response
- 20-30% irritation (mild-mod)*

**less severe than 5-Fluorouracil*

Split-face study design showing the effects of Solaraze and 5-fluorouracil (5-FU) treatment[1]



▲ Solaraze treatment, appearance after 90 days

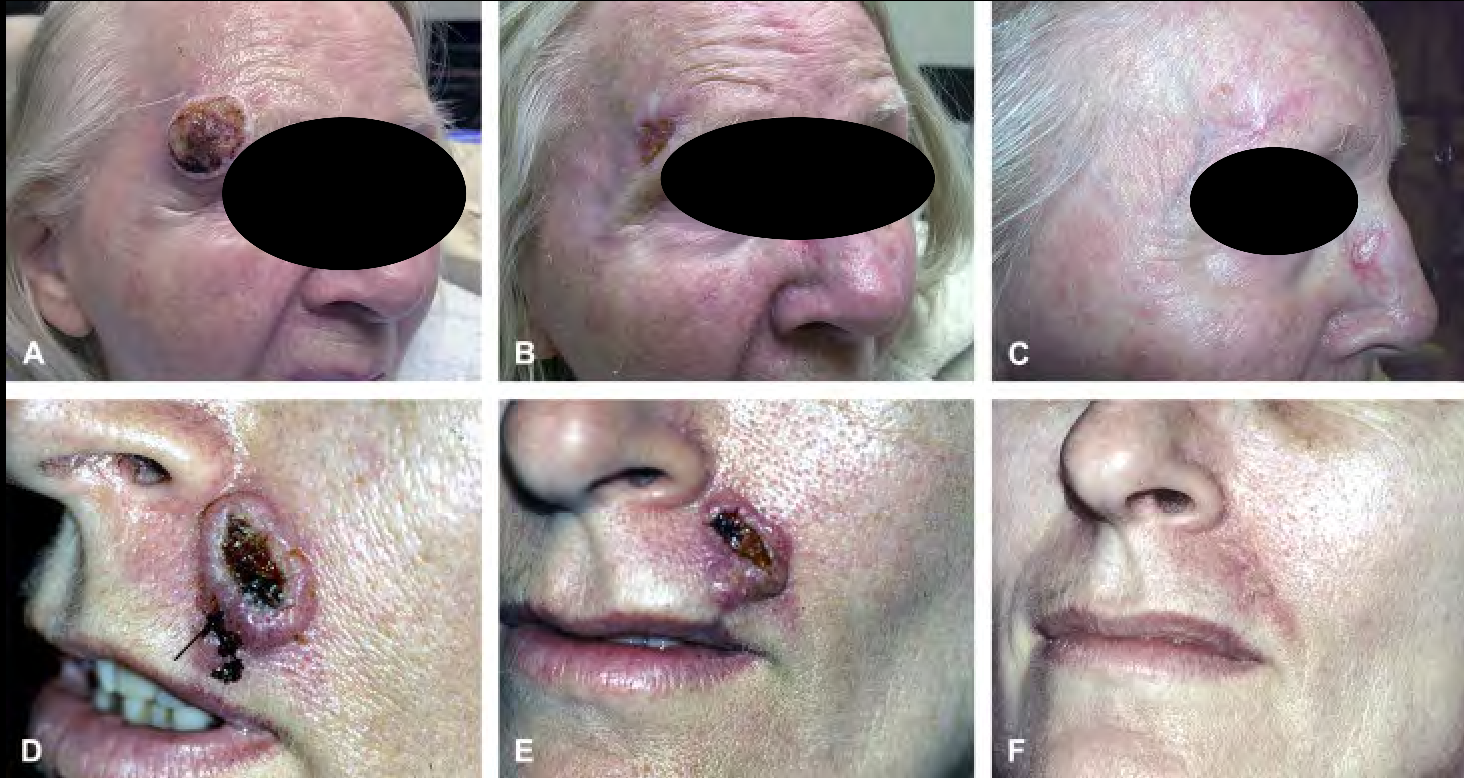


▲ Efudix treatment, appearance after 28 days

Intralesional methotrexate

- Inhibits DNA synthesis
- 92% complete response rate
- Inexpensive
- Anaesthesia not required
- Pancytopaenia in pts with ESRF (2)
- Diagnostic biopsy and FBE
- 1ml of 12.5 - 25.0mg/ml injection
- Fortnightly 1 - 4 treatments (average 2)

Intralesional methotrexate



Annest NM et al. Intralesional methotrexate treatment for kerato-acanthoma tumours: A retrospective study and review of the literature. J Am Acad Dermatol 2007;56(6):989-993

Skin and Cancer Foundation
95 Rathdowne Street
Carlton, 3053
Phone: 639-1744 Fax. 639-3575

SKIN AND CANCER FOUNDATION RADIOTHERAPY CLINIC

INFORMATION SHEET

SKIN AND CANCER TREATMENT BY RADIOTHERAPY:

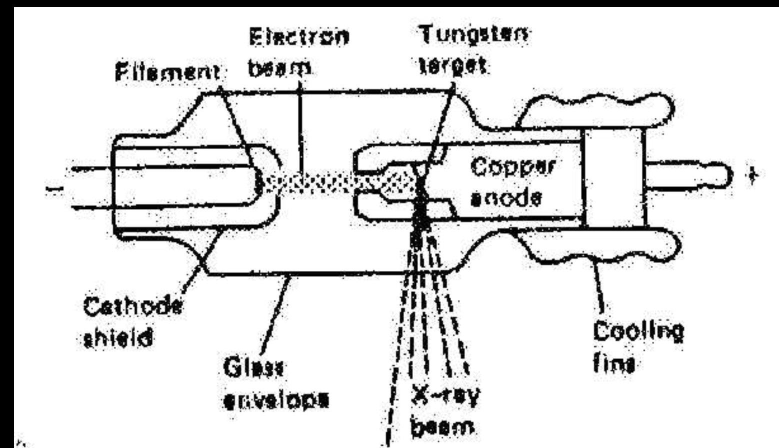
Superficial x-ray therapy has been used in the treatment of skin cancers and other dermatological conditions for over seventy years. In the treatment of skin cancers, radiotherapy has high cure rates equal to surgery. As surgical techniques have improved, the use of radiotherapy has decreased although there is still a significant role for this treatment modality. When surgery is difficult or contra-indicated because of medical conditions, it often is the treatment of choice.

How does X-ray Therapy work?

Radiotherapy for skin cancers use x-rays similar to diagnostic x-rays. They are slightly stronger and used in higher dosage. By carefully dividing the doses over a three week period, it is possible to destroy skin cancer cells while leaving most of the normal tissues cells intact

What happens to me?

At the first visit you will be assessed by the doctor for suitability for treatment with radiotherapy. Treatment areas will be planned and marked out using pencil on the skin. A consent form will be required to be signed. Photographs to document sites of treatment will be taken. Usually, but not always, you will then have your first treatment. The radiotherapy technician will escort you to the radiotherapy room where you will lie down on a bed. Some lead protection to various areas on your body will be attached by tape. Your eyes will be covered with lead to prevent eye damage. The X-ray machine will be positioned appropriately. Treatment will then be given. You cannot feel the x-ray therapy and it is not painful. You will be required to attend two to three times per week for three weeks of treatment. Two weeks after starting treatment you will need to see the doctor again to assess progress of treatment. By this stage a skin reaction will be starting to develop. This skin reaction initially involves redness of the skin but then swelling, crusting and even ulceration may then develop. Instructions on how to care for the treated area will be given. You will then be required to re-attend eight weeks after the initial visit and start of treatment to assess healing. At this stage many of the treated areas will be healed but some cases do take longer. Following this visit your care will be returned to the referring dermatologist.



Relative Indications

- Older patients (> 65 yrs)
- Unfit for surgery or anaesthesia
- Refuse surgery
- Where surgery would result in major loss of function
- Keloid prone areas

Relative Contraindications

- Younger patients
- Hair bearing skin
- Deeply invasive tumours
- Tumours overlying lacrimal gland
- Sites of poor vascularity
- Sites of previous radiotherapy

Guidelines

- **ACN/NHMRC guidelines for management of NMSC 2008**
- **Morton C et al. Guidelines for topical photodynamic therapy. Br J Dermatol Dec 2008**

Non-surgical therapies

Cryotherapy
Aldara (5% Imiquimod) cream
Efudix (5-Fluorouracil) cream
Solaraze (3% Diclofenac) gel
Intralesional MTX
Photodynamic therapy
Superficial radiotherapy

Treatment selection

- Tumour factors
  - type, size, depth, site, behaviour
- Patient factors
  - compliance, dexterity, preference
- Toxicity
- Efficacy
- Cost
- Accessibility