



SCUOLA DERMATOLOGICA
S E R G I O C H I M E N T I

Aggiornamenti sugli algoritmi terapeutici per la cheratosi attinica

Ketty Peris

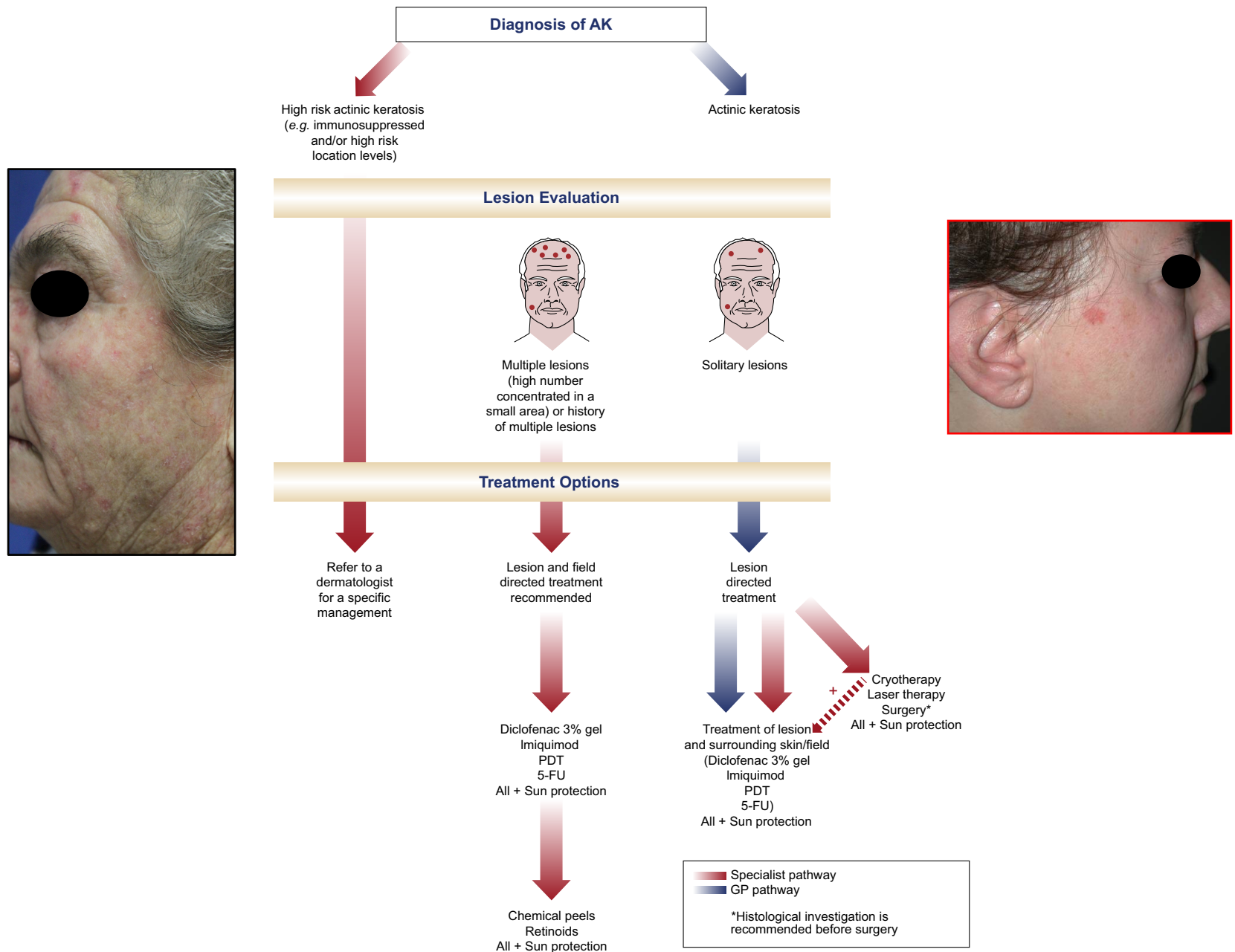
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Goals of AK therapy

- ❖ Eradicate as many clinical and subclinical AK lesions as possible
- ❖ Achieve clinical remission that is as prolonged as possible
- ❖ Provide a good cosmetic result
- ❖ Prevent the progression to invasive SCC

Treatment algorithm for actinic keratosis

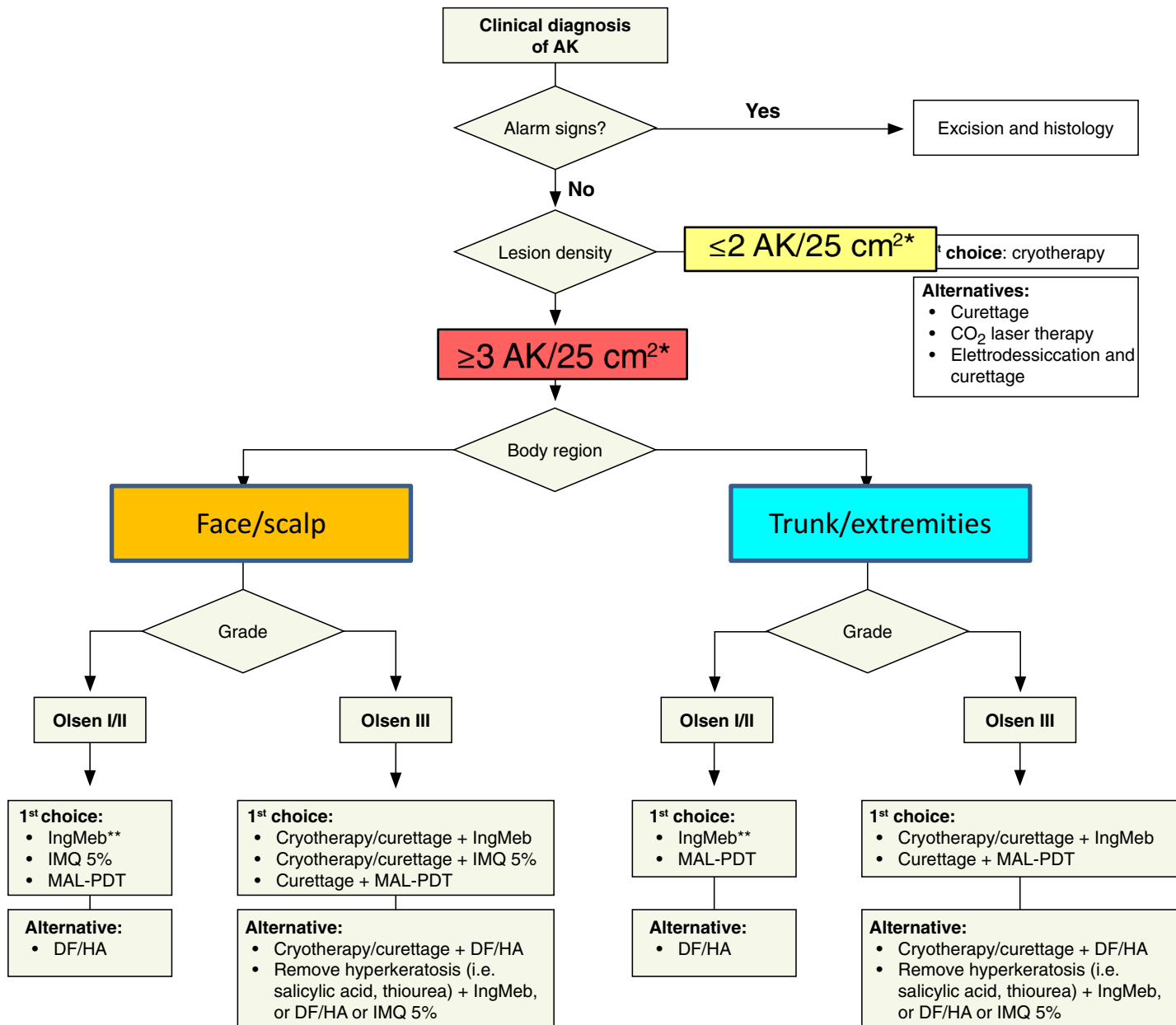


TREATMENT ALGORITHM FOR AK MANAGEMENT, DEPENDING ON LESION NUMBER AND APPEARANCE

Evaluation of lesions

Evaluation of lesions				
	Isolated AK			Multiple AK
	Non-hyperkeratotic AK	Hyperkeratotic AK	Suspicious AK	Non-hyperkeratotic AK
1 st line	▼ • Cryotherapy • Curettage / electrocoagulation	▼ • Cryotherapy • Curettage / electrocoagulation	▼ • Biopsy + exeresis • Biopsy *	▼ • Resurfacing -manual -salicylic acid/urea
				▼ • Topical treatments -5% 5-fluorouracil -3% diclofenac sodium -5% imiquimod -150 µg/g and 500 µg/g ingenol mebutate • Physical treatments -laser -photodynamic therapy
2 nd line	• Surgery if recurrence / resistance			• Physical treatments combined with topical treatments or surgery

*Confirmation of diagnosis of actinic keratosis (AK): Refer to treatment algorithm
 AK, actinic keratosis



*Field-directed therapies may also be considered for a large single lesion when its borders cannot be delimited accurately or in patients who failed previous treatments with cryotherapy (i.e. recurrence in the same area within 12 months). **Single or multiple cycles depending on the extent of the affected area

S3 Guidelines recommendations

Decreasing strength of recommendation	Single AK lesions (≤5)	Multiple AK lesions ≥6	Field cancerization	Immuno-compromised patients with AK
Strong	Cryotherapy	3.75% imiquimod MAL-PDT/ALA-PDT 0.5% 5-FU Ingenol mebutate 0.015%-0.05%		
Weak	Curettage 0.5% 5-FU/5% 5-FU 0.5% 5-FU + 10% SA 3.75% imiquimod 5% imiquimod Ingenol mebutate MAL-PDT/ALA-PDT	Cryotherapy 3% diclofenac in 2.5% HA 5% 5-FU 0.5% 5-FU + 10% SA 5% imiquimod 2.5% imiquimod CO2-laser, Er:YAG-laser		Cryotherapy curettage 5% 5-FU 5% imiquimod MAL-PDT/ALA-PDT
NO	3% diclofenac 2.5% imiquimod CO2-laser Er:YAG-laser	Curettage		3% diclofenac 0.5% 5-FU 0.5% 5-FU + 10% SA 2.5%/3.75% imiquimod Ingenol mebutate
Sunprotection in all patients subgroups				

Structured Expert Consensus on Actinic Keratosis: Treatment Algorithm Focusing on Daylight PDT

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-  AK definition/diagnosis and factors influencing AK treatment decision making
-  A set of 3 clinical cases whereby participants were required to assess the nature of AK, list their preferred management options, and express their view on the appropriateness of dl-PDT use

ISOLATED AK I/II



**MULTIPLE AK I-III IN AN
AREA OF FIELD
CANCERIZATION**



**C/dI-PDT
5-FU
Imiquimod
Ingenol Mebutate**

**MULTIPLE AK I-III AND FIELD
CANCERIZATION**



**C/dI-PDT
5-FU
Imiquimod**

**Cryotherapy
C-PDT
Imiquimod
5-FU
Ingenol Mebutate**

Diagnosis

Diagnosis of AK

Isolated lesions

Multiple lesions/field of actinic damage

Prevention

Preventative measures

- Careful education of sun protection (behaviours, clothing and hats) for all and particularly for immunocompromised patients
- Correct application of high SPF and UVA-PF sunscreens

Biopsy

Biopsy

- Considered for all suspicious (infiltrated and/or painful and/or inflamed ± hyperkeratotic) lesions

Treatment^{1,2}

Lesion-directed treatment

Treatment options⁴:

Conventional PDT
Cryotherapy
Curettage
Electrosurgery/CO₂ laser
Imiquimod 5%
Ingenol mebutate
5-fluorouracil
5-fluorouracil + salicylic acid

Small field of actinic damage³

Treatment options⁴:

Conventional PDT
Daylight PDT⁵
Imiquimod 5%
Ingenol mebutate
5-fluorouracil

Large field of actinic damage³

Treatment options⁴:

Conventional PDT
Daylight PDT⁴
Diclofenac
Imiquimod 3.75%
5-fluorouracil

1. Treatment preferences may vary in different countries due to availability/reimbursement status
2. Treatment options for immunocompromised patients include: cryotherapy and curettage for single lesions, conventional PDT, 5-fluorouracil, and diclofenac for fields of actinic damage. dl-PDT and ingenol mebutate are not included due to lack of clinical data. Imiquimod is not included as a treatment due to safety risks associated with transplant rejection.
3. Hyperkeratotic lesions should be pre-treated separately in advance, or treated with a combined strategy.
4. Treatment options are reported in alphabetical order.
5. Unless AKs are thick and environmental conditions are unsuitable (too cold, too cloudy).

- Published data from RCT are the “gold standard” evidence to support the treatment recommendations

EMA-approved topical therapies for AK

THERAPY	AK TYPE	Tx AREA	TREATMENT REGIMEN	DURATION	LESION CLEARANCE (%)
- 5% 5-FU - 0.5% 5-FU + 10% salycilic acid		25 cm ²	Twice daily Once daily	2-4 weeks Up to 12 wks	75-88
Imiquimod 5% cream	I-II	25 cm ²	3 times a week for 4 wks 4 wks off and 4 wks on, if needed	4 weeks	75.7
Imiquimod 3.75% cream	I-II	100-200 cm ²	Daily 2 weeks on, 2 weeks off, 2 weeks on	2 + 2 weeks	92.2
Ingenol mebutate 150-500 mcg/g gel	I-II	25 cm ²	<u>Face/scalp</u> : 0.015% once daily for 3 consecutive days <u>Trunk/extremities</u> : 0.05% once daily for 2 consecutive days	2-3 days	75-83
Diclofenac 3% gel	ns		Twice daily	60-90 days	54-63
c/dIPDT		100 cm ²	Prepare skin. Apply cream 3 hours under occlusion prior to illumination	1 day	82-91

Factors that drive treatment choice in real life clinical practice

Lesion characteristics

Number



Thickness



Distribution



Factors that drive treatment choice

Patient variables

- Age (comorbidities)
 - Ability to perform home-based treatment
 - Patient's immune status
 - Adherence to the Tx regimen
 - History of previous treatment
-
- Availability of drugs/procedure
 - Dermatologist experience

Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology

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ABSTRACT

Actinic keratosis (AK) is a chronic skin disease in which multiple clinical and subclinical lesions co-exist across large areas of sun-exposed skin, resulting in field cancerisation. Lesions require treatment because of their potential to transform into invasive squamous cell carcinoma. This article aims to provide office-based dermatologists and general practitioners with simple guidance on AK treatment in daily clinical practice to supplement existing evidence-based guidelines. Novel aspects of the proposed treatment algorithm include differentiating patients according to whether they have isolated scattered lesions, lesions clustered in small areas or large affected fields without reference to specific absolute numbers of lesions. Recognising that complete lesion clearance is rarely achieved in real-life practice and that AK is a chronic disease, the suggested treatment goals are to reduce the number of lesions, to achieve long-term disease control and to prevent disease progression to invasive squamous cell carcinoma. In the clinical setting, physicians should select AK treatments based on local availability, and the presentation and needs of their patients. The proposed AK treatment algorithm is easy-to-use and has high practical relevance for real-life, office-based dermatology.

ARTICLE HISTORY

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KEYWORDS

Diclofenac; field cancerisation; 5-fluorouracil; imiquimod; ingenol mebutate; photodynamic therapy

AK CLASSIFICATION

ISOLATED LESION

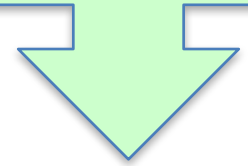


isolated individual lesions
scattered on separate body
areas

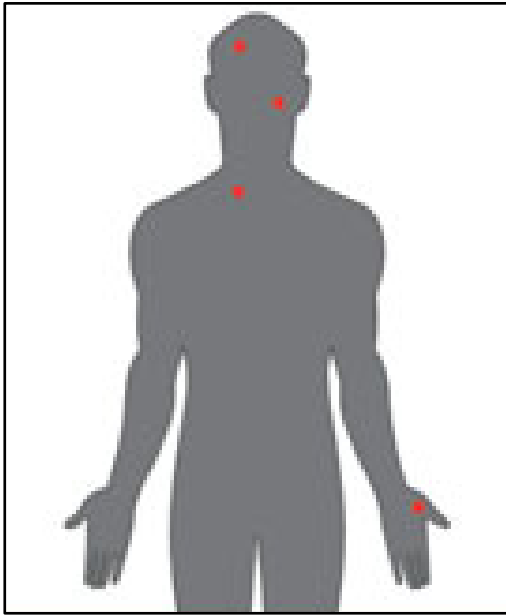
MULTIPLE LESIONS CLUSTERED INTO A SMALL FIELD



MULTIPLE LESIONS ACROSS A LARGE FIELD (e.g ENTIRE FACE OR SCALP)

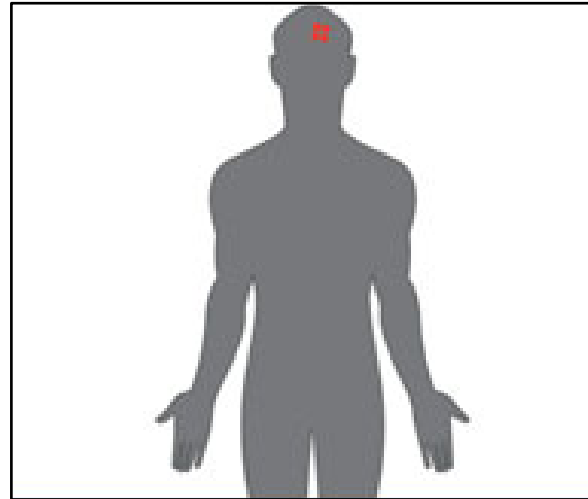


Lesion-directed therapies for *single or scattered lesions*



- Cryotherapy
- Topical active drugs
- Laser (CO₂; Er:Yag)
- Curettage

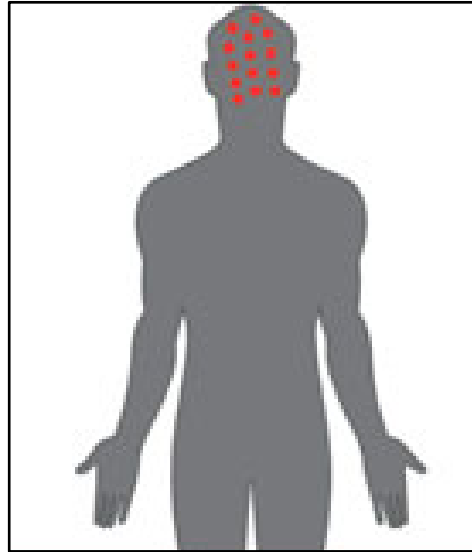
Clustered-directed therapies (areas $\leq 25 \text{ cm}^2$)



- Imiquimod 5%
- 0.5% 5-FU / 10% salicylic acid
- Ingenol Mebutate

All large field-directed therapies can be used to treat clusters

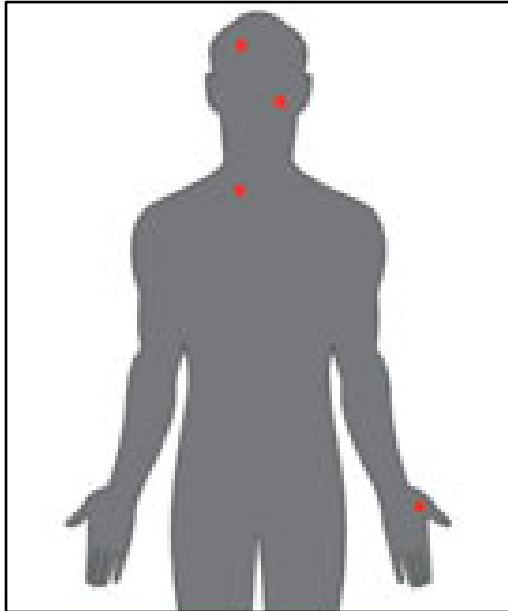
Large field-directed therapies for *multiple lesions*



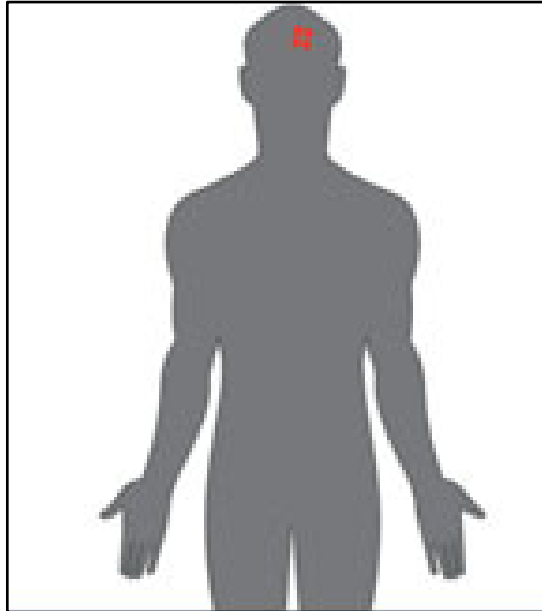
- IMQ 3.75%
- 5-FU
- Diclofenac gel
- PDT

Clustered-directed therapies may be used to treat large fields in successive treatment cycles

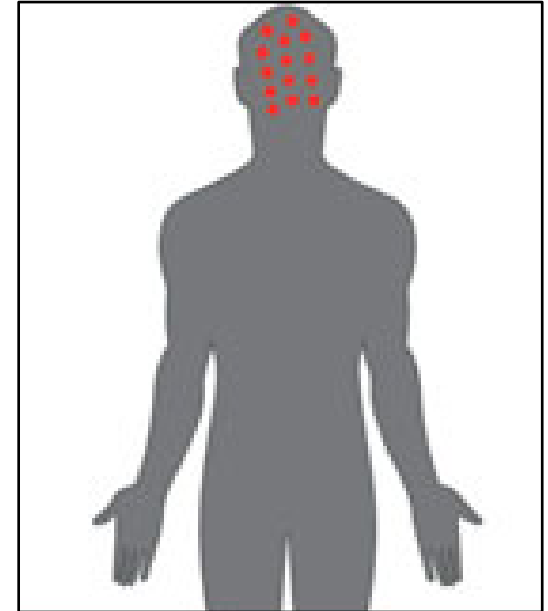
SCATTERED LESIONS



CLUSTERED LESIONS IN A SMALL FIELD



CLUSTERED LESIONS IN A LARGE FIELD



Lesion-directed therapies

Cluster-directed therapies

Large field-directed therapies

TREATMENT SUCCESS EVALUATION AFTER 3 TO 6 MONTHS

Real-life efficacy and safety of ingenol mebutate for the treatment of actinic keratosis of the face and scalp: A single arm retrospective study

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Maria Concetta Fargnoli^b and Ketty Peris^a

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Lesion clearance rate: 81.3% (vs 78% in RCT)



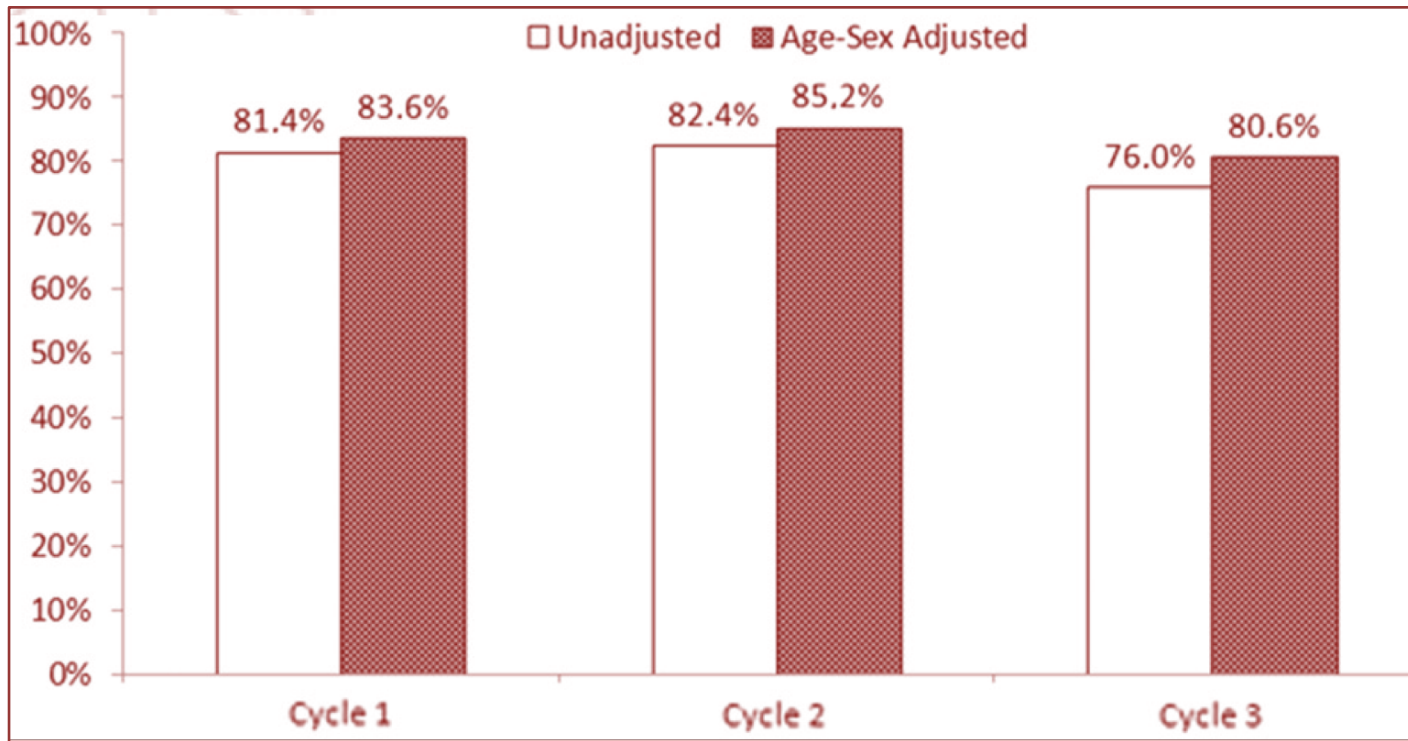
Day 0



Week 8

- Scalp lesions had a higher clearance rate compared to RCT (80% vs 53%)

- No differences in clearance rate for patients who were *previously treated* compared to naïve patients
- No differences according to patients' age, sex and baseline number of AK lesions
- No difference of efficacy *across treatment cycles*



IMIQUIMOD 5%

- Can be used to treat *small clusters of lesions* in a 25 cm² area
- Self-applied 3 times/week for 4 wks; 4 wks free interval, II 4wks course
- Can detect and treat both clinical and subclinical lesions
- Clearance rate: 75%
- Used to treat large affected fields (i.e. full face or balding scalp) in sequential treatment courses (high cost)

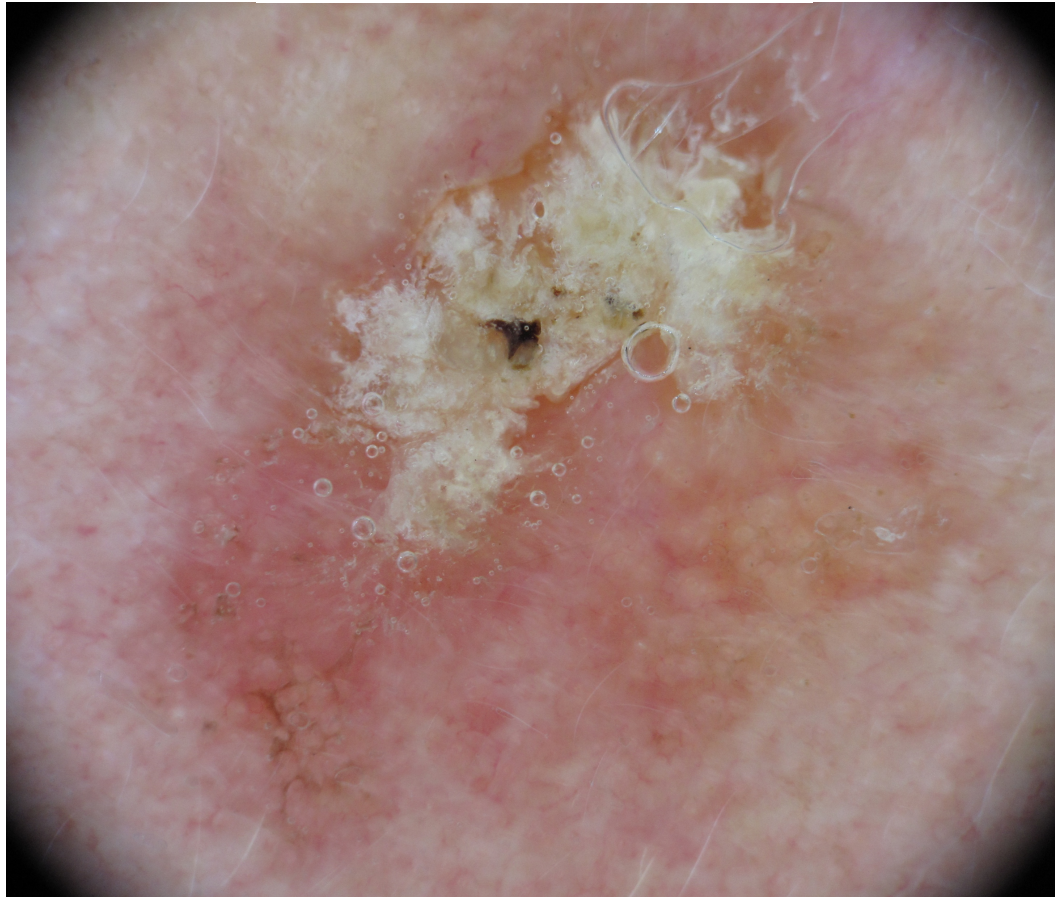
IMIQUIMOD 3.75%

- Can be used to treat *large affected fields* (i.e. full face or balding scalp) in one treatment course
- Self-applied once daily for 2 wks treatment cycles separated by a 2-wks free interval
- Can detect and treat both clinical and subclinical lesions
- 81.8% median percentage reduction in AK lesions from baseline
- Sustained clinical response over long-term

Diclofenac 3% in 2.5% hyaluronic acid

- NSAD which inhibits cyclooxygenase 2
- Treat *clustered lesions* and *field cancerisation*
- Overall lesion clearance rates reported in RCTs: 54–63%
- Advantage: good tolerability with only mild irritant side effects (pruritus, erythema and dry skin; rare: contact dermatitis)
- Treatment duration is long (60-90days): difficult for many patients to fully comply

Hyperkeratotic AK



Before any specific treatment

- Urea 10-30% cream
- Salicylic acid 10%
- Gentle curettage

TREATMENT OF ACTINIC CHEILITIS



- Cryosurgery
- 5% 5-FU
- MAL-PDT followed by IMQ
- Ingenol Mebutate
- Surgical vermilionectomy

NO RCT !

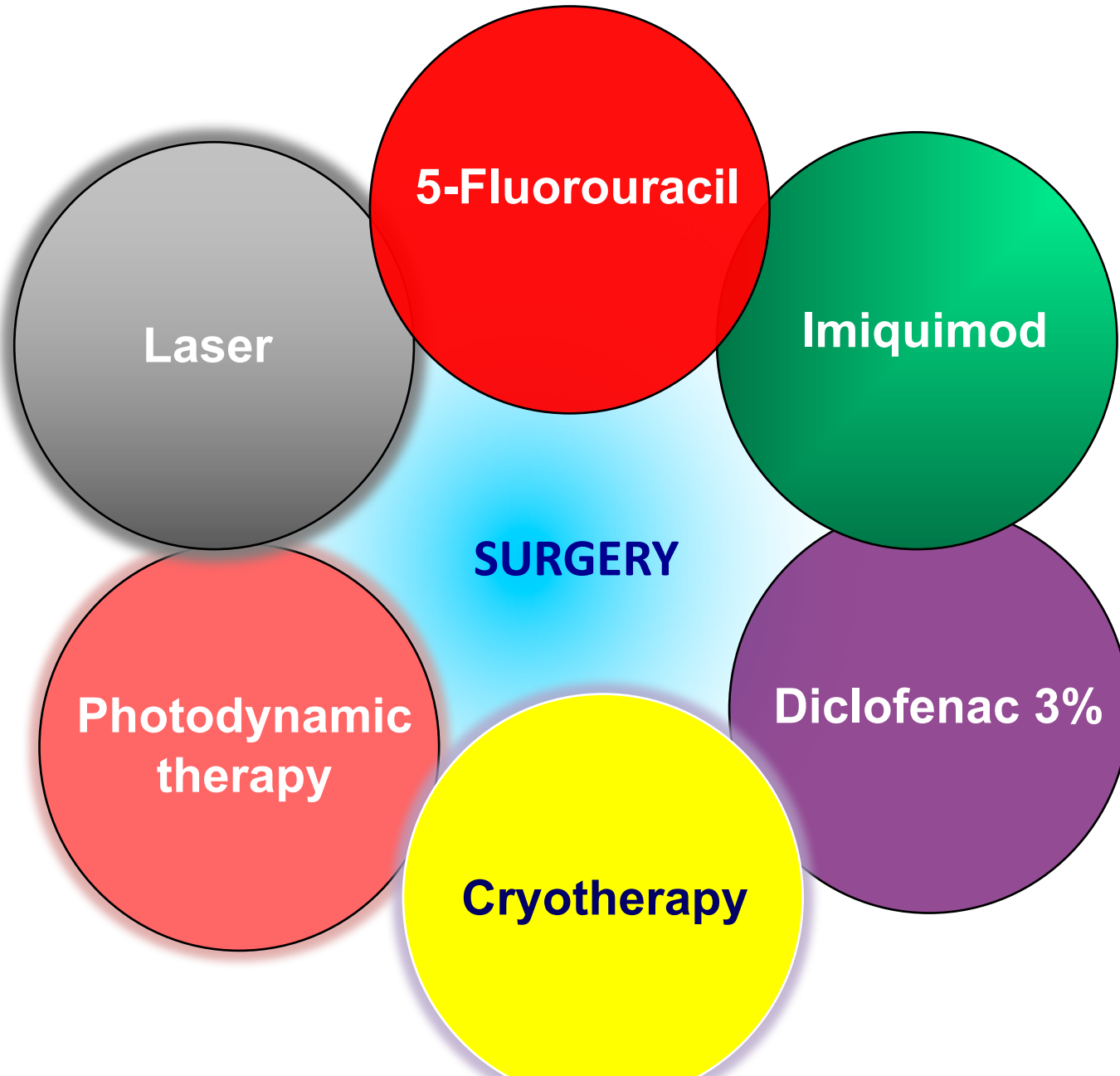
AK treatment in OTR

- Cryotherapy
- Curettage and electrodesiccation
- PDT
- Imiquimod*
- Ingenol mebutate**
- Diclofenac 3%
- Systemic retinoids

*off label

**no studies

Combined or sequential treatments



Combined or sequential treatments

- **Field-treatment** followed by cryo to target individual, resistant lesions
- **Lesion-directed** treatment followed by field-directed therapy, used to treat the actinic damage in the surrounding area
 - Cryosurgery followed by imiquimod 3.75%
 - Cryosurgery followed by 5-fluorouracil
 - PDT followed by imiquimod 5%
 - 5-FU followed by ALA-PDT
 - Diclofenac 3% followed by PDT

Gilbert DJ 2005; Price NM 2007; van der Geer S 2009; Shaffelburg M 2009; Jorizzo JL 2010; Sotiriou E 2011; Ondo AL 2012; Held L 2012, Serra-Guillen C 2012; Hoover WD 2014

CONCLUSIONS

- Deliver simple yet complete information about the modality of self-administration (apply to the target area or the whole area, e.g. full scalp or face) and the expected course of therapy
- Routine follow-up evaluation (every 3-6 months) to examine skin carefully and identify new, early AK lesions as well as other skin cancers
- Sunprotection! Instruct the patient to avoid excessive sun-exposure and to use sunscreen daily