Non-melanoma skin cancer:

- Topische behandelingen
- Preventieve behandelingen

Tine Strobbe

Incidentie en impact NMSC

Meest voorkomende vorm van kanker wereldwijd

Incidentie stijgt

Onder-rapportage

1/3 van alle kanker diagnosen elk jaar

grote impact (kosten, hulpverleners)

Belang van preventie en vroegtijdige detectie

Risico op recidief na NMSC

risico recidief na NMSC: 41% na 5 jaar

risico recidief na meerdere NMSC: 82% na 5 jaar

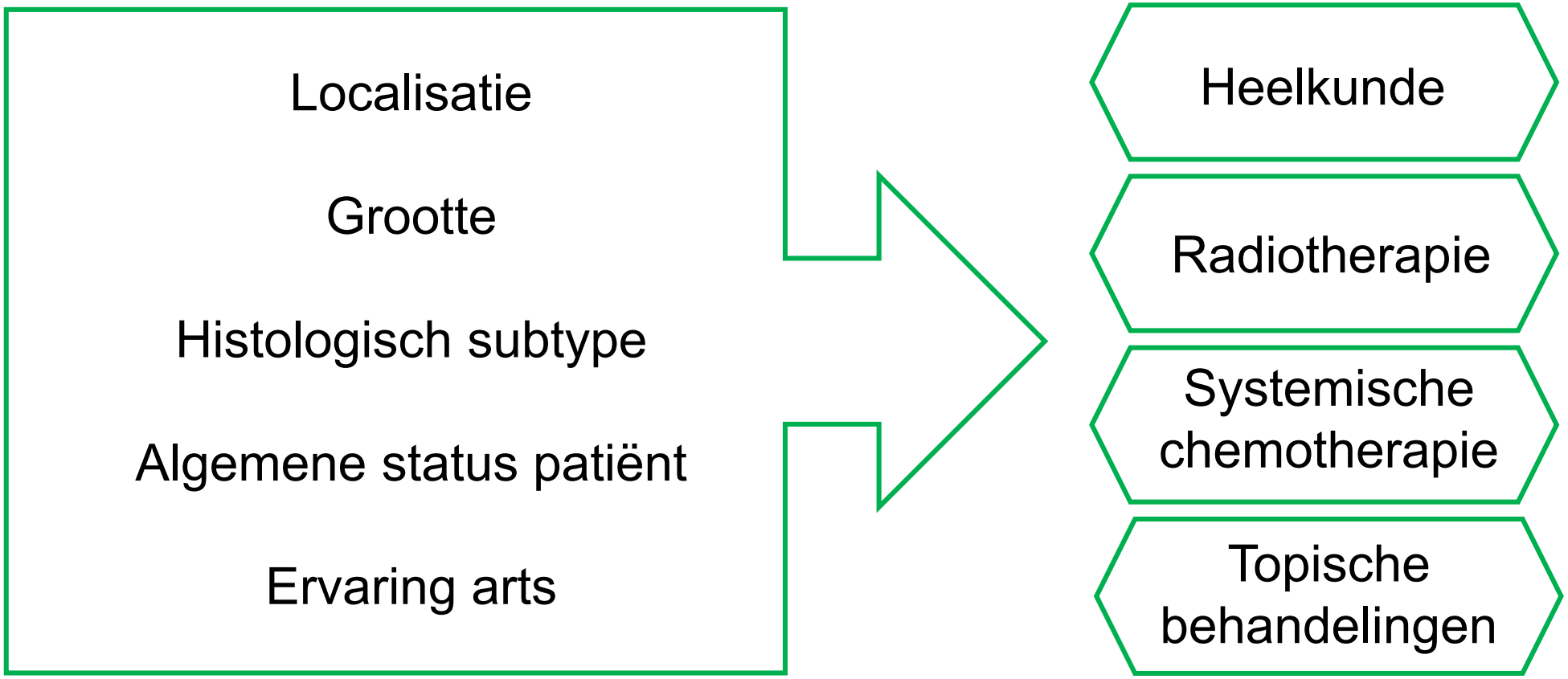
risico recidief na SCC: 50%, meestal 1ste jaar

Cave immuno-supressie en hematologische kankers

Belang van preventie en vroegtijdige detectie

Am Fam Physician. 2020;102(6):339-346
Dtsch Arztblatt Int 2019; 116:616-26

Keuze behandeling NMSC



Voor- en nadelen topische behandelingen

Gelocaliseerde ziekte in vroeg stadium

Kan zelf toegepast worden

Niet invasief

Meerdere precancereuze letsels samen behandelen

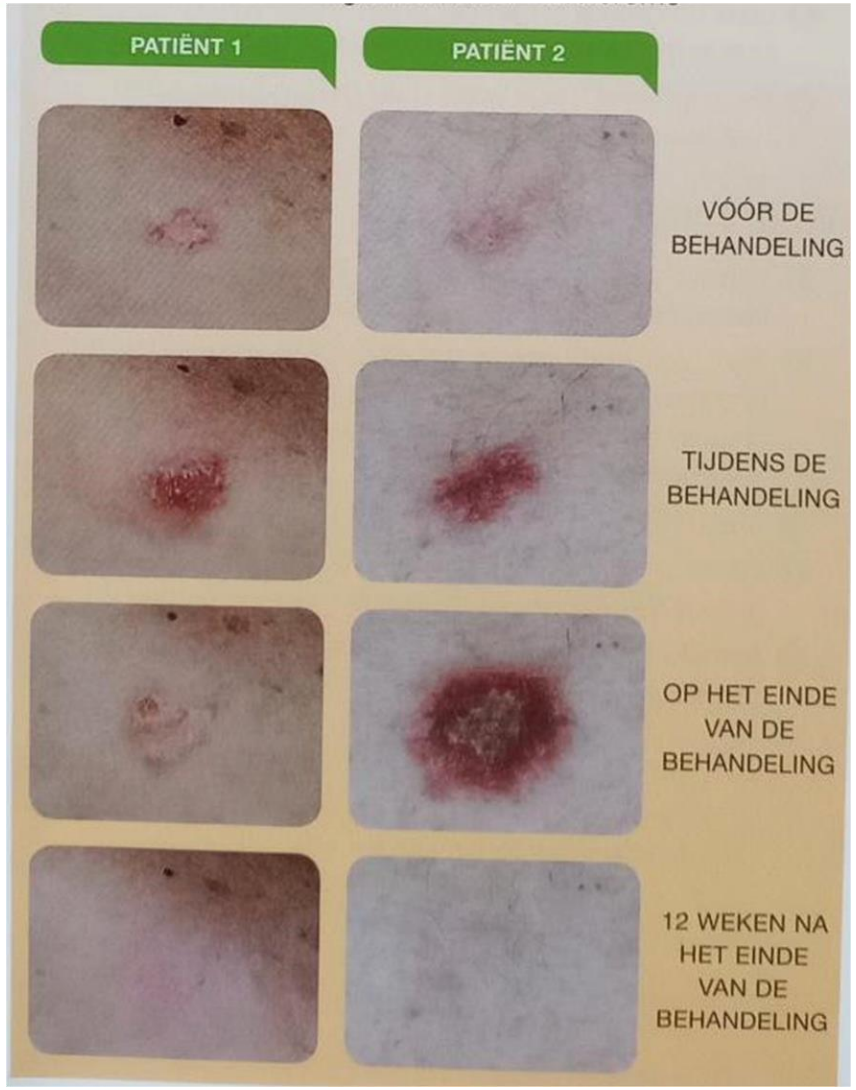
Goede cosmetische outcome

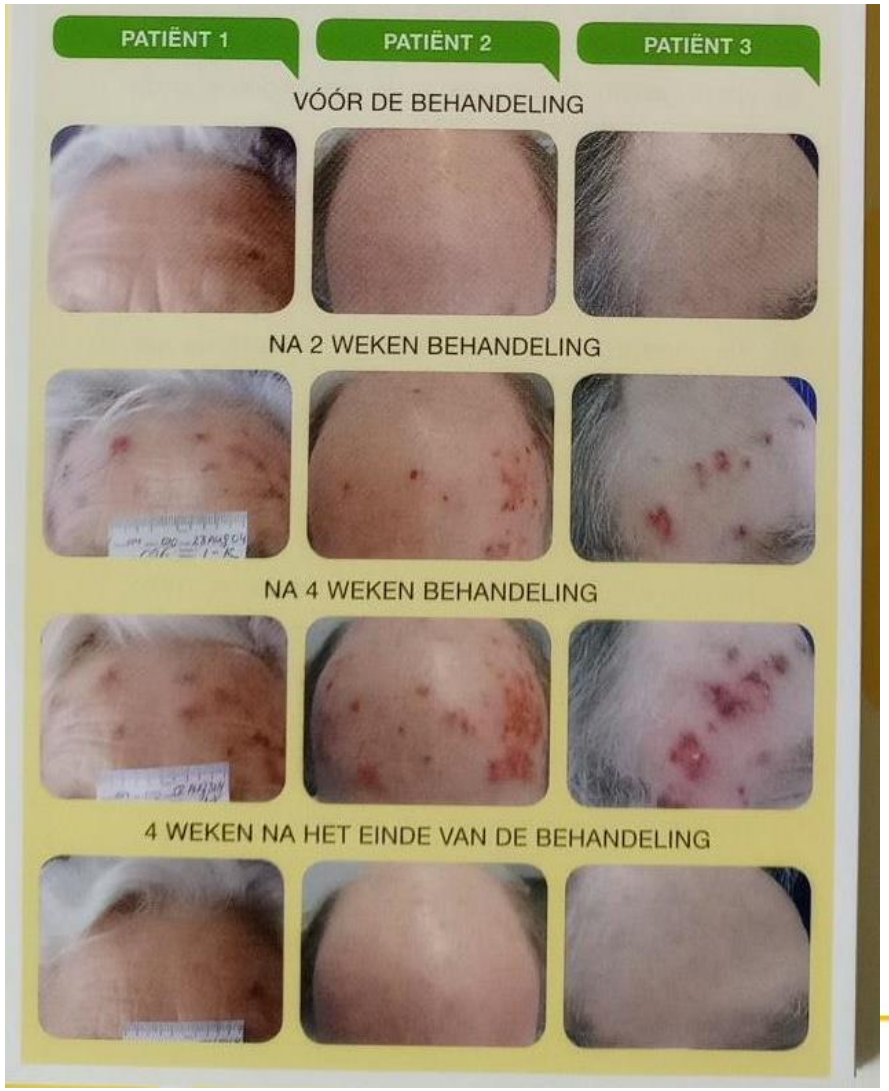
drug penetration

Compliance

Lokale bijwerkingen (inflammatie, irritatie)

Lokale bijwerkingen





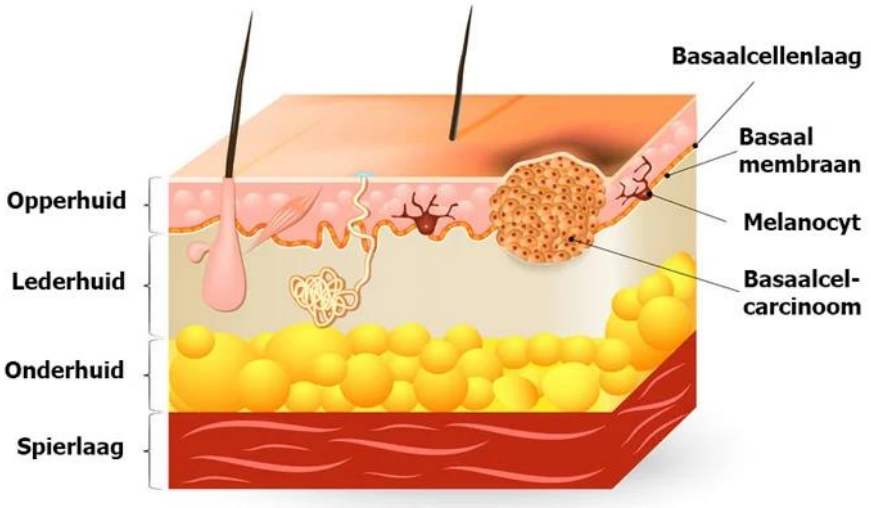
Overzicht topische behandelingen

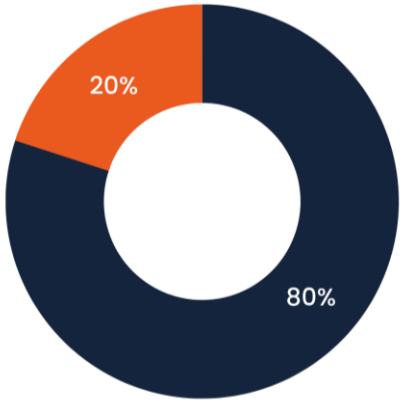
Table 1. Overview of common topical pharmacological treatments for non-melanoma skin cancer and precancerous lesions.

Therapeutic Agent	Dosage Form	Strength	Brand Names	Mode of Action	Common Indications	Limitations	Physico-Chemical Properties	Ref.
5-Fluorouracil (5-FU)	Cream	5%	Efudex® Carac®	Interferes with DNA synthesis by blocking thymidylate synthase	Bowen's disease (SCC in situ); superficial BCC; AK	Skin irritation; photosensitivity	Log P (−0.85); molecular weight (130.078 g/mol); melting point (291.8 °C)	[31,42]
Imiquimod (IMQ)	Cream	5%	Aldara®	Induces immune response against cancer cells	Superficial BCC; genital warts; AK	Local skin reactions; psoriasis	Log P (2.6); molecular weight (240.30 g/mol); melting point (295 °C)	[37,43]
Diclofenac sodium	Gel	3%	Solaraze®	Inhibits COX-2 enzyme, reducing prostaglandin E2 synthesis	AK	Local skin irritation; digestive adverse events	Log P (4.26); molecular weight (318.13 g/mol); melting point (286 °C)	[44]
Ingenol mebutate	Gel	0.015%	Picato®	Induces local lesion cell death; promotes an inflammatory response	AK	Local skin irritation	Log P (3.12); molecular weight (430.5 g/mol); melting point (153.5 °C)	[45]
Tirbanibulin	Ointment	1%	Klisyri®	Disrupts microtubules by direct binding to tubulin	AK	Local skin irritation; sun sensitivity	Log P (N/A); molecular weight (g/mol); melting point (N/A)	[46]

Pharmaceutics **2023**, *15*, 2577

Basocellulair carcinoom





Zichtbaar

Trage groei

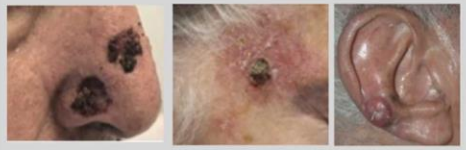
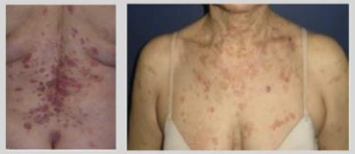
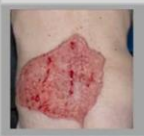
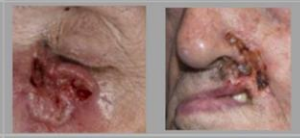
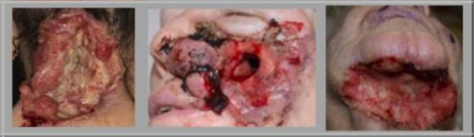
Destructief

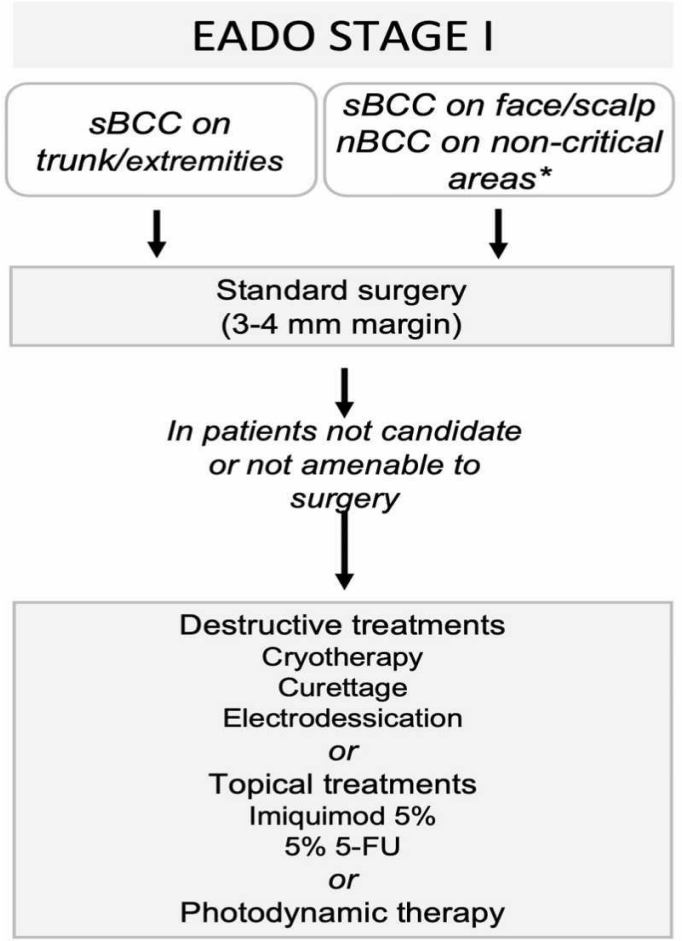
Table 2. Differences between high-risk and low-risk basal cell carcinoma [3,15].

	Low Risk	High Risk
Histological subtype	– Superficial – Macronodular	– Morpheaform – Infiltrative – Micronodular
Perineural/perivascular infiltration	No	Yes
Size	<5 cm	>5 cm
Location	Remaining	– Centrofacial – Periocular – Ears
Other	Primary naïve tumour without associated high-risk factors	– Relapsing – Immunosuppression

Dtsch Arztblatt Int 2019; 116:616-26

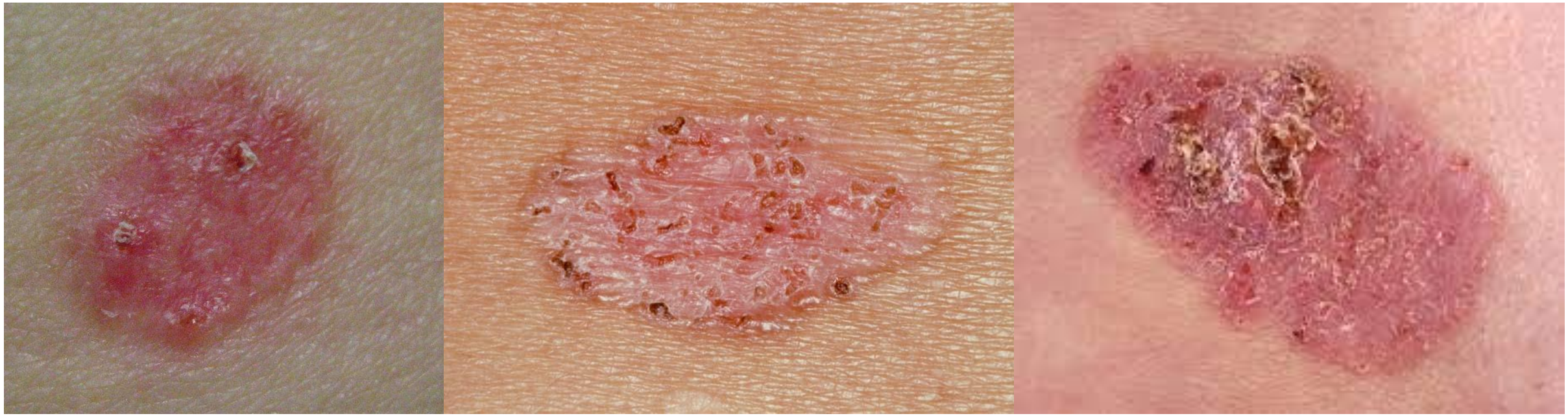
BCC: Plaats topische behandelingen

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*



K. Peris et al. European consensus-based interdisciplinary guidelines for diagnosis and treatment of basal cell carcinoma-update 2023; European Journal of Cancer 192 (2023) 113254

BCC: Plaats topische behandelingen



BCC: Topische behandelingen

- RCT bij sBCC:

	Treatment succes at 1 year	Tumor free survival after 5 years
Imiquimod 5x/w 6 weken	83,4%	80,5%
5-FU 2x/d 4 weken	80,1%	70%
MAL-PDT 2x met 1 week tussen	72,8%	62,7%

- resultaten onafhankelijk van dikte en aantasting adnexen:

K. Peris et al. European consensus-based interdisciplinary guidelines for diagnosis and treatment of basal cell carcinoma-update 2023; European Journal of Cancer 192 (2023) 113254

Bijwerkingen:

Imiquimod	5-FU	MAL-PDT
Lokaal erytheem, zwelling Erosies, korsten Irritatie, jeuk 5% grieperig gevoel	Lokaal erytheem, zwelling Erosies, korsten Irritatie, jeuk	Pijn/discomfort tijdens belichting

BCC: Topische behandelingen

5-FU

- cytotoxisch
- dysruptie van DNA synthese (inhibitie thymidylaat synthase)

- studie:
  - 93% succes rate na behandeling 113 sBCC met topisch 2x daags
  - 90% histologische genezing (gemiddelde genezing 10 weken)

Imiquimod

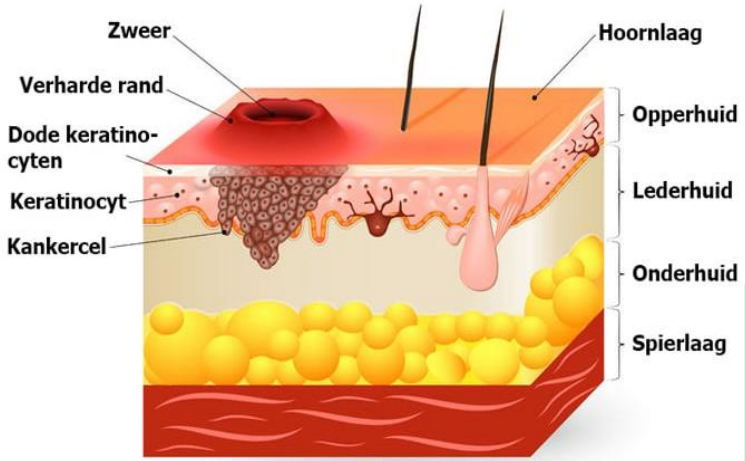
-immunomodulerend
- agonist van Toll-like receptor 7

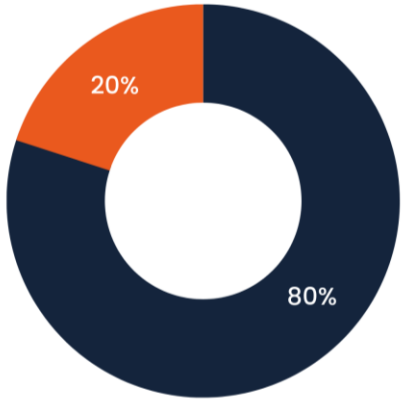
- studie:
  - 90% histologische genezing bij 1x/d 6 weken
  - 82% histologische genezing bij 5x per week 6 weken

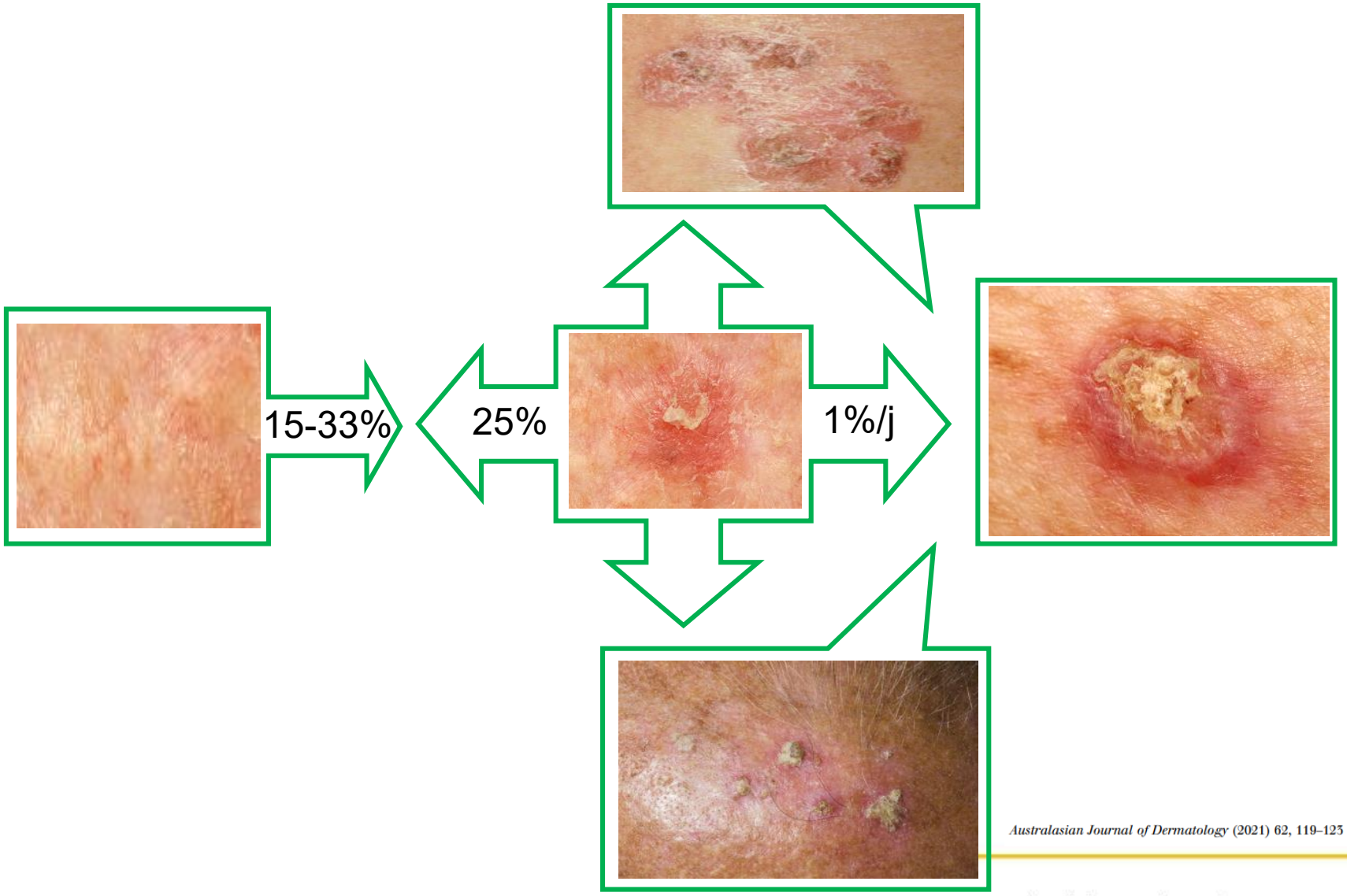
- terugbetaling

Pharmaceutics **2023**, *15*, 2577

Spinocellulair carcinoom

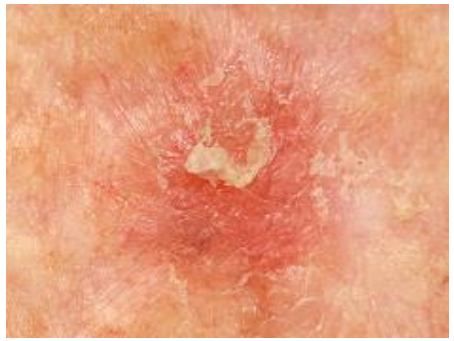






Australasian Journal of Dermatology (2021) 62, 119–125

Aktinische keratose



keratotisch letsel

op chronisch zonblootgestelde huid

droog, ruw, soms gepigmenteerd

variabel in grootte en dikte

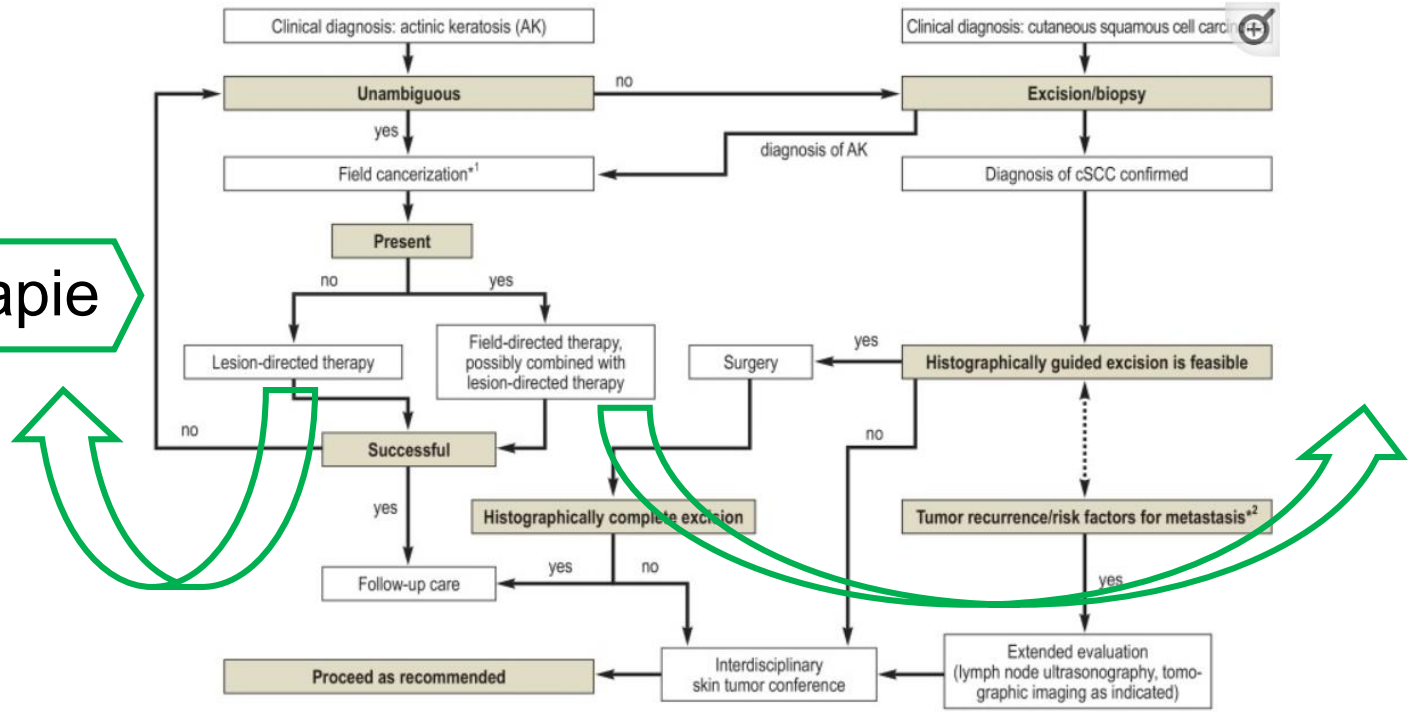
voornaamste zichtbare marker voor solaire schade

meest betrouwbare indicator voor zon gerelateerde huidkankers, vnl SCC

risicofactoren voor ontwikkelen SCC zijn:
immunosupressie, voorgeschiedenis van huidkanker, hoge cumulatieve UV blootstelling, aantal aanwezige letsels, dikte letsels

Behandelings algoritme

Figure 2



Diagnostic and therapeutic algorithm for actinic keratosis and cutaneous squamous cell carcinoma

*1Field cancerization: multiple actinic keratoses and evidence of ultraviolet-induced damage in a contiguous area of skin

*2Risk factors: tumor thickness >6 mm, or tumor thickness >2 mm with additional risk factors (histologic grade = G3, perineural or desmoplastic growth, localization on lower lip or ear, immune suppression), or positive clinical finding (e.g., palpable regional lymph node enlargement)

Dtsch Arztblatt Int 2019; 116:616-26

Cryotherapie

PDT

5-FU

Imiquimod

Diclofenac

Ingenol Mebutate

Tirbanibuline

Keuze behandeling AK:

Table 2

Factors affecting the choice of treatment for actinic keratosis

Patient factors	Lesion factors	Treatment factors
– Immune suppression – Comorbidities – Medications – Patient preference – Treatment compliance	– Site (e.g., face, scalp, lower lip, limbs) – Clinical consistency (e.g., thickness of keratinization) – Size of lesion and of affected area	– Lesion- or field-directed – Application by patient or by medical staff – Duration of application – Side effects – Availability of equipment (e.g., laser, red-light lamp) – Cost

Dtsch Arztblatt Int 2019; 116:616-26

PDT
2x, 1 week tss

5-FU
2x/d 4w

Imiquimod
3x/w 4w

Diclofenac
1x/d

Tirbanibuline
1x/d 5d

Doel behandeling

Efficiënt voor elimineren AK

Preventie van ontstaan SCC

- PDT
  2x, 1 week tss
- 5-FU
  2x/d 4w
- Imiquimod
  3x/w 4w
- Diclofenac
  1x/d
- Tirbanibuline
  1x/d 5d

5-FU
2x/d 4w

- 4 weken therapie 5-FU: 1ste jaar sterk verlaagde kans ontstaan huidkanker, na 2 jaar geen verschil meer
- kleine studie: calcipotriol + 5-FU gezicht/scalp: tot 3 jaar protectief

Eur J Cancer 2020.01.007

JNCCN vol19 Issue 12; dec 2021

Bowen's disease

- multicenter RCT, uitkomst na 12m:
- 250 ptn, Bowen's disease 4-10mm, niet oor/nagel/neus/rond oog/mucosa

	Letselvrij na 3 maand	Letselvrij na 12 maand
Excisie (0,5 cm marge)	97,6%	97,4%
5-FU (2x daags 4 weken)	93,8%	85,7%
MAL-PDT 2x met 1w tss	88,8%	82,1%

Studie: 5-FU versus MAL-PDT: 69% klaring 5-FU (1dd 1w, 2dd 3w) versus 80% MAL-PDT

Studie: 121 pt HK versus cryotherapie (max 3x met 3-4w tussen), curretage+cauterisatie, 5-FU, Aldara, PDT:

- Efficaciteit beste met heelkunde 100%, laagste voor PDT (62,5%)
- recurrence hoogste met Aldara 33%
- post cryo vaker satelliet letsels rondom

H. Park et al. J Clin Med 2022 PMID 35628868
Ahmady S, et al. JAAD 2024 PMID 37666424

Cosmetisch verschil en verschil in kostprijs

Preventie en vroegtijdige detectie

Incidentie en impact van NMSC te ⬇

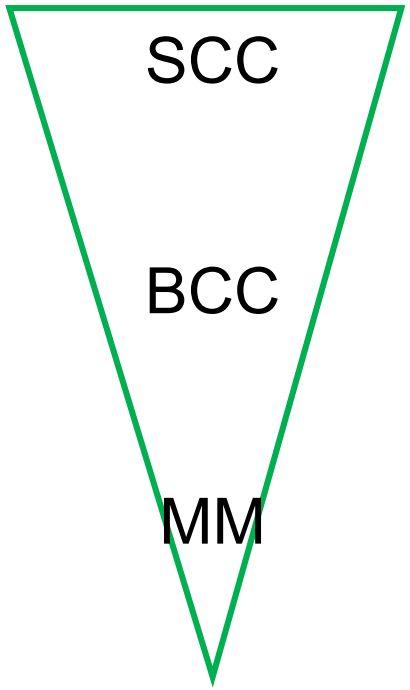
- Verminderen van zonblootstelling is meest effectief
- Gericht screenen van hoog risico populatie
- Zorgvuldige zelf-inspectie
- Systemische fotoprotectie

Table 1. This table summarizes the uses in skin protection, the study results, and the levels of evidence for vit D, NAM, PLE, acitretin, etretinate, isotretinoin, β-carotene, astaxanthin, and celecoxib.

Molecule	Use	Dose	Outcome	Side Effects	Level of Evidence [1]	Refs.
Vit D	NMSC prevention	Highly variable	Insufficient data for conclusive considerations	NR	IB	[19–26]
	MM prevention	400 IU/day	No effectiveness		IB	[28]
NAM	UV-induced immunosuppression prevention	0.5–1.5 g/day	Significant reduction of UV-induced immunosuppression	Diarrhea	IB	[41]
	AK prevention		Reduction of AKs recurrence in at-risk subjects and decrease in number and size of AKs		IB	[42–44]
	NMSC prevention		Reduction in the rate of occurrence of new NMSC		IA	[46,48]
	MM prevention	NR	No significant effectiveness		IB	[46]
PLE	Photoprotection	480 mg/day	Reduction in UV-induced erythema	NR	IB	[52]
	AKs	480–960 mg/day	Improvement of the clearance rate of scalp AKs in patients undergoing PDT		IIA	[57]
	Idiopathic photodermatoses	480 mg/day	Subjective improvement		IIB	[58,59]
	Melasma	480–720 mg/day	Contrasting results		IB	[60,61]
Acitretin	NMSC prevention	15–50 mg/day	Reduction of NMSC incidence in high-risk patients	Dryness and peeling of the skin, hair disorders, headache, epistaxis, osteoporosis, calcification of ligaments, neurological disorders	IB	[48,65–67,69]
Etretinate	Skin cancer prevention	20 mg/day	Reduction of skin cancer incidence in high-risk patients		IB	[48,68]
Isotretinoin	Skin cancer prevention	150 mg/day	Reduction of skin cancer incidence in high-risk patients		IB	[48,71]
β-carotene	Photoprotection	15–180 mg/day	Improved tolerance to sun light in patients affected by erythropoietic protoporphyria	Increased incidence of lung cancer in high-risk patients	IB	[86]
Astaxanthin	Photoprotection	4 mg/day	Increased minimal erythemal dose and reduced skin dryness after UV exposure	NR	IB	[93]
Celecoxib	AK prevention	200 mg twice daily	No effect	Increased blood pressure, myocardial infarction, stroke, or vascular death	IB	[106]
	NMSC prevention		Reduction of BCC and SCC incidence		IB	[106]

[1] Levels of evidence are based on guidelines in the Journal of the American Academy of Dermatology: level IA indicates that evidence is derived from a meta-analysis of randomized controlled trials; level IB indicates that evidence is derived from at least one randomized controlled trial; level IIA indicates that evidence is derived from at least one nonrandomized trial; level IIB indicates that evidence is derived from at least one other type of experimental study; level III data include evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV indicates that evidence is derived from reports or expert opinions, or the clinical experience of respected authorities, or both.

Chemo-preventie huidkanker



BCC

1. Mediterraan dieet en hoge caffeine inname: ?
2. Anti-oxidanten (selenium, vitA, beta-caroteen): geen studies
3. vitamine D: bij tekort aanvullen, doch verder verder nog geen voordeel bewezen voor preventie BCC
4. Nicotinamide: 500mg 2dd 12m: 20% reductie bij immunocompetente ptn met vooraf meedere huidkanker letsels. Effect gelimiteerd tot duur behandeling. Recente studie geen effect bij immuungesupprimeerde ptn
5. Orale retinoiden: lage efficiëntie, geen plaats voor preventie BCC gezien effect/risico balans
6. NSAID, topisch tazotere/Tretinoine: onvoldoende evidentie

K. Peris et al. European consensus-based interdisciplinary guidelines for diagnosis and treatment of basal cell carcinoma-update 2023; European Journal of Cancer 192 (2023) 113254

Biomolecules **2023**, *13*, 1067

Preventie SCC

	Immunocompetent	Immunosupressie (Tx)
Nicotinamide 500mg 2x/d	30% reductie ontstaan nieuwe SCC	/
Neo-Tigason 10-30mg/d	Effectief, maar bijwerkingen	54% reductie ontstaan SCC ! Bijwerkingen ! Rebound na stop
5FU topisch 2x/d 4 weken (ev + calcipotriol)	Enkel eerste jaar effectief	Enkel eerste jaar effectief

Nicotinamide

Preventie van UV-geïnduceerde ATP depetie, waardoor stimulatie DNA repair activiteit in keratinocyten en preventie van immunosupressieve effecten van UV straling

Retinoiden

Reguleren epitheliale maturatie, cellulaire differentiatie en proliferatie, groeistop en apoptose door nuclaire retinoid receptoren te activeren

Biomolecules **2023**, *13*, 1067

AR Rosenberg et al. Skin cancer precursor immunotherapy for squamous cell carcinoma prevention; JCI Insight. 2019;4(6):e125476

Eur J Cancer 2020.01.007

Bedankt voor uw aandacht !