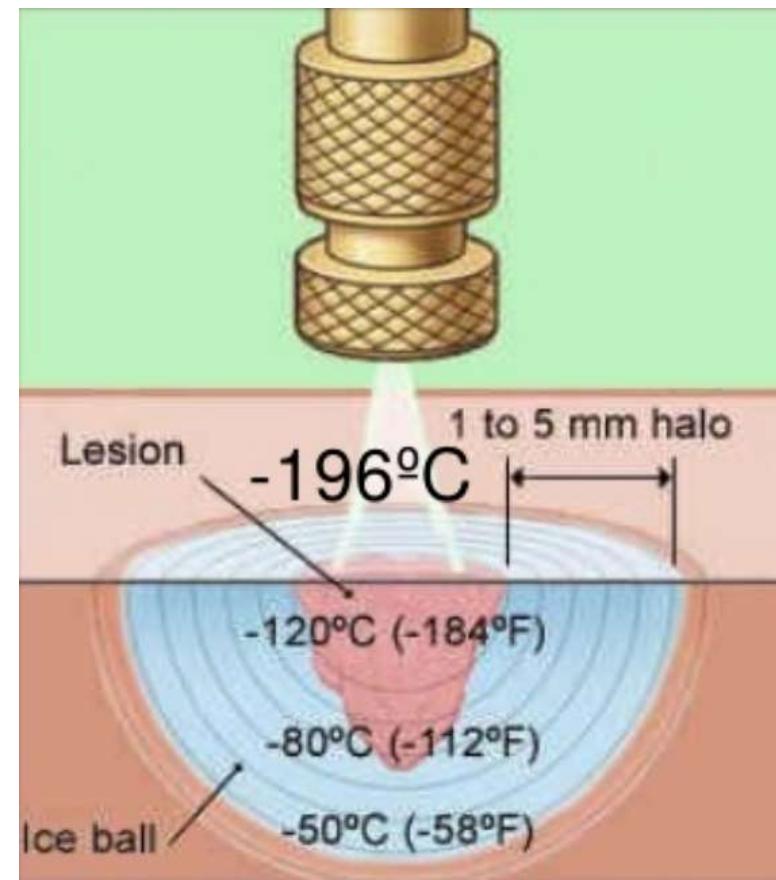
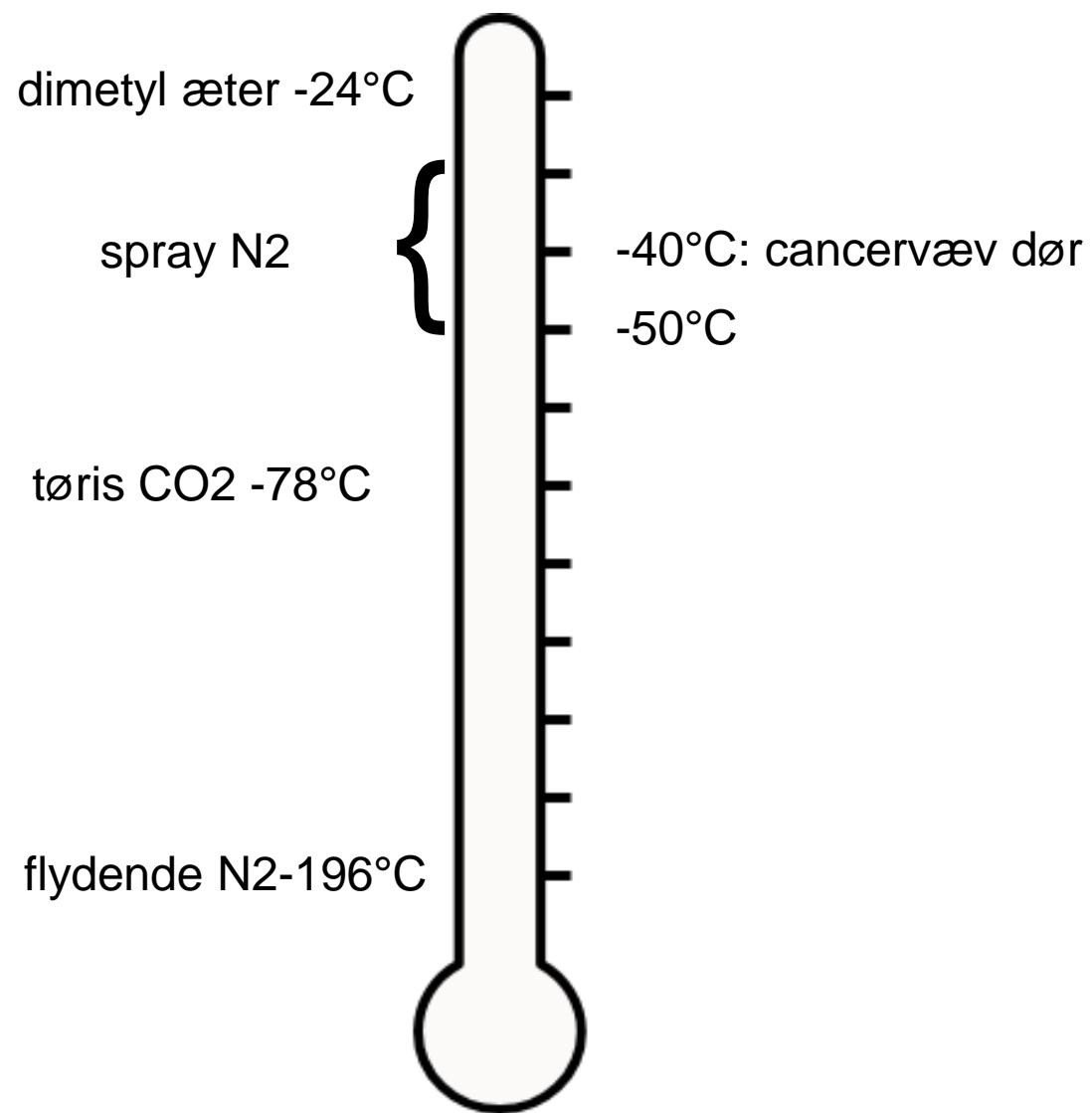


Non-melanom hudkræft Gamle behandlinger

Henrik F. Lorentzen
Munkebjerg 2019

- Kryo-kirurgi
- Curettage
- Imiquimod (aldara + zyklara)
- Ingenol mebutate
- 5 flouro-uracil (efudix [5%] + Actokerall [0,5% inkl. salicylsyre])
- PDT (MAL, 5-ALA nano)

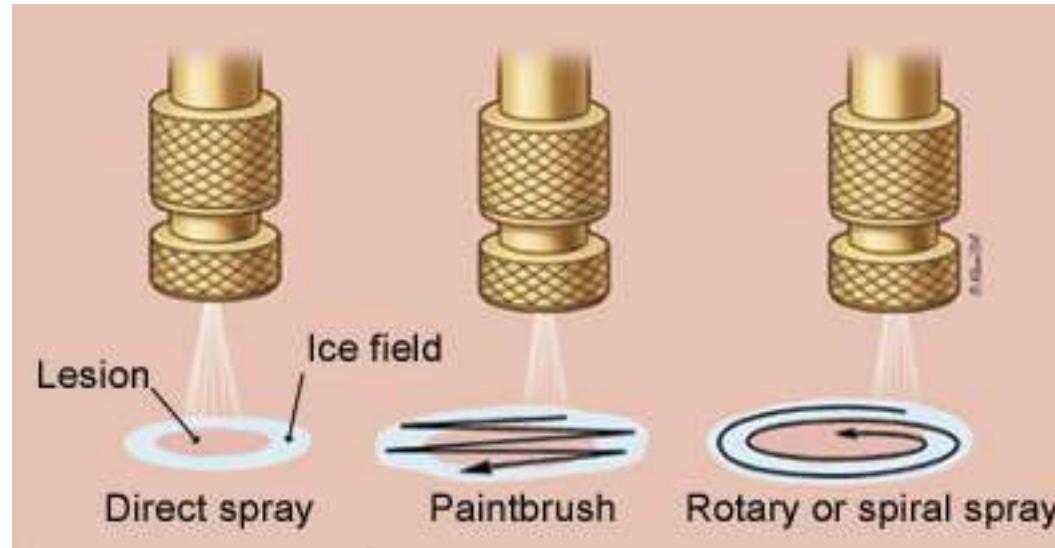
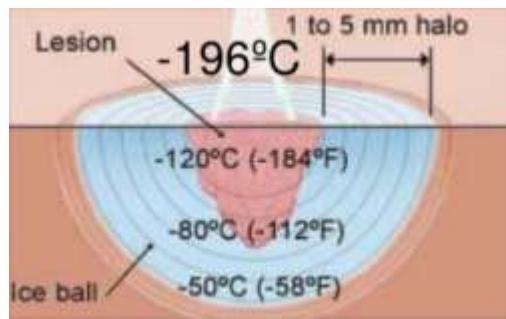
Kryo-kirurgi



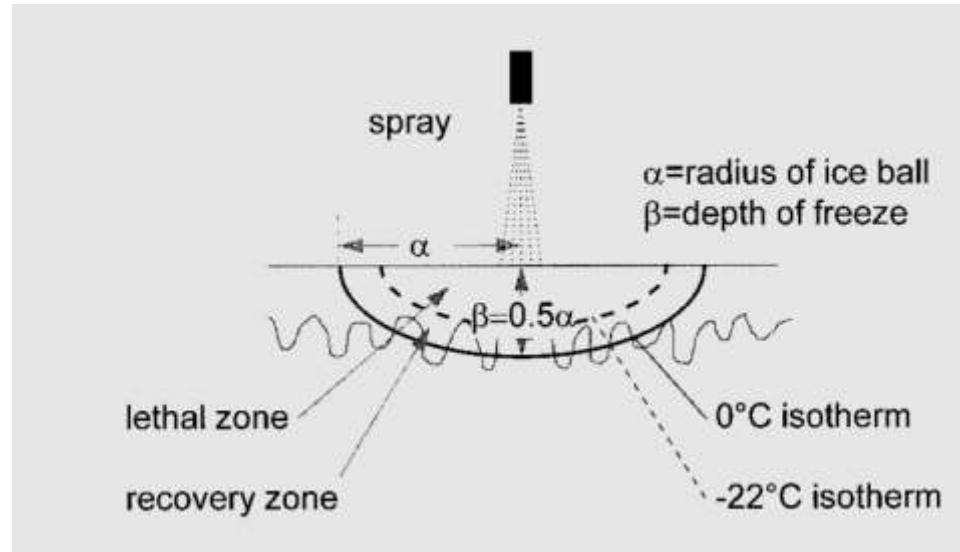
- Let frysning: iskristaller extracellulært. Osmose trækker vand ud af cellerne. Dessication. Utilstrækkeligt for maligne t.
- Hård frysning og fryse-tø cykli: iskristaller intracellulært, skade på cellemembran
- Indirekte virkning: hyperæmi og skade på karvæg i timerne efter behandlingen → mikrotrombosering af kar

Lethal Temperatures for Cells Experiments *in Vivo*—Single F-T Cycles

First author	Year	Cell/tissue	Lethal temp.	F-T program
Gage	1966	Osteocytes, bone, dog	-2°C	5-min F-slow T
Gage	1979	Melanocytes, skin, dog	-4°C	4-min F-slow T
Smith	1974	Liver, rat	-15°C	3-min F-fast T
Rivoire	1996	Liver, pig	-15°C	5-min F-slow T
Lefebvre	1975	Cheek pouch, hamster	-18°C	1-min f-fast T
Dow	1970	Prostate, dog	-20°C	1-s F-slow T
Gage	1982	Skin, dog	-40°C	3-min F-slow T
Yamada	1976	Skin, mouse	-40°C	1-min F-slow T
Gage	1978	Palate, dog	-40°C	3-min F-slow T
Neel	1971	Sarcoma, mouse	-60°C	6-min F-slow T
Staren	1997	Adenocarcinoma, rat	-70°C	7-min F-slow T



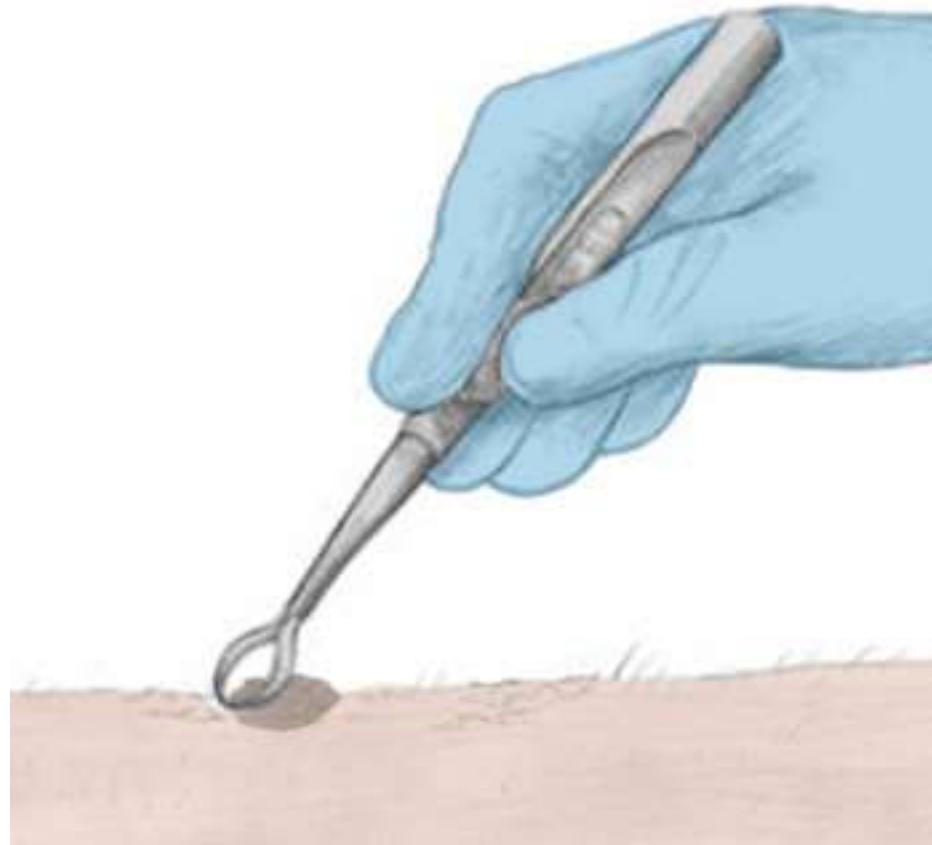
Is-kugle



Ikke standardiseret til større maligne elementer

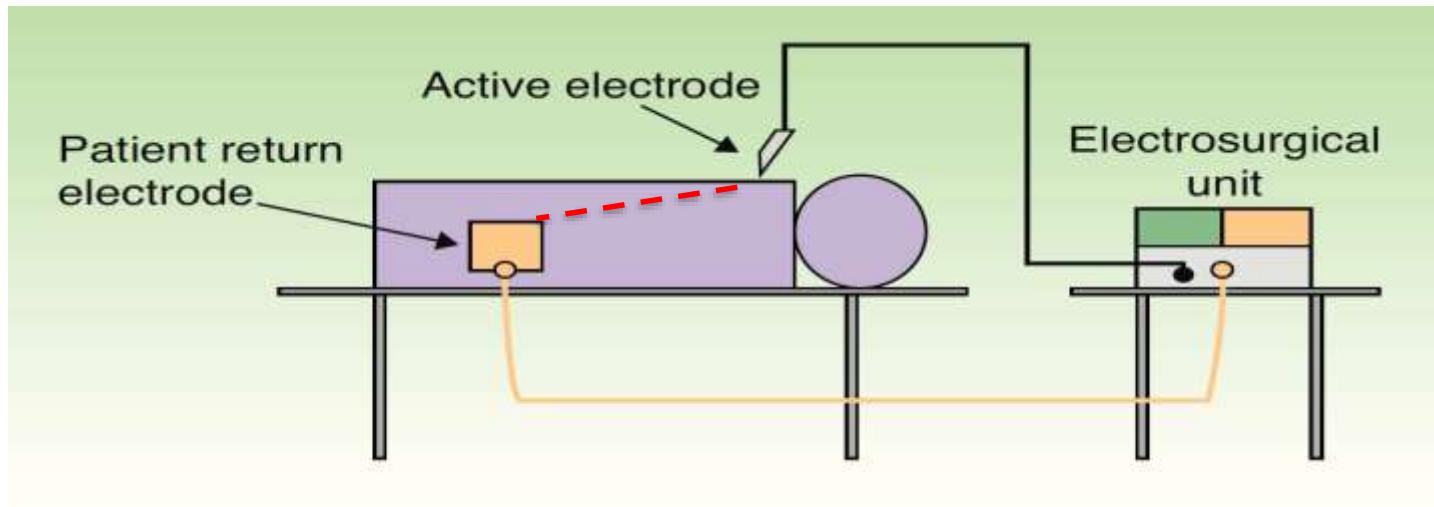
- Actiniske keratoser
- sBCC
- Små nodulære BCC
- Keratin er dårlig varmeleder (hyperkeratotiske tumorer:
debulking m curette, 5FU)

Curettage + el-kaustik

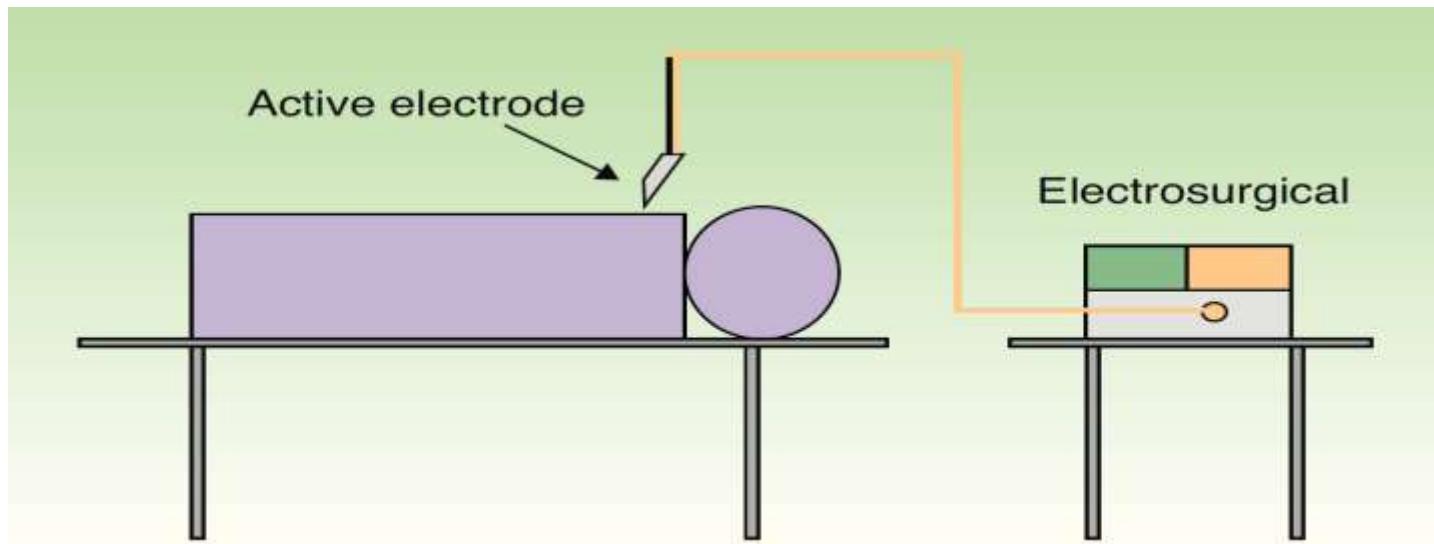


Elkaustik og pace-makere

Unipolær/
monopolær



bipolær



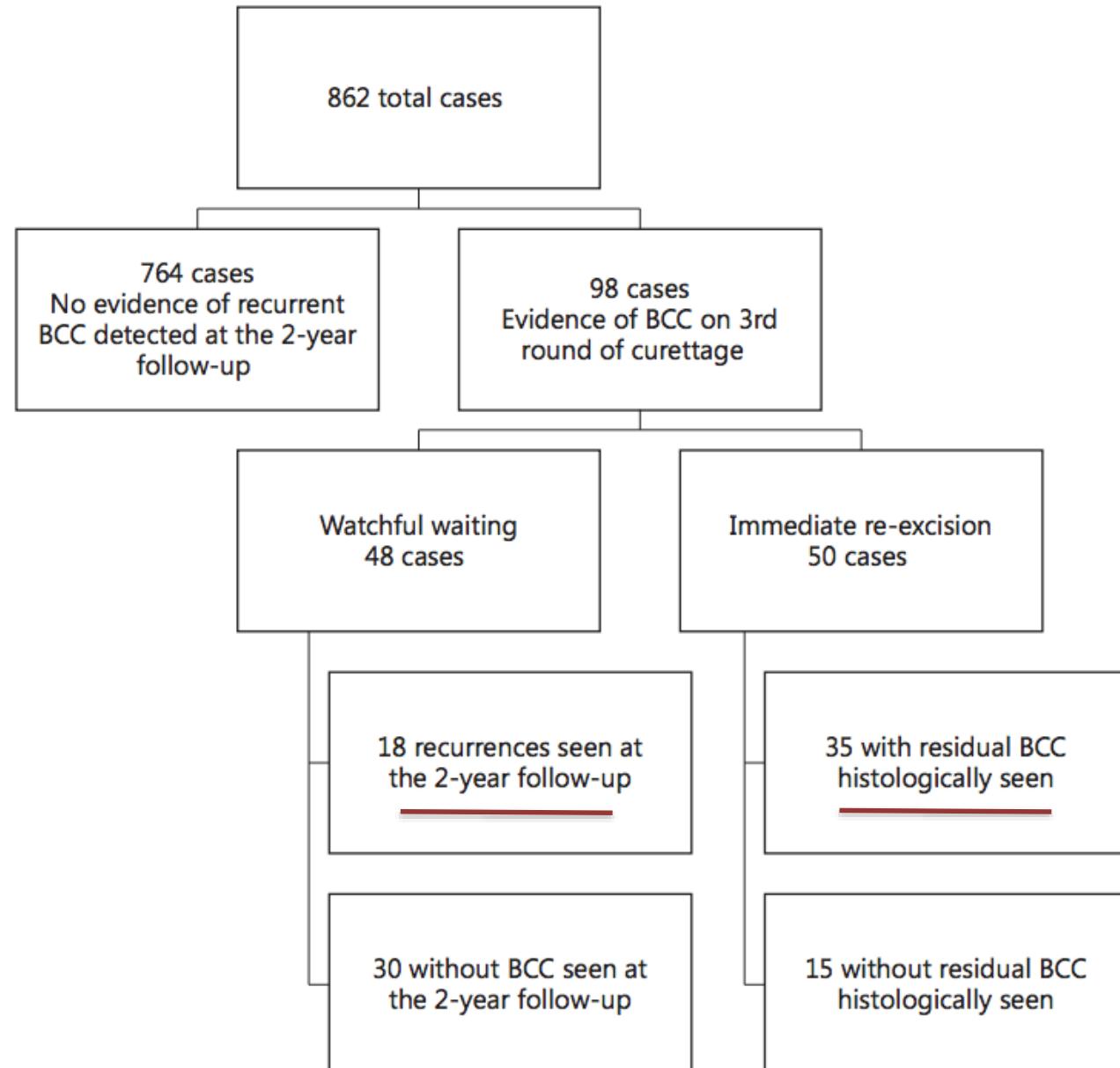
Alle BCC inkl. risikotumorer, risiko-områder og ptt fundet uegnede til kir. el. MMS pga co-morbiditet

Curettage + elektrodessikation x 3

3' curettagemateriale: immunhistokemi Ber-EP4

98:862 Ber-EP4+ [rest BCC] (11%)

53:862 behandlingssvigt (6%)



Curettage primære BCC – recidiv: MMS

Table I. Characteristics of primary basal cell carcinomas included in the study

Location		n	Mean size (range), mm	Mean follow-up time (range), y
High-risk sites (n = 176)	Nose, paranasal, nasal-labial fold	105	8.10 (4-10), SD 2.28	5.44 (2-8), SD 1.11
	Eyelids, canthi	48	7.35 (4-10), SD 2.26	5.22 (2-8), SD 1.22
	Perioral	12	6.85 (4-10), SD 2.13	6.00 (4-8), SD 1.47
	Ears	11	7.98 (4-10), SD 2.20	4.36 (1-8), SD 2.11
Medium-risk sites (n = 81)	Forehead, temples	48	8.31 (4-15), SD 3.60	5.31 (2-8), SD 1.43
	Periauricular areas	14	8.42 (4-15), SD 3.97	5.64 (4-8), SD 1.44
	Malar, cheek	19	9.45 (5-15), SD 2.76	5.05 (3-8), SD 1.50
Total		257		

Rodriguez-Vigil et JAAD 2007

4-5 cykler af cur.+ elkaustik

50 ptt. Lost-to-follow-up
worst case: alle recidiv

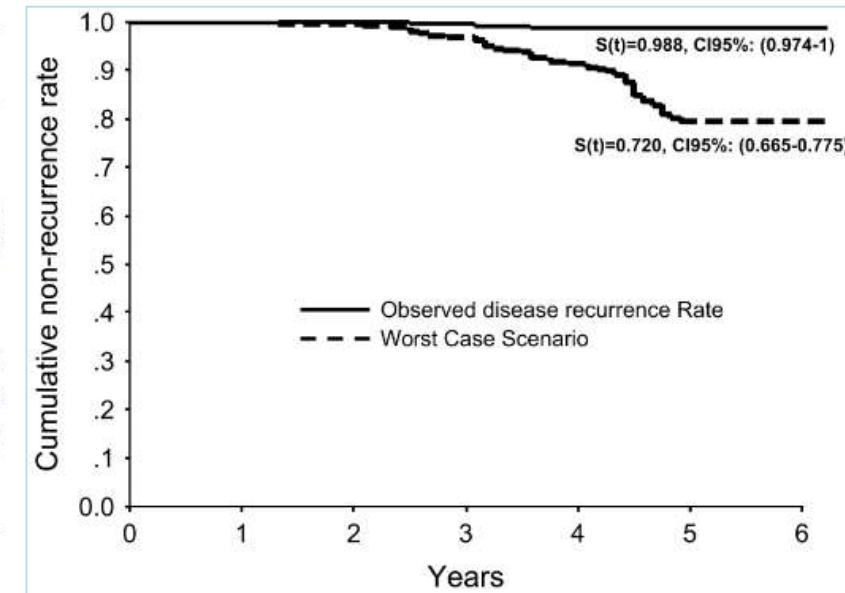
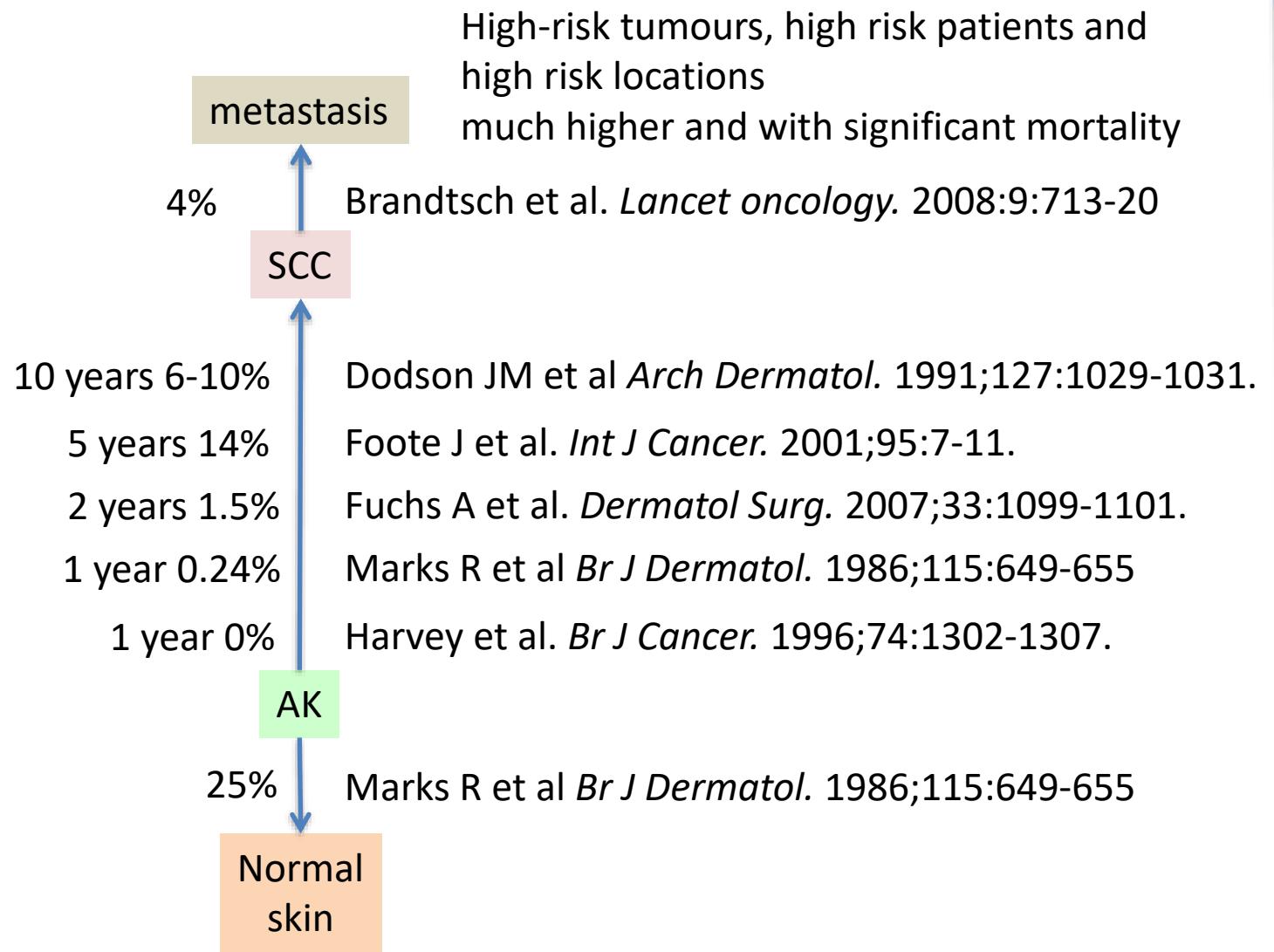


Fig 1. Kaplan-Meier estimate of rate to disease recurrence, including worst-case scenario. *CI*, Confidence interval.

Actinic keratoses progression to SCC



Study endpoints

none

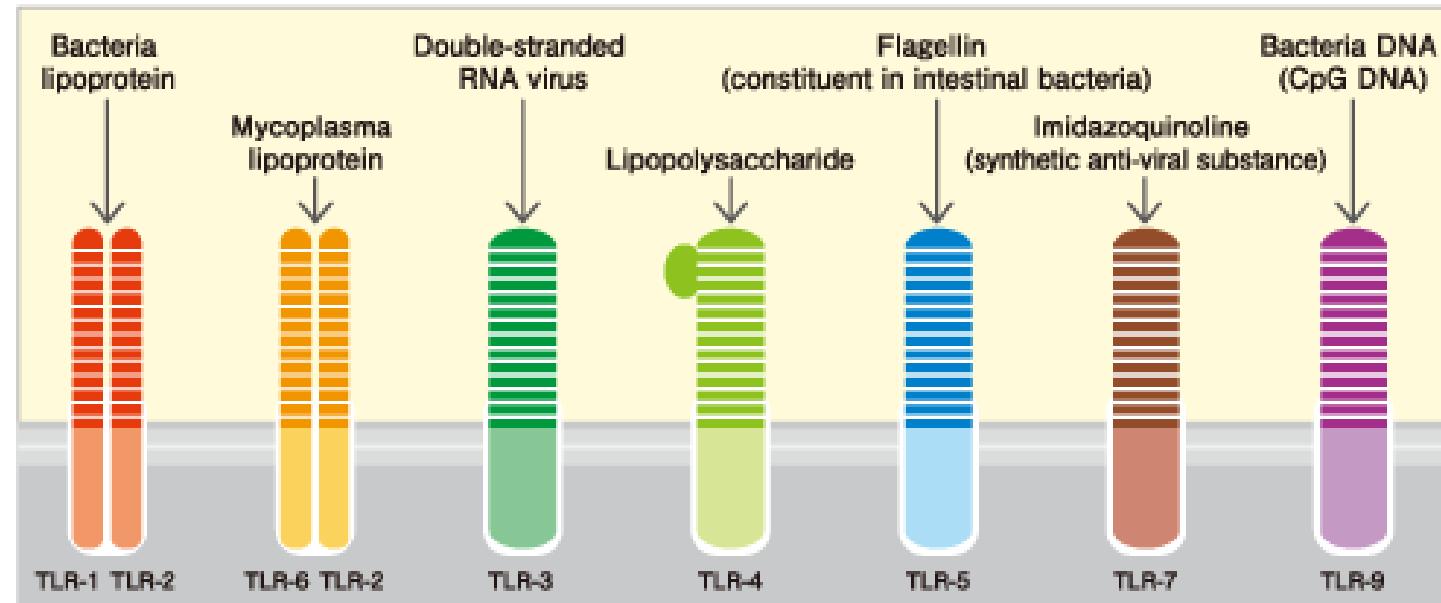
1 abstract: JAAD sep 2018
Kaiser-Permanente: 5.062: 5 FU
638: imiq. 5 år: 1.408 SCC/BCC
Ingen forskel 5FU vs imiq

Reduction in no.
% total clearance

overview

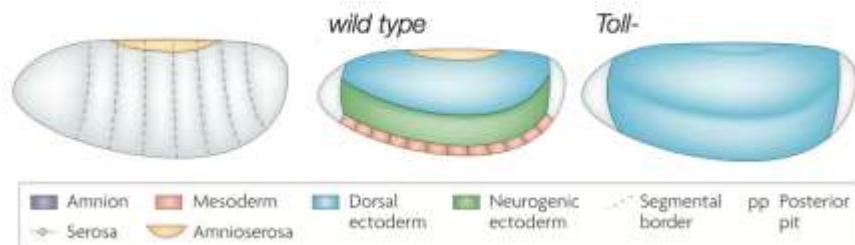
- Medications review
 - Imiquimod (aldara, zyclara)
 - 5 flourouracil (efudix, actikerall)
 - Diclofenac (solaraze)
 - Ingenol mebutate (picato)
 - PDT
- Risk patients (organ transplant recipients)
- Risk areas (eye, genital)
- Retinoids
- Vismodegib / Sonidegib

Imiq. Toll like receptors



Toll-like receptor family and known active ingredients

The Toll mutation in *D. melanogaster*
(C Nusslein-Volhard and colleagues)



drawing from Sommer, Nat Rev Genetics 10:416, 2009

imiquimod Mode of action (MOA)

Cellular activation

- Innate
 - Dendritic cells (APC)
 - NK cells
- Adaptive immune system
 - Cytotoxic T cells
 - B cells

Humoral response

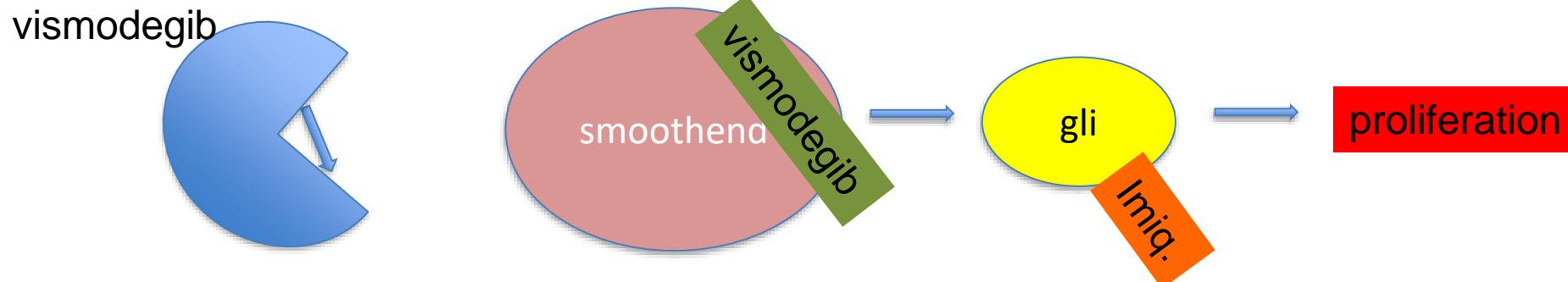
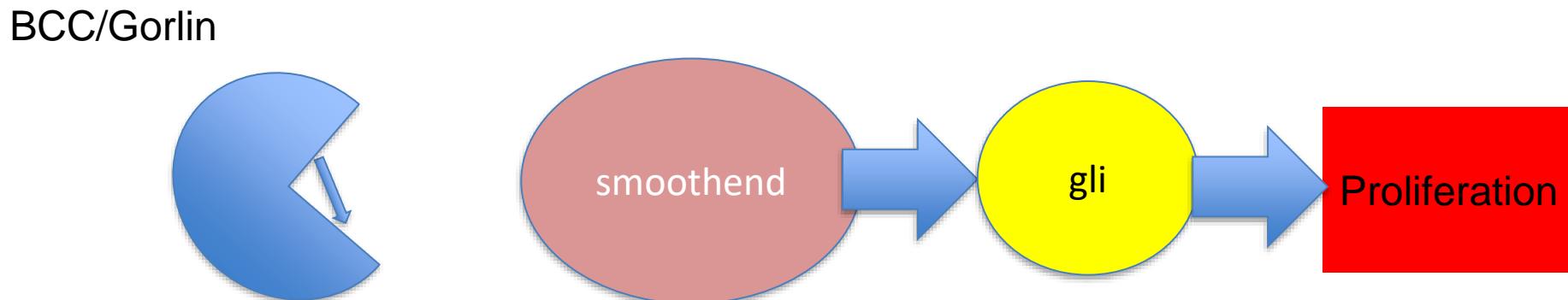
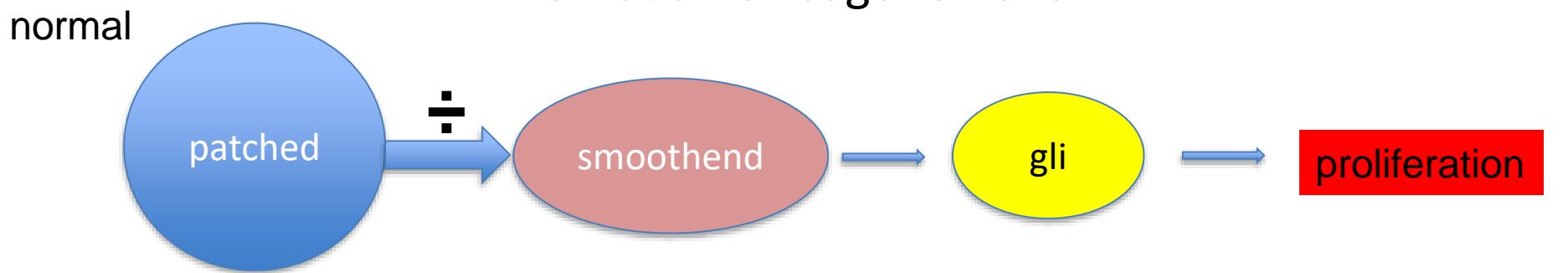
- IFN-gamma
- TNF alfa
- IL-8, IL-12, IL-1, IL-6
- G-CSF, GM-CSF

Apoptosis

- Tumor cells
 - Death receptors ↑

Imiq. MOA hedgehog pathway

Wolf et al. Oncogene 2013



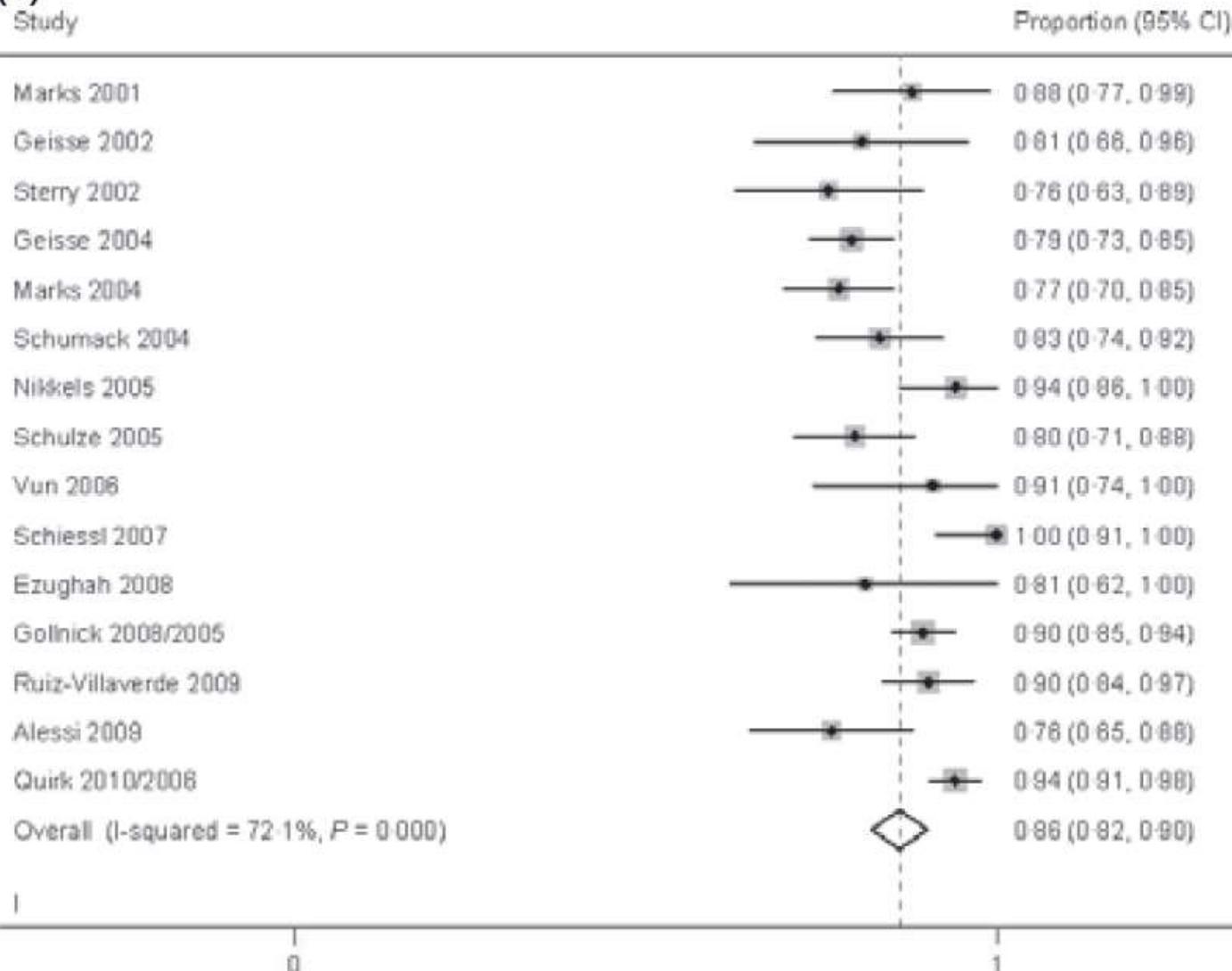
Imiquimod 5% AK

- Meta-analysis (Hadley 2006) 5 studies (Stockflett 2004, Chen 2003, Lebwohl 2004, Szeimies 2004, Korman 2005)
 - Complete clearance 50 %
 - 75 % clearance 65 %
 - Withdrawals AE 3.9 %
 - AE 75 %
 - SAE 4.5 %
- Recurrence (Krawchenco et al 2007)
 - one year sustained clearance 73 % (all treated, 85% responded)
 - Recurrence rate 14 % (initial total clearance)

Imiquimod 5% sBCC

(a)

Study

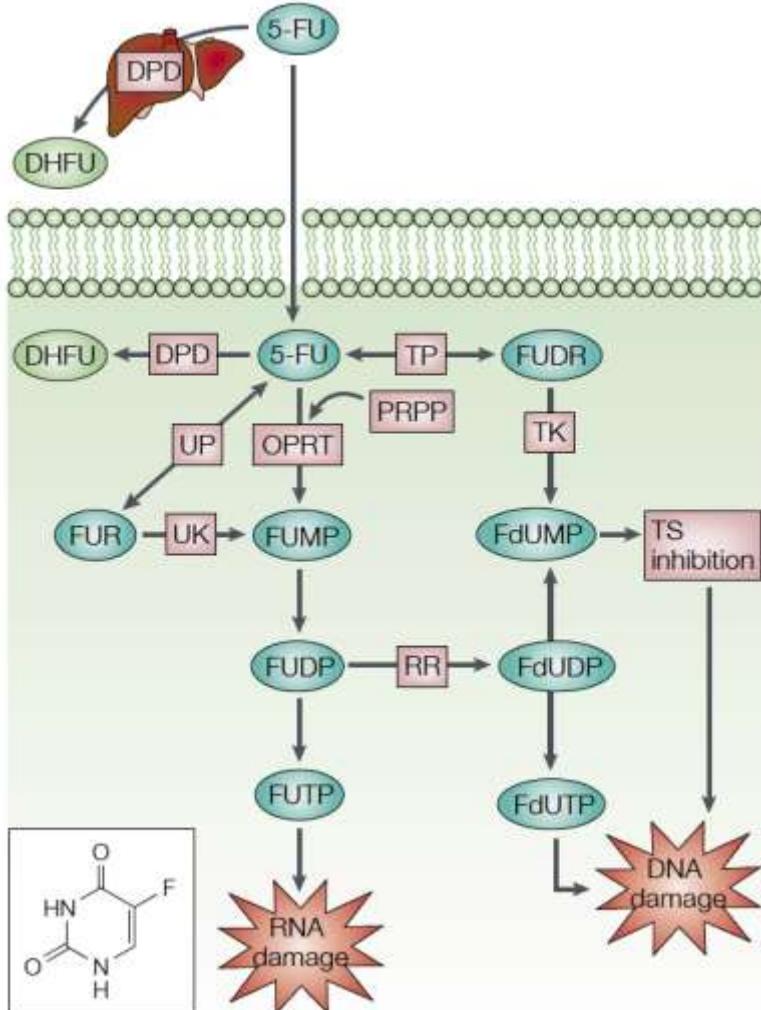


Complete response
86%
Meta-analysis

Roozeboom et al.
BJD 2012; 167: 733-56

Recurrence rate:
12.7%

5-FU MOA



Efudix: a flouro-pyrimidine
Blocks normal function of uracil in
DNA/RNA construction

5-FU actinic keratoses

5% 5-flourouracil creme:

- Recurrence (Krawchenco et al 2007) [proportions with total clearance: 96%]
 - one year sustained clearance 35 % (all treated 96 % responded)
 - Recurrence rate 67 % (initial total clearance)

0.5% 5-FU creme

- 52.6% clearance 4 weeks q.d (Rahvar et al Immunotherapy 2012;4:939-945)

0.5% 5-FU/salicylic acid qd for 12 weeks

- 55.4% clearance (Stockfleth et al. BJD 2011;165:1101-1108)

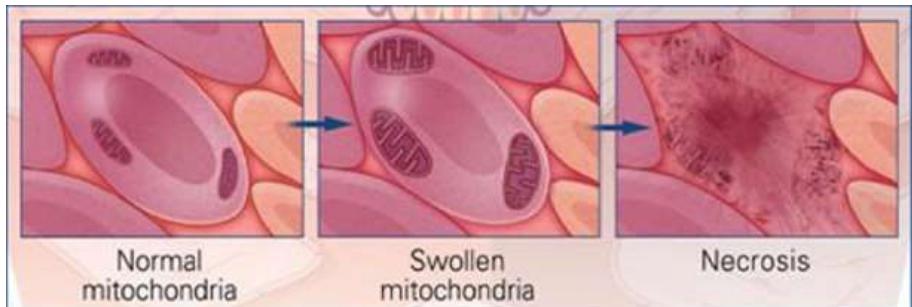
5-FU sBCC

- Gross et al. Dermatol surg 2007; 33: 433-440
- 5% 5-FU b.i.d. For up to 12 weeks
 - Clearance: 90%
 - Side effects: redness and erosion
 - Pain no problem

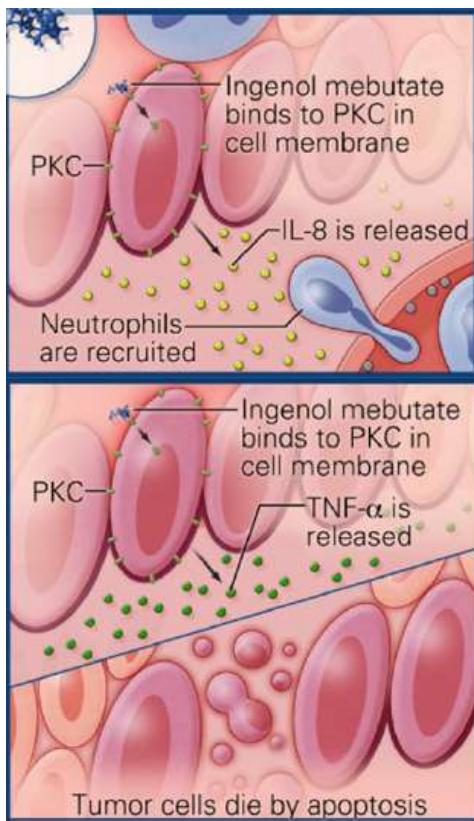
Diclofenac (solaraze®)

- MOA: NSAID COX-2 inhibitor. PGE2↓ in a hyaluronic acid vehicle (<10% absorption)
 - Side-effects: very few. Sun hypersensitivity, allergy
 - Pregnancy III trimester. Rare: kidney failure
 - Advantage: large areas
-
- Meta-analysis: Pirard et al. Arch dermatol res 2005
Clearance: 39.1%
 - Akarsu et al., Clin Exp Dermatol., 2011 36(5):479-84
Clearance: 14.3% at week 24

Ingenol mebutate (picato®)



Hours: calcium release from ER and mitochondria in proliferating keratinocytes. Mitoch. swelling. Primary necr.



IM binds to phosphokinase C receptors → IL-8 → neutrophils

IM binds to phosphokinase C receptors → TNF- α → Apoptosis

Ingenol mebutate AK

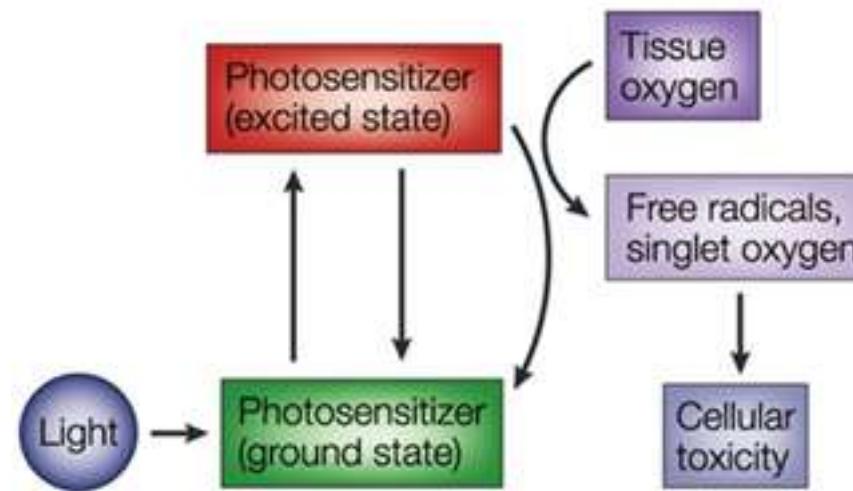
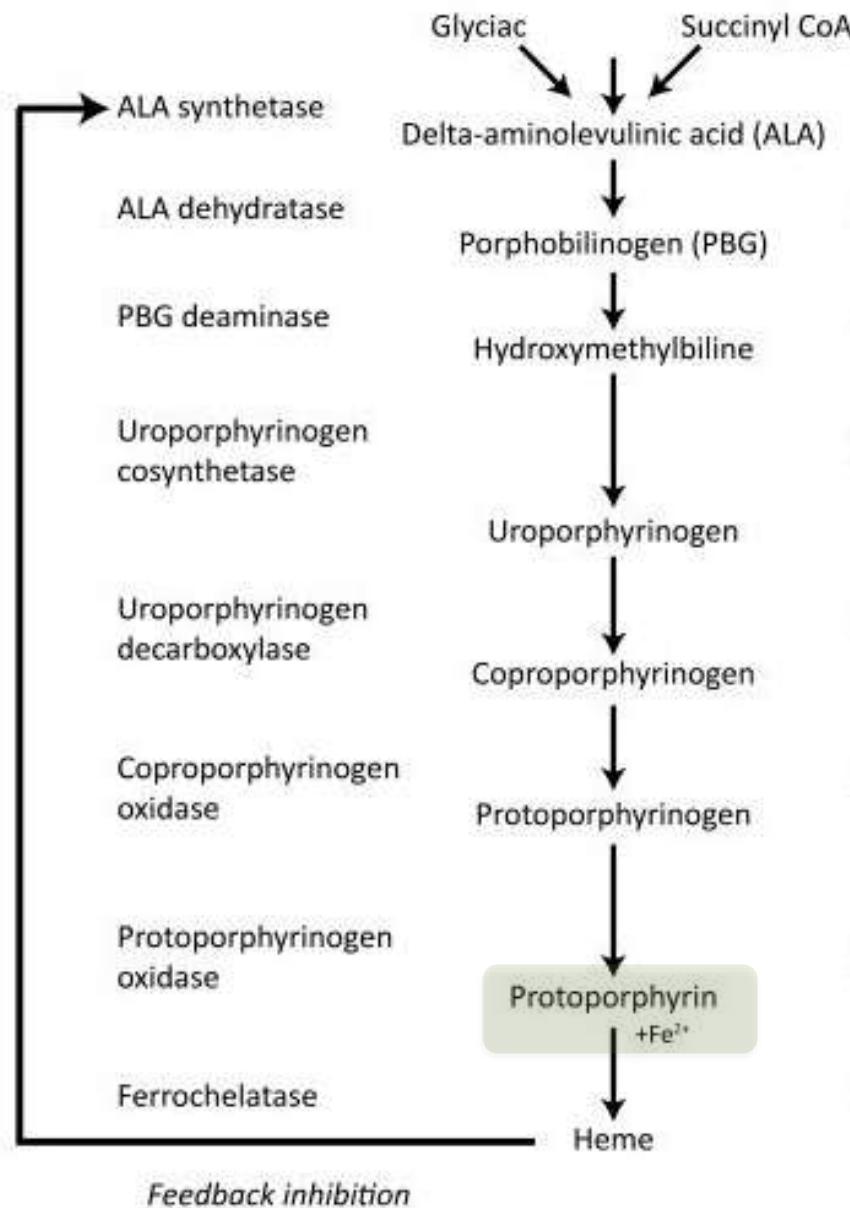
Lebwohl et al. N Engl J Med. 2012;366:1010-9

- Clearance head: 42%
- Clearance trunc and extremities: 34 %

Lebwohl et al. JAMA Dermatol. 2013 Jun;149(6):666-70

- Recurrence rate head 12.8% (initial total clearance)
- Recurrence rate trunc/ex 13.2%

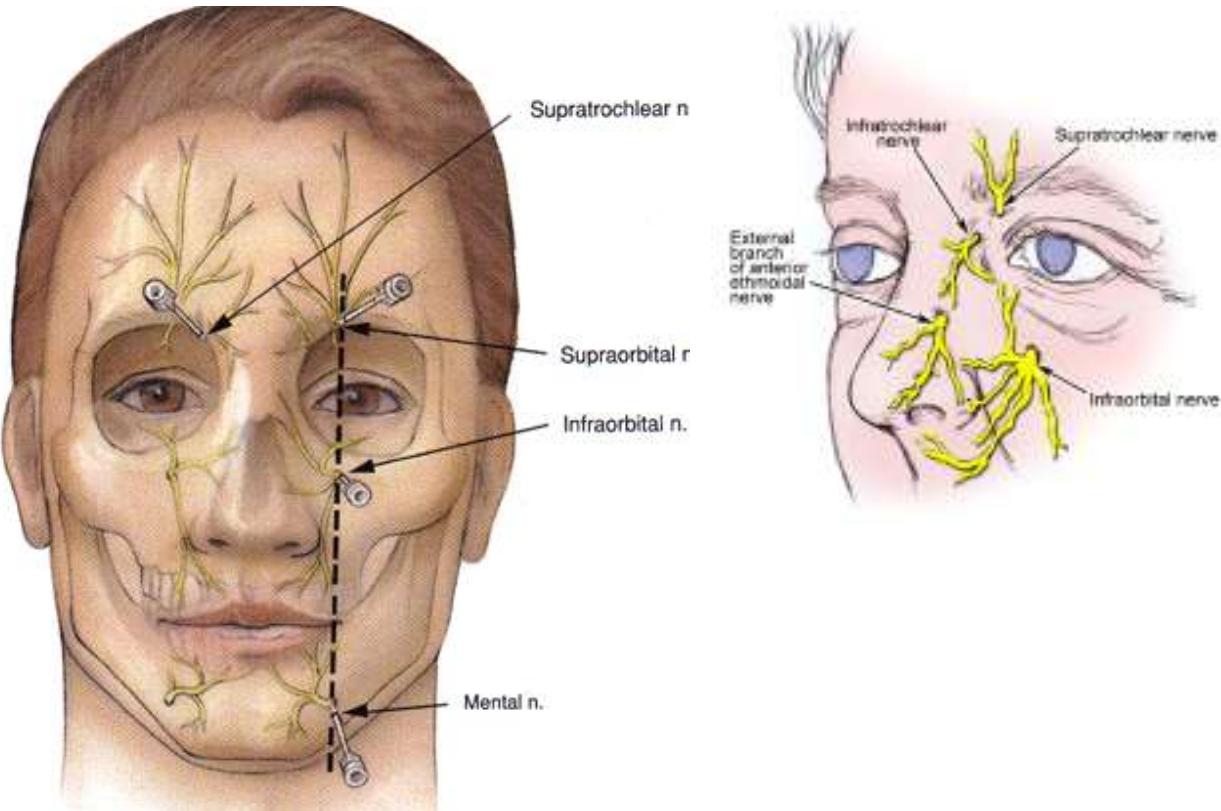
PDT MOA



Dennis et al. Nature Reviews Cancer 2003;3:380-387

Managing pain

- Daylight PDT // Water; cool-air
- Nerve-block (>60 patients. VAS>7 reduced to VAS=0)



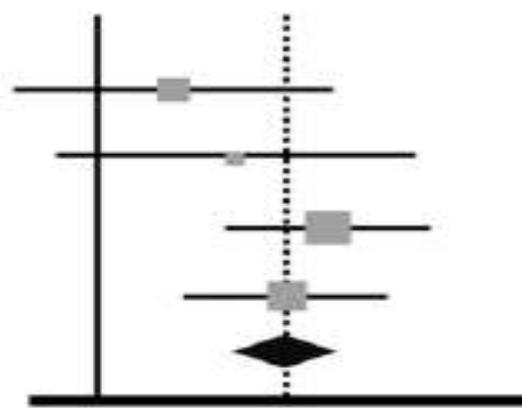
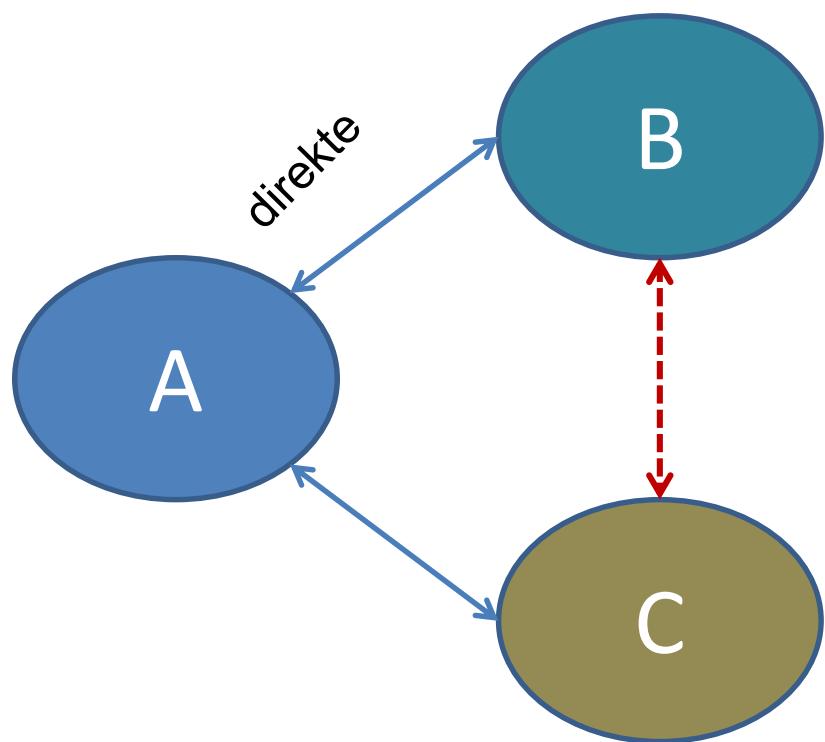
Managing pain: d-PDT



Table 4 Differences in Response Rates Between Conventional and Daylight PDT.

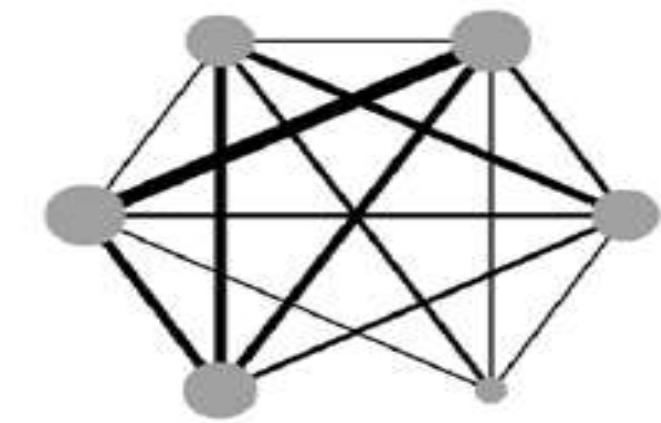
	Rubel et al. ¹⁹	Lacour et al. ²⁰	Global Estimate
Difference in per-protocol analysis	–3.6% 95% CI, –6.8% to –0.3%	–4% 95% CI, –9.5% to 2.4%	–3.69% 95% CI, –6.54% to –0.84%
Difference in intention-to-treat analysis	–3.5% 95% CI, –6.6% to –0.4%	–3.10% 95% CI, –8.6% to 2.4%	–3.40% 95% CI, –6.10% to –0.70%

network meta-analysis



Pairwise meta-analysis

Direct comparison



Network meta-analysis

Direct comparison & Indirect comparison

Treatments of Primary Basal Cell Carcinoma of the Skin

Sep 2018

A Systematic Review and Network Meta-analysis

Aaron M. Drucker, MD, ScM; Gaelen P. Adam, MLIS; Valerie Rofeberg, ScM; Abhilash Gazula, MPH; Bryant Smith, MPH;
 Farah Moustafa, MD; Martin A. Weinstock, MD, PhD; and Thomas A. Trikalinos, MD

Figure 1: Recurrence

First network

Surgical excision	3.3 (1.3-7.8)	
MMS	3.8 (0.7-18.9)	
MMS + IFN	4.6 (0.2-56.2)	
Cryotherapy	21.0 (9.0-41.4)	
Diathermy + curettage	5.9 (0.7-34.9)	
Cryotherapy + curettage	17.1 (3.6-53.4)	
Laser + PDT (MAL)	12.0 (1.8-49.6)	
Laser + PDT (ALA)	25.9 (5.1-69.6)	
External-beam radiation	3.2 (0.6-16.1)	
PDT (MAL)	17.8 (9.1-31.8)	
PDT (ALA)	16.9 (7.3-34.4)	
5-FU	24.7 (7.1-58.4)	
Imiquimod	14.1 (5.4-32.4)	
Curettage	15.4 (2.6-55.3)	

Recidiv efter 1-2 år

BiasOverrepræsentation af
sBCC og

Udenfor risiko-områder

Second network

Surgical excision or MMS	0.6 (0.1-4.0)	
External-beam radiation or brachytherapy	4.6 (2.3-9.0)	

Treatments of Primary Basal Cell Carcinoma of the Skin

Sep 2018

A Systematic Review and Network Meta-analysis

Aaron M. Drucker, MD, ScM; Gaelen P. Adam, MLIS; Valerie Rofeberg, ScM; Abhilash Gazula, MPH; Bryant Smith, MPH;
Farah Moustafa, MD; Martin A. Weinstock, MD, PhD; and Thomas A. Trikalinos, MD

Figure 2: Lack of histologic clearance

First network

Surgical excision	1.7 (0.3-9.9)	←
Cryotherapy	11.7 (3.1-35.3)	
Laser	33.7 (10.9-67.9)	
Laser + PDT (MAL)	37.5 (4.7-87.9)	
PDT (MAL)	14.5 (5.4-33.6)	←
PDT (ALA)	11.0 (2.1-41.4)	←
5-FU	5.5 (0.5-38.8)	←
Imiquimod	28.6 (14.6-48.6)	
Ingenol	77.1 (23.7-97.3)	←
Other medical interventions	78.1 (23.9-97.6)	
No treatment	81.8 (48.3-95.6)	
Placebo	86.3 (72.1-93.9)	

Second network

Surgery + PDT (MAL)	36.4 (14.3-66.1)
Surgery + PDT (MAL) + curettage	20.0 (5.0-54.1)
Surgery + PDT (ALA)	36.4 (14.3-66.1)
Surgery + PDT (ALA) + curettage	18.2 (4.6-50.7)

Third network

Imiquimod + curettage	10.0 (1.4-46.7)
Curettage	40.0 (15.8-70.3)

Treatments of Primary Basal Cell Carcinoma of the Skin

Sep 2018

A Systematic Review and Network Meta-analysis

Aaron M. Drucker, MD, ScM; Gaelen P. Adam, MLIS; Valerie Rofeberg, ScM; Abhilash Gazula, MPH; Bryant Smith, MPH;
 Farah Moustafa, MD; Martin A. Weinstock, MD, PhD; and Thomas A. Trikalinos, MD

Figure 3: Patient-reported good or better cosmetic outcomes

First network

Surgical excision	77.8 (44.8-93.8)
Cryotherapy	51.1 (15.8-85.4) ←
Laser + PDT (MAL)	20.0 (1.9-76.6)
PDT (MAL)	93.8 (79.2-98.3) ←
PDT (ALA)	95.8 (84.2-99.0) ←

Second network

External-beam radiation	96.2 (59.7-99.8)
Imiquimod	96.9 (65.0-99.8)

Third network

Surgical excision or MMS	80.9 (73.3-86.8) ←
External-beam radiation or brachytherapy	66.4 (57.2-74.5) ←

Fourth network

MMS	95.5 (55.2-99.7)
MMS + PDT (MAL)	93.8 (46.1-99.6)

Få
obs**Figure 4: Observer-reported good or better cosmetic outcomes**

First network

Surgical excision	46.7 (19.4-76.1)
Cryotherapy	60.1 (23.1-88.3)
Laser + PDT (MAL)	93.5 (63.5-99.2)
Laser + PDT (ALA)	5.9 (0.5-45.9)
PDT (MAL)	87.9 (73.3-95.1) ←

PDT (ALA)	53.4 (15.9-87.4)
5-FU	57.5 (13.0-92.4)
Imiquimod	61.0 (24.8-88.1)
Placebo/sham	93.3 (41.5-99.6)

Second network

Surgical excision or MMS	78.6 (70.8-84.8) ←
External-beam radiation or brachytherapy	39.8 (31.2-49.1) ←

Network meta-analysis of the outcome ‘participant complete clearance’ in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review

A.K. Gupta^{1,2} and M. Paquet²

5-FU > ALA-PDT ≈ IMI ≈ IMB ≈ MAL-PDT > cryotherapy > DCF/HA > placebo

OPEN  ACCESS Freely available online



A Network Meta-Analysis of the Relative Efficacy of Treatments for Actinic Keratosis of the Face or Scalp in Europe

Stefan Vegter^{1,2*}, Keith Tolley³

BF200 ALA > imiquimod > 5FU

	NMA [†]
Placebo	6.9% (5.5–8.3%)
MAL-PDT	54.8% (33.6–76.0%)
BF-200 ALA	75.8% (55.4–96.2%)
ALA-PDT patch	56.8% (30.5–83.1%)
Cryotherapy	38.2% (12.1–64.3%)
Imiquimod 5% (16 weeks)	63.3% (45.5–81.1%)
Imiquimod 5% (4 weeks)	56.3% (33.8–78.8%)
Diclofenac 3%	24.7% (12.4–37.0%)
5-FU 0.5%	59.9% (38.9–80.9%)
Ingenol mebutate	54.5% (27.8–81.2%)
Imiquimod 3.75% (4 weeks)	39.9% (15.6–64.2%)

Local interventions for actinic keratosis in organ transplant recipients: a systematic review

M.V. Heppt¹, T. Steeb¹, A.C. Niesert,¹ M. Zacher,¹ U. Leiter,² C. Garbe² and C. Berking¹

	PDT	5-FU	imiq	Ingenol-mebutat	solaraze
Total clearance	40-76,4% (*)	11%	27,5-62,1% (#)		41%

(#) Santos-Juanes J. Dermatology 2011
Kasuistik:
Akut tubulær nekrose efter imiquimod

(*) bl.a. K. Togsverd-Bo d-PDT

Retinoid chemoprophylaxis

JOURNAL OF DERMATOLOGICAL TREATMENT, 2018
<https://doi.org/10.1080/09546634.2018.1445194>

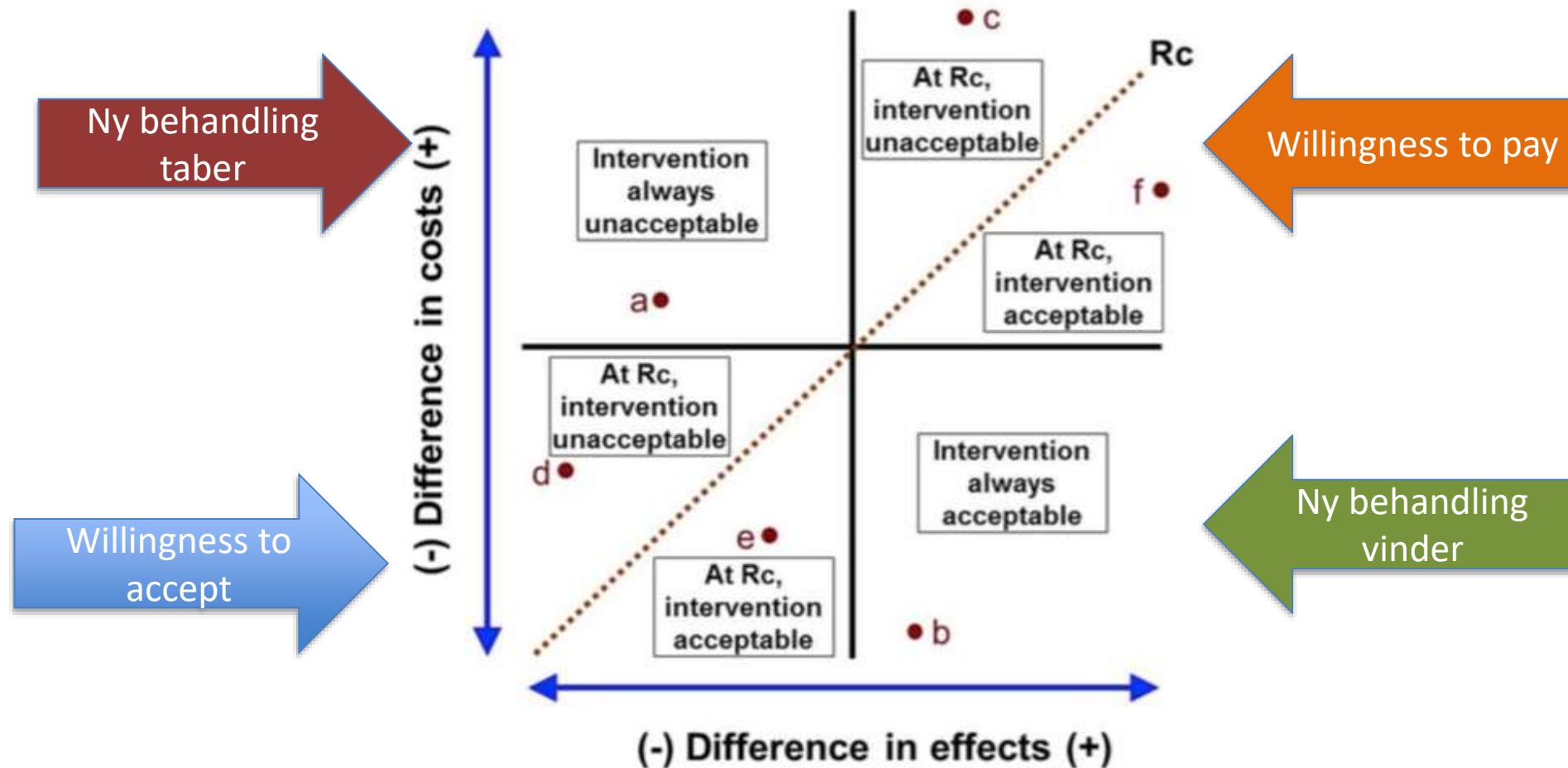
REVIEW ARTICLE

Dermatological indications for the use of isotretinoin beyond acne

Emily Forbat^a, Faisal R. Ali^b and Firas Al-Niaimi^b

1. Cochrane 2007: 2 studies showed increased risk
2. SkiCap-AK study: >10AK + max 2 NMSC: retinol reduce risk of SCC
3. SkiCap.BCC/SCC study: >4 SCC: no effect

$$ICER = \frac{kost(ny) - kost(gammel)}{(effekt(ny) - effekt(gammel))}$$



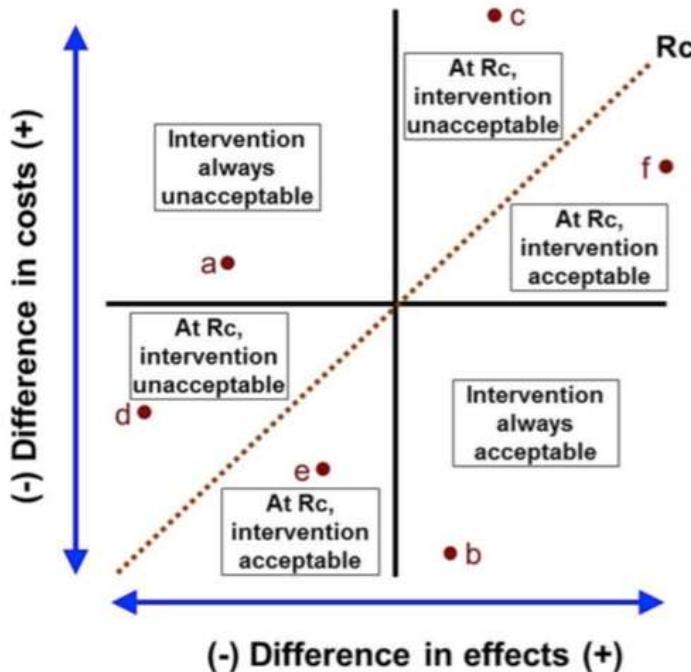
2014

THERAPEUTICS

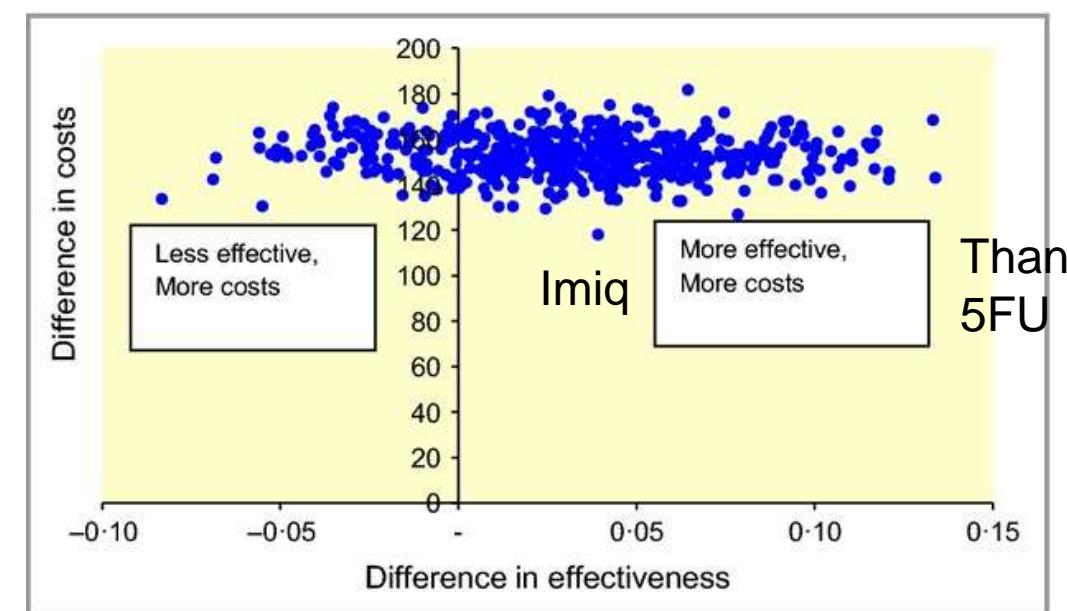
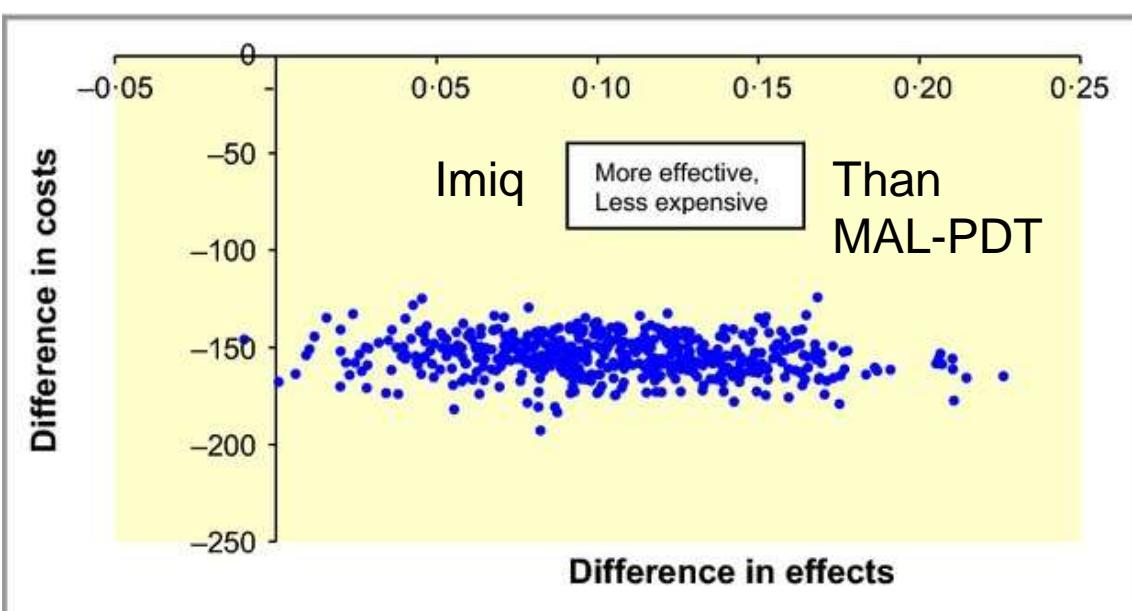
Cost-effectiveness of topical imiquimod and fluorouracil vs. photodynamic therapy for treatment of superficial basal-cell carcinoma Uden for H zone + skalp

A.H.M.M. Arnts,^{1,2} E. Spoorenberg,^{1,3} K. Mosterd,^{1,2} P. Nelemans,⁴ N.W.J. Kelleners-Smeets^{1,2} and B.A.B. Essers⁵

Holland



$$\text{ICER} = (\text{kost_}(ny - gl)/ \text{recidivfri 1 år}) (ny - gl)$$



sammenfatning

- Flere endpoints (recidivfrihed, kosmesis osv)
- Curettage + el-kaustik: studier med gode resultater 3-5 cykli
- Shared decision: pt. præferencer (Ex. kir. ar bedre med tid. Stråle tit ringere)
- Topikale: mange forskellige modaliteter: tilpasses den enkelte pt. (f.eks. Ikke imiq til ps.pt)
- Network meta-analysis: indirekte sammenligning af behandlinger, i stedet for head-to-head
- ICER på danske forhold