

Appendix A. Search Strategy

We searched PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE with an update on November 2, 2018, to identify eligible studies. Searches were supplemented by perusing reference lists of eligible papers and suggestions from stakeholders.

PubMed

((("Bowen's Disease"[Mesh] OR bowen's Or "basal cell carcinoma" or "basal cell carcinomas" or "Carcinoma, Basal Cell"[Mesh] or BCC Or "squamous cell carcinoma" or "squamous cell carcinomas" OR "Carcinoma, Squamous Cell"[Mesh] or SCC OR ((keratinocyte* or "Keratinocytes"[Mesh]) and (carcinoma* or "Carcinoma"[Mesh])) OR "non-melanoma" OR "non melanoma" OR "nonmelanoma") NOT (Oropharynx OR Oropharyngeal neoplasms or "Oropharyngeal Neoplasms"[Mesh] OR Pharynx OR Pharyngeal neoplasms OR "Pharyngeal Neoplasms"[Mesh] or "Lung Neoplasms"[Mesh] or "Urinary Bladder Neoplasms"[Mesh] or "Uterine Cervical Neoplasms"[Mesh] or "Esophageal Neoplasms"[Mesh] or "Laryngeal Neoplasms"[Mesh]))

AND

((((Surger* or surgic*) and (excision or removal)) Or "shave removal" Or "external beam radiation" Or "external-beam radiation" Or brachytherap* or "Brachytherapy"[Mesh] Or chemotherap* OR Sensus OR X-ray OR "X-Ray Therapy"[Mesh] OR radiotherapy OR "Radiotherapy"[Mesh] Or (topical and (medications or chemotherap*)) Or observation Or "watchful waiting" Or ((Mohs or micrographic*) and surgery) Or "Mohs Surgery"[Mesh] Or Curett* or "Curettage"[Mesh] Or diathermy or "Diathermy"[Mesh] Or cauterization or "Cautery"[Mesh] Or Cryotherapy or "Cryotherapy"[Mesh] Or electrodesiccation Or ((CO2 or "carbon dioxide") and laser and therapy) Or "Laser Therapy"[Mesh] Or plesiotherapy Or "Methyl 5-aminolevulinate" or "methyl 5-aminolevulinate" [Supplementary Concept] OR MALA Or "5-aminolevulinic acid" or "Aminolevulinic Acid"[Mesh] Or ALA Or Photodynamic or "Photochemotherapy"[Mesh] or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or "Methotrexate"[Mesh] Or Bleomycin or "Bleomycin"[Mesh] Or imiquimod or "imiquimod" [Supplementary Concept] Or BEC-5 Or diclofenac or "Diclofenac"[Mesh] Or interferon or IFN Or "Ingenol mebutate" or "3-ingenyl angelate" [Supplementary Concept] or PEP005 or PEP-005 or "PEP 005" Or Vismodegib Or Erivedge or "HhAntag691" [Supplementary Concept] or NSC747691 or NSC-747691 or "NSC 747691" or R-3616 or R3616 or "R 3616" or RG-3616 or RG3616 or "RG 3616" or GDC-0449 or GDC0449 or "GDC 0449" Or Sonidegib or Odomzo or "LDE225" [Supplementary Concept] or NVP-LDE225 Or Itraconazole or "Itraconazole"[Mesh] or Sporanox or Orungal or R51211 or R-51211 or "R 51211")

AND

("Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study" [Publication Type] OR ((comparative OR Intervention) AND study) OR pretest* OR pre test* OR posttest* OR post

Drucker et al. Treatments for primary squamous cell carcinoma and squamous cell carcinoma in situ of the skin: a systematic review and network meta-analysis

test* OR prepost* OR pre post* OR “before and after” OR interrupted time* OR time serie* OR intervention* OR ((quasi-experiment* OR quasiexperiment* OR quasi experiment*) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR Clinical Studies OR "Clinical Studies as Topic"[Mesh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR randomized)

NOT

(“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “editorial”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “letter”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or “comment on” or “review”[pt] or “systematic”[sb] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae)

Cochrane

((bowen’s Or bowens OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR “non-melanoma” OR “non melanoma” OR “nonmelanoma”) NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms))

AND

((Surger* or surgic*) and (excision or removal)) Or “shave removal” Or “external beam radiation” Or “external-beam radiation” Or brachytherap* Or chemotherap* OR Sensus OR X-ray OR radiotherapy Or (topical and (medications or chemotherap*)) Or observation Or “watchful waiting” Or ((Mohs or micrographic*) and surgery) Or Curett* Or diathermy or cauterization Or Cryotherapy Or electrodesiccation Or ((CO2 or “carbon dioxide”) and laser and therapy) Or plesiotherapy Or “Methyl 5-aminolevulinate” or "methyl 5-aminolevulinate" or MALA Or “5-aminolevulinic acid” or ALA Or Photodynamic or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or Bleomycin Or imiquimod Or BEC-5 Or diclofenac Or interferon or IFN Or “Ingenol mebutate” or "3-ingenyl angelate" or PEP005 or PEP-005 or “PEP 005” Or Vismodegib Or Erivedge or NSC747691 or NSC-747691 or “NSC 747691” or R-3616 or R3616 or “R 3616” or RG-3616 or RG3616 or “RG 3616” or GDC-0449 or GDC0449 or “GDC 0449” Or Sonidegib or Odomzo or NVP-LDE225 Or Itraconazole or Sporanox or Orungal or R51211 or R-51211 or “R 51211”)

EMBASE

(bowen* OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR non-melanoma OR non melanoma OR nonmelanoma) NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms)

AND

((Surger* or surgic*) and (excision or removal)) Or “shave removal” Or “external beam radiation” Or “external-beam radiation” Or brachytherap* Or chemotherap* OR Sensus

Drucker et al. Treatments for primary squamous cell carcinoma and squamous cell carcinoma in situ of the skin: a systematic review and network meta-analysis

OR X-ray OR radiotherapy Or (topical and (medications or chemotherap*)) Or observation Or “watchful waiting” Or ((Mohs or micrographic*) and surgery) Or Curett* Or diathermy or cauterization Or Cryotherapy Or electrodesiccation Or ((CO2 or “carbon dioxide”) and laser and therapy) Or plesiotherapy Or “Methyl 5-aminolevulinic acid” or "methyl 5-aminolevulinic acid" or MALA Or “5-aminolevulinic acid” or ALA Or Photodynamic or Photochemotherap* Or 5-fluorouracil Or 5-FU Or Methotrexate Or Bleomycin Or imiquimod Or BEC-5 Or diclofenac Or interferon or IFN Or “Ingenol mebutate” or "3-ingenyl angelate" or PEP005 or PEP-005 or “PEP 005” Or Vismodegib Or Erivedge or NSC747691 or NSC-747691 or “NSC 747691” or R-3616 or R3616 or “R 3616” or RG-3616 or RG3616 or “RG 3616” or GDC-0449 or GDC0449 or “GDC 0449” Or Sonidegib or Odomzo or NVP-LDE225 Or Itraconazole or Sporanox or Orungal or R51211 or R-51211 or “R 51211”)

AND

(Clinical trial/ OR Randomized controlled trial/ OR Randomization/ OR Single blind procedure/ OR Double blind procedure/ OR Crossover procedure/ OR Placebo/ OR Randomized controlled trial\$.tw. OR Rct.tw. OR Random allocation.tw. OR Randomly allocated.tw. OR Allocated randomly.tw. OR (allocated adj2 random).tw. OR Single blind\$.tw. OR Double blind\$.tw. OR ((treble or triple) adj blind\$.tw. OR Placebo\$.tw. OR Prospective study/ OR Clinical study/ OR Case control study OR Family study/ OR Longitudinal study/ OR Retrospective study/ OR Prospective study/ OR Randomized controlled trials/ OR Cohort analysis/ OR (Cohort adj (study or studies)).mp. OR (Case control adj (study or studies)).tw. OR (follow up adj (study or studies)).tw. OR (observational adj (study or studies)).tw. OR (epidemiologic\$ adj (study or studies)).tw. OR (cross sectional adj (study or studies)).tw.)

Limits: (human and english language and (adult <18 to 64 years> or aged <65+ years>))

ClinicalTrials.gov

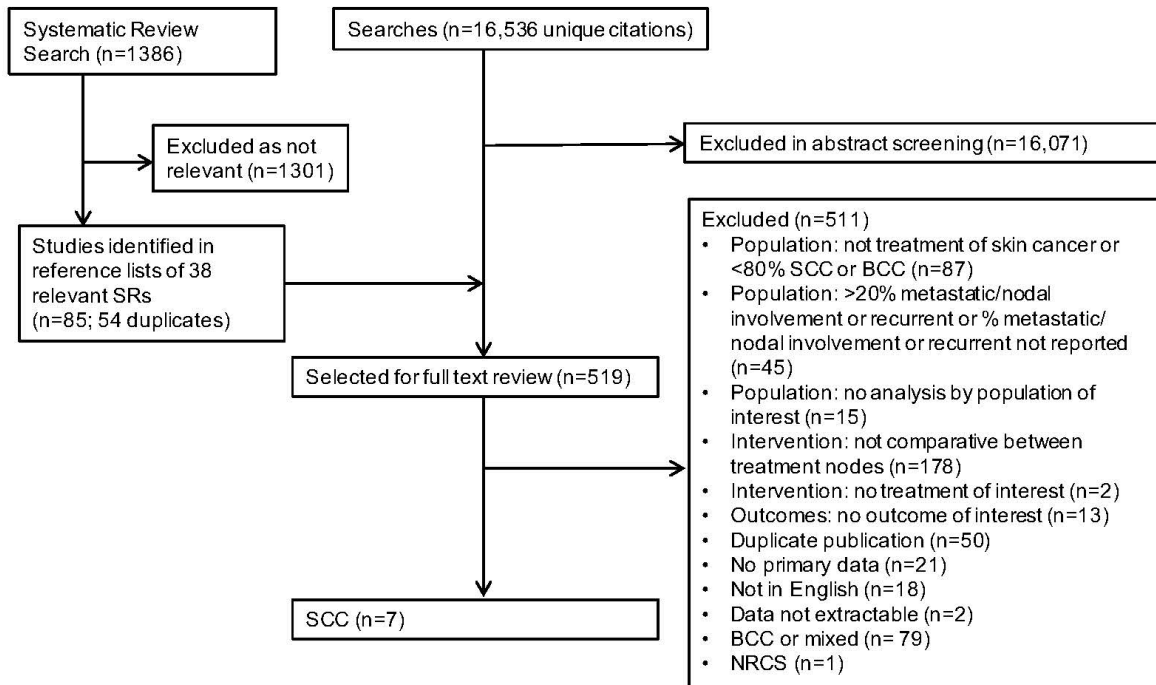
(bowen’s disease OR basal cell carcinoma OR BCC OR squamous cell carcinoma OR SCC OR keratinocyte carcinoma OR “non-melanoma”)

AND (skin OR dermatology OR dermatological OR derma)

ICTRP

bowen’s disease OR basal cell carcinoma OR BCC OR squamous cell carcinoma AND skin OR SCC AND skin OR keratinocyte carcinoma OR non-melanoma AND skin

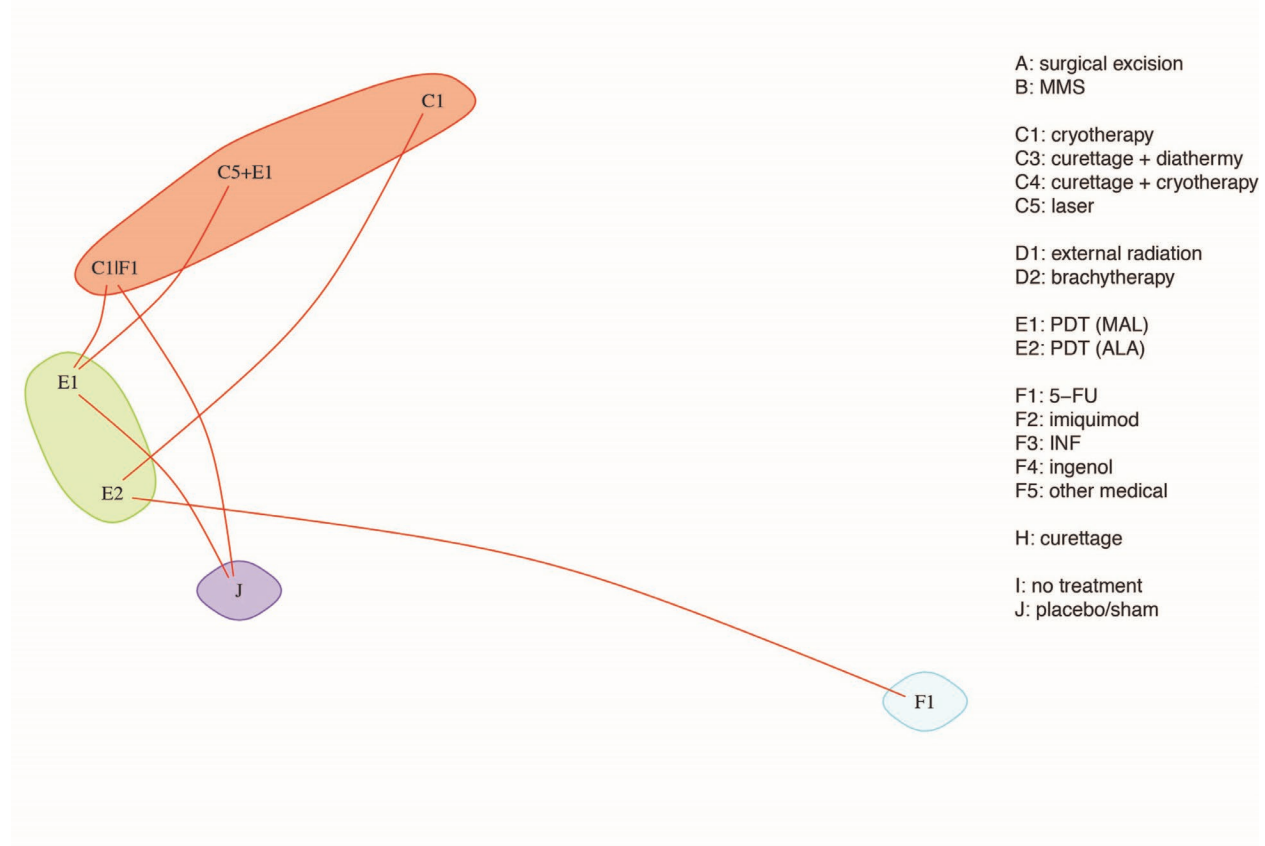
Appendix B. PRISMA flow diagram of included studies



Appendix C. Network graphs

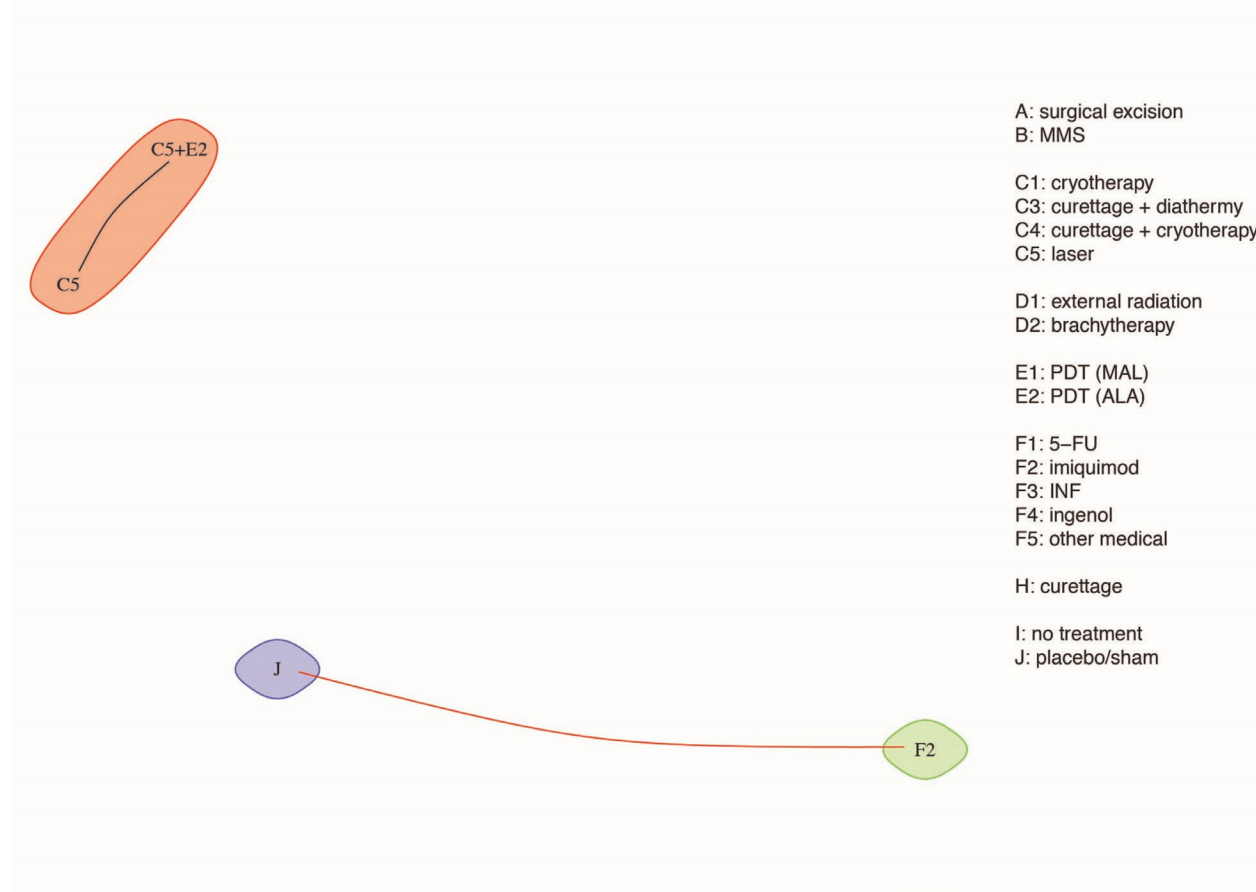
The evidence graphs comprises nodes, depicting specific interventions, and edges (links between nodes). An edge exists when the specific interventions represented by the nodes it connects have been compared head-to-head in ≥ 1 trial. Shaded regions around sets of nodes represent intervention categories.

Figure C1. Evidence graph of RCTs evaluating recurrence in SCCis lesions. The evidence consists of a single connected network. Most nodes represent single interventions but one node consists of Laser + MAL-PDT (C5+E1) and another consists of cryotherapy OR topical 5-fluorouracil (C1|F1).



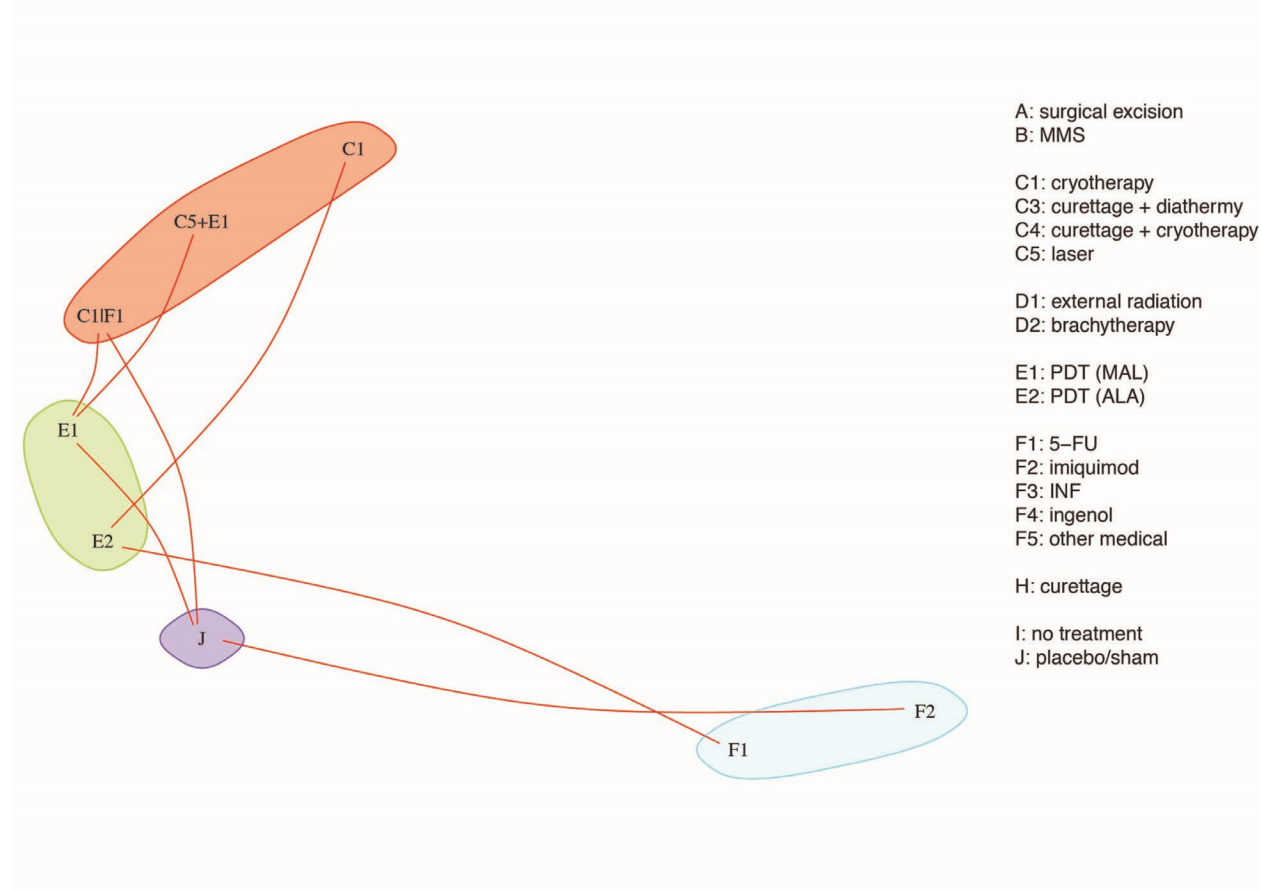
Abbreviations: MMS=mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon; SCCIS=squamous cell carcinoma in situ

Figure C2. Evidence graph of RCTs evaluating lack of histological clearance in SCCis lesions across individual interventions. The evidence consists of two small disconnected networks. One compares Laser + ALA-PDT vs Laser alone and the other compares topical imiquimod vs placebo.



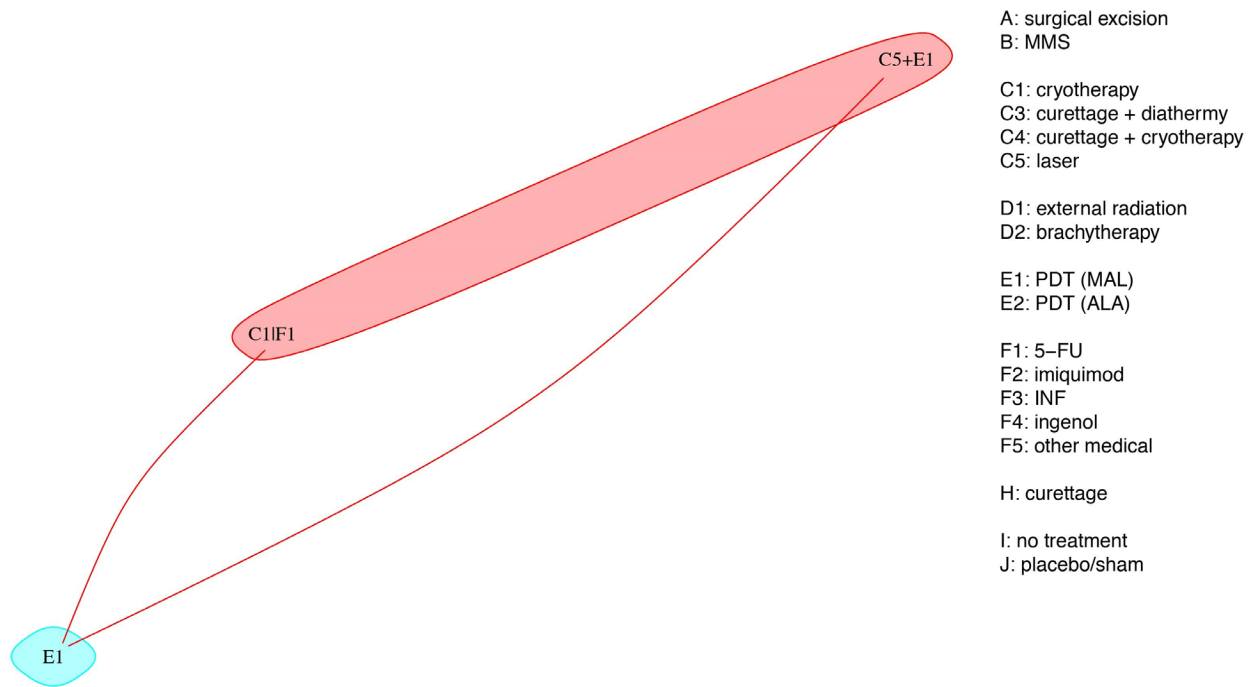
Abbreviations: MMS=mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinic acid, FU= fluorouracil, INF=interferon; SCCIS=squamous cell carcinoma in situ

Figure C3. Evidence graph of RCTs evaluating lack of clinical clearance in SCCis lesions. The evidence consists of a single connected network. Most nodes represent single interventions but one node consists of Laser + MAL-PDT (C5+E1) and another consists of cryotherapy OR topical 5-fluorouracil (C1|F1).



Abbreviations: MMS=mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinic acid, FU= fluorouracil, INF=interferon; SCCIS=squamous cell carcinoma in situ

Figure C4. Evidence graph of RCTs evaluating observer (non-patient) reported cosmetic outcome in SCCis lesions. The evidence consists of a single small network with of cryotherapy OR topical 5-fluorouracil (C1|F1) and Laser + MAL-PDT (C5+E1) connected via comparisons with MAL-PDT (E1) alone.



Abbreviations: MMS=mohs micrographic surgery, PDT=photodynamic therapy; ALA= 5-aminolevulinic acid, MAL=methyl aminolevulinate, FU= fluorouracil, INF=interferon; SCCIS=squamous cell carcinoma in situ

Appendix D. Relative efficacy tables

Table D1. Relative odds ratios for lack of histological clearance of SCCis lesions between individual interventions

(F1) 5-FU	<i>0.01</i> <i>(<0.005, 0.22)</i>		
	(J) placebo		
		(C5) laser	8.33 <i>(0.78, 89.47)</i>
			(C5+E2) laser and PDT (ALA)

Results are given as odds ratios (95% confidence intervals). The odds ratio in each cell represents the odds for lack of histological clearance with the intervention on the left over the odds for lack of histological clearance with the intervention on the right. For example, 5-FU has 0.01 times the odds of failing to histologically clear a lesion compared with placebo. Bold-italic indicates that the result is statistically significant

PDT (ALA)= aminolevulinic acid photodynamic therapy; FU= fluorouracil; SCCis=squamous cell carcinoma in situ.

Drucker et al. Treatments for primary squamous cell carcinoma and squamous cell carcinoma in situ of the skin: a systematic review and network meta-analysis

Table D2. Relative odds ratios for lack of clinical clearance of SCCis between individual interventions

Cryotherapy or 5-FU (C1 F1)	13.7 (2.92, 64.25)	2.11 (0.88, 5.06)	3.04 (0.21, 44.58)	0.04 (0.01, 0.15)
Laser and PDT (MAL) (C5+E1)		0.15 (0.04, 0.56)	0.22 (0.01, 4.18)	<0.005 (<0.005, 0.02)
		PDT (MAL) (E1)	1.44 (0.1, 21.22)	0.02 (0.01, 0.07)
		Imiquimod (F2)		0.01 (<0.005, 0.19)
		Placebo/sham (J)		
		Cryotherapy (C1)	0.28 (0.01, 7.38)	0.06 (<0.005, 1.59)
		PDT (ALA) (E2)		0.21 (0.04, 1.08)
				5-FU (F1)

Results are given as odds ratios (95% confidence intervals). The odds ratio in each cell represents the odds for lack of clinical clearance with the intervention on the left over the odds for lack of clinical clearance with the intervention on the right. For example, MAL PDT has 1.44 times the odds of failing to provide clinical clearance compared with imiquimod. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant. PDT (MAL)= methyl aminolaevulinate photodynamic therapy; PDT (ALA)= aminolevulinic acid photodynamic therapy; FU= fluorouracil; SCCis=squamous cell carcinoma in situ.

Table D3. Relative odds ratios between interventions for SCCis for at least good cosmetic outcome, as assessed by an observer (non-patient)

Cryotherapy or 5-FU (C1 F1)	0.32 (0.07, 1.51)	<i>0.09 (0.02, 0.30)</i>
	Laser and PDT (MAL) (C5+E1)	0.26 (0.04, 1.71)
		PDT (MAL) (E1)

Results are given as odds ratios (95% confidence intervals). The odds ratio in each cell represents the odds of having an observer-rated cosmetic outcome that is at least “good” with the intervention on the left over the odds of having an observer-rated cosmetic outcome that is at least “good” with the intervention on the right. For example, Laser + MAL PDT has 0.26 times the odds of providing a cosmetic outcome that is at least good compared with MAL PDT alone. Cells shaded gray indicate that the estimate is based only on indirect comparisons; bold-italic indicates that the result is statistically significant.

PDT (MAL)= methyl aminolaevulinate photodynamic therapy; FU= fluorouracil; SCCis=squamous cell carcinoma in situ.