British Association of Dermatologists *draft* guidelines for the management of people with squamous cell carcinoma *in situ* (Bowen's disease) 2021

WEB APPENDIX – SUPPLEMENTARY INFORMATION

Appendix A: Systematic Review Protocols

Q1: Interventions

Component	Description
Review question	In people with squamous cell carcinoma *in situ* (Bowen's disease) how clinically effective are the available treatments compared with each other or in combination or with placebo/no treatment?
Objectives	The aim of this review is to assess the clinical effectiveness of various interventions for the management of patients with squamous cell carcinoma in situ, compared with each other or in combination or with placebo/ no treatment.
Population	All people with squamous cell carcinoma *in situ* (Bowen's disease)
Strata	The following groups/interventions will be considered separately if data is available: • Children (0-12 years) and young people (13-17 years) • Immunosuppressed patients • SCC *in situ* of the nail unit • Penile intraepithelial neoplasia (PIN)
Subgroups	The following factors will be considered for subgroup analysis *if heterogeneity is present*: • Gender • Dosing/treatment regimen (e.g. topical schedule, curettage cycles) • Location (head & neck, trunk & lower limb)

Intervention	• Surgical
	  ○ Standard surgical excision
	  ○ Mohs micrographic surgery
	• Destructive
	  ○ Curettage with cautery
	  ○ Cryotherapy/cryosurgery
	• Other
	  ○ Laser
	  ○ Photodynamic therapy (PDT)
	  ○ Radiotherapy
	  ○ Topical therapies (e.g. 5-fluorouracil, imiquimod)
	• Combination therapies

Comparison	• No treatment
	• Surgical
	  ○ Standard surgical excision
	  ○ Mohs micrographic surgery
	• Destructive
	  ○ Curettage with cautery
	  ○ Cryotherapy/cryosurgery
	• Other
	  ○ Laser
	  ○ Photodynamic therapy (PDT)
	  ○ Radiotherapy
	  ○ Sunscreen
	  ○ Topical therapies (e.g. 5-fluorouracil, imiquimod)
	  ○ Placebo
	• Combination therapies

Outcomes (and ranking 1-9)	***Critical*** • Clearance (within 6 months) (9)

	• Sustained clearance/recurrence at 1, 2 or 5 years (9) • Adverse events – serious (e.g. bleeding, severe pain, ulceration) (8) • Quality of life (8) ***Important*** • Cosmetic outcome (6) • Convenience of treatment (6) • Adverse events – minor 4 • Treatment tolerability (e.g. pain) 4 ***Less important*** • Adverse events – less serious (3)
Study design	• RCTs or systematic reviews • Cohort studies • Case-control studies • Case series
Population size and directness	• Sample size n>5 patients • Studies with indirect populations will not be considered
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome

Q2. Rates of cancer

Component	Description
Review question	What are the subsequent rates of keratinocyte cancer in people who have had squamous cell carcinoma *in situ* (Bowen's disease)?
Objectives	To determine the rates of keratinocyte cancer in people who have had squamous cell carcinoma *in situ*
Population	All people who have had squamous cell carcinoma *in situ*
Strata	The following groups/interventions will be considered separately if data is available: • Children (0-12 years) and young people (13-17 years) • Type of keratinocyte cancer • Previous skin cancer • Previous visceral cancer • Previous lymphoma • Immunocompromised patients
Subgroups	The following factors will be considered for subgroup analysis *if heterogeneity is present*: • Age • Gender

Intervention	• Surgical
	  ○ Standard surgical excision
	  ○ Mohs micrographic surgery
	• Destructive
	  ○ Curettage with cautery
	  ○ Cryotherapy/cryosurgery
	• Other
	  ○ Laser
	  ○ Photodynamic therapy (PDT)
	  ○ Radiotherapy
	  ○ Topical therapies (e.g. 5-fluorouracil, imiquimod)
	• Combination therapies

Comparison	• No treatment
	• Surgical
	  ○ Standard surgical excision
	  ○ Mohs micrographic surgery
	• Destructive
	  ○ Curettage with cautery
	  ○ Cryotherapy/cryosurgery
	• Other
	  ○ Laser
	  ○ Photodynamic therapy (PDT)
	  ○ Radiotherapy
	  ○ Sunscreen
	  ○ Topical therapies (e.g. 5-fluorouracil, imiquimod)
	  ○ Placebo
	• Combination therapies

Outcomes (and ranking 1-9)	***Critical*** • Incidence of any keratinocyte cancer (at location of previous SCC *in situ*) in studies with follow-up of ≥6 months since treatment/reference time-point (9) ***Important***

	• Incidence of progression outside original location of previous SCC *in situ* (6) • Incidence of malignancy* (6)
Study design	• RCTs or systematic reviews • Cohort studies • Case-control studies • No case series or case reports
Population size and directness	• Sample size n>5 • Studies with indirect populations will not be considered
Setting	• Primary care • Secondary care • Tertiary care • Community settings in which NHS care is received
Search Strategy	See appendix L
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome
* The clinicians on the GDG did not think that the incidence of other cancers was that important, as although another cancer may be statistically associated, this does not imply causation as the two cannot be linked by scientific evidence. However, the patient representatives were clearly worried about any future cancer, so, it was agreed the incidence of malignancy would be included as an outcome.	

Appendix B: Forest plots

NB: If the outcome being measured is positive i.e. clearance the intervention will appear on the righthand axis of the forest plots. If negative i.e. a mean reduction (due to improvement), the intervention will appear on the left-hand axis of the forest plots.

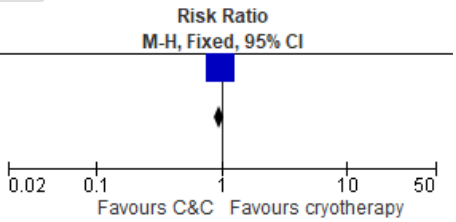
Cryotherapy vs. curettage with cautery (cohort)

Critical

Clearance of treated SCC *in situ* (within 6 months) lesions

	Cryotherapy		C&C			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ahmed, BJD 2000	34	36	43	44	100.0%	0.97 [0.88, 1.06]
Total (95% CI)		**36**		**44**	**100.0%**	**0.97 [0.88, 1.06]**
Total events	34		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)

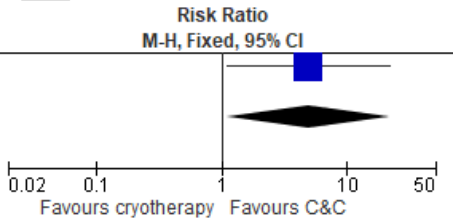


NB: 3 lesions had not yet healed at 6 months

Recurrence at 1 year

	Cryotherapy		C&C			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ahmed, BJD 2000	8	36	2	44	100.0%	4.89 [1.11, 21.60]
Total (95% CI)		**36**		**44**	**100.0%**	**4.89 [1.11, 21.60]**
Total events	8		2			

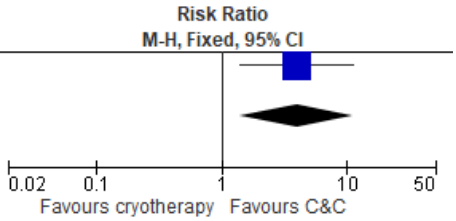
Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)



Recurrence at 2 years

	Cryotherapy		C&C			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ahmed, BJD 2000	13	36	4	44	100.0%	3.97 [1.42, 11.13]
Total (95% CI)		**36**		**44**	**100.0%**	**3.97 [1.42, 11.13]**
Total events	13		4			

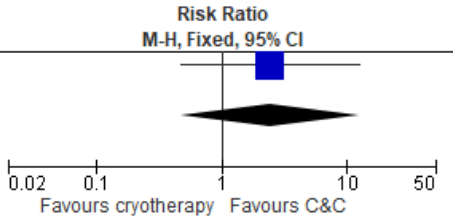
Heterogeneity: Not applicable
Test for overall effect: Z = 2.62 (P = 0.009)



Adverse events – serious: infection requiring antibiotics

	Cryotherapy		C&C			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Ahmed, BJD 2000	4	36	2	44	100.0%	2.44 [0.47, 12.59]
Total (95% CI)		**36**		**44**	**100.0%**	**2.44 [0.47, 12.59]**
Total events	4		2			

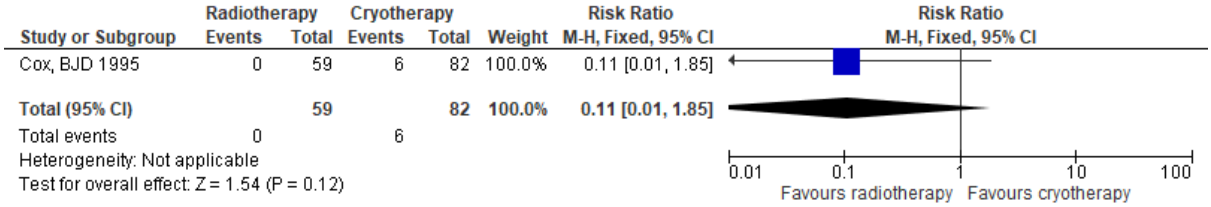
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)



Radiotherapy vs. cryotherapy (retrospective cohort)

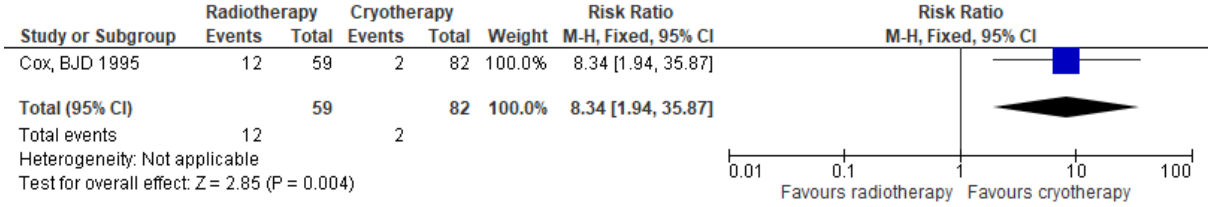
Critical

Recurrence



NB: Note change of scale

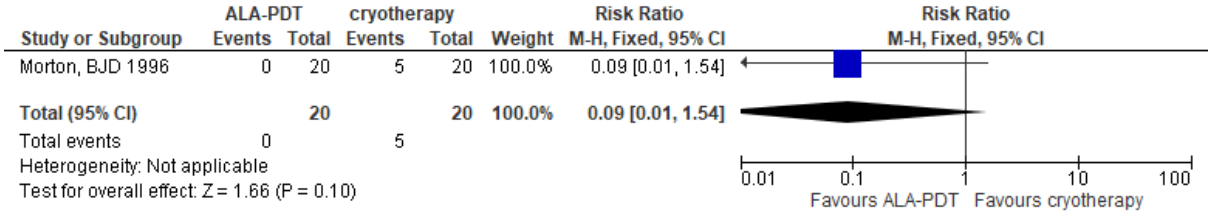
Adverse events – serious (ulceration/failure to heal)



ALA-PDT vs cryotherapy

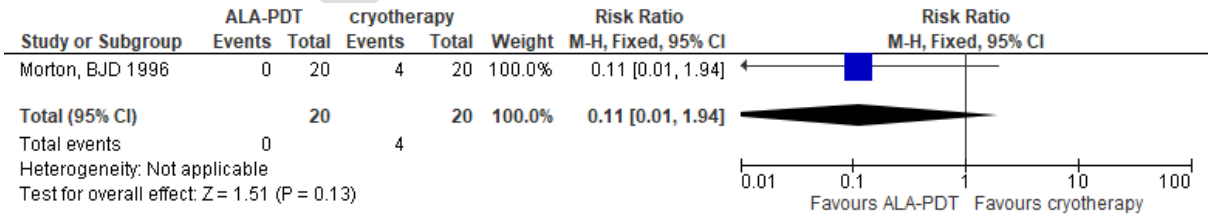
Critical

Adverse events – ulceration



Important

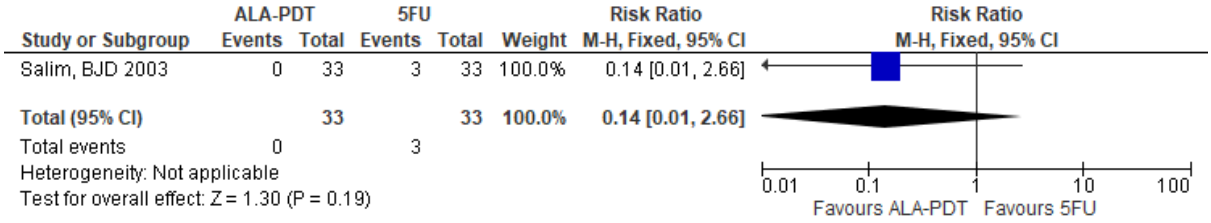
Cosmetic outcome: visible scar at 12 months f/up



ALA-PDT vs topical 5-fluorouracil

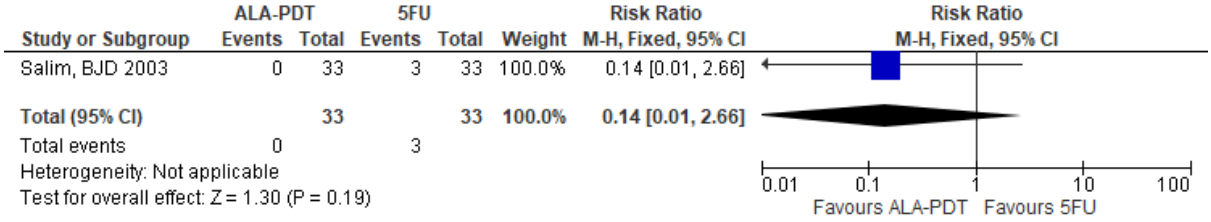
Critical

Adverse events – ulceration



Important

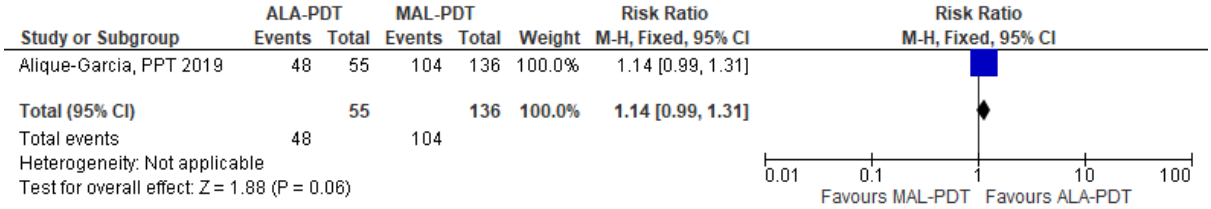
Cosmetic outcome: visible scar at 12 months f/up



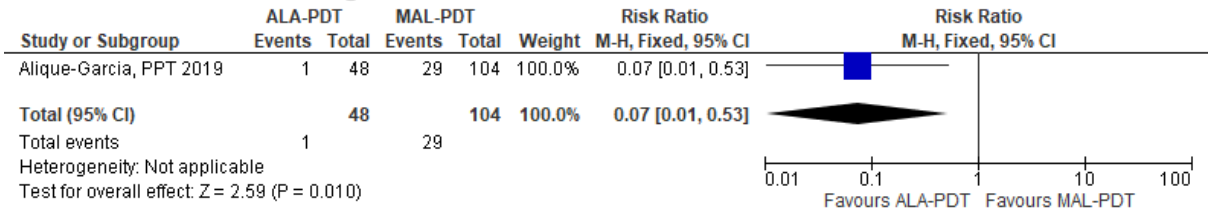
ALA-PDT vs MAL-PDT (cohort)

Critical

Clearance of treated SCC *in situ* (within 6 months) lesions



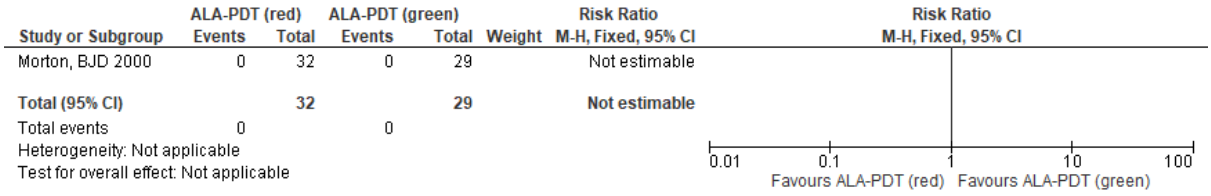
Recurrence



ALA-PDT (red) vs. ALA-PDT (green)

Critical

Serious infection (ulceration)

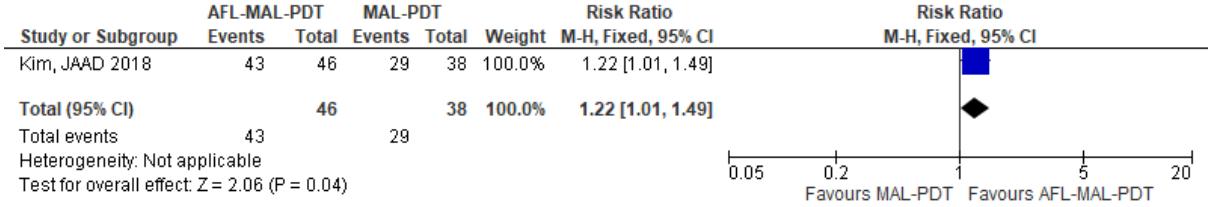


NB: Risk ratio cannot be calculated when there are no events

Ablative fractional laser (AFL)-MAL-PDT vs. MAL-PDT

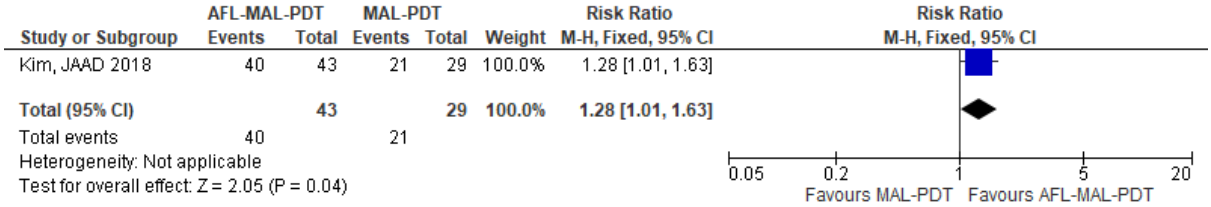
Critical

Clearance of treated SCC *in situ* (3 months) lesions

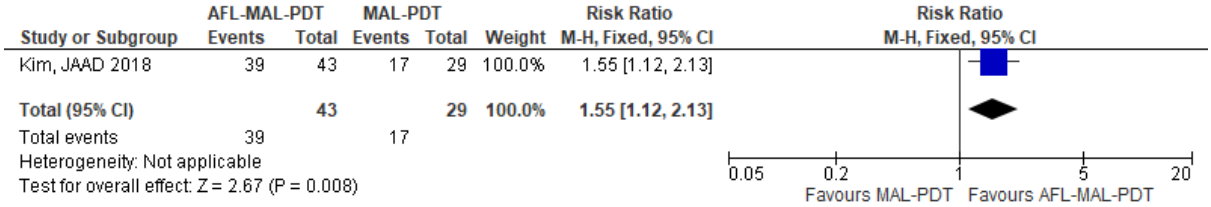


NB: Note change in scale

Sustained clearance of lesions at 1 year

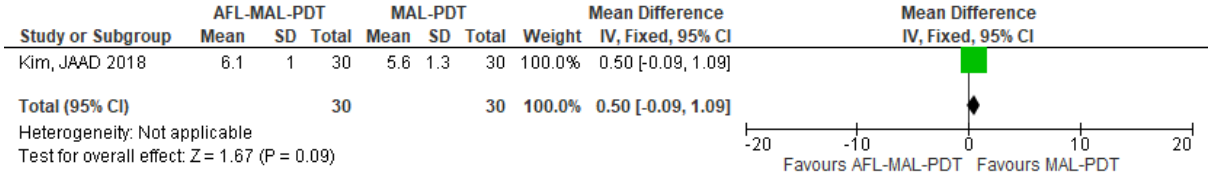


Sustained clearance of lesions at 5 years



Important

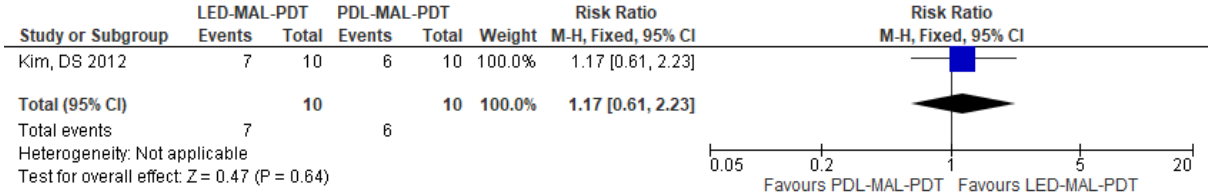
Treatment tolerability: VAS measure of pain (higher the mean the more pain experienced)



Light-emitting diode (LED)-MAL-PDT vs. Pulsed dye laser (PDL)-MAL-PDT

Critical

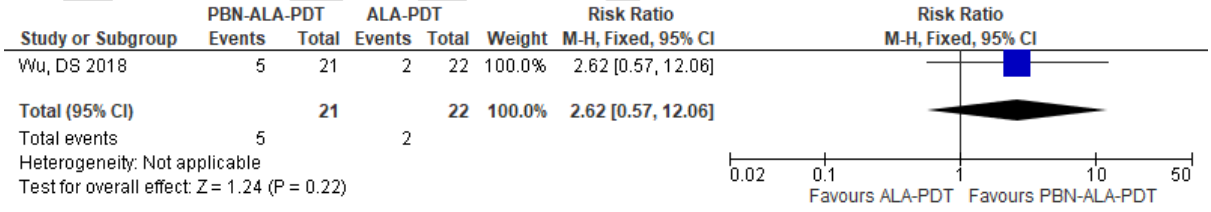
Clearance of treated SCC *in situ* (3 months follow/up) patients



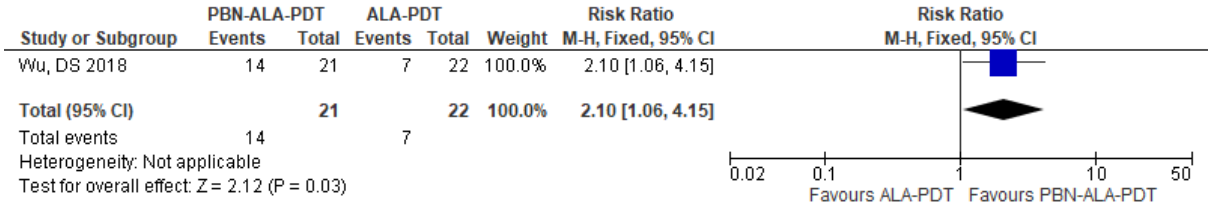
Plum-blossom needling (PBN)-ALA-PDT vs. ALA-PDT

Critical

Clearance of treated SCC *in situ* (4 weeks, 2 treatments) lesions



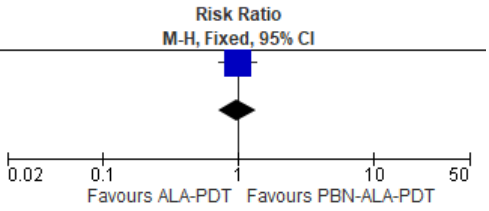
Clearance of treated SCC *in situ* (6 weeks, 3 treatments) lesions



Clearance of treated SCC *in situ* (end of treatment) lesions

Study or Subgroup	PBN-ALA-PDT Events	Total	ALA-PDT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wu, DS 2018	16	21	17	22	100.0%	0.99 [0.71, 1.37]
Total (95% CI)		**21**		**22**	**100.0%**	**0.99 [0.71, 1.37]**
Total events	16		17			

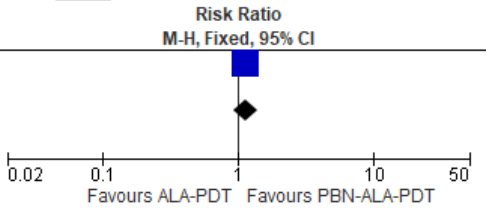
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)



Sustained clearance of lesions at 1 year (patients were followed-up for at least 12 months)

Study or Subgroup	PBN-ALA-PDT Events	Total	ALA-PDT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wu, DS 2018	16	16	15	17	100.0%	1.13 [0.92, 1.38]
Total (95% CI)		**16**		**17**	**100.0%**	**1.13 [0.92, 1.38]**
Total events	16		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)



Appendix C: Linking Evidence To Recommendations (LETR)

REVIEW TITLE/QUESTION: (Q1) In people with squamous cell carcinoma *in situ* (SCC *in situ*) what is the clinical effectiveness, safety and tolerability of available treatments compared with each other or in combination or with placebo/no treatment?	
The wording for recommendations is standardised so that they are clearly identifiable, unambiguous and specific: "Offer[1]" or "Do not offer" (strong recommendation ↑↑ or ↓↓) [an intervention] to patients with [skin disease] + [any relevant conditions] - [1]or similar, e.g. "Use", "Provide", "Take", "Investigate", etc.) "Consider" (weak recommendation ↑) [an intervention] for patients with [skin disease] + [any relevant conditions] The GDG is aware of the lack of high-certainty evidence for some of these recommendations, therefore strong recommendations with an asterisk (*****) are based on available evidence and/or consensus within the GDG and specialist experience. Good practice point (GPP) recommendations are derived from informal consensus.	
Relative values of different outcomes	***Critical*** • Clearance (within 6 months) **(9)** • Sustained clearance/recurrence at 1, 2 or 5 years **(9)** • Adverse events – serious (e.g. bleeding, severe pain, ulceration) **(8)** • Quality of life **(8)** ***Important*** • Cosmetic outcome **(6)** • Convenience of treatment **(6)** • Treatment tolerability (e.g. pain) **(4)** ***Less important*** • Adverse events – minor **(3)** Ranked outcomes according to our guideline development protocol[1] which uses the GRADE methodology (9-7 Critical for decision making; 6-4 Important but not critical for decision making; 3-1 not important for decision making), as agreed and ranked by the patient representatives on the GDG.

Balance between desirable and undesirable effects	Three systematic reviews (SR) were identified. A Cochrane review on the effects of therapeutic interventions for cutaneous SCC *in situ,*[2] a SR and meta-analysis on the treatments for primary cutaneous SCC, including SCC *in situ*[3] and a SR on clearance rates and adverse effects of topical imiquimod or fluorouracil therapy (5-FU) in the treatment of non-melanoma skin cancers (NMSC), including SCC *in situ.*[4] No comparative studies examined surgical methods. The majority of randomised controlled trials (RCTs) related to photodynamic therapy (PDT). In general, the methodological quality of these trials was poor. Overall, they concluded there is very little good-quality research on treatments for SCC *in situ*. The SR concluded that there is limited evidence from individual studies to suggest MAL-PDT is an effective treatment. Although cosmetic outcomes appear favourable with PDT, five-year follow-up data are needed. Significantly more lesions cleared with MAL-PDT compared to cryotherapy. No significant difference in clearance was seen when MAL-PDT was compared with 5-FU, but one study found a significant difference in clearance in favour of ALA-PDT when compared to 5-FU. There was no significant difference in clearance when cryotherapy was compared to 5-FU. The age group, number, and size of lesions and site(s) affected may all influence therapeutic choice; however, there was not enough evidence available to provide guidance on this. There was a discussion within the GDG as what constitutes a small lesion, the original guidelines had defined small as <20 mm.[5] A comparative study of PDT and cryotherapy using patches less than 21 mm in diameter confirmed that lesion size affects the probability that it is completely cleared at first treatment.[6] A later study confirmed larger patches of SCC *in situ* do require more treatments.[7] The GDG decided to retain the definition of a small lesion as <20 mm. More studies are required especially in the immunosuppressed populations as different therapeutic options may be preferable. Firm conclusions about the comparative effectiveness of treatments could not be given. **<u>No treatment</u>** Very few papers looked at no treatment as an option, and those that did often included patients who had died before treatment commenced of other causes or did not attend treatment, rather than being assigned observation. The GDG agreed that in some patients with slowly progressive thin lesions, especially on the lower leg of patients in poor health where healing is poor, observation rather than intervention is more appropriate. In these patients the use of an emollient (especially one containing urea) can reduce scaling and make the lesion less obvious.

Recommendation (GPP) Consider conservative measures in people in poor health and with multiple SCC *in situ* lesions, especially on the lower legs. This includes a moisturiser (preferably urea-based) and skin surveillance, proceeding to biopsy if SCC is suspected.

Topical therapies

5-Fluorouracil (5-FU)

5-FU was first introduced in 1957 as part of a new class of anti-tumour compounds. Early studies of hepatic tumours in rats demonstrated an increased utilization of exogenous uracil in malignant cells. 5-FU, a novel uracil analog, enters the cell via the same facilitated transport mechanism as uracil and is converted into toxic metabolites, which interfere with the normal synthesis of DNA and RNA. In 1970, the topical use of 5-FU was approved, after showing cytotoxic effects in some skin cancers, and proving to be an effective treatment for actinic keratosis and keratoacanthoma. Cytotoxicity with 5-FU occurs only in the rapidly proliferating cells of abnormal skin. Cancerous and precancerous cells require rapid nucleic acid synthesis; and so are more sensitive to the effects of 5-FU than the surrounding normal skin.

Topically applied 5-FU is available in the U.K. as a 5% cream, with a 40 g tube costing £32.90. Its license states once-daily or twice-daily application for 3-4 weeks, repeated as required, although "alternative regimens may be used in some settings". It is to be applied to a maximum area of 500 cm^2, but there is no indication of a treatment margin around a superficial malignant or pre-malignant lesion. Its use is limited by local inflammation with erosion and ulceration, which may last for several weeks. Many of the original studies used different concentrations and regimens, including those described below.

Two of the SRs evaluated the same two RCTs which used the once daily treatment regimen.[2,4] One study demonstrated statistically significantly greater clearance with 5-FU at 12 months when compared with placebo-PDT or cryotherapy, but there was no significant difference when 5-FU was compared to MAL-PDT.[8]

The other study demonstrated statistically significant reduced clearance of lesions with 5-FU compared to ALA-PDT.[9] However, the treatment regime of once daily for 1 week then twice daily for weeks 2 to 4, which could be repeated if necessary, is not commonly used. The clearance rate at initial assessment was 67%, reducing to 48% at 1 year.

There is currently an ongoing RCT due to complete in 2025, comparing surgical excision, PDT and topical 5-FU.[10]

One non-comparative study achieved an 85% clinical clearance with a twice daily treatment for 8 weeks and average follow-up of 4.6 years.[11] This treatment course is twice the typical treatment length recommended in the UK. Furthermore, even at this high dosing schedule, all SCC *in situ* that failed to respond to this treatment were located in high-risk areas (e.g. finger, ear, cheek and penis). Only 50% of 42 males with primary and recurrent Erythroplasia of Queyrat achieved clearance with 5 recurrences within 5 months.[12]

The most recently published retrospective study included 46 people with 72 lesions, cumulative treatment failure probability (95% CI) was reported as 13.1 (6.7-24.7) at 1 year and 15.5 (8.3-27.9) at both 2 years and 5 years.[13] A number of other non-comparative studies showed varying recurrence rates 7.3-23.5%.[14,15]

Several studies used 5-FU in combination with another treatment, including cryotherapy and CO_2 laser.[16,17] (See Combination section)

Imiquimod:

Topical imiquimod, an imidazoquinoline, is an immune response modifier. It does not have any direct antiproliferative action but acts via a Toll-like receptor to induce secretion of pro-inflammatory cytokines, including IFN-α, IFN-γ, IL-12 and TNF. This promotes a Th1 cell mediated immune response with the generation of cytotoxic effectors, resulting in the clearance of skin cancer cells. This immune stimulation may also precipitate systemic flu-like symptoms and underlying autoimmune conditions, such as eczema, psoriasis and vitiligo. It is not licensed for the treatment of SCC *in situ,* but its use in dermatology is well documented. A 12-sachet pack costs £48.60.

The application regime for actinic keratoses is three times per week for 4 weeks, and for superficial basal cell carcinoma (BCC) is five times per week for 6 weeks. For BCC, the cream is to be applied to the lesion and for 10 mm beyond it, although there is no margin specified for actinic keratoses. Given the wide variation in treatment regimens described below, the GDG agreed to keep to the standard treatment regimen as for actinic keratoses, acknowledging that prolonged treatment may be necessary.

One study evaluated daily application of imiquimod 5 days a week, while the other four evaluated once daily application. Treatment duration ranged from 9-16 weeks. The RCT compared imiquimod to placebo and demonstrated statistically greater clearance rates with imiquimod compared to placebo.[18] The imiquimod group did not report any recurrences at 12 months, however 2/16 in the placebo group had developed early invasive SCC at 18 months.[18]

Studies that included SCC *in situ* confined to the trunk and extremities reported higher clearance rates than did studies that included SCC *in situ* in high-risk locations.[18-21] The largest non-comparative study included 56 patients treated daily for 9 weeks and achieved a 75% clinical clearance rate at 19 months.[21] The highest clearance rate, 88% at 6 month clinical follow-up was achieved with a daily application for a mean 12 weeks (range 4-16); all recurrent SCC *in situ* were initially larger than 20 mm in diameter.[22] Long-term follow-up was not available for any of these studies.

One non-comparative study evaluated imiquimod followed by CO_2 laser excision in 10 males with carcinoma *in situ* of the penis.[23] (See combination section)

Regarding cosmesis, topical therapy has been stated to achieve superior cosmetic results compared with surgical treatments in cosmetically sensitive areas in BCC. This was not supported by one SR, where scarring was reported in 8% to 16% of patients with SCC *in situ* treated topically with 5-FU (or 15% of BCC patients treated topically with imiquimod).[4] One study reported that only 76% of patients treated with 5-FU reported an excellent cosmetic outcome at 12 months, compared with 94% for PDT.[8] Permanent hypopigmentation has been reported in 67% of patients treated with imiquimod for BCC (55 patients treated for BCC, followed up after 5 years).[24]

Ingenol mebutate

A single comparative study (n=19) reported 12.5% clearance with ingenol mebutate monotherapy compared to 88.9% with fractional CO_2 laser treatment followed by topical ingenol mebutate.[25] Since then in January 2020 marketing authorisation was suspended for ingenol mebutate by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) and it is no longer available in Europe. This was due to emerging evidence suggesting possible links between use of the product with an increased risk of developing skin cancers.

Tazarotene

A single non-comparative study (n=15) reported clearance of 46.7%.[26]

Summary:

Topical therapy is associated with many adverse effects, including poor cosmetic outcome. For some elderly patients, it may be more difficult to administer. In some instances, it may cost more than other well-established therapies. 5-FU is less effective than PDT but not significantly different from cryotherapy, depending on the protocol used. It is more practical than surgery for larger lesions, especially at poor healing sites. It produces lower clearance rates at high-risk sites. Follow-up data for 5-FU is available up to 5 years, with approximately 15% recurrence rate, but there is no long-term data for imiquimod.

	The evidence for 5-FU is better than for imiquimod although, based on the available evidence, the strength of recommendation for either is weak. There is insufficient evidence to recommend tazarotene or ingenol mebutate. Also, with the loss of marketing recommendation of the latter it would not be recommended due to risk of progression to skin cancer. **Recommendation (↑↑)** Offer topical 5% 5-fluorouracil monotherapy to people with SCC *in situ,* for small lesions (e.g. <2 cm) in low-risk sites, and in those who will not or cannot undergo alternative treatments. Initiate a standard regimen of once or twice daily application for 3-4 weeks. Counsel patients regarding the side effects of local inflammation, ulceration and potential scarring. (see recommendation two below) **Recommendation (GPP)** Consider topical 5% 5-fluorouracil monotherapy in people with SCC *in situ,* for larger lesions in low-risk sites, and in those who will not or cannot undergo treatment with other better-established therapies. Initiate a standard regimen of once or twice daily application for up to 4 weeks. Counsel patients regarding the side effects of local inflammation, ulceration and potential scarring. (see recommendation directly below) **Recommendation (↑)** Consider biopsy and/or the next treatment option if there has been no response to topical 5-fluorouracil after 4 weeks, once the residual inflammation has settled. **Recommendation (↑)** Consider topical 5% 5-fluorouracil monotherapy in people with SCC *in situ* for larger lesions on poorly healing sites (e.g. the lower legs of older patients) as a practical alternative to surgical treatments. Initiate a standard regimen of twice daily application for up to 4 weeks. (see recommendation directly above) **Recommendation (↑)** Consider topical 5% imiquimod in people with SCC *in situ* at low-risk sites, when there is no suitable alternative. Consider once-daily application, three times per week for 4 weeks, although prolonged treatment for 12 weeks may be required. Efficacy may be reduced in immunocompromised people. **No recommendation** (**Θ**) There is insufficient evidence to recommend tazarotene or ingenol mebutate to treat people with SCC *in situ.* Also, with the loss of the marketing recommendation of the latter, it would not be recommended due to the risk of progression to skin cancer. **Future research recommendation:** RCTs evaluating topicals, standard surgical excision, curettage with cautery, PDT and cryotherapy.

Destructive

Curettage with cautery

Under local anaesthesia, a surgical curettage can be performed to remove the epidermis and dermis. An electrocautery device is then used for haemostasis and also to cause destruction of a superficial layer of underlying tissue. This sequence can be repeated for a total of two or three cycles, to varying depths of subcutaneous tissue, perhaps improving success rates. The procedure is therefore 'operator-dependent'. Studies have not routinely commented on the number of cycles performed or peripheral margins used. In some clinical settings, curettage can be performed after the first assessment for both diagnosis and treatment. However, unlike a punch biopsy which reliably samples the full thickness of the skin and underlying fat, a histology report from a curettage specimen may be too superficial to exclude invasive disease. A histology report may end with the phrase 'invasion cannot be excluded', forcing the clinician to consider a subsequent surgical procedure if there was clinical doubt to begin with.

One prospective, non-randomized case-comparison study compared curettage and cautery with cryotherapy. Most lesions were on the lower leg (74%). There was no difference in clearance, although a few lesions with both treatments took over 6 months to heal. Curettage and cautery was associated with a significantly shorter healing time [median time to healing 35 vs. 46 days (39 vs. 90 days for lesions on the lower leg)], less pain, fewer complications and a lower recurrence rate at median follow-up of 2 years when compared with cryotherapy (9.1% vs 36,1%).[27]

The largest non-comparative retrospective study reported a lower recurrence rate of 2% (1/52) after a minimum follow-up of 4 years.[28] The majority of lesions were on the head and neck, with only 25% on the leg. A slightly smaller cohort with 44.9% of lesions on the extremities reported a recurrence rate of 4.3% (2/46) after a mean follow-up of 28.6 months.[29] The remaining three small studies (n=38) gave a range of recurrence rates, no recurrences at 1 year in 8 patients,[30] 10% (1/10) at 2 years[31] and 20% (4/20).[14]

This treatment is one of the simplest, safest and most effective methods of dealing with people with SCC *in situ*, but its success is determined by the skill of the operator.[32]

Recommendation (↑↑) Offer curettage with cautery as a first-line treatment option to people with small SCC *in situ* lesions, especially if diagnosis is desirable.

Recommendation (GPP) Consider curettage with cautery on an individual basis in people with SCC *in situ* with larger lesions. Consider patient factors (age, location, skin health) and discuss the risks of prolonged healing and potential ulceration.

Future research recommendation: RCTs evaluating curettage with cautery, topicals, standard surgical excision and cryotherapy

Cryotherapy/cryosurgery

Liquid nitrogen can be applied to a lesion, creating an expanding zone of freezing to minus 196 degrees centigrade. An initial zone of redness and inflammation is created, followed shortly afterwards by blistering indicating cell death. Differing treatment regimens exist, and the GDG agreed on one 'freeze-thaw' cycle of 20 seconds being adequate, although this may vary with anatomical location. The reported studies are not uniform in the duration of freezing, the number of freeze-thaw cycles, and the peripheral margins used. There is no strong evidence to recommend any particular regimen.

The Cochrane review evaluated two RCTs concerning the use of cryotherapy in immunocompetent patients.[2] One study demonstrated no statistically significant difference in clearance rates or recurrences at 1 year when compared to 5-FU, but statistically significantly greater clearance with MAL-PDT at 12 months when compared with cryotherapy.[8] A second RCT showed no inferiority of cryotherapy to ALA-PDT, with post-study analysis to correct for differences in lesion size between groups demonstrating superiority of PDT to cryotherapy.[6]

One prospective, non-randomised case-comparison study compared cryotherapy with curettage and cautery. There was no difference in clearance, although healing time was significantly longer for cryotherapy [median time to healing 46 vs. 35 days (90 vs.39 days for lesions on the lower leg)]. A few lesions with both treatments took over 6 months to heal, however, there were more infections, requiring antibiotics and a higher recurrence rate with cryotherapy.[27] However, the cryotherapy treatment used was not typical (two freeze thaw cycles rather than one on the lower leg) and more aggressive (only started counting the freeze time after the area was completely frozen). The authors also commented on how this technique could be changed to improve healing by shorter freeze times over a wider area. Technique and experience is important for cryotherapy of SCC *in situ* of the lower leg.

A retrospective comparison study looking at lower leg lesions compared cryotherapy with external beam radiotherapy. Wound healing was better with cryotherapy with only 2% failing to heal compared to 20% with radiotherapy, however,

there was a 6% recurrence with cryotherapy compared to 0% with radiotherapy.[33] All the local recurrences were small in comparison with the initial lesion, so excision with primary closure was possible.

In a prospective non-comparative study of 85 patients with 128 SCC *in situ* (54.7% on the lower leg) achieved 100% clearance with cryotherapy and 0.8% recurrence during a follow-up ranging from 6 months up to 5 years.[34] Smaller retrospective studies reported varying recurrence rates, 0% (0/21) at 1 year,[30] 1.6% (1/64) at 5 years,[35] and 8.3% (2/24).[29]

Clearance rates vary widely, probably reflecting differences in the techniques and regimens used. Freeze-thaw cycle (FTC) rates for cryotherapy varies amongst different sites and clinician experience. There is no strong evidence to suggest definitive recommendations. However, comparative studies have found recurrence rates are lower with one to three 20 second FTC (10% at 1 year) compared to two 5-10 second FTC (36% at 1 year).[6] Cryotherapy may be useful in low-risk situations, where people with SCC *in situ* prefer to avoid surgery or cumbersome topical treatment, but this must be balanced against the need of a cure against the potential adverse effects of aggressive FTCs.

Cryotherapy is a simple and quick method of treatment, with the advantage of accessibility in the outpatients setting. More recently studies have looked at combining it with topical therapies (See Combination section)

Recommendation (↑↑) Offer cryotherapy as a first-line treatment option to people with small SCC *in situ* lesions (except for lesions on the lower leg). (see recommendation directly below).

Recommendation (GPP) Employ a single cryotherapy cycle of freezing for 20-30 seconds, or two cycles of 10-20 seconds, for SCC *in situ* lesions (time begins at the creation of a freezing zone). The duration selected may depend on the device used and anatomical location. Advise patients that cryotherapy may be associated with more discomfort, poorer healing and greater recurrence than curettage with cautery.

Recommendation (GPP) Consider cryotherapy on an individual basis, in people with SCC *in situ* with larger lesions, and those on the lower leg (see previous recommendation). Consider patients factors (age, location, skin health) and discuss the risks of prolonged healing and potential ulceration. The time of freezing may need to be shortened to avoid complications, but is associated with a reduction in effectiveness.

Future research recommendation: Trials to investigate optimum duration of freezing, number of freeze-thaw cycles, and use of a pre-determined peripheral margin.

Future research recommendation: RCTs evaluating cryotherapy, curettage with cautery, PDT, topicals and standard surgical excision.

Photodynamic therapy (PDT)

There are only a few studies that confirm PDT is more clinically effective than cryotherapy or topicals. The Cochrane review evaluated seven RCTs concerning the use of topical PDT in immunocompetent patients.[2] In three studies, [36-38]PDT was compared with cryotherapy or topical 5-FU. One study demonstrated statistically significantly greater clearance with MAL-PDT at 12 months when compared with placebo-PDT or cryotherapy, but there was no significant difference when MAL-PDT was compared to 5-FU.[8] Another study demonstrated statistically significantly greater clearance of lesions with ALA-PDT versus 5-FU,[36] and the remaining RCT showed no inferiority of ALA-PDT to cryotherapy, with post-study analysis to correct for differences in lesion size between groups demonstrating superiority of PDT to cryotherapy.[6]

One study demonstrated superiority of laser enhanced PDT over CO_2 laser alone.[39]

In the remaining three studies,[6,8,36] the comparator was a different protocol for delivering PDT with superiority of red light compared with green,[36] but with no clear evidence to support a split illumination schedule for ALA-PDT in two studies, one failing to demonstrate superiority,[37] and the other including actinic keratosis lesions as well as SCC *in-situ*.[38]

There is currently an ongoing RCT due to complete in 2025, comparing surgical excision, PDT and topical 5-FU.[10]

Lesion size impacts on clearance rate with 82% of lesions up to 14 mm clear at 12 months reducing with increasing size to only 55% of lesions 30 mm or larger.[8] Larger plaques over 30 mm responded to a cycle of MAL-PDT, 2 treatments 7 days apart, clearing 90% of 23 lesions and observing recurrence in only 3 up to 12 months reducing clearance to 83%. Another study of identical design initially clearing 90% of 37 lesions, noting 4 recurrences after 12 months reducing clearance rate to 78%.[40,41] Very large lesions however are less responsive with lack of clearing in two patients with lesions >100 mm diameter,[42] although sequential ALA-PDT followed by imiquimod cleared another case of giant SCC *in-situ*. Patients with multiple plaques of SCC *in-situ* do not show a reduced efficacy to treatment.[7]

Body site does not appear to impact the efficacy of PDT, with protoporphyrin IX accumulation identical in SCC *in situ* located on acral and nonacral sites.[43]

PDT has cleared SCC *in-situ* in challenging sites including digits, peri-ocular, nipple, subungal and in an area of radiation dermatitis.[44-46]

Twenty-four month follow-up is available in certain studies with 68-85% clear,[47-49] and 76-81% clear in two large case series followed for a median of 16-18 months.[50,51] A mean follow-up of 50 months in a small study observed an 11% recurrence rate, all within initial 12 months.[52]

Severe atypia and higher age were associated with increased risk of treatment failure following PDT in a retrospective study re-examining histology and clinical features of patients treated with PDT over 5 years, assessing 98 lesions.[53] Failure to correctly perform PDT may also impact efficacy with a national prospective observational study of MAL-PDT in France noting incorrect delivery of treatment in 23% of patients presenting with SCC in-situ, with a single rather that 2 session approach to treatment the main variance from recommended protocol.[54]

Three additional RCTs and one cohort were identified. One RCT compared Plum-blossom needling (PBN)-ALA-PDT with ALA-PDT. PBN-ALA-PDT required fewer treatment sessions and achieved clearance quicker.[55] PBN may improve the efficacy of ALA-PDT by enhancing ALA delivery for SCC in situ treatment.[55] A second RCT compared ablative fractional laser (AFL)-MAL-PDT with MAL-PCT, clearance and sustained clearance at 1 & 5 years was significantly better with AFL-MAL-PDT, especially in those with lower extremity lesions.[56] Diameters larger than 20 mm and lesions with a history of previous treatment were independent factors for treatment failure.[56] The third RCT compared light-emitting diode (LED)-MAL-PDT with pulsed dye laser (PDL)-MAL-PDT with no difference in clearance between the two treatments.[57]

The cohort study compared ALA-PDT with MAL-PDT, there was no significance in clearance, however, there were far more recurrences with MAL-PDT.[58]

None of the studies looked at the use of daylight PDT as a treatment for people with SCC *in situ*.

The GDG decided there was enough comparative evidence so the non-comparative PDT papers were excluded. Three non-comparative papers used PDT in combination with another treatment (see Combination section).

Recommendation (↑↑) Offer PDT as a treatment option to people with SCC *in situ*, particularly for poorly healing or cosmetically sensitive skin sites, multiple lesions and large area lesions.

No recommendation (**Θ**) There is insufficient evidence to support the use of daylight PDT as a treatment option for people with SCC *in situ*.

Future research recommendation: RCTs evaluating PDT, topicals, and standard surgical excision.

Laser

An ablative laser can be used to cause surgical destruction of the epidermis and dermis. This uses the principle of selective photothermolysis, which requires an intricate knowledge of laser physics. The chromophore of the CO_2 laser is water, causing vaporisation of cells at a specified depth. Efficacy of laser treatment is therefore 'operator-dependent', and requires experience with the specific laser system and its variable treatment parameters. In a study by Humphreys *et al*., eight of 13 lesions were cleared with CO_2 laser. The mean thickness of the five refractory lesions was significantly greater than that of the completely vaporised lesions (0.65 mm vs 0.41 mm, p=0.01). Given that the dermis is approximately 1 mm below the surface, this may reflect caution of the operator in minimising the risk of scarring caused by laser penetration into the dermal layer. The risk remains that a lesion is under-treated and may later recur or progress to invasive malignancy. Given the cosmetic benefits and avoidance of surgical morbidity, laser should be considered where the service is available. As the procedure is both destructive and haemostatic, it is useful on the lower legs of older patients, reducing the risk of bleeding. However, there has been no direct comparison with curettage regarding risks of infection and ulceration.

The Cochrane review evaluated one RCT which demonstrated superiority of laser enhanced PDT over CO_2 laser alone.[39] However, experience of laser in treating people with SCC *in situ* is restricted largely to small case series.

Three prospective case series used CO_2 laser. The largest treated 16 patients with 25 lesions on legs.[59] All cleared and there were no recurrences during the 6 month follow-up, however, three have since been referred back with progression to invasive SCC within 12 months of discharge from follow-up. A second smaller case series treated six SCC *in situ* of the digit.[60] All cleared and there no recurrences during a mean follow-up of 28.6 months. Cosmetic outcome was reported as excellent with preservation of function. A third study of 13 patients had a lower clearance rate with only 61.5% (8/13) achieving histological clearance.[61] Residual tumour in the centre of the specimen was seen in the other five. Mean thickness these was significantly greater than that of the completely vaporized lesions (0.65 vs 0.41mm; p=0.01).

A larger retrospective study also used CO_2 laser to treat 44 people with 49 SCC *in situ* lesions.[62] Clearance after one treatment was reported in 83.3%. The remainder needed additional treatments, with 97.7% achieving clearance. Three recurrences occurred, two within 1 year (evolution time of the third is unknown, presented 1 year 5 months).

Another retrospective case used neodymium yttrium-aluminium-garnet (ND:YAG) laser to treat seven patients and CO_2 laser to treat 12 patients with SCC *in situ* of the penis.[63] Clearance after one treatment was reported in 84.2% with three patients requiring repeat treatment because of incomplete clearance after 2-4 months. Five recurrences occurred within the mean follow-up of 25 months, ND:YAG (1) and CO_2 (4). Cosmetic outcome was excellent.

Laser is considered suitable for potentially more challenging treatment sites including the digits and genitalia. The cosmesis aspect is good. However, this service is not available everywhere, with machines costing around £100,000. It is also operator dependent. Expert opinion from the UK indicates that curettage and cautery is an equally acceptable and practical alternative, causing both removal of the lesion and coagulation of the base. As this modality is destructive, with no histology generated, it should only be used in cases where the clinical diagnosis is clear, or where a representative biopsy specimen has been taken.

Recommendation (↑) Where this service is available, consider laser treatment in people with SCC *in situ* where other treatments have failed or are not suitable. Ablative CO_2 laser may be more effective than non-ablative Neodymium:YAG.

Future research recommendation: Comparison study of laser and curettage, regarding clearance rate, recurrence and cosmetic outcome.

Surgical

There were no comparative studies identified. There is currently an ongoing RCT due to complete in 2025, comparing surgical excision, PDT and topical 5-FU.[10]

Standard surgical excision

Eight non-comparative studies were identified,[13,29,30,35,64-66] including one small prospective study of 12 patients which reported 100% sustained clearance at 1 year.[66] One incidence of secondary infection and wound dehiscence was reported in this study.

The remaining seven were all retrospective studies and included 1254 lesions treated with surgical excision, and only reported recurrence rates.[13,29,30,35,64,65,67] The study with the longest follow-up included 608 patients, of which 241 with 288 lesions were treated with surgical excision and reported a cumulative probability of treatment failure of 4.9% (2.9-

8.1) at 5 years.[13] This compared with 22.3% (17.9-27.6) for PDT (296 patients with 450 lesions) and 15.5% (8.3-27.9) for 5-FU (46 patients with 72 lesions). All recurrences after surgical excision developed in the first 3 months. Recurrences following 5-FU remained more or less stable after 1 year, whereas late recurrences post-PDT developed even after 3 years.

The other studies reported recurrence at different time points. The largest study included 299 patients with 407 lesions and reported an overall 2.7% recurrence rate (with a higher rate of 8.8% in immunocompromised patients) at a mean follow-up of 35 months.[67] A smaller study reported a similar rate 2.8% (3/109) at a mean follow-up of 31 months.[29] A third study showed a lower recurrence rate of 2.3% (2/86) at a mean follow-up of 35 months,[65] while another reported no recurrences in 125 lesions at a mean follow-up of 66 months.[35]

The remaining two studies reported recurrence at one year. The larger study reported a recurrence rate of 1.95% (4/205)[30] while the smaller one reported no recurrences (0/34).[64] These are lower than the cumulative treatment failure probability of 4.9 (2.9-8.1) at 1 year reported in a long-term study.[13]

Only four studies referred to the size of surgical margin used in the excision.{Hassan, 2014 #2568;Westers-Attema, 2014 #377;Overmark, 2016 #289;Jansen, 2018 #114} Two studies used the standard surgical excision then suggested for SCC of 5 mm for some or all excisions.{Westers-Attema, 2014 #377;Jansen, 2018 #114} Westers-Attema *et al.* also used the smaller 3 mm margin for some excisions. They also evaluated whether a 5 mm margin was appropriate, or if a smaller margin may be sufficient, by theoretically reducing the margin of those treated with a 5 mm margin and seeing what the reduction in success rate was. With a reduction of 1 mm the success rate decreased by 7.8%, with a reduction of 2 mm the success rate decreased by 21.6%.{Westers-Attema, 2014 #377} In the other two studies, the margin varied between 0-5 mm (with 53/125 below the recommended margin of at least 2 mm) in one study and between 5-10 mm in the other.{Hassan, 2014 #2568;Overmark, 2016 #289}

A prospective study of 20 patients from Japan used ultrasonic surgical aspiration to treat SCC *in situ* not suitable for standard surgical excision. All cleared and no sign of recurrence were found at 1 year.[68]

Standard surgical excision is a simple, rapid and effective treatment for lesions of limited size, located in a suitable area. It allows for verification of the diagnosis and confirmation of the intraepithelial nature of the lesion. Cosmetic outcome, body site, healing potential and vascularity of the area need to be considered.

Recommendation (↑↑) Offer standard surgical excision to people with SCC *in situ* if there is diagnostic uncertainty regarding invasive disease.

Recommendation (↑↑) Offer standard surgical excision (5 mm margin), where anatomically possible, to people with SCC *in situ* where morbidity from surgery is low, or for recurrent or refractory disease.

No recommendation (**Θ**) There is insufficient evidence to support the use of ultrasonic aspiration to treat people with SCC *in situ.*

Future research recommendation: RCTs evaluating standard surgical excision, topicals and PDT.

Mohs micrographic surgery (MMS)
Six non-comparative studies were identified.[29,69-73] One large multicentre prospective study of 270 patients with SCC *in situ* (133 primary, 137 recurrent), the majority of which were head and neck SCC *in situ* (93.3%) reported recurrence rate.[70] The overall reported 5-year recurrence rate for the 95 patients (35.2%) who completed the 5 year follow-up was 6.3% (2.5% for primary and 9.1% for recurrent SCC *in situ*). Nearly all cases were referred for MMS due to poorly defined margins, recurrence or previously incompletely excised SCC *in situ.*

A recurrence rate of 2.4% was reported in a smaller retrospective study of 83 patients, the majority of which were head and neck SCC in situ (91.5%) at a mean follow-up of 28.6 months.[29]

Three small retrospective studies of SCC *in situ* of the nail unit (n=25) looked at recurrence at different time points.[69,71,72] Reporting a recurrence rate of 16.7% (1/6) at 1 year,[69] 12.5% (1/8) at 2 years[72] and 9.1% (1/11) at 5 years.[71] The remaining study looked at penile SCC *in situ* (23 primary, three recurrent) reported one recurrence at 9 months in the 23 primary penile SCC *in situ* and one recurrence at 15 months in the three recurrent penile SCC *in situ*.[73]

Overall, the recurrence rates following MMS is similar to that for standard surgical excision. However, the patient populations were different as these were at high-risk anatomical locations. MMS may be indicated for digital SCC *in situ* (around the nail in particular) and for some cases of genital (especially penile) SCC *in situ* for its tissue-sparing benefits. There may also be a role for MMS in recurrent or incompletely excised lesions.

Recommendation (↑) Consider Mohs micrographic surgery in people with SCC *in situ* when tissue conservation is important, such as periocular and digital sites.

Recommendation (GPP) Where Mohs micrographic surgery is not available or not appropriate consider active treatment with any suitable alternative on an individual basis. This includes standard surgical excision, curettage with

cautery, PDT, 5% 5-fluorouracil, 5% imiquimod, laser and cryotherapy. Discuss the risk of functional impairment, including that posed by recurrence and its subsequent treatment.

Radiotherapy

Radiotherapy includes the use of superficial X-rays, brachytherapy, and superficial/low energy photons. It has a role in SCC *in situ* that is either recurrent or refractory to other treatments. It is useful at certain anatomical locations where surgery may not be appropriate due to cosmesis (e.g. scalp) or function (e.g. digits). In many departments, radiotherapy is primarily used for invasive disease. However, there are studies that support its use in non-invasive malignancy (see below). Regarding recalcitrant or recurrent SCC *in situ*, there is a risk that the biopsy sample may not be representative, and perhaps the lesion is already transforming into invasive malignancy. Doses and fractionation in radiotherapy/brachytherapy may be the same for SCC *in situ* as for invasive SCC in such a clinical scenario, and the referring clinician should be mindful to assess the risk of invasive disease. Sometimes a lower spectrum of doses is used, especially on delicate areas such as the digit or groin. As with all radiotherapy, re-treatment can be challenging due to the risk of long-term radiotherapy related toxicity.

Brachytherapy can be delivered as a superficial application (also called contact brachytherapy or plesiotherapy) for any surface, including those with an irregular or curved contour. This often involves a custom-made mould made of polymers, resin, wax or thermoplastic material. This provides a secure and reproducible frame for positioning the delivery catheters. The American Brachytherapy Society lists suitable sites for moulds including scalp, face, pinna, lip and external auditory canal.[74] It has the advantage over external-beam radiotherapy in that it can be delivered in a hypo-fractionated course, two or three times a week, rather than daily. Doses are delivered in a short time, with a rapid fall in dose beyond the radioactive source, thereby increasing tumour control while sparing the surrounding tissue.

The GEC-ESTRO ACROP recommendations in skin brachytherapy were based only on low-level evidence, based on retrospective cohort studies.[75] There were no prospective studies and an absence of SR or RCTs. It concludes that in skin tumours (including SCC) with a depth < 5 mm, non-invasive contact brachytherapy is effective. Expert opinion from the UK indicates that brachytherapy can be used to successfully treat SCC *in situ*, using a similar treatment protocol as for SCC.

One cohort study looking at lower leg lesions compared external beam radiotherapy with cryotherapy. There were no recurrences with radiotherapy, compared to 6% with cryotherapy, however, wound healing was worse with radiotherapy with 20% failing to heal compared to 2% with cryotherapy.[33] Lesion diameter was greater in the non-healing group, but

this difference was not statistically significant; older age and higher radiotherapy dose were both ($p < 0.05$) associated with poor healing.

Three small prospective studies used various radiotherapy techniques, including Bucky's rays, soft X-ray therapy and radioactive skin patches.[76-78] The largest with 52 people with 77 lesions used soft X-ray therapy, all cleared within 6 months, with one recurrence at 1 year and one additional recurrence 2 years both in anogenital skin. Functional and cosmetic results were good. There was 70.6% (12/17) clearance with Bucky's rays, cosmetic results were considered good.[76] With radioactive skin patches eight people with 29 lesions achieved clearance with no recurrence during a follow-up of 10-26 months.[78]

Three non-comparative retrospective studies (n=74 lesions) showed similar results to Cox *et al.* with 12.2% failing to heal.[79-81] All, except the two lost to follow-up showed clearance within 6 months. Two of these papers reported recurrence, in the larger study 44 lesions there was one recurrence after 1 year and a further two recurrences at 2 years[80] the smaller with 16 lesions had no recurrences after a mean follow-up of 27.5 months.[79] A fourth study reported one recurrence in 62 lesions.[82]

A small retrospective study including 16 people with 19 lesions using Grenz rays reported 94.7% clearance, with one recurrence at year.[83] There were no further recurrences at either 2 years or 5 years for those that had been followed up for that long (three followed up <2 years, six followed up <5 years), cosmetic results were reported as excellent for 12, good for four and fair for one.

Only two case reports were identified that used high dose brachytherapy to successfully treat SCC *in situ* of the digit with a possible focal positive, deep margin,[84] and recurrent SCC *in situ* of the scalp.[85] In addition a conference abstract reported complete response with a median follow-up of 32 months for 12 patients with SCC *in situ* in an observational, retrospective study.[86] A high level of satisfaction was achieved, with 91% reporting excellent or good cosmetic result.

Various radiotherapy techniques have been used to treat people with SCC *in situ*, with no standardized protocol. Both high- and low-dose regimens appear equally efficacious.[87]

Disadvantages include patient inconvenience and poor healing, particularly on the leg with external beam radiotherapy. Advantages are that it can be used to treat areas where surgical modalities are challenging.

Recommendation (↑↑) Refer immunocompetent people with SCC *in situ* for consideration for radiotherapy where the lesion is recurrent or refractory to other treatments, or where surgery is not appropriate or associated with high morbidity.

Recommendation (GPP) Consider referring immunocompetent people with SCC *in situ* for consideration of brachytherapy to treat curved surfaces and areas of poor healing, such as the digit and lower legs.

Recommendation (↑↑) For immunocompetent people with SCC *in situ* lesions located on the lower legs, use treatments other than radiotherapy (apart from brachytherapy), dur to prolonged healing time. Offer topical 5% 5-fluorouracil, PDT, laser, curettage with cautery or surgery.

Future research recommendation Studies on the effectiveness and complication rates of brachytherapy, including at challenging sites such as the digits and lower legs.

Other approaches

Two small case series. One looked at hyperthermic treatment with chemical pocket warmers (n=8) with 75% clinical clearance, but 37.5% histologic clearance and one recurrence at one year.[88] The second looked at Solamum melongena peel extract ointment applied twice daily for 12 weeks to eight arsenic-induced SCC *in situ*.[89] The lesions reduced in size but not cleared. There is insufficient evidence to recommend either of these treatments.

Combination therapies

A variety of combination therapies have been reported. Five RCTs included at least one combination arm. One demonstrated superiority of laser enhanced PDT over CO_2 laser alone.[39] Another compared Plum-blossom needling prior to ALA-PDT (PBN-ALA-PDT) with ALA-PDT. PBN-ALA-PDT required fewer treatment sessions and achieved clearance quicker.[55] PBN may improve the efficacy of ALA-PDT by enhancing ALA delivery for SCC in situ treatment.[55] The third compared ablative fractional laser assisted MAL-PDT (AFL-MAL-PDT) with MAL-PDT, clearance and sustained clearance at 1 & 5 years was significantly better with AFL-MAL-PDT, especially in those with lower extremity lesions.[56] Diameters larger than 20 mm and lesions with a history of previous treatment were independent factors for treatment failure.[56]

One within-patient RCT (n=21 with 58 lesions) compared Er:YAG AFL assisted MAL-PDT (Er:YAG AFL-PDT) with MAL-PDT.[90] Er:YAG AFL-PDT was significantly more effective (93.8%) than MAL-PDT (73.1%; p=0.031) and the recurrence rate at 1 year was also lower 6.7% compared to 31.6%. A second small within-patient RCT (n=6) compared continuous ablative CO_2 laser-assisted MAL-PDT (CL-MAL-PDT) with fractional (FL) ablative CO_2 laser-assisted MAL-PDT (FL-MAL-PDT).[91] The same four patients had complete clearance at 3 months, with three with sustained clearance at 1 year. The other two had partial clearance at 6 months, with one achieving complete clearance at 1 year.

Only 11 case series were large enough to be considered.

One retrospective non-comparative study looked at cryotherapy followed by topical 5-FU, 81.2% (31/38) achieved clearance, with two recurrences at a mean follow-up of 6.8 months.[17]

Several retrospective studies examined combining imiquimod and cryotherapy. In two studies (n=35) cryotherapy was performed 2-3 weeks after starting imiquimod treatment, clearance was achieved in all.[92,93] In the 29 who completed 1 year follow-up, clearance was sustained in 26. There were no further recurrences in the 14 who had completed 2 years follow-up. In another study of eight males with penile intraepithelial neoplasia cryotherapy was followed by imiquimod.[94] Only two cleared within 6 months. All did eventually clear, however, mean time to clearance was 16 months (range 4-39), sustained clearance was achieved in all 6 that were followed up for 1 year.

In a study of ten males with carcinoma *in situ* of the glans penis topical imiquimod was followed by CO_2 laser ablation.[23] Clearance at 6 months was achieved in six cases and stable disease in two. Sustained clearance at 1 year was achieved by all 6 and at 2 years by the three that had completed 2 years follow-up (other three follow-up < 2 years). Treatment was well tolerated, and cosmetic outcomes were judged satisfactory by the patients.

Ablative fractional laser-assisted delivery of topical 5-FU was used to successfully treat 16 non-genital SCC *in situ*.[16] There was one recurrence in the 12 followed up for 1 year.[95] Treatment was convenient and the majority felt the cosmetic outcome was better than before the treatment.[16,95]

Fractional CO_2 laser treatment followed by topical ingenol mebutate had 88.9% clearance compared to only 12.5% for topical ingenol mebutate monotherapy.[25] However ulceration occurred with 33.3% treated with this combination with 44.4% left with a scar. Marketing authorization for ingenol mebutate has been suspended by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) on 27th January 2020.

Two small studies used ablative CO_2 fractional laser followed by PDT (n=20).[96,97] Seventeen obtained clearance within 6 months. Of these one cleared after one PDT session, three after two sessions, seven after three sessions and five after four sessions. One required six PDT sessions to achieve clearance. Mean follow-up was less than a year with one study and only just over a year with the other. There were no recurrences in the eight that were followed up for 1 year. There were no serious adverse events and cosmetic outcome was favourable.

One prospective study of 10 patients with 44 advanced SCC *in situ* lesions used the combination of simple shaving before three weekly sessions of ALA-PDT.[98] All achieved sustained clearance at 1 year. Cosmetic outcome was measured at several time points, and was reported as good at 12 weeks, excellent at 6 months and better than at 6 months at 1 year. Improvement in DLQI at 12 months follow-up was significant ($p<0.001$).

There is limited evidence on combination therapy for SCC *in situ* and further research is required. There is insufficient evidence to recommend a particular combination (examples of combinations that could be used can be found in the table below).

Combination	n	Clearance by 6 months	Sustained clearance	Recurrence	Other
Topical 5% imiquimod followed by CO_2 laser ablation[23] (non-comparative)	10 carcinoma *in situ* of the glans penis	6/10 (60%)	6/6 at 1 year 3/3 at 2 years (other 3 f/up <2 years)	Not reported	Other 4: stable disease (2), progressive disease (2). One stopped treatment due to scrotal ulceration. Form and curvature of the glans and coronal sulcus were conserved, and the anatomic outcome was judged satisfactory by the patients.
Cryotherapy followed by 5% imiquimod[94] (non-comparative)	8 penile	2/8 (25%)	6/6 at 1 year (other 2 f/up <1 year) 5/5 at 2 years f/up (other 3 f/up <2 years)	No sign of recurrence during f/up	All did eventually clear. Mean time to clearance: 16 months (range 4-39)
Combination cryotherapy and 5% imiquimod[92] (non-comparative)	21 (with 24 lesions)	24/24 (100%)	21/24 at 1 year 12/12 at 2 years (other 9 f/up <2 years) 1/1 at 5 years (other 20 f/up <5 years)	3 small focal relapses (<10 mm)	Satisfactory cosmetic outcome even for extensive lesions (with the exception of hypopigmentation to a variable degree)
Combination cryotherapy and 5% imiquimod[93] (non-comparative)	8 (with 11 lesions)	11/11 (100%)	5/5 at 1 year (other 3 f/up <1 year)	No recurrence during f/up	Attrition: 3 lost to f/up

			2/2 at 2 years (other 6 f/up <2 years)		
Ablative fractional laser-assisted delivery of topical fluorouracil[16,95] (non-comparative)	16 lesions	16/16 (100%)	Not reported	1/12 at 9 months	4 lost to f/up No adverse events
Cryotherapy followed by topical 5% fluorouracil[17] (non-comparative)	38	31/38 (81.2%)	Not reported	2/31 at mean f/up 6.8 months	No adverse events
ER:YAG AFL-assisted MAL-PDT[90] (within-patient RCT)	21 with 35 lesions	90.9%	84.9% at 1 year	6.7%	Attrition: 2 excluded before randomisation, 1 violated protocol. Cosmetic outcome excellent or good in 90.6%
Combination ALA-PDT + CO_2[39] (RCT)	10 with 11 lesions	8/11 (72.7%)	1/8 (12.5%)	Not reported	The remaining 3 lesions showed partial response after three treatments. Cosmetic outcome very good, 80% patients were satisfied.
Combination CL-CO_2 + MAL-PDT[91] (within-patient RCT)	6	4/6 (66.6%)	3/4* at 1 year	No recurrence during f/up	Other 2 showed partial response but had complete response at 1 year f/up. *Attrition; 1 after 6 months f/up
Combination FL-CO_2 + MAL-PDT[91] (within-patient RCT)	6	4/6 (66.6%)	3/4* at 1 year	No recurrence during f/up	Other 2 showed partial response but had complete response at 1 year f/up. *Attrition; 1 after 6 months f/up
Combination Plum-blossom needling (PBN)-ALA-PDT[55] (RCT)	21 lesions	16/21 (76.2%)	16/16 (100%)	No recurrence during f/up	Attrition; 3 lesions. Other 2 remained stable → surgically excised.

Combination simple shaving and PDT[98] (non-comparative)	10 with 44 advanced lesions (unsuitable for surgical excision)	44/44 (100%)	44/44 (100%)	Not reported	>30 mm in diameter, with unclear boarders, ulcers and multiple occurrences Excellent cosmetic outcome
Fractional CO_2 laser treatment followed by topical ingenol mebutate[25] (non-comparative)	9	8/9 (88.8%%)	Not reported	Not reported	3/9 (33.3%) ulceration 4/9 (44.4%) scarring
Ablative CO_2 fractional laser followed by PDT[96] (non-comparative)	10	8/10 (80%)	5/9 at 1 year (other 4 f/up <1 year)	No recurrence during f/up	One required >6 months to clear, no response in other. Favourable cosmetic outcome, no adverse events
Ablative CO_2 fractional laser followed by PDT[97] (non-comparative)	10	9/10 (90%)	3/10 at 1 year (other 7 f/up <1 year)	No recurrence during f/up	One required >6 months to clear. Favourable cosmetic outcome, no adverse events
Ablative fractional laser (AFL)-assisted MAL-PDT[56] (RCT)	46 lesions	43/46 (93.5%)	40/43 at 1 year 39/43 at 5 years	9.3%	All patients experienced local adverse reactions that resolved within 7 days after PDT without complications

Recommendation (↑) Consider combination therapy if monotherapy with 5% 5-fluorouracil, 5% imiquimod, PDT, laser, cryotherapy, or curettage with cautery fail, and surgery is not appropriate or associated with excessive morbidity (see above table).

Future research recommendation: RCTs evaluating **c**ombination treatment.

Certainty of evidence

The overall certainty of the evidence for each outcome was assessed using the GRADE criteria. The following summarizes the overall certainty of evidence for the critical outcomes considered. For details of reasons for downgrading the certainty of the evidence please refer to the relevant GRADE evidence profiles (Appendix D).

	Systematic reviews
	See Appendix H
	Comparative studies
	High –
	Moderate AFL-MAL-PDT vs. MAL-PDT
	Low –
	Very low Cryotherapy vs. curettage with cautery
	Radiotherapy vs. cryotherapy
	ALA-PDT vs cryotherapy
	ALA-PDT vs. topical 5-FU
	ALA-PDT vs. MAL-PDT
	LED-MAL-PDT vs. PDL-MAL-PDT
	PBN-ALA-PDT vs. ALA-PDT
	Non-comparative studies
	Very low Standard surgical excision
	Mohs micrographic surgery
	Topical Imiquimod
	Combination cryotherapy and topical 5-FU
	Combination cryotherapy and topical imiquimod
	Combination topical imiquimod and CO_2 laser
	Combination CO_2 laser and topical ingenol mebutate
	Combination CO_2 laser and PDT
	Combination shaving and ALA-PDT
Patient values and preferences	The BAD works with patients on all its guidelines and encourages patients to share their experiences of a particular treatment, condition or treatment approach. The viewpoints below are shared from the perspectives of individual patients with SCC *in situ*. Between them they had been treated multiple times for SCC *in situ* on various sites including face,

	hands and legs and had experience of topicals, curettage with cautery, cryotherapy, PDT, standard surgical excision and MMS. Outcomes (expectation of the patient) The treatment options and any side effects should be explained to the patient. Experience The patients always felt well informed in making decisions prior to treatment. Initial treatment was usually topicals which they have received many times. They felt benefits were slow and gradual at best, but when it occurred the unpleasant side effect of itch was almost intolerable despite using anti itching cream. Subsequent treatments to the same site included cryotherapy or curettage with cautery and then photodynamic treatment. When standard surgical excision was required it was always the first-line treatment. The patient representatives felt monitoring was important. They felt it was hard to know if their response to various treatments has been different to the majority of other patients undergoing the same treatment. They did not think some treatments worked for them. i.e. photodynamic therapy on the hands and feet.

Cost

Therapy costs will vary depending on the location of services, staffing, volume of procedures and local protocols (e.g. frequency of biopsies prior to non-surgical therapies). Comparative data remains limited and dependent on assumptions over therapy protocol and pathways of care.

A cost-minimization analysis based on costs incurred by the U.K. NHS was published in 2003, comparing cryotherapy, curettage with cautery, excision, laser ablation, PDT and 5-FU, in the treatment of people with SCC *in situ*.[99] Assumptions included the expectation of diagnostic biopsy in all cases managed by non-surgical options. It did not include the costs of any complication or those incurred by people with SCC *in situ*, their families or carers.

Treatment	Cost in 2003
Cryotherapy (3 treatments)	£392
Curettage with cautery	£200
Standard surgical excision	£200
Laser ablation	£312
PDT (2 treatments)	£457[†]
Topical 5-FU	£287

[†]Costed on more expensive light sources that are currently used.

A cost comparison based on published clearance/morbidity data (excluding the cost of a diagnostic biopsy) estimated the cost of successfully treating a single SCC *in situ* to be £119 for PDT, £145 for cryotherapy and £171 for topical 5-FU, which included additional clinic visits to manage complications.[100]

Cost pressures are most likely to be from increased prevalence of SCC *in situ* and organizational changes that impact on the availability of hospital-delivered therapies.

The above figures are 20-years old and may not reflect current practice. For example, many small and low-risk lesions may be treated with 5-FU and then discharged from secondary care, with advice to return if recurrence. Of note, PDT is relatively cost-effective, and may not be routinely considered in clinical practice due to a perception of high cost. Although it requires investment with a specialist nurse and equipment, a functioning PDT clinic can see several patents in a session with low ongoing costs. A local audit at Nottingham showed that the PDT service is underutilised, and clinicians may need reminding of this effective treatment when discussing with patients.

Poor healing and ulceration will add to the cost of treatment.

Other considerations	Peak incidence of the disease occurs in the seventh decade of life and most studies have shown a slight female preponderance.[29,101-104] The majority of studies report that SCC *in situ* occurs mainly on sun-exposed sites, with more recent studies suggesting the most common being the head and neck (29-54%),[29,70,103-105] though the lower limb seems to be affected more in females than males.[29,101,106] Older, UK based studies, have reported that the majority of patients (60-85%) have SCC *in situ* on the lower legs which may indicate that the sun exposure pattern is different in countries with lower rates of sunshine.[101,102] Less common variants include pigmented, subungual, periungual, palmar and verrucous SCC *in situ*. Variants exist on genital and perianal locations and are termed 'penile intraepithelial neoplasia' (PIN) and 'anal intraepithelial neoplasia' (AIN) respectively, each with their own specialist treatment pathway. **Investigation** In routine clinical practice the diagnosis is made on clinical grounds. Dermoscopy examination commonly reveals surface scaling, coiled vessels ('glomerular' vessels) and/or red clods ('globular' vessels), with the pigmented variant displaying small brown dots and globules.[107-112] If there is diagnostic doubt, or confirmation is required before undergoing a certain type of treatment, a punch biopsy can be performed to show full thickness epidermal dysplasia on histology. Biopsies should be taken from a representative area of the lesion, and several may be required for larger lesions. If a curette biopsy is performed, this should include the full thickness of the epidermis and dermis, to establish whether there is any invasive disease amounting to a cutaneous SCC. Curettage may therefore be used for both treatment and diagnosis, and perhaps preferable to a punch biopsy in certain clinical settings. Pagetoid and acantholytic variants are rare histological subtypes.[113-115] **Recommendation (↑)** Consider punch biopsy or diagnostic excision when clinical and dermoscopic features are not sufficient for diagnosis of SCC *in situ.* **Recommendation (GPP)** Curettage may be performed, for both treatment and diagnosis, depending on the clinical scenario and operator judgment. Histology specimens should include the deep margin if an assessment of potentially invasive tumour is required. **Immunosuppression** Patients who are organ transplant recipients (OTR) are at increased risk of non-melanoma skin cancers (NMSC), due to the reduced function of immune cells in the skin. OTRs experience not only a higher incidence of NMSC when compared with the general population but also a higher incidence of SCC compared with BCC. SCC is considered more immunogenic than BCC and therefore more susceptible to a loss of immune surveillance. Such patients are therefore more susceptible to sun-induced skin damage, including SCC *in situ*.

Definitive radiotherapy treatment should *not* be considered first-line in OTRs.[116] OTRs often develop multiple NMSC and previous radiotherapy to a particular site will preclude this as a future treatment option. Primarily, patients should undergo surgery with the aim, especially with a high-risk SCC, to achieve oncological excision margins taking into consideration the cosmetic and functional outcome. However, definitive radiotherapy may be considered an acceptable option if extensive surgery is required in a patient with multiple medical comorbidities or where there are multiple and widespread lesions. Also, if patients refuse surgery, then radiotherapy is an option. Therefore, radiotherapy is felt to be a poor choice for most immunosuppressed patients but may be appropriate in individual cases. Surgical modalities are the primary choice, where feasible.

Imiquimod is an immune response modifier, that stimulates an immune response to target pre-cancerous cells. Its action is dependent of a healthy and functional immune system. A randomised trial of 43 immunosuppressed patients with actinic keratosis, found a complete clearance rate of 62% (18/29), with application 3x weekly for 16 weeks.[117] This figure is slightly less than that for the SCC *in situ* studies described above, even though the AK lesions were presumably thinner lesions. Therefore, imiquimod (which is not licensed for this indication) should be considered a secondary treatment, after more effective modalities have been considered.

5-FU has a direct cytotoxic effect on pre-cancerous cells. The concern is that the resulting inflammatory response may be more severe in OTRs. This is not shown in the literature, with eight patients developing mostly mild side-effects.[118] In a randomised trial of eight patients (both AK and SCC *in situ*), PDT was found to be more effective than 5-FU, and with a superior clearance rate, cosmetic outcome and patient preference. Even still, the 5-FU group only experienced mild symptoms (visual analogue scale <1/4) albeit for the entire 3-week duration of treatment.[119] Therefore, 5-FU is an effective treatment in immunosuppressed patients and should be considered a primary option.

Other modalities should be used with the same consideration as for non-immunocompromised patients, CO_2 laser has been used without excess pain or inflammation.[120] Laser delivery of PDT may be a useful combination therapy.[121] There is perhaps a higher risk of infection following surgery, curettage or cryotherapy, but with modern theatre practices and antibiotics this may not be a problem clinically. The option of Mohs micrographic surgery may be restricted in patients who are immunocompromised due to HIV infection, as fresh tissue processing by the pathology staff is limited by safety concerns, However, this is being addressed due to issues surrounding equality of access to treatment.

Recommendation (GPP) Consider topical 5% 5-fluorouracil in immunocompromised people with SCC i*n situ* as a practical treatment for multiple and recurring lesions.

Recommendation (GPP) Consider PDT in immunocompromised people with SCC i*n situ* as an effective, well tolerated and repeatable treatment for multiple and frequently recurring lesions.

Recommendation (GPP) Consider cryotherapy, curettage with cautery or standard surgical excision as treatment options for immunocompromised people with SCC *in situ*.

Recommendation (↑) Consider topical imiquimod in people with SCC *in situ* lesions located on the lower legs who are inappropriate for, contraindicated or with inadequate response to topical 5% 5-fluorouracil, PDT, laser, curettage with cautery or surgery (see **R30**).

Recommendation (GPP) Reserve radiotherapy for immunocompromised people with SCC *in situ* where the lesion has progressed to invasive SCC.

Future research recommendation: Further trials to investigate the efficacy and safety of treatments in immunocompromised people, in particular, 5% imiquimod and laser.

Choice of therapy for people with SCC *in situ* will be affected by access to therapy, preference for home-based or hospital-delivered therapies and therapy cost to the person with SCC *in situ* and the healthcare provider. Prescription of topical agents for the treatment of people with SCC *in situ* is available in both primary and secondary care. Standard surgical excision, curettage with cautery and cryotherapy are widely available in secondary care and topical PDT is most often located in specialized departments. MMS, radiotherapy and laser are restricted to tertiary specialist centres. All treatment options and any side effects should be explained to patients, and they should be educated on subsequent skin surveillance for local recurrence or new skin cancers.

Recommendation (GPP) Provide educational material or a patient information leaflet on SCC *in situ* and for any proposed treatment modality e.g. www.skinhealthinfo.org.uk/a-z-conditions-treatments/.

REVIEW TITLE/QUESTIONS: (2) What are the subsequent rates of keratinocyte cancer in people who have had SCC *in situ*?

The wording for recommendations is standardised so that they are clearly identifiable, unambiguous and specific: "Offer[1]" or "Do not offer" (strong recommendation ↑↑ or ↓↓) [an intervention] to patients with [skin disease] + [any relevant conditions]

- [1]or similar, e.g. “Use”, “Provide”, “Take”, “Investigate”, etc.) “Consider” (weak recommendation ↑) [an intervention] for patients with [skin disease] + [any relevant conditions]	
Relative values of different outcomes	***Critical*** • Incidence of any keratinocyte cancer (at location of previous SCC *in situ)* in studies with follow-up of ≥6 months since treatment/reference time-point **(9)** ***Important*** • Incidence of progression outside original location of previous SCC *in situ* **(6)** • Incidence of malignancy **(6)** Ranked outcomes according to our guideline development protocol[1] which uses the GRADE methodology (9-7 Critical for decision making; 6-4 Important but not critical for decision making; 3-1 not important for decision making), as agreed between clinicians and patient representatives on the GDG. The GDG’s main consideration was keratinocyte cancer, as this is biologically more likely. SCC can arise from SCC *in situ* directly, and the incidence of BCC is interesting from the point of view of risk stratification. The clinicians didn’t think that the incidence of other cancers was that important. For example, a colon cancer or blood lymphoma may be statistically associated, but this does not imply causation as the two cannot be linked by scientific evidence. There will also be confounding factors such as UV exposure and lifestyle. However, the patient representatives were clearly worried about any future cancer. So, the incidence of malignancy was retained as an outcome.
Balance between desirable and undesirable effects	**Incidence of any keratinocyte cancer (at location of previous SCC *in situ*) in studies with follow-up of ≥6 months since treatment/reference time-point** All reported cases were of SCC. It was not always clear if the reported SCC occurred at the location of the previous SCC *in situ* or elsewhere. A couple of papers that did report an invasive SCC carcinoma developing from an SCC *in situ* 2/498 (0.4%) did not report what treatment had been received.[29,122]

All treatments except CO_2 laser appeared to reduce risk of SCC at the site of a previous SCC *in situ* compared to no treatment, however, the number of people with SCC *in situ* treated with CO_2 laser was small.

However, Jaeger *et al.* observed 83 NMSC in 1147 patients and noted an increased risk in males (SIR 5.0: 95% CI 3.7-6.7) compared to females [Standardized incidence ratio (SIR) 3.7: 95% Confidence interval (CI) 2.6-5.1].[103] Also, people diagnosed as having SCC *in situ* under 60 years old, particularly men, appeared to be at higher risk of NMSC than those diagnosed as having SCC *in situ* at or after 60 years old.

Incidence of progression outside original location of previous SCC *in situ*

Only three papers reported this, and very little detail was given.

Metastatic spread of SCC *in situ* occurred in one patient who had had surgical excision at 15 months, progression to SCC at 7 years, died of widespread metastases 1 year later.[64]

Progression to SCC outside field occurred in 16/151 [single (8), 2 (3), 4 (1), 6 (2), 8 (1), 10 (1)] patients who received PDT.[123] Many of these patients were at risk of SCC (12/16 had a prior history of SCC) and the possibility that the lesion had mixed histology at baseline cannot be excluded. In addition, 5/16 were immunocompromised and 7 developed SCC both on PDT field and outside field. Median time to development of 1st SCC outside field after the first PDT session (IQR) was 10.3 months (4.3-21.1).

Four patients out of 44 experienced a new squamous skin lesion at a distant site after primary radiotherapy (n=32) or adjuvant radiotherapy after local ablative therapy or incomplete excision (n=12).[80] One had been diagnosed simultaneously with SCC and SCC *in situ* at different sites initially and metastatic disease was found at other sites at approximately the same time as the marginal SCC recurrence.

Incidence of malignancy

Some early papers suggested an association between SCC *in situ* and internal malignant neoplasms.[124-126] However, these papers had problems with their methodology[127] and subsequent

	publications have shown people with SCC *in situ* do not appear to have a significant increased risk of internal malignant neoplasms.[103,128] However, Jaeger *et al.* observed elevated risks for lung cancer among men who had SCC *in situ* diagnosed before the age of 60 years (SIR 4.6: 95% CI 1.5-10.8), for leukaemia among men who had SCC *in situ* diagnosed ≥60 years (SIR 3.5: 95% CI 3.5 (1.1-8.2) and among men whose skin lesion was diagnosed at a sun-protected anatomic site (SIR 3.7: 95% CI 1.5-7.5).[103] These associations and the male excess of leukaemia's following SCC *in situ* need further study. These were not reported by treatment received. <u>Summary</u> There is no clear guide to paths for follow-up. People with SCC *in situ* given topicals are typically discharged with treatment. Those receiving other treatments are discharged following completion of the treatment. In most cases follow-up is not required, however, the individual should be educated on how to check their skin for any recurrence or a new skin cancer appearing and if this occurs the individual should return to their general practitioner. Most people with SCC *in situ* can be discharged following the completion of their treatment with advice on skin surveillance and sun protection, however, follow-up may be required in certain circumstances depending on immunocompetence status, size of lesion, treatment modality and anatomical location. **Recommendation (GPP)** Discharge people with SCC *in situ* following completion of treatment, with education on skin surveillance and sun protection, with advice to return to their general practitioner if recurrence or new skin cancer. **Recommendation (GPP)** Consider following up people with SCC *in situ* on an individual basis based on clinical judgment, factoring in lesion size, treatment modality, anatomical location and immunosuppression.
Certainty of evidence	The certainty of the evidence for each outcome was assessed using the GRADE criteria. The majority of studies were very low-certainty retrospective case series. Only one small RCT was included, but with no events on the treatment arm the evidence is of low certainty. For details of reasons for downgrading the certainty of the evidence please refer to the relevant GRADE evidence profiles (Appendix D).

	Patient values and preferences	Patients were worried about the risk of developing other cancers not just keratinocyte cancers and felt monitoring was important.

Recommendation (GPP) Discharge people with SCC *in situ* following completion of treatment, with education on skin surveillance and sun protection, with advice to return to their general practitioner if recurrence or new skin cancer.

Recommendation (GPP) Consider following up people with SCC *in situ* on an individual basis based on clinical judgment, factoring in lesion size, treatment modality, anatomical location and immunosuppression.

Appendix D: GRADE evidence profiles

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Cryotherapy compared to curettage with cautery for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cryotherapy	curettage with cautery	Relative (95% CI)	Absolute (95% CI)		
Clearance (within 6 months)												
1	observational studies	serious [a]	not serious	not serious	not serious [b]	none	34/36 (94.4%)	43/44 (97.7%)	**RR 0.97** (0.88 to 1.06)	**29 fewer per 1,000** (from 117 fewer to 59 more)	⨁◯◯◯ VERY LOW	CRITICAL
Recurrence 1 year												
1	observational studies	serious [a]	not serious	not serious	serious [c]	none	8/36 (22.2%)	2/44 (4.5%)	**RR 4.89** (1.11 to 21.60)	**177 more per 1,000** (from 5 more to 936 more)	⨁◯◯◯ VERY LOW	CRITICAL
Recurrence 2 years												
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	13/36 (36.1%)	4/44 (9.1%)	**RR 3.97** (1.42 to 11.13)	**270 more per 1,000** (from 38 more to 921 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cryotherapy	curettage with cautery	Relative (95% CI)	Absolute (95% CI)		
Adverse events - serious - infection requiring antibiotics												
1	observational studies	serious [a]	not serious	not serious	very serious [c]	none	4/36 (11.1%)	2/44 (4.5%)	**RR 2.44** (0.47 to 12.59)	**65 more per 1,000** (from 24 fewer to 527 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. No clinical important difference - between MIDs
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Radiotherapy compared to cryotherapy for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy	cryotherapy	Relative (95% CI)	Absolute (95% CI)		
Recurrence												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	0/59 (0.0%)	6/82 (7.3%)	**RR 0.11** (0.01 to 1.85)	**65 fewer per 1,000** (from 72 fewer to 62 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events - serious (ulceration)												
1	observational studies	very serious [a]	not serious	not serious	not serious	none	12/59 (20.3%)	2/82 (2.4%)	**RR 8.34** (1.94 to 35.87)	**179 more per 1,000** (from 23 more to 850 more)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

ALA-PDT compared to cryotherapy for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALA-PDT	cryotherapy	Relative (95% CI)	Absolute (95% CI)		
Adverse events - serious (ulceration)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/20 (0.0%)	5/20 (25.0%)	**RR 0.09** (0.01 to 1.54)	**228 fewer per 1,000** (from 248 fewer to 135 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALA-PDT	cryotherapy	Relative (95% CI)	Absolute (95% CI)		
Cosmetic outcome: visible scar at 12 months f/up												
1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	0/20 (0.0%)	4/20 (20.0%)	**RR 0.11** (0.01 to 1.94)	**178 fewer per 1,000** (from 198 fewer to 188 more)	⊕◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ALA-PDT compared to topical 5-FU for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALA-PDT	topical 5FU	Relative (95% CI)	Absolute (95% CI)		
Adverse events - serious (ulceration)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/33 (0.0%)	3/33 (9.1%)	**RR 0.14** (0.01 to 2.66)	**78 fewer per 1,000** (from 90 fewer to 151 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cosmetic outcome: visable scar at 12 months f/up												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/33 (0.0%)	3/33 (9.1%)	**RR 0.14** (0.01 to 2.66)	**78 fewer per 1,000** (from 90 fewer to 151 more)	⊕◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ALA-PDT compared to MAL-PDT for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALA-PDT	MAL-PDT	Relative (95% CI)	Absolute (95% CI)		
Clearance (within 6 months)												
1	observational studies	not serious	not serious	not serious	serious [a]	none	48/55 (87.3%)	104/136 (76.5%)	**RR 1.14** (0.99 to 1.31)	**107 more per 1,000** (from 8 fewer to 237 more)	⨁◯◯◯ VERY LOW	CRITICAL
Recurrence 1 year												
1	observational studies	not serious	not serious	not serious	not serious	very strong association	1/48 (2.1%)	29/104 (27.9%)	**RR 0.07** (0.01 to 0.53)	**259 fewer per 1,000** (from 276 fewer to 131 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

ALA-PDT (red) compared to ALA-PDT (green) for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALA-PDT (red)	ALA-PDT (green)	Relative (95% CI)	Absolute (95% CI)		
Adverse events - serious (ulceration)												
1	randomised trials	serious [a]	[b]	not serious	[b]	none	0/32 (0.0%)	0/29 (0.0%)	not estimable		[b]	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Unable to assess inconsistency, imprecision or outcome due to lack of events in either arm

AFL-MAL-PDT compared to MAL-PDT for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AFL-MAL-PDT	MAL-PDT	Relative (95% CI)	Absolute (95% CI)		
Clearance (3 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	43/46 (93.5%)	29/38 (76.3%)	**RR 1.22** (1.01 to 1.49)	**168 more per 1,000** (from 8 more to 374 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Sustained clearance 1 year												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	40/43 (93.0%)	21/29 (72.4%)	**RR 1.28** (1.01 to 1.63)	**203 more per 1,000** (from 7 more to 456 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Sustained clearance 5 years												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	39/43 (90.7%)	17/29 (58.6%)	**RR 1.55** (1.12 to 2.13)	**322 more per 1,000** (from 70 more to 662 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment tolerability: VAS measure of pain												
1	randomised trials	not serious	not serious	not serious	not serious [b]	none	30	30	-	MD **0.5 higher** (0.09 lower to 1.09 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
b. No clinical important difference - between MIDs

LED-MAL-PDT compared to PDL-MAL-PDT for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LED-MAL-PDT	PDL-MAL-PDT	Relative (95% CI)	Absolute (95% CI)		
Clearance (3 months follow-up) patients												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/10 (70.0%)	6/10 (60.0%)	**RR 1.17** (0.61 to 2.23)	**102 more per 1,000** (from 234 fewer to 738 more)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

PBN-ALA-PDT compared to ALA-PDT for SCC *in situ*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PBN-ALA-PDT	ALA-PDT	Relative (95% CI)	Absolute (95% CI)		
Clearance (4 weeks, after 2 treatments)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	5/21 (23.8%)	2/22 (9.1%)	**RR 2.62** (0.57 to 12.06)	**147 more per 1,000** (from 39 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clearance (6 weeks, after 3 treatments)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14/21 (66.7%)	7/22 (31.8%)	**RR 2.10** (1.06 to 4.15)	**350 more per 1,000** (from 19 more to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Clearance (end of treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PBN-ALA-PDT	ALA-PDT	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	16/21 (76.2%)	17/22 (77.3%)	**RR 0.99** (0.71 to 1.37)	**8 fewer per 1,000** (from 224 fewer to 286 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sustained clearance at 1 year (end of follow-up)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	16/16 (100.0%)	15/17 (88.2%)	**RR 1.13** (0.92 to 1.38)	**115 more per 1,000** (from 71 fewer to 335 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix E: Summary of included comparative studies

E.1 SYSTEMATIC REVIEWS

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Y/N)	The review collects the type of studies you consider relevant to the guideline review question (Y/N)	The literature search is sufficiently rigorous to identify all the relevant studies (Y/N)	Study quality is assessed and reported (Y/N)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Y/N)	What types of studies are included in the review? (RCTs/cohort studies/mixed)
Drucker, A. M. *et al*. J Am Acad Dermatol 2020.[3]	Yes	Yes	Yes, up to Nov 2018 (PubMed, EMBASE, Cochrane SR & trials) In English	Yes	Yes	RCTs and comparative non-randomised controlled studies

Comments: A systematic review and network meta-analysis of treatments for primary cSCC, including SCC *in situ*. The paper was a summary and update of a report for the US Agency for Healthcare Research and Quality (https://www.ncbi.nlm.nih.gov/books/NBK487552/). Studies with <10 lesions in total or with arms that had ≤5 lesions were excluded. Non-English studies were also excluded, as there were very few of them and there is empirical evidence that excluding them typically has minimal impact on conclusions.[129] Some of the outcome measures match or are close to those set in the guideline: recurrence, cure rates, cosmetic outcome, quality of life (QoL) and adverse events. Most of the studies included were at moderate or high risk of bias.

Summary: Six RCTs on SCC *in situ* with a total of 418 participants were included.[6,8,9,18,39,90] No RCTs were found evaluating patient-reported cosmesis or QoL. No non-randomised controlled studies were identified. Confidence intervals (CI) for all comparisons except with placebo, for recurrence were wide enough to include very large effects in either direction.

Laser plus MAL-PDT provided better clinical clearance of SCC in situ than MAL-PDT alone or a physician's choice between cryotherapy and topical 5-fluorouracil.[8] Other non-placebo comparisons for clinical clearance had wide CI crossing the null.

MAL-PDT is more likely to achieve good or better observer-reported cosmesis than a physician's choice between cryotherapy and topical 5-fluorouracil.[8]

There were no RCTs investigating surgical modalities, which are a first-line treatment.

Conclusion: No treatment recommendation could be made with an A grade (consistent good-quality patient orientated evidence). Additional comparative evidence is needed to inform treatment decisions for patients with SCC *in situ*.

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Y/N)	The review collects the type of studies you consider relevant to the guideline review question (Y/N)	The literature search is sufficiently rigorous to identify all the relevant studies (Y/N)	Study quality is assessed and reported (Y/N)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Y/N)	What types of studies are included in the review? (RCTs/cohort studies/mixed)
Bath-Hextall, F. J. *et al.* Cochrane Database Syst Rev 2013.[2]	Yes	Yes	Yes, up to September 2012 (CENTRAL, MEDLINE, EMBASE, PsycINFO, LILACS)	Yes	Yes	RCTs

Comments:
Cochrane review on the effects of therapeutic interventions for histologically proven cutaneous SCC *in situ*. People with anogenital Bowen's disease were excluded. Some of the outcome measures match or are close to those set in the guideline: complete clearance of lesions (after the first treatment cycle)/each treatment cycle), recurrence rate at 12 months and >12 months, cosmetic outcome, quality of life assessment and adverse outcomes. No studies examined surgical methods. In general, the methodological quality of the trials was poor.

Summary:
Nine RCTs with 363 participants were included in the review. Six matched our protocol, one compared MAL-PDT vs. cryotherapy vs. 5-FU vs placebo PDT,[8] one compared ALA-PDT vs. cryotherapy,[6] one compared ALA-PDT vs 5-FU,[9] one compared ALA-PDT single illumination verses ALA-PDT two-fold illumination,[37] one compared ALA-PDT red light vs. green light,[36] and one compared imiquimod vs. placebo.[18]

One study demonstrated statistically significantly greater clearance of lesions of SCC *in situ* with MAL-PDT when compared with placebo-PDT (RR 1.68, 95% CI 1.12 to 2.52; n = 148) or cryotherapy (RR 1.17, 95% ci 1.01 to 1.37; n = 215), but there was no significant difference when MAL-PDT was compared to 5-FU.[8] One study demonstrated statistically significantly greater clearance of lesions with ALA-PDT vs. 5-FU (RR 1.83, 95% CI 1.10 to 3.06; n = 66), but no statistically significant difference in recurrence rates at 12 months (RR 0.33, 95% CI 0.07 to 1.53).[9]

Cryotherapy showed no statistically significant difference in clearance rates (RR 0.99, 95% CI 0.78 to 1.26; n=127) or recurrences at 1 year (RR 1.48 95% CI 0.53 to 4.17) when compared to 5-FU in one study.[8]

One study compared imiquimod to placebo and demonstrated statistically greater clearance rates in the imiquimod group (9/15 lesions) compared to placebo (0/16) (Fisher's Exact P value <0.001). The imiquimod group did not report any recurrences at 12 months, however 2/16 in the placebo group had developed early invasive SCC at 18 months.[18]

Conclusion:

Overall, there is very little good-quality research on treatments for SCC *in situ*. There is limited evidence from individual studies to suggest MAL-PDT is an effective treatment. Although cosmetic outcomes appear favourable with PDT, five-year follow-up data are needed. Significantly more lesions cleared with MAL-PDT compared to cryotherapy. No significant difference in clearance was seen When MAL-PDT was compared with 5-FU, but one study found a significant difference in clearance in favour of ALA-PDT when compared to 5-FU. There was no significant difference in clearance when cryotherapy was compared to 5-FU.

The lack of quality data for surgery and topical cream therapies has limited the scope of this review to one largely about PDT studies. The age group, number, and size of lesions and site(s) affected may all influence therapeutic choice; however, there was not enough evidence available to provide guidance on this. More studies are required in the immunosuppressed populations as different therapeutic options may be preferable.

Specific recommendations cannot be made from the data in this review, so we cannot give firm conclusions about the comparative effectiveness of treatments

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question (Y/N)	The review collects the type of studies you consider relevant to the guideline review question (Y/N)	The literature search is sufficiently rigorous to identify all the relevant studies (Y/N)	Study quality is assessed and reported (Y/N)	An adequate description of the methodology used is included, and the methods used are appropriate to the question (Y/N)	What types of studies are included in the review? (RCTs/cohort studies/mixed)
Love, W. E. *et al.* Arch Dermatol 2009.[4]	Yes	Yes	Yes	Yes	Yes	Mixed

Comments: Systematic review to determine clearance rates and adverse effects of topical imiquimod or fluorouracil therapy in the treatment of non-melanoma skin cancers (NMSC), including SCC *in situ*. Prospective, retrospective, and case studies in English, containing a minimum of four subjects and a 6-month follow-up or post-treatment histologic evaluation.

Summary: Ten studies, three RCTs and seven non-comparative studies were included in this review. Five studies, one RCT[18] and four non-comparative studies[19-22] with 98 SCC *in situ*'s were treated with imiquimod and five studies, two RCTs[8,9] and three non-comparative studies[11,130,131] with 134 SCC *in situ* were treated with fluorouracil.

Imiquimod: One study evaluated daily application of imiquimod 5 days a week, while the other four evaluated once daily application. Treatment duration ranged from 9-16 weeks. The RCT reported at 73% histologic clearance rate at 12 weeks.[18] Studies that included SCC *in situ* confined to the trunk and extremities reported higher clearance rates that did studies that included SCC *in situ* in high-risk locations.[18-21] The largest study included 56 patients treated daily for 9 weeks achieved a 75% clinical clearance rate at 19 months.[21] The highest clearance rate, 88% at 6 month clinical follow-up was achieved with an average daily application of 12 weeks; all recurrent SCC *in situ* were initially larger than 2 cm in diameter.[22] Long-term follow-up was not available for any of these studies.

Fluorouracil: Both RCTs used the same treatment regimen, once daily for 1 week, then twice daily for 3 weeks and achieved 48%[9] and 56%[8] clinical clearance rates at 12 months. One non-comparative study achieved an 85% clinical clearance with a twice daily treatment for 8 weeks and average follow-up of 4.6 years.[11] All SCC *in situ* that failed to respond to this treatment were located in high-risk areas (e.g. finger, ear, cheek and penis).

Adverse effects were tabulated and reported by drug not by type of NMSC. However, while none of the imiquimod papers were cited, all the fluorouracil reported adverse effects related to the SCC *in situ* papers. Topical therapy is associated with many adverse effects, produces lower clearance rates, may be more difficult to administer and, in some instances, cost more than other well-established therapies.

Conclusion: Evidence supports the use of topical fluorouracil as a monotherapy for SCC *in situ*. The recommendation is limited to small SCC *in situ* in low-risk locations in patients who will not or cannot undergo treatment with other better-established therapies. Topical imiquimod is not recommended as a primary monotherapy for SCC *in situ*. Based on the available evidence, the strength of any recommendations for the use of these two agents in the primary treatment of SCC *in situ* is weak.

E.2 Randomized controlled trials (either not covered by the SR or for outcomes not included in the SR)

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Morton, C. A. *et al. Br J Dermatol* 1996.[6] RCT, hospital, UK. Funding: No details given.	n = 19 (40 lesions) SCC *in situ* 16 F: 3 M Mean age (range): 76 years (62-88) Site: legs (33), face (5), hand (2) Inclusion criteria: biopsy proven SCC *in situ* Exclusion criteria: previously treated lesions, lesions >21 mm in diameter	**ALA-PDT** Repeat at 2 months if required **Cryotherapy** 20 seconds freeze after initial icefield formation, repeat at 2 months with option for further repeat after another 2 months if required	**Adverse events – ulceration** ALA-PDT: 0 Cryotherapy: 5 **Cosmetic outcome visible scar at 12 months f/up** ALA-PDT: 0 Cryotherapy: 4	Attrition: none. Small numbers. **Outcomes covered by SR** Sustained clearance of treated SCC *in situ* (1 year) Treatment tolerability - pain
Salim, A. *et al. Br J Dermatol* 2003.[9] RCT, 2 centres, UK. Funding: No details given.	n = 40 (66 lesions) SCC *in situ* 32 F: 8 M Mean age (range): 76 years (65-88) Site: legs (33), arms (4), face (4) Inclusion criteria: biopsy proven SCC *in situ* Exclusion criteria: previously treated lesions, lesions >21 mm in diameter	**ALA-PDT** Repeat at 2 months if required **Topical 5-fluorouracil** applied once daily for 1 week, then twice daily for 3 weeks	**Adverse events – ulceration** ALA-PDT: 0 5FU: 3 **Cosmetic outcome visible scar at 12 months f/up** ALA-PDT: 0 5FU: 3	Attrition: None. **Outcomes covered by SR** Clearance (within 6 months) Sustained clearance of treated SCC *in situ* (1 year) Treatment tolerability - pain

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Morton, C. A. *et al. Br J Dermatol* 2000.[36] Parallel groups, RCT, single centre, UK. Funding: No details given other than development of the lamp was supported by the Cancer Research Campaign (UK).	n = 19 (70 patches) [Sex not recorded] Mean age: 73 years (range 50-87) Site: all lower limb Inclusion criteria: biopsy proven SCC in-situ Exclusion criteria: no lesion previously treated, lesions up to 21 mm diameter	**ALA-PDT (red) (32)** Repeat at 2 months if required, xenon short arc lamp 630±15nm **ALA-PDT (green) (29)** Repeat at 2 months if required, xenon short arc lamp 540±15nm	**Adverse events – ulceration** ALA-PDT (red): 0/32 ALA-PDT (green): 0/29	Attrition: 3/19 (9 lesions) - one lost to F/up and 2 died from chronic unrelated disease. Treatments were well tolerated by both arms **Outcomes covered by SR** Clearance (within 6 months) Sustained clearance of treated SCC *in situ* (1 year) Treatment tolerability - pain
Kim, H. J. *et al. J Am Acad Dermatol* 2018.[56] RCT (NCT03320447), outpatient Dermatology department, university hospital (May 2011-Mat 2012), South Korea. Funding: Supported by the Basic Science Research Program through the National Research Foundation of Korea and funded by the Ministry of Science, ICT & Future Planning (NRF-2017R1D1A1B03032999).	n=60 with 84 SCC *in situ* lesions AFA-MAL-PDT arm (46 lesions) 17 F: 13 M Mean age (SD): 71.83 (12.59) years Skin type: III (2), IV (21), V (7) Mean maximal diameter (SD): 11.59 mm (6.95) Differentiation: Well/moderate (35), poor (11) MAL-PDT arm (38 lesions) 19 F: 11 M Mean age (SD): 69.93 (13.11) years	**Ablative fractional laser (AFL)-assisted MAL-PDT** Before PDT, the lesions were scraped gently, and scales and crust were removed by curettage. The AFL treatment was performed with a 2940-nm erbium:yttrium-argon-garnet ablative fractional laser at a 550- to 600-μm ablation depth with level 1 coagulation, 22% treatment density, and a single pulse. The MAL-PDT, red light-emitting diode lamp total	**Clearance (within 6 months) 3 months** AFL-MAL-PDT: 43/46 MAL-PDT: 29 **Sustained clearance/recurrence at 1, 2 or 5 years** 1 year AFL-MAL-PDT: 40 MAL-PDT: 21 5 years AFL-MAL-PDT: 39 MAL-PDT: 17	All patients experienced local adverse reactions that resolved within 7 days after PDT without complications. The most common local adverse events were erythema, crusting, hyperpigmentation, pruritus, and burning sensations. The occurrence of adverse events was slightly higher in the AFL-MAL-PDT group than in the MAL-PDT group, but there was no significant difference. The overall clearance rate for the AFL-MAL-PDT group at both 12 and 60 months was

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
	Skin type: III (3), IV (22), V (5) Mean maximal diameter (SD): 13.18 mm (6.38) Differentiation: Well/moderate (30), poor (8) Inclusion criteria: >18 years with histopathologically verified SCC *in situ* on a lower extremity Exclusion criteria: pregnancy or lactation; history of calcium metabolic disorders, porphyria, malignant melanoma, or a tendency for melasma or keloid formation; use of an immunosuppressive drug; use of a medication known to cause photosensitivity; other treatment for SCC *in situ* in the past 4 weeks; allergy to MAL and lidocaine	light dose 37 J/cm^2. Single session **MAL-PDT** Same regimen. Two sessions one week apart F/up: 5-years	**Treatment tolerability: Pain per VAS mean (SD)** AFL-MAL-PDT: 6.1 (1) MAL-PDT: 5.6 (1.3)	significantly higher for small lesions (≤20 mm) (97.3% 12 & 60 months;) than for large lesions (>20 mm) (44.44% 12 months; 33.33% 60 months) (p=0.017 12 months; p=0.005 60 months). There was also a significant correlation between history of previous treatment and overall clearance rate for the AFL-MAL-PDT group at 60 months (p=0.027).

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Wu, Y. *et al. Dermatol Surg* 2018.[55] RCT, skin disease hospital (Jan 2013-Jun 2015), China. Funding: No significant interest with commercial supporters.	n=24 with 43 lesions 12 F: 12 M Mean age (SD): 55.5 (10.1) years Inclusion criteria: Histopathological diagnosed lesions: patients not suitable or not willing to undergo surgery were informed of substitution therapies and chose ALA-PDT for treatment. Exclusion criteria: Pregnant or lactating, histories of photosensitivity or allergies to photosensitizers.	**Combination Plum-blossom needling (PBN)-ALA-PDT** (21 lesions) Vertical skin tapping until spot bleeding occurred with PBN* and then the crusts were removed. The punctate haemorrhages on the skin were wiped 0.9% NaCl solution, and were compressed until the bleeding stopped, before applying 10% ALA cream and narrow-band light-emitting diode irradiation (lambda = 633 +/- 10 nm; 100-200 J/cm). Patients returned after each treatment session to determine whether another PDT session was required. **ALA-PDT monotherapy** (22 lesions) Same regimen Once a target lesion had achieved complete response (CR), the treatment was considered complete; otherwise, the treatment sessions were repeated to a maximum of 6 sessions.	**Clearance (with 6 months)** 4 weeks (after 2 treatments) PBN-ALA-PDT:5/21 ALA/PDT: 2/22 6 weeks (after 3 treatments) PBN-ALA-PDT:14/21 ALA/PDT: 8/22 End of treatment: PBN-ALA-PDT:16/21 ALA/PDT: 17/22 **Sustained clearance at 1 year†** PBN-ALA-PDT:16/16 ALA/PDT: 15/17 2 had relapsed at 6-month f/up	Attrition: 4 patients (5 lesions): 3 PBN-ALA-PDT, 2 ALA-PDT *The PBN is a small hammer-like tool comprising 7 needles that are 4 mm long, 0.5 mm wide, and placed at 4 mm intervals in the needle head. Mean number of treatments (SD): PBN-ALA-PDT: 2.88 (0.8) ALA-PDT: 3.4 (0.7) **Adverse events** Mean value of patient reported 11-point pain intensity–numeric rating scale after 1st treatment was 4.5 for both groups †After completing the treatment sessions, the patients visited monthly for a minimum of 12 months. At these visits, 2 dermatologists, who were not involved in the patient's treatment, examined and photographed the skin, and the size(s) of the lesion(s) and any treatment reactions, including pain, were recorded.

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Kim, B. S. *et al. Dermatol Surg* 2012.[57] RCT, skin disease hospital (Jan 2013-Jun 2015), Korea. Funding: No significant interest with commercial supporters.	n= 50* including 20 with 36 SCC *in situ* lesions LED-MAL-PDT 6 F: 4 M Mean age (range): 68.1 years (56-82) PDL-MAL-PDT 8 F: 2 M Mean age (range): 73.2 years (53-86) Inclusion criteria: ≥18 years with biopsy-proven primary SCC *in situ* diagnosed within the previous 3 months Exclusion criteria: porphyria, pregnancy, lactation, and allergy to aminolevulinic acid	**Light-emitting diode (LED)-MAL-PDT** Superficial lesions were prepared using gentle, bloodless debridement with a curette. 630-nm diode lamp, 37 J/cm^2 with an irradiance of 50 mW/cm^2. All lesions received up to five treatments 1 to 2 weeks apart. No other treatment was allowed at the end of treatment or during the 3-month follow-up period. **Pulsed dye laser (PDL)-MAL-PDT** Wavelength of 585 nm, pulse width 450 ms, same regimen F/up: 3 months	**Clearance (within 6 months) patients (Histopathologic response 3 months)** LED-MAL-PDT: 6/10 PDL-MAL-PDT: 7/10	*30 actinic keratosis Treatment tolerability: VAS Mean score: LED-MAL-PDT: 4.5 PDL-MAL-PDT: 1.5 Adverse events were reported for the whole and not separated by disease. These were well tolerated, but there was a pause in treatment in five cases and the use of pain relievers in seven during the LED treatments. All of these reactions resolved within 2 weeks after treatment without further complications.

E.3 Non-randomized comparative trials

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Ahmed, I. *et al. Br J Dermatol* 2000.[27] Prospective cohort, two hospitals, UK. Funding: None.	n=67 (with 80 lesions) with clinical diagnosis of SCC *in situ** 55 F: 12 M Mean age: 74 years (range 46-89) Site: lower leg (59), other limbs (8), trunk (6), head and neck (7) Mean size of lesion: 336 mm^2 (range 30-1890) Exclusion criteria: Patients with recurrent lesions and those on immunosuppression	**Cryotherapy** (36) Liquid nitrogen spray giving two freeze-thaw cycles, each freeze cycle being maintained for 5±10 seconds after the formation of an ice ball to the intended margin. **Curettage with cautery (C&C)** (44) Curettage under local anaesthesia, and electrocautery was then used for haemostasis. Mean f/up: 22 months (range 6-24)	**Clearance (within 6 months)** Cryotherapy: 36/36 (2 not healed) C&C: 44/44 (1 not healed) **Recurrence at 1, 2 years** 1 year Cryotherapy: 8/36 C&C: 2/44 2 year Cryotherapy: 13/36 C&C: 4/44 **Adverse events – serious – infection requiring antibiotics** Cryotherapy: 4/36 C&C: 2/44	Attrition: 19 (with 21 lesions) lost to f/up (10 cryotherapy, 11 C&C *73 patients were enrolled, 6 were subsequently excluded, 2 lost to f/up before assessment, 2 died, 2 SCC *in situ* not confirmed **Treatment tolerability** Postoperative pain: 24 hours: 51/80 (64%) those treated with cryotherapy 10.4x more likely to report pain. Also 5.5x for lower leg lesions. 7 days: 41/80 (51%) no difference 6 weeks: 10/80 (12.5%) those treated with cryotherapy on the lower legs 4.7x more likely to report pain None of the patients reported the level of pain to be very severe. **Mean time to healing** Cryotherapy: 69 days (range 14-210). 12 lesions took more than 90 days to heal. C&C: 53 days (range14-330). Six lesions took more than 90 days to heal.

<table>
<tr><th>Study/ design</th><th>Population</th><th>Intervention & Comparator</th><th>Outcomes</th><th>Comments & additional data not in usable format</th></tr>
<tr>
<td>Cox, N. H, et al. Br J Dermatol 1995.[33]

Retrospective, comparative (1986-92 radiotherapy: 1990-92 cryotherapy), UK.

Funding: None.</td>
<td>Radiotherapy
n=91 with 141 skin tumours* on the lower leg, including 59 SCC in situ
Mean age (range):
74 years (54-97)
84% F: 16% M

Cryotherapy
n=49 with 82 lower leg SCC in situ
Mean age (range):
69 years (52-91)
85% F: 15% M</td>
<td>Radiotherapy
External beam radiotherapy
26 different combinations of total dose, number of fractions and duration of treatment were used. Most commonly 2 x 1200cGy in 6 weeks (NSD 1347 rets). 2 x 1400cGy in 6 weeks (NSD 1572 rets), or 1800cGy single exposure (NSD 1800 rets).

Cryotherapy
Liquid nitrogen spray cryotherapy was administered as two 20 second applications from freezing, with a 5-minute thaw period between treatments. Tumour diameters were measured, and staged therapy was performed by treating overlapping fields at 2-month intervals for broader lesions. A maximum diameter of 2 cm was treated at any time-point.</td>
<td>Recurrence

Radiotherapy: 0
Cryotherapy: 6

All were small in comparison with the initial lesion, so that excision with primary closure was feasible, whereas this had not been possible initially.

Adverse events – serious (ulceration due to radionecrosis or failure to heal)†

Radiotherapy: 12
Cryotherapy: 2</td>
<td>*63 invasive carcinomas, 15 unspecified keratoses & 4 other tumours

Cryotherapy
<table>
<tr><th rowspan="2">Lesion diameter (cm)</th><th rowspan="2">No of lesions</th><th colspan="3">No of stages</th></tr>
<tr><th>1</th><th>2</th><th>3</th></tr>
<tr><td>0-0.9</td><td>45</td><td>45</td><td>-</td><td>-</td></tr>
<tr><td>1.0-1.9</td><td>20</td><td>14</td><td>4</td><td>2</td></tr>
<tr><td>2.0-2.9</td><td>9</td><td>3</td><td>4</td><td>2</td></tr>
<tr><td>3.0-3.9</td><td>8</td><td>-</td><td>7</td><td>1</td></tr>
</table>
†Interpretation should take into account the greater proportion of broad and thick lesions in the radiotherapy group, but the results clearly indicate much poorer healing following radiotherapy.</td>
</tr>
</table>

<table>
<tr><th>Study/ design</th><th>Population</th><th>Intervention & Comparator</th><th>Outcomes</th><th>Comments & additional data not in usable format</th></tr>
<tr>
<td>Alique-Garcia, S. et al. Photodiagnosis Photodyn Ther 2019.[58]

Prospective, observational study, university hospital (June 2011-June 2017), Spain.

Funding: None.</td>
<td>n=171 with 191 SCC in situ

95 F: 76 M
Mean age: 74.31 years
Location: head and neck (93), lower extremity (58), upper extremity (19), trunk (15), genital (6)

Inclusion criteria: ≥18 years, with a clinical, dermoscopic and histological diagnosis of SCC in situ

Exclusion criteria: Porphyria or photosensitivity, presence of a genetic skin cancer disorder, allergic reaction to ingredients of the photosensitizer’s precursor, immunosuppression, pregnancy or lactation and history of previous treatment on SCC in situ lesions.</td>
<td>(BF-200 ALA)-PDT
One cycle of two sessions in one week. LED lamp emitting red light (635 nm wavelength) for 8 min, reaching a final total dose of 37 J/cm^2. A second treatment cycle was performed in cases of clinical persistence at 12 weeks.

MAL-PDT
Same regimen

F/up: 52 weeks</td>
<td>Clearance (with 6 months)

ALA-PDT: 48/55
MAL-PDT: 104/136

Recurrence 1 year

ALA-PDT: 1/48
MAL-PDT: 29/104</td>
<td>Histological resolution was confirmed in 60% of patients, the remainder rejected a post-treatment biopsy.

Adverse events – serious (severe pain that required interruption of treatment)

ALA-PDT: 3 patients
MAL-PDT: 3 patients

Treatment tolerability (VAS)
<table>
<tr><th></th><th>Low (1-3)</th><th>Medium (4-7)</th><th>High (8-10)</th></tr>
<tr><td>ALA-PDT</td><td>58%</td><td>35%</td><td>7%</td></tr>
<tr><td>MAL-PDT</td><td>52%</td><td>39%</td><td>9%</td></tr>
</table>
Adverse events – minor (most frequent):
ALA-PDT: Erythema (43.63%), desquamation (32.73%) and superficial wounds (10.91%)
MAL-PDT: Erythema (41.91%), desquamation (37.5%) and superficial wounds (13.97%)</td>
</tr>
<tr>
<td>Lee, D. W. et al. J Dermatol 2018.[25]

Prospective, single centre (January</td>
<td>n=19 SCC in situ

9 F: 10 M
Mean age (range): 68.4 years (36-86)</td>
<td>Fractional CO_2 laser treatment followed by topical ingenol mebutate
0.015% gel on facial lesions for 3 consecutive days and 0.05% gel on</td>
<td>Clearance (within 6 months)

Combination: 8/9*
Ingenol mebutate: 1/8*</td>
<td>Attrition: 2

*Combination: PR (1)
Ingenol mebutate: PR (4), NR (3)</td>
</tr>
</table>

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
2015-October 2017), Korea. Funding: No details given.	Site: face (6), trunk (4), hand (1), fingers (3), legs (4), toe (1)	other sites for 2 days, with a 5 mm application margin around the visible lesion **Topical ingenol mebutate** Same regimen. F/up range: 2-18 months	**Adverse events – serious: ulceration** Combination: 3 Ingenol mebutate: 0	Long-term post-inflammatory hyperpigmentation: Combination: 4 Ingenol mebutate: 2 No recurrence to date
			Cosmetic outcome: scar Combination: 4 Ingenol mebutate: 0	Marketing authorisation for ingenol mebutate has been suspended by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) on 27th January 2020.

Appendix F: Within-patient randomised controlled trials (not covered by the SR)

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Genouw, E. *et al.* Laser-assisted photodynamic therapy for superficial basal cell carcinoma and Bowen's disease: a randomized intrapatient comparison between a continuous and a fractional ablative CO2 laser mode. *J Eur Acad Dermatol Venereol* 2018; **32**: 1897-905. Within-patient RCT (NCT03012009), (Jan 2015-Mar 2016), Belgium. Funding: None.	n= 15 with 30 treatment areas of inoperable, histologically verified sBCC (9) or SCC *in situ* (6) 8 F: 7 M Median age (range): 73 years (46-87) Skin type: I (2), II (12), III (1) Inclusion criteria: Histologically proven and inoperable with a size larger than 5 cm^2 or had two smaller lesions.* Exclusion criteria: pregnancy or lactation, age below 18, history of an allergic reaction to local anaesthesia and history of side-effects related to laser or PDT.	**Continuous (CL) ablative CO_2 laser-assisted MAL-PDT** Laser treatment was followed by MAL application and illumination occurred 3 hours later. This treatment was repeated after 2 weeks. **Fractional (FL) ablative CO_2 laser-assisted MAL-PDT** Same regimen F/up: 12 months	**Clearance (within 6 months)** **CR at 3-month f/up** CL-CO_2 + MAL-PDT: 4/6 FL-CO_2 + MAL-PDT: 4/6 Same patients cleared, other 2 showed partial clearance at both sites. **Sustained clearance 1 year** **CR at 12-month f/up** CL-CO_2 + MAL-PDT: 3/4 FL-CO_2 + MAL-PDT: 3/4	Attrition: 1 SCC *in situ* patient (CR at 3-month f/up) lost to subsequent f/up due to health problems not related to the study. *Large lesions were subdivided into two treatment areas to make intra-patient comparison possible. Pain, side effects and aesthetics reporting wasn't separated by type of lesion. • Less pain was observed with FL + MAL-PDT. • Side-effects were not significantly different between CL + MAL- PDT and FL + MAL-PDT (P = 0.219–1.000). • No significant difference in aesthetics was found 3, 6 or 12 months post-treatment according to the patients and blinded expert (P = 0.075–1.000).

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data not in usable format
Ko, D. Y. *et al.* A randomized trial comparing methyl aminolaevulinate photodynamic therapy with and without Er:YAG ablative fractional laser treatment in Asian patients with lower extremity Bowen disease: results from a 12-month follow-up. *Br J Dermatol* 2014; **170**: 165-72. Within-patient RCT, single centre (March 2011-March 2012), Korea. Funding: Research funds from university.	n=21 with 58 SCC *in situ* lesions 11 F: 10 M Mean age (SD): 68.9 (13.2) years Skin type: III (2), IV (15), V (4) Site: lower extremity	**Er:YAG AFL-PDT** One session Er:TAG AFL therapy with 550–600 µlm ablation depth, level 1 coagulation, 22% treatment density and a single pulse, then MAL-PDT. **MAL-PDT** Two sessions 7 days apart	**Clearance (within 6 months) (3 months)** Er:YAG AFL-PDT: 29/32 MAL-PDT: 18/26	Attrition: 3/21, two dropped out prematurely: one because of health problems and one because of loss to follow-up. One patient discontinued treatment because of protocol violation. **Outcomes covered by SR** Recurrence of SCC *in situ* (1 year), Adverse events – serious, Quality of Life, Cosmetic outcome, Treatment tolerability

Appendix G: Narrative findings for non-comparative studies

Study/ design	Population	Intervention: various	Outcomes	Comments & additional data not in usable format
Jansen, M. H. *et al.* Bowen's disease: long-term results of treatment with 5-fluorouracil cream, photodynamic therapy or surgical excision. *Acta Derm Venereol* 2018; **98**: 114-5. Retrospective, single centre (January 2008-December 2013), The Netherlands. Funding: No details given.	n=608 with 841 SCC *in situ* lesions 347 F: 261 M Mean age (SD): 73 years (10.8) Immunosuppressed: 72 Site: Head neck region (298), ear (32), upper extremities (164), lower extremities (205), trunk (142) Size: ≤10 mm (497), 11-≤30 mm (240), >30 mm (10), unknown (94) Inclusion criteria: Histological confirmation of SCC *in situ* Exclusion criteria: SCC *in situ* on genitalia/mucous membranes or lesions found nearby an invasive skin cancer.	**Surgical excision** (241 with 288 lesions)* tumours were excised with a 5 mm margin **PDT** (296 with 450 lesions)* **Topical 5-FU** (46 with 72 lesions) **Other (cryotherapy, topical imiquimod or curettage**) (25 with 31 lesions) Median f/up (range): 18 months (0-87)	**Recurrence (1 year) cumulative treatment failure probability (95% CI)** Surgical excision: 4.9 (2.9-8.1) PDT: 13.4 (10.4-17.1) Topical 5-FU: 13.1 (6.7-24.7) **Recurrence (2 years) cumulative treatment failure probability (95% CI)** Surgical excision: 4.9 (2.9-8.1) PDT: 17.0 (13.5-21.3) Topical 5-FU: 15.5 (8.3-27.9) **Recurrence (5 years) cumulative treatment failure probability (95% CI)**	*Numbers quoted in the paper surgical excision (296) & PDT (241) are incorrect. Numbers are taken from table in supplementary that gives baseline details has surgical excision (241) & PDT (296), these agree with denominator required to give correct percentage progression for PDT. After adjustment for differences in baseline characteristics between the treatment groups, PDT is associated with a significantly higher risk of treatment failure than SE (HR 2.71 with 95% CI: 1.52–4.83). 5-FU also showed increased risk compared with SE (adjusted HR 2.22, 95% CI: 0.98–5.04). A slightly higher, statistically non-significant, risk was found for PDT compared with 5-FU (adjusted HR 1.22, 95% CI: 0.62–2.41).

Study/ design	Population	Intervention: various	Outcomes	Comments & additional data not in usable format
			Surgical excision: 4.9 (2.9-8.1) PDT: 22.3 (17.9-27.6) Topical 5-FU: 15.5 (8.3-27.9)	
Overmark, M. *et al.* Retrospective study of treatment of squamous cell carcinoma in situ. *Acta Derm Venereol* 2016; **96**: 64-7. Retrospective, single centre (January-December 2006), Finland. Funding: No details given.	n=239 with 263 SCC *in situ* lesions 136 F: 103 M Mean age (range): 77 years (35-97) Site: head & neck (70%), trunk (10%), upper extremities (11%), lower extremities (10%) Immunosuppressed: 44 Previous skin cancer: 136 (AK (106), SCC *in situ* (68), SCC (30), BCC (85), malignant melanoma (4)) Inclusion criteria: histologically confirmed lesions. Exclusion criteria: patients whose diagnosis was changed after treatment to invasive skin malignancy or who had refused treatment.	**Surgical excision** (125) Recommended excision margins ≥2 mm (in 53 cases the margin was less) **Cryotherapy** (64) 2 freeze-thaw cycles after curettage **PDT (**74) Two MAL-PDT sessions 7-14 days apart Mean f/up (range): 66 months (2-93)*	**Recurrence** Mean time to recurrence (range): 64 months (6-92) Surgical excision: 0 Cryotherapy: 1 PDT: 10	At time of biopsy 146 had other skin malignancies or premalignant lesions. Surgery was used on the trunk (65%) more often than on other body sites. PDT was most often used on the lower extremities (54%). It is likely that larger and more indurated lesions in this area were treated with PDT due to contraindications to surgery and cryotherapy. *124 patients died during this period of causes unrelated to the skin cancer. Six cases of invasive SCC. Treatment for recurrence: surgery (5), imiquimod (3), PDT (2), cryotherapy (1).

<table>
<tr><th>Study/ design</th><th>Population</th><th>Intervention: various</th><th>Outcomes</th><th>Comments & additional data not in usable format</th></tr>
<tr>
<td>Morley, G. L. et al. A comparative study examining the management of Bowen's Disease in the United Kingdom and Australia. Dermatol Res Pract 2015; 2015: 421460.

Retrospective, 2 centres (July 2012-June 2013, UK & Australia.

Funding: No details given.</td>
<td>n=247 (149 with 155 lesions (13 recurrences) UK, 98 with 151 lesions (17 recurrences) Australia)

UK
66 F: 83 M
Mean age (range): 79 years (40-97)

Australia
40 F: 58 M
Mean age (range): 76 years (36-99)</td>
<td>Surgical excision (205)
103 UK, 102 Australia

Curettage (8)
8 UK

Cryotherapy (21)
14 UK, 7 Australia

PDT (6)
3 UK, 3 Australia

Radiotherapy (1)
1 Australia

Topical 5-FU (51)
20 UK, 31 Australia

Topical imiquimod (8)
5 UK, 3 Australia

No treatment* (6)
2 UK, 4 Australia</td>
<td>Recurrence (1 year)

4 (1 UK, 3 Australia)

Surgical excision 2/205
1 UK, 1 Australia

Topical 5-FU 1/51
1 Australia

Topical imiquimod 1/8
1 Australia</td>
<td>*Observation follow-up/did not attend/decreased</td>
</tr>
<tr>
<td>Hansen, J. P. et al. Bowen's Disease: a four-year retrospective review of epidemiology and treatment at a university center. Dermatol Surg 2008; 34: 878-83.</td>
<td>n=299 with 406 SCC in situ (399 primary, 7 recurrent)

106 F: 193 M
Mean age (range): 69.8 years (33-99)
Site: Scalp (17), ear (59), forehead/temple (50), cheek (44), eyelid (6), lips (5), nose (12), neck (26), anterior trunk (33), back (14), upper</td>
<td>Surgical excision (elliptical) (109)

Mohs micrographic surgery (83)

Shave excision (79)

Punch excision (14)
Curettage and fulguration (46)</td>
<td>Recurrence (histological*)

15

Surgical excision: 3/109
Mohs micrographic surgery: 2/83</td>
<td>The male predominance may be due to the male-dominated farming community of the state. There was slight predilection for the left side which may be a result of increase sun exposure on the left while operating a vehicle.

Treatment by site of SCC in situ:
<table>
<tr><td></td><td>Head & neck</td><td>Extremities</td></tr>
<tr><td>Mohs Surgery</td><td>91.5%</td><td>7.2%</td></tr>
<tr><td>Other Surgery</td><td>49.5%</td><td>39.1%</td></tr>
<tr><td>Destruction</td><td>31.5%</td><td>44.9%</td></tr>
</table>
</td>
</tr>
</table>

Study/ design	Population	Intervention: various	Outcomes	Comments & additional data not in usable format
Retrospective, single centre (January 1999-January 2003), USA. Funding: No significant interest with commercial supporters.	extremity (110), lower extremity (30) Exclusion criteria: Tumour associated with human papillomavirus, found on mucous membranes or genitalia or found within or at the margins of an invasive skin malignancy	**Curettage** (3) **Cryotherapy** (24) **Electrodesiccation** (16) **Topical 5-FU** (24) **Topical imiquimod** (6) **Not recorded** (2) Mean f/up (range): 28.6 months (2-75)	Shave excision: 5/79 Curettage and fulguration: 2/46 Cryotherapy: 2/24 Topical 5-FU: 1/24 No recurrence was observed for the other modalities.	<table><tr><td>Topical</td><td>46.7%</td><td>50%</td></tr><tr><td>Total</td><td>54%</td><td>34.6%</td></tr></table> 91.5% of those treatment by Mohs micrographic surgery were on the head and neck. *One invasive SCC
Westers-Attema, A. *et al.* Bowen's disease: A six-year retrospective study of treatment with emphasis on resection margins. *Acta Derm Venereol* 2014; **94**: 431-5. Retrospective, single centre (January 2002-December 2007, The Netherlands. Funding; No details given.	n=185 with 212 SCC *in situ* Mean age (SD): 70 (12.0) years 122 F: 90 M Immunosuppressed: 29 Mean diameter <10 mm (51), ≥10 mm (114), unknown (47) Site: Ears (10), other head/neck (51), trunk (44), upper extremity (44), lower extremity (63) Exclusion criteria: Tumours found on mucous membranes or genitalia or found within the margins of an invasive skin malignancy	**Surgical excision** (86) Mean f/up (range): 35 months (0-99) **Cryotherapy** (3) **PDT** (98) **Topical 5-FU** (11) **Other treatment/no treatment** (14)	**Recurrence** Surgical excision 2 Other 10 (surgical excision was performed after failure of another therapy in 10 cases)	In 79/96 of excised SCC *in situ* the lesion was completely excised. After incomplete excision, patients were treated with re-excision (15) or 5-FU (2). 71/96 SCC *in situ* were excised with a known clinical safety margin, therapy failure was 7%. In the remaining 25 where the margin was unknown therapy failure was 48%. A margin of 5 mm was used in 54 cases and a smaller margin of 3 mm was used in 17 cases. Complete excision was achieved in 51/54 (94.4%) with a 5 mm margin and 15/17 (88.2%) with a 3 mm margin. The theoretical implication of reducing the margin was evaluated. If the margin had been 4 mm, 47/54 (87.0%) would have been completely excised, if the margin had been 3 mm this reduces to 40/54 (74.1%).

Study/ design	Population	Intervention: various	Outcomes	Comments & additional data not in usable format
Sturm, H. M. Bowen's disease and 5-fluorouracil. *J Am Acad Dermatol* 1979; **1**: 513-22. Retrospective, single centre (1965-1976), USA. Funding: No details given.	n=64 with 66 SCC *in situ* lesions Topical 5-FU arm 22 F: 19 M Mean age (range): 58.5 years (34-83) Site: head and neck (65%), upper/lower extremities (35%) Median size (range): 35 mm (15-120) Inclusion criteria: Histological diagnosis of SCC *in situ*	**Surgical excision** (4) **Desiccation and curettage** (20) **X-ray radiation** (1) **Topical 5-FU** (41)	**Recurrence** Surgical excision: 2/4 Desiccation and curettage: 4/20 Topical 5-FU: 3/41	Ill-defined margins meant that the margins of the lesions were not adequately treated which led to recurrence.

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
Hassan, I. *et al.* Surgical excision in Bowen's disease. *Iran J Dermatol* 2014; **17**: 101-3. Prospective, single centre, India. Funding: No details given.	n=12 7 F: 5 M Age range: 50-70 years Site: anteromedial aspect of the thigh, anterior abdomen and legs Diameter: 10-30 mm Inclusion criteria: Histological diagnosis of SCC *in situ*	**Surgical excision** including either fusiform excision, W-plasty, or Z-plasty. Excision was performed up to the level of subcutis with a 5-10 mm margin. After adequate undermining, the wounds were stitched using vicryl or silk sutures. A local dressing was applied and oral antibiotics were prescribed to all the patients for 7-10 days.	**Clearance (within 6 months)** 12/12 **Sustained clearance (1 year)** 12/12 **Adverse events** secondary infection and wound dehiscence: 1	10/12 had previously used topical imiquimod for more than 3 months but reported progression of the lesions associated with pain and pruritus.

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
		F/up: 1 year (ongoing, planning 5 year f/up)		
Drake, A. L. *et al.* Variations in presentation of squamous cell carcinoma in situ (Bowen's disease) in immunocompromised patients. *J Am Acad Dermatol* 2008; **59**: 68-71. Retrospective, single centre (January 1999-January 2003), USA. Funding: None.	n=299 with 407 SCC *in situ* 106 F: 193 M Mean age (range): 69.8 years (30-99) Immunocompromised: 57* Mean diameter (SD): 11mm (9) Site: Normal immune function: head/neck (176), trunk (27), extremities (98) Immunocompromised: head/neck (43), trunk (20), extremities (62)	**Surgical excision** Mean f/up: 35 months	**Recurrence** 11 Immunocompromised: 5 (including one invasive SCC) Normal immune function: 6	*Including 43 organ transplant recipients, 7 patients with acute and chronic leukemia, and 6 patients with immune-suppressing infections or autoimmune disease The mean follow-up duration of 35 months may underestimate the recurrence rate.
Hugo, N.E. *et al.* Bowen's disease: Its malignant potential and relationship to systemic cancer. *Plast Reconstr Surg* 1967; **39**: 190-4. Retrospective, single centre (September 1932- June 1965), USA. Funding: No details given.	n=38 SCC *in situ* 19 F: 19 M Mean age: 62.4 years Inclusion criteria: histological diagnosis of SCC *in situ*	**Surgical excision** (34) **Electrodesiccation** (2) **X-radiation** (1*) **No treatment** (1†)	**Recurrence local (1 year)** Surgical excision: 0/34 Electrodesiccation: 0/2	*partial regression of the lesion was obtained †SCC *in situ* found at autopsy Metastatic spread of SCC *in situ* in one patient who had had surgical excision at 15 months, progression to SCC at 7 years, died of widespread metastases 1 year later.

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
Otani K *et al.* Treatment of Bowen disease using the ultrasonic surgical aspirator. *Plast Reconstr Surg* 2001; **108**: 68-72. Prospective, single centre (1991-?), Japan. Funding: No details given.	n=20 with SCC *in situ* not suitable for surgical treatment 8 F: 12 M Mean age (range): 77.5 years (61-91) Inclusion criteria: diagnosis of SCC *in situ* by two histopathologists	**Ultrasonic surgical aspirator** Local anesthesia administered. Ultrasonic surgical aspirator set at 70 was applied directly to the lesion surface using small, circular stokes until lesion totally excised (visually). Biopsied to confirm visual findings. Mean f/up (range): 20 months (12-26)	**Clearance (within 6 months)** 20/20 **Recurrence (1 year)** None	No signs of recurrence have been found during f/up.
Machan M, *et al.* Penile squamous cell carcinoma: Penis-preserving treatment with Mohs micrographic surgery. *Dermatol Surg* 2016; **42**: 936-44. Retrospective, single centre (1983-2013), USA. Funding: No details given.	n=42 with 44 penile SCC* (including 23 SCC *in situ* and 3 recurrent SCC *in situ*) SCC *in situ* Mean age (range): 63.3 years (29-88) recurrent SCC *in situ* Mean age (range): 54.6 years (45-72)	**Mohs micrographic surgery** Mean number of excision levels required for complete removal of the tumour (range): 1.96 (1-5) SCC *in situ* Mean f/up (range): 92.7 months (4-269) recurrent SCC *in situ* Mean age (range): 53 months (1-144)	**Clearance (within 6 months)** SCC *in situ* 23/23 recurrent SCC *in situ* 3/3 **Recurrence** 2 SCC *in situ*: 1 (9 months) recurrent SCC *in situ:*1 (15 months)	Attrition: 4 SCC *in situ* lost to follow-up *14 invasive SCC & 8 recurrent invasive SCC For 4 patients with SCC *in situ* of the glans which tracked down the urethra, a ventral meatotomy and urethrotomy was performed to provide exposure for a complete circumferential layer of tissue to be excised. All 4 patients required urethral dilation postoperatively secondary to urethral stricture, normal function was restored.

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
Wollina U. Bowen's disease of the nail apparatus: a series of 8 patients and a literature review. *Wien Med Wochenschr* 2015; **165**: 401-5. Retrospective, single centre (January 2001-July 2015), Germany. Funding: None.	n=8 SCC in situ of the nail apparatus 2 F: 6 M Mean age (range): 60 years (40-84) Site: single finger (5), single tow (2), polydactylous of fingers and toes (1*)	**Mohs micrographic surgery** Delayed Mohs technique. F/up: at least 48 months to 5 years.	**Recurrence (2 years)** 1 finger **Recurrence (5 years)** **(3 years)** 1 polydactylous of fingers and toes	In all cases, final diagnosis was delayed for 9 months. Working diagnosis: onychomycosis, psoriasis, eczema, verruca, and posttraumatic onychodystropy. None of these patients developed invasive SCC of the nail apparatus. *Hunt WT *et al.* Multiple-digit periungual Bowen's disease: a novel treatment approach with radiotherapy. Clin Exp Dermatol. 2013;38: 857–61.
Young LC *et al.* Mohs' micrographic surgery as treatment for squamous dysplasia of the nail unit. *Australas J Dermatol* 2012; **53**: 123-7. Retrospective, single centre (2000-2010), Australia.	n=13 with 14 squamous dysplasia of the nail unit (including 11 SCC *in situ*)* 4 F: 7 M Mean age (range): 49.9 years (32-75) Site: thumb (3), 2nd (2), 3rd (4), 4th (1), 5th (1) Recurrent: 8†	**Mohs micrographic surgery** Mean number of excision levels/sections required for complete removal of the tumour (range): 1.45 (1-2)/3 (2-5) Mean f/up (range): 45.8 months (6-120)	**Recurrence (5 years)** **(30 months)** 1 invasive SCC **(96 months)** 1 SCC *in situ*	* Bowenoid actinic keratosis (1), SCC (2) †Previous treatment: cryotherapy, topical imiquimod, topical 5-fluorouracil, photodynamic therapy and surgical excision.

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
Funding: No details given.			**Cosmetic outcome (rated by patients)** Highly satisfactory: 7 Fair: 2 Unsatisfactory: 1 (due to persistent swollen appearance) N/A:1 (recurrence treated with amputation)	No complications, e.g. wound infection were documented. Metastases were not demonstrated in any.
Leibovitch I *et al.* Cutaneous squamous carcinoma in situ (Bowen's disease): treatment with Mohs micrographic surgery. *J Am Acad Dermatol* 2005; **52**: 997-1002. Prospective, multicentre (1993-2002), Australia. Funding; None.	n=270 SCC *in situ* histologically diagnosed 79 F: 191 M Mean age (range): 64 years (27-92) Recurrent: 137* Site: scalp (13), forehead (24), temple (28), periocular (48), maxilia (4), cheek (14), auricular (69), mastoid (3), nose (29), lips (4), chin & mandible (5), neck (11), upper limbs (13), trunk (3), genital (2) Size (cm): <1 (44), 1-1.9 (88), 2-2.9 (74), 3-3.9 (29), 4-4.9 (11), 5-5.9 (4), 6-7.9 (8), not known (12)	**Mohs micrographic surgery** Mean number of excision levels required for complete removal of the tumour (SD): 2.0 (0.9) F/up: 5 years	**Recurrence (5 years) for the 95 patients who completed the 5 year f/up** 6 Primary (1), recurrent (5)	* Previous treatment: Surgical excision (44), cryotherapy (94), curettage & cautery (18) The tumour was initially misdiagnosed in 20% of cases: BCC (34) & SCC (20). Defect sizes in previously recurrent tumours were larger than primary tumours (p=0.0003). Reason for referral: poorly defined tumour (86), recurrent tumour (84), tumour site (66), tumour (12), incomplete tumour excision (10), no details available (12) No cases of perineural invasion
Sau P *et al.* Bowen's disease of the nail bed and periungual area. A clinicopathologic analysis of	n=7 SCC *in situ* of the nail bed 1 F: 6 M Mean age (range): 53 years (39-64)	**Mohs micrographic surgery** (6) **Topical 5% fluorouracil then Mohs micrographic surgery** (1)* Mean f/up (range): 27.7 months (6-84)	**Recurrence (1 year)** 1 (8 months) Retreated with Mohs	Patients presented with the clinical features of verruca vulgaris (3), nail dystrophy and onycholysis (2), paronychia (1), acral melanoma (1).

Study/ design	Population	Intervention: surgical	Outcomes	Comments & additional data not in usable formal
seven cases. *Arch Dermatol* 1994; **130**: 204-9. Retrospective, single centre, USA. Funding: No details given.	Race; white (6), black (1) Site: thumb (1), 2nd (1), 3rd (4), 4th (1)		**Recurrence (2 years)** 1 (18 months) Retreated with Mohs	*residual SCC in situ was found 6 weeks after topical therapy

Study/ design	Population	Intervention: destructive	Outcomes	Comments & additional data not in usable format
Drexler I *et al.* Adnexal cancerization in actinic keratosis and cutaneous Bowen's disease: Incidence, degree and clinical implications. *Eur J Dermatol* 1997; **7**: 427-31. Retrospective, single centre, Germany. Funding: No details given.	n=90* including 16 with SCC *in situ* received questionnaire. 75 returned including 10 with SCC *in situ*	**Curettage** Mean depth of curettage (range): 0.75 mm (0.35-1.10) Mean f/up (range): 18 months (12-24)	**Recurrence (2 years)** Patients were asked to re-examine the respective area with regard to possible reappearance. If suspicion of local recurrence was reported, this was confirmed by their attending dermatologist. 1 (24 months)	*74 actinic keratosis
Honeycutt WM *et al.* Treatment of squamous cell carcinoma of the skin. *Arch Dermatol* 1973; **108**: 670-2.	n=417 SCC of the skin and lower lip including 52 SCC *in situ* 21 F: 31 M Site: forehead (8), nose (7) cheek (11), ear (3), neck (5), arm (4), leg (13), foot (1)	**Curettage with cautery** Minimum f/up: 4 years	**Recurrence** 1/52	Recurrence was successfully retreated with curettage and cautery

Study/ design	Population	Intervention: destructive	Outcomes	Comments & additional data not in usable format
Retrospective, single centre (1964-1968), USA. Funding: No details given.	Size: <20 mm (44), >20 mm (7), not recorded (1)			
Holt PJ. Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol* 1988; **119**: 231-40. Prospective, single centre (1981-1986), UK. Funding: No details given.	n=301 with 395 NMSC including 85 with 128 SCC *in situ** Site: scalp (2), temple (6), ear helix (1), mastoid (2), forehead/eyebrows (3), cheek (3), nose (4), lower lip (2), neck (1), back (4), glans penis (1), arm (3), forearm (3), hand/fingers (19), thin (3), calf/shin (70), foot (1) Size: 20 lesions were larger than 2 cm.	**Cryotherapy** Single freeze-thaw cycle, with a freeze time of 30 seconds. Tumours of the head and neck usually healed within 4-6 weeks, cosmetic results were outstanding. Hand and fingers healed in a similar fashion. Lesions on the calf and shin healed more slowly, sometimes taking 6 months. F/up range: 6 months – 5.5 years	**Recurrence (1 year)** 1 (6 months) on the calf 2x1 cm Excised, reported as showing islands of SCC in the dermis with no overlying epidermal change **Cosmetic outcome** Outstanding. Patients were consistently pleased with the results and no patient who subsequently developed skin cancer at other sites refused cryotherapy when this was offered. **Treatment tolerability** Patients tolerated this treatment well.	Attrition: 24 lost to follow-up post 1985 (last seen after 18-36 months f/up no recurrences) *174 with 225 BCC, 34 SCC, 8 keratoacanthoma Complication: hypertrophic scar 20x7 mm traversing the treatment field. Flatted over next 7 months except at one pole where a nodule persisted which became exquisitely tender. Excised, histology showed changes of a traumatic neuroma.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Covadonga Martinez-Gonzalez M *et al.* Bowen's disease treated by carbon dioxide laser. A series of 44 patients. *J Dermatolog Treat* 2008; **19**: 293-9. Retrospective, single centre (February 2003-November 2006) Spain. Funding: No details given.	n=44 with 49 SCC *in situ* 33 F: 11 M Mean age (range): 76.2 years (37-89) Site: forehead (2), ear (2), abdomen (1), chest (1), arm (4), hand (3), digit (1), leg (32), thigh (2), foot (1) Immunosuppressed: 12	**CO_2 laser** Super-pulsed mode, focalized at 2 W/cm^2 Mean f/up (range): 18.8 months (8-52)	**Clearance (within 6 months)** 43/44 (48/49 lesions) **Recurrence** 3 (4 months, 6 months & 1 year 5 months*) **Adverse events/Cosmetic outcome** 1 Keloid scar	Clearance after one treatment was achieved in 38 patients *Patient only attended 1 month f/up, then presented at 1 year 5 months with recurrence, with unknown evolution time
Dave R, *et al.* Treatment of Bowen's disease with carbon dioxide laser. *Lasers Surg Med* 2003; **32**: 335. Prospective, single centre, UK. Funding: no details given.	n=16 with 25 biopsy proven SCC *in situ* on the legs	**CO_2 laser** F/up: 6 months	**Clearance (within 6 months)** 25/25 8 lesions took longer than 4 weeks to heal, all healed by 8 weeks	No recurrence at 6 month f/up, however, 3 have been referred back with SCC within 12 months of discharge from f/up.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
van Bezooijen BP *et al.* Laser therapy for carcinoma in situ of the penis. *J Urol* 2001; **166**: 1670-1. Retrospective, single centre (1986-2000), The Netherlands. Funding: No details given.	n=19 SCC *in situ* of the penis Mean age (range): 52 years (21-86)	**Neodymium: YAG** (1986-93) (7) or **CO_2 laser** (1994-2000) (12) Mean f/up (range): 32 months (1-95)	**Clearance (within 6 months)** 16* **Recurrence** 5 at an average f/up of 25 months (range 6-75) YAG: (1) CO_2 laser: 4 **Cosmetic outcome** Excellent	No complications, neither sexual or urinary function impaired. *after 2-4 months 3 patients received repeat treatment because of incomplete clearance Infiltrating carcinoma (1) after 6 years
Tantikun N. Treatment of Bowen's disease of the digit with carbon dioxide laser. *J Am Acad Dermatol* 2000; **43**: 1080-3. Prospective, single centre (1992-8), Thailand. Funding: No details given.	n=6 SCC *in situ* of the digit 3 F: 3 M Mean age (range): 63.5 years (49-80) Site: thumb (1), 3rd (2), 4th (1), 5th (2) Skin type: IV (6) Immunosuppressed: 0	**CO_2 laser** Spot size of 3 mm at 5 to 8 W. Mean f/up (range): 28.8 months (6-92)	**Clearance (within 6 months)** 6/6 **Recurrence** None during f/up **Cosmetic outcome** Excellent, with preservation of function	4/6 had a long history of exposure to arsenic from herbal medicines: 2 already had SCCs and 1 developed multiple BCCs & SCCs on back, arms & legs 6 years after treatment. 1 had had long-term radiation therapy on digit 50 years earlier.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Humphreys TR *et al.* Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ with a high-energy pulsed carbon dioxide laser. *Arch Dermatol* 1998; **134**: 1247-52. Prospective, single centre, USA. Funding: No details given.	n= 21 with 30 superficial neoplasms, including 13 SCC *in situ** Mean age (SD): 76.6 (11.1) years Average size length/width (SD): 1.33 (0.51) cm/1.02 (0.38) cm Average total thickness (SD): 0.57 (0.28) mm Site: head & neck (4), trunk (6), arms or legs (3) Exclusion criteria: Patients in poor health precluding surgery, pregnant, or <18 years; with lesions smaller than 0.5 or large lesions whose excision would result in disfigurement or functional compromise; inadequate initial biopsy specimens that precluded measurement of tumour depth.	**CO_2 laser** 2 (6) or 3 (7) passes of a pulsed CO_2 laser (500 mJ, 2-4 W) using a 3-mm collimated handpiece	**Clearance (within 6 months)** 8† 2 passes: 4/6 3 passes: 4/7	*17 superficial BCC †residual tumour in the centre of the specimen seen in other 5: thick stratum corneum with underlying SCC *in situ* (1), persistent abnormal hyperplastic epithelium (2), abnormal keratinocytes extending down follicular epithelium (2). Mean thickness these was significantly greater than that of completely vaporized lesions (0.65 vs 0.41mm; *p*=0.01).
Herman JM *et al.* Radiotherapy using a water bath in the treatment of Bowen's disease of the digit.	n=9 with 14 SCC *in situ* lesions on the digit 6 F: 3 M	**Radiotherapy** Digits were immersed in a water bath and treated with photon irradiation. The median radiation dose delivered was 50 Gy	**Clearance (within 6 months)** 14/14	7/14 were circumferential and radiotherapy was determined to be the only alternative to amputation.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Radiother Oncol 2008; **88**: 398-402. Retrospective, single centre (1999-2004), USA. Funding: No details given.	Median age (range): 77 years (29-87) All Caucasian Recurrent: 2 Median size (range): 27.5 mm (10-50)	(range 25-66 Gy) in 2.5 Gy fractions (range 2-3 Gy). Median f/up (range): 25 months (0.4-52)	**Adverse events – serious: ulceration** Grade 4: 2 **Adverse events – minor:** mild erythema or dry desquamation (grade 1): 6 moist desquamation or edema (grade 2): 6 Candida infection (1)	All locally controlled at last f/up so no recurrences. None developed metastatic disease. Full range of motion and strength was maintained, except for one patient with three circumferential lesions (two digits, one thumb) who developed mild weakness and numbness in their fingertips.
Lukas VanderSpek LA *et al.* Radiation therapy for Bowen's disease of the skin. *Int J Radiat Oncol Biol Phys* 2005; **63**: 505-10. Retrospective, single centre (April 1985-November 2000), Canada. Funding: No details given.	n=44 with SCC *in situ* 15 F: 29 M Mean age (SD): 67.7 (14.5) years Site: scalp (9), face (12), trunk (6), extremity (12), perianal (3), penis (2) Median size (range): 2.65 cm^2 (0.07-34.56) Immunosuppressed: 10 Previous skin cancer (RT/no RT): 10/5 Exclusion criteria: Patients with an incidental diagnosis of SCC in situ that was not treated but who had concurrent,	**Radiotherapy (primary therapy)** (32) **Radiotherapy (residue disease after local ablative therapy or incomplete excision)** (12†) Orthovoltage X-rays (39) Electrons (3); Cobalt (2). There was no standard fractionation regimen; high dose (24), low dose (20) Median f/up (range): 30 months (0-148)	**Clearance (within 6 months)** 42/44* **Recurrence (1 year)** 1 at 0.2 years **Recurrence (2 years)** 2‡ at 1.1 & 1-1.5 years	*Attrition: 2 lost to f/up †Previous adjuvant treatment: topical creams (7), excision (2), cryotherapy (2), curettage and electrodesiccation (1) ‡SCC. One had been diagnosed simultaneously with SCC and SCC in situ at different sites initially and metastatic disease was found at other sites at approximately the same time as the marginal SCC recurrence. At last f/up 32 patients were known to be alive. Median overall survival was estimated to be 8.4 years (95%

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
	nonrelated cancer that was treated.		**Adverse events – serious: ulceration** 3: non-healing ulcer 2 years after RT (1), deformity of the underlying nailbed and occurrence of ulcer (1), non-healing ulcer and underlying bone damage requiring amputation of finger due to radiation necrosis (1)	CI 6.4-NA) and the 5-year overall survival rate was 68% (95% CI 52%-90%).
Dupree MT *et al.* Radiation therapy for Bowen's disease: lessons for lesions of the lower extremity. *J Am Acad Dermatol* 2001; **45**: 401-4. Retrospective, single centre (1993-1997, USA. Funding: No details given.	n=11 with 16 SCC *in situ* lesions 11 M Median age (range): 75 years (58-93) Site: head (8), neck (1), back (2), lower extremities (4), penis (1)	**Radiotherapy** Median time-dose-fractionation value of 105 (range, 93-108) Median f/up (range): 27.5 months (9-57)	**Clearance (within 6 months)** 11/11	
			Recurrence None	
			Adverse events – serious: ulceration 4 nonhealing ulcers all on lower extremities	
			Adverse events – minor moist and dry desquamation: 15	

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
			moderate to severe erythema: 10 cellulitis: 2 mild hypopigmentation: 2 telangiectasia: 2 fibrosis: 2	
Chung YL *et al.* Treatment of Bowen's disease with a specially designed radioactive skin patch. *Eur J Nucl Med* 2000; **27**: 842-6. Prospective, single centre (1996-1998), Korea. Funding: No details given.	n=8 with 29 SCC *in situ* 1 F: 7 M Mean age (range): 63.9 years (45-78) Site: palm (1), buttock (3), thigh (3), multiple sites (1)	**Radiotherapy** Skin patch coated with high-energy beta-emitter holmium-166 was applied to the surface of skin cancer for 30-60 minutes for a total radiation dose of 35 Gy (3500 rads). Range of f/up: 10-26 months.	**Clearance (within 6 months)** 8 **Sustained clearance** No recurrences during f/up **Cosmetic outcome** Good cosmetic and functional results	Desquamation, erythema or ulceration developed in most of the patients 1-2 weeks after ^{166}Ho patch therapy. Some patients complained of a burning sensation and mild pain after treatment, but this subsided spontaneously within 1 month. Some showed hypopigmentation of the treated lesions, this also disappeared spontaneously within 1 year after treatment. F/up biopsies were performed 1-5 months after therapy and did not show any signs of SCC *in situ*.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Caccialanza M *et al.* Results and side effects of dermatologic radiotherapy: a retrospective study of irradiated cutaneous epithelial neoplasms. *J Am Acad Dermatol* 1999; **41**: 589-94. Retrospective, single centre (1982-1995), Italy. Funding: No details given.	n=1188 with 2002 primary epithelial malignant neoplasms*, including 62 SCC *in situ* 592 F: 596 M Mean age (range): 72.96 years (32-96) Site: face/head (1235), neck/trunk (688), limbs (119), other (15)	**Radiotherapy** Contact (1855), superficial (125) and intermediate (22) X-ray. Dose 200-500 cGy/fraction Mean f/up (range): 33.1 months (11-240)	**Recurrence** 1/62 In squamocellular evolution	*BCC (1763), SCC (109), keratoacanthomas (48), metatypic (9), keratosis in evolution (7), erythroplasia of Queyrat (3), trichlemnial cyst in evolution (1) **Clearance** Complete remission in 98.7% (3 partial response & 12 lesions did not respond) **Adverse events** Acute complications: 1.94% Chronic complications: 0.34% all treated lesions **Cosmetic outcome** Good (1195), acceptable (549), not acceptable (217), not evaluated (43)
Blank AA *et al.* Soft-X-ray therapy in Bowen's disease and erythroplasia of Queyrat. *Dermatologica* 1985; **171**: 89-94. Prospective, single centre (1968-1983), Switzerland.	n= 52 with 77 lesions including 73 SCC *in situ* and 4 erythroplasia of Queyrat 17 F: 35 M Mean age (range): 65 years (37-90) Site: head & neck (23), trunk (11), extremities (25), anogenital skin (18) Size: 0-10 cm^2 (28), 10-20 cm^2 (38), 20-90 cm^2 (11)	**Radiotherapy** Soft X-ray therapy 30 kV/0.5 Al filter (68), 40 kV/1.0 Al filter (8), 60 kV/0.2 Cu filter (1). Cumulative surface dose: 3,200 R (9), 3,600 R (2), 4,000 R (40), 4,400 R (7), 4,800 R (13), 5,200 R (1), 5,600 R (2) Mean f/up (range): 3 years (1-11)	**Clearance (within 6 months)** 77 **Recurrence (1 year)** 1 (8 months) penile erythroplasia of Queyrat **Recurrence (2 years)** 1 (16 months) SCC *in situ* of the vulva	3 patients had previously had internal malignant tumours: anal carcinoma 12 years before anogenital SCC *in situ* (1); laryngeal carcinoma 26 years before SCC *in situ* of the foot (1); laryngeal carcinoma 2 years before multiple cutaneous tumours (SCC, *SCC in situ*, carcinoma of Bowen) and bronchial carcinoma 5 years later.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
			Cosmetic outcome Functional and cosmetic results were good in all cases	
Stevens DM *et al.* Treatment of Bowen's disease with grenz rays. *Int J Dermatol* 1977; **16**: 329-39. Retrospective, single centre (1955-1975), USA. Funding: No details given.	n=16 with 19 SCC in situ lesions 9 F: 7 M Mean age (range): 68.9 years (28-80) Site: head (5), neck (1), upper extremities (2), hand (3), digit (2), trunk (3), lower extremities (2), foot (1)	**Radiotherapy** Grenz rays. Total dose was 5000 rads (18) or 5500 rads (1), delivered in fractionated doses of 500 rads each, administered 2 or 3 times per week. Mean f/up (range): 6 years (1.5-12)	**Clearance (within 6 months)** 18/19 **Sustained clearance at 1 year** 17/18* **Sustained clearance at 2 years** 14/17 Other 3 f/up <2 years **Sustained clearance at 5 years** 11/17 Other 6 f/up <5 years **Cosmetic outcome** (17) Excellent: 12 Good: 4 Fair: 1	Other methods of treatment of SCC *in situ* (1955-1968): Surgical excision (15), mean f/up (range) 4 years (0-7) 3 recurrences; Curettage-electrodessication (83), mean f/up (range) 2.25 years (0-18) 8 recurrences; 5-FU (2), mean f/up (range) 4 years (2-6); Other (11) mean f/up (range) 3.5 years (0-9), no recurrences. One lesion did not respond: Excised. F/up 12 years no recurrence. Retrospective review of first biopsy specimen showed 5.6 mm in thickness and it was reinterpreted to be an invasive SCC. *One with a total depth of 1.4 mm recurred at 4 months. Retreated by curettage-electrodesiccation. F/up 7 years no recurrence.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Trnka J. Local effect of Cytembena and Bucky's rays on superficial basaliomas and Bowen's disease. *Neoplasma* 1971; **18**: 467-70. Prospective, single centre, Czechoslovakia. Funding: No details given.	n=140 superficial carcinomas* including 17 SCC *in situ*	**Radiotherapy: Cytembena & Bucky's rays** Cytembena solution containing 6.25 mg/1ml of 1% mesocian solution injected in. Irradiated within 1 hour with single 1500-r dose of Bucky Rays exposure (3 minutes; 12 kV; 15 mA)	**Clearance (with 6 months)** 12 (71%) **Cosmetic outcome** Considered very good	*123 basaliomas
Alnajjar HM *et al.* Treatment of carcinoma in situ of the glans penis with topical chemotherapy agents. *Eur Urol* 2012; **62**: 923-8. Retrospective, prospective database (2001-2011), UK. Funding: None.	n=86 primary and recurrent carcinoma *in situ* of the glans penis (Erythroplasia of Queyrat), 44 received topical treatment* Mean age (range): 62.6 years (47.5-77.7) Caucasians (42), Indian (2) Viral features: 34	**Topical 5 fluorouracil (1st line)** (42) Application to the lesion for 12 hours every 48 hours for 28 days **Topical imiquimod (2nd line)** (11) Same regimen. Mean f/p (range): 34 months (12-180)	**Clearance (within 6 months)** 25† One 5-FU course: 16 Two 5-FU courses: 4 Three 5-FU courses: 1 One IQ course: 4 **Sustained clearance** 20 no recurrence to date 5 recurrences (mean time to recurrence 5 months) **Adverse events – serious: ulceration**	*circumcision (27), wide local excision (8), glans resurfacing (7) †Partial response (PR) (6), no response (NR) (13). Biopsy was performed on 22 patients with PR or NR after first course: SCC (2), carcinoma *in situ* (12), hyperplasia & warty changes (4), inflammation (3), viral wart (1)

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
			IQ: 1 scrotal ulceration and bleeding (treatment course stopped) **Adverse events** 5FU: local toxicity (4), adverse events (unspecified (5)	
Welch ML *et al.* 5-fluorouracil iontophoretic therapy for Bowen's disease. *J Am Acad Dermatol* 1997; **36**: 956-8. Prospective, single centre, USA. Funding: No details given.	n=26 SCC *in situ* 10 F: 17 M (as reported in paper) Mean age (range): 74 years (62-95) Site: head & neck (4), trunk & upper extremities (13), lower extremities (9) Mean size: 11x12 mm Inclusion criteria: Biopsy-proven SCC *in situ,* with persistent clinical evidence of initial lesion after the biopsy site healed. No prior attempts at treatment of the lesion. Exclusion criteria: lesions on the scalp, male beard area, glans penis and female genitalia	**Topical 5-Fluorouracil iontophoretic therapy** Iontophoresis of 1% lidocaine with epinephrine 1:100,000 into the lesion at 4 mA for 7.5 minutes (30 mA/min) to produce vasoconstriction. Next, a pad saturated with 5-FU was placed over the lesion and iontophoresis was applied at 4 mA for 10 minutes (40 mA/min). Different-sized delivery pads were used to maximize overlap of the lesions. In all cases, the periphery of the pad was more than 5 mm outside the clinically apparent tumour margin. Eight treatment sessions over 4 weeks.	**Clearance (within 6 months)** Clinical: 26 Histological: 25* **Cosmetic outcome (after treatment but before excision)** Uniformly good or excellent	*At 3-month follow-up excision of the entire treatment site was performed, sent for serial sectioning, stained and evaluated for any histologic evidence of bowenoid changes. One on lower extremity had residual histologic changes consistent with SCC *in situ.* An allergic reaction to 5-FU developed in one patient after the seventh treatment; that resolved with topical steroids.

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Limmer BL. Bowen disease: treatment with topical 5 fluorouracil. *Cutis* 1975; **16**: 660-3. Retrospective (5 years), USA. Funding: No details given.	n=17 SCC *in situ* Non-genital skin (12) 4 F: 8 M Mean age (range): 61.4 years (31-94) Site: infraorbital (2), temple (1), cheek (1), popliteal fossa (1), anterior thorax(1), posterior thorax (1), deltoid (1), areola nipple (1), wrist (1), finger (1), buttock (1) Genital (5) 5 F Mean age (range): 34.8 years	**Topical 5 fluorouracil** 1% or 2% solution or 5% cream was applied to lesions involving non-genital skin twice daily. Mean duration of therapy (range): 34 days (21-42) Mean f/up (range): 34.8 months (10-53) Genital lesions were treated with cream in 1% or 5% concentration. Mean duration of therapy (range): 10 days (7-10) Mean f/up (range): 29.8 months (14-48)	**Sustained clearance at 2 years** Non-genital At least 8/12 **Recurrence (at f/up)†** Non-genital skin 4*/12 Genital skin 3/5	Not easily treated surgically due to size and location of lesions, cosmetic results or sexual function. *One was successfully retreated and has sustained clearance for 27 months †All with recurrence also had other tumours [BCC; BCC & SCC; BCC, SCC & keratoacanthoma; mixed tumour parotid gland; carcinoma in situ -cervix (3)] not clear when these occurred i.e. if these were concurrent or not. Two patients without recurrence of SCC in situ also had other tumours (Bowen's at different site; SCC & BCC)
Jansen GT et al. Bowenoid conditions of the skin: Treatment with topical 5-fluorouracil. *South Med J* 1967; **60**: 185-8.	n=13 SCC *in situ* 5 F: 8 M Mean age (range): 59.1 Years (30-80)	**Topical 5% or 20% fluorouracil** Applied twice daily without occlusion to the involved areas for 4 weeks	**Clearance (within 6 months)** 12/13	Attrition: Treatment stopped in one patient (vulva) as they were intolerant to treatment. *3 (face (1), penis (2)), at f/up a small area of persisting SCC *in*

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Prospective, single centre, USA. Funding: No details given.	Site: ear (3), face (2), neck (1), trunk (1), back (1), foot (1), penis (2), vulva (2)	Mean f/up (range): 13.75 months (1-36)	**Sustained clearance at 1 year** 5/12* Other 4 f/up <1 year	*situ*/recurrence identified, retreated. Complete resolution.
Alessi SS *et al.* Treatment of cutaneous tumors with topical 5% imiquimod cream. *Clinics (Sao Paulo)* 2009; **64**: 961-6. Retrospective, single centre (2003-2008), Brazil. Funding: No details given.	n= 89 with 123 cutaneous tumours, including 13 SCC *in situ* & 2 erythroplasia of Queyrat 50 F: 39 M Mean age (range): 63.1 years (11-82) White (60) Site: face (54), lower lip (1), neck (6), back (18), trunk (18), legs (13), arms (10), axillae (1), penis (2) Comorbidities: 19 with 29 lesions (including 6 SCC *in situ*, 1 erythroplasia of Queyrat)	**Topical imiquimod** 5% imiquimod cream applied 5-7 times a week, until the time the tumour was dermined to be clinically cured or the treatment was stopped due to failure (minimum treatment threshold 6 weeks) SCC *in situ* median f/up: 15.4 months SCC *in situ with comorbidities* median f/up: 20 months Erythroplasia of Queyrat f/up range: (3-26 months)	**Clearance (within 6 months)** SCC *in situ*: 4/7† Erythroplasia of Queyrat: 0/1† With comorbidities SCC *in situ*: 3/6† Erythroplasia of Queyrat: 1/1 **Recurrence** No recurrence **Cosmetic outcome** Good **Adverse events** Side effects were tolerable	*BCC, SCC & trichoepithelion †SCC *in situ*: NP (3), Erythroplasia of Queyrat: PR (1), SCC *in situ* with comorbidities: PR (1), NP (2)

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Bardazzi F *et al.* A pilot study on the use of topical tazarotene to treat squamous cell carcinoma in situ. *J Am Acad Dermatol* 2005; **52**: 1102-4. Prospective, single centre, Italy. Funding: No details given.	n=15 with SCC *in situ* 6 F: 9 M Mean age (range): 73 years (52-92) Site: head (2), trunk (6), extremities (7)	**Topical tazarotene** 0.1% gel once daily for a maximum of 6 months F/up: 3 months	**Clearance (within 6 months)** 7* **Adverse events – serious: severe local skin irritation which forced withdrawal** 1	Attrition: 5, disqualification for lack of compliance (4), adverse events (1) *partial response (3) No recurrence was observed in the 7 with complete resolution at 3 months f/up. Other adverse events were limited to mild local erythema, edema, or both within 2 weeks of therapy (6)
Sarah QS *et al.* Effect of solanum melongena peel extract in the treatment of arsenic-induced Bowen's disease. *Bangladesh J Pharmacol* 2018; **13**: 309-15. Prospective, single centre (September 2016-January 2018) NCT 03122561, Bangladesh. Funding: No details given.	n=8 arsenic-induced SCC *in situ* 5 F: 3 M Mean age (SD): 53.1 years (6.6) Inclusion criteria: >18 and <65 years, consumption of a high concentration of arsenic water (>50µg/L) for more than 6 months. Exclusion criteria: any drug allergy, or food allergy specifically *S. melongena*; pregnancy or lactation; patients who had received any arsenicosis treatment within the last 3 months.	**Topical *Solanum melongena* peel extract ointment** Twice daily for 12 weeks	**Clearance (within 6 months)** 0	Attrition: 2 (lost to follow-up) **Mean size of lesion (SD):** Before: 3.8 cm (1.9) After: 2.5 cm (1.7) *p*=0.0003

Study/ design	Population	Intervention: other	Outcomes	Comments & additional data not in usable format
Hiruma M *et al.* Hyperthermic treatment of Bowen's disease with disposable chemical pocket warmers: a report of 8 cases. *J Am Acad Dermatol* 2000; **43**: 1070-5. Retrospective, single centre (January 1993-December 1997), Japan. Funding: No details given.	n=8 with SCC *in situ* 2 F: 6 M Mean age (range): 71.5 years (58-92) Site: finger (1), abdomen (1), thigh (1), knee (2), ankle (2) Mean area: 7.43 cm^2	**Hyperthermic treatment: Disposable chemical pocket warmers** Applied daily with pressure directly to the lesion site while the patient was awake. Mean daily treatment 8.8 hours. The clinical course was observed for 4-5 months then the lesion was then excised and histopathologically examined.	**Clearance (within 6 months)** Clinical: 6/8* Histologic: 3/8† **Recurrence at 1 year** Histologic: 1/3	Chemical pocket warmers contain alkaline sulfide and iron carbide and, when removed from their airtight pouches, react with the atmospheric oxygen, with the result that they generate heat. They remain active for approximately 10 hours. * Partial response (1), no response (1) †isolated tumour cells (3), no change (2)

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Torelli T. *et al.* Treatment of carcinoma in situ of the glans penis with topical imiquimod followed by carbon dioxide laser excision. *Clin Genitourin Cancer* 2017; **15**: e483-e7.	n=10 carcinoma *in situ* of the glans penis (erythroplasia of Queyrat) Mean age (range): 55.1 years (41-66) Human papillomavirus-related lesions: 7	**Topical imiquimod followed by CO_2 laser ablation** Self-application of a small dose of imiquimod on the lesion for 12 hours every 48 hours. 4 months of therapy (9), 1 stopped after 6 weeks. Response to treatment was assessed by laser resection, with	**Clearance (within 6 months)** 6/10* **Sustained clearance at 1 year** 6/6	*stable disease (2), progressive disease (2) †All patients experienced a mild local toxicity (burning erythema) but no major adverse effects.

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Prospective, single centre (2010-2015), Italy. Funding: No details given.	Inclusion criteria: small (<3 cm), mucosal and superficial lesions of the glans Exclusion criteria: recurrent (<1 year) lesions, urethral extension beyond the meatus, penile shaft tumour (Bowen's disease), previous or concomitant occurrence of other malignancies.	incision of the lateral and deep margins and peripheral vaporization of the wound. The lateral margins were incised at a mean distance of 5 mm beyond the macroscopic lesion borders. The laser excision depth was 3 mm, and the bioptic depth of the wound bed was about 1 mm. Mean f/up (range): 26 months (12-58)	**Sustained clearance at 2 years** 3/6 Other 3 f/up <2 years **Cosmetic outcome** Form and curvature of the glans and coronal sulcus were conserved and the anatomic outcome was judged satisfactory by the patients. **Treatment tolerability** Treatment was well tolerated **Adverse events – serious: ulceration** 1 treatment stopped due to scrotal ulceration	One who had previous had pagetoid carcinoma *in situ* developed liver metastasis. All patients were alive at the last f/up.
Soong LC *et al.* Cryosurgery + 5% 5-fluorouracil for treatment of superficial Basal Cell Carcinoma and Bowen's disease. *J Cutan Med Surg* 2018; **22**: 400-4.	n=68 with 79 lesions, including 38 with SCC *in situ**	**Combination cryotherapy followed by 5-fluorouracil** Cryotherapy 10 second freeze, then a 1 month healing phase, followed by a 3-week course of	**Clearance (within 6 months)** 31	Attrition: 5 SCC *in situ* lost to f/up *41 superficial BCC

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Retrospective, single centre (September 2012-June 016), Canada. Funding: None.	Site: head and neck (21), truck (4), lower limbs (6), forearm or hands (2)† Inclusion criteria: biopsy-proven, previously untreated SCC *in situ*, immunocompetent	5% 5-fluorouracil applied twice a day. Mean f/up (range): 6.8 months (4-16)	**Adverse events** No adverse events reported on clinical chart documentation	†Those lost to f/up not included Two showed recurrence at f/up (treated with Mohs micrographic surgery or wide local excision)
Shaw KS *et al.* Combination of imiquimod with cryotherapy in the treatment of penile intraepithelial neoplasia. *JAAD Case Rep* 2017; **3**: 546-9. Retrospective, single centre (January 2010-March 2017), USA. Funding: Memorial Sloan Kettering Cancer Center Dermatology Research Fund.	n=8 penile intraepithelial neoplasia (SCC *in situ* (5), erythroplasia of Queyrat (2), Bowenoid papulosis (1)) Mean age (range): 45.1 years (26-65) Site: shaft (4), shaft & glans (2), foreskin, shaft (1), base & shaft (1) HIV positive: 3 (treated concomitantly with highly active antiretroviral therapy)	**Combination cryotherapy followed by imiquimod** Two freeze/thaw cycles, 10 seconds, followed by at-home treatment with topical imiquimod 3 to 5 times a week for at least 8 weeks (reduced to 1-3 times a week in the maintenance phase). Mean number of cryotherapy sessions (range): 5.1 (2-11) Mean number of months using imiquimod (range): 7.8 (2-13) Additional treatments*: 5-FU twice a day for 2 weeks (4), elective circumcision (2), laser therapy (1) Mean f/up (range): 24 months (5-59)	**Clearance (within 6 months)** 2/8 [All did clear, however, mean time to clearance was 16 months (range 4-39)] **Sustained clearance (1 year)** 6/6 Other 2 f/up <1 year **Sustained clearance (2 years)** 5/5 Other 3 f/up <2 years	Two patients had concurrent SCC involving the rectal and anal skin. No patients exhibited signs of recurrence during f/up. *In addition, patients were advised to use concurrent hydrocortisone 2.5% cream, petroleum jelly, ketoconazole cream, and mupirocin ointment during the treatment period to decrease skin irritation.
Gaitanis G *et al.* Immunocryosurgery - an effective combinational	n=24* with SCC *in situ* 21 (with 24 lesions)	**Combination cryotherapy and imiquimod**	**Clearance (within 6 months)** 24/24	Attrition: *3 did not complete treatment (and

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
modality for Bowen's disease. *Dermatol Ther* 2016; **29**: 334-7. Retrospective, single centre (January 2009-December 2014), Greece. Funding: EU (European Regional Development FundERDF) and Greek national funds.	9 F: 12 M Mean age (SD): 74.4 (8.0) years Site: face/scalp (14), neck/trunk (6), arm (2), leg (2) Immunosuppressed: 1 Mean maximum diameter (range): 45.8 mm (9-200)	Imiquimod 5% cream was applied daily on lesion and a 5 mm rim around it in 5-week treatment cycles; cryotherapy (liquid N2 , open spray; 2 cycles, 15 second each) was performed at the end of the second week of each treatment cycle. Median f/up (range): 24 months (6-60)	**Sustained clearance at 1 year** 21/24 **Sustained clearance at 2 years** 12/12 Other 9 f/up <2 years **Sustained clearance at 5 years** 1/1 Other 20 f/up <5 years **Cosmetic outcome** Satisfactory even for extensive lesions (with the exception of hypopigmentation to a variable degree)	are not included in the baseline characteristics) All 21 lesions with diameter <80 mm cleared after one cycle, whilst the three tumours with a diameter ≥100 mm needed two treatment cycles for complete response
Gaitanis G *et al.* Cryosurgery during imiquimod cream treatment ("immunocryosurgery") for Bowen's disease of the skin: a case series. *Acta Derm Venereol* 2010; **90**: 533-4.	n=8 with 11 SCC *in situ* biopsy-proven lesions 5 F: 3 M Mean age (range): 71.9 years (52-87) Site: forehead (1), temple (2), mandible (1),	**Combination cryotherapy and imiquimod** Imiquimod 5% cream was applied daily on lesion and a 5 mm rim around it for a total of 5-9 weeks; at the clinic visit 2–3 weeks after starting imiquimod treatment cryotherapy (liquid N2, open	**Clearance (within 6 months)** 11/11 **Sustained clearance (1 year)** 5/5	Attrition: died from unrelated causes after 6 month f/up (2), lost to further f/up after 6 month f/up (1) No recurrences were observed during f/up

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Retrospective, single centre (January-December 2007), Greece. Funding: supported by Special Research Account Program, University of Ioannina, number 22195.	infraorbital (1), supraclavicular (1), thumb (1), carpal area (1), dorsal hand (2), tibia (1)	spray, two freeze-thaw cycles, including10–20 seconds each) was performed.	Other 3 f/up <1 year; 3 lost to f/up **Sustained clearance (2 years)** 2/2 Other 6 f/up <2 years	
Nguyen BT *et al.* Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ on the trunk and extremities with ablative fractional laser-assisted delivery of topical fluorouracil. *J Am Acad Dermatol* 2015; **72**: 558-60. Prospective, single centre, USA. Funding: None. Follow-up paper: Hsu SH *et al.* Ablative fractional laser-assisted topical fluorouracil for the treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ: a follow-up study. *Dermatol Surg* 2016; **42**: 1050-3.	n=28 including 16 *SCC in situ* lesions* Predominantly Caucasian men (Hsu (2016) reports all were Caucasian men) Mean age (range): 71 years (43-89) Site: trunk (14), arms (9), legs (6), hands/feet (1) Mean size: 1.56 cm^2 Inclusion criteria: lesions < 2 cm	**Ablative fractional laser-assisted delivery of topical fluorouracil** Single pass with the Ultrapulse carbon dioxide laser DeepFX handpiece at 0.12-mm spot size, 10 mJ per pulse, single pulse, 5% density, followed by a single application of topical 5-fluorouracil 5% under occlusion for 7 days. Mean f/up (range): 15 months (9-21)	**Clearance (within 6 months)** 16/16 **Recurrence at 1 year:** 1/12 (>9 months) **Adverse events – serious** None **Cometic outcome (all)** Better than before (23), same (7) **Convenience of treatment (all)** Easy/very easy	*14 superficial BCC Attrition: 6 patients were unable to follow-up (4 SCC *in situ* & 2 BCC): died (1), declined (1), moved away (2), withdrew to general debility (2) Cosmetic outcome reported in Hsu (2016) (1=worse, 2=same, 3=improved). Mean (SD): 2.75 (0.45) Convenience of treatment reported in Hsu (2016) (1=not easy, 2=somewhat easy, 3=very easy). Mean (SD): 2.94 (0.25) Cosmetic & convenience same in both papers but reported differently

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Sung JM *et al.* Photodynamic therapy with epidermal ablation using fractional carbon-dioxide laser in the treatment of Bowen's disease: A case series. *Photodiagnosis Photodyn Ther* 2017; **19**: 84-5. Prospective, single centre. Funding: None.	n=10 SCC *in situ* 3 F: 7 M Mean age (range): 63.3 years (48-77) Skin type: IV/V Site; trunk (1), buttock (1), finger (1), leg (6), scrotum (1)	**Combination ablative CO_2 fractional laser followed by PDT** Just before applying the topical photosensitizer, all lesions were treated with ablative CO_2 fractional laser, following the application of MAL and light exposure. 4 week interval between treatment sessions. Mean f/up (range): 12.4 months (3-29)	**Clearance (within 6 months)*** 8/10 1/10 after 1 PDT session 3/10 after 2 PDT sessions 2/10 after 3 PDT sessions 1/10 after 4 PDT sessions **Sustained clearance 1 year** 5 Other 4 f/up <1 year **Adverse events – serious** None **Cosmetic outcome** Favourable	Mean number of treatments to CR (SD): 3 (1.41) * One required 6 PDT sessions. No response in one. Histological confirmation was obtained for 7. Adverse events: minor Burning sensation and pain during light exposure (3)
Kim SK *et al.* Photodynamic therapy with ablative carbon dioxide fractional laser for treating Bowen disease. *Ann Dermatol* 2013; **25**: 335-9. Prospective, single centre, Korea. Funding: grant 2010-0022412 from the Ministry of	n=10 SCC *in situ* 5 F: 5 M Mean age (range): 61.9 years (35-80) Skin type: IV/V Site; face (4), trunk (1), extremities (4), penis (1)	**Combination ablative CO_2 fractional laser followed by PDT** Just before applying the topical photosensitizer, all lesions were treated with ablative CO_2 fractional laser, following the application of MAL and irradiation with red light. Mean f/up (range): 10.4 months (6-18)	**Clearance (within 6 months)*** 9/10 5/10 after 3 PDT sessions 4/10 after 4 PDT sessions **Sustained clearance 1 year** 3 Other 7 f/up <1 year **Adverse events – serious** None	Mean number of treatments to CR (SD): 3.7 (1.7) *Penile shaft lesion required 8 treatment sessions. Histological confirmation was obtained for 8, the other 2 refused skin biopsy No recurrences during f/up.

Study/ design	Population	Intervention: combination	Outcomes	Comments & additional data not in usable format
Education, Science, and Technology.			**Cosmetic outcome** Favourable	
			Treatment tolerability Generally well tolerated, except for some mild burning sensation during the procedure	
Liu D *et al.* Simple shaving combined with photodynamic therapy for refractory bowen disease. *Photodiagnosis Photodyn Ther* 2019; **26**: 258-60. Prospective, single centre, China. Funding: None, but supported by the National Natural Science Foundation of China (grant number 81430075).	n=10 with 44 advanced* SCC *in situ* lesions 3 F: 7 M Mean age (range): 62 years (46-81) Site: tempus (4): face (3), abdomen (1), waist (1), trunk (1)	**Combination simple shaving and PDT** After local anaesthesia, the lesions were shaved once *in situ* as deep as the superficial dermal layer, before the first PDT session. ALA-PDT 3 sessions at 1-week intervals. F/up: At least 12 months	**Clearance (within 6 months)** 44/44	*>30 mm in diameter, with unclear boarders, ulcers, multiple occurrences and those on the face and neck unsuitable for extended resection by surgery. **DLQI (SD)** Mean baseline: 21.20 (2.348) 12 months: 4.70 (2.058) Average healing time was 10.4 days.
			Sustained clearance at 1 year 44/44	
			Quality of life: change in DLQI at 12 months f/up t test=25.909: $p<0.001$	
			Cosmetic outcome 12 weeks: Good 6 months: Excellent 12 months: Better than at 6 months	
			Treatment tolerability Mean VAS score for pain was 3.1 points (mainly mild).	

Follow-up

Reference	Clearance (lesions)	Follow-up	Recurrence (lesions)	Progression
Hassan I, *et al. Iran J Dermatol* 2014; **17**: 101-3.	Surgical excision: 12/12	1 year	Surgical excision 0/12	
Ahmed I, *et al. Br J Dermatol* 2000; **143**: 759-66	Cryotherapy: 36/36 (2 not healed) C&C: 44/44 (1 not healed)	2 years	Cryotherapy: 13/36 C&C: 4/44	
Patel GK, *et al. J Am Acad Dermatol* 2006; **54**: 1025-32.	Topical imiquimod: 11/15 Placebo cream: 0/16	9 months	Topical imiquimod: 0/11 Placebo cream: N/A	Placebo cream: 2/16 progression to early invasive SCC
Morton CA, *et al. Br J Dermatol* 1996; **135**: 766-71.	PDT: 20/20 Cryotherapy: 16/20	12 months (2 monthly intervals)	PDT: 0/20 Cryotherapy: 2/16	
Morton, C. *et al. Arch Dermatol* 2006; **142**: 729-735.	MAL-PDT: 103/124 Cryotherapy: 73/91 Topical 5-fluorouracil 24/36 Placebo-PDT: 4/19	12 months	MAL-PDT: 15/103 Cryotherapy: 15/73 Topical 5-fluorouracil: 4/24 Placebo: 2/4	
Salim, A. *et al. Br J Dermatol* 2003; **148**: 539-43.	ALA-PDT: 29/33 Topical 5-fluorouraci: 22/33	12 months	ALA-PDT: 2/29 Topical 5-fluorouracil: 6/22	
Morton CA, *et al. Br J Dermatol* 2000; **143**:767-72.	ALA-PDT (red): 30/32 ALA-PDT (green): 21/29	12 months	ALA-PDT (red): 2/30 ALA-PDT (green): 7/21	
Alique-Garcia S, *et al. Photodiagnosis Photodyn Ther* 2019; **28**: 192-4.	ALA-PDT: 48/55 MAL-PDT: 104/136	12 months	ALA-PDT: 1/48 MAL-PDT: 29/104	
de Haas ERM, *et al. Arch Dermatol* 2007; **143**: 264-5.	PDT (single illumination): 20/25 PDT (2-fold illumination): 22/25	12 months	PDT (combined): 2/42	
Ko DY, *et al. Br J Dermatol* 2014; **170**: 165-72.	ER:YAG AFL-PDT: 29/32 MAL-PDT: 18/26	12 months	ER:YAG AFL-PDT: 2/29 MAL-PDT: 5 or 6/18	
Kim HJ, *et al. J Am Acad Dermatol* 2018; **79**: 860-8.	AFL-MAL-PDT: 43/46 MAL-PDT: 29/38	5 years	AFL-MAL-PDT: 4/43 MAL-PDT: 12/29	
Wu Y, *et al. Dermatol Surg* 2018; **44**: 1516-24.	PBN-ALA-PDT: 16/21 ALA-PDT: 17/22	12 months	PBN-ALA-PDT: 0/16 ALA-PDT: 2/17	
Cai H, *et al. Lasers Med Sci* 2015; **30**:1505-10.	Combination ALA-PDT + CO_2: 8/11 CO_2: 7/11	6 months	Combination ALA-PDT + CO_2: 1/8 CO_2: 5/7	
Genouw E, *et al. J Eur Acad Dermatol Venereol* 2018; **32**: 1897-905.	Combination CL-CO_2 + MAL-PDT: 4/6 Combination FL-CO_2 + MAL-PDT: 4/6	12 months	Combination CL-CO_2 + MAL-PDT: 0/4 Combination FL-CO_2 + MAL-PDT: 0/4	

Q2 Rates of cancer

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Jansen MH, *et al.* Bowen's disease: long-term results of treatment with 5-fluorouracil cream, photodynamic therapy or surgical excision. *Acta Derm Venereol* 2018; **98**: 114-5. Retrospective, single centre (January 2008-December 2013), The Netherlands. Funding: No details given.	n=608 with 841 SCC *in situ* lesions 347 F: 261 M Mean age (SD): 73 years (10.8) Immunosuppressed: 72 Site: Head neck region (298), ear (32), upper extremities (164), lower extremities (205), trunk (142) Size: ≤10 mm (497), 11-≤30 mm (240), >30 mm (10), unknown (94) Inclusion criteria: Histological confirmation of SCC *in situ* Exclusion criteria: SCC *in situ* on genitalia/mucous membranes or lesions found nearby an invasive skin cancer.	**Surgical excision** (241 with 288 lesions) **PDT** (296 with 450 lesions) **Topical 5-FU** (46 with 72 lesions) **Other (cryotherapy, topical imiquimod or curettage)** (25 with 31 lesions) Median f/up (range): 18 months (0-87)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** 8 progressed into an invasive SCC 3-42 months post-treatment Surgical excision:0 PDT: 7 Topical 5-FU: 1	* Numbers quoted in the paper surgical excision (296) & PDT (241) are incorrect. Numbers are taken from table in supplementary that gives baseline details has surgical excision (241) & PDT (296), these agree with denominator required to give correct percentage progression for PDT.
Overmark M *et al.* Retrospective study of treatment of squamous cell carcinoma in situ. *Acta Derm Venereol* 2016; **96**: 64-7.	n=239 with 263 SCC *in situ* lesions 136 F: 103 M Mean age (range): 77 years (35-97) Site: head & neck (70%), trunk (10%), upper	**Surgical excision** (125) Excision margins ≥2 mm **Cryotherapy** (64) 2 freeze-thaw cycles after curettage **PDT (**74)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** Surgical excision*: 1 SCC Cryotherapy: 2 SCC	At time of biopsy 146 had other skin malignancies or premalignant lesions. Surgery was used on the trunk (65%) more often than on other body sites. PDT was most often used on the lower extremities (54%). It is likely that larger and

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Retrospective, single centre (January-December 2006), Finland. Funding: No details given.	extremities (11%), lower extremities (10%) Immunosuppressed: 44 **Previous skin cancer**: 136 (AK (106), SCC *in situ* (68), SCC (30), BCC (85), malignant melanoma (4)) Inclusion criteria: histologically confirmed lesions. Exclusion criteria: patients whose diagnosis was changed after treatment to invasive skin malignancy or who had refused treatment.	Two MAL-PDT sessions 7-14 days apart Mean f/up (range): 66 months (2-93). 124 patients died during this period of causes unrelated to the skin cancer.	PDT: 3 SCC Treatment: surgical excision (5), patient died before treatment (1)	more indurated lesions in this area were treated with PDT due to contraindications to surgery and cryotherapy. * Excision margin 4.5 mm
Hansen JP, *et al.* Bowen's Disease: a four-year retrospective review of epidemiology and treatment at a university center. *Dermatol Surg* 2008; **34**: 878-83. Retrospective, single centre (January 1999-January 2003), USA. Funding: None.	n=299 with 406 SCC *in situ* (399 primary, 7 recurrent) 106 F: 193 M Mean age (range): 69.8 years (33-99) Site: Scalp (17), ear (59), forehead/temple (50), cheek (44), eyelid (6), lips (5), nose (12), neck (26), anterior trunk (33), back (14), upper extremity (110), lower extremity (30) Exclusion criteria: Tumour associated with human papillomavirus, found on mucous membranes or genitalia or found within or at	**Surgical excision(elliptical)** (109) Mean f/up (range): 31.5 months (2-70) **Mohs micrographic surgery** (83) Mean f/up (range): 26.3 months (2-66) **Shave excision** (79) Mean f/up (range): 33.4 months (4-72) **Punch excision** (14) Mean f/up (range): 28.6 months (2-75)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** One invasive SCC	**Recurrence (histological) 15/406** Elliptical excision: 3/109 Mohs micrographic surgery: 2/83 Shave excision: 5/79 Curettage and fulguration: 2/46 Cryotherapy: 2/24 Topical 5-FU: 1/24

Study/ design	Population	Intervention	Outcomes	Comments & additional data
	the margins of an invasive skin malignancy	**Curettage and fulguration** (46) Mean f/up (range): 28.7 months (3-71) **Curettage** (3) Mean f/up (range): 28.7 months (12-37) **Cryotherapy** (24) Mean f/up (range): 30.7 months (4-75) **Electrodesiccation** (16) Mean f/up (range): 28.3 months (10-53) **Topical 5-FU** (24) Mean f/up (range): 23.6 months (2-52) **Topical imiquimod** (6) Mean f/up (range): 10 months (3-17) **Not recorded** (2) Mean f/up (range): 28.6 months (2-75)		
Drake AL, *et al.* Variations in presentation of squamous cell carcinoma in situ (Bowen's disease) in immunocompromised patients. *J Am Acad Dermatol* 2008; **59**: 68-71.	n=299 with 407 SCC *in situ* 106 F: 193 M Mean age (range): 69.8 years (30-99) Immunocompromised: 57*	**Surgical excision** Mean f/up: 35 months	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment**	*Including 43 organ transplant recipients, 7 patients with acute and chronic leukemia, and 6 patients with immune-suppressing infections or autoimmune disease **Recurrence** 11

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Retrospective, single centre (January 1999-January 2003), USA. Funding: None	Mean diameter (SD): 11mm (9) Site: Normal immune function: head/neck (176), trunk (27), extremities (98) Immunocompromised: head/neck (43), trunk (20), extremities (62)		One invasive SCC in immunocompromised patient NB: same centre as Hansen JP *et al. Dermatol Surg* 2008; **34**: 878-83 so could be same patient.	Immunocompromised: 5 Normal immune function: 6
Hugo NE, *et al.* Bowen's disease: Its malignant potential and relationship to systemic cancer. *Plast Reconstr Surg* 1967; **39**: 190-4. Retrospective, single centre (September 1932- June 1965), USA. Funding: No details given.	n=38 SCC *in situ* 19 F: 19 M Mean age: 62.4 years Inclusion criteria: histological diagnosis of SCC *in situ*	**Surgical excision** (34) **Electrodesiccation** (2) **X-radiation** (1) **No treatment** (1)	**Incidence of progression outside original location of previous SCC *in situ*** Surgical excision: 1/34 metastatic spread of SCC *in situ* to the glands of the left inguinal area at 15 months* **Incidence of malignancy** 5† 1 bronchogenic carcinoma (7 years later) 1 carcinoma of the bladder (5 years later)	*radical resection of the inguinal nodes. Several more SCC in situ on the legs excised 7 years later. Lymphatic metastases in the right inguinal area (SCC). Radical resection of the right inguinal nodes. Died of widespread metastases 1 year later. †In all cases there was no relationship between time of appearance of the SCC *in situ* and the diagnosis of the systemic cancer. In the other 3 (bronchogenic carcinoma, carcinoma of the colon and lymphosarcoma) both diseases manifested themselves within 1 year of each other, but no details of which occurred first.
Young LC *et al.* Mohs' micrographic surgery as treatment for squamous dysplasia of the nail unit. *Australas J Dermatol* 2012; **53**: 123-7.	n=13 with 14 squamous dysplasia of the nail unit (including 11 SCC *in situ*)* 4 F: 7 M Mean age (range): 49.9 years (32-75)	**Mohs micrographic surgery** Mean f/up (range): 45.8 months (6-120)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment**	* Bowenoid actinic keratosis (1), SCC (2) †Previous treatment: cryotherapy, topical imiquimod, topical 5-fluorouracil, photodynamic therapy and surgical excision.

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Retrospective, single centre (2000-2010), Australia. Funding: No details given.	Site: thumb (3), 2nd (2), 3rd (4), 4th (1), 5th (1) Recurrent: 8†		1 invasive SCC (30 months)	No complications, e.g. wound infection were documented. Metastases were not demonstrated in any.
Lee KC *et al.* Characteristics of squamous cell carcinoma in situ of the ear treated using Mohs micrographic surgery. *Dermatol Surg* 2012; **38**: 1951-5. Retrospective, single centre (2005-2011), USA. Funding: No details given.	n= 73 SCC *in situ* of the ear 9 F: 163 M Mean age: 71 years Recurrent: 13* Site: left (93), right (73) Mean initial size (range): 1.2cm^2 (0.21-13 cm^2)	**Mohs micrographic surgery**	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** No tumours in this study required further systemic examination for metastatic disease, nor did any tumours demonstrate perineural invasion**.**	*Previous treatment: cryotherapy or topical modalities, e.g., 5-fluorauracil The study did not collect data on recurrent SCCs of SCC *in situ* of the ear.
Bell HK, Rhodes LE. Bowen's disease--a retrospective review of clinical management. *Clin Exp Dermatol* 1999; **24**: 338-9. Retrospective, comparative (January 1995-January 1996), UK. Funding: None. F/up: From June 1995-July 1997 the patients made up to eight visits (median four)	n=68 with 92 SCC *in situ* lesions Ratio: 2.7 F: 1 M Median age (range): 71 (40-100) Lower leg (73%)	**Curettage with cautery** (22%) **Cryotherapy** (34%) **Topical 5-FU** (12%) 15 patients received more than one of these treatments and three received all three **Excision** (3 patients) **Radiotherapy** (1 patient)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** 1 invasive SCC*	For those patients who received a single treatment modality clearance rates were: curettage and cautery 93%, 5FU 87%, cryotherapy 61% *No recurrence with either curettage with cautery or 5FU

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Holt PJ. Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol* 1988; **119**: 231-40. Retrospective, single centre (1981-1986), UK. Funding: No details given.	n=301 with 395 NMSC including 85 with 128 SCC *in situ** Site: scalp (2), temple (6), ear helix (1), mastoid (2), forehead/eyebrows (3), cheek (3), nose (4), lower lip (2), neck (1), back (4), glans penis (1), arm (3), forearm (3), hand/fingers (19), thin (3), calf/shin (70), foot (1)	**Cryotherapy** Single freeze-thaw cycle, with a freeze time of 30 seconds. Tumours of the head and neck usually healed within 4-6 weeks, cosmetic results were outstanding. Hand and fingers healed in a similar fashion. Lesions on the calf and shin healed more slowly, sometimes taking 6 months. F/up range: 6 months – 5.5 years	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** One recurrence at 6 months, excised, reported as showing islands of SCC in the dermis with no overlying epidermal change. **Incidence of malignancy** Hypertrophic scar 20x7 mm traversing the treatment field. Flatted over next 7 months except at one pole where a nodule persisted which became exquisitely tender. Excised, histology showed changes of a traumatic neuroma.	Attrition: 24 lost to follow-up post 1985 (last seen after 18-36 months f/up no recurrences) *174 with 225 BCC, 34 SCC, 8 keratoacanthoma
Dave R, *et al.* Treatment of Bowen's disease with carbon dioxide laser. *Lasers Surg Med* 2003; **32**: 335. Prospective, single centre, UK. Funding: No details given. Lasers Surg Med (Suppl 13) 2001;53	n=16 with 25 biopsy proven SCC *in situ* on the legs	**CO_2 laser** F/up: 6 months	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** 3 have been referred back with SCC within 12 months of discharge from f/up	Clearance 100%, no recurrence at 6 month f/up

Study/ design	Population	Intervention	Outcomes	Comments & additional data
van Bezooijen BP *et al.* Laser therapy for carcinoma in situ of the penis. *J Urol* 2001; **166**: 1670-1. Retrospective, single centre (1986-2000), The Netherlands. Funding: No details given.	n=19 SCC *in situ* of the penis Mean age (range): 52 years (21-86)	**Neodymium: YAG** (1986-93) (7) or **CO_2 laser** (1994-2000) (12) Mean f/up (range): 32 months (1-95)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** Infiltrating carcinoma (1) at 6 years	Treated with partial penile amputation and sentinel node procedure
Ratour-Bigot C *et al.* Squamous cell carcinoma following photodynamic therapy for cutaneous bowen's disease in a series of 105 patients. *Acta Derm Venereol* 2016; **96**: 658-63. Retrospective, single centre (2007-2013), France. Funding: No details given.	n=105 with 151 SCC *in situ* 64 F: 41 M Median age (IQR): 75 years (63-81) Immunocompromised: 25 Site: head & neck area (59), trunk (20), upper limbs (34), lower limbs (37) Prior history of SCC: 35	**PDT** Median sessions (range): 2 (1-6) Median f/up (IQR): 14 months (6-30)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment*** SCC (16 with 19 lesions: single (11), 2 (5), 4 (1), 5 (1), 7 (1)) † Immunocompromised: 8 Prior history of SCC: 8 **Incidence of progression outside original location of previous SCC *in situ*** SCC (16 with 48 lesions: single (8), 2 (3), 4 (1), 6 (2), 8 (1), 10 (1))† Immunocompromised: 5 Prior history of SCC: 12	*Many of the patients were at risk of SCC and the possibility that the lesion had mixed histology at baseline cannot be excluded. 7 developed SCC both on PDT field and outside field. Median time to development of 1st SCC on a PDT field after 1st PDT session (IQR) was 6.0 months (2.7-11.8) and outside field after 1st PDT session (IQR) was 10.3 months (4.3-21.1). †On PDT field, invasive (30), microinvasive (7): outside field, invasive (34), microinvasive (12) histology not available (2)

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Lukas VanderSpek LA *et al.* Radiation therapy for Bowen's disease of the skin. *Int J Radiat Oncol Biol Phys* 2005; **63**: 505-10. Retrospective, single centre (April 1985-November 2000), Canada Funding: No details given	n=44 with SCC *in situ* 15 F: 29 M Mean age (SD): 67.7 (14.5) years Site: scalp (9), face (12), trunk (6), extremity (12), perianal (3), penis (2) Median size (range): 2.65 cm^2 (0.07-34.56) Immunosuppressed: 10 Previous skin cancer (RT/no RT): 10/5 Exclusion criteria: Patients with an incidental diagnosis of SCC in situ that was not treated but who had concurrent, nonrelated cancer that was treated.	**Radiotherapy (primary therapy)** (32) **Radiotherapy (residue disease after local ablative therapy or incomplete excision)** (12†) Orthovoltage X-rays (39) Electrons (3); Cobalt (2). There was no standard fractionation regimen; high dose (24), low dose (20) Median f/up (range): 30 months (0-148)	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** 2 SCC‡ **Incidence of progression outside original location of previous SCC *in situ*** Four patients experienced a new squamous skin lesion at a distant site, including one on the cheek‡	*Attrition: 2 lost to f/up †Previous adjuvant treatment: topical creams (7), excision (2), cryotherapy (2), curettage and electrodesiccation (1) ‡One had been diagnosed simultaneously with SCC and SCC *in situ* at different sites initially and metastatic disease was found at other sites at approximately the same time as the marginal SCC recurrence.
Patel GK, *et al.* Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2006; **54**: 1025-32. Double-blind RCT, out-patients department, UK. Funding: unrestricted research grant 3M Healthcare Ltd.	n=31 with biopsy-proven cutaneous SCC *in situ* one lesion was treated Topical 6 F: 9 M Mean age (range): 74 years (54-83) Mean size (SD): 429 (489) mm Placebo 14 F: 2 M Mean age (range): 74 years (60-86)	**Topical imiquimod** (15) Lesion was cleaned with tap water and dried before application of imiquimod 5% cream daily at night for 16 weeks. **Placebo (vehicle cream)** (16) Same regimen	**Incidence of any keratinocyte cancer (at location of previous SCC in situ) in studies with a follow-up of ≥ 6 months since treatment** 2 on the placebo arm had progression to early invasive SCC	Clearance rates were imiquimod 73%, placebo 0%

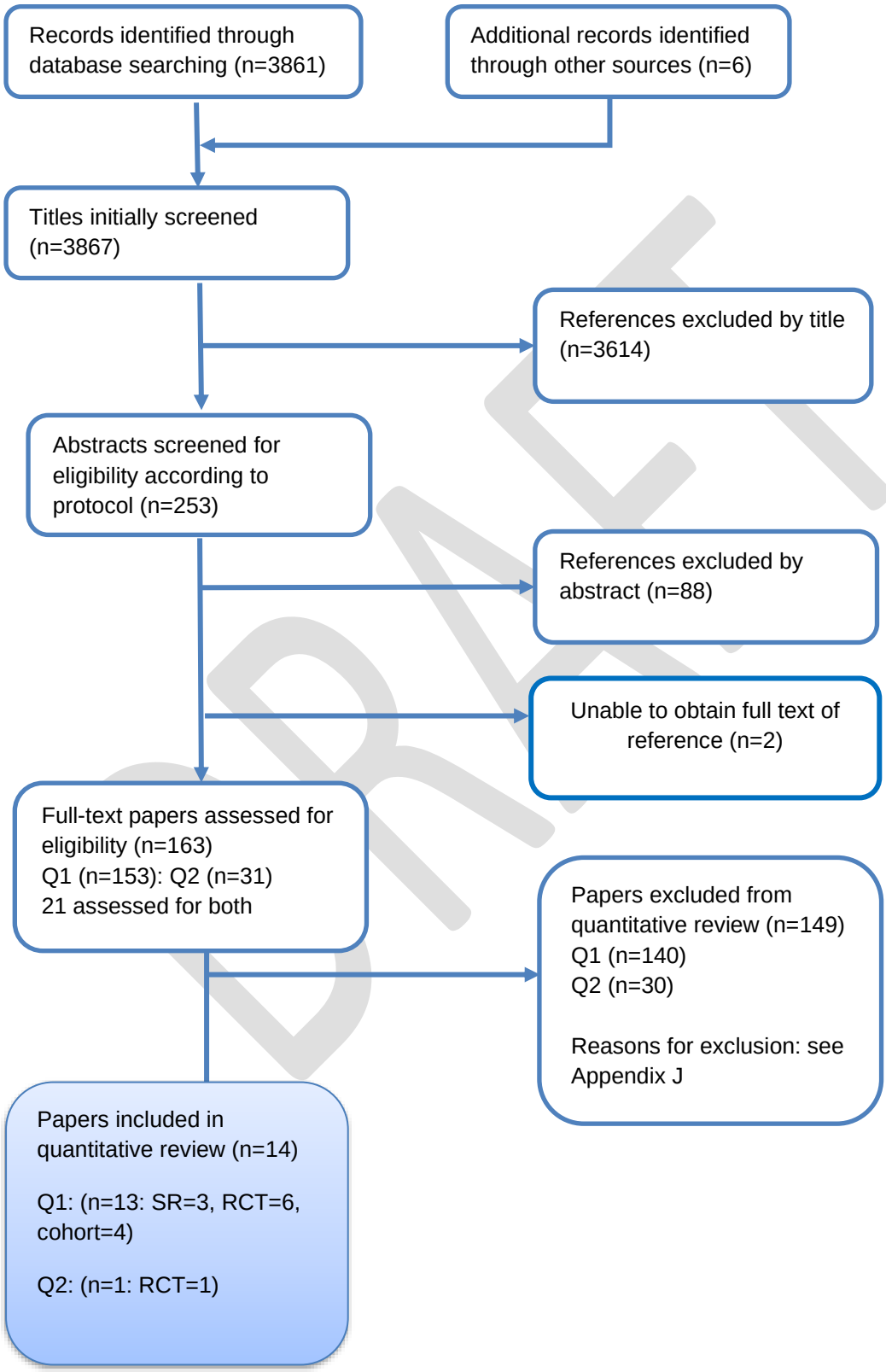
Study/ design	Population	Intervention	Outcomes	Comments & additional data
F/up: 9 months	Mean size (SD): 248 (166) mm Inclusion criteria: Adults, with a post-biopsy lesion of ≥ 1 cm^2 and ≤ 20 cm^2. A lease 1 cm away from the eye. Exclusion criteria: History of immunosuppression, organ transplantation or psoriasis.			
Jaeger AB *et al.* Bowen disease and risk of subsequent malignant neoplasms: a population-based cohort study of 1147 patients. *Arch Dermatol* 1999; **135**: 790-3. Retrospective, single centre (1978-1993), Denmark. Funding: supported by grants from the Grosserer L. F. Foghts Foundation, the Danish Medical Research Council, and the Danish Cancer Society (grant 96-100-17).	n=1147 SCC *in situ* 703 F: 444 M Mean age (range): 73 years (20-99) Site: face, head & neck (461), trunk (162), upper extremities (218), lower extremities (198), multiple (81), not specified (27)	Mean f/up: 4.7 years (2465 person years)	**Incidence of any keratinocyte cancer (at location of previous SCC *in situ*) in studies with a follow-up of ≥ 6 months since treatment** 83 NMSC F: 38 (SIR 3.7: 95% CI 2.6-5.1) M: 45 (SIR 5.0: 95% CI 3.7-6.7) **Incidence of malignancy** 115 F: 51 (SIR 0.9: 95% CI 0.7-1.2) M: 64 (SIR 1.3: 95% CI 1.01-1.7)	Patients diagnosed as having SCC *in situ* <60 years, particularly men, appeared to be at higher risk of NMSC than those diagnosed as having SCC *in situ* ≥60 years. Also, an excess of lung cancer was restricted to men diagnosed as having SCC *in situ* <60 years (SIR = 4.6; n = 5). All cases of leukaemia occurred in patients diagnosed as having SCC *in situ* <60 years. Incidence of melanoma 3 F (SIR 2.6: 95% CI 0.5-7.7)

Study/ design	Population	Intervention	Outcomes	Comments & additional data
Kovács A *et al.* Bowen's disease: statistical study of a 10 year period. *J Dermatol* 1996; **23**: 267-74. Retrospective, single centre (January 1984-December 1993). Funding: Not known.	n=74 SCC *in situ* 38 F: 36 M Mean age: 66.8 years Multiple lesions: 15 Site: sun-exposed areas (head, neck and hands) (1/5th)	Not stated in abstract	Invasive carcinomas developing from SCC *in situ* (8) 63.3% lenticular type	Unable to get full text – done from abstract Other associated malignant tumours (3), other benign skin lesions (13)
Graham JH *et al.* Bowen's disease and its relationship to systemic cancer. *AMA Arch Derm* 1959; **80**: 133-59. Retrospective, single centre, USA. Funding: No details given.	n=35 with 48 SCC *in situ* lesions (via autopsy or were known to have died) 3 F: 32 M Mean age (range): 54 years (38-87) Caucasian (35) Site: head (21), neck (1), trunk (6), extremities (14), pelvic region (6)	**Surgical excision (1st line)** Mean duration of lesions from onset to surgery (range): 7.8 years (5 months-30 years)	**Incidence of any keratinocyte cancer (not clear if same site) in studies with a follow-up of ≥ 6 months since treatment** Senile keratosis: 1 (at 7 years) SCC: 2 (at 5 & 10 years) BCC: 2 with 3 lesions (at 8, 12 & 14 years) Sweat-gland carcinoma (3 years) **Incidence of malignancy** Impossible to work out, 28 had an internal cancer at some point, some were only found at autopsy.	18 had a number of other premalignant and malignant cutaneous lesions: SCC (15), senile keratoses (10), BCC (10), SCC occurring in senile keratosis (3), malignant melanoma (2), adenoacanthoma (1), sweat-gland carcinoma (1), adnexal carcinoma (1). Only 6 were confirmed to occur >1 year after diagnosis of SCC *in situ* (2 unknown, 3 unconfirmed prior cutaneous cancer, 8 concurrently-within 1 year) 31 (89%) of the patients had primary cancer in one or more locations.

Info only

Study/ design	Population	Intervention & Comparator	Outcomes	Comments & additional data
Eimpunth S, *et al.* Squamous Cell Carcinoma In Situ Upstaged to Invasive Squamous Cell Carcinoma: A 5-Year, Single Institution Retrospective Review. *Dermatol Surg* 2017; **43**: 698-703. Retrospective, single centre (March 2007-February 2012), USA. Funding: No details given.	n=395 with 566 SCC *in situ* lesions 202 F: 364 M Mean age (range): 68.7 years (35-99) Immunosuppressed: 240 Site: forehead and cheek (215), ear, nose, lips and eyelids (102), scalp and neck (98) body (151) Size: 0-10 mm (293), 11-20 mm (206), >20 mm (67)	**Mohs micrographic surgery**	**Upstaged to invasive SCC:** 92	**Confirmed SCC in situ:** 474
Knackstedt TJ *et al.* Frequency of squamous cell carcinoma (SCC) invasion in transected SCC in situ referred for Mohs surgery: The Dartmouth-Hitchcock experience. *Int J Dermatol* 2015; **54**: 830-3. Retrospective, single centre (January-December 2012), USA. Funding: No details given.	n=51 with biopsy-proven transected SCC *in situ* Mean age: 73 years Mean preoperative tumour area; SCC *in situ* (SD):0.68 cm^2 (0.61) & 1.02 cm^2 (0.58) invasive SCC Site: H-zone (25), lower lip (8), cheek/forehead (16), high-risk hand/foot (2)	**Mohs micrographic surgery**	**Upstaged to invasive SCC:** 5 Invasive SCC (3), SCC highly suspicious for invasion (2)	

Appendix H: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram – study selection



Appendix I: Critical appraisal of included systematic reviews – AMSTAR2

Drucker, A. M. J Am Acad Dermatol 2020.[3]	Bath-Hextall, F. J. Cochrane Database Syst Rev 2013.[2]	Love, W. E. Arch Dermatol 2009.[4]
1. Did the research questions and inclusion criteria for the review include the components of PICO?		
Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
Yes, CRD42016043353	Partial, Yes	Partial, Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
Yes	Yes	No
4. Did the review authors use a comprehensive literature search strategy?		
Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?		
6.		
Yes	Yes	Yes
7. Did the review authors perform data extraction in duplicate?		
One reviewer extracted, a second verified extractions	Yes	Yes
8. Did the review authors provide a list of excluded studies and justify the exclusion?		
Yes (Appendix B to full report)	Yes	No
9. Did the review authors describe the included studies in adequate detail?		
Yes (Appendices C, D, E, G, I to full report)	Yes	Partial Yes
10. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
Yes (Appendix F to full report)	Yes	No
11. Did the review authors report on the sources of funding for the studies included in the review?		
Yes (Appendix C to full report)		No
12. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		
Yes	No meta-analysis conduced	No meta-analysis conducted
13. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
Yes (in full report)	No meta-analysis conduced	No meta-analysis conduced
14. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?		

Drucker, A. M. J Am Acad Dermatol 2020.[3]	Bath-Hextall, F. J. Cochrane Database Syst Rev 2013.[2]	Love, W. E. Arch Dermatol 2009.[4]
Yes (in full report)	Yes	No
15. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		
Yes (in full report)	Yes	No
16. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?		
No	No meta-analysis conducted	No meta-analysis conducted
17. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?		
Yes	Yes	Yes

Appendix J: Papers excluded from quantitative analysis

Q1: Interventions

Reference	Reasons for exclusion
Aguilar, M. J Eur Acad Dermatol Venereol 2010, 24: 1431-1436.	Economic assessment of the treatment of sNMSC (sBCC and SCC *in situ*) results not reported separately
Aguilar-Bernier, M. Photodermatol Photoimmunol Photomed 2019, 35: 208-213.	Higher quality evidence available
Alessi, S.S. Clinics (San Paulo) 2009, 64: 961-6.	Non-comparative (n=13 lesions): See Appendix G
Alnajjar, H. M. Eur Urol 2012, 62: 923-928.	Non-comparative (n=44): See Appendix G
Anderson, F. E. Med J Aust 1969, 2: 385-388.	Included in Love, Arch Dermatol (2009)
Andersson, L. Scand J Urol Nephrol 1967, 3: 303-306.	Too few patients (n=2)
Arlette, J. P. Br J Dermatol 2003, 149 Suppl 66: 43-49.	Too few patients (n=5)
Attili, S. Br J Dermatol 2009, 161: 170-3.	Higher quality evidence available
Axcrona, K. Scand J Urol Nephrol 2007, 41: 507-510.	Higher quality evidence available
Bardazzi, F. J Am Acad Dermatol 2005, 52: 1102-1104.	Non-comparative (n=15): See Appendix G
Bargman, H. J Cutan Med Surg 2003, 7: 101-105.	Included in Love, Arch Dermatol (2009)
Bath-Hextall, F. J. Cochrane Database Syst Rev 2008.	Superceeded by Bath-Hextall (2013)
Belisario, J. C. Cutis 1970, 6: 401-412.	No raw data: high cure rate reported
Bell, H. K. Clin Exp Dermatol 1999, 24: 338-9.	Retrospective (n=68 with 92 lesions), data not in extractable format
Blank, A. A. Dermatologica 1985, 171: 89-94.	Non-comparative (n=52): See Appendix G
Britton, J. E. Br J Dermatol 2005, 153: 780-784.	Higher quality evidence available
Caccialanza, M. J Am Acad Dermatol 1999, 41: 589-94.	Non-comparative (n=62): See Appendix G
Caccialanza, M. Skin Cancer 1993, 8: 115-118.	Unable to obtain full text
Cai, H. Lasers Med Sci 2015, 30: 1505-10.	Included in Drucher, J Am Acad Dermatol (2020)
Cairnduff, F. Br J Cancer 1994, 69: 605-608.	Higher quality evidence available
Calzavara-Pinton, P. G. Br J Dermatol 2008, 159: 137-144.	Higher quality evidence available
Cavicchini S. Int J Dermatol 2011, 50: 1002-5.	Higher quality evidence available
Chung, Y. L. Eur J Nucl Med 2000, 27: 842-846.	Non-comparative (n=8): See Appendix G

Clayton, T. H. Eur J Dermatol 2006, 16: 39-41.	Higher quality evidence available
Covadonga Martinez-Gonzalez, M. J Dermatolog Treat 2008, 19: 293-299.	Non-comparative (n=44 with 49 lesions): See Appendix G
Dave, R. Lasers Surg Med 2003; 32: 335.	Non-comparative (n=16): See Appendix G
de Haas, E. R. M. Arch Dermatol 2007, 143: 264-5.	Included in Bath-Hextall, Cochrane Database Syst Rev (2013)
Deen, K. Australas J Dermatol 2017, 58: 86-92.	Not systematic, checked for additional references, none Identified
Dijkstra, A. T. J Eur Acad Dermatol Venereol 2001, 15: 550-554.	Higher quality evidence available
Downs, A. M. R. Br J Dermatol 2009, 161: 189-190.	Higher quality evidence available
Dragieva, G. Transplantation 2004, 77: 115-121.	Too few patients (n=4)
Drake, A. L. J Am Acad Dermatol 2008, 59: 68-71.	Non-comparative (n=299): See Appendix G
Drexler, I. Eur J Dermatol 1997, 7: 427-431.	Non-comparative (n=10): See Appendix G
Drug Ther Bull 2009, 47: 113-6.	Not systematic, checked for references none identified
Dupree, M. T. J Am Acad Dermatol 2001, 45: 401-404.	Non-comparative (n=11): See Appendix G
Eimpunth, S. Dermatol Surg 2017, 43: 698-703.	No outcomes of interest, looking at upstaging
Fader, F. J. Dermatol Surg 2002; 28: 97-99.	Too few patients (n=3)
Gaitanis, G. Acta Derm Venereol 2010, 90: 533-534.	Non-comparative (n=8): See Appendix G
Gaitanis, G. Case Rep Dermatol Med 2018, 2018: 9423949.	Too few patients (n=4)
Gaitanis, G. Dermatol Ther 2016, 29: 334-337.	Non-comparative (n=24): See Appendix G
Genouw, E. J Eur Acad Dermatol Venereol 2018, 32: 1897-1905.	Within-patient RCT (n=6 lesions): See Appendix F
Goldberg, L. H. Dermatol Surg 2011, 37: 858-861.	Case report
Gomez, C. Photodiagnosis Photodyn Ther 2019, 26: 295-299.	Higher quality evidence available
Gordon, K. B. Dermatol Surg 1996, 22: 723-728.	Too few patients (n=5)
Gracia-Cazana, T. Acta Derm Venereol 2018, 98: 116-118.	Higher quality evidence available
Graham, J. H. AMA Arch Derm 1961, 83: 738-58.	When recurrence occurred not stated
Gupta, G. Br J Dermatol 1999, 141: 385-386.	Higher quality evidence available
Haddad, R. Photodiagnosis Photodyn Ther 2004, 1: 225-230.	Higher quality evidence available
Hambly, R. Br J Dermatol 2017, 177: e55-e57.	Higher quality evidence available

Hansen, J. P. Dermatol Surg 2008, 34: 878-883.	Non-comparative (n=299): See Appendix G
Hassan, I. Iran J Dermatol 2014, 17: 101-103.	Non-comparative (n=12): See Appendix G
Herman, J. M. Radiother Oncol 2008, 88: 398-402.	Non-comparative (n=9): See Appendix G
Hill, T. G. Plast Reconstr Surg 1987, 79: 1008.	Letter reply to Koyama (1987) no raw data
Hirata, Y. J Dermatol 2011, 38: 748-754.	Higher quality evidence available
Hiruma, M. J Am Acad Dermatol 2000, 43: 1070-1075.	Non-comparative (n=8): See Appendix G
Holt, P. J. Br J Dermatol 1988, 119: 231-240.	Non-comparative (n=85): See Appendix G
Honeycutt, W.M. Arch Dermatol 1973, 198: 670-2.	Non-comparative (n=52): See Appendix G
Hsu, S. H. Dermatol Surg 2016, 42: 1050-1053.	Follow-up of Nguyen (2015): See Appendix G
Hugo, N. E. Plast Reconstr Surg 1967, 39: 190-194.	Non-comparative (n=38): See Appendix G
Humphreys, T. R. Arch Dermatol 1998, 134: 1247-1252.	Non-comparative (n=13): See Appendix G
Ibbotson, S. H. Photodermatol Photoimmunol Photomed 2012, 28: 235-9.	Higher quality evidence available
Jansen, G. T. South Med J 1967, 60: 185-188.	Non-comparative (n=13): See Appendix G
Jansen, M. H. Acta Derm Venereol 2018, 98: 114-115.	Non-comparative (n=608): See Appendix G
Jones, C. M. J Am Acad Dermatol 1992, 27: 979-982.	Higher quality evidence available
Kim, S. K. Ann Dermatol 2013, 25: 335-339.	Non-comparative (n=10): See Appendix G
Knackstedt, T. J. Int J Dermatol 2015, 54: 830-833.	No outcomes of interest, looking at upstaging
Ko, D. Y. Br J Dermatol 2014, 170: 165-72.	Within-patient RCT (n=21 with 70 lesions): See Appendix F for outcome not included in Drucher, J Am Acad Dermatol (2020)
Koh, C. S. L. Hong Kong J Dermatol Venereol 2012, 20: 53-59.	Higher quality evidence available
Landthaler, M. J Dermatol Surg Oncol 1986, 12: 1253-1257.	Too few patients (n=2)
Lee, K. C. Dermatol Surg 2012, 38: 1951-1955.	No outcomes of interest, looking at characteristics
Leibovitch, I. J Am Acad Dermatol 2005, 52: 997-1002.	Non-comparative (n=270): See Appendix G
Limmer, B. L. Cutis 1975, 16: 660-663.	Non-comparative (n=17): See Appendix G

Liu, D. Photodiagnosis Photodyn Ther 2019, 26: 258-260.	Non-comparative (n=10): See Appendix G
Lopez, N. J Dermatolog Treat 2012, 23: 428-430.	Higher quality evidence available
Lu, Y.G. Photodiagnosis Photodyn Ther 2014, 11: 122-6.	Higher quality evidence available
Lukas VanderSpek, L. A. Int J Radiat Oncol Biol Phys 2005, 63: 505-510.	Non-comparative (n=44): See Appendix G
Machan, M. Dermatol Surg 2016, 42: 936-944.	Non-comparative (n=26); See Appendix G
Mackenzie-Wood, A. J Am Acad Dermatol 2001, 44: 462-470.	Included in Love, Arch Dermatol (2009)
Mandekou-Lefaki, I. Arch Dermatol 2009, 145: 1431-1438.	Included in Love, Arch Dermatol (2009)
Martorell-Calatayud, A. Actas Dermosifiliogr 2011, 102: 605-15.	Not SCC *in situ*
Matsumoto, A. J. Dermatol Surg 2018, 44: 613-20.	Outside scope: SR on risk factors that contribute to recurrence not treatment
Mikhail, G. R. Arch Dermatol 1974, 110: 267-270.	Too few patients (n=4)
Mizutani, K. Photodermatol Photoimmunol Photomed 2012, 28: 142-6.	Outside scope: comparing different ways of giving same treatment
Modi, G. Dermatol Surg 2010, 36: 694-700.	Case report
Morley, G. L. Dermatol Res Pract 2015, 2015: 421460.	Non-comparative (n=247): See Appendix G
Morton, C. A. Arch Dermatol 2001, 137: 319-324.	Higher quality evidence available
Morton, C. A. Australas J Dermatol 2005, 46 Suppl 3: S11; discussion S23-15.	Initial abstract of Morton (2006)
Morton, C. Arch Dermatol 2006, 142: 729-735.	Included in Drucher, J Am Acad Dermatol (2020), Bath-Hextall, Cochrane Database Syst Rev (2013) & Love, Arch Dermatol (2009)
NCT https://clinicaltrials.gov/show/nct00384124 2006.	Unable to find published results for this trial
NCT https://clinicaltrials.gov/show/nct00605709 2008.	Trial withdrawn: topical creams
NCT https://clinicaltrials.gov/show/nct01912976 2013.	Results published in Ko D. Y. *et al.* Br J Dermatol 2014; 170: 165-72.
NCT https://clinicaltrials.gov/show/nct03012009 2016.	Unable to find published results for this trial
NCT https://clinicaltrials.gov/show/nct03025724 2016.	Results published in Genouw, E. *et al*. J Eur Acad Dermatol Venereol. 2018; 32:1897-1905.
NCT https://clinicaltrials.gov/show/nct03320447 2017.	Results published in Kim, H. J. *et al.* J Am Acad Dermatol 2018; 79:860-8.
NCT https://clinicaltrials.gov/show/nct03909646 2019.	Study ongoing, estimated primary completion date 12 2021 & study completion 12 2025

Nguyen, B. T. J Am Acad Dermatol 2015; 72: 558-60.	Non-comparative (n=16): See Appendix G
O'Connell, K. A. Photodiagnosis Photodyn Ther 2018, 24: 109-14.	Not systematic, checked for additional references, two identified
Otani, K. Plast Reconstr Surg 2001, 108: 68-72.	Non-comparative (n=20): See Appendix G
Overmark, M. Acta Derm Venereol 2016, 96: 64-67.	Non-comparative (n=239): See Appendix G
Pagliaro, J. Dermatol Surg 2004, 30: 63-66.	Outside scope: looking at if cold air analgesia reduces pain in PDT: within-patient RCT (sBCC and SCC *in situ* results not separated)
Paoli, J. Acta Derm Venereol 2006, 86: 418-421.	Higher quality evidence available
Patel, G. K. J Am Acad Dermatol 2006, 54: 1025-1032.	Included in Drucher, J Am Acad Dermatol (2020), Bath-Hextall, Cochrane Database Syst Rev (2013) & Love, Arch Dermatol (2009)
Patel, M. J. Br J Dermatol 2007, 156 Suppl 3: 53-56.	Too few patients (n=5)
Pedrosa, J. A. Int Urol Nephrol 2014, 46: 1551-1555.	Too few patients (n=5)
Peris, K. J Am Acad Dermatol 2006, 55: 324-327.	Included in Love, Arch Dermatol (2009)
Piccolo, D. Biomedicines 2018, 6	Higher quality evidence available
Prinz, B. M. Transplantation 2014, 77:790-1.	Too few patients (n=4)
Ratour-Bigot, C. Acta Derm Venereol 2016, 96: 658-663.	Higher quality evidence available
Rosen, T. Dermatol Surg 2007, 33: 427-431; discussion 431-422.	Included in Love, Arch Dermatol (2009)
Sarah, Q. S. Bangladesh J Pharmacol 2018, 13: 309-315.	Non-comparative (n=8): See Appendix G
Sau, P. Arch Dermatol 1994, 130: 204-209.	Non-comparative (n=7): See Appendix G
Shaw, K. S. JAAD Case Rep 2017, 3: 546-549.	Non-comparative (n=8): See Appendix G
Shuttleworth, D. J Dermatol Treat 1989, 1: 65-68.	Cohort (n=20) mixed actinic keratosis/SCC *in situ* results not reported separately
Smith, K. J. Dermatol Surg 2001, 27: 143-146.	Too few patients (n=5)
Smith, K. J. Dermatol Surg 2001, 27: 561-564.	Too few patients (n=5)
Soong, L. C. J Cutan Med Surg 2018, 22: 400-404.	Non-comparative (n=38): See Appendix G
Stevens, D. M. Int J Dermatol 1977, 16: 329-339.	Non-comparative (n=16): See Appendix G
Stone, N. Br J Dermatol 1999, 140: 987-978.	Included in Love, Arch Dermatol (2009)

Sturm, H. M. J Am Acad Dermatol 1979, 1: 513-522.	Non-comparative (n=64): See Appendix G
Sung, J. M. Photodiagnosis Photodyn Ther 2017, 19: 84-85.	Non-comparative (n=10): See Appendix G
Tantikun, N. J Am Acad Dermatol 2000, 43: 1080-1083.	Non-comparative (n=6): See Appendix G
Tarstedt, M. J Eur Acad Dermatol Venereol 2016, 30: 420-423.	Higher quality evidence available
Torelli, T. Clin Genitourin Cancer 2017, 15: e483-e487.	Non-comparative (n=10): See Appendix G
Towery, L. E. G Ital Dermatol Venereol 2019, 154: 114-119.	Outside scope: not treatment. Looking at patient reported outcomes
Trnka, J. Neoplasma 1971, 18: 467-470.	Non comparative (n=17): See Appendix G
Truchuelo, M. J Eur Acad Dermatol Venereol 2012, 26: 868-874.	Higher quality evidence available
Truchuelo, M. T. J Eur Acad Dermatol Venereol 2014, 28: 86-93.	Observational retrospective study on the value of fluorescence
van Bezooijen, B. P. J Urol 2001, 166: 1670-1671.	Non-comparative (n=19): See Appendix G
Varma, S. Br J Dermatol 2001, 144: 567-574.	Higher quality evidence available
Victoria-Martinez, A. M. Actas Dermosifiliogr 2017, 108: e9-e14.	Too few patients treated with combination (n=4), higher quality evidence available for monotherapy
Wang, Y. Chin-Ger J Clin Oncol 2009, 8: 726-728.	Too few patients (n=4)
Welch, M. L. J Am Acad Dermatol 1997, 36: 956-958.	Non-comparative (n=26): See Appendix G
Westers-Attema, A. Acta Derm Venereol 2014, 94: 431-435.	Non-comparative (n=185): See Appendix G
Westers-Attema, A. Dermatology 2015, 230: 55-61.	Higher quality evidence available
Wilkie, T. F. Br J Plast Surg 1961, 14: 205-210.	Case report
Wollina, U. Wien Med Wochenschr 2015, 165: 401-405.	Non-comparative (n=8): See Appendix G
Wong, T. W. Dermatol Surg 2001, 27: 452-456.	Too few patients (n=4)
Young, L. C. Australas J Dermatol 2012, 53: 123-127.	Non-comparative (n=11): See Appendix G
Zaar, O. J Eur Acad Dermatol Venereol 2017, 31: 1289-1294.	Higher quality evidence available
Zygogianni, A. Rev Recent Clin Trials 2012, 7: 42-6.	Not systematic, checked for additional references, none identified

Q2. Rates of cancer

Reference	Reasons for exclusion
Bath-Hextall, F. J. Cochrane Database Syst Rev 2013: Cd007281.	The one paper that reports progression Patel (2006) is already included
Bell, H. K. Clin Exp Dermatol 1999, 24: 338-9.	Non-comparative (n=68): See Appendix G
Chuang, T. Y. Am J Prev Med 1990, 6: 238-43.	Awaiting paper
Cox, N. H. Br J Dermatol 1995, 133: 60-65.	SCC found at time of treatment
Dave, R. Lasers Surg Med 2003; 32: 335.	Non-comparative (n=16): See Appendix G
Drake, A. L. J Am Acad Dermatol 2008, 59: 68-71.	Non-comparative (n=299): See Appendix G
Drexler, I. Eur J Dermatol 1997, 7: 427-431.	No outcomes of interest
Eimpunth, S. Dermatol Surg 2017, 43: 698-703.	No outcomes of interest, looking at upstaging
Gottlieb, B. Cutis 1975, 16: 108-110.	No outcomes of interest
Graham, J. H. AMA Arch Derm 1959, 80: 133-159.	Non-comparative (n=35): See Appendix G
Graham, J. H. Arch Dermatol 1961, 83: 738-758.	Over 40% already had other lesions, results not separated and time points not specified
Hansen, J. P. Dermatol Surg 2008, 34: 878-883.	Non-comparative (n=299): See Appendix G
Holt, P. J. Br J Dermatol 1988, 119: 231-240.	Non-comparative (n=85 with 128 lesions): See Appendix G
Hugo, N. E. Plast Reconstr Surg 1967, 39: 190-194.	Non-comparative (n=38): See Appendix G
Jaeger, A. B. Arch Dermatol 1999, 135: 790-793.	Non-comparative (n=1147): See Appendix G
Jansen, M. H. Acta Derm Venereol 2018, 98: 114-115.	Non-comparative (n=608): See Appendix G
Kao GF. Arch Dermatol 1986; 122: 1124-6.	Editorial
Kovács A, J Dermatol 1996; 23: 267-74.	Unable to obtain full text
Lee, K. C. Dermatol Surg 2012, 38: 1951-1955.	Non-comparative (n=73): See Appendix G
Lukas VanderSpek, L. A. Int J Radiat Oncol Biol Phys 2005, 63: 505-510.	Non-comparative (n=44): See Appendix G
Lycka BAS. Int J Dermatol 1989; 28: 531-3.	Outside scope: SR on association with internal carcinoma
Matsumoto, A. J. Dermatol Surg 2018, 44: 613-20.	Outside scope: SR on risk factors that contribute to recurrence
Newsom, E. Dermatol Surg 2019, 45: 1345-1352.	Outside scope: rate of occult invasion in biopsy specimen

Obalek, S. J Am Acad Dermatol 1986, 14: 433-444.	No outcomes of interest
Overmark, M. Acta Derm Venereol 2016, 96: 64-67.	Non-comparative (n=239): See Appendix G
Ratour-Bigot, C. Acta Derm Venereol 2016, 96: 658-663.	Non-comparative (n=105): See Appendix G
Reizer, G. T. J Am Acad Dermatol 1994, 31: 596-600.	Outside scope: Incidence of SCC *in situ* and concurrent NMSC
Tokez, S. JAMA Dermatol 2020, 156: 81.	Overall incidence, not reported by treatment received
van Bezooijen, B. P. J Urol 2001, 166: 1670-1671.	Non-comparative (n=19): See Appendix G
Young, L. C. Australas J Dermatol 2012, 53: 123-127.	Non-comparative (n=11): See Appendix G

Appendix K: Methodology

Developing the review questions and outcomes

Review questions were developed using the PICO framework (patient, intervention, comparison and outcome) for intervention reviews. The use of this framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the technical team and refined and validated by the GDG. The questions were based on the key clinical areas.

A total of two systematic review questions were identified (see Appendix A).

Full literature searches, critical appraisals and evidence reviews were completed for both the review questions.

Searching for evidence

Clinical literature search

Systematic literature searches were undertaken to identify the published clinical evidence relevant to the review questions; these were undertaken according to the parameters stipulated within the protocols. Databases were searched using relevant medical subject headings (MeSH), free-text terms and study-type filters, where appropriate. Where possible, searches were restricted to articles published in the English language; studies published in languages other than English were not reviewed. All searches were conducted in PubMed, MEDLINE, EMBASE and Cochrane databases to identify key articles relevant to the questions. All searches for this draft version were completed on 18th September 2019 and will be updated after consultation to ensure recommendations remain current to the best available evidence; search terms and strategies are detailed in Appendix L.

Identifying and appraising evidence of effectiveness

The technical team identified potentially relevant studies for the review question from the search results by reviewing the titles. Two members of the GDG then reviewed the abstracts of these studies using the inclusion/exclusion criteria in the systematic review protocol(s). Full papers were then obtained for those agreed as potentially relevant.

The full papers were then reviewed against the inclusion/exclusion criteria in the systematic review protocol(s) to identify studies that addressed the review question.

The systematic reviews were critically appraised using the AMSTAR tool (see Appendix I) and the studies were critically appraised using the appropriate study design checklists as specified in Developing NICE guidelines: the manual.[132]

Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in Appendix A. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Type of studies

See relevant systematic review protocols (Appendix A).

Type of analysis

Relevant data were extracted from the studies using the Review Manager (RevMan) 5.3 software package.[133] Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate the risk ratios (relative risk). The absolute risk difference was also calculated using GRADEprofiler 3.6 software package,[134] using the event rate in the control arm of the results.

When possible, meta-analyses were conducted to combine the data given in all studies for each of the outcomes of interest for the review question (see Appendix A).

Where relevant, the GDG specified that certain data should be stratified, meaning that studies that varied on a particular factor were not combined and analysed together. Where stratification was used, this is documented in the individual systematic review protocols (see Appendix A).

Appraising the quality of the evidence by outcomes

The evidence for outcomes from the included randomized controlled trials (RCTs) was evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (www.gradeworkinggroup.org/). The software was used to assess the quality of each outcome, considering individual study quality and the meta-analysed results.

Each outcome was first examined for each of the quality elements listed and defined in Table K.1.

Table K.1: Description of quality elements in GRADE for intervention studies

Quality element	**Description**
Risk of bias *(i.e. study limitations)*	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional and assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. The 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide

	confidence intervals may denote a result that is consistent with conflicting interpretations (for example, a result may be consistent with both clinical benefit AND clinical harm) and thus, be imprecise.
Publication bias	Publication bias is a systematic under/overestimation of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an over-estimate of the effectiveness of that outcome.
Other issues	Sometimes, randomization may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be considered. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the four main elements (risk of bias, indirectness, inconsistency and imprecision) used to assess overall certainty of the evidence were appraised for each outcome are given below. Publication or other biases were only taken into consideration in the quality assessment if it was apparent.

a) Risk of bias
The key domains of bias for RCTs are listed in Table K.2. Each outcome had its risk of bias assessed within each paper first. For each outcome, if there were no issues with any of the domains, the risk of bias was given a rating of "0". If there were issues with just one domain, the risk of bias was given a "serious" rating of "-1", but if there was risk of bias in two or more domains the risk of bias was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by considering the weighting of studies according to study precision.

Table K.2: Principal domains of bias in randomized controlled trials

Limitation	Explanation
Selection bias – sequence generation and allocation concealment	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of 1) knowledge of that participant's likely prognostic characteristics and 2) a desire for one group to do better than the other.
Performance and detection bias – lack of patient and healthcare professional blinding	Patients, care-givers, those adjudicating and/or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of group can influence 1) the experience of the placebo effect, 2) performance in outcome measures, 3) the level of care and attention received, and 4) the methods of measurement or analysis, all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from loss of data beyond a certain level which is not accounted for. Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from

	the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: Stopping early for benefit observed in randomized trials, particularly in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes Lack of washout periods to avoid carry-over effects in crossover trials Recruitment bias in cluster randomized trials

b) Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (Chi square $p<0.1$ or I^2 inconsistency statistic of >50%), but no plausible explanation could be found, the certainty of the evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of "-1" if the I^2 was 50-74%, and a 'very serious' score of "-2" if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an $I^2 < 50$), the GDG took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation, the certainty of the evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

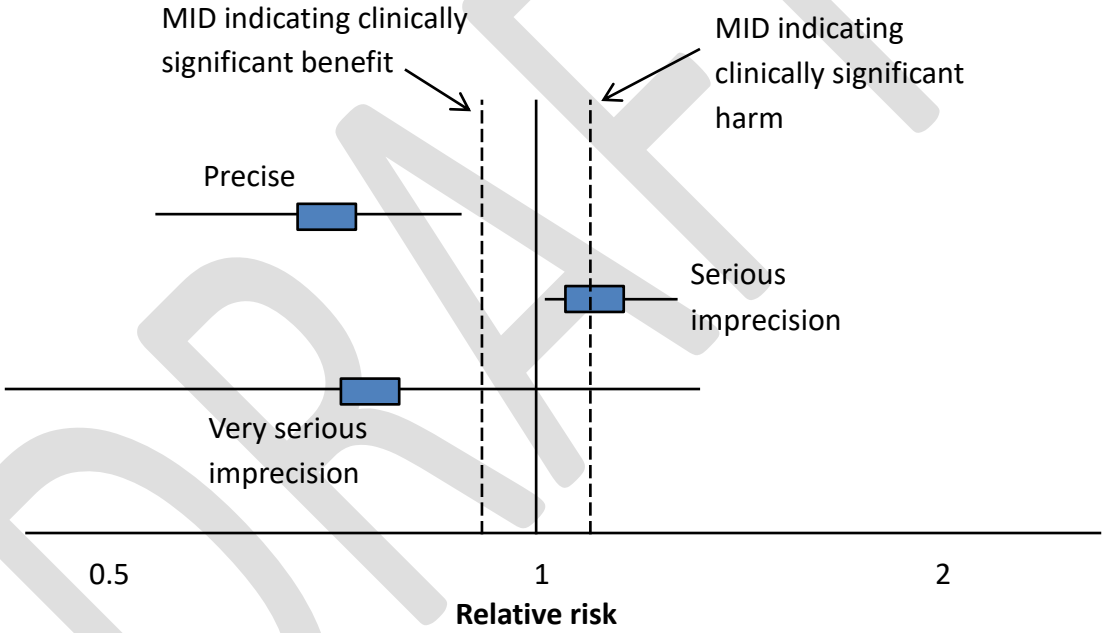
c) Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size or may affect the balance of harms and benefits considered for an intervention. As for risk of bias, each outcome had its indirectness assessed within each paper first. For each paper, if there were no sources of indirectness, this was given a rating of 0. If there was indirectness in just one source (for example in terms of population), indirectness was given a 'serious' rating of -1, but if there was indirectness in two or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of -1 each for that outcome, the overall score for that outcome would probably tend towards -1.

d) Imprecision

The criteria applied for imprecision were based on the confidence intervals for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. For categorical/dichotomous outcomes, if either of the 95% confidence intervals of the overall estimate of effect crossed one of the MID lines, imprecision was regarded as serious and a 'serious' score of -1 was given. This was because the overall result, as represented by the span of the confidence intervals, was consistent with two interpretations as defined by the MID (for example, no clinically important effect and either clinical benefit or harm). If both MID lines were crossed by either or both the confidence intervals, then imprecision was regarded as very serious and a 'very serious' score of -2 was given. This was because the overall result was consistent with three interpretations defined by the MID (no clinically important effect and clinical benefit and clinical harm). This is illustrated in Figure K.1.

Figure K.1: Illustration of precise and imprecise outcomes



The position of the MID lines is ideally determined by values as reported in the literature. "Anchor-based" methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or "anchoring" them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, the minimum amount of change in an outcome necessary to make a patient decide that they felt their quality of life had "significantly improved" might define the MID for that outcome (e.g. DLQI ≥4 for psoriasis). MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life, or health. For categorical/dichotomous variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, as so are not amenable to patient-centred "anchor" methods.

In the absence of literature values, the alternative approach to deciding on MID levels is the "default" method, as follows:

For categorical/dichotomous outcomes, the MIDs are taken as RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm. No appropriate MIDs for the outcomes were found in the literature and the GDG agreed that the default MID was appropriate.

Non-comparative studies

When higher quality studies with a comparator arm are lacking, data and information from case series are presented as 'tabulated narrative findings' (Appendix G). The assessment of these studies is more subjective and therefore consensus opinion amongst clinical experts on the GDG played a more important role.

Grading the certainty of clinical evidence

Once an outcome had been appraised for the main certainty elements, an overall certainty grade was calculated for that outcome. The scores from each of the main certainty elements (0, -1 or -2) were summed to give a score that could be anything from 0 (the best possible) to -3 (the worst possible, as scores were capped at -3). This final score was then added to the starting grade that had originally been applied to the outcome by default, based on study design.

For example, all RCTs start as 'HIGH' (0 points) and the overall certainty became 'MODERATE', 'LOW' or 'VERY LOW' if the overall score was -1, -2 or -3 points, respectively. The significance of these overall ratings is explained in Table K.3. The reasons used for downgrading were specified in the footnotes of the GRADE tables. On the other hand, observational interventional studies started at 'LOW', and so a score of -1 would be enough to take the grade to the lowest level of 'VERY LOW'. Observational studies could, however, be upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect, as long as they had not been downgraded already due to risk of bias.

Table K.3 Overall certainty of outcome evidence in GRADE

Level	**Description**
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low	Any estimate of effect is very uncertain

For each comparison, e.g. drug A vs. placebo, the certainty of the body of evidence is determined by the majority of the lowest certainty rating amongst the ***critical*** outcomes; these are featured in the LETR table (Appendix C).

Practical and economic considerations

Where relevant, cross-references were made to NICE guidance and associated health economic evaluation. Drug acquisition costs, resource use and practical considerations based on the experience of the GDG were also considered. Formal health economic analyses were not performed.

Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Summaries of the clinical and overall certainty of the evidence (Appendix D)
- Evidence tables of the reviewed literature (Appendices E, F & G)
- Forest plots (Appendix B)

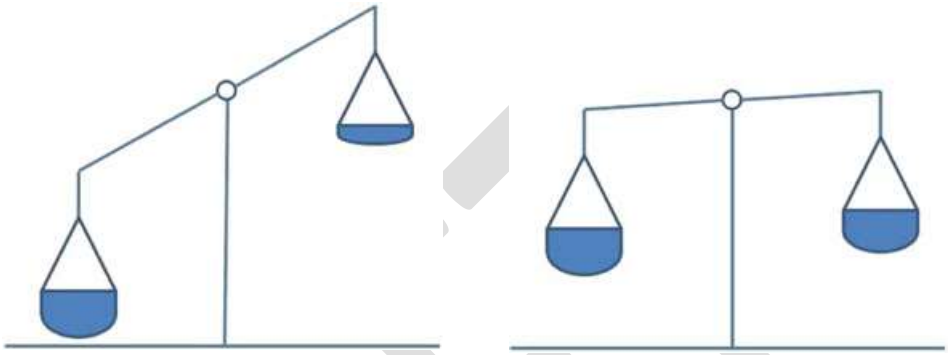
Recommendations were drafted based on the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms, costs between different courses of action and patient values and preferences. The clinical benefit over harm (clinical effectiveness) focused on the ***critical*** outcomes when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the GDG's, and patient values and preferences), and the confidence the GDG had in the evidence (evidence certainty). The GDG assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical evidence was of poor certainty, conflicting or absent, the GDG drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, practical and economic considerations, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see ***Future research recommendations (FRRs)*** Appendix C).

The GDG considered the appropriate 'strength' of each recommendation. This took into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' (↑↑) in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people (see Figure K.2a) and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms (see Figure K.2b), and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effects and others

are not. For clinicians, this indicates the need to consider the pros/cons for the patient in context of the evidence and that variation in practice is expected. In these circumstances, the recommendation is generally weaker (🡅), although it may be possible to make stronger recommendations about specific groups of patients, or when experience and expertise in the GDG called for it despite the weaker evidence (e.g. when certain interventions are well established in clinical practice with no recent high-certainty RCTs, or when conducting an RCT would be unethical).

Figure K.2 Illustration for (a) strong and (b) weak recommendations



(a) Strong recommendations (b) Weak recommendations

For patients	Most people in this situation would want the recommended course of action and only a small proportion would not	Many people in this situation would want the suggested course of action, but many others would not
For clinicians	Most people should receive the intervention	Consider pros/cons for patient in context of the evidence
For quality monitors	Useful as a performance indicator	Poor indicator (variability in practice expected)

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions healthcare professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the words ‘Offer’, ‘Assess’, ‘Advise’, ‘Discuss’, etc. were used for strong recommendations and ‘Consider’ for weaker recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care

The main considerations specific to each recommendation are outlined in the LETR table(s) (Appendix C).

Future research recommendations (FRRs)

Where areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population

- national priorities
- potential impact on the NHS and future guidance
- ethical and technical feasibility

VALIDATION PROCESS

The draft document was made available for a 1-month consultation to all relevant stakeholders identified by the GDG, including healthcare professionals and patient support groups. All comments were reviewed by the GDG and the recommendations were revised if appropriate (for example, in light of important new evidence or other considerations not previously considered by the GDG). Following further review, the finalized version was peer-reviewed by the Clinical Standards Unit of the BAD (which includes the Therapy & Guidelines sub-committee) prior to submission to the British Journal of Dermatology.

FUNDING

Development of this guideline has been funded independently by the BAD.

Appendix L: Search Strategy

PubMed (1966- current + selective coverage back to 1865) search carried out on 18.09.2019

Search no.	Keywords
1	meta-analys* OR “systematic review*” OR controlled clinical trials, randomized [MeSH Terms] OR randomi* controlled trial* OR randomi* control trial* OR RCT* OR non-randomi* controlled trial* OR non-randomi* control trial* OR controlled clinical trial* OR clinical monitor* OR case series OR case control* OR open stud* OR cohort stud*
2	“Bowen’s disease”[MeSH Terms] OR “Bowen’s disease” OR “Bowens disease” OR “Bowen disease” OR “squamous cell carcinoma in situ” OR “squamous carcinoma in situ” OR “intraepidermal squamous cell carcinoma” OR “intraepidermal squamous carcinoma” OR “intraepidermal carcinoma”
3	"erythroplasia of Queyrat"[All Fields] OR ("erythroplasia"[MeSH Terms] OR "erythroplasia"[All Fields]) OR Queyrat[All Fields]
4	2 OR 3
5	1 AND 4
6	therapy OR therapies OR treatment OR management OR intervention* OR topical OR surgery OR surgeries OR surgical OR excise* OR excised OR excision OR Mohs surgery [MeSH Terms] OR Mohs
7	4 AND 6
8	fluorouracil [MeSH Terms] OR 5-fluorouracil OR fluorouracil
9	4 AND 8
10	cryotherapy[MeSH terms] OR cryotherapy OR “liquid nitrogen”
11	4 AND 10
12	electrodesiccation OR electrocautery OR curettage[MeSH Terms] OR curettage OR cautery[MeSH Terms] OR cautery OR cauterisation OR cauterization
13	4 AND 12
14	imiquimod[MESH Terms] OR imiquimod OR “ingenol mebutate” OR “ingenol 3 angelate” OR Picato
15	4 AND 14
16	“photodynamic therapy” OR PDT
17	4 AND 16
18	“laser therapy”[MeSH Terms] OR ”laser therapy” OR “low level laser therapy”
19	4 AND 18
20	radiotherapy[MeSH Terms] OR radiotherapy OR “radiotherapy”
21	4 AND 20
22	5 OR 7 OR 9 OR 11 OR 13 OR 15 OR 17 OR 19 OR 21
23	Limit 22 to English-language publications
24	23 (From 1966 to 18.09.2019)

Medline (1946-current) & EMBASE (1947-current) (Proquest/DialogDatastar) search carried out on 18.09.2019

Search no.	Keywords
1	meta-analys$2 OR (systematic pre/0 review$1) OR (randomi$3 pre/0 control$3 pre/0 trial$1) OR RCT$1 OR (non-randomi$3 pre/0 control$3 pre/0 trial$1) OR (control$3 pre/0 clinical pre/0 trial$1) OR (clinical pre/0 monitor$3) OR (case pre/0 series) OR (case pre/0 control$1) OR (open pre/0 stud$3) OR (cohort pre/0 stud$3)
2	MESH.EXACT(“Bowens disease”) OR EMB.EXACT(“Bowen disease”) OR (Bowen$2 pre/0 disease) OR (squamous pre/0 cell pre/0 carcinoma pre/0 in pre/0 situ) OR (squamous pre/0 carcinoma pre/0 in pre/0 situ) OR (intraepidermal pre/0 squamous pre/0 cell pre/0 carcinoma) OR (intraepidermal pre/0 squamous pre/0 carcinoma) OR (intraepidermal pre/0 carcinoma)
3	(erythroplasia pre/1 Queyrat) OR (erythroplasia AND Queyrat) OR Erythroplasia
4	2 OR 3
5	1 AND 4
6	therap$3 OR treatment OR management OR intervention$1 OR topical OR surger$3 OR surgical OR excis$3 EMB.EXACT("chemosurgery") OR MESH.EXACT("Mohs surgery") OR "Mohs" OR EMB.EXACT(“micrographic surgery”)
7	4 AND 6
8	MESH.EXACT(“Fluorouracil”) OR EMB.EXACT(“fluorouracil”) OR 5-fluorouracil
9	4 AND 8
10	MESH.EXACT(“Cryotherapy”) OR EMB.EXACT(“cryotherapy”) OR cryotherapy OR (liquid pre/0 nitrogen)
11	4 AND 10
12	electrodessication OR electrocautery OR EMB.EXACT(“cauteri$1ation”) OR MESH.EXACT(“curettage”) OR EMB.EXACT(“curettage”) OR curettage OR MESH.EXACT(“cautery”) OR EMB.EXACT(“cautery”) OR cautery
13	4 AND 12
14	MESH.EXACT (“Imiquimod”) OR EMB.EXACT (“Imiquimod”) OR imiquimod OR Ingenol pre/0 mebutate OR (ingenol pre/0 3 pre/0 angelate) OR Picato
15	4 AND 14
16	EMB.EXACT(“photodynamic therapy”) OR (photodynamic pre/0 therapy) OR PDT
17	4 AND 16
18	MESH.EXACT(“Laser therapy”) OR (laser pre/0 therapy) OR MESH.EXACT(“laser therapy, low-level”) OR EMB.EXACT(“low level laser therapy”)
19	4 AND 18
20	MESH.EXACT(“Radiotherapy”) OR EMB.EXACT(“radiotherapy”) OR radiotherapy
21	4 AND 20
22	5 OR 7 OR 9 OR 11 OR 13 OR 15 OR 17 OR 19 OR 21
23	Limit 22 to English-language publications
24	23 [From 1946 to 18.09.2019 (Medline) OR 1947 to18.09.2019 (EMBASE)]

Cochrane database (1990-current) search carried out on 18.09.2019

Search no.	Keywords
1	[mh “Bowen* Disease”] OR (“Bowen’s disease”):ti,ab,kw OR OR (squamous cell carcinoma in situ):ti,ab,kw
2	erythroplasia of Queyrat OR “erythroplasia of Queyrat” OR (erythroplasia AND Queyrat) OR erythroplasia
3	1 OR 2
4	3 (all publications up to 18.09.2019)

Appendix M: Audit standards, data items and data collection

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