Aus der Klinik und Poliklinik für Dermatologie und Allergologie der

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# Evidenzbasierte und patientenorientierte Therapieentscheidungen bei aktinischer Keratose

Dissertation

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München, den 2. Mai 2022

Theresa Steeb

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# Abkürzungsverzeichnis

| | |
|---|---|
| AGREE II | Appraisal of Guidelines for Research and Evaluation II |
| AGREE-REX | Appraisal of Guidelines for Research and Evaluation - Recommendation EXcellence |
| AK | Aktinische Keratose(n) |
| AKASI | Actinic keratosis area and severity index |
| AK-FAS | Actinic keratosis field assessment scale |
| ALA | Aminolävulinat |
| AWMF | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften |
| CI | Konfidenzintervall (confidence interval) |
| $CO_2$-Laser | Kohlendioxid-Laser |
| DELBI | Deutsches Leitlinien-Bewertungsinstrument |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| IMB | Ingenolmebutat |
| IMQ | Imiquimod |
| KIN | Keratinozytäre intraepitheliale Neoplasie |
| MAL | Methyl-Aminolävulinat |
| MD | Mittlere Differenz |
| PDT | Photodynamische Therapie |
| PEK | Plattenepithelkarzinom |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RCT | Randomisierte kontrollierte Studie (randomised controlled trial) |
| RR | Relatives Risiko |
| SPSS | Statistical Package for the Social Sciences |
| STROBE | STrengthening the Reporting of OBservational studies in Epidemiology |
| UV | Ultraviolett |
| VAS | Visuelle Analogskala |

# Abbildungsverzeichnis

# Publikationsliste

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# 1. Einleitung

Die aktinische Keratose (AK) ist eine häufig vorkommende präkanzeröse Hautveränderung bei hellhäutigen Menschen infolge chronischer Sonnenexposition und zählt zu den häufigsten Gründen, einen Dermatologen[1] zu konsultieren [1-3]. Schätzungen zufolge entfielen in Deutschland im Jahr 2011 8,3% der hundert am häufigsten ambulant behandelten dermatologischen Diagnosen auf die AK [3]. Sie hat ihren Ursprung in den basalen Keratinozyten der Epidermis der Haut und ist auch unter den Synonymen solare Keratose, senile Keratose oder Lichtkeratose bekannt [4, 5].

## 1.1 Epidemiologie und Ätiologie der aktinischen Keratose

Genaue Daten zur Prävalenz der AK in Deutschland sind schwer zu erheben, da diese Diagnose bislang nicht systematisch in den Krebsregistern erfasst wird. Es liegt allerdings eine Schätzung bei 90.800 Arbeitnehmenden auf Basis von Daten der gesetzlichen Krankenkassen aus dem Jahr 2008 vor, wonach die Prävalenz in allen Altersgruppen 2,7% beträgt und mit zunehmendem Alter ansteigt (11,5% in der Altersgruppe der 60- bis 70-Jährigen) [3, 4]. Männer waren dabei häufiger betroffen als Frauen (3,9% vs. 1,5%) [3, 4]. Insgesamt wird geschätzt, dass ca. 1,7 Millionen Menschen in Deutschland wegen einer AK in Behandlung sind, allerdings ist der tatsächliche Anteil aufgrund der fehlenden systematischen Erfassung sowie unbehandelter Fälle vermutlich beträchtlich höher [3]. In Australien beträgt die geschätzte Prävalenz bei Erwachsenen zwischen 30 und 69 Jahren ungefähr 40%; in Europa wurden Prävalenzdaten für Personen, die älter als 40 Jahre sind, auf 1,4 - 6% für Frauen und 15% für Männer geschätzt [6-9]. Allerdings liegen auch hier kaum Daten aufgrund einer fehlenden Erfassung vor.

Insgesamt steigt die Erkrankungsrate von AK, insbesondere in der älteren Bevölkerung [2, 3]. Die Ursachen hierfür sind der demografische Wandel mit einem höheren Anteil der älteren Bevölkerung sowie das veränderte Freizeitverhalten mit häufigerer und längerer Exposition gegenüber ultravioletter (UV) Strahlung des Sonnenlichts [5]. Dieser Zusammenhang konte in zahlreichen Studien belegt werden [2, 3, 10, 11]. Auch die Prävalenz bei Arbeitnehmenden mit beruflich bedingter UV-Lichtexposition (Außenberufe, „Outdoorworker") ist höher als bei solchen mit vorwiegender Bürotätigkeit [12]. Daher wird das Vorliegen der AK in bestimmten Berufsgruppen wie zum Beispiel dem Baugewerbe und Handwerk, der Land- und Forstwirtschaft oder der Fischerei und Seefahrt seit 2015 in Deutschland als Berufskrankheit (BK 5103, § 9 Abschnitt 1 des 7. Buches des Sozialgesetzbuches) anerkannt [13-15].

## 1.2 Klinische Manifestation und Einteilung der aktinischen Keratose

Die AK manifestiert sich meist als 0,3 - 1,0 cm durchmessender rötlicher, manchmal auch gelblicher oder bräunlicher Fleck bis Plaque mit einer rauen, schuppigen Oberfläche [16, 17]. Primär tritt sie an den Sonnenterrassen der Haut wie dem Kapillitium, Gesicht, Dekolleté und den Extremitäten auf (Abb. 1) [2].



**Abbildung 1:** AK am Kapillitium (links) und Handrücken (rechts)
(Fotos Hautklinik Erlangen)

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[1] Aus Gründen der besseren Lesbarkeit wird in dieser Dissertation das generische Maskulinum verwendet. Es werden weibliche und anderweitige Geschlechteridentitäten ausdrücklich mitgemeint.

Sie kann vereinzelt in Form von isolierten, solitären Läsionen, aber auch gruppiert und konfluierend in einem Hautareal vorkommen. Liegen multiple AK zusammen mit klinisch nicht sichtbaren (subklinischen) AK in einem zusammenhängenden von UV-Lichtschädigung gezeichnetem Hautareal, bezeichnet man dies als Feldkanzerisierung [4, 18-21]. Allerdings fehlt für diesen oft genutzten Terminus eine allgemein gültige und anerkannte Definition.

Die Diagnose einer AK erfolgt in der Regel klinisch durch Inspektion und Palpation, in unklaren Fällen wird die Verdachtsdiagnose über eine Gewebeprobe histopathologisch gesichert. Zur Einordnung der AK stehen eine Auswahl verschiedener klinischer und histologischer Klassifikationssysteme zur Verfügung. Meistens wird die AK in Grad I-III klinisch nach Olsen [22] und histologisch nach Röwert-Huber eingeteilt [23]. Eine andere Einteilung jüngeren Datums ist die histomorphologische Klassifikation der basalen Proliferationsmuster in die Abstufungen PRO I bis PRO III, die nicht mit dem histologischen Einstufungssystem AK I-III korreliert [24-26]. Cockerell et al. haben den Begriff „keratinozytäre intraepitheliale Neoplasie" (KIN) vorgeschlagen. Er basiert sowohl auf klinischen als auch histologischen Merkmalen und klassifiziert AK in KIN1 bis KIN3 [23, 27]. Seit 2017 gibt es mit dem „*actinic keratosis area and severity index*" (AKASI) und der „*actinic keratosis field assessment scale*" (AK-FAS) zwei weitere klinische Klassifikationssysteme, welche auch die Feldkanzerisierung des Kopfes/Gesichts anhand von verschiedenen Parametern (z.B. Erythem, Dicke und Verteilung beim AKASI) berücksichtigen [28-31]. An sämtlichen bestehenden Klassifikationssystemen wird kritisiert, dass sie nicht geeignet sind, die Prognose bzw. das Progressionsrisiko vorherzusagen.

## 1.3 Notwendigkeit einer Therapie: Spontanregression versus Risiko für eine Progression in ein Plattenepithelkarzinom

Eine spontane Regression der AK ohne Therapie kann auftreten [9, 32, 33]. Die publizierten Spontanremissionsraten werden auf 15 - 63% pro Jahr geschätzt, insbesondere wenn keine Anzeichen für eine Feldkanzerisierung vorliegen [32]. Andererseits kann sich eine AK zu einem invasiven Plattenepithelkarzinom (PEK) der Haut entwickeln [34]. Bis zu zwei Drittel aller PEK entstehen aus einer AK [34-36]. In einer systematischen Übersichtsarbeit quantifizierten Werner et al. maligne Progressionswerte von 0% bis 0,075% pro Läsion und Jahr bzw. 0,53% bei Patienten, die bereits an einem nicht-melanozytären Hautkrebs erkrankt waren [32].

Aufgrund der möglichen Spontanregression ist abzuwägen, ob die Behandlung jeder AK indiziert ist oder ob auch ein beobachtendes Abwarten ohne Therapie vertreten werden kann [32]. Das Vorliegen von multiplen AK, Anzeichen einer chronischen, UV-bedingten Hautschädigung, eine begleitende Feldkanzerisierung, eine ausgeprägte basale Proliferation in der Histologie sowie weitere Risikofaktoren wie höheres Alter, männliches Geschlecht und Immunsuppression erhöhen jedoch das Progressionsrisiko maßgeblich [24, 32, 37]. In internationalen Leitlinien wird die frühzeitige Therapie der AK empfohlen, da sie eine potenzielle Vorstufe von nicht-melanozytärem Hautkrebs ist und es nach dem aktuellen Wissensstand unmöglich ist vorherzusagen, welche AK sich zu einem invasiven PEK entwickeln wird und welche nicht [4, 38, 39].

## 1.4 Therapie der aktinischen Keratose

Zur Therapie der AK stehen zahlreiche verschiedenartige Interventionen zur Verfügung. Sie umfassen sowohl chirurgisch-ablative als auch topisch-medikamentöse Verfahren und können entweder läsions- oder feldgerichtet sein [4, 20]. Läsionsgerichtete Interventionen sind für die Behandlung einzelner bzw. isolierter AK geeignet [4]. Im Gegensatz dazu sind feldgerichtete Verfahren bei multiplen AK und Feldkanzerisierung zu bevorzugen, da sie auch auf subklinische Veränderungen eines aktinisch

geschädigten Feldes abzielen [4]. Dies ist insbesondere wichtig, da AK zunehmend als chronische Flächenerkrankung verstanden werden. Wenn in der Umgebung von AK daher ein Tumorfeld klassifiziert werden kann, hat dies unmittelbare Auswirkungen auf die Wahl der Therapie [4, 20]. Die Abgrenzung zwischen multiplen AK und Feldkanzerisierung ist oftmals nicht eindeutig, was die fehlende allgemein anerkannte Definition der Feldkanzerisierung noch zusätzlich erschwert [4]. Derzeit sind zahlreiche läsions- und feldgerichtete Therapieoptionen mit einem unterschiedlichen Effektivitäts- und Sicherheitsprofil in Deutschland verfügbar (Abb. 2) [4].
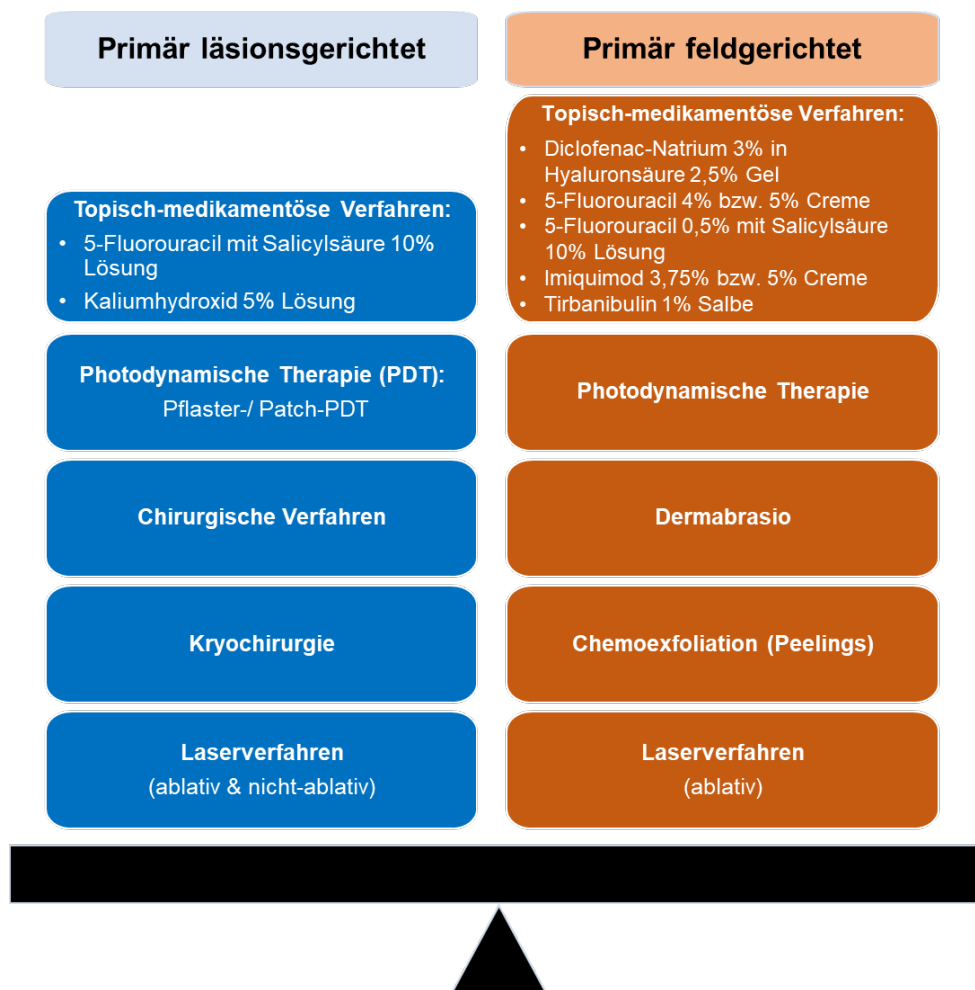


**Abbildung 2:** Übersicht über die in Deutschland verfügbaren und zugelassenen läsions- und feldgerichteten Verfahren zur Therapie von AK (Stand: 20.12.2021, in Anlehnung an [4])

Die Vielzahl an Therapiemöglichkeiten der AK ist allerdings „Fluch und Segen" zugleich: Ein unmittelbarer Vergleich dieser einzelnen Therapiemöglichkeiten ist häufig nur begrenzt möglich, da viele Interventionen in klinischen randomisierten kontrollierten Studien (RCT) nicht direkt miteinander verglichen werden. Außerdem unterscheiden sich die Interventionen in ihrer Art und Anwendung deutlich voneinander. Da die in Studien gewählten Endpunkte und Erhebungszeitpunkte sehr heterogen sind, sind auch indirekte Vergleiche erschwert [40, 41]. Daher ist auch eine hierarchische Darstellung, beispielsweise in Form von Algorithmen, bislang nicht zweckmäßig bzw. praktikabel. Stattdessen müssen bei der Therapiewahl verschiedene Aspekte berücksichtigt und gegeneinander abgewogen werden, um eine bestmögliche individualisierte Therapieempfehlung zu generieren (Abb. 3) [4].
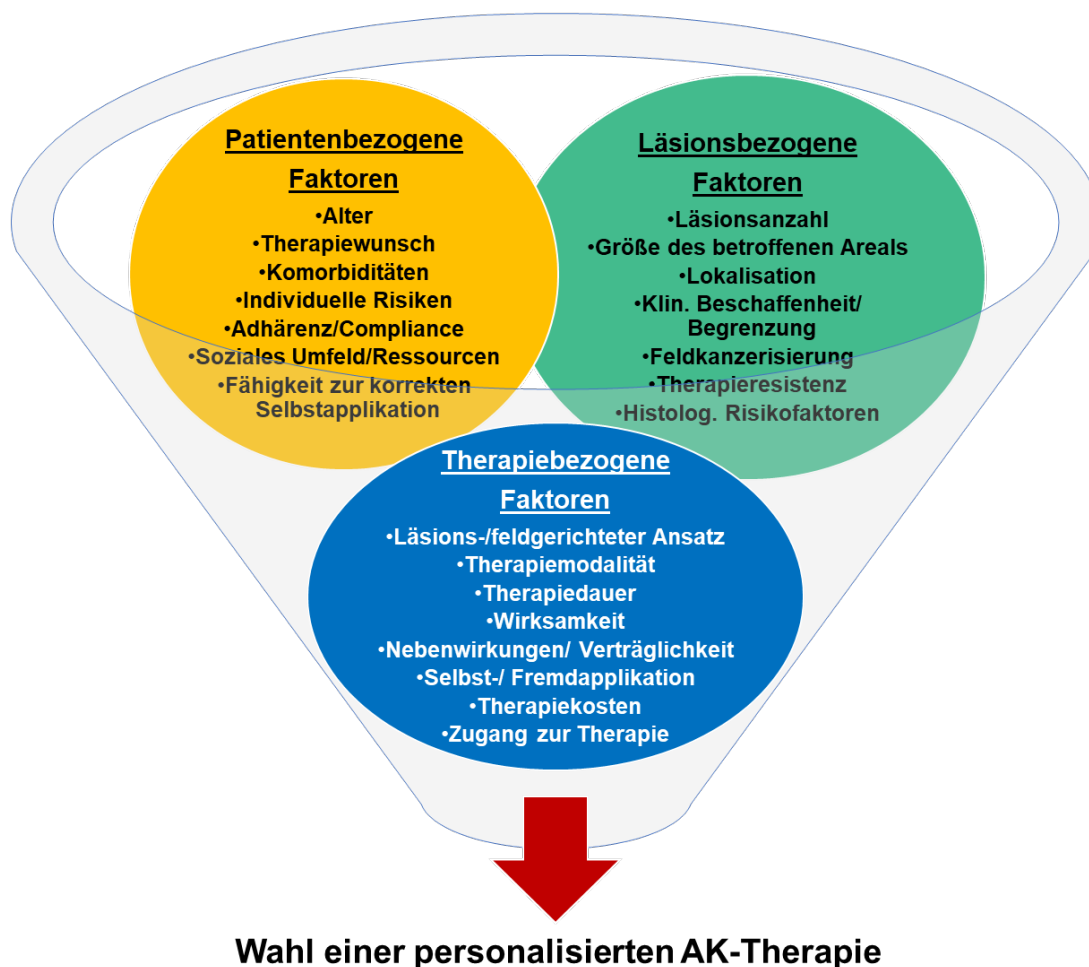
**Patientenbezogene Faktoren**
- Alter
- Therapiewunsch
- Komorbiditäten
- Individuelle Risiken
- Adhärenz/Compliance
- Soziales Umfeld/Ressourcen
- Fähigkeit zur korrekten Selbstapplikation

**Läsionsbezogene Faktoren**
- Läsionsanzahl
- Größe des betroffenen Areals
- Lokalisation
- Klin. Beschaffenheit/ Begrenzung
- Feldkanzerisierung
- Therapieresistenz
- Histolog. Risikofaktoren

**Therapiebezogene Faktoren**
- Läsions-/feldgerichteter Ansatz
- Therapiemodalität
- Therapiedauer
- Wirksamkeit
- Nebenwirkungen/ Verträglichkeit
- Selbst-/ Fremdapplikation
- Therapiekosten
- Zugang zur Therapie

**Wahl einer personalisierten AK-Therapie**

**Abbildung 3:** Übersicht zu verschiedenen Faktoren mit Einfluss auf die Therapieentscheidung bei AK [4, 10]

Zu diesen Aspekten gehören zum einen patientenbezogene Faktoren wie z.B. Alter, Komorbiditäten, Immunsuppression, Komedikation, Wunsch bzw. Präferenz der Patienten sowie Therapieadhärenz [4]. Zu den läsionsbezogenen Faktoren zählen die Anzahl von AK, deren Lokalisation (Kapillitium, Gesicht, Extremitäten, Stamm), die klinische Beschaffenheit (Graduierung nach Olsen, hyperkeratotische Läsionen) sowie die Größe des betroffenen Areals einschließlich des Vorhandenseins einer Feldkanzerisierung [4]. Außerdem fließen therapiebezogene Faktoren in die Wahl der Behandlung ein, wie z.B. Modalität, Art der Anwendung, Dauer, Kosten und Erstattungsfähigkeit, Effektivität, Nebenwirkungen sowie der Zugang zu der Therapie [4]. Auch die Erfahrung, Präferenz sowie die vorhandenen Ressourcen des behandelnden Arztes haben einen maßgeblichen Einfluss auf die Therapiewahl. Darüber hinaus sind neben den genannten Faktoren für die Wahl der Therapie der AK auch evidenz- bzw. leitlinienbasierte sowie patientenorientierte Aspekte wichtige Dimensionen, auf die im Folgenden näher eingegangen wird.

## 1.4.1 Evidenz- und leitlinienbasierte Therapieentscheidungen bei aktinischer Keratose

### 1.4.1.1 Kombinationstherapien

Eine weitere wichtige Dimension in der Therapieentscheidung ist die vorhandene Evidenz zur Effektivität und Sicherheit von verfügbaren Interventionen. Interventionen für AK werden in der klinischen Praxis häufig miteinander kombiniert, um die Stärken und Vorteile der jeweiligen Einzeltherapien zu vereinigen bzw. die individuellen Schwächen der therapie-, patienten- oder läsionsbezogenen Faktoren auszugleichen. Die Überlegung hinter einer Kombination von zwei oder mehreren Interventionen ist

außerdem, dass höhere Abheilungsraten erreicht werden können. Es wird vermutet, dass aufgrund unterschiedlicher Wirkmechanismen der Einzeltherapien synergistische Effekte erzielt werden können [42-46]. Daher werden beispielsweise oft läsionsgerichtete Verfahren wie die Kryochirurgie oder ablative Laserverfahren zur Vorbehandlung einer feldgerichteten Therapie mit topischen, arzneimittelgestützten Verfahren bei dicken, hyperkeratotischen AK eingesetzt, um eine effektive und schnelle Behandlung von klinisch manifesten Läsionen mit einer Therapie von subklinischen Veränderungen zu verbinden [4, 45, 47-55]. Es wird davon ausgegangen, dass die Kombination eine bessere Wirkstoffpermeation bei einzelnen, hyperkeratotischen Läsionen ermöglicht [45, 56]. Umgekehrt können nach einer primär feldgerichteten Therapie noch verbleibende bzw. therapieresistente AK mit einem läsionsgerichteten Ansatz erneut behandelt werden [4, 45]. Auch eine Vorbehandlung bei topischen Ansätzen durch ein Microneedling (= Walze bzw. mechanischer Stempel mit multiplen kleinen Nadeln, welche die oberflächliche Epidermis durchstechen) zur Erhöhung der Wirkstoffpermeation sowie die Kombination von zwei feldgerichteten Ansätzen sind möglich [45, 57]. Tatsächlich sind multiple Kombinationen von fast allen verfügbaren Interventionen denkbar.

Die photodynamische Therapie (PDT) mit 5-Aminolävulinat (ALA) oder seinem Ester Methyl-Aminolävulinat (MAL) nimmt bei der Kombination von Interventionen einen hohen Stellenwert ein. Dies ist darin begründet, dass sie sowohl läsions- als auch feldgerichtet eingesetzt werden kann, wodurch sich vielfältige Kombinationsmöglichkeiten ergeben [46]. Außerdem ist die PDT eine hochwirksame und etablierte Behandlung für multiple AK oder die Feldkanzerisierung mit einem ausgezeichneten kosmetischen Ergebnis [44, 58, 59]. Die in einer Creme eingesetzten Wirksubstanzen dringen in das Stratum corneum ein und reichern sich in proliferierenden Zellen an, wo sie in photosensitive Porphyrine, u.a. Protoporphyrin IX, umgewandelt werden [60, 61]. Durch die anschließende Bestrahlung mit sichtbarem Licht entsteht toxischer Singulett-Sauerstoff. Zu den unerwünschten Nebenwirkungen gehören allerdings lokale Schmerzen während der Bestrahlung, die die Patientenzufriedenheit deutlich mindern [62]. Außerdem ist die PDT bei dickeren Läsionen meist unzureichend wirksam, da die Photosensibilisatoren nicht tief genug bei hyperkeratotischen Läsionen eindringen können. Dies macht eine physikalische Vorbehandlung (z.B. Kürettage) vor der PDT erforderlich. Um diese Nachteile auszugleichen, kann die PDT mit einer läsionsspezifischen Vorbehandlung z.B. durch ablative Laserverfahren kombiniert werden [42-44, 56]. Ablative fraktionierte Laser, darunter Erbium:YAG- oder Kohlendioxid ($CO_2$)-Laser, erhitzen das behandelte Gewebe auf bis zu 100 °C und verdampfen dadurch mikroskopisch kleine, vertikale Kanäle in der Haut, die das Eindringen und die Anreicherung von MAL bzw. ALA in dysplastischen Zellen erleichtern (sogenannte laserunterstützte Medikamentenabgabe) [43, 63].

Eine weitere in der Praxis oftmals eingesetzte Kombinationsmöglichkeit stellt die Behandlung der AK zunächst mittels Kryochirurgie gefolgt von einer topisch-medikamentösen Therapie dar [45, 52-55]. Hierbei wird ebenfalls ein läsionsgerichteter Ansatz (Kryochirurgie) mit einem feldgerichteten Ansatz wie z.B. der PDT oder topischen Medikamenten vereint, um einen synergistischen Nutzen zu erzielen [45, 52-55, 64]. Die Kryochirurgie ist eine schnelle und einfach durchzuführende Methode zur Therapie von einzelnen AK [65]. Zur Behandlung wird flüssiger Stickstoff (-196 °C) zur Vereisung des Gewebes im Sekundenbereich in ein bis drei Gefrier-Tau-Zyklen eingesetzt, um die AK zu zerstören. Die Ergänzung durch eine feldgerichtete Behandlung soll dazu beitragen, auch subklinische Läsionen zu erreichen. Hierfür steht eine Vielzahl effektiver topisch-medikamentöser Interventionen zur Verfügung. Insbesondere bei dickeren Läsionen sind sie jedoch durch eine schlechtere Wirkstoffpermeation oftmals nur unzureichend wirksam [45, 52-55]. Weiterhin zählt zu den Nachteilen einer feldgerichteten Therapie eine häufig längere Anwendungsdauer, welche die Adhärenz verringern kann [4]. Die Kombination aus Kryochirurgie und anschließender topisch-medikamentöser Behandlung soll den Vorteil bieten, dass die Wirkstoffe der Topika nach Entfernung der Keratosen durch die Kryochirurgie leichter und gezielter einwirken können und somit zu einem besseren Behandlungsergebnis führen [51, 53, 54, 64, 66, 67].

Allerdings wird der Einsatz von Kombinationstherapien bei AK auch kontrovers diskutiert, da die jeweiligen Monotherapien bei nicht vorbehandelten Läsionen bereits sehr wirksam sind und so unnötig mehr Ressourcen verwendet werden. Dies resultiert in einer Überbehandlung und einer Zunahme der Therapiekosten. Weiterhin könnte sich die Toxizität erhöhen [4, 38, 45]. Daher ist die Frage, ob Kombinationstherapien bei der Behandlung von AK gegenüber Monotherapien bevorzugt werden sollten, nach wie vor Gegenstand der Forschung. Bislang mangelt es an evidenzbasierten Synthesen in Form von systematischen Übersichtsarbeiten und Meta-Analysen sowie Empfehlungen zur tatsächlichen Effektivität und Sicherheit von Kombinationstherapien für AK, obwohl verfügbare Evidenz einen entscheidenden Aspekt in der Wahl der Therapie repräsentiert. Die deutsche S3-Leitlinie „Aktinische Keratose und Plattenepithelkarzinom der Haut" bezieht neben anderen Leitlinien zu dieser wichtigen Fragestellung aktuell ebenfalls nicht ausreichend Stellung, weshalb der Einsatz von Kombinationstherapien bisher ausschließlich auf Basis von Expertenmeinungen, Einzelstudien oder Einzelfallberichten individuell erfolgt [4, 38]. Daher werden evidenzbasierte Arbeiten zur Entscheidungsfindung in der Wahl von (Kombinations-) Therapien benötigt.

**Methodische Aspekte im Rahmen der Erstellung von evidenzbasierten Synthesen**

Bei der evidenzbasierten Aufarbeitung in Form von systematischen Übersichtsarbeiten oder Meta-Analysen ist ein transparentes, methodisches Vorgehen erforderlich. Daher ist eine Orientierung an den Vorgaben *der Cochrane Collaboration* und der *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) Arbeitsgruppe notwendig [68, 69]. Weiterhin ist bei der Aufbereitung und Publikation der Ergebnisse ein standardisiertes Vorgehen analog zu den Checklisten des *equator networks* zur Erstellung von systematischen Übersichtsarbeiten und Meta-Analysen (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)) wichtig [70]. Ein potentielles Risiko für eine Verzerrung (Bias) von eingeschlossenen RCT sollte immer von mindestens zwei Wissenschaftlern mit dem *Cochrane Risk of Bias Tool* als „niedrig", „unklar" oder „hoch" evaluiert werden, während die Qualität der Evidenz der Endpunkte als „hoch", „moderat", „niedrig" bzw. „sehr niedrig" mit der GRADE-Methodik und der Software GRADEpro GDT ebenfalls von mindestens zwei Wissenschaftlern hinsichtlich der fünf Kriterien Risiko für Bias, Inkonsistenz, fehlende Präzision, Indirektheit und Publikationsbias bewertet werden sollte [68, 69]. Die Bewertung des Risikos für Bias umfasst Aspekte hinsichtlich eines Selektionsbias (Generierung der Randomisierungssequenz, verdeckte Gruppenzuteilung), Performance Bias (Verblindung von Teilnehmern und Studienpersonal), Detection Bias (Verblindung der Endpunkterhebung), Attrition Bias (unvollständige Daten zu Endpunkten), Reporting Bias (selektives Berichten zu Endpunkten) sowie andere Ursachen für Bias [68]. Die Einschätzung des Risikos für eine Verzerrung bzw. der Qualität der Evidenz ist bedeutend für die Interpretation der Effektschätzer.

## 1.4.1.2 Medizinische Leitlinien

Neben der Evidenz aus Meta-Analysen und systematischen Übersichtsarbeiten wird die Wahl der Therapie der AK durch die Empfehlungen und Inhalte medizinischer Leitlinien beeinflusst. Da in den letzten Jahrzehnten weltweit eine Vielzahl verschiedener Interventionen für die Behandlung von AK zugelassen wurde, ist es für Ärzte oftmals schwierig, eine geeignete Therapie für den individuellen Patienten auszuwählen. Daher sind aktuelle medizinische Leitlinien wichtige Quellen oder Nachschlagewerke, die bei der Auswahl von evidenzbasierten und geeigneten Behandlungsoptionen unterstützen. Die bereitgestellten Empfehlungen sollten jedoch in einem strukturierten Prozess mit interdisziplinärer Beteiligung auf Grundlage einer standardisierten Methodik von höchster Qualität (z.B. systematische Literaturidentifikation mit anschließendem Konsensusverfahren) entwickelt werden, um die Aktualität, Verlässlichkeit und Evidenzbasierung der Leitlinien zu gewährleisten [71, 72].

Bislang wurden mehrere internationale Leitlinien zur Therapie der AK veröffentlicht, die durch unterschiedliche methodische Ansätze entwickelt wurden und sich dadurch in der Evidenzstufe unterscheiden [4, 38, 39, 73-76]. Darüber hinaus existieren zahlreiche Expertenreviews sowie Leitlinien speziell für Interventionen, wie z.B. die PDT [44, 58, 59, 77, 78]. Bei der Erstellung von Leitlinien für AK sind die Entwickler insbesondere neben der Vielzahl an unterschiedlichen Interventionen auch mit der daraus resultierenden Masse an Literatur konfrontiert. Im Indikationsgebiet der AK, insbesondere für die Therapie der AK, existieren neben vielen Beobachtungsstudien auch zahlreiche RCT, die nicht immer methodisch korrekt durchgeführt wurden. Ein weiteres Dilemma ist, dass die Interventionen selten in direkten Vergleichsstudien miteinander verglichen werden. Auch erschwerte bislang das Fehlen standardisierter Endpunkte einschließlich festgelegter Erhebungszeitpunkte den Vergleich von Interventionen [41]. Daher sprechen sich Leitlinienentwickler bislang gegen eine Hierarchisierung der Therapien aus [4, 38].

Für den behandelnden Arzt ist es daher oftmals schwierig, aufgrund der Vielzahl an Leitlinien und Expertenreviews den Überblick zu behalten und geeignete Leitlinien von hoher methodischer Qualität zu identifizieren und für seine zukünftige Wahl der Therapie zu konsultieren. Es ist mittlerweile gängige Praxis, die methodische Güte von Leitlinien mit standardisierten Instrumenten zu bewerten, da auch die Wirksamkeit und der Nutzen von Leitlinien von deren Qualität abhängt [79-83]. Am weitesten verbreitet und anerkannt ist das internationale Instrument *Appraisal of Guidelines for Research and Evaluation II* (AGREE II), welches auch von der Weltgesundheitsorganisation befürwortet wird [84, 85]. Zu den 6 Domänen gehören 1) Geltungsbereich und Zweck, 2) Beteiligung von Interessengruppen, 3) Genauigkeit der Leitlinienentwicklung, 4) Klarheit der Gestaltung, 5) Anwendbarkeit sowie 6) Redaktionelle Unabhängigkeit [85]. Die Bewertung erfolgt auf einer 7-Punkte-Skala von 1 (stimme überhaupt nicht zu) bis 7 (stimme voll und ganz zu) durch mindestens 2, am besten jedoch 4 Bewerter um die Reliabilität der Bewertung zu erhöhen [85]. Vor kurzem wurde außerdem *AGREE-REX: Recommendation Excellence* als Ergänzung zu AGREE II vorgestellt [86]. AGREE-REX ist ein neu entwickeltes Instrument zur Bewertung der klinischen Glaubwürdigkeit und Umsetzbarkeit von Leitlinien. Das Instrument besteht aus 9 Fragen, die in die 3 Domänen 1) klinische Anwendbarkeit, 2) Werte und Präferenzen und 3) Umsetzbarkeit gruppiert sind, sowie 2 Items zur Gesamtbewertung [86]. Die Bewertung erfolgt analog zu AGREE II. In Deutschland findet auch das Deutsche Leitlinien-Bewertungsinstrument (DELBI) Einsatz in der Bewertung von Leitlinien, allerdings ist es international nicht so verbreitet wie AGREE [83]. DELBI wurde von der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) und dem Ärztlichen Zentrum für Qualität in der Medizin entwickelt und besteht aus insgesamt 8 Domänen mit 34 Fragen, welche sich weitestgehend mit den Domänen von AGREE II überschneiden [83]. Allerdings fragt DELBI zusätzlich ab, ob die zu bewertende Leitlinie im deutschen Gesundheitssystem anwendbar ist [83].

Von den derzeit aktuell verfügbaren, internationalen, evidenz- und konsensusbasierten Leitlinien zur Behandlung von AK wurde die methodische Qualität bis dato nicht systematisch mit internationalen, standardisierten Instrumenten evaluiert. Die Identifizierung möglicher Schwächen und Stärken der verfügbaren Leitlinien für die Therapie der AK durch das etablierte Instrument AGREE II sowie das erst kürzlich publizierte AGREE-REX kann dazu beitragen, die deutsche Leitlinie bei der nächsten Aktualisierung nachhaltig zu verbessern und somit einen entscheidenden Beitrag für zukünftige Leitlinienarbeit zu leisten.

## 1.4.2 Patientenorientierte Therapieentscheidungen bei aktinischer Keratose

Weiterhin ist der Erfolg der individuellen Behandlung wie in den in Abbildung 3 beschriebenen Faktoren maßgeblich vom Patienten selbst abhängig. Fast alle Interventionen zur Behandlung von AK sind mit

Nachteilen für den Patienten assoziiert, darunter z.B. Schmerzen, Kosten, eine lange Behandlungsdauer, ein verändertes ästhetisches Erscheinungsbild oder lokale Hautreaktionen [4]. Diese Aspekte können die zugrundeliegenden Motive der Patienten beeinflussen, sich einer bestimmten Intervention zu unterziehen bzw. die Therapie gemäß den Behandlungsanweisungen durchzuführen und haben somit einen entscheidenden Einfluss auf die Effektivität der Behandlung [4, 40, 87-90]. Insbesondere bei selbst zu applizierenden Topika ist eine gute Therapieadhärenz und die Fähigkeit zur korrekten Anwendung des Patienten entscheidend für den Therapieerfolg [4].

In einem sogenannten diskreten Entscheidungsexperiment wurden bereits Patientenpräferenzen für topische Behandlungen bei AK untersucht [87]. Die Mehrheit der 109 Patienten aus Großbritannien war bereit, eine gewisse Verringerung sowohl der präventiven als auch kosmetischen Wirksamkeit zu akzeptieren, um die Belastung durch das Behandlungsschema, die Intensität der Hautreaktion und andere Nebenwirkungen zu vermindern [87]. Darüber hinaus untersuchte eine kürzlich publizierte systematische Übersichtsarbeit patientenberichtete Endpunkte bei der topischen Therapie von AK [90]. Ein patientenberichteter Endpunkt ist ein Endpunkt, der direkt vom Patienten berichtet wird und den Gesundheitszustand und die Erfahrungen zu einer bestimmten Behandlung erhebt [90]. Lediglich eine Studie wurde identifiziert, welche ein speziell für AK entwickeltes, validiertes Instrument zur Erfassung von patientenberichteten Endpunkten verwendet hatte, nämlich den *„Actinic Keratosis Quality of Life questionnaire"* [90, 91]. Weiterhin zeigte die Arbeit, dass die Adhärenz und die Patientenzufriedenheit bei kürzeren Behandlungsschemata besser ist [90].

Somit ist die Wahl der Therapie der AK auch maßgeblich von dem zu behandelnden Patienten abhängig und sollte bei der Entscheidung im Sinne einer partizipativen Entscheidungsfindung unbedingt berücksichtigt werden. Überraschenderweise wurden patientenbezogene Motive und Erwartungen an alle derzeit in Deutschland verfügbaren Behandlungsmöglichkeiten von AK in einem Echtwelt-Kontext bislang wenig erforscht, obwohl sie ein wesentliches Hindernis für die Adhärenz darstellen können [87, 88, 92, 93]. Eine Publikation definierte beispielsweise für die Selektion einer feldgerichteten Therapie sechs Patientenprofile, welche auf den Erfahrungen eines Expertengremiums bestehend aus 22 Dermatologen basierten [88]. Hierzu zählten unter anderem der „desinteressierte, uninformierte Typ", welcher sich primär eine schnelle und effektive Behandlung wünscht, der Typ, der sich um das Erscheinungsbild während bzw. nach der Behandlung sorgt, der „interessierte, informierte Typ", welcher gerne zusätzliche Informationen zur Behandlung wünscht oder auch der Typ, der sich um Nebenwirkungen sorgt und dementsprechend eine sichere Behandlung und frühzeitige Nachsorge wünscht [88]. Innerhalb dieses Forschungsteams wurden ebenfalls Entscheidungskriterien und Patientencharakteristika zur patientenorientierten Therapie der Feldkanzerisierung durch 6 Dermatologen im Rahmen eines Expertentreffens entwickelt [94]. Außerdem wurden 3 Patiententypologien definiert. Zu den patientenrelevanten Kriterien für die Behandlungsentscheidung gehörten unter anderem die Wirksamkeit, Praktikabilität, Sicherheit, Therapiedauer, Kosmesis, Patientenpräferenz, Adhärenz und Komorbiditäten [94]. Eine große Schwäche dieser Arbeiten ist allerdings, dass keine Echtweltdaten einbezogen wurden. Patienten selbst oder Patientenvertreter wurden nicht in das Gremium eingebunden. Es sind daher keine repräsentativen Meinungen der tatsächlichen Zielgruppe in die Entwicklung eingeflossen. Tatsächlich bestand das Expertengremium ausschließlich aus Ärzten. Weiterhin beschränkten sich die Profile nur auf Patienten, die eine feldgerichtete Therapie erhalten sollten oder von Feldkanzerisierung betroffen sind [88, 94].

Daher besteht ein Bedarf, die Einstellung zur Therapie der AK aus tatsächlicher Patientensicht in Deutschland in einem Echtwelt-Kontext zu untersuchen, um diese besser zu verstehen. Dieses Wissen kann dazu beitragen, die partizipative Entscheidungsfindung für zukünftige Behandlungen von Patienten mit AK zu stärken und hierdurch die Therapie zu verbessern.

# 2. Zielsetzungen der Arbeit

Die vorliegende Dissertation hatte vor dem Hintergrund der Therapieentscheidungen das übergeordnete Ziel, die evidenzbasierte und patientenorientierte Wahl der Therapie bei AK zu stärken und nachhaltig zu verbessern, um eine Basis für die klinische Entscheidungsfindung für Ärzte und Patienten im Rahmen einer partizipativen und personalisierten Entscheidungsfindung bereitzustellen.

Im Rahmen der vier Veröffentlichungen dieser Dissertation wurden folgende Teilziele festgelegt (Abb. 4):

1. Synthese der Evidenz zur Wirksamkeit und Sicherheit von ausgewählten Kombinationstherapien (lasergestützte PDT und Kryochirurgie in Kombination mit primär feldgerichteten Topika) für AK gemäß den Kriterien der evidenzbasierten Medizin (*Veröffentlichung I und Veröffentlichung II*).
2. Systematische Identifikation der derzeit aktuellen, internationalen und evidenzbasierten Leitlinien für die AK-Behandlung sowie Bewertung der methodischen Qualität mit standardisierten Instrumenten, um methodische Stärken und Schwächen für zukünftige Leitlinienarbeit abzuleiten (*Veröffentlichung III*).
3. Explorative Erforschung der Motivation von Patienten an die AK-Therapie in Deutschland anhand einer multizentrischen Querschnittserhebung in einem Echtwelt-Kontext (*Veröffentlichung IV*).
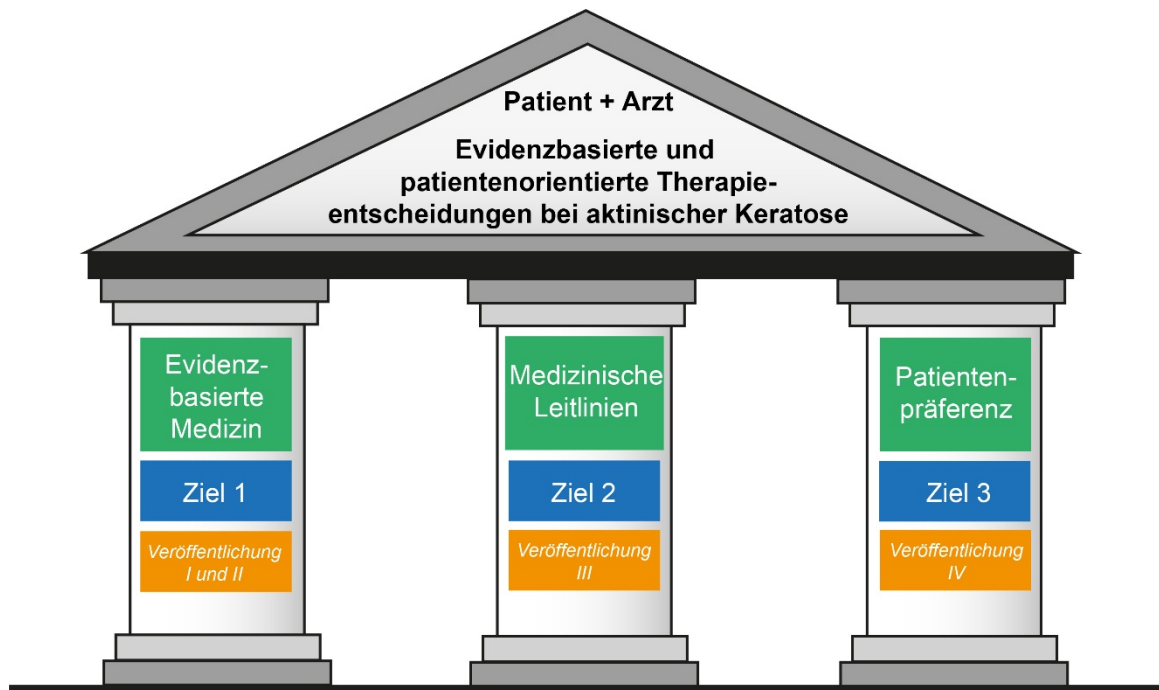


**Abbildung 4:** Einordnung der vier Veröffentlichungen der Dissertation zu den verschiedenen Zielen und Dimensionen für evidenzbasierte und patientenorientierte Therapieentscheidungen bei AK

# 3. Veröffentlichungen

## 3.1 Veröffentlichung I

In der Veröffentlichung "*Laser-assisted photodynamic therapy for actinic keratosis: A systematic review and meta-analysis*" (Steeb et al. 2019, *J Am Acad Dermatol,* IF: 8,3) haben wir die verfügbare Evidenz zur Wirksamkeit und Sicherheit der lasergestützten PDT erstmals gemäß den Kriterien der evidenzbasierten Medizin in einer systematischen Übersichtsarbeit und Meta-Analyse synthetisiert (Ziel 1) [95].

Vorab haben wir ein Protokoll zum methodischen Vorgehen bei der internationalen Online-Datenbank Prospero für Protokolle für systematische Übersichtsarbeiten und Meta-Analysen registriert (CRD42018087854). Wir haben uns hierbei und bei der weiteren Durchführung stark an den Vorgaben der *Cochrane Collaboration*, der GRADE-Arbeitsgruppe und den Vorgaben nach *PRISMA* orientiert [68-70]. Daraufhin wurde eine sensitive, systematische Literaturrecherche in den medizinischen Datenbanken Medline, Embase und Central sowie für graue Literatur in den gängigen Studienregistern durchgeführt. Die identifizierten Treffer wurden in eine EndNote-Library überführt. Nach Entfernung von Duplikaten wurden die Treffer von zwei Autoren unabhängig voneinander zunächst in einem Titel-Abstrakt-Screening auf die vorab definierten Ein- und Ausschlusskriterien gemäß PICO-Schema (*population, intervention, control, outcome*) geprüft und daraufhin einem Volltext-Screening unterzogen. Wir haben inter- und intraindividuelle RCT eingeschlossen, in denen Patienten bzw. ganze Behandlungsareale (als Cluster) mit klinisch oder histologisch diagnostizierten AK mit einer Kombination aus einem ablativen oder nicht ablativen Laser und einer PDT behandelt wurden. Weiterhin sollten diese RCT Daten zu vorab definierten Endpunkten wie beispielsweise der läsionsspezifischen Abheilungsrate oder zur Schmerzintensität (erhoben auf einer visuellen Analogskala (VAS) von 0 (keine) bis 10 (extreme Schmerzen)) nach zwei bis sechs Monaten nach Therapieende berichten. Hinsichtlich des PDT-Protokolls haben wir RCT eingeschlossen, die eine Rotlicht- oder eine Tageslicht-PDT mit ALA oder MAL als Photosensibilisator durchgeführt haben. Die Ergebnisse der eingeschlossenen Studien wurden zunächst extrahiert und dann mit Hilfe eines "Random-Effects-Modell" mit der Software RevMan 5.3 aggregiert [96], um relative Risiken (RR) für dichotome bzw. mittlere Differenzen (MD) für kontinuierliche Endpunkte mit 95% Konfidenzintervallen (CI) zu berechnen. Ein potentielles Risiko für Bias der RCT wurde von zwei Wissenschaftlern mit dem Cochrane Risk of Bias Tool als „niedrig", „unklar" oder „hoch" eingeschätzt, während die Qualität der Evidenz der Endpunkte als „hoch", „moderat", „niedrig" bzw. „sehr niedrig" mit der GRADE-Methodik und der Software GRADEpro GDT ebenfalls von diesen hinsichtlich fünf Kriterien (Risiko für Bias, Inkonsistenz, fehlende Präzision, Indirektheit, Publikationsbias) bewertet wurde [68, 69]. Eine Herausforderung dieser Veröffentlichung umfasste von einer methodischen Perspektive gesehen die Synthese von sowohl intra- als auch interindividuell konzipierten RCT. In intraindividuellen Studien werden nicht einzelne AK-Läsionen, sondern Behandlungsbereiche randomisiert. Obwohl die einzelnen Läsionen nicht auf die spezifischen Behandlungen randomisiert wurden, wurden sie für die Analysen der Arbeit als cluster-randomisiert betrachtet. Da keiner der eingeschlossenen RCT Clusterkorrelationen oder Designeffekte berichtete, wurden die jeweiligen berechneten Ergebnisse der Meta-Analysen zusätzlich einer Sensitivitätsanalyse ohne intraindividuelle RCT unterzogen, um einen möglichen Effekt der Synthesen einzuschätzen.

Unsere Literaturrecherche ergab 817 Treffer, von denen sieben RCT mit einer Stichprobengröße von n=240 den Auswahlkriterien entsprachen und in eine qualitative Analyse bzw. vier in eine Meta-Analyse eingeschlossen wurden. Zwei der Studien untersuchten die Intervention bei Organtransplantierten. Die lasergestützte PDT zeigte signifikant höhere läsionsbezogene Abheilungsraten als die PDT-Monotherapie (RR 1,33; 95% CI 1,24 - 1,42; I² = 25%). Eine Sensitivitätsanalyse mit ausschließlich interindividuellen RCT zeigte einen ähnlichen Effekt (RR 1,41; 95% CI, 1,27 - 1,56; I² = 0%). Außerdem gab es keinen

signifikanten Unterschied in der Schmerzintensität zwischen der lasergestützten PDT und der Monotherapie (MD 0,31; 95% CI -0,12 - 0,74; I² = 0%). Allerdings wurde die Evidenz für diese beiden Endpunkte als niedrig eingeschätzt. Weitere Endpunkte wurden inkonsistent berichtet. Die eingeschlossenen Studien zeigten ein hohes Risiko für Verzerrung, hauptsächlich aufgrund fehlender Verblindung. Zusätzlich kann als Limitation die klinische Heterogenität der eingeschlossenen Studien hinsichtlich der verschieden eingesetzten PDT-Protokolle und die Variabilität der eingesetzten Lasersysteme kritisiert werden. Darüber hinaus war die Teststärke möglicherweise aufgrund der begrenzten Stichprobengröße zu gering, um Unterschiede bezüglich der läsionsbezogenen Abheilungsrate zu identifizieren. Die Synthese und Bewertung der Effektivität auf Ebene der einzelnen Läsionen kann die tatsächliche Power verzerren, da in der Regel Stichprobenkalkulationen auf der Basis der Studienteilnehmer und nicht auf der Basis der Gesamtzahl der AK-Läsionen bei der Planung einer klinischen Studie beruhen. Dies ist jedoch ein statistischer Fallstrick, der auf der Ebene der einzelnen Studien auftritt, in denen die Berechnung läsionsspezifischer Ansprechraten ohne weitere statistische Anpassungen gängige Praxis zu sein scheint.

Zu den Herausforderungen bei dieser systematischen Übersichtsarbeit und Meta-Analyse zählte die Masse an Literatur durch die sensitiv gestalteten, systematischen Suchstrings sowie die Evidenzsynthese und Interpretation unter kritischer Würdigung der Qualität der Evidenz der Endpunkte sowie dem individuellen Risiko für Bias [68, 69]. Zusätzlich gestaltete sich die Auswahl geeigneter Endpunkte schwierig, da die Berichterstattung von AK-spezifischen Endpunkten in der Publikationslandschaft sehr heterogen ist und zum Zeitpunkt der Protokollerstellungen noch kein *core outcome set* (Katalog an Endpunkten) für AK konsentiert bzw. publiziert war [93].

Zusammenfassend zeigt diese Arbeit, dass die lasergestützte PDT effektiver und dabei nicht schmerzhafter als eine alleinige PDT ist. Daher kann sie für schwer zu behandelnde AK wie hyperkeratotische, akral lokalisierte Läsionen oder AK bei Organtransplantierten eingesetzt werden. Diese Arbeit bietet somit eine Grundlage für die klinische und partizipative Entscheidungsfindung von Dermatologen und Patienten sowie eine mögliche Begründung für die Übernahme der behandlungsbezogenen Kosten für die lasergestützte PDT durch die Krankenkassen.

## Beitrag zur Veröffentlichung I

Die Veröffentlichung wurde von mir zusammen mit Herrn Priv. Doz. Dr. med. Markus Heppt geplant und durchgeführt. Hierzu gehörten die Definition der Ein- und Ausschlusskriterien sowie die Registrierung des Protokolls bei Prospero. Zusammen mit Herrn Dr. med. J. Gabriel Schlager habe ich die systematische Literaturrecherche einschließlich der Erstellung des Suchstrings, das Titel-/Abstrakt-Screening, die Beschaffung der Volltexte mit anschließendem Volltextscreening unter Anwendung der Einschlusskriterien, die Datenextraktion sowie die Einschätzung des Risikos für Bias und die Bewertung der Evidenz der Endpunkte ausgeführt. Da diese Arbeitsschritte bei einer systematischen Übersichtsarbeit und Meta-Analyse gemäß den Kriterien der evidenzbasierten Medizin immer von mindestens zwei Gutachtern unabhängig voneinander durchzuführen sind, bin ich zusammen mit Herrn Dr. med. J. Gabriel Schlager Erstautorin dieser Publikation. Die gewonnenen Daten wurden von mir mit der Software RevMan 5.3 analysiert, interpretiert und mit Herrn Priv. Doz. Dr. med. Markus Heppt besprochen. Das Protokoll sowie das Manuskript einschließlich der Grafiken wurden in seiner ersten Fassung eigenständig von mir erstellt und zunächst nach Vorschlägen von Herrn Dr. med. J. Gabriel Schlager und Priv. Doz. Dr. med. Markus Heppt korrigiert, woraufhin ich das Manuskript nach weiteren Vorschlägen der Ko-Autoren nochmals revidiert und zur Publikation eingereicht habe. Die Ko-Autoren Frau Prof. Dr. med. Carola Berking und Herr Prof. Dr. med. Dr. h.c. mult. Thomas Ruzicka haben zur Durchführung der systematischen Übersichtsarbeit und Meta-Analyse beraten und Hilfestellung gewährt, das Manuskript kritisch revidiert und die wissenschaftliche Infrastruktur bereitgestellt. Herr Priv. Doz. Dr. med. Markus

Heppt stand darüber hinaus bei Diskrepanzen in der Auswahl der Volltexte gemäß den Einschlusskriterien, der Bias- und Evidenz-Bewertung sowie Datenextraktion zur Verfügung. Herr Christoph Kohl stand unterstützend bei speziellen Fragestellungen zur statistischen Auswertung zur Verfügung.

## Sonstiges

Die Ergebnisse dieser Arbeit wurden 2018 auf dem 28. Deutschen Hautkrebskongress in Stuttgart vorgestellt und mit dem Posterpreis der Arbeitsgemeinschaft Dermatologische Onkologie ausgezeichnet.

## 3.2 Veröffentlichung II

In Veröffentlichung II haben wir eine systematische Übersichtsarbeit mit Meta-Analyse durchgeführt, um den aktuellen Wissensstand zur Effektivität und Sicherheit der Kryochirurgie in Kombination mit primär feldgerichteten Topika im Vergleich zur Kryochirurgie alleine zu untersuchen (Ziel 1, Heppt, Steeb et al. 2019, *Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis*; *Br J Dermatol*; IF 7,0 [97]).

Zunächst haben wir für diese Fragestellung ein Protokoll in Prospero registriert (CRD42018102026). Diese Arbeit haben wir analog zur Veröffentlichung I durchgeführt; das methodische Vorgehen ist weitgehend identisch [70, 95]. Wir haben eine systematische Literaturrecherche in den medizinischen Datenbanken Medline, Embase und der Cochrane Library sowie in Studienregistern durchgeführt, um RCT zu identifizieren, in denen Patienten (interindividuelles Design) bzw. ganze Behandlungsareale (intraindividuelles Design) mit klinisch oder histologisch diagnostizierten AK zu einer Behandlung mit der Kryochirurgie alleine oder gefolgt von einer topischen Therapie randomisiert wurden. Die primären Endpunkte umfassten Effektivitätsendpunkte wie z.B. die vollständige (100%) und partielle (≥ 75%) patientenbezogene Abheilungsrate, während als sekundärer Endpunkt die Tolerabilität bestimmt wurde, definiert als die Anzahl der Patienten, die die Behandlung gemäß dem Studienprotokoll abschlossen und diese nicht aufgrund von behandlungsinduzierten, unerwünschten Ereignissen abbrachen. Alle Endpunkte mussten frühestens 2 Monate und nicht später als 6 Monate nach Behandlungsende berichtet werden. Die Ergebnisse der einzelnen Studien wurden mit Hilfe eines "Random-Effects-Modells" und der Software RevMan 5.3 [96] zu RR mit 95% CI zusammengefasst. Um den Einfluss auf die Effektschätzung zu berücksichtigen, haben wir eine Sensitivitätsanalyse durchgeführt, indem die Meta-Analyse nur mit interindividuellen Studien wiederholt wurde. Interventionsspezifische stratifizierte Analysen wurden zusätzlich durchgeführt, wenn zwei oder mehr Studien identifiziert wurden, die dieselben Vergleiche von topischen Interventionen mit Kryochirurgie untersuchten. Die Bewertung des Risikos für Bias sowie die Qualität der Evidenz der Endpunkte haben wir analog zur Meta-Analyse zur lasergestützten PDT vorgenommen [68, 69, 95].

Von 1758 identifizierten Publikationen entsprachen neun RCT mit einer Gesamtstichprobengröße von 1644 Patienten den Einschlusskriterien. Vier Studien analysierten die Kryochirurgie gefolgt von Imiquimod- (IMQ) Creme und zwei Studien die Kryochirurgie kombiniert mit Ingenolmebutat (IMB) Gel. Die verbleibenden Studien untersuchten die Kryochirurgie und Diclofenac-Natrium 3% in Hyaluronsäure 2,5% Gel, 5-Fluorouracil-Creme 0,5% oder ALA-PDT. Die Meta-Analyse zeigte, dass die Kryochirurgie in Kombination mit einem topischen Ansatz signifikant höhere vollständige patientenbezogene Abheilungsraten als die Kryochirurgie alleine erzielte (RR 1,74; 95% CI 1,25 - 2,43; I² = 73%). Eine Sensitivitätsanalyse mit ausschließlich interindividuellen RCT bestätigte diesen Effekt (RR 1,68; 95% CI 1,19 - 2,35; I² = 77%). Die Vertrauenswürdigkeit der Evidenz für diesen Endpunkt wurde allerdings aufgrund eines hohen Risikos für Bias, statistischer Heterogenität und geringer Präzision als niedrig eingeschätzt. Die Anzahl der Patienten, die die Behandlung gemäß Studienprotokoll abschlossen und die Studie nicht wegen Nebenwirkungen abbrachen, war in beiden Gruppen ähnlich (RR 0,98; 95% CI 0,95 -

1,01; I² = 75%). Die Evidenz wurde aber durch ein hohes Risiko für Bias und Inkonsistenz herabgestuft und als sehr gering bewertet. Eine Sensitivitätsanalyse ohne intraindividuelle RCT zeigte einen ähnlichen Effekt (RR 0,98; 95% CI 0,94 - 1,02; I² = 84%). Eine weitere Sensitivitätsanalyse wies zudem darauf hin, dass die Unterschiede der methodischen Qualität der RCT ursächlich für die statistische Heterogenität waren. Die weiteren vorab definierten Endpunkte waren statistisch nicht signifikant. Eine interventionsspezifische stratifizierte Analyse war für die Kryochirurgie plus IMB und IMQ möglich. Beide Kombinationsbehandlungen zeigten keine signifikanten Unterschiede hinsichtlich der patientenbezogenen Abheilungsrate im Vergleich zur Kryochirurgie allein (IMB: RR 3,51; 95% CI 0,22 - 56,52, I² = 77%, IMQ: RR 2,46; 95% CI 0,63 - 9,57, I² = 87%). Auch die Anzahl der Patienten, die die Behandlung aufgrund von unerwünschten Ereignissen abbrachen, war in beiden Gruppen ähnlich (IMB: RR 0,99; 95% CI 0,97 - 1,01, I² = 0%, IMQ: RR 0,99; 95% CI 0,97 - 1,01, I² = 0%). Insgesamt wurde das Risiko für Bias aufgrund einer selektiven Berichterstattung und einer fehlenden Patientenverblindung als hoch bewertet. Weiterhin ist die Interpretation der Ergebnisse kritisch hinsichtlich eines möglichen Sprachbias zu sehen, da ausschließlich englisch- und deutschsprachige Publikationen in dieser Übersichtsarbeit eingeschlossen wurden. Eine weitere Limitation bedingt die klinische Heterogenität zwischen den RCT, da die Durchführung der Kryochirurgie in allen Studien wenig standardisiert war und unterschiedliche Gefrier-Auftau-Zyklen und Gefrierzeiten angewendet wurden. Zusätzlich dazu wurde eine Vielzahl von topischen Wirkstoffen mit unterschiedlichen Wirkmechanismen und Anwendungsdauern untersucht bzw. in einer Off-Label-Anwendung eingesetzt.

Eine Herausforderung dieser Arbeit war die gemeinsame Analyse von inter- und intraindividuellen RCT. Eine angemessene Anpassung der Standardfehler war wie bei der Meta-Analyse zur lasergestützten PDT nicht möglich, da in den intraindividuellen Studien keine Clusterkorrelationen und Designeffekte berichtet wurden. Um diesen Effekt zu berücksichtigen, wurde nach Ausschluss der intraindividuellen Studien für jeden Endpunkt eine Sensitivitätsanalyse durchgeführt, die jeweils vergleichbare Ergebnisse aufzeigte.

Zusammenfassend deuten die Ergebnisse auf die Überlegenheit einer Kombination der Kryochirurgie mit Topika hinsichtlich der Effektivität bei gleicher Tolerabilität hin. Darüber hinaus unterstreichen die Ergebnisse die Bedeutung der Behandlung des gesamten betroffenen Hautareals bei Patienten mit multiplen AK und Feldkanzerisierung. Außerdem heben die Ergebnisse hervor, dass die Kryochirurgie als alleinige Therapieform bei schwer zu behandelnden Läsionen möglicherweise nicht ausreicht. Somit hat diese Studie als Grundlage für die Entscheidungsfindung von Dermatologen eine direkte Auswirkung auf die Patientenversorgung in der täglichen klinischen Praxis.

## Beitrag zur Veröffentlichung II

Die Veröffentlichung II wurde von mir zusammen mit Herrn Priv. Doz. Dr. med. Markus Heppt einschließlich der Definition der Ein- und Ausschlusskriterien geplant und durchgeführt. Der Suchstring für die systematische Recherche in den medizinischen Datenbanken sowie das Protokoll wurde initial von mir erstellt und nach Rücksprache mit Priv. Doz. Dr. med. Markus Heppt modifiziert. Weiterhin wurde von mir in Zusammenarbeit mit Herrn Priv. Doz. Dr. med. Markus Heppt die systematische Literaturrecherche inklusive Titel-/Abstrakt-Screening, Volltextbeschaffung und Volltextscreening, Datenextraktion, Analyse sowie die Bewertung des Risikos für Bias und der Evidenz der Endpunkte durchgeführt. Da diese Arbeitsschritte zur Sicherung einer hohen Qualität bei systematischen Übersichtsarbeiten und Meta-Analysen gemäß den Kriterien der evidenzbasierten Medizin immer von mindestens zwei Gutachtern unabhängig voneinander durchzuführen sind, teile ich mit Herrn Priv. Doz. Dr. med. Markus Heppt bei dieser Veröffentlichung die Erstautorenschaft. Die gewonnenen Daten wurden zunächst von mir mit der Software RevMan 5.3 analysiert und interpretiert und im Anschluss mit Herrn Priv. Doz. Dr. med. Markus Heppt diskutiert. Das Publikationsmanuskript einschließlich der Grafiken wurde in seiner ersten Fassung von mir zunächst eigenständig erstellt, nach Vorschlägen von Herrn Priv. Doz. Dr. med. Markus Heppt

sowie den Ko-Autoren verbessert, in die finale Fassung gebracht und zur Publikation eingereicht. Die Ko-Autoren Frau Prof. Dr. med. Carola Berking und Herr Prof. Dr. med. Dr. h.c. mult. Thomas Ruzicka haben das Manuskript kritisch revidiert, zur Durchführung der systematischen Übersichtsarbeit und Meta-Analyse beraten und Hilfestellung gewährt, sowie die wissenschaftliche Infrastruktur bereitgestellt. Frau Prof. Dr. med. Carola Berking hat darüber hinaus bei Unstimmigkeiten in der Auswahl der Studien im Rahmen des Volltextscreenings beraten.

## 3.3 Veröffentlichung III

In den letzten Jahrzehnten wurde eine Vielzahl von Interventionen für die Behandlung von AK zugelassen. Aktuelle medizinische Leitlinien sind daher wertvolle Quellen zur Unterstützung des Arztes in der Auswahl eines evidenzbasierten und geeigneten Behandlungsschemas. Es existieren jedoch zahlreiche Behandlungsleitlinien sowie Expertenreviews, die mit unterschiedlichen methodischen Herangehensweisen erstellt wurden. Diese Vielfalt macht es für Ärzte oftmals schwierig, die methodisch beste Leitlinie zu identifizieren und aus dieser eine geeignete Therapie für den individuellen Patienten auszuwählen. Die Veröffentlichung „*A critical appraisal of evidence- and consensus-cased guidelines for actinic keratosis*" (Wessely, Steeb et al. 2021, *Curr Oncol*, IF: 3,7) hatte zum Ziel, die derzeit aktuellen, internationalen und evidenzbasierten Leitlinien für die AK-Behandlung zunächst zu identifizieren und deren methodische Qualität anschließend zu bewerten, um methodische Stärken und Schwächen für zukünftige Leitlinienarbeit abzuleiten (Ziel 2) [98].

Zunächst haben wir eine systematische Literaturrecherche nach evidenz- und konsensusbasierten Leitlinien (entsprechend dem deutschen „S3-Niveau") zur Behandlung von AK vorgenommen, die innerhalb der letzten 5 Jahre veröffentlicht wurden und derzeit noch gültig sind. Hierfür wurden Leitliniendatenbanken (z.B. *Guideline International Network*) sowie die medizinischen Datenbanken Medline und Embase durchsucht. Zwei Autoren prüften die Treffer auf die vorab definierten Ein- und Ausschlusskriterien. Daraufhin wurde die methodische Qualität von sechs Gutachtern unabhängig voneinander mit den anerkannten und validierten Bewertungsinstrumenten für Leitlinien AGREE II und der neu entwickelten Ergänzung AGREE-REX auf einer 7-Punkte-Likert-Skala bewertet [86, 99-101]. Die verschiedenen Bewertungen wurden gemäß den Vorgaben der AGREE II- und AGREE-REX-Instruktionen (siehe Einleitung) für jede Domäne summiert [86, 99-101]. Die Gesamtpunktzahlen jeder Domäne wurden dann als Prozentsatz der maximal erreichbaren Punktzahl für diese Domäne berechnet und reichte von 0% (schlechteste) bis 100% (beste mögliche Bewertung) [86, 99-101]. Neben einer deskriptiven Analyse wurden mit dem Kruskal-Wallis (H)-Tests Subgruppenunterschiede zwischen den Leitlinien untersucht, während eine Spearman-Korrelation eingesetzt wurde, um die Beziehung zwischen den einzelnen Domänen zu untersuchen. Die statistischen Analysen wurden mit der Software Statistical Package for the Social Sciences (SPSS) Version 24 vollzogen [102].

Von insgesamt 2612 Treffern entsprachen drei Leitlinien aus Kanada, Deutschland und dem Vereinigten Königreich den Einschlusskriterien und wurden mit den zwei Instrumenten bewertet. Die deutsche Leitlinie erreichte die höchsten Punktzahlen und erfüllte 65% bis 92% der Kriterien in AGREE II und 67% bis 84% in AGREE-REX, während die kanadische Leitlinie 31% bis 71% der Kriterien in AGREE II und 33% bis 46% in AGREE-REX erreichte und somit erhebliche methodische Mängel aufwies. Die meisten der AGREE II- und AGREE-REX-Domänen korrelierten signifikant positiv miteinander. Die Domänen "Beteiligung der Interessengruppen" und "Werte und Präferenzen" wurden insgesamt als methodische Schwachstellen identifiziert. Diese Domänen benötigen daher bei zukünftigen Leitlinienvorhaben zu AK besondere Aufmerksamkeit und Verbesserung. Die kanadische und deutsche Leitlinie unterschieden sich darüber hinaus in fast allen AGREE-Domänen statistisch signifikant voneinander.

Eine mögliche Erklärung für die gute Bewertung der deutschen Leitlinie ist, dass die AWMF und die Deutsche Krebsgesellschaft, die für die Entwicklung onkologischer Leitlinien in Deutschland verantwortlich sind, nicht nur begleitende Unterstützung des Leitlinienkoordinationsteams gewährleisten, sondern auch ein methodisches Regelwerk für die Leitlinienautoren vorgeben, an das sich diese halten müssen. Dieses Regelwerk orientiert sich darüber hinaus an AGREE II. Zu diskutieren ist bei dieser Arbeit, dass ausschließlich die methodische Qualität der Leitlinien bewertet wurde und nicht der Inhalt oder die Empfehlungen selbst. Weiterhin ist die Vorgehensweise der Bewertung kritisch zu sehen, da diese nicht verblindet hinsichtlich des Herkunftslandes der Leitlinie stattgefunden hat und alle Gutachter aus Deutschland stammen. Allerdings waren alle Gutachter hinsichtlich der Bewertung der anderen Gutachter verblindet. Zusätzlich waren drei Autoren dieser Arbeit an der Entwicklung der deutschen S3-Leitlinie „Aktinische Keratose und Plattenepithelkarzinom der Haut" beteiligt. Sie übernahmen allerdings keine Rolle bei der aktiven Bewertung der Leitlinien, um keine systematische Verzerrung zu verursachen. Darüber hinaus kann die sprachliche Beschränkung auf Englisch und Deutsch zum Ausschluss relevanter Leitlinien geführt haben und ein Risiko für einen Selektions- bzw. Sprachbias darstellen. Neben der Masse an identifizierter Literatur im Rahmen der systematischen, sensitiven Recherche und Anwendung der Einschlusskriterien zählte neben dem Umgang mit potentiellen Interessenskonflikten die Bewertung durch insgesamt sechs verschiedene Reviewer und deren Übereinstimmung zu den Hürden bei diesem Projekt.

Nichtsdestotrotz verdeutlichen die Ergebnisse dieser Arbeit, dass die deutsche Leitlinie als Vorbild für die Entwicklung bzw. Aktualisierung zukünftiger Leitlinien unter Berücksichtigung bzw. Verbesserung der schlecht bewerteten Domänen dienen kann. Weiterhin sollten die Ergebnisse bei der derzeitigen Aktualisierung der deutschen S3-Leitlinie unbedingt beachtet werden. Somit haben die Ergebnisse dieser Arbeit in der Zukunft auch unmittelbare Auswirkungen auf die klinische und partizipative Entscheidungsfindung bei der Behandlung der AK.

## Beitrag zur Veröffentlichung III

Die Veröffentlichung III wurde von mir zusammen mit Herrn Priv. Doz. Dr. med. Markus Heppt in Anlehnung an bereits durchgeführte, publizierte Leitlinienevaluationen der Arbeitsgruppe zum kutanen Melanom [80] und Aderhautmelanom [79] entworfen und durchgeführt. Ebenso wurden die gewonnenen Daten von mir zusammen mit Frau Anja Wessely analysiert und interpretiert. Die systematische Literaturrecherche erfolgte durch mich in Absprache mit Herrn Priv. Doz. Dr. med. Markus Heppt, während die Erhebung der Daten durch Frau Anja Wessely, Herrn Dr. med. Franz Heppt, Frau Dr. med. Annkathrin Hornung, Herrn Matthias Kaufmann, Herrn Dr. med. Elias Koch und Herrn Dr. med. Frédéric Toussaint erfolgte. Ich habe bewusst nicht an der Bewertung der Leitlinien teilgenommen, da ich an der Entwicklung und Aktualisierung der deutschen S3-Leitlinie „Aktinische Keratose und Plattenepithelkarzinom der Haut" beteiligt war bzw. bin und durch diesen potentiellen Interessenskonflikt keine systematische Verzerrung der Bewertungen bewirken wollte. Das Manuskript wurde in seiner ersten Fassung von mir, Frau Anja Wessely und Herrn Priv. Doz. Dr. med. Markus Heppt erstellt, nach Anmerkungen der Ko-Autoren revidiert, finalisiert und zur Publikation eingereicht. Bei potentiellen Rückfragen zur Durchführung und Interpretation der Ergebnisse stand ich mit der Erstautorin Frau Anja Wessely in regem Austausch. Die Grafiken wurden von Frau Anja Wessely in Rücksprache mit mir erstellt. Die Ko-Autoren Frau Prof. Dr. med. Carola Berking und Herr Dr. med. Michael Erdmann haben zur Durchführung der Arbeit beraten und Hilfestellung gewährt und das Manuskript kritisch revidiert. Frau Prof. Dr. med. Carola Berking hat darüber hinaus die wissenschaftliche Infrastruktur bereitgestellt.

## 3.4 Veröffentlichung IV

Die Motivation für eine Behandlung von AK, die individuelle Erwartung an die Therapie und Präferenzen aus Sicht der Patienten haben einen entscheidenden Einfluss auf den Erfolg der Behandlung. Das Wissen ist insbesondere wichtig, um die Akzeptanz und Adhärenz der Behandlung zu erhöhen. Überraschenderweise wurde diesen patientenbezogenen Aspekten in Deutschland in einem Echtwelt-Kontext bisher wenig Aufmerksamkeit geschenkt. Daher war das Ziel der Veröffentlichung „*Treatment motivations and expectations in patients with actinic keratosis: a German-wide multicenter, cross-sectional trial*" (Steeb et al. 2020, *J Clin Med*, IF: 5,7), Einblicke in die Einstellung zur Therapie zu gewinnen, indem Erwartungen und Motive zur Therapie der AK aus Patientensicht in Deutschland in einem Echtwelt-Kontext explorativ untersucht wurden (Ziel 3) [103].

Zur Ableitung bzw. Gruppierung von Patientenprofilen einschließlich Behandlungsmotivationen und - erwartungen von Patienten mit AK haben wir eine deutschlandweite Querschnittsstudie an insgesamt 14 Hautkliniken durchgeführt. Nach Einholung des Ethikvotums sowie Erstellung und Pilotierung des anonymisierten Fragebogens haben wir diesen an teilnahmeberechtigte Patienten mit AK ab 18 Jahren ausgegeben. Der Fragebogen umfasste neben der Abfrage von soziodemografischen Daten auch Items, die verschiedene Behandlungsmotive sowie Erwartungen an die AK-Behandlung beschreiben. Diese wurden mit Hilfe einer VAS erfasst und umfassten einen Wertebereich von 0-10, wobei 0 keine Zustimmung und 10 eine hohe Zustimmung bedeutete. Die statistische Auswertung erfolgte mit der Software SPSS Version 24 [102]. Neben der deskriptiven Statistik wurden Subgruppenunterschiede zwischen zwei Gruppen mit dem t-Test oder dem Mann-Whitney-U-Test untersucht. Für den Vergleich von mehr als zwei Gruppen wurde eine einfaktorielle Varianzanalyse oder der Kruskal-Wallis-Test eingesetzt. Der Zusammenhang zwischen dem Grad der Übereinstimmung von Patientenmotiven und Erwartungen an die AK-Therapie haben wir mit der Spearman-Korrelation untersucht. Ein zweiseitiger p-Wert $< 0,05$ wurde als statistisch signifikant angesehen. Darüber hinaus haben wir uns bei der Erstellung dieser Arbeit an der *STrengthening the Reporting of OBservational studies in Epidemiology* (STROBE) Checkliste des *equator networks* orientiert [104].

Insgesamt lagen Daten von 403 Patienten mit einem medianen Alter von 77 Jahren (Bereich 43 - 94) vor. Die höchsten Werte für die Motivation zur Therapie wurden für die Items "Vermeiden der Weiterentwicklung zu invasivem Hautkrebs" (Mittelwert ± Standardabweichung; 8,98 ± 1,46) und "Arzt empfiehlt Therapie" (8,10 ± 2,37; p < 0,01) berichtet. Eine Subgruppenanalyse zeigte, dass Patienten im Alter von ≥ 77 Jahren und solche mit ≥ 7 Läsionen aufgrund einer geringeren intrinsischen und extrinsischen Motivation ein hohes Risiko hatten, sich keiner Behandlung zu unterziehen. Bei den Aspekten, die die Therapieerwartung der Patienten beschrieben, erreichten die Items "effektive Läsionsabheilung" (8,36 ± 1,99), "Sicherheit der Behandlung" (8,20 ± 2,03) und "Erstattung der Behandlungskosten durch Krankenkasse" (8,00 ± 2,41; p < 0,01) die höchsten Werte. Zusätzlich dazu wurden vier Gruppierungen (Cluster) von Motivations- und Erwartungsprofilen durch eine Hitzekarte („*Heatmap*") der Korrelationsanalyse identifiziert.

Diese Ergebnisse müssen allerdings vorsichtig interpretiert werden, da die Stichprobengröße relativ klein ist und da die Studienpopulation nicht zufällig, sondern in Abhängigkeit von der Verfügbarkeit von Patienten in den Universitätskliniken rekrutiert wurde. Die meisten Fragebögen stammten von Patienten des Universitätsklinikums München, möglicherweise führt diese Überrepräsentation zu einer Verzerrung der Ergebnisse. Daher sind die Ergebnisse möglicherweise nicht vollständig auf die Allgemeinbevölkerung übertragbar und unterliegen wahrscheinlich dem Risiko eines Selektions- sowie eines Erinnerungs-Bias.

Nichtsdestotrotz bietet diese Arbeit ein patientenbasiertes, heuristisches Werkzeug für eine personalisierte Behandlungsentscheidung bei Patienten mit AK. Die Kenntnis der unterschiedlichen Patientenprofile kann

dazu beitragen, die Therapieadhärenz von Patienten zu verbessern. Somit könnten die Ergebnisse ein zukünftiges personalisiertes Management der AK ermöglichen. Dadurch haben die Ergebnisse auch unmittelbare Auswirkungen auf die klinische und partizipative Entscheidungsfindung für zukünftige Behandlungen von Patienten mit AK.

## Beitrag zur Veröffentlichung IV

Die Veröffentlichung IV wurde von mir zusammen mit Herrn Priv. Doz. Dr. med. Markus Heppt und Frau Prof. Dr. med. Carola Berking entworfen. Der Fragebogen wurde in seiner ersten Fassung von mir entwickelt und zusammen mit Herrn Priv. Doz. Dr. med. Markus Heppt und Frau Prof. Dr. med. Carola Berking überarbeitet, woraufhin ich einen Pretest zur Finalisierung des Fragebogens durchführte. Das Einholen des Ethikvotums der Ethikkommission München wurde durch mich und Herrn Priv. Doz. Dr. med. Markus Heppt übernommen. Die Datenerhebung erfolgte durch mich sowie die Ko-Autoren (Frau Prof. Dr. med. Dagmar von Bubnoff, Herr Prof. Dr. med. Thomas Dirschka, Herr Dr. med. Konstantin Drexler, Herr Dr. med. Conrad Falkenberg, Frau Prof. Dr. med. Jessica Hassel, Herr Dr. med. Kinan Hayani, Frau Dr. med. Svea Hüning, Frau Dr. med. Katharina Kähler, Frau Prof. Dr. med. Sigrid Karrer, Herr Dr. med. Christian Krammer, Frau Prof. Dr. med. Ulrike Leiter, Frau Diana Lill, Herr Enklajd Marsela, Herr Dr. med. Andreas Meiwes, Frau Prof. Dr. med. Dorothée Nashan, Frau Dr. med. Suzan Stürmer (geb. Nasifoglu), Herr Dr. med. Lutz Schmitz, Frau Dr. med. Judith Sirokay, Herr Dr. med. Alexander Thiem, Herr Prof. Dr. med. Jochen Utikal, Herr Priv. Doz. Dr. med. Alexander Zink sowie Herr Priv. Doz. Dr. med. Markus Heppt). Die Dateneingabe bzw. -codierung wurde von mir durchgeführt und durch Frau Anja Wessely bzw. Matthias Harlaß kontrolliert. Die Auswertung und Interpretation der Ergebnisse erfolgte zunächst selbstständig durch mich. Daraufhin wurden die Ergebnisse mit Herrn Priv. Doz. Dr. med. Markus Heppt besprochen, während die Grafiken in Zusammenarbeit mit Frau Anja Wessely erstellt wurden. Das Manuskript wurde in seiner ersten Fassung von mir als alleinige Erstautorin erstellt und von Herrn Priv. Doz. Dr. med. Markus Heppt korrigiert. Nach Einholen von Feedback der Ko-Autoren zum Publikationsmanuskript wurde dieses durch mich revidiert, finalisiert und zur Publikation eingereicht. Die Ko-Autorin Frau Prof. Dr. med. Carola Berking hat darüber hinaus zur Durchführung der Querschnittsstudie beraten und Hilfestellung gewährt sowie die wissenschaftliche Infrastruktur bereitgestellt. Außerdem hat Frau Prof. Dr. med. Carola Berking den Kontakt zu den an der Querschnittsstudie teilnehmenden Zentren hergestellt.

# 4. Ausblick

AK repräsentieren eine chronische Erkrankung und bedingen aufgrund ihrer Häufigkeit eine hohe Krankheitslast [2-4, 38]. Es ist anzunehmen, dass die Erkrankungsrate aufgrund des demografischen Wandels weiterhin steigen wird. Somit wird die Auswahl der Behandlungsoptionen auch in Zukunft eine zentrale Rolle in der Entscheidungspraxis von Ärzten einnehmen [4]. Dies ist nicht nur in der Vielzahl an Therapiemöglichkeiten begründet, sondern auch an dem dynamischen Feld der Therapie mit sowohl neuen als auch ruhenden Zulassungen. So entschied beispielsweise die Europäische Arzneimittel-Agentur zusammen mit dem Bundesinstitut für Arzneimittel und Medizinprodukte im Januar 2020, die Zulassung von IMB als Vorsichtsmaßnahme auszusetzen und das Präparat auf dem deutschen Markt vorerst nicht mehr zu vertreiben [105, 106]. Dies wurde mit den Ergebnissen einer Langzeitanalyse begründet, welche eine höhere Inzidenz von PEK unter IMB im direkten Vergleich zu IMQ bei insgesamt 484 Patienten zeigte (IMB 3,3% vs. IMQ 0,4%). Auch in vier weiteren Studien mit insgesamt 1234 Patienten zeigte sich, dass die mit dem IMB-verwandten Ester Ingenoldisoxat behandelten Patienten eine höhere Inzidenz an Hauttumoren aufwiesen als die Patienten der Kontrollgruppe, die lediglich das Vehikel erhielten (7,7% vs. 2,9%) [105]. Somit steht in Europa eine Therapiemöglichkeit weniger zur Verfügung, allerdings wurden in der Zwischenzeit andere Interventionen zur Therapie der AK zugelassen, wie beispielsweise

Kaliumhydroxid 5% Lösung, 5-Fluorouracil 4% Creme sowie Tirbanibulin 1% Salbe. Letztere wurde im Juli 2021 von der Europäischen Arzneimittel-Agentur zugelassen und zeigte in zwei Phase-III-RCT mit 702 Patienten patientenbezogene Abheilungsraten von 44% bis 54% im Vergleich zu 5% bis 16% für die Kontrollgruppe bei einem guten Sicherheitsprofil, das vergleichbar mit bereits verfügbaren Topika ist [107, 108]. Ebenfalls gibt es beispielsweise erste Machbarkeitsstudien zur Therapie mit Mikrowellen [109]. Somit ist es wahrscheinlich, dass in absehbarer Zukunft auch weitere Kombinationen von Therapieansätzen getestet werden können.

Auch bereits etablierte Ansätze wie die PDT werden kontinuierlich weiterentwickelt. So wurden beispielsweise alternative Protokolle mit wiederverwendbaren Textilien wie einem biophotonischen Helm als Lichtquelle („Phosistos Protokoll") [110, 111] entwickelt. Außerdem wurden niedrigschwellige Ansätze wie die PDT „to go" vorgestellt, die die Patienten selbst zuhause anwenden können [112, 113]. Auf der anderen Seite können Langzeitergebnisse aus Phase-IV-Studien oder nicht-interventionellen Studien die publizierten Effektivitäts- und Sicherheitsdaten der Zulassungsstudien in ein neues Licht stellen, wie beispielsweise im Fall von IMB [114]. Dies muss zwangsläufig zu einem Überdenken bestehender Behandlungsmuster führen.

Die Vielzahl an Therapiemöglichkeiten wird weiterhin Fluch und Segen zugleich sein. Zusätzlich werden die Endpunkte sehr heterogen erfasst und berichtet, was neben dem generellen Vergleich der Interventionen auch die Zusammenfassung mehrerer Studien im Zuge von Meta-Analysen und die Leitlinienarbeit erschwert. Ein erster Schritt zur Verbesserung eines standardisierten Vergleichs der Therapien ist das kürzlich publizierte, sogenannte *core outcome set* für AK, ein Katalog an Endpunkten, die zukünftig immer in klinischen Studien berichtet werden sollen [93]. Es wurden sechs Endpunkte konsentiert: (1.) Vollständige Abheilung der AK, (2.) Prozentsatz an abgeheilten AK, (3.) Schweregrad der Nebenwirkungen, (4.) Patientenperspektive hinsichtlich der Wirksamkeit, (5.) vom Patienten berichtete zukünftige Behandlungspräferenz und (6.) Rezidivrate. Es wird zusätzlich empfohlen, das Ansprechen auf die Behandlung nach 2 bis 4 Monaten und die Rezidivrate nach 6 bis 12 Monaten zu berichten. Außerdem soll die Progressionsrate von AK zu einem PEK immer bei Langzeitstudien berichtet werden [93].

Ein weiterer Meilenstein könnte die Entwicklung einer internationalen *living guideline* für AK sein, die für sämtliche Fragestellungen und Therapieansätze die Evidenz synthetisiert und somit einen wichtigen und kontinuierlich aktualisierten Evidenzkörper als Zusatz für bestehende nationale Leitlinien repräsentieren würde [115, 116].

# 5. Zusammenfassung

Aktinische Keratosen (AK) sind häufige präkanzeröse Hautveränderungen bei Menschen mit hellem Hauttyp. Sie entstehen durch kumulative Exposition gegenüber ultravioletter Strahlung an sonnenbelichteter Haut. In Deutschland sind Schätzungen zufolge mehr als 10% aller 60- bis 70-Jährigen von AK betroffen, wobei der tatsächliche Anteil wahrscheinlich sehr viel höher ist. Da AK in ein invasives kutanes Plattenepithelkarzinom (PEK) übergehen können, wird eine frühzeitige Behandlung empfohlen.

Die vorliegende Dissertation umfasst vier publizierte Studien, welche die evidenzbasierte und patientenorientierte Entscheidungsfindung zur Behandlung von AK verbessern sollen. Die ersten beiden Publikationen fassen als systematische Übersichtsarbeiten mit Meta-Analysen erstmals den aktuellen Wissensstand zur Wirksamkeit und Sicherheit ausgewählter Kombinationstherapien bei AK zusammen. Hierzu fehlte bislang eindeutige Evidenz und auch die derzeit verfügbaren Leitlinien sprechen keine konkreten Empfehlungen aus. Die lasergestützte photodynamische Therapie (PDT) zeigte signifikant höhere läsionsbezogene Abheilungsraten als die PDT-Monotherapie bei gleicher Schmerzintensität. Die Kryochirurgie in Kombination mit einer topischen Intervention war der Monotherapie hinsichtlich der Wirksamkeit durch signifikant höhere patientenbezogene Abheilungsraten bei ähnlicher Verträglichkeit überlegen. Die Publikationen bieten somit eine Grundlage für die klinische Entscheidungsfindung für Ärzte und Patienten.

Den evidenzbasierten Arbeiten zu Kombinationstherapien schließt sich eine systematische Identifizierung und anschließende Bewertung der methodischen Qualität der aktuell verfügbaren internationalen evidenz- und konsensusbasierten Leitlinien zur Behandlung der AK an. Die kritische Bewertung durch sechs Gutachter mit den Instrumenten AGREE II und AGREE-REX zeigte, dass die S3-Leitlinie aus Deutschland die höchsten Werte erreichte, gefolgt von der Leitlinie aus dem Vereinigten Königreich und Kanada. Somit repräsentiert die deutsche Leitlinie unter Berücksichtigung der identifizierten Schwachstellen eine mögliche Adaptationsgrundlage für zukünftige AK-Leitlinien bzw. Aktualisierungen.

Weiterhin hängt der individuelle Behandlungserfolg maßgeblich von patientenbezogenen Faktoren ab, die die zugrundeliegende Motivation von Patienten beeinflussen, sich für eine bestimmte Intervention zu entscheiden oder sich kontinuierlich an den Behandlungsablauf zu halten. Daher wurde die Motivation sowie die Erwartungen an die Therapie von AK aus Patientensicht in einer multizentrischen, deutschlandweiten Querschnittsstudie untersucht. Insgesamt konnten vier Cluster mit unterschiedlichen Motivations- und Erwartungsprofilen aus Daten von 403 Patienten abgeleitet werden. Die meisten Patienten stimmten zu, sich einer Behandlung zu unterziehen, um die Entwicklung in ein invasives kutanes PEK zu vermeiden oder weil der behandelnde Arzt eine Therapie empfiehlt. Darüber hinaus stimmten die meisten Patienten zu, dass sie eine effektive Läsionsabheilung bzw. eine sichere Therapie erwarten oder dass die behandlungsbedingten Kosten von ihrer Krankenkasse erstattet werden. Diese Arbeit ergänzt die evidenzbasierten Studien mit Daten aus einem Echtwelt-Kontext aus Deutschland im Sinne einer ganzheitlichen Anschauung der Therapie von AK.

Insgesamt liefern die Ergebnisse der vier Publikationen den praktisch tätigen Dermatologen sowie den Patienten mit AK Informationen und unterstützen sie bei der Wahl der besten, evidenzbasierten und patientenorientierten Behandlung. Die in dieser Dissertation vorgestellten Publikationen ergänzen die bestehende S3-Leitlinie zu AK und haben unmittelbare Auswirkungen auf die klinische und partizipative Entscheidungsfindung für zukünftige Behandlungen von Patienten mit AK. Außerdem bietet die Publikation zur Leitlinienevaluation anderen Entwicklern von Leitlinien die Möglichkeit, Schwachstellen zu identifizieren und die eigene Leitlinienarbeit zu unterstützen, um die beste verfügbare Evidenz sowohl für die Behandler als auch für Patienten mit AK zu gewährleisten.

# 6. Summary (English)

Actinic keratoses (AK) are common precancerous lesions of the skin in fair-skin individuals. They arise as a result of cumulative exposure to ultraviolet radiation on sun-exposed areas. In Germany, AK affect approximately more than 10% of all 60- to 70-year-olds, although the actual proportion is probably much higher. As AK may progress to invasive cutaneous squamous cell carcinoma, early treatment is recommended.

This doctoral thesis comprises four published studies to improve evidence-based and participatory decision-making for the treatment of AK. The first two publications are systematic reviews with meta-analyses and summarize the current evidence on the efficacy and safety of selected combination therapies for AK. Until now, clear-cut evidence regarding combination therapies for AK have been lacking and the available guidelines also did not make any specific recommendations. Overall, laser-assisted photodynamic therapy (PDT) revealed significantly higher lesion-specific clearance rates than PDT monotherapy while being equally painful. Besides this, cryosurgery in combination with a topical approach was superior compared to monotherapy in terms of efficacy due to significantly higher participant complete clearance rates with a similar tolerability. Thus, the two publications provide a solid basis for clinical decision-making for physicians and patients.

The evidence-based projects on combination therapies were followed by a systematic identification and evaluation of the methodological quality of currently available international evidence- and consensus-based guidelines for the treatment of AK. The critical appraisal of six reviewers using the instruments Appraisal of Guidelines for Research and Evaluation (AGREE II) and Appraisal of Guidelines for Research and Evaluation - Recommendation EXcellence (AGREE-REX) showed that the S3-guideline from Germany achieved the highest scores, followed by the guideline from the United Kingdom and Canada. Thus, taking into account the identified weaknesses, the German guideline may serve as a possible adaptation basis for future AK guidelines and updates.

Finally, the motivation as well as the expectations towards AK therapy from the patient's point of view were investigated in a multicenter, cross-sectional study including 403 patients in Germany. The individual treatment success depends significantly on patient-related factors that influence the underlying motivation of patients to choose or to continuously adhere to a particular intervention. Overall, four clusters with distinct motivation and expectation profiles were deduced. Most patients agreed to undergo AK treatment to avoid progression to invasive cutaneous squamous cell carcinoma or because the treating physician recommends treatment. Furthermore, most patients agreed to expect an effective lesion clearance, a safe therapy or that the treatment-related costs are reimbursed by their health insurance, when choosing an intervention. This work complements the evidence-based studies with real-world data from Germany in terms of a holistic perspective on AK therapy. Hence, the entire project also has a direct impact on patient care in daily clinical practice.

Overall, the results of the four publications provide the treating dermatologists and patients with AK with new information and thus support them to choose the most suitable evidence-based and patient-oriented treatment regimen. The publications presented in this thesis complement the existing German evidence- and consensus-based guideline on AK and will ultimately contribute to shared decision-making. Moreover, the appraisal of guidelines offers other guideline developers to identify weaknesses and to advance future guideline development in order to guarantee best available evidence for both clinicians and patients with AK.

# 7. Veröffentlichung I

**Laser-assisted photodynamic therapy for actinic keratosis: a systematic review and meta-analysis**

**Veröffentlicht in:**

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# Laser-assisted photodynamic therapy for actinic keratosis: A systematic review and meta-analysis

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**Background:** Photodynamic therapy (PDT) is an effective intervention for actinic keratosis and field cancerization. Ablative fractional lasers may facilitate the delivery of photosensitizers and thereby improve the effects of PDT.

**Objective:** To summarize the current evidence on the efficacy and safety of laser-assisted PDT.

**Methods:** We performed a systematic literature research in Medline, Embase, and the Cochrane Central Register of Controlled Trials and hand-searched pertinent trial registers for eligible randomized controlled trials. Results from individual studies were pooled by using a random-effects model. The risk of bias was estimated with the Cochrane Risk of Bias Tool, and the quality of evidence of the outcomes was assessed with the Grading of Recommendations, Assessment, Development, and Evaluation approach.

**Results:** Of 817 records initially identified, 7 randomized controlled trials were included in the qualitative analysis and 4 were included in the meta-analysis. Laser-assisted PDT showed significantly higher clearance rates than did PDT monotherapy (risk ratio, 1.33; 95% confidence interval, 1.24-1.42; $I^2$ = 25%; $P$ < .01). There was no difference in pain intensity between laser-assisted PDT and other interventions (mean difference, 0.31; 95% confidence interval, −0.12 to 0.74; $I^2$ = 0%; $P$ = .16). The included studies showed a high risk of bias.

**Limitations:** The clinical heterogeneity of included studies.

**Conclusion:** Laser-assisted PDT is more efficient but not more painful than PDT or laser treatment only. ( J Am Acad Dermatol 2019;80:947-56.)

*Key words:* actinic keratosis; carbon dioxide laser; erbium:yttrium-argon-garnet laser; general oncology; meta-analysis; photodynamic therapy; senile keratosis; solar keratosis; systematic review.

Actinic keratoses (AKs) are precancerous lesions of the skin as a consequence of long-term sun exposure.[1,2] They can progress into cutaneous squamous cell carcinoma (cSCC), although the risk is presumably low.[3] International guidelines recommend the treatment of AKs because predicting whether a lesion will become invasive cSCC is not possible.[4]

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) or its ester methyl-aminolevulinate (MAL) is a highly effective treatment for multiple AKs or field cancerization with an excellent cosmetic outcome.[5,6]

However, 1 of the main side effects is local pain during illumination, which can limit treatment adherence and patient satisfaction.[7] Other limiting factors include the thickness of the individual lesions, as hyperkeratotic lesions are poorly penetrated by the photosensitizing agent, requiring pretreatment with curettage before PDT.

PDT as a field-directed approach may be combined with lesion-targeted pretreatment by ablative and non-ablative laser devices (laser-assisted PDT). An ablative fractional laser (AFXL) creates microscopic vertical channels that may facilitate the penetration and enrichment of ALA or MAL in dysplastic cells, a concept that has been termed *laser-assisted drug delivery*. However, whether laser-assisted PDT is really more effective than PDT alone has been a subject of debate, and clear-cut evidence from randomized controlled trials (RCTs) is lacking. Here, we have performed a systematic review to summarize the current evidence for laser-assisted PDT for AK.

## MATERIALS AND METHODS
### Protocol and registration
The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=87854). The register identifier is PROSPERO 2018 CRD42018087854. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[8] and the Cochrane Handbook For Systematic Reviews.[9]

### Eligibility criteria
Patients with the clinical and/or histopathologic diagnosis of AK were included. They were to be treated with a combination of PDT and laser therapy. Both MAL and ALA were allowed as photosensitizers. Ablative and nonablative laser devices were eligible. We included only RCTs in which study participants (interindividual trials) or entire body parts (intraindividual trials) were investigated. Pseudorandomized trials, observational studies, retrospective studies, crossover studies, and case series were excluded.

## CAPSULE SUMMARY

- This meta-analysis suggests that photodynamic therapy combined with ablative laser treatment for actinic keratosis is more efficient but not more painful than either therapy alone.

- Laser-assisted photodynamic therapy is an attractive option for patients with multiple actinic keratoses or field cancerization.

### Search strategy and data sources
We searched the electronic databases Medline and Embase (both via Ovid) as well as the Cochrane Central Register of Controlled Trials to identify all relevant records until January 24, 2018. Additionally, we searched the following trial registers for the keywords *actinic keratosis* or *actinic keratoses*: the metaRegister of Controlled Trials (ISRCTN registry [www.controlled-trials.com]), US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch/), and European Union Clinical Trials Register (www.clinicaltrialsregister.eu/); the last search was conducted on February 20, 2018. For ongoing trials and completed trials without data publication, principal investigators or trial sponsors were contacted to obtain preliminary or unpublished data. Reference lists of the included records were screened.

### Study selection
Two authors (J.G.S. and T.S.) independently screened the titles and abstracts identified in the electronic database searches to determine their eligibility. Trial registers were hand-searched and assessed for eligibility by 1 author (T.S.). For records that were considered relevant according to the title and abstract screening, full-text articles were obtained and the inclusion and exclusion criteria were applied. Whenever discrepancies arose, resolution was achieved by discussion with a third independent author (M.V.H.).

### Outcomes
The primary outcomes were the lesion-specific complete clearance rate and local adverse events), as determined by the number of patients or treated areas with skin irritation. Secondary outcomes were cosmetic outcome, which was quantified as the number of patients or treatment areas with skin dyspigmentation; patient satisfaction, which was rated globally as "satisfied" or "very satisfied"; and pain as a result of treatment, which was reported on a visual analogue scale from 0 (none) to 10 (extreme pain). All outcomes had to have been reported at

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| | |
|---|---|
| *Abbreviations used:* | |
| AFXL: | ablative fractional laser |
| AK: | actinic keratosis |
| ALA: | 5-aminolevulinic acid |
| CI: | confidence interval |
| cSCC: | cutaneous squamous cell carcinoma |
| dPDT: | photodynamic therapy with daylight |
| MAL: | methyl-aminolevulinate |
| OTR: | organ transplant recipient |
| PDT: | photodynamic therapy |
| RCT: | randomized controlled trial |
| RR: | risk ratio |

least 2 months but no more than 6 months after the end of treatment.

### Data collection, synthesis, and management

Information regarding each of the included study's design, baseline characteristics, intervention, risk of bias, and primary and secondary outcomes was collected and summarized by 2 authors independently (T.S. and J.G.S.) with the use of RevMan 5.3 software.[10]

Wherever possible and suitable, we performed a meta-analysis of quantitative data by using RevMan 5.3.[10] We used the random-effects model, as clinical and methodologic heterogeneity between the studies was likely. We expressed dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous outcomes as mean differences with 95% CIs. To analyze the lesion-specific clearance rate in intraindividual trials, we considered the lesions of a given treatment randomized as a cluster. To address the influence on the effect estimate, we performed sensitivity analysis by repeating meta-analysis with only interindividual trials. Where possible, we calculated the data following the intention-to-treat principle. If meta-analysis for an outcome was impossible, we described the results qualitatively (Table I[11-17]).

### Risk of bias assessment and quality of evidence assessment

Two authors (J.G.S. and T.S.) independently assessed the risk of bias of the included studies with the Cochrane Risk of Bias Tool.[9] Discrepancies were thoroughly discussed and resolved with the full texts and supplementary material. The quality of evidence for each outcome was rated by the same authors by using GRADEpro Guideline Development Tool software (www.gradepro.org).[18] If at least 10 RCTs reported a specific comparison, we intended to assess publication bias by creating a funnel plot.

## RESULTS
### Study identification

Our literature search identified 817 references; 14 records underwent full-text review after title and abstract screening and removal of duplicates. Seven records were excluded because they had an uncontrolled design,[19] did not meet the inclusion criteria,[20-22] or did not present any relevant data.[23,24] One more duplicate was identified[25] (Fig 1). Finally, 7 RCTs with a total sample size of 240 met the eligibility criteria. Of the 7 studies, 6 assessed MAL[12-17] and 1 assessed ALA[11] as a photosensitizer. Regarding the type of laser, 3 studies investigated an erbium:yttrium-argon-garnet laser[12,14,17] and the remaining 4 investigated a carbon dioxide ($CO_2$) laser.[11,13,15,16]

### Clearance rates

Six studies comparing the reported clearance rates achieved by use of laser-assisted PDT with those achieved by use of PDT monotherapy.[11,12,14-17] Of the 6 studies, 4 provided sufficient data to perform meta-analysis (Fig 2).[11,12,14,16] Laser-assisted PDT showed significantly higher clearance rates than did PDT monotherapy (RR, 1.33; 95% CI, 1.24−1.42; $I^2$ = 25%; $P$ < .01). A sensitivity analysis with interindividual trials only revealed a similar effect (RR, 1.41; 95% CI, 1.27-1.56; $I^2$ = 0%).

Song et al reported data from an interindividual study with 46 participants.[15] Conventional PDT plus AFXL was more efficient than PDT monotherapy (clearance rate, 71.4% vs 64.7% [the difference was not statistically significant]). In an intraindividual trial with 16 organ transplant recipients (OTRs), Togsverd-Bo et al compared the combination of daylight PDT (dPDT) and AFXL with dPDT or conventional PDT as monotherapy.[17] The areas treated with AFXL and dPDT, dPDT alone, and conventional PDT alone showed median complete response rates of 74% (range, 37%−100%), 46% (range, 0%−75%), and 50% (range, 25%−83%), respectively (a statistically significant difference). We rated the quality of evidence as low (Table II).

### Local skin irritation

None of the studies reported severe adverse events or cases in which patients had to discontinue treatment.

### Dyspigmentation

Dyspigmentation was inconsistently reported. Because of substantial heterogeneity among the trials, we did not perform meta-analysis. The data provided by Choi et al could not be analyzed on

**Table I.** Overview of the reported outcomes of the included studies

| Reference | Laser and/or PDT interventions | Primary outcomes | | Secondary outcomes | | |
|---|---|---|---|---|---|---|
| | | Efficacy lesion clearance, % (n/N) | Local adverse events | Skin dyspigmentation, % (n/N) | Patient satisfaction | Pain, VAS score |
| Alexiades[11] (2017) | ALA PDT+ $CO_2$ laser | 87.81% (54/443) | Unclear | 0% (0/10) | NR | mean, 4 |
| | ALA PDT | 70.09% (131/438) | Unclear | 0% (0/10) | NR | mean, 3 |
| Choi et al[12] (2015) | Er:YAG laser + 2 h of MAL PDT | 76.8%; 95% CI 70.1-83.6% (116/151) | Unclear | Unclear | NR | mean ± SD, 5.91 ± 1.27 |
| | Er:YAG laser + 3 h of PDT | 91.7%, 95% CI 87.2-96.2%, (133/145) | Unclear | Unclear | NR | mean ± SD, 6.06 ± 0.71 |
| | 3 h of MAL PDT | 65.6%, 95% CI 57.5-73.8% (86/131) | Unclear | Unclear | NR | mean ± SD, 5.77 ± 1.13 |
| Helsing et al[13] (2013)* | $CO_2$ laser + MAL PDT | 73% (range, 8%-57%) | Unclear | 30% (3/10) | NR | NR |
| | $CO_2$ laser | 31% (range, 8%-57%) | Unclear | 10% (1/10) | NR | NR |
| Ko et al[14] (2014) | Er:YAG laser + MAL PDT | 86.9% (93/107) | Unclear | 100% (20/20) | NR | mean ± SD, 4.765 ± 2.283 |
| | MAL PDT | 61.2% (79/129) | Unclear | 100% (20/20) | NR | mean ± SD, 4.304 ± 1.714 |
| Song et al[15] (2015) | $CO_2$ laser + MAL PDT | 71.4% | NR | NR | NR | NR |
| | MAL PDT | 64.7% | NR | NR | NR | NR |
| Togsverd-Bo et al[16] (2012) | $CO_2$ laser + MAL PDT | 90% (93/103) | Unclear | 40% (6/15) | NR | median, 6.5 (range, 2-10) |
| | MAL PDT | 67% (71/109) | Unclear | 13.3% (2/15) | NR | median, 5.5 (range, 3-8) |
| Togsverd-Bo et al[17] (2015) | Er:YAG laser + dPDT | 74% (range, 37%-100%) | NR | 0% (0/16) | NR | median, 0 (range, 0-3) |
| | dPDT | 46% (range, 0%-75%) | NR | 0% (0/16) | NR | median, 0 (range, 0-1) |
| | MAL PDT | 50% (range, 25%-83%) | NR | 0% (0/16) | NR | median, 5.5 (range, 3-9) |
| | Er:YAG laser | 5% (range, 0%-40%) | NR | 0% (0/16) | NR | median, 0 |

*ALA PDT*, Photodynamic therapy with 5-aminolevulinic acid, *CI*, confidence interval, *CO₂*, carbon dioxide, *dPDT*, daylight photodynamic therapy; *Er:YAG*, erbium:yttrium-argon-garnet; *MAL PDT*, photodynamic therapy with methyl aminolevulinate; *NR*, not reported; *OTR*, organ transplant recipient; *SD*, standard deviation; *VAS*, visual analogue scale.
*This study was identified according to the review protocol but is not reported because it compared laser-assisted PDT with laser monotherapy.
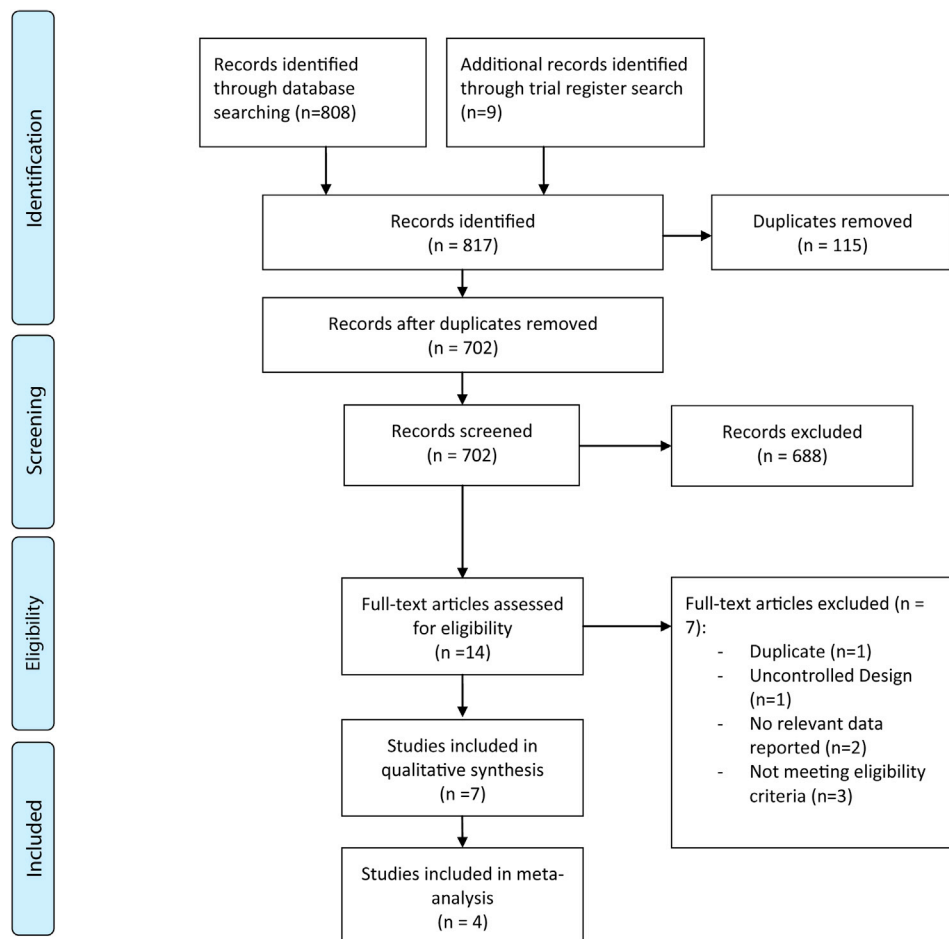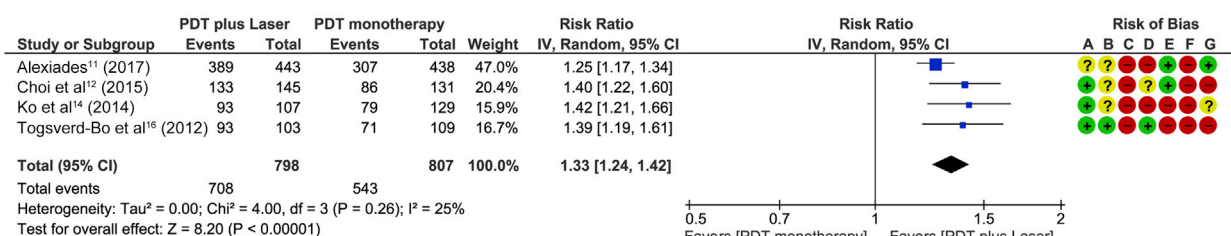
**Fig 1.** Selection process for study inclusion in the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.



Risk of bias legend

**(A)** Random sequence generation (selection bias)
**(B)** Allocation concealment (selection bias)
**(C)** Blinding of participants and personnel (performance bias)
**(D)** Blinding of outcome assessment (detection bias)
**(E)** Incomplete outcome data (attrition bias)
**(F)** Selective reporting (reporting bias)
**(G)** Other bias

**Fig 2.** Risk ratio to have actinic keratoses cleared for the intervention laser-assisted photodynamic therapy (PDT) compared with that for PDT monotherapy. This is a forest plot examining randomized controlled trials. Random-effects analysis was used. The diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). *df*, Degrees of freedom; *IV*, instrumental variable.

account of incoherent reporting.[12] In 2 intraindividual studies with 10 and 16 patients, respectively, no dyspigmentation occurred.[11,17] An interindividual

trial (N = 40) reported that all participants experienced dyspigmentation, irrespective of the intervention.[14]

**Table II.** Summary of evidence table for the outcomes of the comparison laser-assisted PDT versus PDT monotherapy for patients with AK

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence, on a scale of 1 to 4 (GRADE approach) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with PDT monotherapy** | **Risk with laser-assisted PDT** | | | | |
| Clearance rate | 673 per 1000 | 895 per 1000 (834-955) | RR 1.33 (1.24-1.42) | 1605 (4 RCTs) | 2 (low)[†] | Laser-assisted PDT appears to reduce clearance rate. Of note: 1605 treatment areas were randomized, not participants. The 4 RCTs included a total of 129 patients; 25 patients were included in 2 studies with an intraindividual design (ie, the participants served as their own control). The remaining 2 studies had an interindividual design with 52 participants in the intervention group and 53 in the control group. |
| Skin irritation—not reported | None of the included RCTs specifically reported this outcome | | | - | - | - |
| Dyspigmentation | In 2 studies, with 10 and 16 patients, respectively, no dyspigmentation occurred. Another trial (N = 40) reported that all participants experienced dyspigmentation, irrespective of treatment. Another trial reported that dyspigmentation was observed in 6 laser-assisted PDT and in 2 PDT only areas. One study did not provide sufficient data regarding dyspigmentation | | | (5 RCTs) | 1 (very low)[‡§] | We are uncertain about the effect of laser-assisted PDT on dyspigmentation. |

| Patient satisfaction—not reported | None of the included RCTs specifically reported this outcome. | | - | - | - |
|---|---|---|---|---|---|
| Pain assessed with VAS scale (0-10) | The mean pain score was 0 | The mean pain score in the intervention group was 0.31 higher (0.12 lower to 0.74 higher) | - | 104 (2 RCTs) | 2 (low)[‖] | Laser-assisted PDT may result in a small effect that may not be an important (or unimportant) reduction in pain. |

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group grades of evidence are as follows: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low certainty, our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect); and very low certainty, we have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of the effect).

*AK*, Actinic keratosis; *CI*, confidence interval; *RCT*, randomized controlled trial; *PDT*, photodynamic therapy; *RR*, risk ratio; *VAS*, visual analogue scale.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[†]For the study by Alexiades et al,[11] whether the outcome assessment was done in blinded fashion remains unclear. In addition, the study by Ko et al[14] had an open-label design; therefore, detection bias is likely. Dropouts in the laser-assisted PDT group imbalanced the baseline disease severity of the intervention groups. The study of Togsverd-Bo et al[16] was at risk of attrition bias because the results are probably reported for only 12 of 15 patients. Besides, 14 of 15 patients received prior treatment of their AKs, but the authors did not specify the nature and duration of the previous therapy (which may have had an impact on the study results even though the AK treatment had to have ended 4 weeks before the study according to their eligibility criteria). Overall, the studies showed a high risk of bias (−2).

[‡]All studies showed a high risk of performance bias. The studies by Alexiades et al[11] and Ko et al[14] also had a high risk of detection bias, whereas the risk of detection bias for the study by Choi et al[12] remains unclear (−2).

[§]The results were highly inconsistent. In the studies of Alexiades et al[11] and Togsverd-Bo et al[17] no dyspigmentation was reported among the participants (N = 26 [intraindividual design]), whereas Ko et al[14] reported all patients as showing dyspigmentation (N = 40 [interindividual design]).

[‖]Both studies show a high risk of performance bias. Additionally, the study of Ko et al[14] also has a risk of detection bias because of its open-label design (−2).
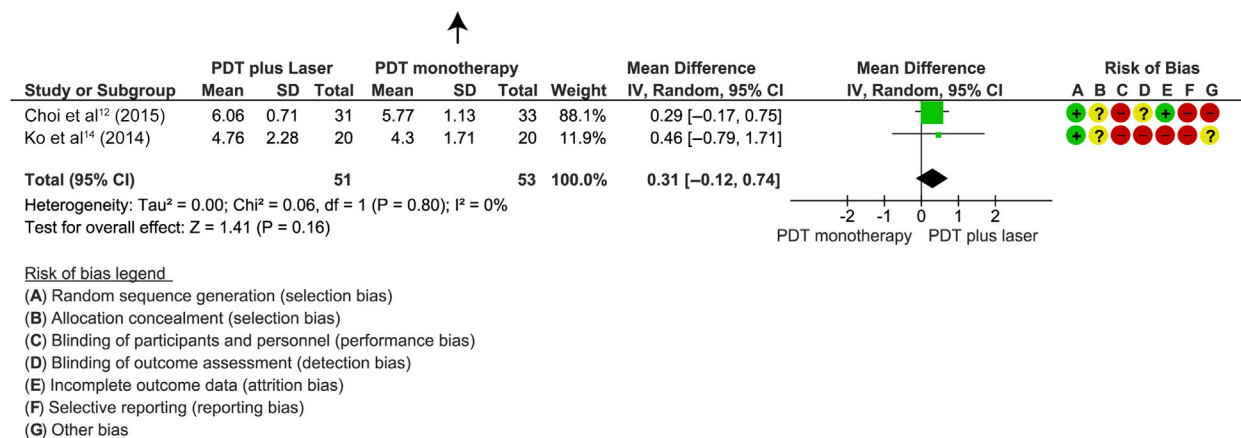
**Fig 3.** Mean differences in pain intensity for the intervention laser-assisted photodynamic therapy (PDT) versus for PDT monotherapy, as assessed on a visual analogue scale. This is a forest plot examining randomized controlled trials with an interindividual design. Random-effects analysis was used. The diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). *df*, Degrees of freedom; *IV*, instrumental variable; *SD*, standard deviation.

Togsverd-Bo et al reported in an intraindividual trial with 15 patients that dyspigmentation was observed in 6 and 2 areas treated with AFXL-PDT and PDT, respectively.[16] The quality of evidence was rated as very low (Table II[11,12,14,16,17]).

**Patient satisfaction**

None of the included studies reported this outcome.

**Pain**

Five studies measured the severity of pain during or immediately after treatment. Two studies with an interindividual design and 104 participants provided sufficient data for meta-analysis, showing no difference in pain intensity between the 2 interventions (mean difference, 0.31; 95% CI, −0.12 to 0.74; $I^2 = 0\%$; $P = .16$) (Fig 3).[12,14] One intraindividual trial with 10 participants reported an average pain intensity score of 4 on the visual analogue scale for the combination therapy and an average score of 3 for PDT monotherapy.[11] However, the authors did not report either CI or whether the effect was significant. In an intraindividual study with 15 patients, Togsverd-Bo et al reported a median pain intensity score of 6.5 (range, 2-10) on the side treated with combination therapy and a median score of 5.4 (range, 3-8) on the area treated with PDT ($P = .023$).[16]

Another intraindividual study showed that there was no difference in pain intensity between the combination of laser and dPDT (median, 0; range, 0-3) compared with dPDT alone (median, 0; range,

0-1) among 16 OTRs.[17] The quality of evidence was rated as low (Table II).

**Bias assessment**

As we included fewer than 10 studies, we did not create a funnel plot and cannot exclude the presence of publication bias. None of the studies provided any cause for serious suspicion of selection bias. Blinding of participants was not performed, which may have resulted in performance bias for subjective outcomes such as pain. Blinding of the outcome assessor was clearly stated in 3 trials. Most studies were free of attrition bias. However, 2 studies had a dropout rate of more than 10% without performance of intention-to-treat analysis. These studies were at high risk of attrition bias. We identified a high risk of selective reporting bias, mostly because trials either reported only *P* values without providing further statistical data or did not adequately report results for predefined outcomes.

**DISCUSSION**

Our results suggest an increased effectiveness of laser-assisted PDT regarding lesion clearance; however, the certainty of the evidence was considered low according to evaluation based on the Grading of Recommendations, Assessment, Development, and Evaluation approach. The increased efficacy of AFXL used as an adjunct to PDT may be explained by 2 different mechanisms. First, laser ablation creates vertical microchannels within the stratum corneum

that facilitate penetration of the photosensitizer and accumulation of protoporphyrin IX.[26,27] Second, AFXL treatment has direct cytotoxic effects on target cells. Despite growing evidence that nonablative devices can also be used with high clearance rates for AK, no trial met the inclusion criteria applied here. Meta-analysis was possible for lesion clearance for the comparison of laser-assisted PDT versus PDT monotherapy, revealing an RR of 1.33 in favor of the combination therapy. A 33% higher chance of lesion clearance is remarkable, as PDT alone is considered a highly effective treatment for AKs and has shown clearance rates of 70% to 90% in several phase III trials. This risk estimate, however, needs to be interpreted with caution owing to high clinical heterogeneity regarding differences in the treatment protocols, variability of the settings of the lasers used, and the fact that some studies were designed as interindividual trials while others were designed as intraindividual trials.

From a methodologic perspective, it is not single AK lesions but treatment areas that are subject to randomization in intraindividual trials. Although individual lesions were not randomized to the specific treatments, we considered them randomized as a cluster for the analysis. Intercluster correlation coefficients were not reported in any trial. Thus, cluster effects of the included studies remain unclear and represent a possible source of bias for the results regarding the lesion-specific response. When only trials with an interindividual design were analyzed, similar results were obtained, underlining the fact that the observed effect is consistent. Furthermore, the results regarding the lesion-specific response may be underpowered. Assessment at the level of individual lesions can falsely inflate the power because it is usually calculated on the basis of the study participants and not on basis of the total number of AK lesions. However, this is a statistical pitfall that arises at the individual trial level, where reporting lesion-specific response rates without further statistical adjustments seems to be common practice.

Regarding tolerability, in most trials, reporting of patient satisfaction, local skin reactions, and dyspigmentation was poor. Thus, we are uncertain of and cannot draw clear conclusions regarding these outcomes. In contrast, pain was well documented. Laser-assisted PDT was not perceived as more painful than PDT only, regardless of whether it was conducted after illumination from light-emitting diodes or in natural daylight (which is a nearly painless alternative to conventional PDT).[28,29]

Two studies investigated OTRs as their population. Because of long-term immunosuppression with reduced immune surveillance, AKs are more likely to progress to cSCC and show lower response to therapy.[30] Although a subgroup analysis was not performed here, the studies performed by Helsing et al and Togsverd-Bo et al showed significantly higher rates of lesion clearance for the combination.[13,17] The low clearance rates observed with PDT only in this study imply that monotherapy may not be sufficient for AK clearance and suggest that laser-assisted PDT should be preferred in OTRs or for difficult-to-treat lesions.

All together, our study showed that ablative laser-assisted PDT provided a higher likelihood of lesion clearance than PDT alone without a significant difference regarding pain. Thus, it may be offered upfront for difficult-to-treat AKs such as hyperkeratotic, acral lesions, or AKs in OTRs.

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**Supplementary Table S I: Search queries**

**Supplementary Table S1A:** Search query in Medline via Ovid

1 actinic keratosis.mp. or exp Keratosis, Actinic/
2 solar keratos*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3 senile keratos*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 field cancerization.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5 exp Precancerous Conditions/ or exp Carcinoma, Squamous Cell/ or exp Skin Neoplasms/
6 field changes.mp.
7 exp RANDOMIZED CONTROLLED TRIAL/ or exp CLINICAL TRIAL/ or trial.mp.
8 1 or 2 or 3 or 4 or 5 or 6
9 7 and 8
10 laser.mp. or exp Lasers/
11 laser therapy.mp. or exp Laser Therapy/
12 exp Photochemotherapy/ or exp PHOTOSENSITIZING AGENTS/ or exp Singlet Oxygen/ or photosensitizing.mp. or exp Porphyrins/
13 photodynamic therapy.mp.
14 photodynamic.mp.
15 pdt.mp.
16 aminolevulinic acid.mp. or exp Aminolevulinic Acid/
17 ALA.mp.
18 MAL.mp.
19 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 9 and 19
21 combined.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22 followed.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23 sequential.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
24 concurrent.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25 assisted.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26 mediated.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27 combination.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
28 21 or 22 or 23 or 24 or 25 or 26 or 27 29 20 and 28
30 limit 29 to english language

**Supplementary Table S1B:** Search query in Embase via Ovid

1 actinic keratosis.mp. or exp actinic keratosis/
2 solar keratosis.mp.
3 senile keratosis.mp.
4 field change.mp.
5 actinically damaged field.mp. 4
6 field-cancerized.mp. or exp precancer/
7 exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "phase 1 clinical trial (topic)"/ or trial.mp. or exp "controlled clinical trial (topic)"/ or exp "phase 3 clinical trial (topic)"/
8 exp argon plasma laser/ or laser/ or exp dye laser/ or laser.mp. or exp neodymium YAG laser/ or exp carbon dioxide laser/ or exp pulsed dye laser/ or exp erbium chromium YSGG laser/ or exp diode laser/ or exp femtosecond laser/ or exp argon laser/ or exp laser surgery/ or exp neodymium laser/ or exp erbium YAG laser/ or exp alexandrite laser/ or exp excimer laser/
9 laser therapy.mp.
10 photodynamic therapy.mp. or exp photodynamic therapy/ or exp photochemotherapy/ or exp phototherapy/
11 exp photosensitizing agent/ or pdt.mp. or exp aminolevulinic acid/
12 methyl aminolevulinate.mp. or exp aminolevulinic acid methyl ester/
13 ALA.mp.
14 MAL.mp.
15 1 or 2 or 3 or 4 or 5 or 6
16 8 or 9 or 10 or 11 or 12 or 13 or 14
17 15 and 16
18 7 and 17
19 followed.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
20 sequential.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
21 combined.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
22 combination.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23 assisted.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24 mediated.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
25 19 or 20 or 21 or 22 or 23 or 24
26 18 and 25
27 limit 26 to english language

**Supplementary Table S1C:** Search query in the Cochrane Library CENTRAL

| | |
|---|---|
| #1 | MeSH descriptor: [Keratosis, Actinic] explode all trees |
| #2 | actinic keratos* (Word variations have been searched) |
| #3 | solar keratos* (Word variations have been searched) |
| #4 | senile keratos* (Word variations have been searched) |
| #5 | MeSH descriptor: [Precancerous Conditions] explode all trees |
| #6 | field cancerization (Word variations have been searched) laser (Word variations have been searched) |
| #7 | pdt (Word variations have been searched) |
| #8 | "photodynamic therapy" (Word variations have been searched) |
| #9 | MAL (Word variations have been searched) |
| #10 | ALA (Word variations have been searched) |
| #11 | MeSH descriptor: [Lasers] explode all trees |
| #12 | MeSH descriptor: [Lasers] explode all trees |
| #13 | MeSH descriptor: [Photochemotherapy] explode all trees |
| #14 | #1 or #2 or #3 or #4 or #5 or #6 |
| #15 | #7 or #8 or #9 or #10 or #11 or 12 or #13 or #14 |
| #16 | #15 and #16 |
| #17 | followed (Word variations have been searched) |
| #18 | combined (Word variations have been searched) |
| #19 | sequential (Word variations have been searched) |
| #20 | combination:ti,ab,kw (Word variations have been searched) |
| #21 | assisted (Word variations have been searched) |
| #22 | mediated (Word variations have been searched) |
| #23 | #18 or #19 #20 or #21 or #22 or #23 |
| #23 | #17 and #24 |

**Supplementary Table II:** Overview of the baseline characteristics of the included studies (n=7)

| Study characteristics | | | | Population | | |
|---|---|---|---|---|---|---|
| **Author and year** | **Design** | **Blinding** | **Interventions** | **Sample size** | **Age (years)** | **Localization of the lesions** |
| **Alexiades 2017** | Intra-individual | Investigator-blinded | One pass of AFXL treatment (fractional ablative $CO_2$ laser used at 10 600 nm, 20 W, 300 mm microbeam diameter, 550 mm dot spacing and 700 ms dwell time), followed by ALA PDT with 15 min ALA incubation and irradiation with blue light for 1.000 s | 10 | 64.20 ± 10.53 | Face |
| | | | ALA PDT with ALA incubation time of 15 min and irradiation with blue light for 1000 s | | | |
| | | | One pass of AFXL treatment (fractional ablative $CO_2$ laser used at 10 600 nm, 20 W , 300 mm microbeam diameter, 550 mm dot spacing and 700 ms dwell time), followed by ALA-PDT with 30 min ALA incubation and irradiation with blue light for 1000 s | 10 | 65.10 ± 11.20 | |
| | | | ALA-PDT with ALA incubation time of 30 min and irradiation with blue light for 1000 s | | | |
| **Choi 2015** | Inter-individual | Investigator-blinded | Er:YAG AFL at 300–550 µm ablation depth, level 1 coagulation, 22 % treatment density and a single pulse. Then application of MAL for 2 h under occlusion and irradiation with a red light-emitting diode at 632 nm and at a dose of 37 J/cm² (N = 29) | 93 | 71.6±9.9 | Face or scalp |
| | | | Er:YAG AFL at 300–550 µm ablation depth, level 1 coagulation, 22 % treatment density and a single pulse. Then application of MAL for 3 h under occlusion and irradiation with a red light-emitting diode at 632 nm and at a dose of 37 J/cm² (N = 31) | | 71.9±7.2 | |
| | | | Application of MAL for 3 h under occlusion and irradiation with a red light-emitting diode at 632 nm and at a dose of 37 J/cm² (N = 33) | | 69.1±8.3 | |
| **Helsing 2013** | Intra-individual | Investigator-blinded | Two passes of AFXL treatment (fractional ablative $CO_2$ laser used at 10600 nm, 30 W and 0.12 mm spot size), followed by MAL-PDT (illumination with red light- | 10 OTRs | 64.1±6.9 | Dorsal hands |

| | | | emitting diode light at 632 nm at a dose of 37 J/cm²) | Kidney: n=8 Liver: n=1 Heart: n=1 | | |
|---|---|---|---|---|---|---|
| | | | Two passes of AFXL treatment (fractional ablative $CO_2$ laser used at 10 600 nm, 30 W and 0.12 mm spot size) | | | |
| **Ko 2014** | Inter-individual | Open | 2940 nm Er:YAG AFL at an ablation depth of 300–550 nm, using level 1 coagulation, 22 % treatment density and a single pulse, followed by application of MAL for 3h under occlusion and illumination with a red light-emitting diode at 632 nm at a dose of 37 J/cm² (N=20) | 40 | 67.8±7.8 | Face |
| | | | Application of MAL for 3 h under occlusion and illumination with a red light-emitting diode at 632 nm at a dose of 37 J/cm² (N = 20) | | | |
| **Song 2014** | Inter-individual | n.r. | Ablative $CO_2$ fractional laser (AFXL) plus PDT with MAL incubation time of 90 min, illumination with red light (N = 24) | 46 | n.r. | n.r. |
| | | | MAL PDT as monotherapy with MAL incubation time of 180 min, illumination with red light (N = 22) | | | |
| **Togsverd-Bø 2012** | Intra-individual | Investigator-blinded | AFXL treatment (fractional ablative $CO_2$ laser at 0.12 mm spot size, 10 mJ per pulse, single pulse, 5 % density), followed by application of MAL for 3 h under occlusion, then illumination with a red light-emitting diode at 632 nm and a light dose of 37 J/cm² | 15 | Mean: 73 (range 59-86) | Face and scalp |
| | | | Application of MAL for 3 h under occlusion, then illumination with a red light-emitting diode at 632 nm and a light dose of 37 J/cm² | | | |
| **Togsverd-Bø 2015** | Intra-individual | Investigator-blinded | AFXL treatment with a 2940 nm ablative fractional Er:YAG laser at 2.3 mJ/pulse, 1.15 W, two stacks, 50 µs pulse-duration, 2.4 % density. Then application of MAL for 2.5 h without occlusion during daylight exposure | 16 OTRs Kidney: n=12 Lung: n=3 Liver: n=1 | Mean: 63 (range 54-76) | Scalp Chest Extremities |
| | | | Application of MAL for 2.5 h without occlusion during daylight exposure | | | |
| | | | Application of MAL for 3 h under occlusion, then illumination with red light-emitting diode lamps with peak irradiance at 630 nm, irradiance of 68 mW/cm², and a total light dose of 37 J/cm² | | | |
| | | | AFXL treatment with a 2940 nm ablative fractional Er:YAG laser at 2.3 mJ/pulse, 1.15 W, two stacks, 50 µs pulse-duration, 2.4 % density | | | |

*AFXL* = ablative fractional laser, *ALA PDT* = photodynamic therapy with 5-aminolevulinic acid, *CO2 laser* = carbon dioxide laser, *Er:YAG laser* = Erbium:YAG laser, *MAL PDT* = photodynamic therapy with methyl aminolevulinate, *n.r.* = not reported, *OTRs* = organ transplant recipients

# 8. Veröffentlichung II

**Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis**

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# Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis

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**Conflicts of interest**

C.B. has been a member of advisory boards for Almirall Hermal, Biofrontera, Galderma, ISDIN and LEO Pharma; has received speakers' honoraria from Almirall Hermal, Galderma and LEO Pharma; and has received funding for clinical research from LEO Pharma. The other authors declare no conflicts of interest.

M.V.H. and T.S. contributed equally.

## Summary

**Background** Actinic keratoses (AKs) are early in situ carcinomas of the skin caused by cumulative sun exposure. Cryosurgery is an easy and practicable lesion-directed approach for treatment of isolated lesions.

**Objectives** To investigate whether an upfront combination of cryosurgery with a topical intervention is superior to cryosurgery alone for treatment of AK.

**Methods** We performed a systematic literature search in MEDLINE, Embase and CENTRAL and hand searched pertinent trial registers for eligible randomized controlled trials until 17 July 2018. Results from individual studies were pooled using a random effects model. The risk of bias was estimated with the Cochrane Risk of Bias Tool and the quality of evidence of the outcomes with the GRADE approach.

**Results** Out of 1758 records initially identified, nine studies with a total sample size of 1644 patients were included. Cryosurgery in combination with a topical approach showed significantly higher participant complete clearance rates than monotherapy [risk ratio (RR) 1·74, 95% confidence interval (CI) 1·25–2·43, $I^2 =$ 73%, eight studies]. The participant partial clearance rate was not statistically different (RR 1·64, 95% CI 0·88–3·03, $I^2 = 77\%$, three studies). The number of patients who completed the study protocol and did not withdraw due to adverse events was equal in both groups (RR 0·98, 95% CI 0·95–1·01, $I^2 = 75\%$, seven studies). The studies were estimated to have high risk for selective reporting bias.

**Conclusions** Our results suggest the superiority of a combination regimen for AK clearance, with equal tolerability. This study highlights the importance of a field-directed approach in patients with multiple AKs or field cancerization.

### What's already known about this topic?

- Cryosurgery is a fast and easy approach for treatment of isolated actinic keratoses.
- A variety of effective field-directed topical interventions are available, but they may lose efficacy in thicker lesions.
- Combining cryosurgery with a topical intervention offers the benefits of a lesion- and field-directed approach.

### What does this study add?

- This meta-analysis suggests the superiority of a combination of cryosurgery and topical interventions for participant complete clearance, without a difference in tolerability, in comparison with cryosurgery alone.
- Cryosurgery in combination with a topical intervention is an attractive and effective option for patients with multiple actinic keratoses or field cancerization.
- Our results highlight the importance of treating the entire actinic field in patients with multiple actinic keratoses.

Actinic keratoses (AKs) are common lesions of the skin caused by long-term exposure to ultraviolet radiation.[1,2] They can progress to cutaneous squamous cell carcinoma, although the risk is presumably low for single lesions.[3] However, if multiple AKs are present and if they are accompanied by signs of chronic actinic damage, the risk of malignant progression increases rapidly.[4,5] Visible AK lesions may be surrounded by tissue that clinically appears unaltered but bears significant ultraviolet-induced histological and genetic abnormalities. This concept has generally been accepted as field cancerization, although an exact clinical definition has not yet been coined.[6]

As it is difficult to predict whether a lesion will become invasive cutaneous squamous cell carcinoma, international guidelines recommend early treatment of AK.[7,8] Cryosurgery is a fast and easy approach to target single lesions in an office-based setting. The procedure usually involves liquid nitrogen and is applied in one to three freeze–thaw cycles. The advantage of this treatment is its ease of application and efficacy in hyperkeratotic lesions.[9] In patients with multiple lesions or field cancerization, topical interventions offer advantages as they are primarily field directed. A variety of agents for the treatment of AKs are available, with distinct mechanisms of action ranging from cytostatic effects to immune activation. The downsides are a longer duration of application and questionable efficacy in patients with thicker lesions, who are commonly excluded from larger trials.

In this context, we were interested to determine whether an upfront combination of cryosurgery followed by a topical intervention is more efficient than cryosurgery alone. We hypothesized that such a combination can combine the benefits of both a field- and lesion-directed approach. To address this question, we performed a systematic review with meta-analysis to summarize the current knowledge on the efficacy and safety of the combination of cryosurgery and topical intervention in comparison with cryosurgery monotherapy in patients with AKs.

## Patients and methods

### Protocol and registration

The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk). The register ID was PROSPERO CRD42018102026. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[10] and the Cochrane Handbook For Systematic Reviews.[11]

### Eligibility criteria

Patients with a clinical or histopathological diagnosis of AK were included. They were to be treated with a combination of cryosurgery and one of the following topical interventions: ingenol mebutate 0·015% or 0·05% gel, imiquimod 3·75% or 5% cream, 5-fluorouracil 0·5% or 5% cream, 5-fluorouracil

0·5% plus salicylic acid 10% in solution, diclofenac 3% in 2·5% hyaluronic acid, and photodynamic therapy with aminolaevulinic acid or its methyl ester. Cryosurgery as monotherapy served as the comparison. We included randomized control trials (RCTs) only in which the study participants (interindividual trials) or entire body parts (intraindividual trials) were investigated. Pseudorandomized trials, crossover trials, observational studies, retrospective studies and case series were excluded. Language restrictions were records in English or German.

### Search strategy and data sources

We searched the electronic databases MEDLINE and Embase (both via Ovid) and the Cochrane Library CENTRAL to identify all relevant records until 10 July 2018 (Table S1; see Supporting Information). Additionally, we searched the following trial registers for the keywords 'actinic keratosis' or 'actinic keratoses': The metaRegister of Controlled Trials (ISRCTN registry, www.controlled-trials.com), the U.S. National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) and the EU Clinical Trials Register (www.clinicaltrialsregister.eu) (last search on 17 July 2018). For ongoing trials and completed trials without data publication, principal investigators or trial sponsors were contacted to obtain preliminary or unpublished data. Reference lists of included records were screened.

### Study selection

Two authors (T.S. and M.V.H.) independently screened for eligibility the titles and abstracts that were identified in the electronic database searches. Trial registers were hand searched and assessed for eligibility by one author (T.S.). For records that were considered relevant according to title and abstract screening, full-text articles were obtained, and inclusion and exclusion criteria were applied by two review authors independently (T.S. and M.V.H.). Whenever discrepancies arose, resolution was achieved by discussion with a third independent author (C.B.).

### Outcomes

The primary outcomes were (i) the participant complete clearance rate and (ii) the participant partial clearance rate, defined as the rate of participants who had all (100%) or ≥ 75% of their lesions cleared, respectively and (iii) the lesion-specific reduction, measured as a continuous outcome and defined as the proportion of cleared lesions after the end of treatment in comparison with baseline (change-from-baseline outcome according to the Cochrane Handbook for Systematic Reviews of Interventions). The secondary outcome was tolerability, defined as the number of participants who completed treatment according to the study protocol and did not discontinue

due to treatment-related adverse events. All outcomes had to be reported at the earliest 2 months and not later than 6 months after the end of treatment.

## Data collection, synthesis and management

Information for each included study regarding design, baseline characteristics, intervention, outcomes and risk of bias were collected and summarized by two authors independently (T.S. and M.V.H.) using Review Manager version 5·3.[12] Wherever possible and suitable, we performed a meta-analysis of quantitative data using Review Manager. We used the random effects model, as clinical and methodological heterogeneity between the studies was likely. Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs), and continuous outcomes as mean differences with 95% CIs. To address the influence of differences in the trial design on the effect estimate, we performed sensitivity analyses by repeating the meta-analysis with only interindividual trials. Where possible, we calculated the data following the intention-to-treat (ITT) principle. If meta-analysis for an outcome was impossible, we described the results qualitatively. Comparator-specific stratified analyses were performed if two or more trials were identified investigating the same comparisons of topical
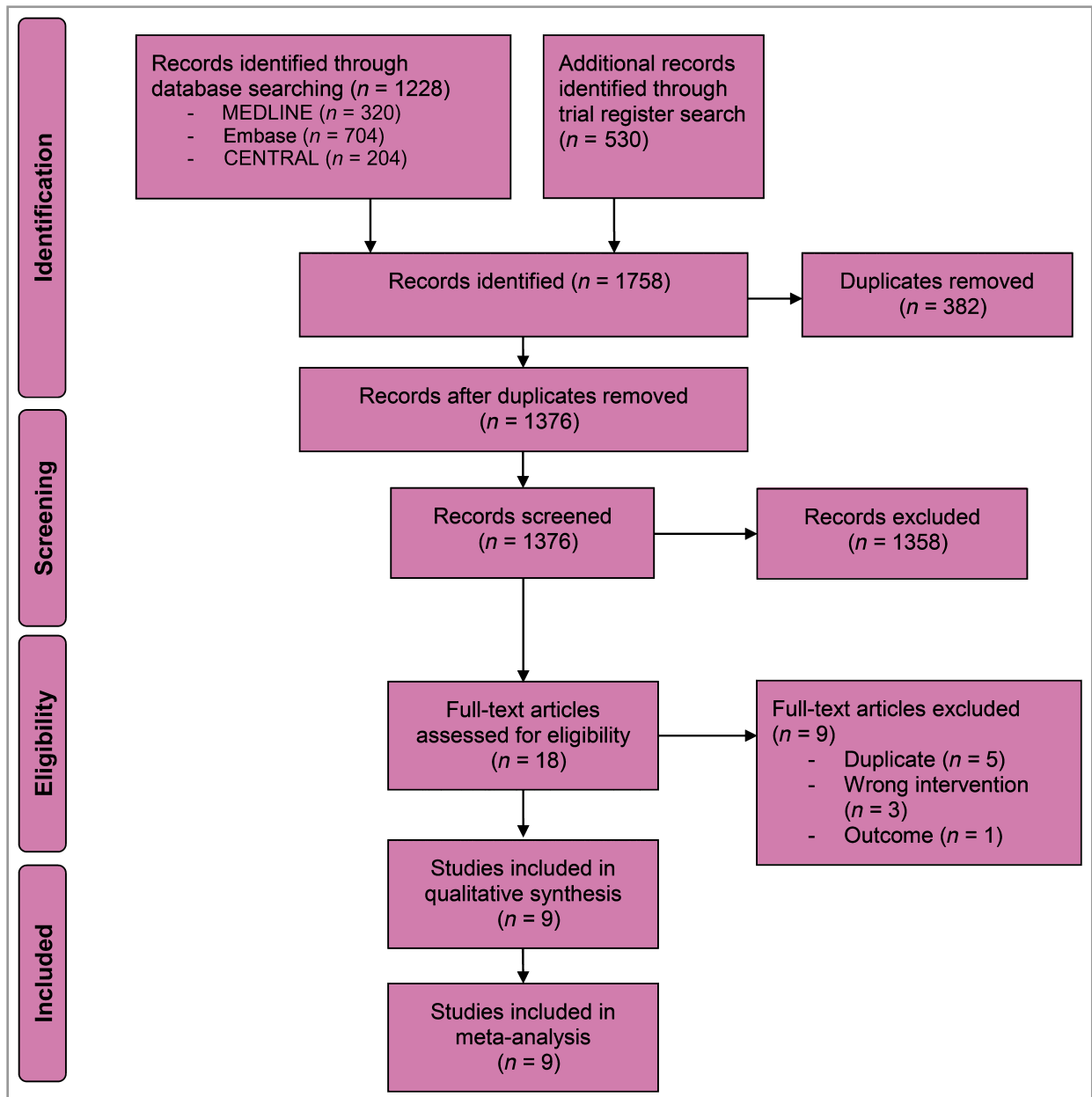


**Fig 1.** PRISMA flowchart of the study. Selection process for study inclusion in the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

interventions with cryosurgery. Subgroup analyses were performed to explore heterogeneity.

### Assessment of risk of bias and quality of evidence

Two authors (M.V.H. and T.S.) independently assessed the risk of bias of the included studies with the Cochrane Risk of Bias Tool.[11] Discrepancies were thoroughly discussed and resolved with the full texts and supplementary material. The quality of evidence for each outcome was rated by the same authors using the software GRADEpro GDT (www.gradepro.org).[13] If at least 10 RCTs reported a specific comparison, we intended to assess publication bias by creating a funnel plot.[11]

## Results

### Study identification

Our literature search identified 1758 references. After title and abstract screening and removal of duplicates, 18 records underwent full-text review. Nine records were excluded, firstly because they did not investigate the interventions of interest (n = 3)[14–16] or did not report one of the predefined outcomes (n = 1).[17] Five more duplicates were additionally identified (Fig. 1).[18–22] Finally, nine RCTs with an overall sample size of 1644 met the eligibility criteria. Four of the nine studies investigated cryosurgery followed by imiquimod (3·75% cream, n = 2;[23,24] 5% cream, n = 2[25,26]) and two studies investigated cryosurgery followed by ingenol mebutate (0·015% gel, n = 1;[27] 0·05% gel, n = 1[28]). The remaining three studies assessed diclofenac 3% in 2·5% hyaluronic acid,[29] 5-fluorouracil 0·5% cream[30] and photodynamic therapy with aminolaevulinic acid after cryosurgery (Table S2).[31] Six of the nine studies had an interindividual[24,25,27,29–31] and three an intraindividual design.[23,26,28] All studies were conducted in North America: eight in the U.S.A. and one in Canada.

### Bias assessment

The studies were at unclear risk for selection bias. Only four studies clearly described the generation of a random sequence for randomization.[24,27,29,30] For the remaining five studies, it was unclear how randomization was achieved.[23,25,26,28,31] None of the included studies described whether allocation concealment was performed. Blinding of participants was not performed in five[23,26,28–30] of the nine included trials, which may result in performance bias for adverse events leading to discontinuation. Blinding of the outcome assessor was explicitly stated in seven trials.[24–28,30,31] Most studies were free of attrition bias.[23,24,26–28,30] However, three studies had a dropout rate of > 10% without performing ITT analysis.[25,29,31] These studies were at high risk for attrition bias. We identified a high risk of selective reporting bias as the included studies often did not report all of the results for their predefined outcomes (Fig. 2 and Fig. S1; see Supporting Information).[23–31]



**Fig 2.** Risk-of-bias evaluation for each included study. The risk-of-bias summary was based on the review authors' judgements about each risk-of-bias item for each included study: '+' = low risk, '−' = high risk, '?' = unclear risk of bias. Berman 2014 refers to reference 27.

Subgroup analyses revealed that differences in the methodological quality were a relevant source of heterogeneity.

### Outcomes

Eight studies were identified reporting participant complete clearance rates.[24–31] Cryosurgery in combination with a topical approach showed significantly higher participant complete clearance rates than cryosurgery monotherapy (RR 1·74, 95% CI 1·25–2·43, $I^2$ = 73%, eight studies) (Fig. 3a). A sensitivity analysis with only interindividual trials revealed a similar effect size and degree of heterogeneity (RR 1·68, 95% CI 1·19–2·35, $I^2$ = 77%, six studies). We rated the quality of evidence for this outcome as low due to the high risk of bias, high heterogeneity and imprecision (Table 1).

Information on the proportion of patients who had $\geq$ 75% of their baseline lesions cleared at the end of treatment was available from three studies.[27,28,30] Participants treated with a combination approach showed no significant difference regarding partial clearance rates compared with cryosurgery only (RR 1·64, 95% CI 0·88–3·03, $I^2$ = 77%, three studies) (Fig. 3b). A sensitivity analysis with only interindividual trials revealed a similar effect (RR 1·31, 95% CI 0·92–1·87, $I^2$ = 59%, two studies). The quality of evidence was rated as very low because of the high risk of bias and high heterogeneity between the studies (Table 1).

Data on lesion-specific reduction were presented in eight of the nine studies.[23–30] However, the results were inconsistently reported and did not allow us to pool the results or perform a meta-analysis. In general, more lesions were cleared with a combination treatment of cryosurgery and a topical intervention (range 73·2–89%) in comparison with monotherapy with cryosurgery (range 39–76%) (Table 2). The quality of evidence was rated as low due to the high risk of bias (Table 1).

Seven studies provided data on adverse events that led to discontinuation of treatment.[24–30] The number of patients who stopped treatment due to treatment-related adverse events was virtually equal in both groups (RR 0·98, 95% CI 0·95–1·01, $I^2$ = 75%, seven studies) (Fig. 3c). A sensitivity analysis excluding intraindividual trials revealed a similar effect (RR 0·98, 95% CI 0·94–1·02, $I^2$ = 84%, five studies). The quality of evidence for this outcome was rated as very low as the studies showed a high risk of bias and high inconsistency (Table 1).
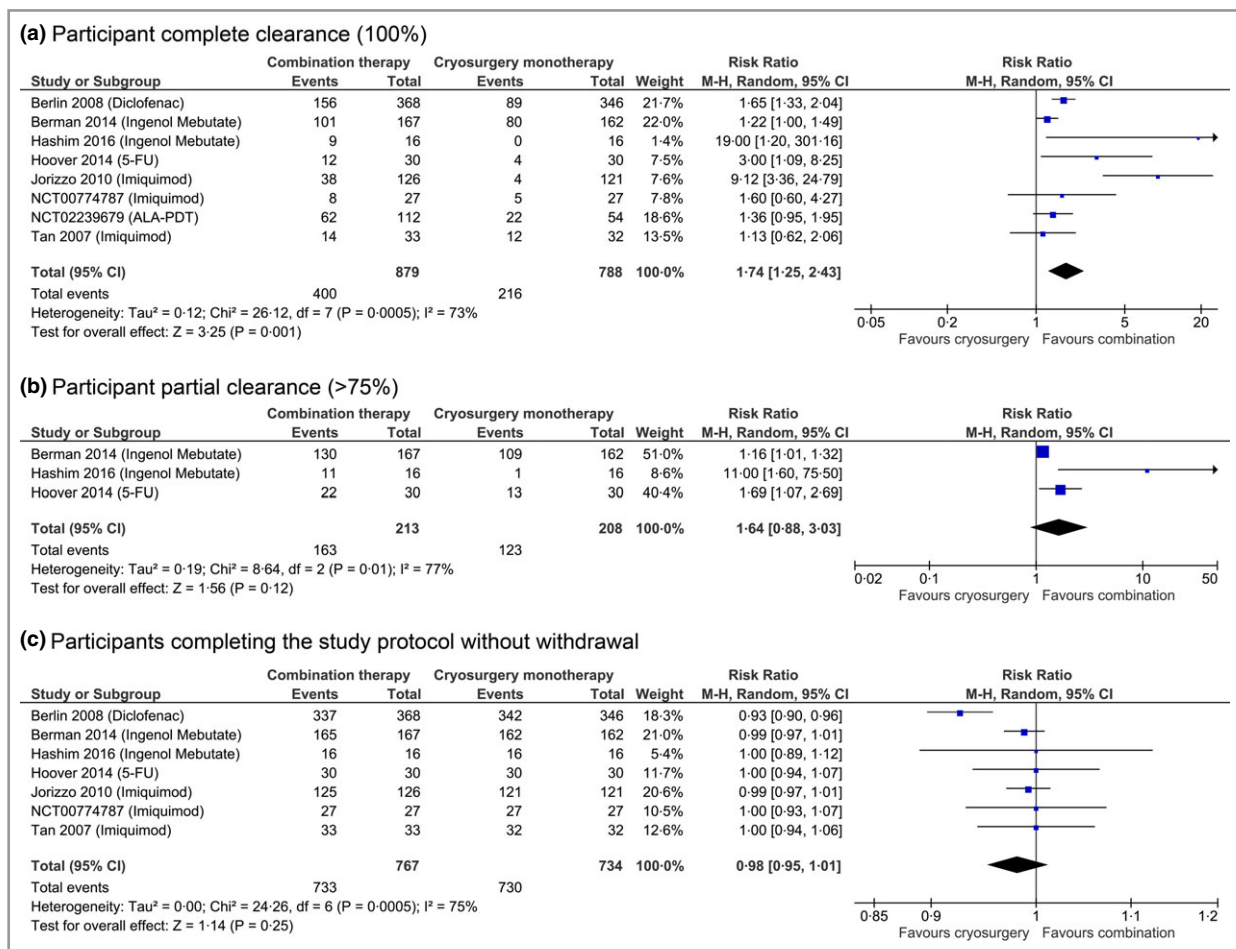


**Fig 3.** Outcome analysis for all included studies. (a) Risk ratio for a participant to have all actinic keratoses (100%) cleared for the intervention cryosurgery and topical intervention in comparison with cryosurgery monotherapy (participant complete clearance). (b) Risk ratio for a participant to have ≥ 75% of all actinic keratoses cleared for the intervention cryosurgery and topical intervention in comparison with cryosurgery monotherapy (participant partial clearance). (c) Risk ratio for a participant to complete treatment according to the study protocol and not discontinue due to treatment-related adverse events for the intervention cryosurgery and topical intervention in comparison with cryosurgery monotherapy, as a measure of tolerability. In all cases, forest plots examining the randomized controlled trials are shown. Random effects analysis was used. The diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). Berman 2014 refers to reference 27. FU, fluorouracil; ALA-PDT, 5-aminolaevulinic acid photodynamic therapy; M-H, Mantel–Haenszel.

Table 1 Summary-of-findings table for the outcomes of the comparison cryosurgery followed by a topical intervention vs. cryosurgery alone in patients with actinic keratosis

| Outcomes | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with cryosurgery alone | Risk with cryosurgery followed by a topical intervention | | | |
| Participant complete clearance | 274 per 1000 | 477 per 1000 (343–666) | RR 1·74 (1·25–2·43) | 1624 (8 RCTs) | ⊕⊕◯◯ LOW[a,b,c] |
| Participant partial clearance | 591 per 1000 | 970 per 1000 (520–1000) | RR 1·64 (0·88–3·03) | 405 (3 RCTs) | ⊕◯◯◯ VERY LOW[d,e] |
| Lesion-specific clearance | The lesion-specific clearance rate ranged from 73·2% to 89% | | | 1644 (9 RCTs) | ⊕⊕◯◯ LOW[a,f] |
| Tolerability | 995 per 1000 | 975 per 1000 (945–1000) | RR 0·98 (0·95–1·01) | 1458 (7 RCTs) | ⊕◯◯◯ VERY LOW[g,h] |

CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence are as follows. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. [a]The risk for selection bias due to random sequence generation remains unclear in the studies Hashim 2016,[28] NCT0774787,[26] NCT02239679[31] and Tan 2007.[25] Allocation concealment was unclear in all eight trials. The studies Berlin 2008,[29] Hashim 2016,[28] Hoover 2014[30] and NCT00774787[26] had a high risk for performance bias as the participants were not blinded. The outcome assessor was not blinded in the study Berlin 2008.[29] Regarding attrition bias, three studies (Berlin 2008,[29] NCT02239679[31] and Tan 2007)[25] demonstrated a high risk, mostly because they did not perform intention-to-treat analysis. The risk for selective reporting remains unclear in the study from Hoover.[30] Five further studies (Berlin 2008,[29] Hashim 2016,[28] Jorizzo 2010,[24] NCT0774787[26] and Tan 2007)[25] had a high risk for selective reporting, mostly because they did not report the outcomes that they had described in the methods part (−2 from the GRADE score). [b]$I^2$ = 73% (−1). [c]The margins of the CIs of three studies (NCT00774787,[26] NCT2239679[31] and Tan 2007)[25] show contrary results (−2). [d]All studies had an unclear risk of selection bias due to unclear allocation concealment. The studies Hashim 2016[28] and Hoover 2014[30] had a high risk of performance bias as blinding of participants was not performed. The study by Hashim 2016[28] had a high risk of selective reporting bias, whereas this risk for bias was unclear for Hoover 2014.[30] Random sequence generation was indefinitely described in the study Hashim 2016[28] (−1). [e]$I^2$ = 77%, CIs are large (−2). [f]The study Goldenberg 2013[17] had a high risk of performance and reporting bias and an unclear risk of selection and detection bias (−2). [g]The risk of selection bias due to random sequence generation remains unclear in the studies Hashim 2016,[28] NCT0774787[26] and Tan 2007.[25] Allocation concealment was unclear in all eight trials. The studies Berlin 2008,[29] Hashim 2016,[28] Hoover 2014[30] and NCT00774787[26] had a high risk of performance bias as participants were not blinded. The outcome assessor was not blinded in the study Berlin 2008.[29] Regarding attrition bias, two studies (Berlin 2008[29] and Tan 2007)[25] demonstrated a high risk, mostly because they did not perform an intention-to-treat analysis. The risk of selective reporting remains unclear in the study Hoover 2014.[30] Five further studies (Berlin 2008,[29] Hashim 2016,[28] Jorizzo 2010,[24] NCT0774787[26] and Tan 2007)[25] had a high risk of selective reporting, mostly because they did not report the outcomes that they had described in the methods part (−2). [h]$I^2$ = 75% (−2).

## Comparator-specific stratified analyses

Comparator-specific stratified analysis was possible for cryosurgery plus ingenol mebutate (two studies)[27,28] and imiquimod (four studies).[23–26] Cryosurgery followed by ingenol mebutate showed no significant differences regarding participant complete clearance rate (RR 3·51, 95% CI 0·22–56·5, $I^2$ = 77, two studies) or partial clearance rate (RR 2·97, 95% CI 0·28–31·0, $I^2$ = 83%, two studies) in comparison with cryosurgery alone. A sensitivity analysis was not performed as only two studies were available for this comparison. The lesion-specific reduction ranged from 82·7% to 85·1% for a combination of cryosurgery and ingenol mebutate (Table 2). The number of patients who stopped treatment due to adverse events was equal in both groups (RR 0·99, 95% CI 0·97–1·01, $I^2$ = 0%, two studies) (Fig. S2; see Supporting Information). The quality of evidence was estimated as very low because of imprecision, high risk of bias and inconsistency

(participant complete and partial clearance), and low due to a high risk of bias of the included studies (lesion-specific reduction, tolerability) (Table S3; see Supporting Information).

The combination of cryosurgery with imiquimod revealed no significant difference of participant complete clearance in comparison with cryosurgery alone (RR 2·46, 95% CI 0·63–9·57, $I^2$ = 87%, three studies). Sensitivity analysis with only interindividual trials showed similar results (RR 3·11, 95% CI 0·31–30·9, $I^2$ = 94%, two studies). The lesion-specific reduction ranged from 73·2% to 79·3% for the combination therapy (Table 2). Tolerability in terms of adverse events leading to discontinuation was similarly distributed in both groups (RR 0·99, 95% CI 0·97–1·01, $I^2$ = 0%, three studies; interindividual trials only: RR 0·99, 95% CI 0·97–1·01, $I^2$ = 0%, two studies) (Fig. S3; see Supporting Information). The quality of evidence was graded as very low (participant complete clearance) due to imprecision, high risk of bias and inconsistency, and low because of a high risk of bias (lesion-

Table 2 Overview of the lesion-specific complete clearance rates in the included studies

| Study | Intervention | Lesion reduction, % ± SD[a] |
|---|---|---|
| Berlin 2008[29] | Cryosurgery + diclofenac | 89 |
| | Cryosurgery monotherapy | 68 |
| Berman 2014[27] | Cryosurgery + ingenol mebutate 0·015% gel | 82·7 |
| | Cryosurgery + vehicle | 75·6 |
| Hashim 2016[28] | Cryosurgery + ingenol mebutate 0·05% gel | 85·1 |
| | Cryosurgery monotherapy | 54·8 |
| Goldenberg 2013[23] | Cryosurgery + imiquimod 3·75% cream | 75·9 |
| | Cryosurgery monotherapy | 39·0 |
| Jorizzo 2010[24] | Cryosurgery + imiquimod 3·75% cream | 77·4 ± 27·6 |
| | Cryosurgery + placebo | 43·3 ± 30·1 |
| NCT00774787[26] | Cryosurgery + imiquimod 5% cream | 73·2 ± 27·1 |
| | Cryosurgery monotherapy | 62·0 ± 30·3 |
| Tan 2007[25] | Cryosurgery + imiquimod 5% cream | 79·3 |
| | Cryosurgery + vehicle | 76·0 |
| Hoover 2014[30] | Cryosurgery + 5-FU 0·5% cream | 84 |
| | Cryosurgery + vehicle | 69 |
| NCT02239679[31] | Cryosurgery + ALA-PDT | n.r. |
| | Cryosurgery + vehicle PDT | n.r. |

FU, fluorouracil; ALA, 5-aminolevulinic acid; PDT, photodynamic therapy; n.r., not reported. [a]Change from baseline outcome, with SD if reported.

specific reduction, tolerability) (Table S4; see Supporting Information). The participant partial clearance was not consistently reported for this subgroup.

## Discussion

In this study we addressed the question of whether a combination approach of cryosurgery plus a topical agent is preferable to cryosurgery alone in patients with AK. Our results revealed the superiority of the combination regarding the outcome participant complete clearance. Statistical analysis showed a significant difference only for complete clearance but not for partial clearance. This may be explained by the fact that the results from only three studies were pooled for the latter outcome, whereas eight trials provided data on participant complete clearance rates. Thus, the estimate for partial clearance may be underpowered.

A quantitative synthesis for lesion-specific reduction was not possible, as data were reported insufficiently and measures of dispersion were lacking. Furthermore, pooling lesion-specific values is not without problems from a methodological point of view, because it is not the individual lesions that are randomized but the patients or entire treatment areas that represent the basis for sample-size calculations. Thus, we decided to describe the lesion-specific reduction qualitatively. Consistently with the participant-specific efficacy results, the lesion-specific reduction was consistently higher for the combination compared with cryosurgery alone, ranging from 73·2% to 89% and from 39% to 76%, respectively. The efficacy for cryosurgery as monotherapy in our analysis was largely concordant with values reported in other RCTs.[32–35]

Krawtchenko *et al.* reported a participant complete clearance rate of 68% of patients treated with cryosurgery, which dropped to 28% at the 12-month follow-up.[34] As we included only efficacy data obtained 2–6 months after the end of treatment, conclusions on the long-term efficacy of the combination of cryosurgery with a topical agent were not possible. Kaufmann *et al.* found a high lesion-specific response rate of 88% for AKs located on the extremities that had been treated with cryosurgery only.[33] This contrasts with our observations. Lesions of the limbs are considered difficult to treat, and efficacy results are usually worse for this localization compared with the face or scalp. Three trials in our analysis included AK on the dorsal hands, revealing rather low clearance rates ranging from 39% to 68%.[23,28,29] This underlines that cryosurgery alone may not be sufficient for sustained lesion clearance and that a combination with topical treatment is preferable here.

Zane *et al.* provided evidence that cryosurgery alone is a highly effective treatment for patients with isolated AK (maximum four lesions) on the face and scalp.[9] In contrast, the baseline AK count in the trials included in our data analysis ranged from 4·6[28] to 12[30] lesions. Hence, we propose that the results are only generalizable to patients with multiple AKs or field cancerization. In cases of single and well-defined lesions, cryosurgery alone remains an effective and practicable approach for both patients and physicians, and adding a topical intervention may not be necessary. In patients with multiple lesions within a larger field with signs of chronic exposure to ultraviolet radiation, subclinical changes are likely to be present adjacent to clinically visible lesions. Here, adding a topical intervention after treating thicker and hyperkeratotic AKs with cryosurgery represents an attractive and tolerable approach to target both visible AKs and the entire actinically damaged field.

The tolerability of the interventions of interest was measured by the number of patients who successfully completed the study protocol and did not withdraw due to treatment-related adverse events. This outcome was applied in several treatment guidelines and meta-analyses to estimate the tolerability and feasibility of interventions for AKs.[7,8] Although there were more patients who discontinued the treatment in the combination group compared with monotherapy, this difference was not statistically significant and the size of the effect was negligible. One exception is the study conducted by Berlin and Rigel, which reported a high dropout rate of patients treated with cryosurgery followed by diclofenac sodium.[29] It is conceivable that the attrition was due to compliance issues, as diclofenac sodium should be applied twice

daily over 90 days, and not explained by treatment-related serious adverse events. Altogether, our analyses suggest that a combination is equally tolerable compared with cryosurgery alone in all subgroups that were analysed by us.

A major limitation of this study is the inclusion of only RCTs and the high clinical and methodological heterogeneity of the interventions. Firstly, the performance of cryosurgery was little standardized throughout all of the studies, and distinct freeze–thaw cycles and freezing times were used. Secondly, a variety of topical agents were used with distinct mechanisms of action and durations of application. Two of the included trials applied the topical interventions in an off-label use as the treatment field was larger than recommended in the summary of product characteristics.[25,28] Furthermore, the size of the treatment areas varied. Some studies investigated an area of 25 cm$^2$, which is regarded as a small or limited field and may not represent a full field-directed approach.[27] This limitation should be kept in mind when generalizing our results to other populations.

Subgroup analysis was possible for the topical agents ingenol mebutate and imiquimod. In both groups, the participant-specific clearance rates of the combination were superior to those of monotherapy with cryosurgery, yet without statistical significance. The effect size for both agents was consistent and similar to the overall analysis. Thus, the lack of significance may be explained by a small sample size and a lack of power. Further important limitations are the language restriction to records published in English or German and the fact that inter- and intraindividual trials were analysed together. A proper adjustment of the standard errors was not possible because cluster correlations and design effects were not reported in the primary intraindividual studies. To address this effect, we performed sensitivity analysis after exclusion of intraindividual trials for each outcome, revealing results comparable with those achieved with all studies. Nevertheless, we cannot exclude that the CIs of our pooled results are artificially narrow and may not reflect the true variability.

Taking the evidence together, this review suggests that a combination of cryosurgery with a topical intervention may be more effective than cryosurgery alone in patients with multiple AKs and field cancerization. Our results underline that cryosurgery alone may not be sufficient to achieve disease control in difficult-to-treat lesions. Furthermore, they highlight the importance of a field-directed approach in patients with multiple AKs.

## Acknowledgments

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Fig S1.** Summary of the evaluation of the included studies for each risk-of-bias item.

**Fig S2.** Subgroup analysis for cryosurgery combined with ingenol mebutate.

**Fig S3.** Subgroup analysis for cryosurgery combined with imiquimod.

**Table S1** Search queries for (a) MEDLINE via Ovid, (b) Embase via Ovid and (c) The Cochrane Library 'CENTRAL'.

**Table S2** Characteristics of the included studies (n = 9).

**Table S3** Summary-of-findings table for the outcomes of the comparison cryosurgery with ingenol mebutate vs. cryosurgery alone (subgroup analysis).

**Table S4** Summary-of-findings table for the outcomes of the comparison cryosurgery with imiquimod vs. cryosurgery alone (subgroup analysis).

**Supplementary Table S1:** Search queries for (a) MEDLINE via Ovid, (b) Embase via Ovid and (c) The Cochrane Library 'CENTRAL'.

| **(a) Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>** <br> **n=320 hits (10.07.2018)** |
|---|
| 1. actinic keratosis.mp. or exp Keratosis, Actinic/ |
| 2. solar keratosis.mp. |
| 3. senile keratosis.mp. |
| 4. field change.mp. |
| 5. actinically damaged field.mp. |
| 6. exp Precancerous Conditions/ or field-cancerized.mp. |
| 7. actinic keratoses.mp. |
| 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 |
| 9. cryotherapy.mp. or exp CRYOTHERAPY/ |
| 10. cryosurgery.mp. or exp CRYOSURGERY/ |
| 11. cryopeel*.mp. |
| 12. exp RANDOMIZED CONTROLLED TRIAL/ or exp CLINICAL TRIAL/ or trial.mp. |
| 13. 8 and 12 |
| 14. fluorouracil.mp. or exp FLUOROURACIL/ |
| 15. fluorouracil derivative.mp. |
| 16. efudix.mp. |
| 17. actikerall.mp. |
| 18. 5-FU.mp. |
| 19. exp Aminoquinolines/ or imiquimod.mp. |
| 20. aldara.mp. |
| 21. zyclara.mp. |
| 22. exp Diterpenes/ or ingenol mebutate.mp. |
| 23. picato.mp. |
| 24. diclofenac.mp. or exp DICLOFENAC/ |
| 25. solaraze.mp. |
| 26. solacutan.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 27. ingenolmebutat.mp. |
| 28. ingenol mebutate.mp. |
| 29. photodynamic therapy.mp. or exp Photochemotherapy/ |
| 30. exp Aminolevulinic Acid/ or aminolevulinate.mp. or exp Photosensitizing Agents/ |
| 31. methyl aminolevulinic acid.mp. |
| 32. MAL.mp. |
| 33. ALA.mp. |
| 34. BF-200 ALA.mp. |
| 35. Ameluz.mp. |
| 36. Alacare.mp. |
| 37. Metvix.mp. |
| 38. Luxerm.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 39. 9 or 10 or 11 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 |
| 40. 13 and 39 |

41. combined.mp.

42. followed.mp.

43. sequential.mp.

44. concurrent.mp.

45. assisted.mp.

46. mediated.mp.

47. combination.mp.

48. adjunct.mp.

49. after.mp.

50. 41 or 42 or 43 or 44 or 45 or 46 or 47

51. 40 and 50

52. limit 49 to (english or german)

**(b) Embase <1974 to 2018 July 9>**
**N=704 hits (10.07.2018)**

1. actinic keratosis.mp. or actinic keratosis/

2. solar keratosis.mp.

3. senile keratosis.mp.

4. field change.mp.

5. actinically damaged field.mp.

6. field-cancerized.mp. or exp precancer/

7. actinic keratoses.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. trial.mp. or exp "phase 4 clinical trial (topic)"/ or exp controlled clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or exp "controlled clinical trial (topic)"/ or exp "phase 3 clinical trial (topic)"/

10. cryotherapy.mp. or exp cryotherapy/

11. 8 and 9

12. exp cryosurgery/ or cryosurgery.mp.

13. cryopeel*.mp. or exp skin surgery/

14. exp fluorouracil/ or exp fluorouracil plus salicylic acid/ or exp fluorouracil derivative/ or fluorouracil.mp.

15. efudix.mp.

16. actikerall.mp.

17. 5-FU.mp.

18. exp imiquimod/ or imiquimod.mp.

19. aldara.mp.

20. zyclara.mp.

21. ingenol mebutate.mp. or exp ingenol mebutate/

22. picato.mp.

23. diclofenac.mp. or exp diclofenac/ or exp diclofenac derivative/

24. solaraze.mp.

25. solacutan.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

26. photodynamic therapy.mp. or exp photodynamic therapy/

27. exp phototherapy/

28. aminolevulinate.mp. or exp aminolevulinic acid/

29. exp aminolevulinic acid methyl ester/ or methyl aminolevulinic acid.mp.

30. MAL.mp.

31. exp nanoemulsion/ or exp photosensitizing agent/ or BF-200 ALA.mp.

32. Ameluz.mp.

33. Alacare.mp.

34. Metvix.mp.

35. Luxerm.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

36. ALA.mp.

37. 10 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. followed.mp.

39. sequential.mp.

40. combined.mp.

41. combination.mp.

42. assisted.mp.

43. mediated.mp.

44. adjunct.mp.

45. after.mp.

46. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

47. 11 and 37 and 46

48. limit 47 to (english or german)

**(c) CENTRAL (The Cochrane Library)**
**n=204 hits (10.07.2018)**

| | |
|---|---|
| #1 | MeSH descriptor: [Keratosis, Actinic] explode all trees |
| #2 | actinic keratos* |
| #3 | solar keratos* |
| #4 | senile keratos* |
| #5 | MeSH descriptor: [Precancerous Conditions] explode all trees |
| #6 | field cancerization |
| #7 | cryotherapy |
| #8 | cryosurgery |
| #9 | cryopeel* |
| #10 | fluorouracil |
| #11 | 5-FU |
| #12 | diclofenac |
| #13 | ingenolmebutate |
| #14 | ingenol mebutate |
| #15 | imiquimod |
| #16 | actikerall |
| #17 | photodynamic therapy |
| #18 | phototherapy |
| #19 | aminolevulinate |
| #20 | aminolevulinic acid |
| #21 | methyl aminolevulinic acid |
| #22 | MAL |
| #23 | ALA |
| #24 | Ameluz |
| #25 | Alacare |
| #26 | Metvix |
| #27 | nanoemulsion |
| #28 | photosensitizing agent |
| #29 | BF-200 ALA |
| #30 | Luxerm |
| #31 | efudix |
| #32 | solaraze |
| #33 | solacutan |
| #34 | picato |
| #35 | actikerall |

```
#36      aldara
#37      zyclara
#38      #1 or #2 or #3 or #4 or #5 or #6
#39      #7 or #8 or #9 or #10 or #11 or 12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or
#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or
#35 or #36 or #37
#40      #38 and #39
#41      followed
#42      combined
#43      sequential
#44      combination:ti,ab,kw
#45      assisted
#46      mediated
#47      #41 or #42 or #43 or #44 or #45 or #46
#48      #40 and #47
#49      randomized controlled trial
#50      #49 and #48
```

**Supplementary Table S2:** Characteristics of the included studies (n = 9).

| Study | Design | Intervention | Mean AK count at baseline | Sample size | Localization of lesions | Time of assessment |
|---|---|---|---|---|---|---|
| **Diclofenac** | | | | | | |
| **Berlin 2008** | Multicentre, randomized, inter-individual, open-label phase 4 | Cryosurgery with a single freeze-thaw cycle and 4-second to 10-second freeze time. After 15 days, application of diclofenac sodium 3% gel for 90 days (n=368) | 8.9 | n=714 | Forehead<br><br>Scalp<br><br>Hands | Day 135 |
| | | Cryosurgery alone with a single freeze-thaw cycle and 4-second to 10-second freeze time (n=346) | 8.2 | | | |
| **Ingenol Mebutate** | | | | | | |
| **Berman 2014** | Multicentre, randomized, double-blind, inter-individual, phase 3 | Cryosurgery using the spray technique; after 3 weeks, application of ingenol mebutate 0.015% gel once daily for 3 consecutive days (n=167) | 5.7 | n=329 | Face<br><br>Scalp | 11 weeks |
| | | Cryosurgery using the spray technique; after 3 weeks, application of vehicle gel once daily for 3 consecutive days (n=162) | 5.8 | | | |
| **Hashim 2016** | Single-centre, randomized, intra-individual | Cryosurgery with two continuous sprays of liquid nitrogen for five seconds with a five-second interval between sprays, followed by application of ingenol mebutate 0.05% gel once daily for 2 consecutive days | 5.4, sd = 3.1 | n=16 | Dorsal hands | Day 57 |
| | | Cryosurgery with two continuous sprays of liquid nitrogen for five seconds with a five-second interval between sprays | 4.6, sd = 2.1 | | | |
| **Imiquimod** | | | | | | |
| **Goldenberg 2013** | Single-centre, randomized, intra-individual | Cryotherapy using two sprays; five seconds each, with a five-second rest interval; following cryotherapy, application of imiquimod 3.75% cream two weeks on, two weeks off, two weeks on use | 6.3, sd = 3.6 | n=20 | Dorsal hands<br><br>Forearms | Week 14 |

| | | Cryotherapy using two sprays, five seconds each, with a five-second rest interval | 5.5, sd = 2.6 | | | |
|---|---|---|---|---|---|---|
| **Jorizzo2010** | Multicentre, randomized, double-blind, placebo-controlled, inter-individual | Cryosurgery per investigator's usual practice, followed by application of imiquimod 3.75% cream on two weeks on, two weeks off, two weeks on regimen (n=126) | 16.1, sd = 5.8 | n=247 | Face Scalp | 26 weeks |
| | | Cryosurgery per investigator's usual practice, followed by application of vehicle cream on two weeks on, two weeks off, two weeks on regimen (n=121) | 15.8, sd = 5.8 | | | |
| **NCT00774787** | Single-centre, randomized, assessor-blinded, intra-individual, phase 4 | Cryotherapy followed by application of imiquimod 5% cream 3 times per week for 4 weeks | 8.7, sd = 2.2 | n=27 | Face | Week 8 |
| | | Cryotherapy alone | 8.5, sd = 2.3 | | | |
| **Tan 2007** | Single-centre, randomized, double-blind, inter-individual | Cryosurgery with a 3-5-second freeze cycle with liquid nitrogen, followed by the application of imiquimod 5% cream twice weekly for 8 weeks (n=33) | 8.5, sd = 3.2 | n=65 | Face Scalp | Week 22 |
| | | Cryosurgery with a 3-5-second freeze cycle with liquid nitrogen, followed by the application of vehicle cream twice weekly for 8 weeks (n=32) | 8.1, sd = 3.6 | | | |
| **5-Fluorouracil** | | | | | | |
| **Hoover 2014** | Single-centre, randomized, investigator-blinded, vehicle-controlled, inter-individual | Three weeks after cryosurgery once daily application of 5-FU cream 0.5% for 1 week (n=30) | 12 (median), IQR = 9 | n=60 | Face Scalp | Week 8 |
| | | Three weeks after cryosurgery once daily application of vehicle cream for 1 week (n=30) | 12 (median), IQR = 10 | | | |
| **Photodynamic therapy with ALA** | | | | | | |

| NCT02239679 | Multi-centre, randomized, double-blind, inter-individual | Cryotherapy with liquid nitrogen per investigator's usual practice followed by 2 or 3 treatments of ALA-PDT (application of 20% ALA for 3 hours, illumination with 10 J/cm² blue light delivered at 10 mW/cm²) (n=112) | n.r. | n=166 | Face | Week 12 |
|---|---|---|---|---|---|---|
| | | Cryotherapy with liquid nitrogen per investigator's usual practice followed by 2 or 3 treatments of vehicle PDT. (n=54) | n.r. | | | |

**Abbreviations:** ALA = 5-aminolevulinic acid, IQR = interquartile range, n.r. = not reported, sd = standard deviation

**Supplementary Table S3:** Summary-of-findings table for the outcomes of the comparison cryosurgery with ingenol mebutate vs. cryosurgery alone (subgroup analysis).

| Outcomes | Anticipated absolute effects[*] (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with cryosurgery alone** | **Risk with cryosurgery followed by ingenol mebutate** | | | |
| Participant complete clearance | 449 per 1.000 | **1000 per 1.000** (99 to 1.000) | **RR 3.51** (0.22 to 56.53) | 345 (2 RCTs) | ⊕◯◯◯ VERY LOW a,b,c |
| Participant partial clearance | 618 per 1.000 | **1000 per 1.000** (173 to 1.000) | **RR 2.97** (0.28 to 30.96) | 345 (2 RCTs) | ⊕◯◯◯ VERY LOW a,c,d |
| Lesion complete clearance | The lesion complete clearance rate ranged from 82.7% to 85.1% for the combination therapy. | | | 345 (2 RCTs) | ⊕⊕◯◯ LOW a |
| Tolerability | 1.000 per 1.000 | **990 per 1.000** (970 to 1.000) | **RR 0.99** (0.97 to 1.01) | 345 (2 RCTs) | ⊕⊕◯◯ LOW a |

*****The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

---

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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## Explanations

a. The study Hashim 2016 showed a risk for performance and reporting bias. Selection bias was unclear in both studies. (-1)
b. I²=77% (-2)
c. Confidence intervals are very broad (-2).
d. I²=83% (-2).

**Supplementary Table S4:** Summary-of-findings table for the outcomes of the comparison cryosurgery with imiquimod vs. cryosurgery alone (subgroup analysis).

| Outcomes | Anticipated absolute effects[*] (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with cryosurgery alone** | **Risk with cryosurgery followed by imiquimod** | | | |
| Participant complete clearance | 117 per 1.000 | **287 per 1.000** (74 to 1.000) | **RR 2.46** (0.63 to 9.57) | 339 (3 RCTs) | ⊕◯◯◯ VERY LOW a,b,c |
| Participant partial clearance - not reported | - | - | - | - | - |
| Lesion complete clearance | The lesion specific clearance rate ranged from 73.2% to 79.3% for the combination therapy. | | | 359 (4 RCTs) | ⊕⊕◯◯ LOW a |
| Tolerability | 1.000 per 1.000 | **990 per 1.000** (970 to 1.000) | **RR 0.99** (0.97 to 1.01) | 339 (3 RCTs) | ⊕⊕◯◯ LOW a |

**\*The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

## Explanations

a. All studies have a risk for selective reporting. Besides Tan 2007 has a high risk for attrition bias and unclear risk for selection bias. The study NCT00774787 did not provide enough information to estimate the risk for selection bias (-2).
b. I²=87% (-2).
c. Confidence intervals have contrary margins. (-2)

**Supplementary Figure 1:** Summary of the evaluation of the included studies for each risk-of-bias item.
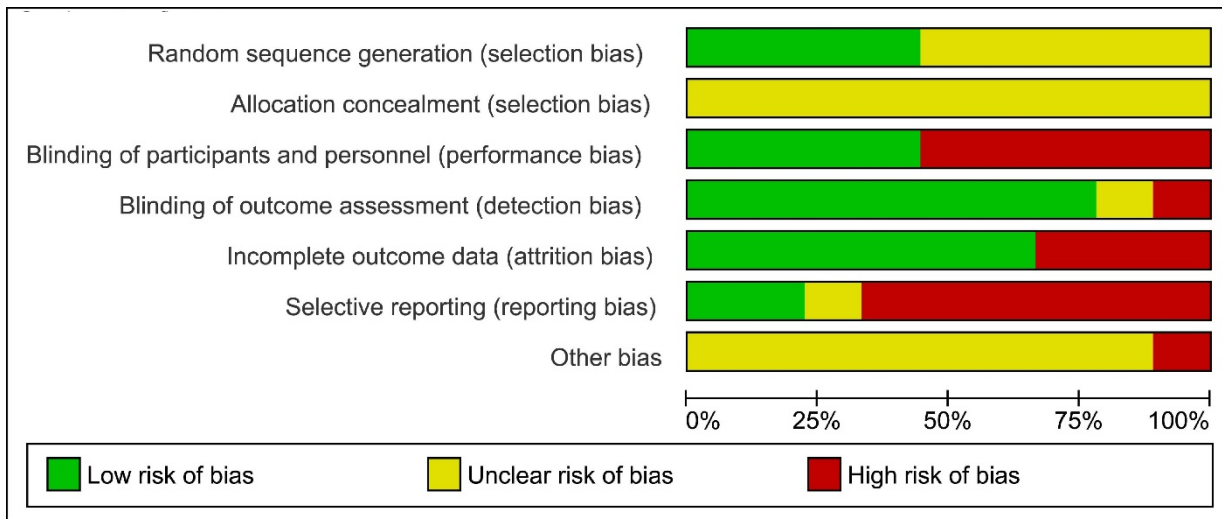
**Supplementary Figure 2:** Subgroup analysis for cryosurgery combined with ingenol mebutate.

(a) Participant complete clearance (100%)

| Study or Subgroup | Cryosurgery and IMB Events | Total | Cryosurgery monotherapy Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Berman 2014 (Ingenol Mebutate) | 101 | 167 | 80 | 162 | 61.6% | 1.22 [1.00, 1.49] | |
| Hashim 2016 (Ingenol Mebutate) | 9 | 16 | 0 | 16 | 38.4% | 19.00 [1.20, 301.16] | |
| **Total (95% CI)** | | 183 | | 178 | 100.0% | 3.51 [0.22, 56.53] | |
| Total events | 110 | | 80 | | | | |

Heterogeneity: Tau² = 3.25; Chi² = 4.26, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.88 (P = 0.38)

Favours cryosurgery    Favours cryosurgery + IMB

(b) Participant partial clearance (>75%)

| Study or Subgroup | Cryosurgery and IMB Events | Total | Cryosurgery monotherapy Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Berman 2014 (Ingenol Mebutate) | 130 | 167 | 109 | 162 | 58.2% | 1.16 [1.01, 1.32] | |
| Hashim 2016 (Ingenol Mebutate) | 11 | 16 | 1 | 16 | 41.8% | 11.00 [1.60, 75.50] | |
| **Total (95% CI)** | | 183 | | 178 | 100.0% | 2.97 [0.28, 30.96] | |
| Total events | 141 | | 110 | | | | |

Heterogeneity: Tau² = 2.46; Chi² = 6.06, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 0.91 (P = 0.36)

Favours cryosurgery    Favours cryosurgery + IMB

(c) Participants completing the study protocol without withdrawal

| Study or Subgroup | Cryosurgery and IMB Events | Total | Cryosurgery monotherapy Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Berman 2014 (Ingenol Mebutate) | 165 | 167 | 162 | 162 | 97.0% | 0.99 [0.97, 1.01] | |
| Hashim 2016 (Ingenol Mebutate) | 16 | 16 | 16 | 16 | 3.0% | 1.00 [0.89, 1.12] | |
| **Total (95% CI)** | | 183 | | 178 | 100.0% | 0.99 [0.97, 1.01] | |
| Total events | 181 | | 178 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

Favours cryosurgery    Favours cryosurgery + IMB

70

**Supplementary Figure 3:** Subgroup analysis for cryosurgery combined with imiquimod.

(a) Participant complete clearance (100%)

| Study or Subgroup | Cryosurgery and Imiquimod | | Cryosurgery monotherapy | | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | | |
| Jorizzo 2010 (Imiquimod) | 38 | 126 | 4 | 121 | 31.9% | 9.12 [3.36, 24.79] | |
| NCT00774787 (Imiquimod) | 8 | 27 | 5 | 27 | 32.1% | 1.60 [0.60, 4.27] | |
| Tan 2007 (Imiquimod) | 14 | 33 | 12 | 32 | 35.9% | 1.13 [0.62, 2.06] | |
| | | | | | | | |
| Total (95% CI) | | 186 | | 180 | 100.0% | 2.46 [0.63, 9.57] | |
| Total events | 60 | | 21 | | | | |

Heterogeneity: Tau² = 1.24; Chi² = 15.29, df = 2 (P = 0.0005); I² = 87%
Test for overall effect: Z = 1.30 (P = 0.19)

0.01　0.1　1　10　100
Favours cryosurgery　Favours cryosurgery + IMI

(b) Participants completing the study protocol without withdrawal

| Study or Subgroup | Cryosurgery and Imiquimod | | Cryosurgery monotherapy | | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | | |
| Jorizzo 2010 (Imiquimod) | 125 | 126 | 121 | 121 | 80.7% | 0.99 [0.97, 1.01] | |
| NCT00774787 (Imiquimod) | 27 | 27 | 27 | 27 | 7.9% | 1.00 [0.93, 1.07] | |
| Tan 2007 (Imiquimod) | 33 | 33 | 32 | 32 | 11.4% | 1.00 [0.94, 1.06] | |
| | | | | | | | |
| Total (95% CI) | | 186 | | 180 | 100.0% | 0.99 [0.97, 1.01] | |
| Total events | 185 | | 180 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)

0.85　0.9　1　1.1　1.2
Favours cryosurgery　Favours cryosurgery + IMI

# 9. Veröffentlichung III

72

**A critical appraisal of evidence- and consensus-based guidelines for actinic keratosis**

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*Article*

# A Critical Appraisal of Evidence- and Consensus-Based Guidelines for Actinic Keratosis

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**Abstract:** Actinic keratoses (AK) are common lesions of the skin that can be effectively treated with several lesion- and field-directed treatments. Clinical practice guidelines assist physicians in choosing the appropriate treatment options for their patients. Here, we aimed to systematically identify and evaluate the methodological quality of currently available guidelines for AK. Guidelines published within the last 5 years were identified in a systematic search of guideline databases, Medline and Embase. Then, six independent reviewers evaluated the methodological quality using the tools "Appraisal of Guidelines for Research and Evaluation" (AGREE II) and "Recommendation EXcellence" (AGREE-REX). The Kruskal–Wallis (H) test was used to explore differences among subgroups and Spearman's correlation to examine the relationship between individual domains. Three guidelines developed by consortia from Canada, Germany and the United Kingdom were eligible for the evaluation. The German guideline achieved the highest scores, fulfilling 65 to 92% of the criteria in AGREE II and 67 to 84% in AGREE-REX, whereas the Canadian guideline scored 31 to 71% of the criteria in AGREE II and 33 to 46% in AGREE-REX. The domains "stakeholder involvement" and "values and preferences" were identified as methodological weaknesses requiring particular attention and improvement in future guideline efforts.

## 1. Introduction

Actinic keratoses (AK) are common lesions of chronically sun-damaged keratinocytes in the epidermis, the upper layer of the skin [1]. They are most commonly found in areas that have been chronically exposed to ultraviolet (UV) radiation such as the head, face and the dorsal hands [2]. Affected areas usually present as red, scaly plaques with a rough surface [2]. AK can further progress to invasive squamous cell carcinoma of the skin [3]. However, it is currently not possible to predict which AK may progress and which do not, thus, consequent treatment of AK is recommended by several international practical guidelines, especially in high-risk patients [4–6].

Over the last decades, a broad variety of options have been licensed for AK treatment. They include lesion-directed options as cryotherapy and fractional laser therapy, which are suitable to treat single

AK lesions. Another approach comprises field-directed treatments, which are usually deployed to treat larger areas of sun-damaged skin, for instance photodynamic therapy (PDT), which may be also effective in other skin diseases such as acne vulgaris, as recently shown by Del Duca et al. [7], microneedling and application of various topicals. Additionally, monotherapies can be combined for a stronger effect to achieve better results especially in difficult-to-treat or therapy-resistant AK patients [8–12]. The vast number of available and approved therapies may be both a blessing and a curse. Thus, up-to-date medical practical guidelines are valuable tools that help to select the most suitable and evidence-based approach for the individual patient with additional consideration of their personal preferences [13]. However, the provided recommendations should be developed in a structured process based on a sound methodological quality to ensure reliability and engagement.

In this study, we aimed to assess the methodological strengths and weaknesses of all currently available international guidelines on AK treatment using the two assessment instruments "Appraisal of Guidelines for Research and Evaluation (AGREE) II" and "AGREE-REX: Recommendation EXcellence" [14,15]. The widely used AGREE II appraisal tool from 2009 is an updated version of AGREE that was originally released in 2001. AGREE II consists of 23 items that are grouped in the six quality domains "scope and purpose", "stakeholder involvement", "rigor of development", "clarity of presentation", "applicability" and "editorial independence" as well as two items assessing the overall quality of the respective guideline. Recently, the AGREE-REX instrument was launched to complement guideline evaluation with AGREE II. AGREE-REX covers the topics clinical credibility and implementability and also assesses how values and preferences of target users, patients, policy and the guideline developers themselves have influenced the development of the recommendations.

## 2. Materials and Methods

### 2.1. Eligibility Criteria

In our appraisal, we only included guidelines developed by national or international consortia focusing on more than one option for the management of AK. They had to be published within the last 5 years, i.e., 2015–2019, as we only wanted to evaluate the most up-to-date guidelines. Furthermore, only English or German publications were included. Guidelines that had already expired or were not developed based on a systematic literature search followed by a structured consensus process, e.g., expert consent-based guidelines, were excluded.

### 2.2. Search Strategy and Selection of Guidelines

In order to identify potential guidelines for the evaluation, we systematically searched several guideline databases as well as Medline and Embase (both via Ovid) until 23 October 2019. The search included the terms "actinic keratosis/keratoses", "solar keratoses", "field cancerization", "senile keratoses" and "precancerous lesions". Besides, cross-references of included guidelines were screened as well. The detailed search strategies are shown in Supplementary Tables S1 and S2. The search results were screened for double hits. After their elimination, the remaining titles, abstracts or editorials were screened by two authors (M.V.H., T.S.), if they met the predefined eligibility criteria. Full-text guidelines of potentially relevant records were obtained and checked for eligibility again.

### 2.3. Data Extraction and Rating of the Guidelines

Background information including title, consortia and/or authors, country of origin, publication date, methodological approach and scope of all eligible guidelines were collected. Then, six independent reviewers (A.W., F.H., A.H., M.K., E.K., F.T.) evaluated their methodological quality using AGREE II and AGREE-REX as described previously [16]. Using AGREE II, the quality of each of the 23 items was assessed on a 7-point scale ranging from 1 ("strongly disagree") to 7 ("strongly agree") and similarly, the guideline's overall quality was evaluated on a 7-point scale ranging from lowest to highest possible quality. Furthermore, the question "I would recommend this guideline for use" was answered by each

reviewer with "yes", "yes, with modifications" or "no". The 9 items supplied by AGREE-REX were also assessed on a 7-point scale ranging from 1 ("lowest quality") to 7 ("highest quality") as described previously [16]. All evaluations using AGREE II and AGREE-REX were blinded towards the other evaluators' assessments and performed independently. The platform "My AGREE Plus" provided by the AGREE consortium on https://www.agreetrust.org/ (last access: 31 May 2020) was used for evaluating the guidelines with the AGREE II instrument, whereas internally piloted data extraction spreadsheets (Microsoft Excel 2010) were used for the evaluation with AGREE-REX.

*2.4. Analysis*

Scores were calculated for each domain according to the instructions provided in the AGREE II and AGREE-REX instrument user manuals [15,17]. Total scores were expressed as percentages ranging from 0% as the worst to 100% as the best possible evaluation for each domain. Mean ± standard deviation (SD) was calculated for descriptive analyses. The Kruskal–Wallis (H) test was used to explore differences among subgroups and Spearman's correlation to examine the relationship between individual domains and items of the instruments. *p*-values < 0.05 were considered statistically significant. Ratings were grouped in the three categories "strongly agree" (6 and 7 points), "partly agree" (3 to 5 points) and "strongly disagree" (1 and 2 points) and Fleiss' Kappa was calculated in order to assess the interrater agreement of the six reviewers [18]. SPSS Statistics (version 24, IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

## 3. Results

*3.1. Guideline Identification*

We initially identified 2612 records when searching the databases (Figure 1). After the elimination of double hits (*n* = 126) and title and abstract screening, nine records remained for full-text review. Six records were excluded, as they had already expired (*n* = 2) [19,20], only dealt with cutaneous squamous cell carcinoma (*n* = 1) [21], were not evidence-based (*n* = 1) [22] or did not meet our language eligibility (*n* = 1) [23]. Another record was dismissed, as it was a review summary and not a guideline [24]. Finally, the following three guidelines met our eligibility criteria and, therefore, were included in our assessment: the guideline of the Canadian Non-Melanoma Skin Cancer Guidelines Committee [4], the guideline of the British Association of Dermatologists from the United Kingdom (UK) [6] and the guideline developed by the Association of the Scientific Medical Societies in Germany (AWMF) and the German Cancer Society (DKG) [5,10,25]. The full-length German guideline is also available in English in the "Supporting Information" section of the short version [10].

*3.2. Evaluation of the Guidelines*

The interrater agreement of the six reviewers regarding AGREE II and AGREE-REX was rated as fair with a Fleiss' Kappa of 0.299 (95% CI 0.263–0.336).

*3.3. AGREE II*

3.3.1. Scope and Purpose

This domain evaluates whether the main objectives of the guideline and the population for whom it was developed are clearly described. The average score was 5.17 (±1.49, Figure 2). The German guideline achieved the highest score fulfilling 89% of the criteria of this domain. The Canadian guideline was rated lowest with 48% and the UK guideline was rated in between achieving 71%. The German and the Canadian guideline significantly differed from each other (*p* = 0.01).
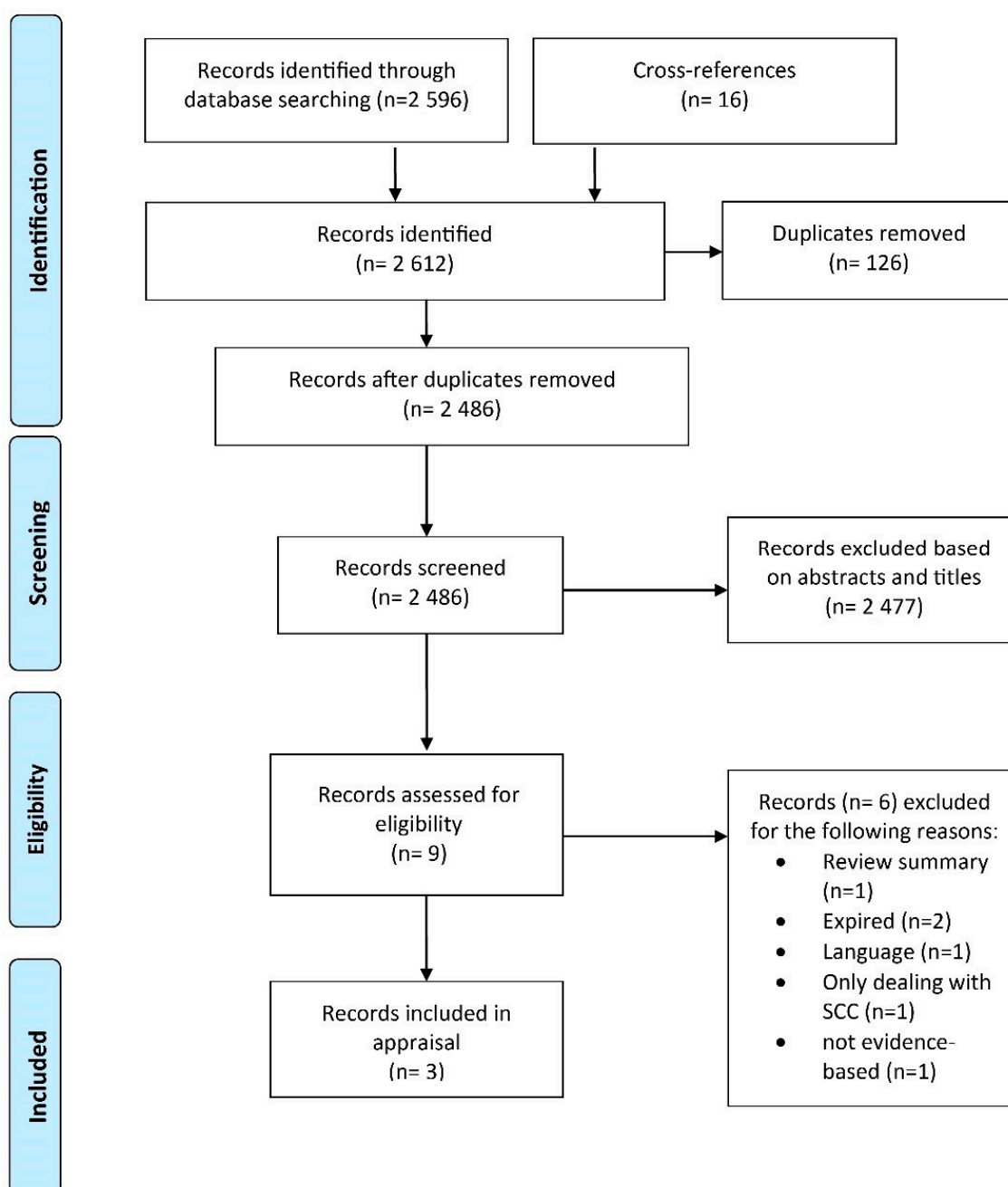
**Figure 1.** Flow chart of the guideline identification process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

### 3.3.2. Stakeholder Involvement

This domain covers the topics involvement of appropriate stakeholders and whether the views of the users that should deploy the guideline are represented. The average score was 4.39 (±1.86). The German guideline achieved a very high value of 92%, while the UK and Canadian guidelines achieved only 37 and 41%, respectively. The German guideline significantly differed from both the Canadian ($p = 0.012$) and the UK guideline ($p = 0.009$).

### 3.3.3. Rigor of Development

The methodological approaches including a systematic and transparent identification of evidence are covered by the items of this domain. The mean score was 4.99 (±1.44). Again, the German guideline

was rated as the one with the best methodological quality achieving 89% whereas the UK and the Canadian guidelines were rated worse with 63 and 48%, respectively. The German guideline also significantly differed from the Canadian guideline in this domain ($p = 0.006$).

### 3.3.4. Clarity and Presentation

This domain evaluates the presentation of the provided recommendations including the clarity of recommendations or if key recommendations can be easily found in the guideline text at a glance. The mean score was 6.02 (±0.87). Both the German and the UK guideline fulfilled almost all criteria (89 and 91%, respectively) and also the Canadian guideline fulfilled more than 2/3 of the criteria (71%).

| Guideline / Domain | Canada | Germany | UK | Mean score ± SD |
|---|---|---|---|---|
| **AGREE II** | | | | |
| Scope and purpose | 48 | 89 | 71 | 5.17 ± 1.49 |
| Stakeholder involvement | 41 | 92 | 37 | 4.39 ± 1.86 |
| Rigor of development | 48 | 89 | 63 | 4.99 ± 1.44 |
| Clarity of presentation | 71 | 91 | 89 | 6.02 ± 0.87 |
| Applicability | 31 | 65 | 58 | 4.08 ± 1.20 |
| Editorial independence | 63 | 92 | 78 | 5.64 ± 1.23 |
| Overall assessment | 63 | 83 | 47 | 4.79 ± 1.12 |
| **AGREE-REX** | | | | |
| Clinical applicability | 45 | 84 | 65 | 4.89 ± 1.20 |
| Values and preferences | 33 | 67 | 46 | 3.92 ± 1.16 |
| Implementability | 46 | 78 | 68 | 4.83 ± 1.11 |

**Fulfilled criteria:**

| | |
|---|---|
| < 40% | |
| 40 – 54% | |
| 55 – 69% | |
| 70 – 84% | |
| 85 – 100% | |

**Figure 2.** Heat map illustrating "Appraisal of Guidelines for Research and Evaluation" (AGREE II) and "Recommendation EXcellence" (AGREE-REX) scores of the three actinic keratoses (AK) guidelines evaluated by six independent reviewers.

### 3.3.5. Applicability

Processes concerning guideline implementation are evaluated in this domain. The mean score was 4.08 (±1.20). The German and UK guidelines achieved similar results (65 and 58%), while the Canadian guideline achieved the lowest rates fulfilling only 31% of the criteria. The German and Canadian guidelines also significantly differed in this domain ($p = 0.004$).

### 3.3.6. Editorial Independence

The role of funding and competing interest of the experts that were involved in the development process is evaluated in this domain. The mean score was 5.64 (± 1.23). Again, the German guideline was rated as the best (92%) followed by the UK (78%) and Canadian guideline (63%). Similar to the other domains, the Canadian and the German guidelines were rated to be significantly different of each other ($p = 0.035$).

### 3.3.7. Overall Assessment

This domain evaluates the overall quality and whether the reviewer would recommend to use the guideline in practice. The mean score was 4.79 (±1.12), and the German guideline was rated as the one with the best overall quality (83%). The UK and Canadian guidelines were rated lower with 63 and 47%, respectively. All reviewers recommended to use the German guideline without any modifications. The use of the UK guideline was also recommended, but half of the reviewers rated to use it with modifications. In contrast, the ratings regarding the recommendation to use the Canadian guideline were ambiguous: two reviewers rated to use it, two to use it with modifications while another two reviewers recommended not to use this guideline.

### *3.4. AGREE-REX*

### 3.4.1. Clinical Applicability

This domain assesses whether the recommendations were developed based on a thorough review of the existing literature and whether they are applicable for the intended users (e.g., physicians, patients). The mean score was 4.89 (±1.20). The fulfilled criteria in this domain ranged from 45% (Canada) and 65% (UK) to 84% (Germany). In this domain, the German and the Canadian guidelines significantly differed from each other ($p = 0.002$).

### 3.4.2. Values and Preferences

This domain evaluates whether the preferences of the intended users, patients, policy/decision-makers and guideline developers have been taken into consideration during the guideline development process. The mean score was 3.92 (±1.16). The German guideline achieved 67%, whereas the UK and the Canadian guidelines were rated similar (46 and 33%, respectively). Here, the German and Canadian guidelines significantly differed again ($p = 0.004$).

### 3.4.3. Implementability

This domain asks how suitable the recommendations are for the patients and/or the health care system in which they should be implemented. The mean score of this domain was 4.83 (±1.11). The German guideline achieved the highest rates with 78%. The UK guideline was rated lower with 68%, and the Canadian guideline was rated with the lowest scores (46%). The German and Canadian guidelines also significantly differed in this domain ($p = 0.004$).

### *3.5. Correlations of the AGREE II and AGREE-REX Domains*

Most of the AGREE II and the AGREE-REX domains were significantly positively correlated with each other (Figure 3). The domain "scope and purpose" was highly positively correlated with the

domains "rigor of development" (r = 0.84) and "clinical applicability" of the AGREE-REX tool (r = 0.86). Additionally, the domain "stakeholder involvement" was highly correlated with the domains "rigor of development" (r = 0.81) and "values and preferences" (r = 0.83). Furthermore, the domains "clinical applicability" and "implementability" showed a high positive correlation (r = 0.84).

| Correlation coefficient r: | | AGREE II | | | | | | AGREE-REX | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Scope and Purpose | Stakeholder Involvement | Rigor of Development | Clarity of Presentation | Applicability | Editorial Independence | Clinical applicability | Values and preferences | Implementability |
| **AGREE II** | Scope and Purpose | 1.000 | 0.614** | 0.844** | 0.732** | 0.733** | 0.709** | 0.858** | 0.502* | 0.655** |
| | Stakeholder Involvement | | 1.000 | 0.806** | 0.296 | 0.674** | 0.635** | 0.692** | 0.831** | 0.651** |
| | Rigor of Development | | | 1.000 | 0.645** | 0.756** | 0.712** | 0.866** | 0.669** | 0.789** |
| | Clarity of Presentation | | | | 1.000 | 0.471* | 0.459 | 0.672** | 0.257 | 0.498* |
| | Applicability | | | | | 1.000 | 0.411 | 0.763** | 0.757** | 0.782** |
| | Editorial Independence | | | | | | 1.000 | 0.592** | 0.488* | 0.493* |
| **AGREE-REX** | Clinical applicability | | | | | | | 1.000 | 0.651** | 0.836** |
| | Values and preferences | | | | | | | | 1.000 | 0.745** |
| | Implementability | | | | | | | | | 1.000 |

Correlation coefficient r legend: < 0.39, 0.4 – 0.54, 0.55 – 0.69, 0.7 – 0.84, > 0.85

**Figure 3.** Correlations among the AGREE II and AGREE-REX domains. *: $p < 0.05$, **: $p < 0.01$.

## 4. Discussion

AK are one of the most commonly diagnosed conditions in dermatology [26]. Due to the overwhelming number of available treatment options, choosing the most appropriate intervention for each patient can be challenging. In this study, we evaluated currently available guidelines on AK using the appraisal instruments AGREE II and AGREE-REX. The AGREE II tool and its previous version AGREE have already been successfully used in other evaluations in the field of dermatology and guideline development [27,28]. In an evaluation of published guidelines by the European Dermatology Forum (EDF), the assessment with AGREE highlighted that evidence- and consensus-based guidelines ("S3 level") generally received the highest score in comparison to guidelines derived through either a structured consensus process, a systematic literature assessment or on informal consensus only [27]. Thus, identifying evidence- and consensus-based guidelines and their methodological strengths and weaknesses is essential for improving the overall quality of national as well as international guidelines that can be used as a template for country-specific adaptions.

Surprisingly, although AK are a very common health problem especially in fair-skinned patients and account for large disease burden form a public health care perspective, we only identified three currently valid evidence- and consensus-based guidelines dealing with this topic, which were published within the last 5 years and matched our pre-defined eligibility criteria. The detailed international guideline on AK treatment developed by the International League of Dermatological Societies (ILDS) and published in 2015 was not included in this evaluation, as it had already expired in July 2018 [19].

Developing guidelines and keeping them up-do-date is labor- and cost-intensive. In the field of AK, developers are confronted with a vast number of treatment options including several monotherapies

as well as combinations of them. Scanning all the evidence available is time-consuming and difficult. Besides, the quality of the body of evidence varies across interventions, making it difficult to compare the efficacy of different approaches and derive recommendations. However, regular updating is crucial for maintaining the quality of the provided guidance as seen in the case of ingenol mebutate (IMB), which was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a topical intervention for AK in 2012 [29]. Recently, the EMA decided to suspend its usage in January 2020, as a post-marketing surveillance study had shown that patients treated with IMB showed a higher incidence of skin cancer compared to imiquimod. Surprisingly, all evaluated guidelines recommended the use of IMB, but only the German guideline was amended in March 2020 in order to provide a footnote to no longer recommend the use of IMB [5]. This example underlines that continuous updating of guidelines is indispensable for state of the art patient care.

The German guideline achieved the highest scores in all domains of AGREE II and AGREE-REX ranging from 65% (applicability) to 92% (stakeholder involvement and editorial independence). On the other hand, the Canadian guideline was rated as the guideline with the poorest methodological quality in our appraisal with scores ranging from 31% (applicability) to 71% (clarity of presentation). Overall, the domain "clarity of presentation" was rated best among all evaluated domains ranging from 71% (Canadian guideline) to 91% (German guideline), indicating that the recommendations provided by the guidelines are unambiguous and clear and can be easily found in the guideline texts. In contrast, the domains "applicability" and "values and preferences" achieved the lowest scores ranging from 31 to 65% and 33 to 67%, respectively. Interestingly, these two domains also achieved only low scores in a recent appraisal of currently available evidence- and consensus-based melanoma guidelines [30], indicating that guideline developers may not pay sufficient attention to these domains in general and tend to neglect them. As the German evidence- and consensus-based guideline is being updated at the moment [10,25], it is of utmost importance to improve this weakness in the update.

Major differences between the guidelines were observed in the evaluation of the domain "stakeholder involvement". Here, the German guideline achieved a good result of 92%, whereas both the UK and the Canadian guideline were rated worse, achieving only 37 and 41%, respectively. The lack of participation of important target groups may severely hamper the implementation of the recommendations into the real world setting. Thus, when updating these guidelines, developers should particularly focus on this part to improve the overall quality in the future. Especially patient representatives should ultimately be involved in the development of guidelines and might be actively approached through patient support groups.

Overall, the German guideline achieved the highest scores in all domains in both instruments. This might be due to the fact that the AWMF and DKG, which guide the process of oncological guideline development in Germany, provide not only support but also build a solid methodological framework of rules for the guideline authors they have to adhere to. Besides, the German guideline provided by far the most detailed Supplementary Materials including very detailed descriptions, which facilitated the identification of relevant content for the appraisal. According to the UK guideline [6], the AGREE II instrument also served as a guide for its development. This might explain why the UK guideline achieved better results compared to the Canadian guideline, although both guideline texts are similarly short.

This study has several limitations. We only evaluated the methodological quality of the guidelines, but not the content or the medical content of the recommendations themselves. This might be problematic as seen in the abovementioned case of IMB. Furthermore, we cannot fully exclude that the six reviewers may have been biased as all of them are from Germany. Additionally, three members of this research team (T.S., C.B., M.V.H.) were at least partly involved in the development process of the evaluated German guideline. However, these three were not part of the appraisal team and did not evaluate the quality of any guideline. Furthermore, the language restrictions to English and German may have led to the exclusion of relevant guidelines and may have introduced risk for selection bias.

## 5. Conclusions

Taken together, we identified three currently available guidelines on AK treatment that were published within the last five years. Two of them showed substantial methodological weaknesses. Only the German guideline, which was rated as the best in this evaluation, fulfilled most of the evaluated criteria and, therefore, may be used as a role model for developing or updating future guidelines. Paying special attention to the domains "applicability" and "values and preferences" that achieved low scores in all three guidelines is required.

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*Supplementary materials*

# A Critical Appraisal of Evidence- and Consensus-Based Guidelines for Actinic Keratosis

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**Supplementary Table S1:** Overview of the guideline databases searched for "aktinische keratose, actinic keratosis, actinic keratoses, solar keratoses, senile keratoses, field cancerization, precancerous lesions".

| Guideline database | Initial hits |
|---|---|
| EADV homepage | 3 |
| Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften: AWMF (https://www.awmf.org/leitlinien/leitlinien-suche.html) | 13 |
| Ärztliches Zentrum für Qualität in der Medizin: ÄZQ (leitlinien.de) | 0 |
| Guidelines International Network: GIN (g-i-n.net) | 3 |
| Agency for Healthcare Research and Quality: NGC (guidelines.gov/) | 11 |
| Scottish Intercollegiate Guidelines Network: SIGN (sign.ac.uk/) | 1 |
| National Institute for Health and Care Excellence: NICE (guidance.nice.org.uk/CG/Published) | 1 |
| Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) http://www.akdae.de | 21 |
| Dutch Guidelines (oncoline.nl/index.php?language=en) | 0 |
| NCCN (https://www.nccn.org/) | 0 |
| Cross-references | 16 |

**Supplementary Table S2:** Overview of the search strategy in Medline and Embase via Ovid.

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**Search query in Medline (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to October 22, 2019; n = 959 hits)**

1. practice guideline.mp. or exp Practice Guideline/

2. health planning guideline.mp. or exp Health Planning Guidelines/

3. exp Guideline/ or guideline.mp. or exp Guideline Adherence/

4. guidance.mp.

5. evidence-based medicine.mp or exp Evidence-Based Medicine/

6. care pathway.mp.

7. consensus.mp. or exp Consensus Development Conference/ or exp Consensus Development Conferences, NIH as Topic/

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. actinic keratosis.mp. or exp Keratosis, Actinic/

10. solar keratosis.mp.

11. senile keratosis.mp.

12. field change.mp.

13. actinically damaged field.mp.

14. exp Precancerous Conditions/ or field-cancerized.mp.

15. actinic keratosis.mp.

16. 9 or 10 or 11 or 12 or13 or 14 or 15

17. 8 and 16

**Search query in Embase (Embase 1974 to 2019 October 22 n=1,584 hits)**

1. actinic keratosis.mp. or actinic keratosis/

2. solar keratosis.mp.

3. senile keratosis.mp.

4. field change.mp.

5. actinically damaged field.mp.

6. field-cancerized.mp. or exp precancer/

7. actinic keratosis.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. practice guideline.mp. or exp practice guideline/

10. health care planning.mp. or exp health care planning/

11. clinical pathway.mp. or exp clinical pathway/

12. guidance.mp.

13. exp consensus/ or consensus.mp.

14. decision making.mp. or exp decision making/

15. exp consensus/ or exp consensus development/ or consensus development.mp.

16. evidence-based medicine.mp. or exp evidence based medicine/ or medical decision making/

17. 8 and 16

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# 10.  Veröffentlichung IV

**Treatment motivations and expectations in patients with actinic keratosis: a German-wide multicenter, cross-sectional trial**

**Veröffentlicht in:**

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*Article*

# Treatment Motivations and Expectations in Patients with Actinic Keratosis: A German-Wide Multicenter, Cross-Sectional Trial

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**Abstract:** Patient-centered motives and expectations of the treatment of actinic keratoses (AK) have received little attention until now. Hence, we aimed to profile and cluster treatment motivations and

expectations among patients with AK in a nationwide multicenter, cross-sectional study including patients from 14 German skin cancer centers. Patients were asked to complete a self-administered questionnaire. Treatment motives and expectations towards AK management were measured on a visual analogue scale from 1–10. Specific patient profiles were investigated with subgroup and correlation analysis. Overall, 403 patients were included. The highest motivation values were obtained for the items "avoid transition to invasive squamous cell carcinoma" (mean ± standard deviation; 8.98 ± 1.46), "AK are considered precancerous lesions" (8.72 ± 1.34) and "treating physician recommends treatment" (8.10 ± 2.37; $p < 0.0001$). The highest expectation values were observed for the items "effective lesion clearance" (8.36 ± 1.99), "safety" (8.20 ± 2.03) and "treatment-related costs are covered by health insurance" (8.00 ± 2.41; $p < 0.0001$). Patients aged ≥77 years and those with ≥7 lesions were identified at high risk of not undergoing any treatment due to intrinsic and extrinsic motivation deficits. Heat mapping of correlation analysis revealed four clusters with distinct motivation and expectation profiles. This study provides a patient-based heuristic tool for a personalized treatment decision in patients with AK.

## 1. Introduction

Long-term exposure to ultraviolet (UV) radiation can lead to the formation of actinic keratoses (AK) in light-skinned individuals [1,2]. Lesions present as diffuse red and keratotic or scaling plaques with a rough, sandpaper-like surface on chronically sun-exposed areas such as the face, ears, arms, and dorsal hands [2,3]. AK lesions are considered precursors of invasive cutaneous squamous cell carcinoma (cSCC), although the conversion risk for an individual lesion to progress into cSCC is estimated low [4]. The presence of multiple lesions, marked basal proliferation in histology, and additional signs of chronic UV damage on the adjacent skin increases the risk for progression considerably, and spontaneous regression is less likely to occur [5–7]. As it is clinically not possible to exactly predict which AK will become invasive cSCC, international treatment guidelines recommend early and consequent treatment [8,9]. Today, numerous interventions with varying efficacy and safety profiles are licensed for the management of AK. These comprise lesion-directed therapies such as excision or cryosurgery as well as field-directed therapies including photodynamic therapy (PDT) or topical interventions, which target a whole area of skin bearing multiple AK and aim at clearing subclinical changes [10].

However, the individual effect of the respective treatment strongly depends on patients' willingness and consent to adhere to the treatment regimen. Almost all AK treatments carry a therapeutic burden such as pain, adverse events, costs, treatment duration, altered cosmetic appearance, local skin reactions or inconvenience of application. These factors may influence the underlying motives of patients to be willing to undergo or choose a specific intervention [11]. Understanding treatment motivation, expectations, and individual patient preferences critically influence the treatment success. Besides, these factors are important to improve the acceptability of and compliance to treatment regimens [11,12]. Surprisingly, the patient-centered motives and expectations towards AK treatment have received little attention until now but can represent a major barrier for treatment adherence [13–15]. Here, we report the results of a German-wide, multicenter, cross-sectional study to gain insight into the management of AK by investigating patient attitudes, expectations, and motives.

## 2. Materials and Methods

### 2.1. Study Design and Ethics Approval

A multicenter, cross-sectional study that included patients from 14 German skin cancer centers was conducted between May and August 2019. This study was approved by the institutional review board of the University Hospital (LMU Munich) on 7 June 2019 (approval number 19-356 KB, Supplementary A1). We closely adhered to the STROBE statement for cross-sectional studies for the reporting of this study (Supplementary A2) [16,17].

### 2.2. Setting and Participants

Adult patients (≥18 years) presenting with AK in the participating centers were asked either by a physician or a nurse to complete a self-administered four-page questionnaire (purposive sampling, Supplementary A3). As the first page of the questionnaire included questions related to previous treatments, number, and localization of AK, patients were allowed to ask the physician for advice and to obtain patient-specific information, if necessary. Participation was voluntary and all participants gave verbal informed consent before completing the questionnaire. Refusals were not documented, and no incentives were provided. Relatives or accompanying persons were excluded from the study. Each patient was allowed to participate only once in the survey (cross-sectional design).

### 2.3. Survey

As no validated survey tools for the objective of our study existed, the questionnaire was developed *de novo* based on a literature review and thorough dermatologic expert consulting. The questionnaire included items on previous treatments for AK, localization and number of lesions, immunosuppression, underlying motives to undergo AK treatment and expectations and wishes towards therapy as well as basic demographic information (age, gender, marital status, health insurance status, profession). Patients with an increased UV exposure due to their long-term profession were categorized as at high risk for developing skin cancer. For the questions related to motives and expectations towards AK treatment, patients were asked to rate the level of agreement on a continuous visual analogue scale (VAS) ranging from 0 (do not agree) to 10 (fully agree). The full questionnaire is available in Supplementary A3. The questionnaire was pre-tested and validated for clarity and comprehension by independent researchers who were not involved in the design of the original questionnaire and volunteering patients without AK. Unclear items were thoroughly discussed and rephrased until a consensus on clarity was reached. Based on this feedback, questions were simplified, the questionnaire was shortened and finally, the questionnaire was revised to its final version. Completed questionnaires were sequentially numbered for data entry purposes but were not linked to any identifying patient information to assure irreversible anonymity.

### 2.4. Data Analysis

We calculated an estimated sample size of at least $n = 320$ required for this explorative study design as suggested by Tabachnik and Fidell by multiplying the number of the questionnaires' items by factor 10 [18]. Statistical analyses were conducted with SPSS (IBM SPSS Statistics version 24, IBM Corporation, Armonk, NY, USA). Descriptive analyses included means with standard deviations (SD) or medians and interquartile ranges (IQR). Categorical variables were expressed as frequencies and percentages. Subgroup differences between two groups were explored with the student's *t*-test or Mann-Whitney-U-test. For the comparison of more than two groups, one-factor analysis of variance followed by Scheffé procedure or the Kruskal-Wallis test was used. The relationship between the level of agreement of patient motives and expectations towards AK therapy were examined with Spearman's correlation. A two-sided *p*-value $< 0.05$ was considered statistically significant in all cases. Missing values were excluded pairwise. Besides, missing data were addressed by indicating the number of participants considered in each analysis.

## 3. Results

### 3.1. Characteristics of the Study Population

A total of 403 patients were included. The majority was male (73.7%; 294/399) and the median age at the time of the visit was 77 years with a range from 43 to 94 years. 73.5% (291/396) of the patients were married, 15.7% (62/396) were widowed followed by 5.6% who were divorced (22/396) or single/unmarried (5.3%; 21/396). Besides, most patients had statutory health insurance (76.8%, 304/396). 7.9% (30/382) of patients stated to take immunosuppressive medication, the majority (*n* = 17) due to organ transplantation. Of these, 11 patients were renal transplant recipients, one had a transplanted liver and five transplant recipients did not provide information regarding their transplanted organ. The remaining patients stated to have an autoimmune disease (16.7%, *n* = 5) or to take immunosuppressive medications due to other reasons, such as rheumatoid arthritis (*n* = 1) or ankylosing spondylitis (*n* = 1), representing a risk population for the development of AK (Table 1). The majority of patients (91.0%; 303/333) were classified as not having an increased risk for skin cancer. Patients presented predominantly with AK located in the face or scalp (65.6%; 261/398). In contrast, 23.9% (95/398) had AK both on the scalp and facial sites as well as in non-head and non-facial regions. The remaining 10.6% (42/398) showed AK only on the extremities or trunk. Nearly half of the patients had 1–3 AK treated at the time of the visit (47.6%, 167/351), followed by ≥7 AK (29.9%, 105/351) and 4–6 AK (22.5%, 79/351). Overall, 83.6% (331/396) of the patients reported at least one pre-treatment, whereas 15.4% (61/396) did not have any prior treatment and 1% (4/396) could not remember. Nearly half of the patients (46.4%; 153/330) voted to have had their AK treated at least once with diclofenac sodium 3% in hyaluronic acid 2.5% gel, followed by PDT (38.8%; 128/330) and surgical excision (37.3%; 123/330) (Supplementary Figure S1).

**Table 1.** Baseline characteristics of the study population.

| Sample | % (*n*) |
|---|---|
| **Sex (*n* = 399)** | |
| Female | 26.3 (105) |
| Male | 73.7 (294) |
| **Age (*n* = 395)** | |
| years (median, range) | 77 (43–94) |
| years (mean ± standard deviation) | 75.10 ± 9.45 |
| **Family status (*n* = 396)** | |
| Single/unmarried | 5.3 (21) |
| Married | 73.5 (291) |
| Divorced | 5.6 (22) |
| Widowed | 15.7 (62) |
| **Risk exposure for skin cancer (*n* = 333)** | |
| Yes | 9.0 (30) |
| No | 91.0 (303) |
| **Health insurance (*n* = 396)** | |
| Statutory health insurance | 76.8 (304) |
| Private health insurance | 23.2 (92) |
| **Immunosuppression (*n* = 382)** | |
| No | 92.1 (352) |
| Yes | 7.9 (30) |
| Organ transplant recipient | 56.7 (17) |
| Autoimmune disease | 16.7 (5) |
| Other | 26.7 (8) |

**Table 1.** *Cont.*

| Sample | % (*n*) |
|---|---|
| **Previous treatment of AK (*n* = 396)** | |
| Yes | 83.6 (331) |
| No | 15.4 (61) |
| Unsure | 1.0 (4) |
| **Last treatment of AK (*n* = 292)** | |
| months (median, range) | 6 (0–300) |
| months (mean ± standard deviation) | 18.62 ± 32.35 |
| **Number of AK to be treated at the visit (*n* = 351)** | |
| 1–3 | 47.6 (167) |
| 4–6 | 22.5 (79) |
| ≥7 | 29.9 (105) |
| **Outdoor profession (*n* = 333)** | |
| Yes | 9.0 (30) |
| No | 91.0 (303) |
| **Localization of AK (*n* = 398)** | |
| Scalp | 57.3 (228) |
| Face | 61.6 (245) |
| Trunk | 8.0 (32) |
| Extremities | 31.4 (125) |
| Only face/scalp | 65.5 (261) |
| Only trunk/extremities | 10.6 (42) |
| All sites | 23.9 (95) |

### 3.2. Items of Treatment Motivation

Patients strongly agreed to undergo treatment to avoid the transition of AK to invasive cSCC (mean ± standard deviation: 8.98 ± 1.46) or since AK are considered precancerous lesions (8.72 ± 1.34) (Figure 1A). Interestingly, patients also agreed to undergo treatment due to the physician's recommendation (8.10 ± 2.37) or because medical guidelines recommend treatment (7.19 ± 2.67). In contrast, patients rather disagreed that cosmetic reasons (2.49 ± 2.84) and treatment due to the desire of third parties such as relatives (3.35 ± 3.45) were motivating factors ($p < 0.0001$). Other reasons specifically mentioned by the patients in a free-text field included aesthetic restrictions in general (*n* = 3), improvement of the professional appearance (*n* = 1), pain relief (*n* = 3), or improvement of quality of life (*n* = 1). Next, we investigated whether the treatment motivations varied according to clinical and socio-demographic parameters and performed subgroup analyses. Significant differences among the subgroups are shown in Figure 2A. Further information can be obtained from the supplementary results (Appendix A.1).

**A**



**B**
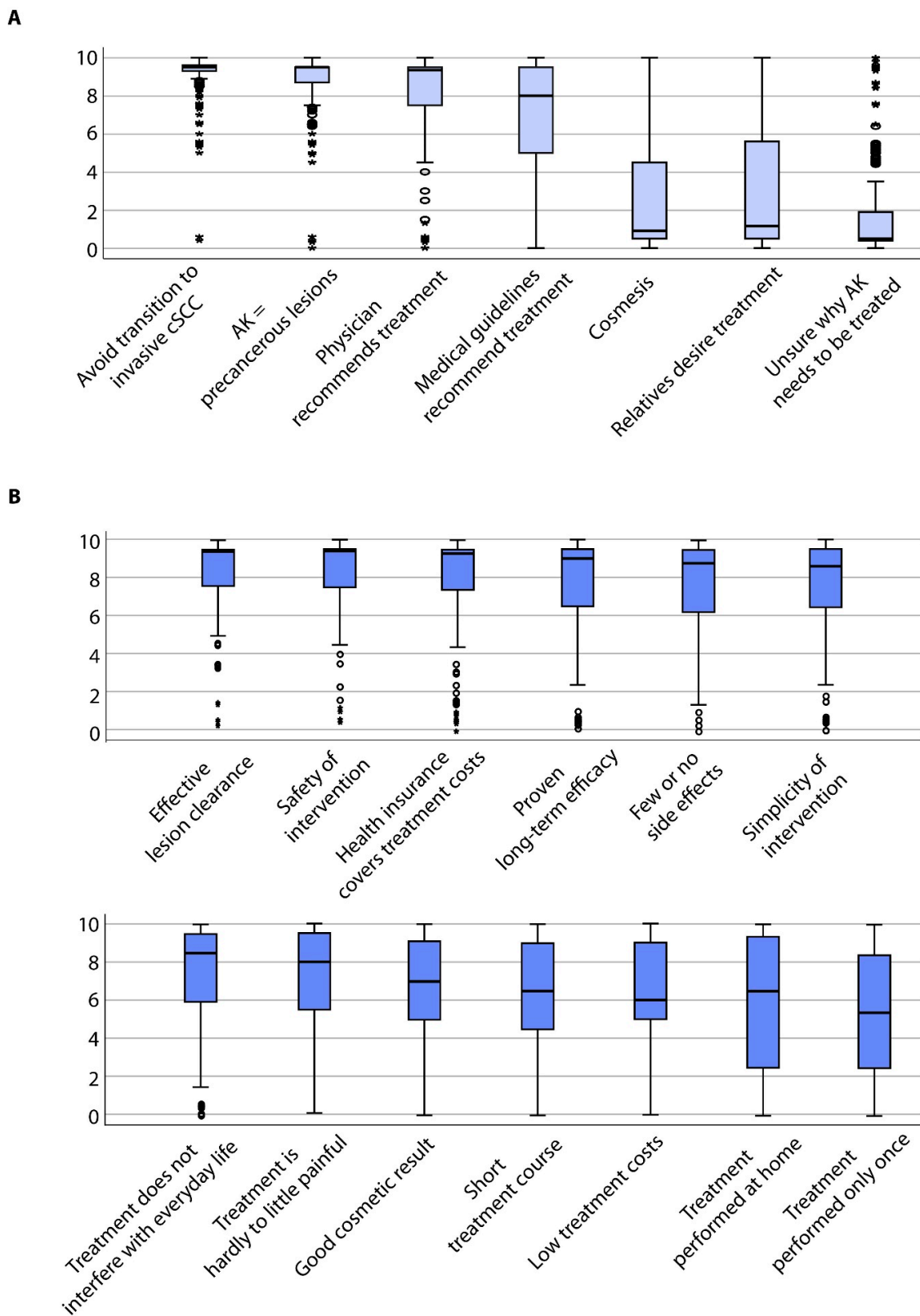


**Figure 1.** Boxplots showing all patients' specific evaluation on (**A**) motivation for therapy of their actinic keratoses (AK) and (**B**) on expectations towards therapy of their AK.
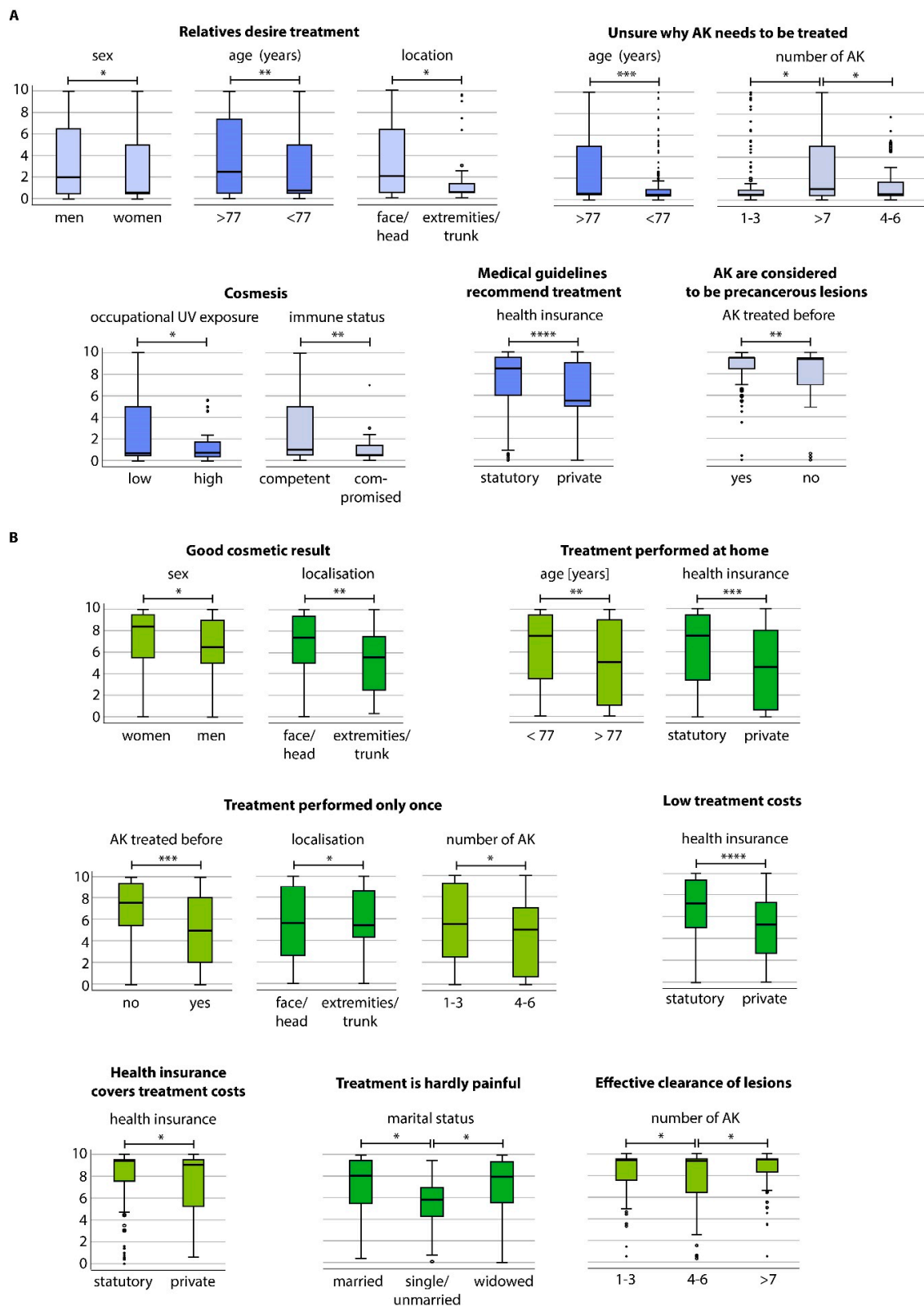
**Figure 2.** Boxplots showing patients' specific subgroup evaluation on (**A**) motivation for a therapy of their AK and (**B**) on expectations for the therapy of AK; *p*-values: * <0.05; ** <0.01; *** =0.001; **** =0.000.

### 3.3. Items of Treatment Expectation

Patients strongly expected effective AK lesion clearance (8.36 ± 1.99) (Figure 1B). Safety of the individual interventions was also considered important (8.20 ± 2.03), followed by the coverage of treatment-related costs by health insurance funds (8.00 ± 2.41). Furthermore, patients expected that the treatment has a proven long-term efficacy (7.80 ± 2.32) and few or no side effects (7.77 ± 2.33). Further patient preferences included simplicity of the individual intervention (7.70 ± 2.39), no interference with everyday life (7.43 ± 2.55) and that the treatment is hardly to minimally painful (7.25 ± 2.58). Additionally, patients estimated a good cosmetic outcome (6.60 ± 2.77), short treatment course (6.31 ± 2.97) and little costs (6.24 ± 2.83) as important. Lower values were obtained for home-based treatment (5.77 ± 3.56) and a one-time treatment procedure (5.40 ± 3.35; $p < 0.0001$). Further reasons that were specifically addressed by patients in the free-text field included the wish for regular surveillance and better education regarding the dangers and avoidance of sunlight by physicians ($n = 2$), long-term clearance ($n = 6$) or no occurrence or spread of skin cancer ($n = 6$).

Next, we performed subgroup analysis for the motivation items. Significant differences among the subgroups are shown in Figure 2B. In particular, patients aged >77 years and those with >7 lesions were unsure why treatment was indicated. Further information can be obtained from the supplementary results (Appendix A.2).

### 3.4. Correlation Analysis of Motivation and Expectation Items

To identify distinct patient profiles and clusters of patient subgroups, we performed Spearman's correlation of the individual motivation and expectation items. As most items were correlated with each other, we focused on correlations that were most strongly correlated (i.e., r > 0.5 or r < −0.2). The recommendation of the physician for treatment was positively correlated with the motivation to have AK treated as they are considered precancerous lesions (r = 0.547) (Figure 3). Furthermore, the item "avoid progression to invasive cSCC" was also correlated with the motivation to treat AK because they are perceived precancerous lesions (r = 0.670). There was also a trend that patients who agreed to desire a short treatment wished for treatment to be performed only once (r = 0.557). Patients voting a proven long-term effect as important tended to rate effective lesion clearance to be important (r = 0.682) as well as safe treatment (r = 0.639). Effective lesion clearance was additionally positively correlated with safe treatment (r = 0.535). Another correlation was identified for treatments with hardly or no adverse events and simplicity of treatment (r = 0.606). There was also a correlation between the desire for an intervention that does not interfere with daily life and one that is perceived to be hardly or not painful (r = 0.557). Additionally, the item "unclear why AK needs to be treated" and age were slightly significantly correlated with each other. All correlations were statistically highly significant ($p < 0.01$).

### 3.5. Clustering Treatment Motivation and Expectation Items to Define Distinct Patient Populations

Based on the heat map of these data, we identified two distinct clusters for treatment motivation (clusters 1 + 2) and treatment expectation (clusters 3 + 4), respectively (Figure 3). Cluster 1 comprised the items "physician's recommendation", "AK as precancerous condition", and "avoid transition to invasive cSCC (Table 2). Cluster 2 was dominated by the negatively correlated items "unclear why AK need to be treated", "physician's recommendation", "AK as precancerous condition", and "avoid transition to invasive cSCC". Within this cluster "unclear why AK need to be treated" and "desire of relatives" was positively correlated with each other. Cluster 3 comprised "simplicity", "safety", "few adverse events", "little painfulness" and "no impairment in daily life", and cluster 4 "safety", "few adverse events", "little painfulness", "effective lesion clearance", and "long-term efficacy". All items of clusters 1, 3, and 4 were positively correlated.
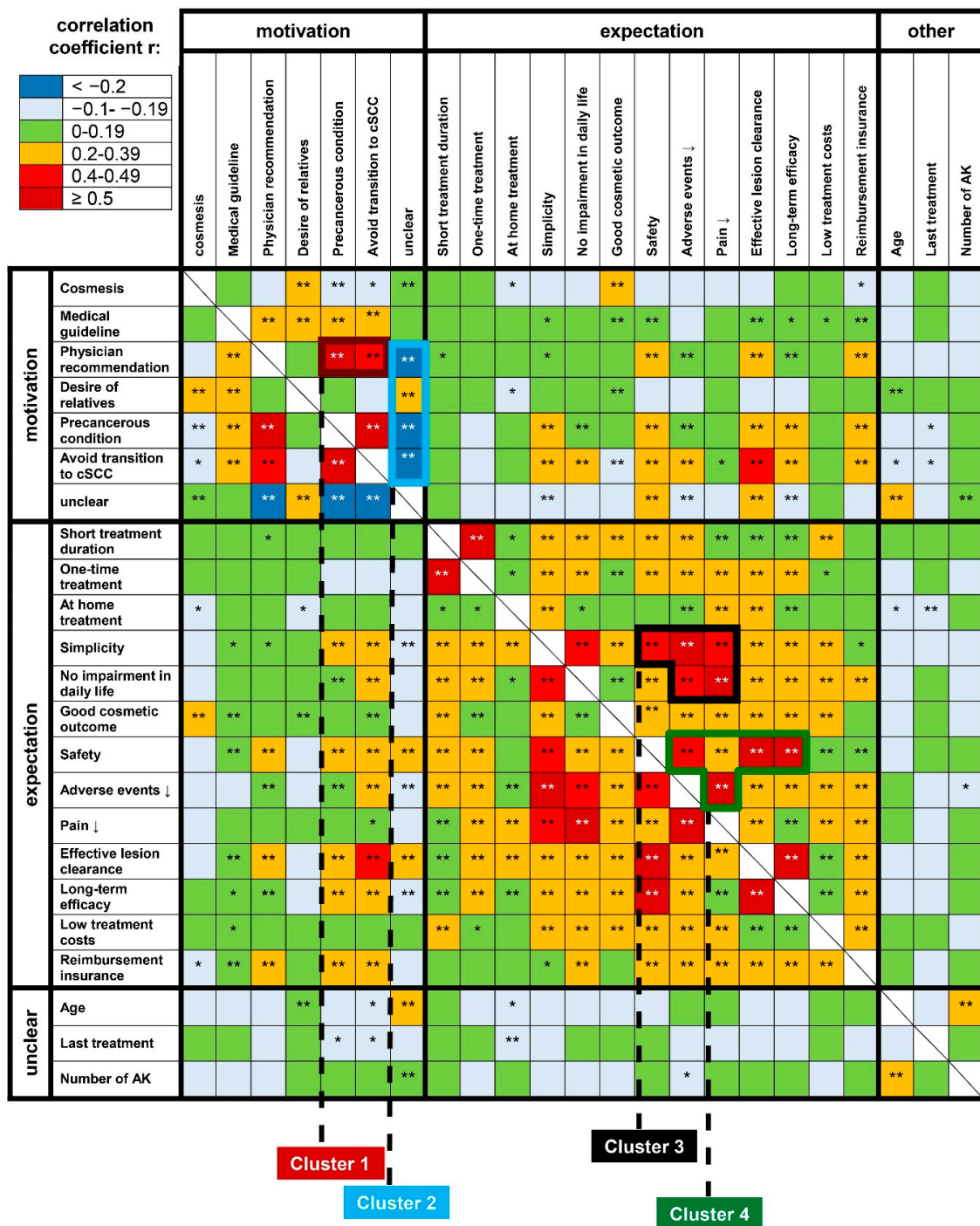
**Figure 3.** Heat-map showing the correlations of patients' motives and expectations towards AK management. The correlation coefficients were used to indicate the strength of the correlation. Four patient clusters were identified (black frames).

**Table 2.** Summary of treatment motivation and treatment expectation profiles.

| | Treatment Motivation | | Treatment Expectation | |
|---|---|---|---|---|
| | **Cluster 1** | **Cluster 2** | **Cluster 3** | **Cluster 4** |
| **Leading item** | Physician recommendation | Unclear why AK need treatment | Simplicity / No impairment in daily life | Safety |
| **Associated items** | (+) AK = precancerous condition Avoid transition to cSCC | (−) Physician recommendation AK = precancerous condition Avoid transition to cSCC / (+) Desire of relatives | (+) Safety Few adverse events Little painfulness / (+) Few adverse events Little painfulness | (+) Long-term efficacy Effective lesion clearance Few adverse events Little painfulness |
| **Patient characteristic** | Well informed about condition Fear of AK progress | Indifferent to condition May be approached by relatives Intrinsic and extrinsic motivation deficits | The convenient patient Motivated for treatment if it does not interfere with daily life | Discerning and rational-thinking patient Highly motivated but with high expectations of treatment |
| **Degree of motivation** | High | Low | Moderate | High |
| **Degree of expectation** | Moderate | Low | High | High |

## 4. Discussion

This cross-sectional study was designed to investigate individual, patient-centered motives and expectations towards the treatment of AK which have not received much attention until now but should ultimately be considered when a treatment choice is made. Furthermore, we aimed to identify distinct patient profiles that could provide a valuable and heuristic resource to facilitate personalized decision-making in the daily routine. For the first time, we define distinct patient profiles for the treatment of AK based on primary patient-derived data. A previous study defined six profiles based on the experience of an expert panel. However, patients themselves or patient representatives were not involved when the profiles were derived [19]. In analogy to other dermatologic conditions, we believe that it is indispensable to use patient-derived data as a primary source to outline specific profiles and to guide patient-centered treatment [20,21]. Thus, we collected data on the treatment motivation and expectation from a large cohort of 403 patients distributed among 14 major centers for AK care within Germany. Overall, the highest motivation for AK treatment was to avoid the transition to invasive cSCC, because AK are considered precancerous lesions, and because the treating physician recommends treatment. These motivation items also achieved uniformly high values on the VAS in the subgroup analysis. The highest expectation values were obtained for effective lesion clearance, the safety of the intervention, and that the treatment costs are covered by health insurance. We conclude that these factors should be considered and highlighted for any treatment decision.

Nowadays, choosing an appropriate and individualized intervention often largely depends on the knowledge, expertise, and preference of the practitioner as well as reimbursement status and may be insufficiently aligned with the individual desire of the patient [22,23]. In a recent qualitative study among physicians, cryosurgery was cited as the predominant therapy because other forms of therapy were little known or because there was uncertainty about their use [24]. Nevertheless, most

dermatologists in this qualitative survey stated that they were aiming for guideline-based therapy, which was also an important motivation for patients in our study. Among all items of motivation in our survey, it achieved the third-highest average values, albeit with a high degree of variability. Interestingly, this motivation was higher for patients with statutory health insurance than for those with private health insurance. This could be possibly explained by the fact that patients with statutory health insurance suspect that therapy in line with the guidelines is also fully reimbursed and that this does not result in any financial losses for them. A concrete counterexample is conventional PDT, which is uniformly recommended in current treatment guidelines [8,9] but has not yet been reimbursed by the statutory health insurance funds in Germany.

To further dissect and identify specific profiles, we performed subgroup analyses and correlated the motivation and expectation items with each other and with the baseline characteristics. Cosmesis showed rather low motivation values in the overall population. However, it was rated significantly higher in patients with low occupational UV exposure and a non-immunocompromised status. Furthermore, the expectation of a good cosmetic outcome was higher in women and patients with AK located on the face or head. Interestingly, patients whose AK had never been treated before and those with few AK (1–3 lesions) rather expected a one-time treatment, indicating that they may not yet be aware that AK is a chronic condition, which usually requires multiple treatment modalities and lifelong surveillance [5]. We propose that it is critical to provide substantial information framing on the disease course and to ensure sufficient communication and patient education for this subgroup [25]. Treating physicians must actively approach and educate this subgroup, especially those who undergo AK treatment for the first time.

The correlation analysis between motives and expectations revealed that patients who underwent treatment to prevent progression to invasive cSCC mainly desired an effective, long-lasting, safe, and simple approach that does not interfere with daily life and whose costs are covered by health insurance. Similarly, patients undergoing AK treatment due to the physician's recommendation preferred an effective and safe therapy that is reimbursed by health insurance. In contrast, those who underwent treatment for cosmetic reasons expected a good cosmetic result while being less interested in the efficacy and safety of the procedure. The heat-map of the correlation analyses revealed four clusters with highly positively (clusters 1, 3, 4) and negatively (cluster 2) correlated items. For motivation, we identified two distinct clusters. While cluster 1 appeared easily and highly motivated for treatment both intrinsically and extrinsically by the physician's recommendation, cluster 2 may have a high risk of not undergoing any therapy due to motivation deficits. Older patients (>77 years) and those with ≥7 lesions were particularly unsure why their conditions needed to be treated, although they carry a high risk of developing an invasive cSCC. As they were less motivated by treating physicians, relatives and third parties may be approached to assure adherence to treatment in this subgroup. Although the relatives' desire for treatment was rated rather less important as motivation in the overall population, the values for this item were significantly higher for the subgroups age ≥77 years, men, and localization of lesions on the head or face.

Among treatment expectations, we identified two more clusters whose items were positively correlated. Patients of cluster 3 expected both efficacy and safety measures as well as no impairment in daily living along with the intervention. We conclude that patients of cluster 3 are therefore moderately motivated for treatment if everyday life is not affected by the interventions chosen. In contrast, safety, efficacy, and tolerability were the main domains for patients of cluster 4. Although these patients appear highly motivated to undergo treatment, they also have high expectations towards the interventions. We believe that considering and balancing these preferences will help to ensure adherence to treatment and facilitate ideal treatment outcomes.

We are aware that this study has several limitations. The sample comprised 403 patients recruited during a short period. This sample size is relatively small, and the study population was not sampled randomly but depending on the availability of patients. Most questionnaires have been obtained from the University Hospital Munich, hence this overrepresentation may skew the results, although

we believe that geographic or inter-city diversity can be neglected due to the small size of Germany. Besides, participants with high cumulative sun exposure were underrepresented which may limit the external validity of this study. Thus, the results presented here may not be fully generalizable to the general population and are at risk for sampling bias.

## 5. Conclusions

This study provides a patient-based heuristic tool to facilitate personalized treatment decisions in patients with AK. Considering patient profiles and individual preferences are of paramount importance to ensure patient adherence and to achieve ideal treatment outcomes. Nevertheless, the choice of the intervention should be made on a case-by-case basis and thoroughly discussed to reach an informed treatment consensus.

## Appendix A

**Supplementary results: Subgroup analysis of treatment motivation items and subgroup analysis of treatment expectation items**

*Appendix A.1 Subgroup Analysis of Treatment Motivation Items*

We revealed specific subgroup differences for gender and the willingness to undergo treatment due to the desire of relatives of the patient, i.e., men would rather receive treatment because their partners want them to do so ($p = 0.017$) (Figure 2A). The same motivation item also concerned patients aged ≥77 years in contrast to patients below that age ($p = 0.004$) and patients with AK located in the face or head region compared to trunk or extremities ($p = 0.046$). Additionally, older patients (≥77 years) were rather unsure about the necessity of treatment in comparison to younger patients ($p = 0.001$). Also, patients with ≥7 lesions were rather unsure about the necessity of treatment compared to those with 1–3 ($p = 0.017$) or 4–6 lesions ($p = 0.016$). Indoor workers stated that cosmesis was a

motivation for treatment compared to outdoor workers ($p = 0.039$). Cosmetic outcome was also a pronounced motivation for immunocompetent patients compared to immunocompromised ones ($p = 0.007$). Notably, patients with statutory health insurance rather saw guideline recommendations as treatment motivation compared to those with private insurance ($p = 0.000$). Lastly, patients who have already undergone at least one prior treatment also considered the precancerous nature of AK as motivation ($p = 0.005$).

*Appendix A.2 Subgroup Analysis of Treatment Expectation Items*

Women expected a good cosmetic result compared to men ($p = 0.040$) (Figure 2B). Patients with AK localized in the face or on the scalp also rather expected a good cosmetic outcome in comparison to those with AK on the extremities or trunk ($p = 0.009$). Furthermore, younger patients (<77 years) preferred to undergo treatment at home, whereas older patients preferred treatment at the hospital or practice ($p = 0.006$). Besides, treatment-naïve patients rather expected treatment to be performed only once ($p = 0.001$). Patients with AK located on the face or head area also desired treatment to be performed only once in comparison to those with AK located on every site of their body ($p = 0.031$). Additionally, patients with statutory health insurance preferred home-based treatment in contrast to those with private insurance ($p = 0.001$). Patients with statutory health insurance also expected low treatment costs ($p = 0.000$) and reimbursement by health insurance ($p = 0.018$) compared to private insurance. In comparison to single patients, married ($p = 0.012$) and widowed ones ($p = 0.024$) rather expected treatment to be hardly to little painful. Besides, patients with few AK (1–3) rather voted that treatment be carried out only once in comparison to those with 4–6 lesions ($p = 0.025$). However, in comparison to patients with a medium number of lesions (4–6), patients with 1–3 ($p = 0.039$) and patients with ≥7 lesions ($p = 0.034$) expected effective AK lesion clearance.

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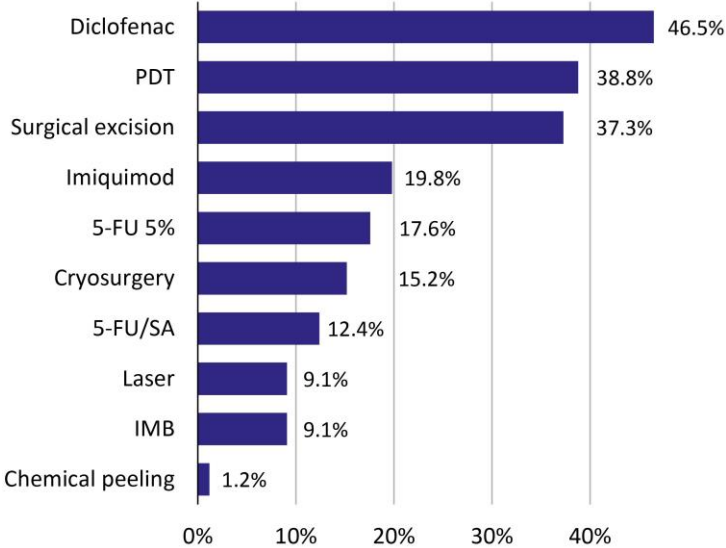**Supplementary Materials:**



**Figure S1.** Bar chart showing the distribution of patients' previous interventions for AK in our sample; abbreviations: 5-FU = 5-fluorouracil; IMB = ingenol mebutate; PDT = photodynamic therapy; SA = salicylic acid.

1

**Supplementary A1**:Ethical approval.



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07.06.2019 Hb /om

Projekt Nr.: **19-356 KB** (bitte bei Schriftwechsel angeben)

**Keine Beratungspflicht**

| | |
|---|---|
| Projekt: | Treatment motivation and expectation among patients with actinic keratosis: a cross-sectional survey |
| Antragsteller: | Prof. Dr. Carola Berking, Klinikum der Universität München, Klinik und Poliklinik für Dermatologie und Allergologie, Frauenlobstr. 9 - 11, 80337 München |
| Untersucher: | Prof. Dr. Carola Berking, Klinikum der Universität München, Klinik und Poliklinik für Dermatologie und Allergologie, Frauenlobstr. 9 - 11, 80337 München |

Sehr geehrte Frau Prof. Berking,

besten Dank für Ihr Schreiben vom 04.05.2019, mit dem Sie um eine Stellungnahme zum o.g. Projekt bitten.

Da Sie Ihre Untersuchungen anhand von Datensätzen durchführen, die irreversibel anonymisiert sind, d. h. dass auch den Bearbeitern kein Rückschluss auf die personenbezogenen Daten der Probanden möglich ist, besteht keine Beratungspflicht durch die Ethikkommission.

Für Ihre Untersuchungen wünsche ich Ihnen viel Erfolg.

Mit freundlichen Grüßen

Prof. Dr. W. Eisenmenger
Vorsitzender der Ethikkommission

**Supplementary A2**: STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

**Profiling treatment motivations and expectations in patients with actinic keratosis: A German-wide multicenter, cross-sectional trial**

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2-3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 3 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 3 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *3* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 3 |
| Study size | 10 | Explain how the study size was arrived at | 3 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 3-4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 3-4 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 3-4 |
| | | (*c*) Explain how missing data were addressed | 4 |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 3-4 |
| | | (*e*) Describe any sensitivity analyses | n.a. |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 4 |
| | | (b) Give reasons for non-participation at each stage | n.a. |
| | | (c) Consider use of a flow diagram | n.a. |

1

| | | | |
|---|---|---|---|
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1, page 4-12 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1, Figures, 4-12 |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 4 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 4-12 |
| | | (*b*) Report category boundaries when continuous variables were categorized | figures |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n.a. |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | supplementary |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 12-14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 14 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 14 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

2

**Supplementary A3**: Befragung von Patienten mit aktinischen Keratosen zur Motivation und Erwartung an die Therapie

Sehr geehrte Damen und Herren,

zunächst möchten wir Ihnen für Ihre Bereitschaft danken, an dieser Befragung teilzunehmen. Im folgenden Fragebogen werden Angaben zu Ihrer Motivation und Erwartung zur Behandlung aktinischer Keratosen erhoben.

Die Beantwortung des Fragebogens ist freiwillig und wird nur wenige Minuten in Anspruch nehmen. Lesen Sie sich die Fragen bitte aufmerksam durch und kreuzen Sie die für Sie zutreffenden Antworten an. Der Fragebogen umfasst insgesamt 4 Seiten.

Bitte füllen Sie Frage 1 bis 4 auf Seite 1 gegebenenfalls zusammen mit Ihrem behandelnden Arzt aus; die restlichen Fragen füllen Sie bitte selbst aus.

Sollten Sie Fragen haben, können Sie sich über die onkologische Ambulanz an Herrn Dr. Markus Heppt wenden. Ihre Angaben werden selbstverständlich vertraulich behandelt und lediglich in anonymisierter Form verarbeitet.

Mit freundlichen Grüßen

Prof. Dr. med. Carola Berking

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3

**Bitte füllen Sie Frage 1 bis 5 auf Seite 1 gegebenenfalls zusammen mit Ihrem Arzt aus!**

**Frage 1a: Wurden Ihre aktinischen Keratosen bereits in der Vergangenheit behandelt?**

☐ Ja → weiter bei Frage 1b    ☐ Nein → weiter bei Frage 2    ☐ weiß nicht→ weiter bei Frage 2

**Frage 1b: Falls ja: <u>Wie</u> wurden Ihre aktinischen Keratosen bereits behandelt? (Mehrfachantworten möglich)**

☐ Photodynamische Therapie
    ☐ konventionelle photodynamische Therapie mit LED
    ☐ Photodynamische Therapie mit Tageslicht

☐ Diclofenac-Natrium 3% in 2.5% Hyaluronsäure-Gel (z.B. Solaraze®, Solacutan®)

☐ 5% 5-Fluorouracil Creme (Efudix®)

☐ 5-Fluorouracil mit Salicylsäure (Actikerall®)

☐ Ingenolmebutat Gel (Picato®)

☐ Imiquimod Creme (z.B. Zyclara®, Aldara®)

☐ Lasertherapie

☐ Chirurgische Entfernung

☐ Kryochirugie (=Vereisung)

☐ Sonstige Therapie
Bitte um Angabe der Behandlung:—————————————————

**Frage 1c: Wann fand die letzte Behandlung Ihrer aktinischen Keratosen statt? (Angabe bitte in Jahren ODER Monaten)**

Vor   \_\_\_\_   Jahren bzw. vor \_\_\_\_ Monaten

**Frage 2: Wie viele aktinische Keratosen sollen heute behandelt werden?**

☐ 1 – 3             ☐ 4 – 6             ☐ ≥7

**Frage 3: Wo befinden sich Ihre aktinischen Keratosen (Mehrfachantworten möglich)**

☐ Kopfhaut        ☐ Körperstamm

☐ Gesicht          ☐ Arm(e) und/oder Bein(e)

4

**Frage 4a: Nehmen Sie regelmäßig immunsupprimierende Medikamente ein?**

☐ Nein → Weiter bei Frage 5 auf Seite 2

☐ Ja → Weiter bei Frage 4b

**Frage 4b: Aus welchem Grund nehmen Sie immunsupprimierende/immunschwächende Medikamente ein?**

☐ Organtransplantation
Bitte um Angabe des transplantierten Organs: _____

☐ Autoimmunerkrankung
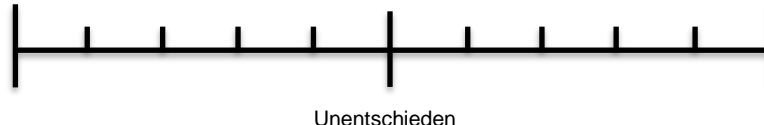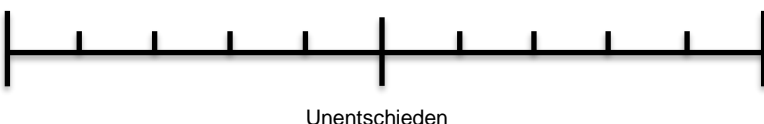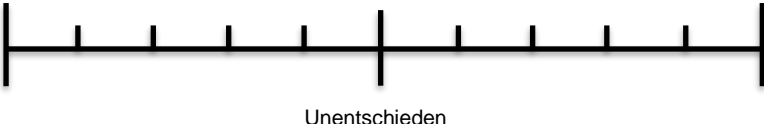
☐ Weitere Gründe: _____

**Frage 5: In dem untenstehenden Block haben wir eine Reihe von Aussagen zu *Ihrer Motivation zu einer Therapie* Ihrer aktinischen Keratosen aufgeführt.**

**Bitte lesen Sie jede Aussage und kreuzen Sie auf der Linie an, inwieweit Sie dieser zustimmen oder nicht zustimmen.**
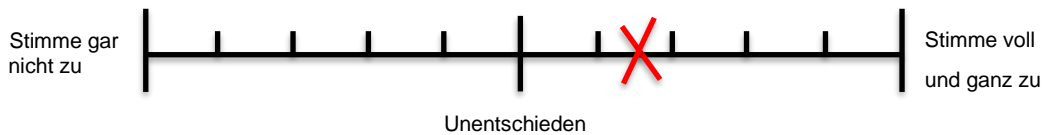


| | |
|---|---|
| Ich lasse meine aktinischen Keratosen aus **kosmetischen** Gründen behandeln. |  |
| Ich lasse meine aktinischen Keratosen behandeln, da der **Arzt** mir eine Therapie empfohlen hat. |  |
| Ich lasse meine aktinischen Keratosen behandeln, da diese als **Krebsvorstufe** angesehen werden. |  |
| Ich lasse meine aktinischen Keratosen behandeln, um eine |  |

5
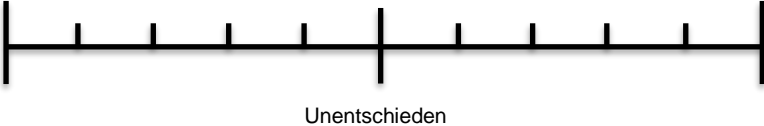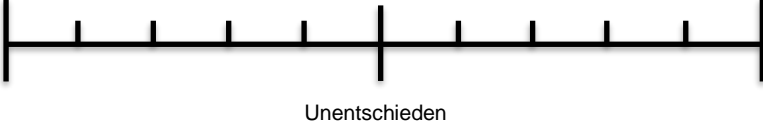
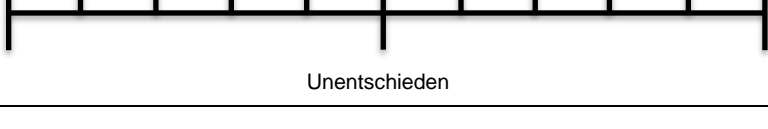| | |
|---|---|
| **Weiterentwicklung in invasiven Hautkrebs** zu vermeiden. | |
| Ich lasse meine aktinischen Keratosen behandeln, weil es in **Behandlungsrichtlinien** (medizinischen Leitlinien) empfohlen wird. | Stimme gar nicht zu      Unentschieden      Stimme voll und ganz zu |
| Ich lasse meine aktinischen Keratosen behandeln, da meine **Angehörigen** eine Therapie wünschen. | Stimme gar nicht zu      Unentschieden      Stimme voll und ganz zu |
| Der Grund, weshalb meine aktinischen Keratosen behandelt werden sollen, ist mir **unklar**. | Stimme gar nicht zu      Unentschieden      Stimme voll und ganz zu |
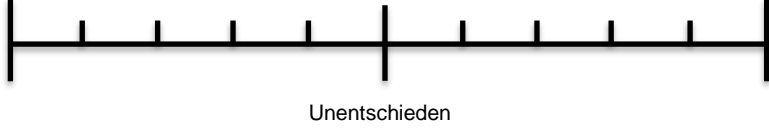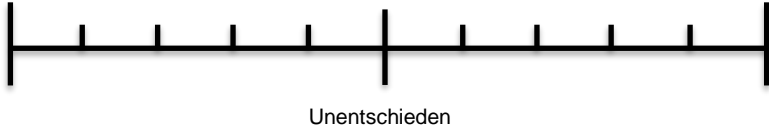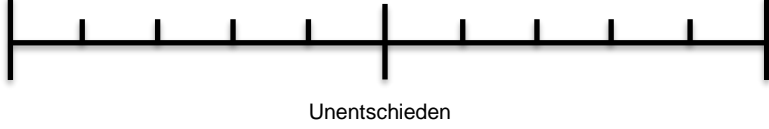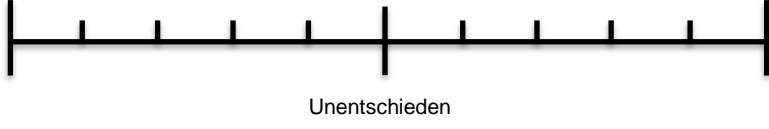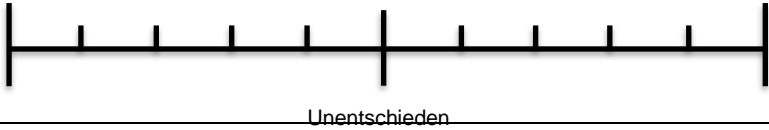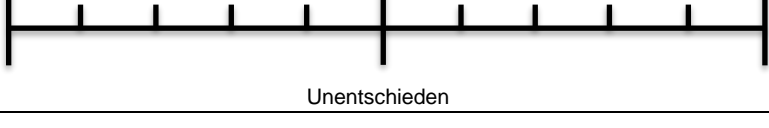
Haben Sie noch **weitere Gründe oder Motivation** für eine Behandlung Ihrer aktinischen Keratosen, die nicht in der Tabelle aufgeführt sind?
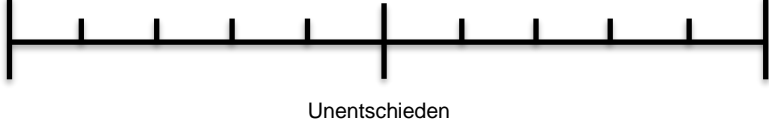
**Weitere Gründe:** _____

**Frage 6: In dem untenstehenden Block haben wir eine Reihe von Aussagen zu einer möglichen Erwartung an die Therapie Ihrer aktinischen Keratosen aufgeführt.**

**Bitte lesen Sie jede Aussage und kreuzen Sie auf der Linie an, inwieweit Sie dieser zustimmen oder nicht zustimmen.**

| | |
|---|---|
| Bei einer Behandlung von aktinischen Keratosen ist für **mich** wichtig: | |
| Behandlungsdauer ist **kurz**. | Stimme gar nicht zu      Unentschieden      Stimme voll und ganz zu |
| Behandlung erfolgt **einmalig**. | Stimme gar nicht zu      Unentschieden      Stimme voll und ganz zu |

6

| | | |
|---|---|---|
| Behandlung kann **zuhause** erfolgen. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung führt zu einer **effektiven Abheilung** der betroffenen Läsionen**.** | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung hat eine nachgewiesene **Langzeitwirkung**. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung ist **sicher**. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung ist **einfach**. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung hat keine bis wenig **Nebenwirkungen**. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung erzielt ein gutes **kosmetisches** Ergebnis. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Die **Kosten** der Behandlung sind niedrig. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |

| | | |
|---|---|---|
| Bei einer Behandlung von aktinischen Keratosen ist für **mich** wichtig: | | |
| Behandlung wird durch die **Krankenversicherung** erstattet. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |
| Behandlung ist kaum bis wenig **schmerzhaft**. | Stimme gar nicht zu | Stimme voll und ganz zu |
| | Unentschieden | |

7

| | |
|---|---|
| Behandlung **beeinträchtigt** mich nicht im Alltag. | Stimme gar nicht zu      \|  \|  \|  \|  \|  \|  \|  \|  \|      Stimme voll und ganz zu<br>Unentschieden |

Haben Sie noch **weitere Erwartungen an die Behandlung** Ihrer aktinischen Keratosen, die nicht in der Tabelle aufgeführt sind?

**Weitere Erwartungen**:

_____

## Zum Schluss noch einige Angaben zu Ihrer Person:

**Sind Sie männlich oder weiblich?**

☐ Männlich                    ☐ Weiblich

**Bitte geben Sie Ihr Alter an:**

☐ _____ Jahre

**Familienstand**

☐ ledig
☐ verheiratet
☐ geschieden
☐ verwitwet

**In welchem Beruf haben Sie die längste Zeit gearbeitet?**

_____

**Wie sind Sie aktuell krankenversichert?**

☐ gesetzlich versichert
☐ privat versichert
☐ keine Versicherung

**Sie sind nun am Ende des Fragebogens angelangt. Vielen Dank für Ihre Teilnahme.**

8

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# Danksagung