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Kutane Nebenwirkungen und Supportivtherapie im Kontext der adjuvanten Bestrahlung des Mammakarzinoms

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Die folgenden aufgelisteten vier Originalarbeiten liegen der kumulativen Habilitationsschrift zu Grunde, welche die wesentlichen Ergebnisse der Publikationen zusammenfasst und diskutiert.

1 **Dejonckheere CS** *, Dejonckheere E *, Layer JP, Layer K, Sarria GR, Koch D, Abramian A, Kaiser C, Lindner K, Bachmann A, Anzböck T, Röhner F, Schmeel FC, Schmeel LC. Barrier Films for the Prevention of Acute Radiation Dermatitis in Breast Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *The Breast* 2023; 71: 31–41. (IF = 3,9). DOI: 10.1016/j.breast.2023.07.001

2 **Dejonckheere CS**, Layer JP, Nour Y, Layer K, Glasmacher AR, Wiegreffe S, Fuhrmann A, Caglayan L, Grau F, Sarria GR, Scafa D, Kock D, Heimann M, Leitzen C, Köksal MA, Röhner F, Müdder T, Dejonckheere E, Schmeel FC, Anzböck T, Lindner K, Bachmann A, Abramian A, Kaiser C, Faridi A, Mustea A, Giordano FA, Stope MB, Schmeel LC. Non-Invasive Physical Plasma for Preventing Radiation Dermatitis in Breast Cancer: Results from an Intrapatient-Randomised Double-Blind Placebo-Controlled Trial. *Clinical and Translational Radiation Oncology* 2023; 44: 100699. (IF = 3,1). DOI: doi.org/10.1016/j.ctro.2023.100699

3 **Dejonckheere CS** *, Abramian A *, Lindner K, Bachmann A, Layer K, Anzböck T, Layer JP, Sarria GR, Scafa D, Koch D, Leitzen C, Kaiser C, Faridi A, Schmeel LC. Objective, Clinician- and Patient-Reported Evaluation of Late Toxicity following Adjuvant Radiation for Early Breast Cancer: Long-Term Follow-Up Results of a Randomised Series. *Journal of Clinical Medicine* 2023; 12: 4212. (IF = 5,0). DOI: 10.3390/jcm12134212

4 **Dejonckheere CS**, Lindner K, Bachmann A, Abramian A, Layer K, Anzböck T, Layer JP, Sarria GR, Scafa D, Koch D, Leitzen C, Kaiser C, Faridi A, Schmeel LC. Do Barrier Films Impact Long-Term Skin Toxicity Following Whole-Breast Irradiation? Objective Follow-Up of Two Randomised Trials. *Journal of Clinical Medicine* 2023; 12: 7195. (IF = 5,0). DOI: 10.3390/jcm12227195

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1 Verzeichnisse

1.1 Inhaltsverzeichnis

1.2 Abkürzungsverzeichnis

aHR	adjusted hazard ratio
BET	brusterhaltende Therapie
BMI	body mass index
bzw.	beziehungsweise
ca.	circa
CRO	Clinician-Reported Outcome
CTCAE	Common Terminology Criteria for Adverse Events
d. h.	das heißt
DRKS	Deutsches Register Klinischer Studien
DNA	Desoxyribonukleinsäure
ggf.	gegebenenfalls
Gy	Gray
HER2	Human Epidermal growth factor Receptor 2
HR	hazard ratio
IMRT	intensitätsmodulierte Strahlentherapie
IORT	intraoperative Bestrahlung
LENT-SOMA	Late Effects on Normal Tissue – Subjective, Objective, Management, Analysis
Linac	Linearbeschleuniger
MASCC	Multinational Association of Supportive Care in Cancer
NIPP	nicht-invasives physikalisches Plasma
OR	odds ratio
PRO	Patient-Reported Outcome
pT1	pathologisches Tumorstadium ≤ 20 mm
RISRAS	Radiation-Induced Skin Reaction Assessment Scale
RTOG	Radiation Therapy Oncology Group
S2k	konsensbasiert
SMD	standardised mean difference
SNP	Einzelnukleotid-Polymorphisme
SSA	Skin Symptom Assessment
Tab.	Tabelle
TGF-β1	transformierender Wachstumsfaktor β1

u. a.	unter anderem
VMAT	volumetrisch-modulierte Bogenbestrahlung
vs.	versus
z. B.	zum Beispiel

1.3 Tabellenverzeichnis

2 Einleitung

2.1 Mammakarzinom

Brustkrebs bleibt mit Abstand die häufigste Krebserkrankung der Frau. Mit über 70.000 Neudiagnosen in Deutschland im letzten Jahr, erkrankt etwa eine von acht Frauen hieran im Laufe ihres Lebens. Weltweit erreichen diese Zahlen jährlich über 2.300.000 und etwa ein Prozent der Neuerkrankungen betrifft Männer (Siegel et al., 2022). Mammakarzinome treten hauptsächlich ab der 6. Lebensdekade auf, sodass das Alter den wichtigsten Risikofaktor darstellt. Neben hormonellen Einflüssen (frühe Menarche bzw. späte Menopause, hormonelle Verhütung, Hormonersatztherapie) spielen auch Übergewicht, Alkohol und Rauchen eine wichtige Rolle (Łukasiewicz et al., 2021).

Seit der Einführung des Mammographie-Screenings im Jahr 2005 wurde ein typischer Anstieg der Neudiagnosen gesehen mit erwartungsgemäß anschließendem Rückgang über die folgenden Jahre. Im Durchschnitt ist die Anzahl an fortgeschrittenen Tumoren, die dabei festgestellt wird jedoch ruckläufig, sodass die zweijährliche Mammographie sich für Frauen vom 50. bis zum 69. Lebensjahr (bald auch darüber hinaus) als kosteneffektive Früherkennungsuntersuchung erwiesen hat, einhergehend mit einer eindeutigen Reduktion der Brustkrebsmortalität in dieser Altersgruppe (Katalinic et al., 2019). Neben der (meist hormonsensibelen) sporadischen Variante des Mammakarzinoms sind auch genetische Aberrationen bekannt, die das Risiko für Mammakarzinome (so oft auch anderer Tumorentitäten) erhöhen. Träger solcher Mutationen profitieren von einer früheren, intensivierten oder ergänzten (z. B. Ultraschall, Magnetresonanztomographie) Vorsorge und in Einzelfällen, bei signifikant erhöhtem Lebenszeitrisiko, ist sogar eine prophylaktische Mastektomie zu erwägen (Shiovitz et al., 2015).

2.2 Strahlentherapie

Die Behandlung von Brustkrebs ist komplex und hat sich über die letzten Dekaden stark erweitert. Abhängig vom Stadium und der Tumorbiologie steht eine Kombination verschiedener Modalitäten wie Chirurgie, Strahlentherapie, Chemo-, Immun-, zielgerichtete und antihormonelle Therapie zur Verfügung. Die Indikation und Reihenfolge werden nach multidisziplinärer Kasusbesprechung in einer Tumorkonferenz

festgelegt. Zentral ist dabei stets eine partizipative und evidenzbasierte Entscheidungsfindung, die ebenso auch individuelle Patientencharakteristika wie Vorerkrankungen, Allgemeinzustand oder Lebenserwartung berücksichtigt.

Die Standardtherapie des Mammakarzinoms im Frühstadium in Deutschland umfasst in der Regel eine brusterhaltende operative Therapie (BET) mit oder ohne Sentinellymphonodektomie. Vier bis sechs Wochen später, nach abgeschlossener Wundheilung und bei Vorliegen des finalen pathologischen Gutachtens, wird bei der Mehrheit der Patienten eine adjuvante Brustbestrahlung empfohlen (Hennequin et al., 2016; Wöckel et al., 2021). Ziel dieser ist es, die Wahrscheinlichkeit eines Lokalrezidivs zu senken, von ca. 10 % auf ca. 1 %, dadurch dass eventuell verbliebene Tumorzellen abgetötet werden (Kunkler et al., 2023). Bei den meisten Subgruppen werden ebenso das metastasenfreie sowie das Gesamtüberleben verbessert, sodass die Bestrahlung gegenwärtig als obligater Bestandteil der Therapie betrachtet wird, da die Kombination aus Brusterhalt und Bestrahlung auch der Mastektomie überlegen ist (Darby et al., 2011; de Boniface et al., 2021).

Zur Auswahl stehen die Ganzbrustbestrahlung, jedoch kann bei älteren Patienten mit einem insgesamt niedrigen Rezidivrisiko auch eine Teilbrustbestrahlung erwogen werden (d. h. ausschließliche Bestrahlung der erweiterten ehemaligen Tumorregion statt der gesamten Brustdrüse). In Deutschland ist die klassische Modalität dieser Brustbestrahlung aktuell die photonenbasierte tangentiale intensitätsmodulierte Strahlentherapie (IMRT) in moderater Hypofraktionierung, mit 15−16 Fraktionen von 2,5−2,67 Gy (einer Gesamtdosis von 40,05−42,7 Gy entsprechend) über ca. drei Wochen (Whelan et al., 2010). In den letzten Jahren hat die moderate Hypofraktionierung die ältere konventionelle Fraktionierung (25−28 Fraktionen von 1,8−2 Gy, einer Gesamtdosis von ca. 50 Gy entsprechend, über fünf bis sechs Wochen) großenteils ersetzt, da mehrere hochqualitative randomisierte Studien eine mindestens vergleichbar gute Tumorkontrolle zeigen konnten bei insgesamt besserer Verträglichkeit und kürzerer Behandlunsgzeit (Whelan et al., 2010; Shaitelman et al., 2015; Schmeel et al., 2020). Eine weitere Verkürzung der perkutanen Strahlentherapie (die sogenannte Ultrahypofraktionierung; z. B. 5 Fraktionen innerhalb einer Woche) ist Thema aktueller Studien, deren Langzeitdaten hinsichtlich lokaler Kontrolle und Spättoxizität aktuell jedoch noch ausstehen (Murray Brunt et al., 2020).

Bei Patienten mit einem erhöhten Rezidivrisiko, entweder aufgrund des Alters (≤ 50 Jahre) oder der Tumorbiologie (> pT1, Grad 3, HER2 positiv, tripelnegativ) kann eine Dosisaufsättigung (ein sogenannter Boost) im Bereich des (clipmarkierten) ehemaligen Tumorbettes die lokale Kontrolle weiter verbessern (Bartelink et al., 2015). Für die exakte Modalität dieses Boosts stehen verschiedene Techniken zur Verfügung: intraoperative Bestrahlung (IORT), Multikatheter-Brachytherapie oder perkutan (entweder simultan-integriert oder sequentiell). In der Mehrzahl der Fälle wird ein perkutaner Boost mit 5−8 Fraktionen von 2 Gy (einer Gesamtdosis von 10−16 Gy entsprechend) sequentiell appliziert, u. a. aufgrund der derzeit stärkeren Datenlage, breiten Erfahrung sowie der allgegenwärtigen Verfügbarkeit der linacbasierten Strahlentherapie.

2.3 Kutane Nebenwirkungen

Durch technische Fortschritte hat sich das Nebenwirkungsprofil der perkutanen Strahlentherapie in den letzten Jahren stark verbessert: so sind schwerwiegende Therapiefolgen während oder nach einer Brustbestrahlung mittlerweile selten geworden. Abhängig vom Zeitpunkt des Auftretens relativ zur Bestrahlung, werden dabei akute von chronischen Nebenwirkungen unterschieden (≤ 90 bzw. > 90 Tage).

2.3.1 Akut

Die häufigste akute Nebenwirkung der Brustbestrahlung ist die Radiodermatitis, die bei bis zu 85 % der Patienten auftritt und meist eine geringe Ausprägung aufweist (ca. 30 % der Fälle moderat bis schwer) (Shaitelman et al., 2015; Schmeel et al., 2020). Die Pathophysiologie der Radiodermatitis ist komplex, aber hauptsächlich auf die Strahlenempfindlichkeit der basalen Keratinozyten der Haut zurückzuführen, was zu einer Unterbrechung der Selbsterneuerungsfähigkeit der Epidermis führt und damit zu einem Verlust der Integrität der Hautbarriere. Hautfalten (z. B. axillär, inframammär) sind aufgrund zusätzlicher mechanischer Reizungen besonders anfällig. Klinisch wird die Radiodermatitis durch Erythem, Überwärmung, Juckreiz, Schmerzen, Ödem, trockene und feuchte Desquamationen charakterisiert, mit konsekutiven Beeinträchtigungen der Lebensqualität und des Selbstbildes (Rzepecki et al., 2018). In schweren Fällen (mit ausgeprägten Erosionen oder Ulzerationen) können außerdem

Unterbrechungen der Strahlentherapie erforderlich sein, welche die Tumorkontrolle aus radiobiologischen Gesichtspunkten negativ beeinflussen (Haruna et al., 2017).

Die Radiodermatitis tritt gemeinhin erst ab der 2. Bestrahlungswoche auf und besitzt danach einen in der Regel sigmoidal verlaufenden Anstieg bis zum Ende der Strahlentherapie. Die maximale Ausprägung kann noch zwischen 1 bis 2 Wochen nach Therapieabschluss persistieren, woraufhin eine langsame spontane Abheilung über mehrere Tage bis Wochen die Regel ist (Chan et al., 2012). Pigmentierungsänderungen im bestrahlten Areal können jedoch für mehrere Wochen oder sogar Monate danach persistieren. Verschiedene Risikofaktoren für eine stärkere Ausprägung der Radiodermatitis sind bekannt, so sind Patienten mit helleren Hauttypen und größeren Brustvolumina durchaus stärker betroffen (Böhner et al., 2020). Auch die Fraktionierung, Kumulativdosis (d. h. Boost), die Technik der Bestrahlung sowie die Patientenlagerung können das Risiko modulieren (Schmeel et al., 2020; Behroozian et al., 2021a; Vesprini et al., 2022). In zwei kürzlich veröffentlichten Publikationen wurde das dermale Mikrobiom, d. h. die bakterielle Besiedlung der Haut, als neuer und potenziell modifizierbarer Risikofaktor für die Radiodermatitis herauskristallisiert (Kost et al., 2023a; Hülpüsch et al., 2024). In einem ersten Bericht zeigten Kost et al., dass eine nasale *Staphylococcus aureus*-Besiedlung mit dem Schweregrad der Radiodermatitis assoziiert sein kann. Darüber hinaus wiesen Hülpüsch et al. nach, dass bei Patienten, die eine schwere Radiodermatitis entwickeln, eine Überbesiedlung mit nicht-spezifischen Hautbakterien beobachtet wurde, bevor schwere Symptome auftraten. Beide Studien legen die weitere Untersuchung der Zusammensetzung des Hautmikrobioms als einen vielversprechenden Weg zu einem lange gesuchten potenziellen prädiktiven Biomarker nahe. Spezifische Prädispositionen von Krebspatienten (z. B. der Immunstatus) sind in der Regel nicht modulierbar, doch könnten diese neuen Erkenntnisse zukünftig leicht anwendbare personalisierte Präventionsstrategien ermöglichen. Die wichtigsten Risikofaktoren sind in Tabelle 1 zusammengefasst.

Tab. 1 Etablierte Risikofaktoren für die maximale Ausprägung einer Radiodermatitis bei der adjuvanten Ganzbrustbestrahlung.

Autor	**Behroozian**	**Böhner**	**Vesprini**	**Schmeel**	**Kost**	**Hülpüsch**	**Keenan**
Jahr	2021a	2020	2022	2020	2023a	2024	2019
n	1 093	142	357	140	76	20	131
Fraktionierung	$p <$ 0,0001	-	$p =$ 0,004	$p =$ 0,024	-	-	$p =$ 0,001
= konventionelle Fraktionierung (25 ×) versus moderate Hypofraktionierung (15 ×)							
bestrahltes Volumen	$p =$ 0,01	$p =$ 0,005	$p <$ 0,001	-	-	-	-
= postoperatives Brustvolumen, z. B. gemessen in der Computertomographie zur Bestrahlungsplanung (in mL) oder alternativ (weniger genau) als Körbchengröße							
Boost	$p =$ 0,01	$p =$ 0,0635	$p <$ 0,001	-	-	-	-
= Dosisaufsättigung im Bereich des ehemaligen Tumorbettes, stimmt überein mit der kumulativen Bestrahlungsdosis							
Hauttyp	-	$p <$ 0,001	-	-	-	-	-
= z. B. mittels Fitzpatrick-Skala, eine Charakterisierung der Haut hinsichtlich der Empfindlichkeit für Sonne, alternativ (genauer) mittels objektiver Messverfahren							
Technik	-	$p <$ 0,05	-	-	-	-	-
= volumetrisch-modulierte Bogenbestrahlung (VMAT) versus sogenannte *sliding window* Technik							
Lagerung	-	-	$p <$ 0,001	-	-	-	-
= klassische Rückenlage versus Bauchlage, nur bei Patienten mit großen Brüsten							
Mikrobiom	-	-	-	-	$p =$ 0,02	$p <$ 0,001	-
= nasale *Staphylococcus aureus*-Besiedlung oder geringe Zahl von kommensalen Hautbakterien auf der Brusthaut vor Beginn der Strahlentherapie							
Hautdosis	-	-	-	-	-	-	$p =$ 0,013
= kann durch dosimetrische Parameter ausgedrückt werden, z. B. das Volumen der Brusthaut, dass mindestens 105 % der verschriebenen Dosis erhält, soll möglichst < 30 mL bleiben ($V_{105\%}$ > 30 mL)							

Eine systematische Überprüfung der Literatur bis 2021 ergab 38 Studien mit insgesamt 15 623 Patienten (Xie et al., 2021). Die Sensitivitätsanalyse zeigte, dass nur BMI als Patientenfaktor und Fraktionierung als Therapiefaktor über alle Studien hinaus konsistent das Radiodermatitisrisiko signifikant beeinflussen. Noch wichtig zu erwähnen ist, dass BMI und Brustvolumen häufig eng mit einander verbunden sind bzw. Frauen mit einem höheren BMI haben generell auch größere Brüste. Ob die anderen Faktoren (wie in Tabelle 1 aufgeführt) das Risiko beeinflussen, ist abhängig vom Studiendesign, Land wo die Studie durchgeführt wurde und von der verwendeten Toxizitätsbewertungsskala. Weitere Faktoren, die das Risiko für eine Radiodermatitis bei der Ganzbrustbestrahlung nicht scheinen zu modulieren, sind die Chemo-, Immun- und antihormonelle Therapie, dies allerdings im Gegensatz zu anderen Tumorentitäten wie z. B. das Nasopharynxkarzinom. Hier zeigte eine Metaanalyse (15 Studien, 1 142 Patienten), dass die Kombination der Strahlentherapie und Chemotherapie das Radiodermatitisrisiko verdoppelt (He et al., 2018). Auch die Bestrahlung der regionalen Lymphabflusswege der Brust beeinflusst das Risiko der Radiodermatitis nicht.

Verschiedene Studien untersuchten außerdem die genetische Prädisposition für die Entwicklung einer Radiodermatitis, im Bereich der sogenannten *radiogenomics*. Bisher war bereits bekannt, dass bestimmte genetische Syndrome, die mit einer gestörten DNA-Reparaturkapazität einhergehen (z. B. Bloom-Syndrom, Ataxia Telangiectasia), die Entwicklungswahrscheinlichkeit für akute Nebenwirkungen einer Strahlentherapie stark erhöhen. DNA-Sequenzierungsstudien haben seitdem auch eine Reihe von Einzelnukleotid-Polymorphismen (*single nucleotide polymorphism* oder SNP) identifiziert, die das Risiko der Radiodermatitis geringfügig erhöhen können (Tabelle 2). Wie bei den Syndromen, sind auch diesen Genen hauptsächlich zuständig für DNA-Reparatur. Eine routinemäßige Umsetzung solcher Bestimmungen im Alltag bleibt bei klinisch noch unklarer Relevanz gegenwärtig allerdings noch aus.

Tab. 2 DNA-Sequenzierungsstudien, die Einzelnukleotid-Polymorphismen (SNP) identifizierten, die das Risiko für die Entwicklung einer Radiodermatitis erhöhen können.

Autor	Jahr	*n*	Entität	Gen	Risiko
Ambrosone	2006	446	Brust	GSTP1	aHR = 2,28
Isomura	2008	156	Brust	IL12RB2 ABCA1	OR = 3,02 OR = 2,45
Mangoni	2011	87	Brust	XRCC3 MSH2 MSH3	HR = ∞ HR = 53,36 HR = ∞
Murray	2011	480	Brust	LIG3	HR = 1,92
Terrazzino	2012	286	Brust	XRCC1 eNOS	OR = 2,24 OR = 2,47
Chen	2017	114	Nasopharynx	XRCC1	OR = 2,86
Mumbrekar	2017	132	Brust	CD44	OR = 2,68

Die ärztliche Bewertung der Radiodermatitis, genauer die Beurteilung des maximalen Schweregrades (sogenannte Clinician-Reported Outcomes oder CROs), dient zeitgleich mehreren Zielen. Erstens vereinfacht sie die eindeutige Dokumentation der Beschwerden und so auch die anschließende Kommunikation zwischen verschiedener in die Behandlung involvierter Gesundheitsdienstleister. Zweitens basieren verschiedene Interventionsalgorithmen auf eben dieser ärztlichen Bewertung und überdies kann auch die Effektivität einer Intervention (im Sinne einer Reduktion des Schweregrades) durch sie eingeschätzt werden. Drittens werden diese ärztlichen Erhebungen in klinischen Studien, die solche Interventionen (oder auch prophylaktische Maßnahmen) untersuchen, oft als primärer Endpunkt herangezogen. Am häufigsten angewendet zur Erfassung von CROs werden die Common Terminology Criteria for Adverse Events (CTCAE) und die Radiation Therapy Oncology Group (RTOG) Kriterien (Cox et al., 1995; Trotti et al., 2003), die für die akute Radiodermatitis in Tabelle 3 dargestellt sind.

Tab. 3 Vergleich zwischen den CTCAE- und RTOG-Kriterien für die akute Radiodermatitis, die beiden am häufigsten angewendeten ärztlichen Schweregradgraduierungen.

Grad	CTCAE	RTOG
0	keine Radiodermatitis	
1	leichtes Erythem oder trockene Desquamation	leichtes Erythem, Epilation, trockene Desquamation, verminderte Schweißbildung
2	mäßiges bis starkes Erythem, fleckige feuchte Desquamation, meist auf Hautfalten beschränkt, mäßiges Ödem	**a**: intensives Erythem, mit oder ohne trockene Desquamation
		b: fleckige feuchte Desquamation, mäßiges Ödem
3	feuchte Desquamation in anderen Bereichen als Hautfalten, Blutung durch geringfügiges Trauma oder Abschürfung	konfluierende feuchte Desquamation in anderen Bereichen als Hautfalten, Lochfraßödem
4	lebensbedrohliche Folgen, Hautnekrose oder Ulzeration der gesamten Dermis, spontane Blutung, Hauttransplantation erforderlich	Ulzeration, Blutung, Nekrose
5	Tod	

Neben der ärztlichen Einschätzung der Radiodermatitis spielen auch die von den Patienten berichteten Ergebnisse zunehmend eine bedeutsame Rolle. Bei den sogenannten Patient-Reported Outcomes (PROs) stammen Informationen bezüglich des Gesundheitszustands eines individuellen Patienten unmittelbar vom Patienten, ohne dass diese Reaktion zusätzlich z. B. durch einen Arzt graduiert oder bewertet wird. Die zusätzliche Erhebung der subjektiven Belastung einer Krankheit oder Behandlung ist wichtig, da mehrere Studien zeigten, dass große Diskrepanzen zwischen beiden Bewertungsmethoden (CRO und PRO) bestehen (Lam et al., 2020; Behroozian et al., 2021b; Jagsi et al., 2022). Dabei geht es hauptsächlich um eine unzureichende Erkennung der subjektiven Beschwerden bzw. deren Einfluss auf die Lebensqualität der

Patienten, was möglicherweise zu einer Unterbehandlung therapie-induzierter Nebenwirkungen führen kann (Di Maio et al., 2015). Insbesondere auch allgemeine Symptome wie Müdigkeit, Erschöpfung und Ängste werden nur selten von den behandelnden Ärzten in den Krankenakten vermerkt (Takala et al., 2021). Eine weitere Studie zeigte, dass diese Untererfassung im Kontext der Radiodermatitis vor allem bei jüngeren Patienten der Fall ist, schwarzer oder nicht-weißer ethnischer Herkunft, konventioneller Fraktionierung und bei Erhebungen durch männliche Ärzte (Jagsi et al., 2022). Wie bei den ärztlichen Erhebungen stehen zur PRO-Erfassung der Radiodermatitis verschiedene Instrumente zur Verfügung, z. B. die Radiation-Induced Skin Reaction Assessment Scale (RISRAS), das Skin Symptom Assessment (SSA) oder der Skindex (Noble-Adams, 1999; Chren, 2012; Behroozian et al., 2023a). Diese Instrumente erfragen die subjektiven Symptome, die mit der Radiodermatitis assoziiert sind wie Juckreiz, Schmerzen, Schwellung, Schuppung und Beeinträchtigungen im alltäglichen Leben, meist anhand einer klassischen Likert-Skala von gar nicht bis sehr stark. Ein Goldstandard für die Erhebung der PROs bei Radiodermatitis ist jedoch noch nicht vorhanden (Behroozian et al., 2021c).

Zur weiteren Beurteilung und Einstufung der Radiodermatitis stehen neuerdings auch objektive Messmethoden zur Verfügung. CROs sind nämlich durch eine inhärente Subjektivität gekennzeichnet, welche mit einer erheblichen Variabilität sowohl zwischen verschiedenen als auch bei ein und demselben Beobachter verbunden ist (was vor allem in nicht-verblindeten Studien problematisch ist). Nicht-invasive, objektive Bewertungsmethoden der Radiodermatitis, die bereits im Kontext der adjuvanten Brustbestrahlung validiert wurden, sind u. a. Bestimmung des Hydrationsgrades und des transepidermalen Wasserverlustes, Spektralphotometrie, Messung des kutanen Blutflusses und optische Kohärenztomographie (Momm et al., 2005; Huang et al., 2015; Robijns et al., 2019; Böhner et al., 2020). Vor- und Nachteile einzelner Methoden sind in Tabelle 4 dargestellt. Solche objektiven Messmethoden werden im klinischen Alltag zwar selten angewendet, sind jedoch gerade im Rahmen klinischer Studien besonders sinnvoll.

Tab. 4 Nicht-invasive, objektive Bewertungsmethoden der Radiodermatitis, validiert im Kontext der adjuvanten Brustbestrahlung.

Methode	Erklärung	Vorteile	Nachteile
Hydratationsgrad der Haut	Wasserhaltevermögen und Hydratation des Stratum corneum bzw. Messung der Kapazität mittels der dielektrischen Methode	ermittelt Informationen über die Funktion der Hautbarriere	teuer
transepidermaler Wasserverlust	Menge an Wasser, die pro Hautfläche aus dem Stratum corneum austritt	ermittelt Informationen über die Funktion der Hautbarriere	teuer
Spektralphotometrie	Ausstrahlung bestimmter Wellenlängen des Lichts, die dem Absorptionsspektrum von Melanin entsprechen, Messung des absorbierten und reflektierten Lichts	sehr schnell, kabellos, tragbar, Informationen über Pigmentierung und Erythem	schwieriger bei Patienten mit einer dunklen Hautfarbe (unterrepräsentiert in Validierungsstudien), korreliert sehr gut mit CRO
Messung des kutanen Blutflusses	in Perfusionseinheiten, d. h. Multiplikation der Anzahl der roten Blutkörperchen innerhalb des gemessenen Volumens (in den oberflächlichen Kapillaren der Haut) mit der	korreliert sehr gut mit CRO (alle Skalen)	hauptsächlich Information über Erythem

	mittleren Geschwindigkeit		
optische Kohärenztomographie	hochauflösende Querschnittsbilder (wie Ultraschall, aber mit Licht statt Schall)	Querschnittsbilder, anatomische Änderungen können dargestellt werden	entsprechende (teure) Ausstattung erforderlich, Datenlage (noch) weniger stark da neuerer Technik

2.3.2 Chronisch

Aufgrund der generellen Zunahme an Therapieoptionen beim Mammakarzinom durch Fortschritte in der Medizin mit begleitenden Überlebensvorteilen, steigt auch das Bewusstsein und Interesse für das Thema der Spättoxizität. Chronische kutane Nebenwirkungen sind mit modernsten Bestrahlungstechniken zwar seltener geworden, bei Auftreten jedoch meist irreversibel mit entsprechend starker und ggf. dauerhafter Beeinträchtigung der Kosmesis, des Selbstbildes und der Lebensqualität. Im Vordergrund der chronischen Radiodermatitis steht die Fibrose, d. h. eine Vernarbung des Bindegewebes, vorrangig durch die strahlenbedingte Verödung der Mikrovaskularisation. Ferner wird das klinische Bild durch Atrophie, Pigmentierungsstörungen (Hyper- oder Hypopigmentierung) und Teleangiektasien (d. h. Äderchen der oberflächlichen Haut) charakterisiert (Fehlauer et al., 2003). Auch Einschränkungen der Schulter- und Armmobilität sowie chronische Schmerzen können dabei auftreten. Eine fachgerechte Diagnostik der Spättoxizität ist aufgrund des langen Intervalls (Monate bis Jahre) zwischen Bestrahlung und Beginn der assoziierten Symptomatik oft zeitverzögert und die Datenlage zur adäquaten Therapie ist sehr limitiert, sodass die Spätfolgen oft als hartnäckig oder sogar therapierefraktär gelten. Wie bei der akuten Toxizität, ist die Pathogenese auch hier komplex. Zentral steht transformierender Wachstumsfaktor β1 (TGF-β1), ein regulatorisches Protein dessen Konzentration bereits innerhalb weniger Stunden nach der Strahlentherapie ansteigt. Vor allem die resultierende Synthese von extrazellulären Matrixbestandteilen, spielt eine gewichtige Rolle bei der Entwicklung der strahleninduzierten fibrotischen Veränderungen (Martin et al., 2000; Pohlers et al., 2009).

Ein häufig angewendetes einheitliches Erfassungsinstrument für Spätnebenwirkungen ist der Late Effects on Normal Tissue – Subjective, Objective, Management, Analysis (LENT-SOMA) (Seegenschmiedt et al., 2000). Im Vergleich mit älteren (ausschließlich CRO-basierten) Instrumenten werden die Reaktionen der Haut nach einer Strahlentherapie bei LENT-SOMA höher eingestuft, sodass von einer sensitiveren Messmethode ausgegangen werden kann (Hoeller et al., 2003). Zur genaueren Einstufung der subjektiven Beschwerden steht von den CTCAE-Kriterien außerdem eine PRO-Variante zur Verfügung (PRO-CTCAE) (Basch et al., 2014).

Auch andere Organen in der Nähe des bestrahlten Volumens (Herz, Lunge, Rippen) können Spätfolgen einer Radiotherapie davontragen. Aufgrund der technischen Fortschritte in der Strahlentherapie (IMRT, bildgestützte Strahlentherapie, Atemanhaltetechnik, Oberflächenscanning) hat sich die Prävalenz stark reduziert. Chronische Fatigue tritt bei gut einem Drittel der therapierten Brustkrebspatienten auf (Maass et al., 2021; Di Meglio et al., 2022).

Ein besonderes dermales Phänomen ist die sogenannte *recall* Dermatitis, eine seltene akute inflammatorische Reaktion (klinisch wie die akute Radiodermatitis) die sich jedoch erst spät manifestiert (manchmal sogar erst nach mehreren Jahren). Die Hautreaktion bezieht sich auf die ehemalige Bestrahlungsregion und kann durch Medikamente (meist Chemotherapien wie z. B. Anthrazykline oder Taxane) ausgelöst werden. Nach Absetzen dieser Auslöser ist die Reaktion in der Regel selbstlimitierend (Bhangoo et al., 2022).

2.4 Supportivtherapie

Eine adäquate Supportivtherapie und das Management von therapieassoziierten Nebenwirkungen ist ein wichtiger Bestandteil jeder holistischen onkologischen Therapie geworden. Da Risikofaktoren oft nur schwierig moduliert werden können, steht die Prophylaxe im akuten Kontext im Vordergrund, wo versucht wird, den Beginn der Radiodermatitis zu verzögern, die maximale Ausprägung zu mildern und die Abheilung zu beschleunigen.

Verschiedene nationale und internationale Fachgesellschaften haben sich mit der Erfassung von Leitlinien zur Supportivtherapie der kutanen Nebenwirkungen beschäftigt. Ein direkter Vergleich dieser Empfehlungen bestätigt jedoch eine große Unstimmigkeit mit starken Unterschieden in den empfohlenen Vorgehensweisen (Finkelstein et al., 2022). Letzteres hat sich außerdem auch bestätigt in einer Umfrage der Strahlentherapiegesellschaft im deutschsprachigen Raum, wo eine starke Variation in der Prophylaxe und Therapie der Radiodermatitis durch Ärzte beobachtet wurde (Layer et al., 2023a; Layer et al., 2023b).

Bei den Basismaßnahmen zur Radiodermatitisprophylaxe steht die Reduktion des oberflächlichen, epidermalen Zellverlustes im Mittelpunkt. Dies wird u. a. durch lockere und luftdurchlässige Kleidung sowie Duschen mit lauwarmem Wasser und normales Waschen mit vorsichtigem Abtrocknen erreicht. Eine pflegende (z. B. harnstoffhaltige) Lotion oder Creme ohne allergisierende Substanzen ist ratsam (*good clinical practice*). Puder sollte aufgrund des Austrocknungspotentials generell vermieden werden, aber auf Deodorant im Rahmen der gewohnten Körperpflege muss nicht verzichtet werden.

Eine Vielzahl an zusätzlichen topischen Maßnahmen wurde bisher im Kontext der Radiodermatitis untersucht. Die rezent publizierte Multinational Association of Supportive Care in Cancer (MASCC) Leitlinie, erstellt von 42 internationalen Experten und basierend auf gegebener Evidenz bis September 2020 (235 Originalpublikationen, davon 149 randomisierte Studien), konnte nur eine begründete Empfehlung für sechs prophylaktische Maßnahmen abgeben: Photobiomodulationstherapie, Mepitel- und Hydrofilm, Mometason, Betamethason und Olivenöl (Behroozian et al., 2023b). Zu den meisten Interventionen kann also aufgrund unzureichender oder sogar widersprüchlicher Evidenz kein Statement gegeben werden, was hauptsächlich durch methodische Einschränkungen der einzelnen Studien zu erklären ist:

- heterogene Kollektive im Hinblick auf Patientencharakteristika und geplante Strahlentherapie (Behandlungsort, Dosis und Fraktionierung);
- Fehlen einer einfachen oder doppelten Verblindung;
- uneinheitliche oder nicht-definierte Standardhautpflege;
- Fehlen einer Placebokontrolle mit identischer Trägersubstanz;
- fehlende Prädefinition der Endpunkte (Prophylaxe versus Therapie);

- fehlende Prüfung der Compliance bzw. des Verzichts auf weitere topische Therapien, die die Ergebnisse beeinflussen können;
- keine Berücksichtigung oder Angabe der bereits etablierten Risikofaktoren der Radiodermatitis und somit keine entsprechende Stratifizierung der Patienten bzw. Adjustierung für Imbalancen zwischen Studienkohorten;
- fehlende Berücksichtigung von PROs und;
- fehlende Anwendung objektiver Messverfahren dadurch, dass die Interrater-Validität des klinischen Endpunkts nicht berücksichtigt wird.

Nur wenige Studien erfüllen somit die Kriterien für Level of Evidence 1, sodass trotz laufender Forschungsanstrengungen und eines exponentiellen Anstiegs von Studien und Publikationen zum Radiodermatitismanagement in den letzten Jahren nur über wenige Substanzen eine eindeutige Aussage getroffen werden kann, obgleich einige von ihnen initial eine vielversprechende Wirkung bei der Prävention oder Behandlung der Radiodermatitis zeigten (Yee et al., 2018).

Bei den Maßnahmen mit starkem Konsens müssen außerdem die jeweiligen Limitierungen der eingesetzten Methoden berücksichtigt werden. Photobiomodulationstherapie bedarf z. B. einer entsprechend (teuren) Ausstattung mit geschultem Personal für die Durchführung; das Anbringen von Film- und Folienverbänden in Regionen mit erhöhter Transpiration oder Reibung (z. B. axillär, klavikulär) kann schwierig sein und in Einzelfällen können Juckreiz, Hautausschlag und Bläschenbildung auftreten; topische Kortikoide wiederum können die durch die Radiodermatitis verursachten Symptome zwar lindern, werden aufgrund ihres Nebenwirkungsprofils (z. B. mögliche Atrophie der Haut, Entwicklung von Dehnungsstreifen, potenziell erhöhtes Risiko einer Superinfektion oder verzögerten Wundheilung) in praxi nur restriktiv eingesetzt (Haruna et al., 2017).

Supportive Maßnahmen bei den chronischen Nebenwirkungen sind weniger erforscht, u. a. durch die viel komplexere Diagnosestellung sowie die insgesamt geringere Inzidenz, was die Rekrutierung solcher Studien deutlich erschwert. Versuche, den ursächlichen TGF-β1-Pathway direkt oder indirekt zu modulieren, z. B. mittels Pentoxifyllin, Glutamin, Zink oder Hyaluronsäure, waren bisher ohne Erfolg (Jordan et al., 2020). Chronische radiogene Ulzera werden daher nach den allgemeinen Regeln der Wundversorgung therapiert. Über den Einsatz der Photobiomodulationstherapie besteht in

diesem Zusammenhang lediglich anekdotische Evidenz. Hyperbarer Sauerstoff, d. h. die Einatmung von 100 % O_2 bei einem höheren Druck als dem Atmosphärendruck, kann angeboten werden. Durch die bessere Sauerstoffsättigung im Gewebe wird die Angiogenese stimuliert, was die Entwicklung einer Fibrose verhindern kann. In einer randomisierten Studie konnte die Schmerzen nicht wirksam reduzieren, wohl aber die Fibrose (Mink van der Molen et al., 2024). Nur 25 % der Patienten, denen diese Therapie angeboten wurde, hat dies aber zugestimmt, was mit dem hohen Aufwand zusammenhängt (30 bis 40 Sitzungen über einen konsekutiven Zeitraum von 6 bis 8 Wochen, jede Sitzung dauert ca. 100 bis 120 Minuten). Dies führte allerdings dazu, dass die Studie frühzeitig abgebrochen wurde aufgrund der mangelnden Rekrutierung. Auch bei anderen therapierefraktären radiogenen Spätfolgen (z. B. radiogene Zystitis, radiogene Proktitis), kann hyperbarer Sauerstoff angewendet werden (Jordan et al., 2020).

2.5 Zielsetzung

Obwohl die Radiodermatitis die häufigste akute Nebenwirkung im Rahmen adjuvanter Brustbestrahlungen und der Strahlentherapie insgesamt ist, bleibt für viele Patienten eine erhebliche körperliche und psychische Belastung bestehen. Ziel aktueller Studien zum Thema der Radiodermatitis beim Mammakarzinom sollte eine wissenschaftlich fundierte Erprobung potenzieller Präventions- oder Behandlungsmaßnahmen sein, wobei klassische methodische Einschränkungen im Interventions- und Studiendesign erkannt und entsprechend berücksichtigt werden. In den nachfolgenden Originalarbeiten dieser kumulativen Habilitationsschrift wird (1) die Evidenz hinsichtlich einer bereits bestehenden Intervention in der akuten Setting (Film- und Folienverbände) kritisch geprüft und mittels einer Metaanalyse gepoolt und (2) eine potenzielle nebenwirkungsarme und benutzerfreundliche Radiodermatitispräventionsmethode, das nicht-invasive physikalische Plasma, nach zum ersten Mal erfolgter Erprobung am Menschen anschließend in einem größeren Patientenkollektiv untersucht, wobei besonders auf ein umfassendes und störfaktorfreies Studiendesign geachtet wird. Die gleichen methodologischen Stärken werden danach im Kontext der Spätfolgen der Brustbestrahlung angewendet. So werden anschließend (3) Einflüsse der Dosis und Fraktionierung auf das Auftreten der Spättoxizität identifiziert und (4) die Effekte der erwähnten Film- und

Folienverbände auf das Auftreten der Spätfolgen im ehemaligen Patientenkollektiv umfassend untersucht.

3 Ergebnisteil

3.1 Dejonckheere CS et al. Barrier Films for the Prevention of Acute Radiation Dermatitis in Breast Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Breast* 2023; 71: 31–41

Zielsetzung der Arbeit: Polyurethanbasierte Film- und Folienverbände (Mepitel- und Hydrofilm) bilden eine transparente semipermeable mechanische Barriere zwischen der geschädigten Basalschicht der bestrahlten Haut und möglichen zusätzlichen (mechanischen, chemischen oder thermischen) Traumata, was somit die Reparatur des strahlengeschädigten Gewebes beschleunigt. Sie können während der gesamten Dauer der Bestrahlung auf der Haut verbleiben. Bei der nicht-strahleninduzierten Wundbehandlung werden solche Verbände bereits seit Jahrzehnten eingesetzt. Ziel dieser Studie ist es, die verfügbare Evidenz zu Film- und Folienverbänden zur Radiodermatitisprophylaxe im Kontext der Bestrahlung beim Mammakarzinom kritisch zu beurteilen und mittels einer Metaanalyse zu poolen.

Methoden und Ergebnisse: Die internationale Literatur wurde systematisch überprüft und fünf hochqualitative, prospektive, randomisierte Studien (davon zwei aus der eigenen Klinik: Schmeel et al., 2018; Schmeel et al., 2019) wurden in die Metaanalyse inkludiert (663 Patienten). Film- und Folienverbände führten zu einer Verbesserung der CROs und PROs: weniger Grad ≥ 2 Radiodermatitis (11 vs. 42 %; OR = 0,16; p < 0,001) und feuchte Desquamationen (2 vs. 16%; OR = 0,12; p = 0. 006) im Vergleich mit Standardhautpflege sowie weniger subjektive Schmerzen (SMD −0,51; p < 0,001), Juckreiz (SMD −0,52; p = 0,001), Brennen (SMD −0,41; p = 0,011) und Einschränkungen bei täglichen Aktivitäten (SMD −0,20; p = 0,007). Außerdem besteht eine hohe Akzeptanz bei den Patienten sowie ein günstiges Kosten-Nutzen-Verhältnis.

Schlussfolgerungen: Die in dieser Metaanalyse generierte Evidenz deutet darauf hin, dass Film- und Folienverbände eine hervorragende Methode zur Prävention der Radiodermatitis sind im Kontext der Bestrahlung beim Mammakarzinom und unterstützt somit die aktuellen Empfehlungen der MASCC. Die Anwendung sollte daher routinemäßig in Betracht gezogen werden, insbesondere bei Patienten mit Risikofaktoren.

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Barrier films for the prevention of acute radiation dermatitis in breast cancer: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Purpose: Radiation dermatitis (RD) is the most common side effect of adjuvant whole-breast or chest wall irradiation, majorly impacting quality of life in numerous patients. The use of barrier films (polyurethane dressings such as Hydrofilm® and Mepitel® film remaining on the skin for the duration of the radiation treatment) has been investigated as a prophylactic measure in several prospective trials. Here, we critically appraise the available evidence behind preventive barrier film application in the context of breast cancer treatment.
Methods: International literature was reviewed and high-quality randomised controlled trials (RCTs) were included in this meta-analysis.
Results: The results of 5 RCTs (663 patients; >90% Caucasian) were analysed. Overall, barrier films lead to improved clinician- and patient-reported outcomes: fewer grade ≥2 RD (11% vs. 42%; OR = 0.16; $p < 0.001$) and moist desquamation (2% vs. 16%; OR = 0.12; $p = 0.006$), as well as less patient-reported pain (standardised mean difference [SMD] −0.51; $p < 0.001$), itching (SMD −0.52; $p = 0.001$), burning (SMD −0.41; $p = 0.011$), and limitations in daily activities (SMD −0.20; $p = 0.007$). Furthermore, barrier films have a high acceptance rate among patients, as well as a favourable cost-benefit ratio. Possible side effects due to its application are mild and mostly self-limiting. Overall, there was a lack of information on the radiation treatment techniques used.
Conclusion: The evidence presented in this meta-analysis suggests that barrier films are an excellent tool in the prevention of RD among Caucasian patients receiving whole-breast or chest wall irradiation. Its use should therefore be considered routinely in these patients.

1. Introduction

Radiation dermatitis (RD) remains the most common acute side effect of adjuvant whole-breast or chest wall irradiation [1,2]. Its pathophysiology is complex, but disruptions of the skin barrier function through direct DNA damage to the epidermal basal layer cells play a central role. The main extrinsic risk factor for RD is the skin dose. Recent advances in dose-fractionation regimens (e.g. hypofractionation causing fewer damage to healthy tissues without compromising tumour control) and radiation treatment techniques (e.g. higher photon energies, intensity-modulated radiation therapy [IMRT], and volumetric intensity-modulated arc therapy [VMAT]) can reduce this skin dose,

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resulting in fewer and milder RD. In particular, skin folds or areas of frequent arm movement (e.g. the axilla) are most susceptible to radiation-induced skin toxicities due to damage of the keratinised superficial skin layers from friction or maceration. Other extrinsic risk factors for RD in breast cancer irradiation are use of a bolus (leading to skin dose build-up) and boost administration. Proven intrinsic risk factors include large breast size (requiring a higher number of monitoring units, thus leading to increased inflammation), and darker skin complexion (darker skin types naturally tend to have a more rapid pigmentation tendency and accompanying inflammatory reaction) [3–6]. In more severe cases involving moist desquamation, treatment interruptions might be necessary, possibly compromising disease control [7]. Furthermore, the development of RD impairs quality of life and self-image [8–10]. Topical corticosteroids are effective in reducing RD-related symptoms such as pain, burning, or itching, however, their widespread and prolonged use remains limited due to the associated side effect profile [7,11]. More importantly, topical corticosteroids should preferably be used on intact skin only, as they might otherwise even delay wound healing or promote infection when applied in the context of advanced moist desquamation. Other preventive and therapeutic options have been studied, often with conflicting results due to methodological differences, leading to substantial variation in RD management between practitioners and clinics [7,12,13].

Barrier films (e.g. Hydrofilm®, Mepitel® film) have been standard of care in wound management for several decades [14,15]. Both are sterile, transparent, and breathable polyurethane films, which differ in the adhesive used (Hydrofilm has a hypoallergenic polyacrylate, whereas Mepitel film uses a silicone-based adhesive). They can be applied directly on the skin (or wound) and protect it from friction and excess moisture by providing a semi-permeable mechanical barrier between the damaged basal skin layer and any potential additional trauma [16]. RD and especially moist desquamation have a predilection for areas

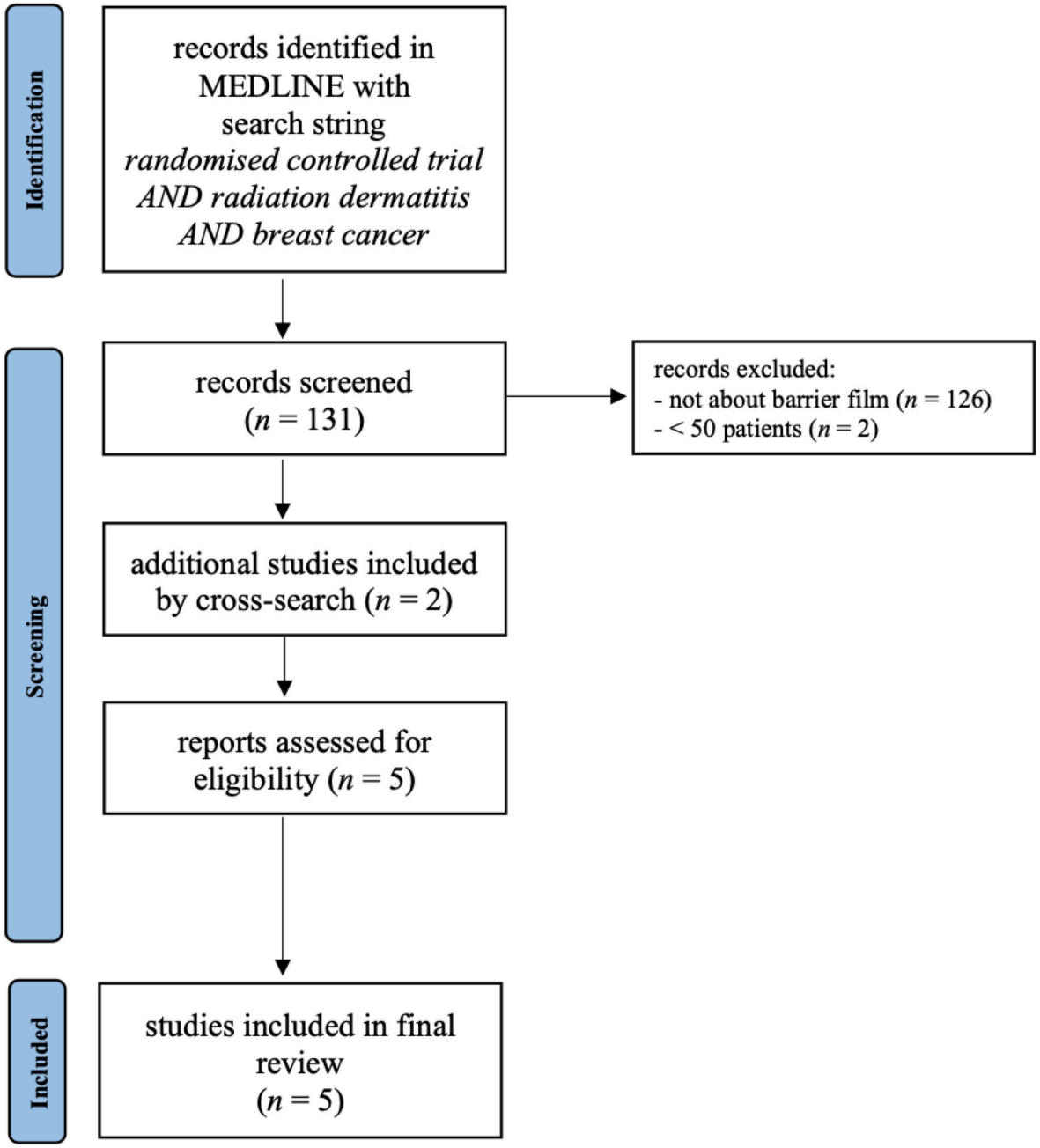


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of literature research and selection.

prone to friction such as the axilla and inframammary fold. The use of barrier films as a protective layer in the context of breast or chest wall irradiation is therefore of major interest, as it facilitates repair of the radiation-damaged tissue while protecting against any additional trauma. Due to their clinically insignificant bolus effect and high patient tolerability (when showering or exercising and regardless of clothing), barrier films can remain on the skin for the entire duration of the radiation course, which promotes patient comfort [17–20].

Initial trials sought to determine the therapeutic effect of barrier films, i.e. they were applied as soon as an RD-associated erythema became apparent [15,21]. Subsequent studies investigated the effect as a prophylactic measure. Herein, we review the data supporting the use of barrier films for the prevention of acute RD in the setting of adjuvant whole-breast or chest wall irradiation.

2. Materials and methods

We conducted a comprehensive literature search of the MEDLINE database, using PubMed as the primary search engine. Studies published between January 1st, 1977 and March 1st, 2023 matching the search string *randomised controlled trial AND radiation dermatitis AND breast cancer* were screened for inclusion based on title and abstract. All randomised controlled trials (RCTs) that investigated the use of barrier films in at least 50 breast cancer patients undergoing irradiation were included. Studies reporting on barrier creams or film-forming gels were excluded from the analysis, as these products possess different properties which would increase the heterogeneity of the results of the intervention. Additional studies were identified by cross-searching the already included articles' references. A flowchart of literature research and selection is shown in Fig. 1.

All included papers were independently appraised by 2 authors (C.S.D. and L.C.S) and data were collected from the manuscripts, supplements, and study protocols (where available). The individual risk of bias was assessed using the revised Cochrane tool for randomised trials [22]. The different domains were independently assessed by two reviewers and a traffic light plot was generated (Supplement 1). This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [23].

Mean, median, standard deviation (SD), and range were calculated for all applicable clinical data. For comparable outcomes between studies, the pooled effect size was estimated by calculating the odds ratio (OR) with a 95% confidence interval (CI), using a random effects model and results were summarised in a forest plot [24]. A p-value <0.05 was considered as statistically significant. Heterogeneity between studies was assessed by calculating I^2 with cut-offs as defined by Higgins et al. [25]. The analysis was carried out using *R* version 4.1.2 (*R* Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Trial, patient, and radiation treatment characteristics

A total of 5 RCTs, reporting on 663 patients, was included in the final analysis [17–20,26]. Of these, 2 investigated Hydrofilm and 3 Mepitel film). Four trials used an intrapatient control, i.e. the irradiated breast or chest wall was divided into a medial and a lateral compartment, and each of these compartments was randomised to receive either barrier film or standard of care. Only the most recent trial used a 2:1 inter-patient random allocation, based on the proposed superiority of Mepitel film demonstrated in the previous trials [20]. Table 1 depicts the general characteristics of the included RCTs.

All included trials recruited patients undergoing whole-breast irradiation following lumpectomy as well as patients receiving chest wall irradiation after mastectomy. Behroozian et al. only included lumpectomy patients if they were at a higher risk of developing acute radiation dermatitis (defined as postoperative bra size ≥36 inches of cup size ≥ C). Conventional fractionation (50 Gy in 25 fractions) and moderate hypofractionation (40−42.6 Gy in 15–16 fractions) were allowed, as well as boost administration (10−16 Gy in 5–8 fractions) and/or the use of a bolus to increase skin dose. If this was the case, patients were stratified accordingly to minimise confounding. Table 2 shows the individual and overall patient and radiation treatment characteristics.

3.2. Intervention properties and bolus effect

Two trials investigated the use of Hydrofilm, a polyurethane film dressing, while the other 3 trials used Mepitel film, a silicone-based polyurethane film. In all trials, barrier film was used from the first day of radiation treatment onwards and a moisturising cream or lotion was used as the standard of skin care control, a common recommendation which is considered good clinical practice [7,27].

Skin dose contributes to the risk of RD development. It is therefore of interest to determine the possible bolus effect of an applied barrier film [6,28]. All trials carried out phantom studies: with application of a barrier film, there is a negligible bolus effect of 0.12 mm, resulting in a clinically insignificant skin dose build-up. Barrier films can thus safely remain on the skin for the entire radiation course, which was the case in all trials.

Table 2
Patient and radiation treatment characteristics across selected trials.

authors	surgery		fractionation		boost (%)	bolus (%)
	lumpectomy (%)	mastectomy (%)	CF (%)	mHF (%)		
Herst et al.	56	44	50	50	36	8
Schmeel et al. (a)	100	0	100	0	31	0
Møller et al.	80	20	25	75	8	20
Schmeel et al. (b)	100	0	0	100	34	0
Behroozian et al.	58[a]	42	7	93	29	13
total	**79**	**21**	**36**	**64**	**27**	**8**

CF = conventional fractionation; mHF = moderate hypofractionation.
[a] In this trial, only patients at a higher risk of developing radiation dermatitis were included. Therefore, patients were only eligible after lumpectomy if they had a postoperative bra size ≥36 inches or cup size ≥ C.

Table 1
General characteristics of the included randomised controlled trials on the prevention of acute radiation dermatitis using barrier films ($n = 5$), including 663 patients.

authors	year	region (centers)	time frame	randomisation	intervention	control	n[a]	reference
Herst et al.	2014	New Zealand (1)	10/2012−04/2013	intrapatient	Mepitel film	aqueous cream	78	[16]
Schmeel et al. (a)	2018	Germany (1)	09/2016−09/2017	intrapatient	Hydrofilm	5% urea lotion	56	[17]
Møller et al.	2018	Denmark (3)	10/2015−04/2016	intrapatient	Mepitel film	moisturising lotion	79	[25]
Schmeel et al. (b)	2019	Germany (2)	03/2018−06/2019	intrapatient	Hydrofilm	5% urea lotion	74	[18]
Behroozian et al.	2022	Canada (3)	01/2020−05/2022	2:1	Mepitel film	aqueous cream	376	[19]

[a] Patients included in the statistical analyses of the respective trials.

Table 3
Clinician-reported outcome.

authors	assessment tool	blinding	barrier film (%)[a]					control (%)[a]				
			G0	G1	G2	G3	MD	G0	G1	G2	G3	MD
Herst et al.	RTOG, RISRAS	none	56	36	8	0	0	0	28	64	8	26
Schmeel et al. (a)	RTOG	none	48	39	13	0	0	13	46	30	11	11
Møller et al.	RTOG	observer	31	62	7	0	N/A	28	58	13	1	N/A
Schmeel et al. (b)	CTCAE v4.03	none	45	46	10	0	0	15	49	37	0	7
Behroozian et al.	CTCAE v5.0, RISRAS, SSA	none	11	73	13	3	8	2	53	32	14	19
total			**38**°	**51**	**10**°	**1**°	**2**°	**11**	**47**	**35**	**7**	**16**

RTOG = Radiation Therapy Oncology Group; RISRAS = Radiation-Induced Skin Reaction Assessment Scale; CTCAE = Common Terminology Criteria for Adverse Events; SSA = Skin Symptom Assessment; G = grade; MD = moist desquamation; N/A = not available.
° $p < 0.01$.
[a] Radiation dermatitis assessment using RTOG/CTCAE.

3.3. Clinician-reported outcome

Clinician-reported outcome has long been regarded as the gold standard for RD assessment [20,29]. Commonly used scoring tools include the Radiation Therapy Oncology Group (RTOG) and the Common Terminology Criteria for Adverse Events (CTCAE) scales, which evaluate skin toxicity on a scale from 0 (no symptoms) to 5 (death) [30,31]. Furthermore, the Radiation-Induced Skin Reaction Assessment Scale (RISRAS), a validated tool to assess the visible extent of skin reaction, can be used by clinicians to evaluate erythema, dry and moist desquamation, and necrosis, using a 4-point Likert scale (0 = not at all; 1 = a little; 2 = quite a bit; 3 = very much) [32]. Finally, 1 trial also used a Skin Symptom Assessment (SSA) scale to record pruritus, pain/soreness, blistering/peeling, erythema, pigmentation, oedema, and trouble fitting brassieres [20].

All but one of the included trials reported a significant difference in RD severity upon radiation treatment completion, favouring barrier film over standard skin care (Møller et al. found no significant difference in their blinded staff evaluation). A pooled and weighted analysis confirms this: 11% of patients developed grade ≥2 RD with barrier film, compared to 42% without (OR = 0.16; 95% CI 0.08–0.34; $p < 0.001$). The benefit of barrier films remained significant in patients developing grade 3 RD (1% vs. 7%; OR = 0.18; 95% CI 0.08–0.39; $p < 0.001$) and moist desquamation (2% vs. 16%; OR = 0.12; 95% CI 0.03–0.54; $p = 0.006$). Table 3 summarises the clinician-reported outcomes for the individual trials, Fig. 2a–f shows the forest plots of the individual and pooled effect sizes.

3.4. Patient-reported outcome

Each of the included trials also assessed patient-reported outcome. The RISRAS contains an evaluation of patient-experienced pain, itching,

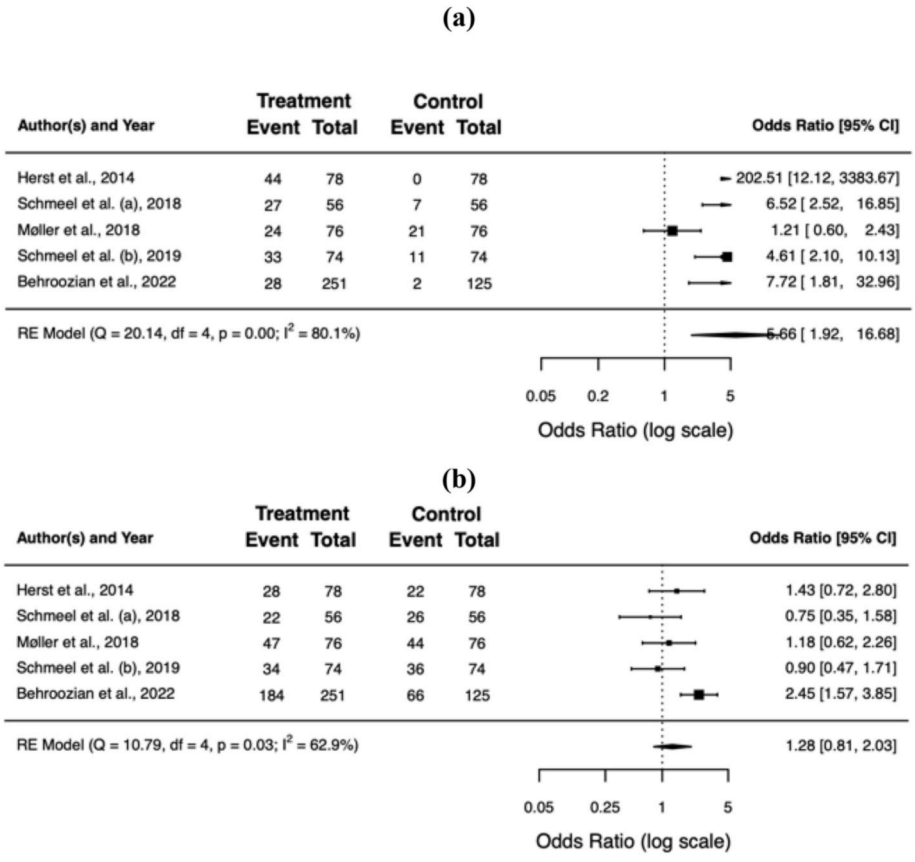


Fig. 2. Forest plots of the individual and pooled effect sizes of developing grade 0 **(a)**, 1 **(b)**, 2 **(c)**, ≥2 **(d)**, or 3 **(e)** RD and moist desquamation **(f)**. Error bars indicate the 95% confidence interval (CI). RD = radiation dermatitis.

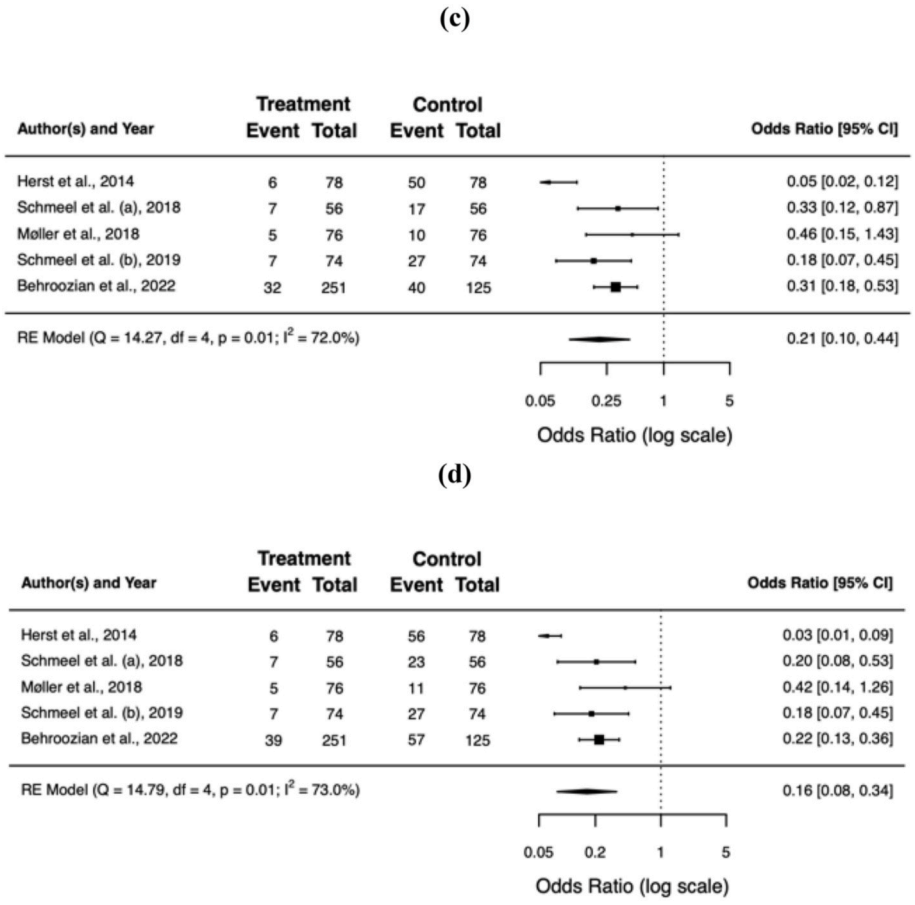


Fig. 2. (*continued*).

burning, and subsequent limitations in daily activities, using a 4-point Likert scale (0 = not at all; 1 = a little; 2 = quite a bit; 3 = very much) [32]. Møller et al. used a patient-reported outcome questionnaire based on the RISRAS. Behroozian et al. also recorded the patient-assessed SSA (same items as clinicians).

Overall, barrier films resulted in a significant reduction of the mean item score for pain (standardised mean difference [SMD] −0.51; 95% CI −0.75, −0.27; $p < 0.001$), itching (SMD −0.52; 95% CI −0.83, −0.20; $p = 0.001$), burning (SMD −0.41; 95% CI −0.73, −0.09; $p = 0.011$), and limitations in daily activities (SMD −0.20; 95% CI −0.20, −0.34; $p = 0.007$). Table 4 summarises the patient-reported outcomes for the individual trials, Fig. 3a–d shows the respective forest plots.

3.5. Objective assessment

Two trials used an objective RD assessment method to corroborate their findings [18,19]: reflectance spectrophotometry is a validated tool to objectively assess skin colour, as it correlates with clinician-reported outcome [33]. Lower L* values describe darker skin (hyperpigmentation), whereas higher a* values are interpreted as an increased erythema intensity. Schmeel et al. performed 5 spectrophotometric readings in each of the breast compartments upon radiation treatment completion.

Overall, the mean a* value was significantly lower in the Hydrofilm compartments (SMD –0.69; 95% CI –1.14, −0.24; $p = 0.003$), which supports the beneficial effect of barrier film on clinician-reported RD severity. Table 5 summarises the outcome of the objective RD assessment, Fig. 4 shows the respective forest plot.

3.6. Topical corticosteroid use

Three trials reported on the use of physician-prescribed topical corticosteroids to alleviate RD-induced symptoms such as pain or itching [18–20]. The pooled rate of patients receiving topical corticosteroids among these trials was 5% for patients or compartments with barrier film vs. 12% for the respective controls (OR = 0.27; 95% CI 0.05−1.52; $p = 0.136$). Table 6 shows the rates for the individual trials, Fig. 5 the respective forest plot.

Topical antibiotic use was documented by 1 trial only [20]. Here, a significant reduction was observed in the Mepitel film group (23% vs. 43%; $p < 0.0001$).

3.7. Tolerability, side effects, and patient experience

All trials reported on the tolerability and side effects of the barrier film used. As such, itching, rash, and the development of blisters under the applied barrier film were documented by each of the included trials, with a mean prevalence of 7%, 5%, and 2%, respectively. Most of these side effects were mild and self-limiting, rarely requiring any additional treatment (other than adjusting, changing, or removing the barrier film). Cutaneous side effects are mainly related to shear stress at the edges of the barrier film due to suboptimal film application. There seems to be a learning curve for healthcare providers regarding barrier film application: Schmeel et al. observed a reduced rate of side effects in their follow-up trial with Hydrofilm when compared to the initial trial performed at the same center [18,19].

Three trials assessed patient-reported experience measures. Overall, there was a high patient acceptance of barrier films. On average, 82% of patients preferred the barrier film over standard of care, while 87%

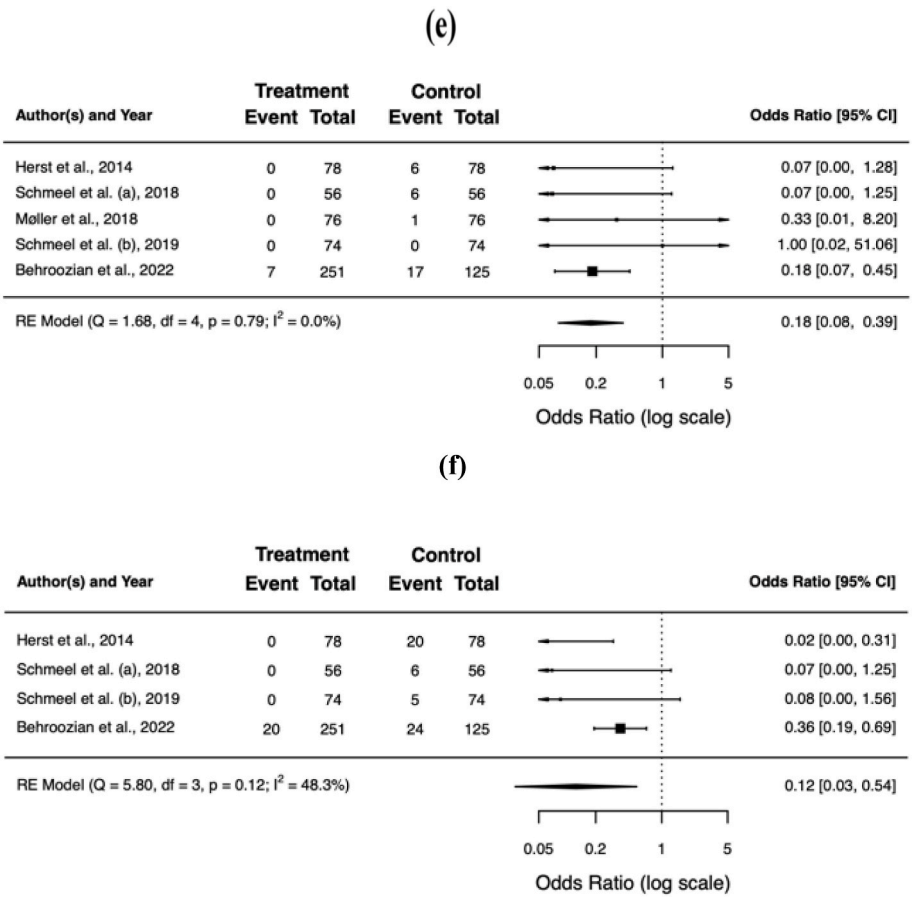


Fig. 2. (*continued*).

Table 4
Patient-reported outcome. Scores in **bold** were statistically significant better for barrier film in the individual trials ($p < 0.05$).

authors	assessment tool	barrier film[b]				control[b]			
		pain	itching	burning	limitation	pain	itching	burning	limitation
Herst et al.	RISRAS	N/A[c]				N/A[c]			
Schmeel et al. (a)	RISRAS	**0.44**	**0.32**	0.44	0.24	0.83	1.00	0.80	0.48
Møller et al.	PROM[a]	**0.59**	**0.70**	**0.45**	0.19	1.08	1.01	0.73	0.25
Schmeel et al. (b)	RISRAS	**0.18**	**0.22**	**0.12**	**0.07**	0.72	0.95	0.74	0.24
Behroozian et al.	RISRAS, SSA	**0.80**	**0.80**	**0.50**	0.30	1.10	1.00	0.70	0.40
total		**0.66**°	**0.67**°	**0.44**°	**0.25**°	**1.02**	**1.00**	**0.72**	**0.37**

RISRAS = Radiation-Induced Skin Reaction Assessment Scale; PROM = patient-reported outcome measures; SSA = Skin Symptom Assessment; N/A = not available.
° $p < 0.05$.
[a] Based on RISRAS.
[b] Mean maximum scores.
[c] Herst et al. only reported the combined (clinician + patient) RISRAS scores.

would recommend its use to other patients to prevent RD. Table 7 shows an overview of the tolerability and patient experience.

3.8. Costs and time

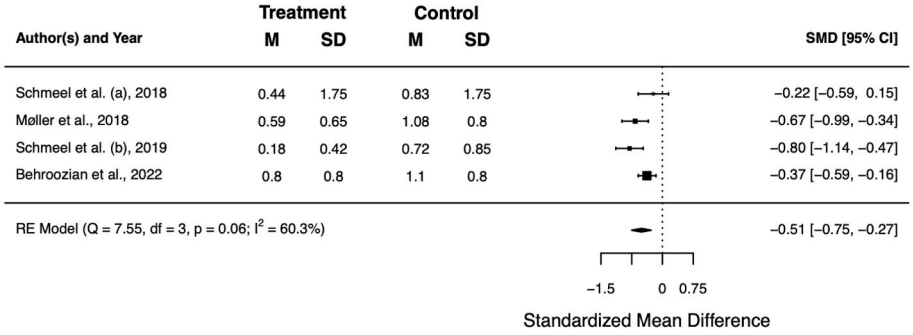
All trials stated either the mean number of barrier films needed per patient over the entire treatment course, or the mean total raw material costs yielded by barrier film use. Behroozian et al. reported the highest number of barrier films per patient, since they included patients after lumpectomy only if they had a postoperative cup size ≥ C. Across all trials, an average of 11 barrier films was needed per patient. Hydrofilm costs were lower in comparison with Mepitel film.

Herst et al. reported an average of 5–10 min to replace a single barrier film, whereas Behroozian et al. calculated a mean time spent adjusting or replacing the barrier film of 51 min for the entire treatment period (55 min for lumpectomy patients and 46 min for mastectomy patients). None of the trials estimated the costs generated by the correct application of the barrier film by a trained healthcare provider. Table 7 shows an overview of the costs generated by barrier films across the individual trials.

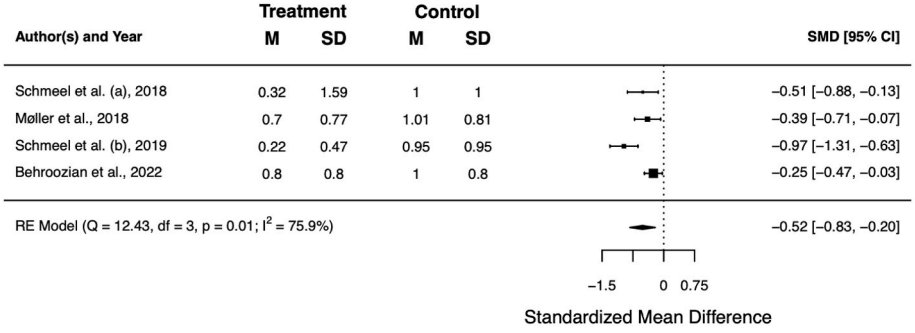
4. Discussion

As the evidence on the use of barrier films for the prevention of acute RD in the context of adjuvant whole-breast or chest wall irradiation emerges, there is a need for a comprehensive appraisal of the available data. We conducted a systematic review of international literature and included 5 high-level RCTs in the quantitative meta-analysis (2 with

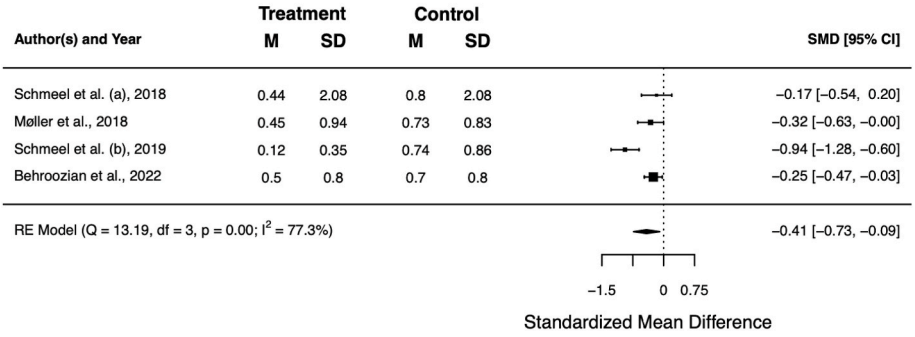
(a)



(b)



(c)



(d)

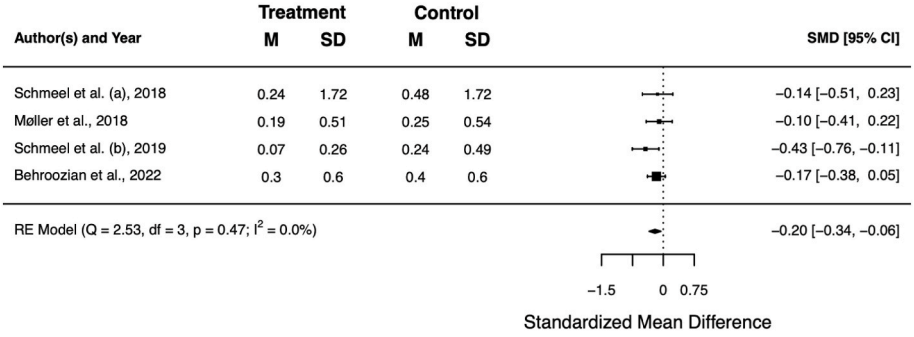


Fig. 3. Forest plots of the mean item score for patient-reported pain **(a)**, itching **(b)**, burning **(c)**, and limitations in daily activities **(d)**. Error bars indicate the 95% confidence interval (CI).

Table 5
Objective assessment of radiation dermatitis using reflectance spectrophotometry. Lower L* values describe darker skin (hyperpigmentation), whereas higher a* values are interpreted as an increased erythema intensity. Scores in **bold** were statistically significant better for barrier film in the individual trials ($p < 0.05$).

authors	barrier film		control	
	L*	a*	L*	a*
Schmeel et al. (a)	N/A	**11.00**	N/A	16.50
Schmeel et al. (b)	**65.31**	**10.83**	59.90	13.16
total	**N/A**	**10.90**°	**N/A**	**14.60**

N/A = not available.
° $p < 0.01$.

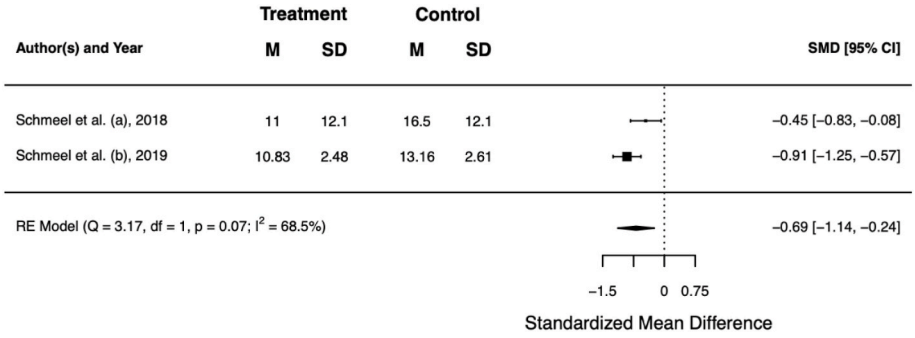


Fig. 4. Forest plot of the mean a* value. Higher values of this objective assessment method are interpreted as an increased erythema intensity. Error bars indicate the 95% confidence interval (CI).

Hydrofilm and 3 with Mepitel film), to assess clinician- and patient-reported benefits of barrier film usage as well as its safety and cost-effectiveness.

Four trials used an intrapatient control receiving standard of care. Apart from the assumed positive impact on patient recruitment (all patients receive the intervention), each patient acts as their own control, which minimises confounding and omits the need for stratification based on factors known to influence the RD risk (e.g. breast size, skin type, use of a bolus, fractionation regimen). Only Behroozian et al. had to stratify patients accordingly, since they recruited a physical control group receiving only standard of care. In the latter trial, there were no significant differences in patient characteristics between the two groups. Lighter skin tones were, however, more common in the group receiving Mepitel film (33% vs. 22%; $p = 0.056$), which is a known protective factor for RD development and could have slightly skewed the results in favour of the intervention [4]. In addition, this trial only included patients at higher risk of developing RD (i.e. patients after lumpectomy with a large postoperative breast size and patients after mastectomy) to maximise the effect size and assess the benefit of Mepitel film in this high-risk subgroup [4,6]. As the number of patients contributed by Behroozian et al. constitutes about 57% of the pooled sample size in this meta-analysis, there might be a slight overestimation of the overall effect size of barrier films.

A further limitation of these RCTs is the overall absence of clinician and/or patient blinding, due to the visible nature of the intervention. Møller et al. were the only trial that implemented a blinded skin assessment (of the bare skin, i.e. after removal of the barrier film) by a trained physician upon radiation treatment completion. Overall, they found no significant difference in RD severity between the medial and lateral breast compartment ($p = 0.100$). Only in the small subgroups of patients undergoing chest wall irradiation ($n = 16$) and conventional fractionation ($n = 20$), there was a significant difference favouring barrier film use ($p = 0.005$ and $p = 0.002$, respectively). This might be related to the intrinsically increased RD risk (both incidence and severity) in these patient populations [4,6]. The primary endpoint of Møller et al., i.e. patient-reported symptoms and experience, was however met.

The lack of blinding might have introduced observational bias in the respective clinician- and patient-reported outcome assessments and is regarded as the main source of bias in these RCTs and the subsequent meta-analysis (Supplement 1). The use of validated non-invasive objective assessment methods (such as reflectance spectrophotometry) might overcome this and should thus be considered in future trials in this context [33,34]. In the case of Schmeel et al., the spectrophotometric readings supported the clinician-reported differences in erythema intensity in favour of barrier film.

Of great added value are the patient-reported outcomes in each of the trials included in this meta-analysis, especially since symptoms caused by RD tend to be significantly underreported by clinicians: Behroozian et al. previously investigated these discrepancies in 777 patients undergoing adjuvant whole-breast or chest wall irradiation and found only low to moderate concordance between patients and clinicians [10]. The authors thus conclude that clinician-reported outcomes alone are insufficient to assess RD (or the subsequent effect of an intervention), as they do not adequately take the impact on a patient's quality of life into account. The RISRAS, which has both a clinician and patient component, is validated and easy to implement in this context [32]. Its use should therefore also be considered in future trials.

Another limitation of the included RCTs is the limited information on treatment techniques such as three-dimensional conformal radiation therapy (3D-CRT), IMRT, or VMAT, and the subsequent absence of stratification based on it. VMAT has been shown to result in significantly lower dermatitis grades when compared to IMRT [4]. Furthermore, the majority (>90%) of patients included in this meta-analysis were of

Table 6
Rate of physician-prescribed topical corticosteroids to alleviate RD-induced symptoms such as pain or itching. Scores in **bold** were statistically significant better for barrier film in the individual trials ($p < 0.05$). Overall, the difference was not significant ($p = 0.136$).

authors	barrier film (%)	control (%)
Schmeel et al. (a)	**0**	11
Schmeel et al. (b)	**0**	7
Behroozian et al.	15	19
total	**5**	**12**

RD = radiation dermatitis.

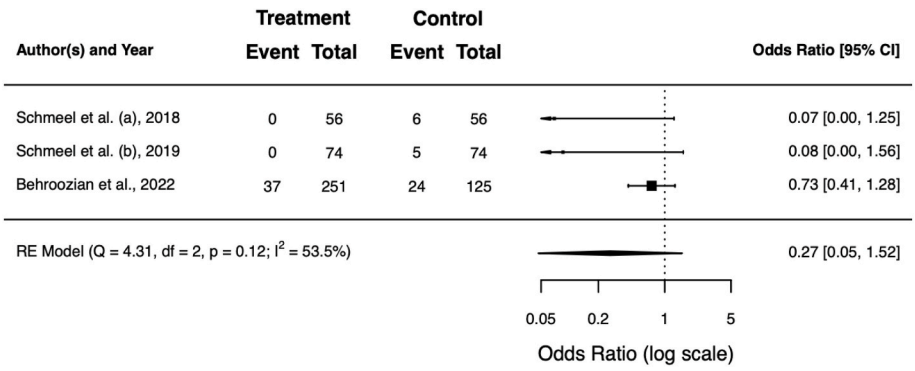


Fig. 5. Forest plot of the topical corticosteroid prescription rate to alleviate RD-induced symptoms. RD = radiation dermatitis.

Caucasian descent and had lighter Fitzpatrick skin types. It is therefore difficult to assess the potential benefits of barrier film in the smaller subgroup of patients with darker skin complexion, a known risk factor for the development of RD [4]. Future trials should aim to assess the respective risk reductions in each of these subgroups.

The overall benefit of barrier films as a prophylactic measure in the context of whole-breast and chest wall irradiation is apparent: improved clinician- and patient-reported outcomes, confirmed by objective measurements, as well as an overall favourable patient experience and cost-benefit ratio make for an excellent tool in the prevention of acute RD, especially in patients with high risk of developing it. The possible side effects of barrier film application such as itching or rash are mild and mostly self-limiting. Care should however be taken to ensure proper tension-free placement on the skin. If multiple barrier films are required to cover the irradiated area (e.g. in patients with large breast size), overlapping of different films should be avoided to prevent increased dose build-up. The negligible bolus effect of a single barrier film implies that they can safely remain on the skin during the entire radiation treatment, which promotes patient comfort.

Challenges with barrier films include difficult application and poor adherence to regions with increased perspiration and friction, such as the axillary and clavicular region in patients undergoing locoregional irradiation – of all areas, these in particular tend to have a predilection for the development of acute RD and moist desquamation [8]. In these patients, more frequent replacement of the barrier film might be necessary, thereby increasing total treatment time and costs. Patients with large breasts also require more frequent adjustments (e.g. due to rolling up of the barrier film at the edges) and replacements of their barrier film for this very reason. Furthermore, care should be taken to prevent distortion of the breast shape, which could otherwise interfere with the radiation treatment setup (Schmeel et al. and Behroozian et al. used weekly cone beam computed tomography to assure correct film application and positioning). Film application and (daily) position control should ideally be carried out by an experienced healthcare provider, which is time-consuming and yields additional costs. The possible interference of barrier films with treatment verification through surface-guided radiotherapy has not been studied so far and should be the aim of future trials.

The use of barrier films as a prophylactic RD measure has also been investigated in the context of head and neck irradiation, but data are sparse. Wooding et al. ($n = 33$) investigated the use of Mepitel film in a randomised intrapatient-controlled trial and found a 27–29% reduction of the combined RISRAS, as well as a 28–37% reduction of the moist desquamation rate (in a New Zealand and a Chinese cohort, respectively) [35]. These results were confirmed by Yan et al. ($n = 39$): with a similar study design, they found respective reductions of 30% and 41% [29]. In the latter trial, 80% of patients preferred Mepitel film over standard of care skin cream. Both trials, however, ran into the same obstacles: the complex anatomy of the head and neck region resulted in poor adherence of the Mepitel film to the skin (especially in patients with stubble or beard), which led to itching and discomfort. For this very reason, the RAREST-01 trial, which sought to further corroborate the use of Mepitel film for RD prevention in head and neck irradiation, was stopped prematurely (46% of patients could not tolerate Mepitel film) [36].

Some systematic reviews on the use of barrier films for RD prevention have been conducted in the past [37–41]. Often, however, there were considerable methodological differences between the included studies, e.g. regarding the nature of the barrier film, irradiated area, skin care control, study design, endpoints, and assessment methods. This lack of standardisation between included studies generally resulted in inconsistent and weak recommendations [12]. A quite comprehensive overview was recently published, on the basis of which Hydrofilm and Mepitel film are recommended for RD prevention by the Multinational Association of Supportive Care in Cancer (MASCC) [41,42]. The latter, however, also investigated the use of barrier creams and film-forming gels, in different oncological contexts, and included trials published before September 2020 only, meaning that the most comprehensive

Table 7
Tolerability, side effects, patient experience, and costs of barrier film use.

authors	side effects with barrier film (%)			experience (%)		costs[b]	
	itching	rash	blisters	preferred	recommend	number of films (*n*)	price (EUR)[c]
Herst et al.	4	0	0	92	N/A	10	71.48
Schmeel et al. (a)	16	8	7	N/A		6	20.00
Møller et al.	9[a]	9[a]	3	76	84	8	N/A
Schmeel et al. (b)	8	5	0	77	89	N/A	20.00
Behroozian et al.	0	1	0	N/A		21	62.73
total	**7**	**5**	**2**	**82**	**87**	**11**	**51.40**

N/A = not available.

[a] Møller et al. only reported the combined prevalence of itching and rash, which was 9%.

[b] Mean per patient to cover the treated breast/chest wall over the entire treatment course. The respective number of films and price for the first 4 trials (where only either the medial or lateral compartment was covered with barrier film) were doubled to estimate the actual number of films and costs for the entire breast/chest wall.

[c] Costs for raw material in the form of barrier film. Costs yielded by application of barrier film by a trained healthcare provider are not included.

barrier film RCT to date was not included [20]. In the current systematic review and meta-analysis, we focussed on RD prevention with two comparable barrier films in the context of whole-breast and chest wall irradiation and only included RCTs with similar skin care controls and quantitatively comparable outcomes. Additionally, we comprehensively evaluated the bolus effect, side effects, patient experience, and cost-benefit ratio, which were not considered in previous reports. Although Hydrofilm and Mepitel film possess some different properties (mainly in terms of the adhesive used), they are applied in the same way and have an identical mechanism of action by creating a mechanical barrier and were, therefore, included in a single meta-analysis. The decision on when to use which barrier film should be based on patient characteristics. Hydrofilm has stronger adhesive potential and could be preferred in complex anatomical regions (e.g. women with larger breasts, skin folds), very active patients, or those who tend to experience more excessive perspiration. Mepitel film, in contrast, is easier to remove and might be preferred in patients with more sensitive or brittle skin. Patient allergies, pricing, clinician preference and experience might also influence the choice of barrier film. Barrier creams and film-forming gels (e.g. StrataXRT® or 3 M Cavilon No Sting Barrier Film®) were explicitly excluded from the analysis as the evidence in the context of breast irradiation is currently limited and these products exhibit substantial differences when compared to regular barrier films, which would have increased the heterogeneity of the included trials and results.

Other promising topical preventive measures in the form of creams or medical devices are currently being investigated in the context of whole-breast and chest wall irradiation [43–45]. Furthermore, advances in patient positioning and radiation treatment planning and delivery (e.g. ultrahypofractionation, partial-breast irradiation) are a valuable approach towards reducing RD burden [46]. The effects of barrier film application should also be explored in these contexts, also focussing on dosimetric aspects of radiation treatment.

5. Conclusion

Barrier films for acute RD prevention improve clinician- and patient-reported outcomes in the context of adjuvant whole-breast or chest wall irradiation, which in turn improves quality of life. Results were consistent across all RCTs included in this meta-analysis, despite certain possible bias due to methodological differences and the general absence of blinding. The use of barrier films should therefore be routinely considered, especially in patients with high risk of developing RD.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.S.D., E. D., and L.C.S. The first draft of the manuscript was written by C.S.D. and reviewed and edited by L.C.S. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics statement

This systematic review of literature and meta-analysis required no ethical approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at. https://doi.org/10.1016/j.breast.2023.07.001.

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3.2 Dejonckheere CS et al. Non-Invasive Physical Plasma for Preventing Radiation Dermatitis in Breast Cancer: Results from an Intrapatient-Randomised Double-Blind Placebo-Controlled Trial. *Clin Transl Radiat Oncol* 2023; 44: 100699

Zielsetzung der Arbeit: Nachdem die Sicherheit und vorläufige Effektivität vom nicht-invasiven physikalischen Plasma (NIPP), eine flüchtige, aus Umgebungsluft erzeugte reaktive Mischung, zur Radiodermatitisprävention im Rahmen von Brustbestrahlungen nachgewiesen wurden, folgte eine prospektive, randomisierte, doppelblinde, placebokontrollierte Studie (Phase 2) in einem größeren Patientenkollektiv.

Methoden und Ergebnisse: Die mediale bzw. laterale Brusthälfte von 64 Patienten wurde randomisiert, um im Zeitraum der Bestrahlung entweder eine tägliche NIPP- (120 Sekunden) oder *sham* Behandlung (d. h. Placebobehandlung mit einem äquivalenten, aber nicht-funktionellem Gerät) zu erhalten. Die gesamte Brust wurde täglich mit Harnstofflotion behandelt. Verblindete CROs und PROs ergaben zwar keine signifikanten Unterschiede zwischen den Brusthälften, aber ein Vergleich mit einem sehr ähnlichen Kontrollkollektiv im Hinblick auf die Radiodermatitisprävalenz aus unserer Klinik (Schmeel et al., 2020) ergab eine signifikante Verbesserung der CROs, PROs und auch der objektiven Radiodermatitisgraduierung mittels Spektralphotometrie: OR = 0,28 (p = 0,014) für Grad ≥ 2 Radiodermatitis nach Abschluss der Bestrahlung zusammen mit weniger Hyperpigmentierung (p < 0,001), Ödem (p = 0,020), trockener (p < 0,001) und feuchter Desquamation (p = 0,017) sowie Schmerzen, Juckreiz und Brennen (jeweils p < 0,001). Die Verträglichkeit des NIPPs war weiterhin ausgezeichnet, denn es wurden keine Nebenwirkungen beobachtet.

Schlussfolgerungen: Obwohl in diesem homogenen Patientenkollektiv keine Unterschiede zwischen den Brusthälften observiert wurden, waren die Gesamtprävalenz und der Schweregrad der akuten Radiodermatitis im Vergleich mit einer prospektiv überwachten Standardhautpflegekohorte deutlich geringer, mit einer signifikanten Verbesserung aller Studienzielgrößen. Diese Daten weisen auf den potenziellen Nutzen des nebenwirkungsarmen NIPPs zur Radiodermatitisprophylaxe hin. Eine randomisierte Studie mit einer physischen Kontrollgruppe ist jedoch gerechtfertigt, um diese vielversprechenden Ergebnisse zu bestätigen.

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Original Research Article

Non-invasive physical plasma for preventing radiation dermatitis in breast cancer: Results from an intrapatient-randomised double-blind placebo-controlled trial

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ABSTRACT

Background and Purpose: To investigate the effect of topical non-invasive physical plasma (NIPP), a volatile mix generated out of ambient air, on prevention of acute radiation dermatitis (RD) during and after whole-breast irradiation (WBI).

Materials and Methods: Lateral and medial breast halves were randomised within each patient to receive either 120 s of NIPP or sham treatment daily during WBI. Standard skin care with urea lotion was applied to the whole breast. Blinded acute skin toxicity was assessed weekly for each breast half separately and included clinician- (CTCAE) and patient-reported (modified RISRAS), and objective (spectrophotometry) assessments. As an additional external control, a comparable standard of care (SoC) patient collective from a previous prospective trial was used.

Results: Sixty-four patients were included. There were no significant differences between breast halves. Post-hoc comparison with a similar SoC control collective revealed OR = 0.28 (95% CI 0.11–0.76; $p = 0.014$) for grade ≥ 2 RD upon WBI completion, along with less hyperpigmentation ($p < 0.001$), oedema ($p = 0.020$), dry ($p < 0.001$) and moist desquamation ($p = 0.017$), pain, itching, and burning ($p < 0.001$ for each). Tolerability of NIPP was excellent and side effects were not observed.

Conclusion: Even though there were no differences between intrapatient-randomised breast halves, the overall incidence and severity of acute radiation-induced skin toxicity were considerably lower when compared to a prospectively collected SoC cohort. Our data suggest the potential benefit of NIPP in RD prevention. A randomised trial with a physical control group is warranted to confirm these promising results (DRKS00026225).

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Introduction

Early breast cancer, one of the most common cancer diagnoses worldwide, involves surgical therapy followed by adjuvant whole-breast irradiation (WBI) in about 70% of cases [1,2]. The most frequent acute side effect of WBI is radiation dermatitis (RD), characterised by erythema, pruritus, pain, and dry or moist desquamation, which occur in up to 85% of patients [3,4]. Severe cases requiring radiation treatment interruption have become rare following advancements in radiation treatment technique (e.g. intensity-modulated radiation therapy [IMRT]) and the exploration of new fractionation regimens (e.g. hypofractionation); however, even mild symptoms are known to impact quality of life and self-image [5–7]. Continuous research efforts are being made, yet potent preventative and therapeutic options are limited, resulting in substantial variation in RD management amongst practitioners and institutions [8–10]. Due to insufficient and sometimes even contradictory evidence, a recommendation can currently only be made for a handful of interventions [11].

Non-invasive physical plasma (NIPP) is an emerging treatment modality for various skin conditions, such as psoriasis, eczema, diabetic ulcers, and different types of dermatitis [12,13]. Physical plasma, the fourth state of matter, is characterised by free electrons and derived from the other states of matter (gas, liquid, solid) by altering temperature or pressure [14]. Contrary to thermal plasma, NIPP is created using a high-frequency alternating field under atmospheric pressure, thereby only reaching body temperatures, rendering it safe for clinical use. Dielectric barrier discharges (DBD) are a type of NIPP, generated out of ambient air, without the need for a carrier gas [15]. The reactive mix of electrons, ions, excited atoms, reactive oxygen species (ROS), and ultraviolet radiation has been shown to positively affect tissue healing in a dose-dependent manner [16]. NIPP treatment is well-tolerated and multiple trials have confirmed its safety [17–19].

ROS play a crucial role in tissue damage mediated by ionising radiation, yet are also significantly involved in NIPP-associated tissue healing and regeneration [20]. A first-in-human benchmarking trial previously reported safety and feasibility of a topical DBD-generated NIPP-based prevention of acute RD [21]. In the current prospective, intrapatient-randomised, double-blind, placebo-controlled trial, we evaluate the effect of NIPP on the incidence and severity of RD and associated symptoms in breast cancer patients undergoing WBI.

Materials and methods

Participants

From March 2022 through September 2023, we conducted a monocentric phase 2 study enrolling breast cancer patients that were scheduled for adjuvant WBI. Inclusion criteria were age $\geq$ 18 years, breast-conserving surgery, and a moderately hypofractionated radiation regimen. A normofractionated sequential boost to the tumour bed was allowed. To avoid bias in RD grading, the following exclusion criteria were defined: synchronous metastatic disease, mastectomy, reconstruction with breast implant, alternative fractionation regimens, history of ipsilateral breast irradiation, any pre-existing dermatological disorder, active dermatitis, current treatment with topical or oral corticosteroids, and patient refusal to participate. Written informed consent was obtained from all included patients. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of the University Bonn in September 2021 (210/21).

Radiation protocol

All patients received 40.05 Gy in 15 fractions of 2.67 Gy each. Patients $\leq$ 50 years or those with risk factors ($\geq$pT2, HER2/neu positive, triple-negative, or poor cell differentiation) regardless of age received a sequential boost to the tumour bed of 16 Gy in 8 fractions of 2 Gy. Target volume delineation followed international standards [22]. The treatment technique used was 6 MV sliding window IMRT or hybrid 6 and 10 MV volumetric modulated (partial) arc therapy and the International Commission on Radiation Units and Measurements recommendations for dose limits of 95–107% were followed. All patients were treated on a TrueBeam STx (Varian Medical Systems, Palo Alto, CA, USA) linear accelerator in a supine position on a breast board. Left-sided WBI was performed in deep inspiration breath-hold (DIBH) for compliant patients. Post-hoc assessment of skin dose to lateral and medial breast halves is described in *Supplementary Fig. 1*.

Intrapatient control and standard skin care

The irradiated breast of each patient was evenly divided into a lateral and medial half. Using computer-generated random permuted blocks with sequentially numbered containers, one half was randomly assigned to receive NIPP treatment, while the other half served as an intrapatient control and received placebo. This design omits the need for stratification based on established risk factors influencing RD incidence and severity, such as breast size or Fitzpatrick skin type [23]. In those requiring a sequential boost, another acknowledged risk factor, breast halves were stratified accordingly (i.e. based on the primary breast half in which the boost area was located). Patients were blinded to their breast half assignment.

Institutional standard skin care with urea-based lotion (UreaRepair PLUS 5%, Eucerin, Beiersdorf, Hamburg, Germany) was applied to the whole breast. All patients were given oral and written information to apply it twice daily from the first day of treatment onwards and were encouraged not to use any complementary topical treatments. Compliance was checked on the scheduled patient visits. At the discretion of the principal investigator, those presenting with grade $\geq$ 2 RD, moist desquamation, or intense pain could be prescribed topical corticosteroids until symptoms resolved.

NIPP protocol

To generate and apply the NIPP, a wireless topical physical plasma device (plasma care, terraplasma medical, Garching, Germany) was employed. The device was pressed loosely on the patient's breast skin with a separate 4 $\times$ 4 cm spacer for each patient and each visit, to achieve an optimal and reproducible distance to the skin (Fig. 1). Based on the initial feasibility trial, the treatment time was set at 120 s, balancing the dose-dependent effect of NIPP with treatment time and using the device's preset program to ensure a constant dose of NIPP. This process was repeated until the entire assigned breast half had received treatment [24]. This process was repeated for the other (control) breast half, using an identical yet non-functional sham device. NIPP was applied daily following every radiation fraction by a trained radiation oncology nurse.

Patient evaluation

a *Clinician-reported outcome*

Patients were evaluated during the standard weekly on-treatment visits and any additional visits requested by the participants were also documented. RD was assessed for each breast half separately, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) [25]. Furthermore, hyperpigmentation, breast oedema, and desquamation (dry or moist) were assessed and recorded (yes–no) for each breast half separately. Upon radiation treatment completion, as well as two and six weeks later, acute toxicity was reassessed. The experienced breast radiation oncologists who performed the clinical assessments were blinded to the initial breast half assignment.

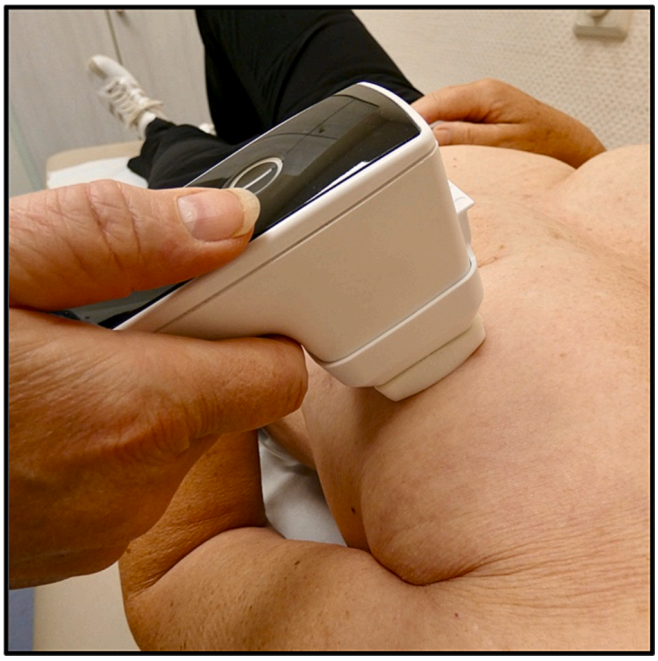

Fig. 1. Generation and application of NIPP on the breast skin. The device is pressed loosely on the skin with a separate 4 × 4 cm spacer for each patient and each visit. NIPP = non-invasive physical plasma. Image from Dejonckheere et al., with permission [21].

b *Patient-reported outcome*

At the end of the radiation course and during the two follow-up visits, the patient-assessed modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS) was recorded [26]. All patients reported their maximum breast-related experience of pain, itching, burning, and limitations in daily activities, for each breast half separately. All items were scored on a 4-point Likert scale: 0 = not at all; 1 = a little; 2 = quite a bit; 3 = very much. During the last follow-up visit, patient-reported experiences were captured with four yes–no statements (*Supplementary Table 1*).

c *Objective assessment*

At baseline, during every visit, on the last day of radiation treatment, as well as during both follow-up visits, five erythema readings were performed with a reflectance spectrophotometer (CR-10 Plus, Konica Minolta, Tokyo, Japan), across both the NIPP-treated and control breast half (*Supplementary Fig. 2*). This compact device has previously been validated to objectively assess acute and chronic RD [23,27–29]. Its automatically performed measurements are based on the Commission Internationale de l'Éclairage system of tristimulus values and describe a measured colour in three coordinates using the L*a*b* system: lower L* values describe darker skin (hyperpigmentation) and higher a* values indicate redness (RD), whereas b* values describe the position on a scale from blue to yellow (of secondary importance in the acute setting).

Trial endpoints

The primary endpoint was the difference in clinician-assessed RD between NIPP and placebo breast halves upon treatment completion. Secondary endpoints were differences in grade ≥ 2 RD, hyperpigmentation, oedema, dry and moist desquamation, patient-reported outcomes, and spectrophotometric values. The evaluation of said endpoints compared to an identical standard of care (SoC) control collective from a previously published prospective trial on acute toxicity was added as a secondary endpoint upon completion of the study [4]. The latter trial had very similar inclusion and exclusion criteria, identical fractionation and radiation treatment technique, and outcome assessment.

Statistical analysis and visualisation of results

As prior studies on this topic are lacking, we estimated a meaningful reduction in clinician-assessed RD severity upon radiation treatment completion of 33%. Assuming at least 80% statistical power and a type I error rate of 5% for the two-tailed *t*-test, a minimum sample size of $n = 63$ was needed for this intrapatient-randomised trial design. Mean, median, standard deviation (SD), and range were calculated for all applicable clinical data. For the pairwise comparison of categorical variables (clinician- and patient-assessed outcomes), the Mann-Whitney-*U* test was used and odds ratios (OR) with 95% confidence intervals (CI) were calculated. Objective spectrophotometric data were compared with Welch's *t*-test, after ensuring homoscedasticity with Levene's test. The statistical significance level was defined as $p < 0.05$. Microsoft Excel (version 16; Microsoft, Redmond, WA, USA), SPSS Statistics (version 27; IBM, Armonk, NY, USA), and GraphPad Prism (version 10; GraphPad Software, San Diego, CA, USA) were used to perform the analyses. GraphPad Prism and Adobe Illustrator 2023 (Adobe Inc., Mountain View, CA, USA) were used to generate graphs. The graphical abstract was created with BioRender.com.

Results

Patient and treatment characteristics

A Consolidated Standards of Reporting Trials (CONSORT) flowchart of patient selection and inclusion is shown in Fig. 2. Sixty-four patients completed the trial per protocol, with a median age (range) of 58 (29–83) years. All patients were female, 97% Caucasian, and Fitzpatrick II was the most common skin type (70%). A sequential boost to the tumour bed was delivered in 59% and 9% received topical corticosteroids to alleviate RD-induced symptoms. The generalised equivalent uniform dose (gEUD) to NIPP and placebo breast skin was similar ($p = 0.734$), implying a homogeneous dose distribution with a subsequent similar probability to develop acute RD.

When compared to the SoC collective, baseline characteristics were very similar. In the SoC collective, fewer patients received a sequential boost (44% versus 59%; $p = 0.081$), the mean breast size was significantly smaller ($p = 0.007$), and fewer patients received neoadjuvant systemic therapy ($p < 0.001$), implying that these patients were at an overall lower risk of developing RD. Patient and radiation treatment characteristics for both collectives are presented in Table 1.

Clinician-reported outcome

Mean ± SD graded severity of RD upon radiation treatment completion was 0.79 ± 0.60 for NIPP halves versus 0.83 ± 0.52 for placebo halves ($p = 0.644$). There were no statistically significant differences between NIPP and placebo halves in terms of physician-assessed RD, hyperpigmentation, oedema, and dry and moist desquamation over the course of treatment and follow-up.

The mean ± SD RD severity upon radiation treatment completion was 1.06 ± 0.71 in the SoC control collective ($p = 0.004$; OR = 0.28 [95% CI 0.11–0.76; $p = 0.014$] for grade ≥ 2 RD). After two weeks, this had dropped to 0.27 ± 0.55 in NIPP patients, however, remained at 1.05 ± 0.70 in SoC controls ($p < 0.001$). At six weeks, there was no significant difference (0.04 ± 0.19 versus 0.10 ± 0.30; $p = 0.156$). Upon treatment completion, there was an overall lower maximum toxicity ($p < 0.001$) with less hyperpigmentation ($p < 0.001$), oedema ($p = 0.020$), and dry and moist desquamation ($p < 0.001$ and $p = 0.017$, respectively) in patients receiving NIPP. Results are summarised in Fig. 3a and Fig. 4*a–c*.

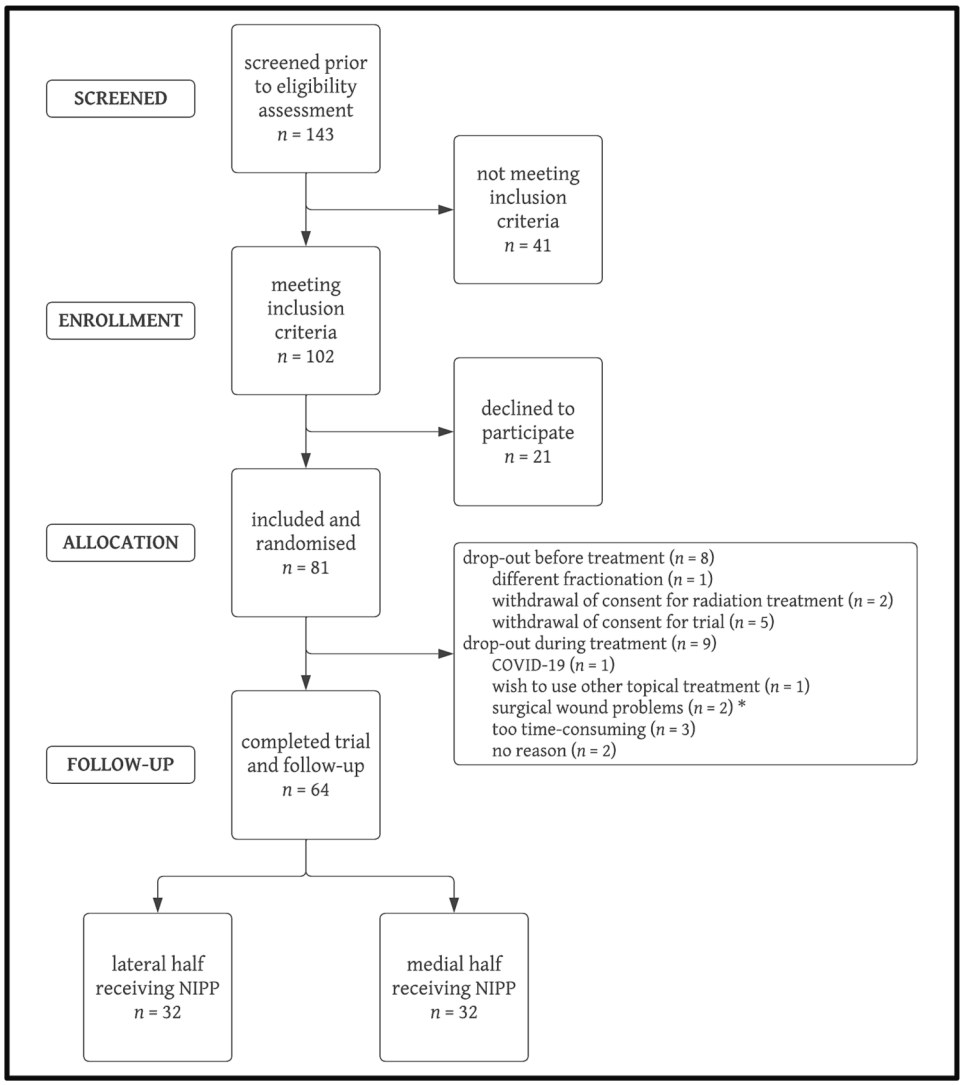

Fig. 2. Flowchart of patient selection and inclusion. NIPP = non-invasive physical plasma. * not related to NIPP use.

Patient-reported outcome

There were no statistically significant differences between NIPP and placebo breast halves in terms of the maximum patient-assessed RD symptoms.

In comparison with the SoC control collective, however, NIPP patients reported significantly less pain, itching, and burning ($p < 0.001$). There was no difference in limitations in daily activities ($p = 0.130$). Results are summarised in Fig. 3b and Fig. 4d.

Objective assessment

Fig. 5a–b shows the evolution of L* and a* values of the irradiated skin over the course of treatment and follow-up. There were no statistically significant differences between NIPP and placebo halves.

On comparison with the SoC control collective, the differences in clinician-reported RD assessment were confirmed: lower a* values for NIPP patients upon treatment completion and at two weeks ($p < 0.001$), indicating less erythema.

Safety and satisfaction

In accordance with the initial feasibility trial, the tolerability of NIPP was excellent and no adverse events or discontinuations due to side effects of NIPP or its combination with WBI were recorded. This was reflected by the positive patient-reported experiences, as shown in *Supplementary Table 1*.

Discussion

Progress in the development of new RD prophylactic and therapeutic agents has been slow, leading to a considerable physical and psychological impact on numerous patients. Topical corticosteroids (mometasone, betamethasone) are effective in reducing RD-related symptoms, however, their widespread and prolonged use remains limited due to the associated side effect profile [30–32]. Care should also be taken if moist desquamation is present, as topical corticosteroids might delay wound healing or promote infection.

Despite some experimental products showing promise in the context of RD prevention or management, few of them proved consistently useful in sufficiently powered randomised trials [11,33]. Furthermore, such trials often recruit heterogeneous patient collectives with varying dose-fractionation regimens and treatment sites, and most lack a uniform control group or adequate placebo control. Another issue is the subjectivity of physician-assessed RD gradings such as CTCAE, with considerable inter- and intra-observer variability, accompanied by significant discrepancies with patient-reported outcomes [34,35]. To accurately investigate prevention and treatment strategies, there is a

Table 1
Overview of patient and radiation treatment characteristics (n = 64) and comparison of baseline characteristics between the current trial (NIPP + SoC) and a similar control trial (identical SoC) [4]. NIPP = non-invasive physical plasma; SoC = standard of care; BMI = body mass index; pT = pathological stage of the primary tumour; Tis = carcinoma in situ; pN = pathological stage of the regional lymph nodes; PTV = planning target volume; SD = standard deviation; gEUD = generalised equivalent uniform dose.

	Current trial	Control trial [a]	*p* [b]
n	64	70	
Median age (range) in years	58 (29–83)	59 (37–84)	0.592
	***n* (%)**		
Female	64 (100)	70 (100)	
Caucasian	62 (97)	70 (100)	0.136
Fitzpatrick skin type			
I	12 (19)		
II	45 (70)		
III	7 (11)		
Median BMI (range) in kg/m^2	25 (18–35)	27 (18–40)	**< 0.001**
Diabetes mellitus	4 (6)	2 (3)	0.343
Active smoking	3 (5)	0 (0)	0.067
Neoadjuvant chemo- or immunotherapy	24 (38)	0 (0)	**< 0.001**
pT-stage			
Tis	20 (31)	6 (9)	
T1	29 (45)	48 (69)	
T2	14 (22)	16 (23)	
T3	1 (2)	0 (0)	**0.004**
pN-stage			
N0	55 (86)		
N1	8 (13)		
N2	1 (2)		
Sequential boost to the tumour bed	38 (59)	31 (44)	0.081
Boost compartment = NIPP half	19 (50)		
Boost compartment = placebo half	19 (50)		
Median PTV Breast (range) in mL	892 (303–2154)	720 (134–1771)	**0.007**
Median PTV Boost (range) in mL	110 (46–291)	192 (50–413)	**< 0.001**
Mean ± SD gEUD in %			0.734[c]
NIPP halves	74.1 ± 4.2		
Placebo halves	74.4 ± 4.9		

[a] Patients in the moderately hypofractionated trial arm.
[b] Difference assessed using Fisher's exact test, Pearson's χ^2, or Student's unpaired *t*-test, as appropriate.
[c] Comparison between NIPP and placebo halves in the current trial.

need for objective RD assessment methods and inclusion of the patient's perspective into clinical trial protocols.

In this prospective, double-blind, placebo-controlled trial, we evaluated the effect of topical NIPP on the incidence and severity of acute RD in a homogeneous patient collective undergoing WBI for breast cancer, using clinician- and patient-reported as well as objective assessment methods.

NIPP shows promising results in the context of several skin conditions and positively affects tissue healing without side effects. In vitro and in vivo studies have revealed that its application to human skin cells does not result in any impairment of cell physiology, cytology, nor DNA integrity, making it safe for clinical use [19,36–39]. A preclinical placebo-controlled trial in irradiated mice showed delayed onset and reduced severity of RD and the only case report published so far showed successful treatment of acute RD following head and neck irradiation [40,41].

When comparing NIPP and placebo breast halves, no significant differences in either clinician- or patient-reported outcomes nor objective assessments were observed. However, the overall incidence and severity of acute skin toxicity were low. A comparison with a very similar patient collective in terms of radiation dose and treatment technique as well as identical SoC supports this: even though patients in the NIPP cohort were at an overall higher risk of developing RD (more sequential boosts and larger breast volumes; both risk factors for RD development), they still developed less frequent and milder acute toxicity [23,42]. An additional comparison with international landmark trials on acute radiation-induced toxicity following hypofractionated WBI with modern treatment techniques further supports the apparent benefit of NIPP in this context (*Supplementary Table 2*). Also in accordance with previous reports on the use of NIPP in comparable clinical settings, side effects were not reported and patient tolerability and acceptance were excellent [18,19]. Treatment time and cost are discussed in more detail in the initial feasibility trial [21].

We reason that the trial design with an intrapatient control breast half may be responsible for the discrepancy between the placebo and SoC controls. Although NIPP was applied to one breast half only, diffusion to the other (placebo) breast half cannot be ruled out, which is the main limitation of this trial. Said design proved useful in previous trials investigating topical therapies for RD prevention [43–45]: each patient acting as their own control promotes patient accrual and omits the need for stratification based on other risk factors for RD development such as breast volume or skin type, limiting confounding in RD grading [23]. To confirm this hypothesis and to accurately investigate the effect of NIPP on RD development (or radiation injury in general), an interpatient-randomised design with a physical control group receiving SoC and sham treatment will be needed [46].

The pathophysiology of RD is complex and the signalling pathways and mechanisms through which NIPP positively affects tissue healing are not yet fully understood. We reason that its primary mode of action in the context of RD mainly involves a reduction of the bacterial load on the irradiated breast skin. Ionising radiation disrupts the skin barrier function and microorganisms or microbial antigens may subsequently trigger an inflammatory response, enhancing the clinical appearance of RD through an increased immune reaction [47]. In this context, patients with *Staphylococcus aureus* colonisation before initiation of radiotherapy are more prone to severe RD development [48]. A recent study supporting these findings investigated the use of chlorhexidine body wash once daily in patients undergoing WBI and observed a significant reduction of RD incidence and severity when compared to standard skin care [49]. NIPP also achieves bacterial decolonisation, both on working surfaces and humans, among other by promoting macrophage ability to eliminate internalised *Staphylococcus* [18,50–52]. Its beneficial effects on diabetic foot ulcers is, among other factors, attributed to the observed immediate reduction of the bacterial load on the damaged skin [13,19,53].

A proposed additional mechanism is that NIPP promotes proliferation and migration of keratinocytes, fibroblasts, and endothelial cells, which facilitates tissue recovery [54]. Accelerated endothelial tube formation improves vascular shear stress which contributes to angiogenesis, in turn enhancing capillary blood flow and increasing local

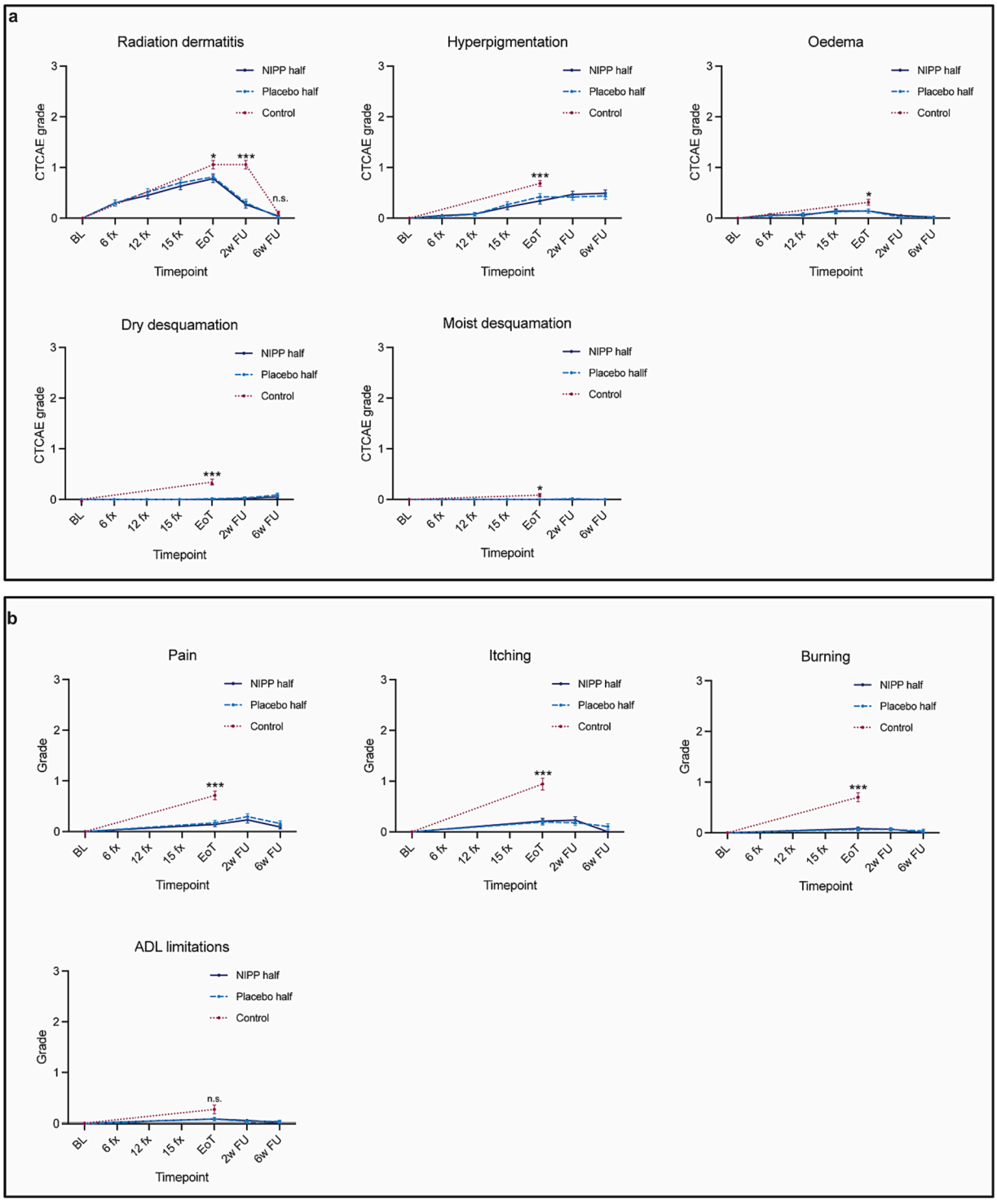

Fig. 3. a–b. Blinded clinician- and patient-reported outcomes over the course of treatment and follow-up. (a) Assessment of clinician-reported acute skin toxicity in terms of radiation dermatitis, hyperpigmentation, breast oedema, dry and moist desquamation, for NIPP (dark blue; full) and placebo (light blue; dashed) breast halves separately, mean grading according to CTCAE (version 5.0) [25]. (b) As in (a), but for patient-reported outcomes in terms of pain, itching, burning, and limitations in daily activities, according to the modified Radiation-Induced Skin Reaction Assessment Scale [25]. The dotted line (purple) represents a comparable standard of care control collective, not receiving NIPP. Error bars represent standard error of the mean. * $p < 0.05$; *** $p < 0.001$; n.s. = not significant. NIPP = non-invasive physical plasma; CTCAE = Common Terminology Criteria for Adverse Events; BL = baseline; fx = fractions; EoT = end of treatment; w = weeks; FU = follow-up. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

oxygen saturation and nutrient supply [55,56]. The expression of wound healing gene signatures alongside significant changes to the human skin barrier lipid stoichiometry are two additional modes of action, which are, however, still poorly understood [57,58].

The main limitation of the current trial is its intrapatient-randomised design, which cannot rule out diffusion of NIPP to the other (placebo) breast half. In order to unequivocally assess the benefit of NIPP in the context of adjuvant WBI, an interpatient-randomised design with a

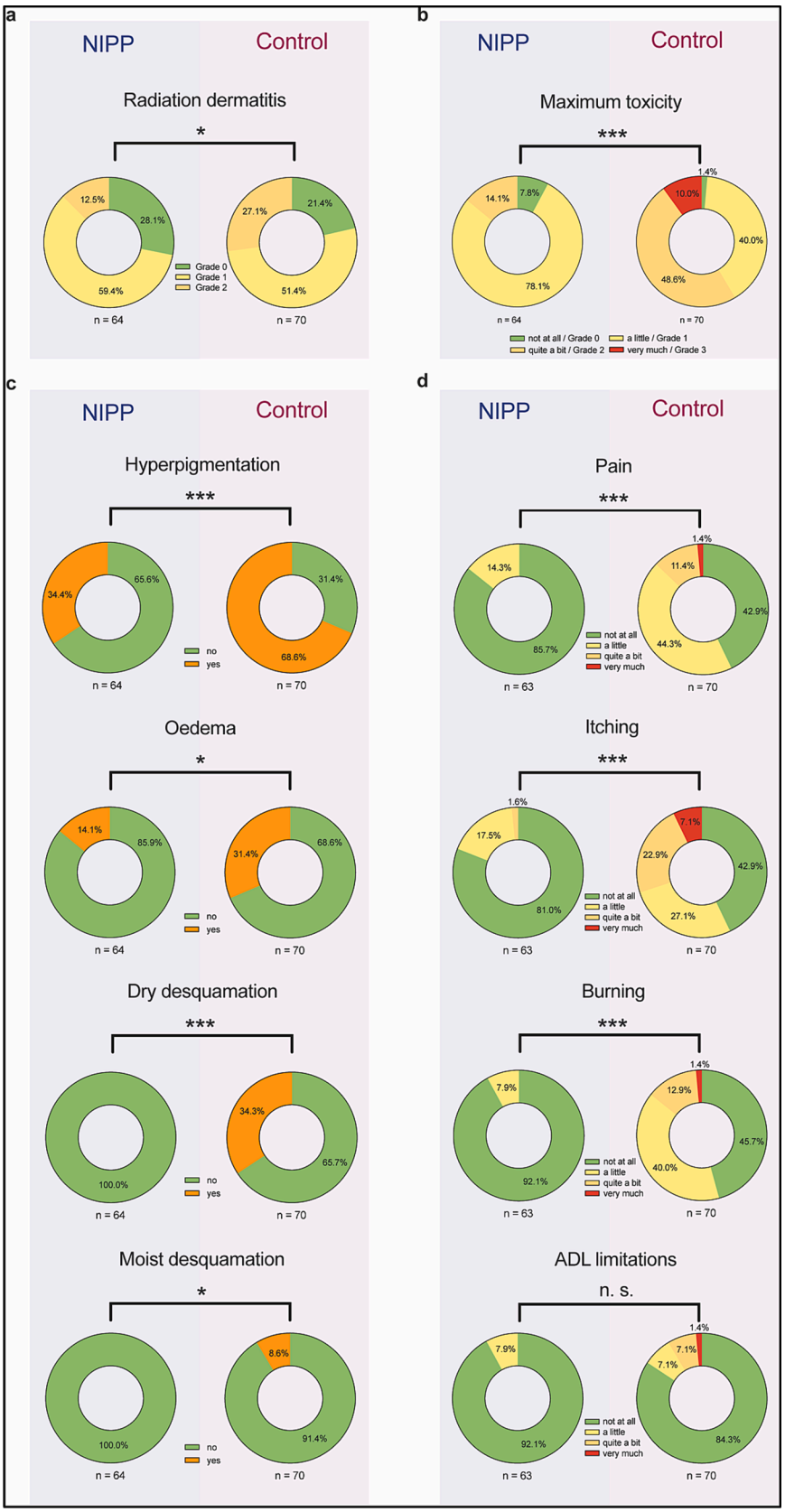

Fig. 4. a–d. Maximum clinician- and patient-reported toxicity. Frequency of radiation dermatitis CTCAE gradings (a), overall maximum observed toxicity grade (b), clinician-reported (c) and patient-reported (d) outcomes, with NIPP (blue; left) and in a comparable SoC control collective (purple; right). Mann-Whitney-*U* test: * $p < 0.05$; *** $p < 0.001$; n.s. = not significant. CTCAE = Common Terminology Criteria for Adverse Events; NIPP = non-invasive physical plasma; SoC = standard of care; ADL = activities of daily living. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

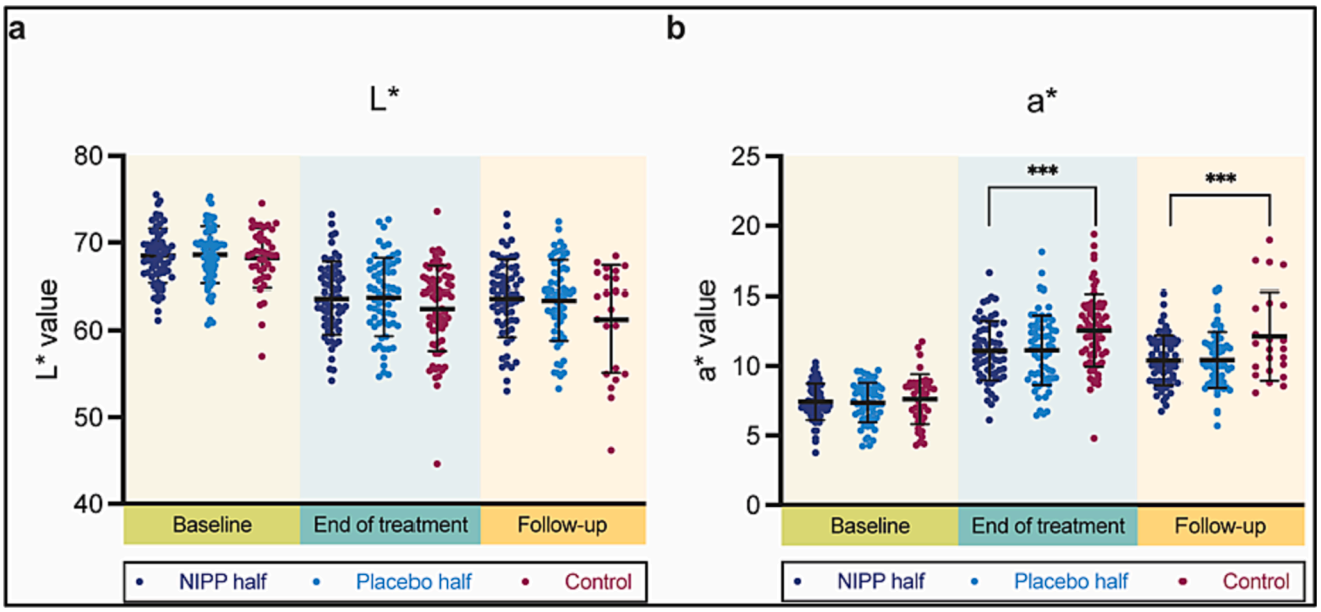

Fig. 5. a–b. Objective spectrophotometric readings (n = 4,600), for NIPP (dark blue) and placebo (light blue) breast halves separately. The purple dots represent a comparable SoC collective, not receiving NIPP. Lower L* values (a) indicate darker skin (hyperpigmentation) and higher a* values (b) imply erythema (radiation dermatitis). Black line and error bars represent mean ± standard deviation. Mann-Whitney-*U* test: *** $p < 0.001$. SoC = standard of care; NIPP = non-invasive physical plasma. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

physical control group receiving placebo will be needed. Furthermore, an additional NIPP dose-escalation should be investigated, as it might yield an even better outcome. Longer treatment times generate more ozone, enabling bacterial decolonisation and increasing the secretion of anti-inflammatory and regenerative signalling molecules, which might improve outcome even further [13,49,59]. The subsequent additional treatment time and costs generated with the device used in this trial might delineate a subset of high-risk patients (i.e. those with risk factors for RD development), in which NIPP is most cost-effective. Lastly, the long-term effects of daily NIPP application will have to be investigated in future trials.

Conclusion

Even though there were no significant differences between intrapatient-randomised breast halves receiving NIPP versus placebo, the overall incidence and severity of acute radiation-induced skin toxicity was considerably lower in comparison with an independent, prospectively-recruited control collective receiving identical SoC. Diffusion of the volatile NIPP towards the placebo half is the most likely explanation for this discrepancy. We provide first evidence supporting the benefits of NIPP as an add-on RD prevention method in the context of adjuvant WBI for breast cancer, while confirming the excellent safety and tolerability from the feasibility trial. A randomised controlled trial with a physical control group is needed to further investigate this promising approach for RD prevention.

Author Contributions

Cas Stefaan Dejonckheere: Investigation, Methodology, Data curation, Formal analysis, writing – original draft. **Julian Philipp Layer:** Formal analysis, Visualization, Writing – review and editing. **Younèss Nour:** Data curation. **Katharina Layer:** Data curation. **Andrea Glasmacher:** Data curation. **Shari Wiegreffe:** Data curation. **Arne Fuhrmann:** Data curation. **Lara Caglayan:** Data curation. **Franziska Grau:** Data curation. **Gustavo Renato Sarria:** Writing – review and editing. **Davide Scafa:** Data curation. **David Koch:** Data curation. **Martina Heimann:** Data curation. **Christina Leitzen:** Data curation. **Mümtaz Ali Köksal:** Data curation. **Fred Röhner:** Data curation. **Thomas Müdder:** Data curation. **Egon Dejonckheere:** Data curation. **Frederic Carsten Schmeel:** Data curation. **Teresa Anzböck:** Data curation. **Kira Lindner:** Data curation. **Anne Bachmann:** Data curation. **Alina Abramian:** Data curation. **Christina Kaiser:** Data curation. **Andree Faridi:** Data curation. **Alexander Mustea:** Data curation. **Frank Anton Giordano:** Data curation. **Matthias Bernhard Stope:** Writing – review and editing. **Leonard Christopher Schmeel:** Conceptualization, Project administration, Investigation, Methodology, Data curation, Writing – review and editing.

Patient Consent Statement

Written informed consent was obtained from all included patients. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of the University Bonn in September 2021 (210/21).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100699.

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3.3 Dejonckheere CS et al. Objective, Clinician- and Patient-Reported Evaluation of Late Toxicity following Adjuvant Radiation for Early Breast Cancer: Long-Term Follow-Up Results of a Randomised Series. *J Clin Med* 2023; 12: 4212

Zielsetzung der Arbeit: Nur wenige Studien haben sich ausführlich mit etwaiger Spättoxizität nach Ganzbrustbestrahlungen befasst. Ziel dieser Studie war es daher, Prävalenz und Schweregrad der strahleninduzierten Spätfolgen zu beurteilen und dabei den Einfluss der Fraktionierung (konventionell vs. moderat hypofraktioniert) zu untersuchen – mit Fokus auf objektiven Messmethoden und -Verfahren.

Methoden und Ergebnisse: Patienten die an einer von uns initiierten, prospektiven, randomisierten Studie über den Einfluss der Fraktionierung auf die akute Radiodermatitis (Schmeel et al., 2020) teilgenommen hatten, wurden eingeladen an dieser Post-hoc-Analyse teilzunehmen. CROs, PROs und nicht-invasive objektive Messmethoden (Spektralphotometrie zur Erfassung und Beurteilung von Pigmentierungsänderungen, Ultraschall zur Beurteilung einer Hautfibrose) wurden dabei erhoben. Vierundsechzig Patienten wurden nach einer medianen Nachbeobachtungszeit von 57 Monaten eingeschlossen (55 % erhielten dabei eine konventionelle Fraktionierung, 45 % eine moderate Hypofraktionierung und über beide Kohorten hinweg 52 % einen Boost). Die Spektralphotometrie zeigte eine signifikante Zunahme der Hautpigmentierung im Vergleich zur Messung vor Bestrahlungsbeginn und im Vergleich zur nicht-bestrahlten Brust wurde eine signifikante Zunahme der Dicke der Kutis (+14 %; $p < 0{,}001$) und Subkutis (+17 %; $p = 0{,}011$) gemessen, die nach konventioneller Fraktionierung stärker ausgeprägt war ($p = 0{,}049$). Der sequentielle Boost führte nur nach konventioneller Fraktionierung zu einer signifikanten Zunahme der lokalen Kutisdicke und des Ödems im Vergleich zu den Nicht-Boost-Regionen derselben Brüste ($p \leq 0{,}001$). Die verblindeten kosmetischen Ergebnisratings waren ebenso besser nach moderater Hypofraktionierung ($p = 0{,}024$).

Schlussfolgerungen: Die moderate Hypofraktionierung führt neben einer erhöhten Kosteneffektivität und kürzeren Behandlungszeit objektiv zu einer geringeren langfristigen Hauttoxizität und sollte somit als Standardfraktionierungsschema nach BET bevorzugt werden. Außerdem wurde der Stellenwert der ultraschallbasierten Erfassung der Hauttoxizität als möglicher Endpunkt für zukünftige Studien bewiesen.

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Objective, Clinician- and Patient-Reported Evaluation of Late Toxicity following Adjuvant Radiation for Early Breast Cancer: Long-Term Follow-Up Results of a Randomised Series

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Abstract: Background and Purpose: This study aimed to differentially assess the frequency and severity of late radiation-induced toxicity following adjuvant whole-breast irradiation for early breast cancer with conventional fractionation (CF) and moderate hypofractionation (mHF). **Materials and Methods:** Patients recruited in a previous randomised controlled trial comparing acute toxicity between CF and mHF without disease recurrence were included in a post hoc analysis. Spectrophotometric and ultrasonographic examinations were performed for an objective evaluation and subsequent comparison of long-term skin toxicity. Furthermore, patient- and clinician-reported outcomes were recorded. **Results:** Sixty-four patients with a median age of 58 (37–81) years were included. The median follow-up was 57 (37–73) months. A total of 55% underwent CF and 45% mHF. A total of 52% received a sequential boost to the tumour bed. A significant decrease in mean L* ($p = 0.011$) and an increase in a* ($p = 0.040$) and b* values ($p < 0.001$) were observed, indicating hyperpigmentation. In comparison with the non-irradiated breast, there was a significant increase in both cutis (+14%; $p < 0.001$) and subcutis (+17%; $p = 0.011$) thickness, significantly more pronounced in CF patients ($p = 0.049$). In CF patients only, a sequential boost significantly increased the local cutis thickness and oedema compared to non-boost regions in the same breast ($p = 0.001$ and $p < 0.001$, respectively). **Conclusions:** mHF objectively resulted in reduced long-term skin toxicity compared to CF. A sequential boost increased the local fibrosis rate in CF, but not in mHF. This might explain the subjectively reported better cosmetic outcomes in patients receiving mHF and reinforces the rationale for favouring mHF as the standard of care.

Keywords: breast cancer; radiation therapy; conventional fractionation; moderate hypofractionation; late toxicity; pigmentation changes; fibrosis; spectrophotometry; ultrasound; breast cosmesis

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1. Introduction

Early breast cancer remains the most common cancer diagnosis worldwide [1]. Treatment usually includes lumpectomy followed by whole-breast irradiation (WBI) to consolidate local control and improve survival [2]. In recent years, moderate hypofractionation (mHF) has been established as a standard of care for WBI; however, its potential benefit over conventional fractionation (CF) regarding late skin toxicity has been investigated by fewer trials [3–6]. Acute skin toxicity, particularly radiation dermatitis, is frequent and

often affects a patient's quality of life [7–10]. Nevertheless, it is mostly self-limiting and usually resolves within weeks after completion of the radiation course. Late toxicity, in contrast, can be irreversible and thus generate a long-lasting impairment in quality of life [11]. Frequent late toxicities include pigmentation changes, telangiectasia, and cutaneous and subcutaneous fibrosis, which are known to affect breast cosmesis [12]. If the regional lymph nodes are included in the radiation field, potential additional risks are posed, i.e., arm lymphoedema, reduced shoulder mobility, or plexopathy. Constitutional symptoms, such as long-term fatigue, arise in up to one-third of patients [13,14].

An increasing body of mature data exists on local control and survival with modern radiation techniques or alternative fractionation regimens. Nonetheless, in-depth evidence on late toxicity has not been thoroughly researched. Hurdles include a lack of non-invasive objective assessment methods, poor correlation between clinician- and patient-reported outcomes (CROs; PROs), and the long intervals between irradiation and onset of symptoms, delaying a timely and accurate diagnosis [8,15].

The aim of this study was to comprehensively assess late radiation-induced toxicity in patients who underwent adjuvant WBI after breast-conserving surgery, using both objective and CRO and PRO measures. Furthermore, differences between CF and mHF were evaluated.

2. Materials and Methods

2.1. Participants

Patients receiving WBI for early breast cancer at our comprehensive university cancer center and other participating clinics between October 2016 and July 2019 were screened for inclusion (n = 143). All patients from this collective had been previously recruited into a randomised controlled trial investigating differences in acute radiation-induced toxicity between CF and mHF [4]. Inclusion criteria for this initial trial were age > 18 years, breast-conserving surgery for breast cancer, and intended WBI, either as CF or as mHF. Exclusion criteria were planned irradiation of regional lymph nodes, history of ipsilateral breast irradiation, mastectomy, reconstruction with breast implant, metastatic disease, active dermatitis in the breast region, pre-existing dermatological disorder, current use of corticosteroids, and refusal to participate.

All patients who had completed the initial trial without treatment interruptions were reassessed for inclusion in this post hoc analysis (n = 140). To reduce the risk of bias in the assessment of late toxicity, the following exclusion criteria were defined: ipsilateral recurrent disease, metastases, contralateral breast irradiation (since the non-irradiated breast is used as control), reconstruction with breast implant, active dermatitis of the breast, any pre-existing dermatological condition, current use of corticosteroids. Patients meeting the inclusion criteria were contacted and invited to participate in this follow-up examination. Prior to their appointment, all patients received a PRO questionnaire by mail. Written informed consent was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki, approved by the Institutional Review Board (184/22) and preregistered in the German Clinical Trials Register (DRKS 00029665).

2.2. Radiation Protocol

All patients received either 50 Gy in 25 fractions of 2 Gy (CF) or 40.05 Gy in 15 fractions of 2.67 Gy (mHF), using 6 MV sliding window intensity-modulated radiotherapy (IMRT) or hybrid 6 and 10 MV volumetric modulated (partial) arc therapy (VMAT) [4]. A sequential normofractionated boost to the tumour bed (16 Gy in 8 fractions of 2 Gy) was given to patients with positive tumour margins, age $\leq$ 50 years, and age $\geq$ 51 in case of a high-grade tumour ($\geq$pT2, HER2/neu positive, triple-negative, poor cell differentiation). The International Commission on Radiation Units and Measurements (ICRU) recommendations for dose limits of 95% to 107% were followed. All patients were treated on a TrueBeam STx (Varian Medical Systems, Palo Alto, CA, USA) linear accelerator in a supine position on

a breast board. Left-sided WBI was performed in deep inspiration breath-hold (DIBH), if feasible.

Standard institutional skin care with a urea-based lotion (Eucerin UreaRepair PLUS 5%, Beiersdorf, Hamburg, Germany) was applied twice daily to the whole breast, from the first day of treatment onwards until completion. Patients presenting with grade ≥ 2 radiation dermatitis with moist desquamation and severe pain during radiation treatment, were prescribed topical corticosteroids, until symptoms resolved.

2.3. Patient Evaluation

2.3.1. Clinical Examination

Biometric data and patient characteristics (comorbidities, smoking habits, breast volume, prior systemic therapies) were collected. Clinical examination was performed by an experienced breast radiation oncologist, scoring relevant Late Effects of Normal Tissue—Subjective, Objective, Management, and Analytic (LENT-SOMA) items (Table A1) [16,17]. Furthermore, the cosmesis of the irradiated breast relative to the untreated contralateral breast was assessed by an experienced breast surgeon as being excellent, fair, good, or poor, according to the Harvard Breast Cosmesis Scale (Table A2) [18]. Clinicians were blinded to the radiation treatment characteristics (fractionation regimen).

2.3.2. Objective Assessments

Pigmentation changes were assessed using a reflectance spectrophotometer (CR-10 Plus, Konica Minolta, Tokyo, Japan). Six readings were performed on the irradiated breast (Figure 1A). This compact device has been previously used to assess pigmentation changes in a non-invasive and objective way [4,19–21]. The automatically performed measurements are based on the Commission Internationale de l'Éclairage (CIE) system of tristimulus values, describing each measured colour (or skin tone) with three coordinates, using the L*a*b* system. The L* value describes the luminance or brightness of the skin, the a* value describes the position of the colour on a scale ranging from red to green, and the b* value describes the position on a scale from blue to yellow. Accordingly, higher L* values describe lighter skin, whereas lower values indicate hyperpigmentation. Higher a* values indicate erythema. Since all patients had been previously enrolled in a randomised controlled trial, baseline spectrophotometric measurements (before radiation treatment initiation) were available.

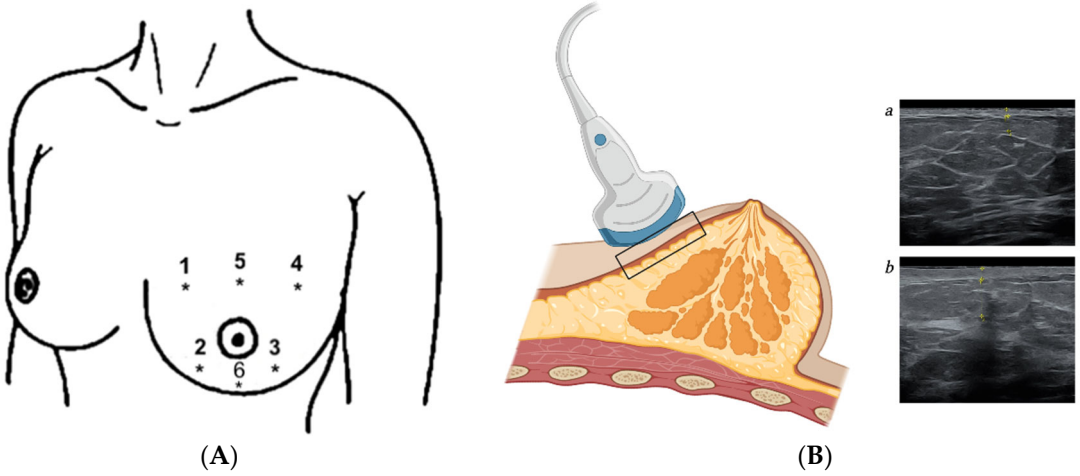

Figure 1. (**A**) Location of the 6 spectrophotometric (1–6) and 4 ultrasound (1–4) measurements. Corresponding ultrasound points were identified and measured on the contralateral breast. (**B**) Quantifying tissue fibrosis using ultrasound. The thickness of the skin (epidermis and dermis), subcutis, and subcutaneous oedema (if present) was measured for the contralateral (**a**) and ipsilateral (**b**) breast. Created with BioRender.com (accessed on 1 March 2023).

The extent of tissue fibrosis was quantified using ultrasound, which has previously proved reliable and valid in this context [22,23]. Patients were in a supine position with the axis of the ultrasound probe perpendicular to the skin surface, applying minimal pressure. To guarantee proper coupling between the patient's skin and the probe, a thin layer of transmission gel was used. All breast examinations were performed in B-mode, using 4–13 MHz ML6-15-D linear array probes on a Voluson E10 (GE Healthcare, Solingen, Germany). The thickness of the skin (epidermis and dermis) and subcutis were measured in each of the breast quadrants (1, 4, 8, and 10 o'clock) of both breasts (Figure 1A,B). In patients who received a sequential boost to the tumour bed, the skin and subcutis thickness in this region were documented separately, using the surgical scar and the original digital radiation treatment plan to determine the exact location. Anatomically, the transition between cutis and subcutis can be determined very precisely, as the cutis consists mainly of keratinocytes, whereas the subcutis is connective and adipose tissue, reflected by a different image morphology in the ultrasound. If subcutaneous oedema was present, this was documented and quantified by ultrasound as well. A single senior breast surgeon with certified expertise in breast ultrasound performed all measurements to avoid interobserver variability. To minimise any potential bias, this physician was blinded to the radiation treatment characteristics (fractionation regimen), as well as the corresponding clinically assessed late toxicity.

2.3.3. Patient-Reported Outcome

Items such as appetite, fatigue, itching, pain, self-image, sexual health, and satisfaction with breast cosmesis were subjectively evaluated using a modified Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire (Table A3) [24]. The severity of each item and its influence on activities of daily living and quality of life were scored on a 5-point Likert scale, separately for the ipsilateral and contralateral breast.

2.4. Endpoints and Statistical Analysis

The patients recruited for this study had already participated in a prospective clinical trial on the acute toxicity of CF versus mHF WBI [4]. We were thus able to draw from a collective previously homogenised by means of randomisation and stratification. The primary endpoint was the incidence of late radiation-induced breast fibrosis, as measured by ultrasonographic skin thickness in both treatment arms.

Mean, median, standard deviation (SD), and range were calculated for all applicable clinical data. Differences in baseline patient characteristics by randomisation arm were assessed using Pearson's χ^2 or the Wilcoxon rank-sum test (if the data were not normally distributed), as appropriate. The comparison of spectrophotometric and ultrasonographic data by randomisation arm was performed with an unpaired two-sample *t*-test, after checking homoscedasticity using Levene's test. To compare with baseline or contralateral values, a paired *t*-test was used. For the comparison of clinician- and patient-assessed scores (categorical variables) among both fractionation regimens or depending on the presence or absence of a sequential boost, Pearson's χ^2 was calculated. If a correlation between CRO or PRO and a continuous variable (i.e., spectrophotometric or ultrasonographic values) was sought, an ANOVA was performed, and correlation was quantified using Pearson's *r*. Finally, concordance between CRO and PRO was quantified with Cohen's κ, using the reference values as proposed by Landis and Koch [25]. The statistical significance level was defined as $p < 0.05$, using SPSS Statistics version 27 (IBM, Armonk, New York, USA) to perform the analyses.

3. Results

3.1. Patient and Treatment Characteristics

The assessments were completed between September 2022 and February 2023. In total, 64 patients (45.7% of the initial cohort) consented to the follow-up examination and

were included in the analysis (Figure 2). All patients were female and Caucasian. Their median age (range) was 58 (37–81) years, and the median time between radiation treatment completion and late toxicity assessment was 57 (37–73) months. A total of 54.7% underwent CF and 45.3% mHF. A total of 51.6% had received a sequential boost to the tumour bed. A total of 6.3% of patients received VMAT, and all other patients underwent IMRT. Patient and treatment characteristics were well balanced between both arms and are summarised in Table 1.

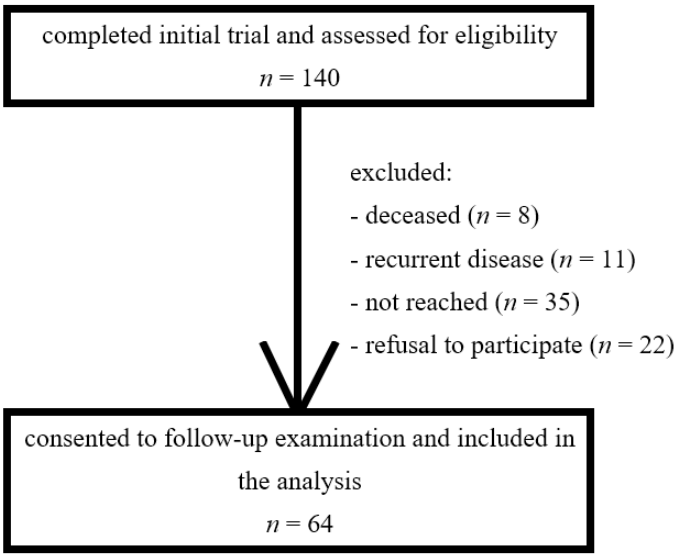

Figure 2. Flowchart of patient selection and inclusion. Patients completing the initial trial [4] were reassessed for eligibility in this follow-up trial. Exclusion criteria were defined as ipsilateral recurrent disease, metastases, contralateral breast irradiation, reconstruction with breast implant, active dermatitis of the breast, any pre-existing dermatological condition, and current use of corticosteroids.

Table 1. Summary of patient and treatment characteristics (*n* = 64).

	Total ***n* = 64**	**CF** ***n* = 35**	**mHF** ***n* = 29**	*p*
median age (range) in years [a]	58 (37–81)			
median follow-up time (range) in months	57 (37–73)			
		%		
female	100	100	100	
Caucasian	100	100	100	
Fitzpatrick skin type [26]				0.829
I	17.2	17.1	17.2	
II	71.9	71.4	72.4	
III	10.9	11.4	10.3	
diabetes mellitus	1.6	0	3.4	0.268
active smoking	17.2	17.1	17.2	0.992
T-stage				0.067
Tis	14.1	14.3	13.8	
T1	67.2	77.1	55.2	
T2	18.8	8.6	31.0	

Table 1. *Cont.*

	Total ***n* = 64**	**CF** ***n* = 35**	**mHF** ***n* = 29**	***p***
N-stage				0.165
N0	85.9	91.4	79.3	
N1	14.1	8.6	20.7	
previous chemotherapy/immunotherapy	35.9	34.3	37.9	0.762
current antihormonal therapy	39.1	42.9	34.5	0.781
sequential boost to the tumour bed	51.6	57.1	44.8	0.326
mean PTV breast (range) in mL	515 (134–1572)	503 (163–1572)	533 (134–1408)	0.984
mean PTV boost (range) in mL	178 (40–505)	183 (40–505)	161 (88–329)	0.912
radiation treatment technique				
sliding window IMRT	98.4	97.1	100	
VMAT	1.6	2.9	0	

CF = conventional fractionation; mHF = moderate hypofractionation; T = stage of the primary tumour; Tis = carcinoma in situ; N = stage of the regional lymph nodes; PTV = planning target volume; IMRT = intensity-modulated radiotherapy; VMAT = volumetric modulated arc therapy. [a] Age at the time of radiation treatment.

3.2. Objective Assessments

3.2.1. Pigmentation Changes

A total of 384 spectrophotometric readings were performed. Compared to baseline skin tone measurements, there was a significant decrease in the mean L* value ($p = 0.011$), indicating darker skin or hyperpigmentation. Furthermore, a significant increase in the mean a* value ($p = 0.040$) and mean b* value ($p < 0.001$) was noted, translating into more red and yellow tones, respectively, but no significant changes regarding the mean differences in the spectrophotometric skin measurements between the two fractionation groups: $p = 0.281$, $p = 0.076$, and $p = 0.559$ for L*, a*, and b*, respectively. Table 2 summarises the spectrophotometry data.

Table 2. Summary of the spectrophotometric data. Mean values of 384 readings.

	Baseline	**Follow-Up**	**Δ Total**	***p***	**Δ CF**	**Δ mHF**	***p***
L*	69.692	69.166	−0.527	0.011	−0.725	−0.290	0.281
a*	6.404	6.631	+0.227	0.040	+0.404	+0.017	0.076
b*	14.191	14.897	+0.707	<0.001	+0.781	+0.619	0.559

CF = conventional fractionation; mHF = moderate hypofractionation.

3.2.2. Tissue Fibrosis

A total of 545 ultrasonographic measurements were conducted. There was a significant increase in both cutis (+14.1%) and subcutis (+17.1%) thickness when compared to the contralateral, non-irradiated breast ($p < 0.001$ and $p = 0.011$, respectively). A total of 17.5% of patients had measurable subcutaneous oedema. The increase in cutis thickness was significantly more pronounced in patients who had previously undergone a conventionally fractionated radiation regimen ($p = 0.049$). For the subcutis, this difference was not significant ($p = 0.088$), but for the combined cutis and subcutis thickness, the effect remained significant ($p = 0.047$). Regarding oedema, there were no differences in the prevalence or extent between both treatment arms ($p = 0.332$) (Table 3).

Table 3. Summary of the ultrasonographic quantification of cutis, subcutis, and oedema thickness (in millimeters). Mean ± SD values of 545 measurements. Comparison with the contralateral, non-irradiated breast.

	Control	Irradiated Breast	*p*	CF	mHF	*p*
cutis	1.640 ± 0.234	1.871 ± 0.476	<0.001	1.985	1.737	0.049
subcutis	2.253 ± 0.771	2.638 ± 1.574	0.011	2.944	2.273	0.088
sum	3.893 ± 0.848	4.509 ± 1.854	0.001	4.928	4.010	0.047
oedema	0	1.929 ± 5.355	0.009	1.294	2.688	0.332

SD = standard deviation; CF = conventional fractionation; mHF = moderate hypofractionation.

When comparing patients with and without a sequential boost to the tumour bed, there was no significant increase in the overall cutis or subcutis thickness ($p = 0.430$ and $p = 0.555$, respectively). However, when comparing boost regions to non-boost regions in the same breasts, there was a significant increase in cutis ($p < 0.001$), combined cutis and subcutis ($p = 0.006$), and oedema ($p = 0.015$) thickness. Considering only patients receiving CF, these increases in the boost region remained significant ($p = 0.001$, $p = 0.026$, and $p < 0.001$, respectively). However, this was not the case in patients who underwent mHF ($p = 0.209$, $p = 0.099$, and $p = 0.817$, respectively) (Table 4).

Table 4. Summary of the ultrasonographic quantification of cutis, subcutis, and oedema thickness (in millimeters). Mean ± SD values of 545 measurements. Effect of a sequential boost to the tumour bed.

	Boost Region			Non-Boost Region			*p* *
	Total	CF	mHF	Total	CF	mHF	
cutis	2.117	2.206	1.983	1.919	2.021	1.767	<0.001
subcutis	2.540	2.639	2.392	2.756	3.108	2.227	0.133
sum	4.657	4.844	4.375	4.675	5.129	3.994	0.006
oedema	3.287	2.489	4.483	2.308	2.101	2.617	0.015

SD = standard deviation; CF = conventional fractionation; mHF = moderate hypofractionation. * Comparing boost region versus non-boost region in all patients, regardless of fractionation arm.

3.3. Clinician-Reported Outcome

None of the mean LENT-SOMA item scores was significantly different between the two fractionation arms (Table 5). The blinded cosmesis assessment was significantly better in patients who underwent mHF ($p = 0.024$) (Table 6). In patients who had previously received a sequential boost to the tumour bed, there was increased clinician-assessed pain ($p = 0.006$) and fibrosis ($p = 0.070$). The blinded cosmesis assessment was not influenced by boost application ($p = 0.441$).

There was a strong correlation between clinician-reported pigmentation changes and spectrophotometric measurements: decreased L* ($r = -0.65$; $p < 0.001$) and increased a* and b* values ($r = 0.48$ and $r = 0.47$, respectively; each $p = 0.001$). Ultrasonographic measurements did not correlate with clinician-reported fibrosis but were, however, associated with oedema ($r = 0.42$; $p = 0.003$ for cutis and $r = 0.40$; $p < 0.001$ for subcutis) and restricted arm movement ($r = 0.29$ and $r = 0.38$ for cutis and subcutis, respectively; each $p < 0.001$). Clinician-reported cosmetic outcome was independent of spectrophotometry but correlated with the ultrasonographic presence of subcutaneous oedema ($r = 0.30$; $p = 0.045$).

Table 5. Mean LENT-SOMA scores for relevant items.

	Total	CF	mHF	*p*
itching	0.079	0.029	0.143	0.095
pain	0.492	0.543	0.429	0.663
sensory discomfort	0.333	0.371	0.286	0.202
pigmentation changes	0.238	0.343	0.107	0.411
telangiectasia	0.111	0.143	0.071	0.332
fibrosis	0.603	0.686	0.500	0.129
retraction/atrophy	0.175	0.257	0.071	0.271
ulcer	0	0	0	-
oedema	0.270	0.229	0.321	0.733
arm lymphoedema	0.032	0.029	0.036	0.872
restricted arm movement	0.302	0.371	0.214	0.646
pain management	0.048	0.086	0	0.438
atrophy management	0	0	0	-
ulcer management	0	0	0	-
oedema management	0.048	0	0.107	0.260
arm lymphoedema management	0.190	0.257	0.107	0.419

CF = conventional fractionation; mHF = moderate hypofractionation.

Table 6. Harvard Breast Cosmesis Scale between the two fractionation arms.

	Total (%)	CF (%)	mHF (%)	*p*
excellent	63.5	57.1	71.4	0.024
good	23.8	34.3	10.7	
fair	9.5	2.9	17.9	
poor	3.2	5.7	0	

CF = conventional fractionation; mHF = moderate hypofractionation.

Patients with worse clinician-reported breast cosmesis were more likely to report feeling less feminine because of their illness or treatment ($p = 0.001$) as well as general dissatisfaction with their breast ($p < 0.001$).

3.4. Patient-Reported Outcome

None of the mean modified PRO-CTCAE item scores was significantly different between the two fractionation arms (Table 7). Patients who had received a sequential boost to the tumour bed reported more coughing ($p = 0.048$), dry skin ($p = 0.050$), and memory deficits ($p = 0.055$). The latter most likely is a mere random event, as a biological explanation is unclear.

3.5. Concordance between CRO and PRO

Several items were reported by both clinicians and patients. For itching and arm lymphoedema, there was only slight concordance ($\kappa = 0.035$ and $\kappa = 0.096$, respectively), whereas the concordance for pain was fair ($\kappa = 0.386$) between clinicians and patients. These discrepancies were similar between the two fractionation arms: $\kappa = 0.031$, 0.155, and 0.395 for CF, and $\kappa = 0.040$, 0.143, and 0.375 for mHF.

Table 7. Mean modified PRO-CTCAE scores.

	Total	CF	mHF	*p*
decreased appetite	0.397	0.571	0.179	0.334
nausea	0.435	0.618	0.214	0.172
cough	0.429	0.314	0.571	0.592
wheezing	0.339	0.229	0.481	0.211
arm swelling (severity)	0.413	0.429	0.393	0.600
arm swelling (interference)	0.254	0.343	0.143	0.783
skin dryness	1.651	1.914	1.321	0.273
itching	1.226	1.294	1.143	0.762
pain (severity)	1.190	1.314	1.036	0.425
pain (interference)	0.746	0.943	0.500	0.412
concentration	1.032	1.114	0.926	0.821
memory	1.016	1.000	1.038	0.743
fatigue (severity)	2.129	2.171	2.074	0.305
fatigue (interference)	1.836	1.882	1.778	0.283
less attractive	0.885	1.029	0.704	0.633
less feminine	0.629	0.714	0.519	0.536
discomfort seeing oneself naked	0.516	0.514	0.519	0.730
dissatisfaction with breast	0.726	0.657	0.815	0.323
discomfort towards partner	0.623	0.735	0.481	0.362

CF = conventional fractionation; mHF = moderate hypofractionation.

4. Discussion

With the development of new radiation techniques or alternative fractionation regimens, both local control and acute toxicity in early breast cancer improved. While differences in acute radiation-induced toxicity are, at least in some instances, better defined, there is only a limited understanding of late toxicity. These potentially irreversible treatment-related side effects do, however, play an important role in long-term cancer survivors, as they may affect the quality of life. Herein, we report the long-term follow-up of a randomised series in which patients underwent either CF or mHF adjuvant WBI after breast-conserving surgery. We address the incidence and severity of late toxicity by using objective clinician- and patient-reported outcome measures, as well as differences between CF and mHF.

Pigmentation changes and fibrosis are well-documented late toxicities following WBI, known to impair breast cosmesis [12]. Following WBI, mean L*a*b* values indicate a significantly increased hyperpigmentation and erythema when compared to baseline, without differences in pigmentation changes between the two treatment arms (neither in the objective assessment nor in the CRO). Previous CRO-based reports did, however, suggest reduced clinician-reported dyspigmentation following mHF when compared to CF [27].

Our series is the first comprehensive objective comparison of the skin composition and condition between different fractionation regimens: the data reflect a significant increase in cutis and subcutis thickness after WBI, consistent with other trials investigating the use of quantitative ultrasound assessments [23,28,29]. The increment was more pronounced in patients who underwent CF. Other reports found no increased risk of clinician-assessed breast induration between CF and mHF at 3 and 5 years [27]. They did, however, observe significantly more fibrosis after a slightly longer median follow-up time of 87 months, implying that the development of fibrosis is an evolving and dynamic process [27]. Offersen et al. also reported a significantly lower incidence of oedema following mHF after the same interval [27].

In the current collective, however, ultrasound still revealed similar rates of subcutaneous oedema in both groups at 57 months.

While a sequential boost to the tumour bed improves local tumour control, there is a dose-dependent risk of moderate and severe fibrosis [12,30–34]. A systematic review and meta-analysis showed that the cosmetic assessment by a panel was better if no boost was applied, yet no difference was found if this assessment was performed by a single physician (as was the case in the current series) [32]. The quantitative breast retraction assessment proposed by the European Organisation for Research and Treatment of Cancer (EORTC), measuring the displacement of the nipple and used as a surrogate for cosmesis, was also not influenced by boost application [32]. Although objective and reliable, it is not a comprehensive cosmetic assessment method, as surgical scars or skin changes are not considered [35].

In our series, a sequential boost led to both increased local skin thickness and subcutaneous oedema, as anticipated. Interestingly, after adjusting for the fractionation regimen, this effect remained significant in patients who underwent CF only, highlighting radiobiological differences between these fractionation regimens. Objective assessments such as ultrasound thus prove useful to evaluate these changes [23]. Our blinded cosmesis assessment was not influenced by a boost application. It was, however, significantly better for mHF, which corroborates previous findings [27,36]. Clinician-reported induration and sensibility changes have also been shown to be less frequent with mHF compared to CF [27]. However, this was not observed in our cohort.

Late PROs were similar between the two fractionation arms and also similar to the recent literature on this topic [37–39]. Importantly, there was only poor to slight concordance between late CRO and PRO, which has previously been described for acute toxicity only [8,40,41]. This discrepancy underlines the need to report both CRO and PRO in future trials.

Multiple landmark trials using contemporary IMRT techniques are available on breast irradiation [27,31,36,42]. In these trials, however, the assessment of late toxicity is solely based on subjective CRO (e.g., colorimetric evaluations, breast palpation), with a high inherent risk of inter- and intra-observer variability. Slight changes in skin composition and condition are rarely detected by classical CRO but can lead to impaired cosmesis or symptoms, prompting the need for more sensitive assessment methods. We previously demonstrated the validity of objective assessment methods such as spectrophotometry in the context of acute radiation-induced toxicity and evaluated the superiority of mHF over CF [4]. Nowadays, PROs are finding their way into modern radiotherapy trials, and some effort is being made to investigate the use of objective assessment methods in the context of acute RD [43]. The need for unbiased, objective late radiation-induced toxicity assessment methods, however, remains [37,38]. Potential hurdles to the widespread implementation of such techniques in future landmark trials might be added costs and time consumption for patients and their healthcare providers. Additional research should focus on these aspects to facilitate the incorporation of sustainable objective assessment methods in upcoming trials and possibly everyday clinical practice.

Our study carries certain limitations. Only 45.7% of the initial cohort was eligible and consented to the follow-up examination. The fact that a quarter of the patients could not be reached together with the strict inclusion criteria to yield a homogeneous patient collective resulted in this relatively small sample size. However, the long follow-up combined with objective measurements provides high-quality data and reduced risk of bias on long-term side effects of WBI and between different fractionation regimens. These substantial advantages along with a homogeneous cohort and the baseline spectrophotometric data strengthen the validity of our study. Future trials should also investigate potential differences in objectively assessed late toxicities depending on the radiation treatment technique used (e.g., three-dimensional conformal radiation therapy versus IMRT).

5. Conclusions

Adjuvant WBI for early breast cancer improves local control substantially and is generally well tolerated, justifying its role across all age groups [44]. As mHF reduces costs

and overall treatment time, as well as patient burden, it should be preferred over CF. While confirming the feasibility of ultrasound-based skin toxicity assessment, we objectively provide proof of the superiority of mHF over CF in terms of late radiation-induced toxicity and cosmesis.

In both long-term CROs and PROs, mHF yields fewer skin toxicity events than CF, regardless of boost application. Our objective results add to the existing body of evidence favouring mHF and might ease an improved informed decision in adjuvant therapy for early breast cancer.

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Appendix A Appendix

Table A1. Relevant Late Effects of Normal Tissue—Subjective, Objective, Management, and Analytic (LENT-SOMA) items [16,17].

	0	Grade 1	Grade 2	Grade 3	Grade 4
itching		occasional and minimal	intermittent and tolerable	persistent and intense	refractory and excruciating
pain		occasional and minimal	intermittent and tolerable	persistent and intense	refractory and excruciating
sensory discomfort		local	largely	general	-
pigmentation changes		local	largely	general	-
telangiectasia		<1/cm^2	1–4/cm^2	>4/cm^2	-
fibrosis		barely palpable increased density	definite increased density and firmness	very marked density, retraction and fixation	-
retraction/atrophy		10–25%	>25–40%	>40–75%	whole breast
ulcer		epidermal only, <1 cm^2	dermal, >1 cm^2	subcutaneous	bone exposed, necrosis
oedema		asymptomatic	symptomatic	secondary dysfunction	-
arm lymphoedema		2–4 cm circumference increase	>4–6 cm circumference increase	>6 cm circumference increase	useless arm, angiosarcoma
restricted arm movement		minimal, without restrictions	moderate, now and then restrictions	strong, often restrictions	very strong, permanent restrictions
pain management		occasional non-narcotic	regular non-narcotic	regular narcotic	surgical intervention
atrophy management		-	-	-	surgical intervention, mastectomy
ulcer management		-	medical intervention	surgical intervention, wound debridement	surgical intervention, mastectomy
oedema management		-	-	medical intervention	surgical intervention, mastectomy
arm lymphoedema management		-	elevate arm, elastic stocking	compression wrapping, intensive physiotherapy	surgical intervention, amputation

Table A2. Harvard Breast Cosmesis Scale [18].

excellent	Treated breast nearly identical to untreated breast.
good	Treated breast slightly different from untreated breast.
fair	Treated breast clearly different from untreated breast but not seriously distorted.
poor	Treated breast seriously distorted.

Table A3. Modified Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire [24].

	None	Mild	Moderate	Severe	Very Severe
In the last 7 days, what was the severity of your decreased appetite at its worst?					
In the last 7 days, what was the severity of your nausea at its worst?					
In the last 7 days, what was the severity of your cough at its worst?					
In the last 7 days, what was the severity of you wheezing at its worst?					
In the last 7 days, what was the severity of your arm swelling at its worst?					
In the last 7 days, how much did arm swelling interfere with your usual or daily activities?					
In the last 7 days, what was the severity of your dry skin at its worst?					
In the last 7 days, what was the severity of your itchy skin at its worst?					
In the last 7 days, what was the severity of your pain at its worst?					
In the last 7 days, how much did pain interfere with your usual or daily activities?					
In the last 7 days, what was the severity of your problems with concentration at their worst?					
In the last 7 days, what was the severity of your problems with memory at their worst?					
In the last 7 days, what was the severity of your fatigue, tiredness, or lack of energy at its worst?					
In the last 7 days, how much did fatigue, tiredness, or lack of energy interefere with your usual or daily activities?					
Have you felt less physically attractive because of your breast?					
Have you felt less feminine because of your illness or treatment?					
Did you have problems seeing yourself naked?					
Were you dissatisfied with your breast?					
Were you uncomfortable showing your body to a partner because of your breast?					
Do you have other symptoms to report? In the last 7 days, what was the severity of this symptom at its worst?					

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3.4 Dejonckheere CS et al. Do Barrier Films Impact Long-Term Skin Toxicity Following Whole-Breast Irradiation? Objective Follow-Up of Two Randomised Trials. *J Clin Med* 2023; 12: 7195

Zielsetzung der Arbeit: Hydrofilm, ein Folienverband auf Polyurethanbasis, kann zur Vorbeugung der akuten Radiodermatitis eingesetzt werden. Langzeitsicherheitsdaten und den Einfluss auf die späte radiogene Hauttoxizität (z. B. Pigmentierungsänderungen, Fibrose) wurden bisher nicht untersucht.

Methoden und Ergebnisse: Patienten, die zuvor an einer von zwei intrapatienten-randomisierten kontrollierten (laterale versus mediale Brusthälfte) Studien zur Verwendung von Hydrofilm zur akuten Radiodermatitisprophylaxe teilgenommen haben (DRKS00029665), wurden erneut nachgesorgt. Es wurden CROs und PROs erhoben, und es erfolgten objektive Untersuchungen der bestrahlten Haut. Zweiundsechzig Patienten (48 % des ursprünglichen Kollektivs) konnten erneut rekrutiert werden, nach einer medianen Nachbeobachtungszeit von 58 Monaten. Nach der Ganzbrustbestrahlung kam es zu einer signifikanten Zunahme der gelben Hauttone im Vergleich zu den Ausgangswerten vor der Strahlentherapie ($p < 0{,}001$) und zu einer signifikanten Zunahme der Dicke der Kutis, der Subkutis und des Ödems ($p < 0{,}001$, $p < 0{,}001$ bzw. $p = 0{,}004$). Bei der Nachuntersuchung gab es keine signifikanten Unterschiede zwischen den Brusthälften mit Hydrofilm oder Standardbehandlung, weder bei den Pigmentierungsänderungen noch bei der Hautfibrose.

Schlussfolgerungen: Diese Daten zeigen zum ersten Mal, dass Hydrofilm im Rahmen der akuten Radiodermatitisprävention sicher eingesetzt werden kann, ohne dass es zu erhöhten Spätnebenwirkungen kommt, was die verbreitete Anwendung weiter unterstützt.

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Do Barrier Films Impact Long-Term Skin Toxicity following Whole-Breast Irradiation? Objective Follow-Up of Two Randomised Trials

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Abstract: Purpose: Hydrofilm, a polyurethane-based barrier film, can be used to prevent acute radiation dermatitis (RD) in adjuvant whole-breast irradiation (WBI) for breast cancer. This cost-effective prophylactic measure is currently being recommended to a growing number of patients, yet long-term safety data and its impact on late radiation-induced skin toxicity such as pigmentation changes and fibrosis have not been investigated. **Methods:** We objectively evaluated patients who were previously enrolled in either of two intrapatient-randomised (lateral versus medial breast halve) controlled trials on the use of Hydrofilm for RD prevention (DRKS00029665; registered on 19 July 2022). **Results:** Sixty-two patients (47.7% of the initial combined sample size) provided consent for this post-hoc examination, with a median follow-up time (range) of 58 (37–73) months. Following WBI, there was a significant increase in yellow skin tones of the entire breast when compared to baseline measurements before WBI ($p < 0.001$) and a significant increase of cutis, subcutis, and oedema thickness ($p < 0.001$, $p < 0.001$, and $p = 0.004$, respectively). At follow-up, there were no significant differences in either pigmentation changes or skin fibrosis between the Hydrofilm and standard of care breast halves. **Conclusion:** These data suggest that Hydrofilm can be safely used in the context of acute RD prevention, without affecting late side effects, supporting its widespread use.

Keywords: hydrofilm; breast cancer; radiotherapy; pigmentation changes; skin fibrosis; objective assessment

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1. Introduction

The most common oncological diagnosis worldwide remains early breast cancer [1]. In about 70% of cases, surgical therapy is followed by adjuvant radiation treatment to improve local tumour control and survival [2,3]. The most common side effect of whole-breast irradiation (WBI) is radiation dermatitis (RD), which occurs in up to 85% of patients and is characterised by erythema, pruritus, pain, and dry or moist desquamation [4,5]. Ongoing improvements in radiation treatment techniques (e.g., intensity-modulated radiation therapy [IMRT]) and the exploration of new fractionation regimens (e.g., hypofractionation) have led to a reduction in the breast skin dose, which in turn results in fewer and milder RD [4,6]. Severe cases necessitating radiation treatment interruption have thus become rare; however, even mild symptoms can impact a patient's quality of life and self-image [7,8]. Even though continuous research efforts are being made, there is a lack of potent preventa-

tive and therapeutic options, leading to substantial variation in RD management amongst practitioners [9–11].

Hydrofilm®, a polyurethane-based barrier film, has been shown to majorly reduce the clinical appearance and patient-experienced symptoms of RD across multiple trials [12–16]. Based on these data, recently published international guidelines recommend its use for RD prevention in the context of adjuvant WBI [17]. Hydrofilm provides a mechanical barrier that protects the underlying radiation-damaged skin layers from additional friction or maceration and facilitates repair. It is a transparent and breathable film with an insignificant bolus effect, which is why it can be left on the skin for the entirety of the radiation treatment, promoting patient comfort. Side effects due to its application are mild and mostly self-limiting.

Apart from acute radiation-induced toxicity such as RD, breast cancer survivors might also be affected by late toxicities such as telangiectasia, pigmentation changes, or (sub)cutaneous fibrosis or induration [18]. These side effects can be irreversible and negatively impact breast cosmesis, which may result in an ongoing impairment of quality of life [19–21]. Evidence on the prevention and treatment of such late cutaneous toxicities is clearly limited. Reasons are manifold and include poor correlation between clinician- and patient-reported outcomes, limited availability of non-invasive objective assessment methods, and delayed diagnosis due to its late onset, inadvertently burdening numerous breast cancer patients [22,23].

Several high-quality trials have investigated the use and benefits of Hydrofilm and other barrier films for the prevention of acute radiation-induced skin toxicity; however, no data on its long-term impact on the irradiated skin exist. Here, we report the long-term follow-up of two previously published intrapatient-randomised controlled trials on the use of Hydrofilm for acute RD. We sought to determine the impact of Hydrofilm on late cutaneous toxicity following WBI, using validated objective assessment methods.

2. Materials and Methods

2.1. Patient Selection

Patients were drawn from two previously published prospective investigator-initiated intrapatient-randomised controlled trials on the use of Hydrofilm for the prevention of acute RD in the context of WBI for breast cancer [12,13]. Inclusion criteria for these initial trials were age > 18 years, breast-conserving surgery for breast cancer, and a fractionation regimen of 50 Gy in 25 fractions (conventional fractionation) or 40.05 Gy in 15 fractions (moderate hypofractionation). A conventionally fractionated sequential tumour bed boost of 16 Gy in 8 fractions was allowed. In order to minimise confounding factors, both trials defined similar exclusion criteria: Neoadjuvant or concomitant chemotherapy, mastectomy, reconstruction with breast implant, history of breast irradiation, metastatic disease, active smoking, active dermatitis, current treatment with oral or topical corticosteroids (known to suppress RD development), alternative fractionation regimens, and refusal to participate. These criteria resulted in two homogeneous patient collectives.

All patients who completed either of the initial trials per protocol were reassessed for inclusion in this post-hoc analysis. The following exclusion criteria were defined: Reconstruction with breast implant, recurrent or metastatic disease, active dermatitis, and current use of oral or topical corticosteroids. Eligible patients were contacted by telephone and invited to participate. All assessments were completed between September 2022 and February 2023, after obtaining a written informed consent from all participants. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Bonn, Germany (184/22).

2.2. Radiation Protocol

All patients previously underwent adjuvant WBI. Those < 50 years or those with risk factors (≥pT2, HER2 positive, triple-negative, or poor cell differentiation, as per German national guidelines), regardless of age, received a sequential boost to the tumour bed. For both trials, the treatment technique used was 6 MV sliding window IMRT or hybrid 6 and

10 MV volumetric modulated (partial) arc therapy (VMAT). The International Commission on Radiation Units and Measurements (ICRU) recommendations for dose limits of 95–107% were followed. If feasible, left-sided WBI was performed in deep inspiration breath-hold (DIBH), with all patients in a supine position on a breast board. Patients were treated on a TrueBeam STx (Varian Medical Systems, Palo Alto, CA, USA) linear accelerator.

2.3. Intervention

In both initial trials, patients acted as their own control: The irradiated breast was divided into a lateral and medial compartment, and these halves were randomised to receive either Hydrofilm or standard of care. Hydrofilm (Paul Hartmann, Heidenheim, Germany) is a sterile polyurethane film with a hypoallergenic polyacrylate adhesive. Phantom studies revealed a clinically insignificant skin dose build-up (<0.1%) with Hydrofilm, which is why it can remain on the skin from the first day of radiation treatment until completion. Institutional standard of skin care consisted of urea lotion (UreaRepair PLUS 5%, Eucerin, Beiersdorf, Hamburg, Germany) twice daily applied from the first day of radiation treatment until completion. Topical corticosteroids were prescribed to patients with grade $\geq$ 2 RD, moist desquamation, and/or intense pain, until symptoms resolved.

2.4. Patient Evaluation

Biometric data and patient characteristics were collected. As clinician- and patient-reported outcomes are difficult to assess for each breast halve separately, especially regarding late skin toxicity, previously validated objective skin assessment methods were used.

(a) Evaluation of Pigmentation Changes with Spectrophotometry

Four erythema readings were performed on the previously irradiated breast (two lateral and two medial) with a reflectance spectrophotometer (CR-10 Plus, Konica Minolta, Tokyo, Japan) (Figure 1). These automatically performed measurements are based on the system of tristimulus values of the Commission Internationale de l'Éclairage (CIE). They describe a measured colour in three coordinates using the L*a*b* system. This technique has been previously validated in the context of acute RD: Lower L* values describe darker skin (hyperpigmentation) and higher a* values indicate redness (RD), whereas b* values describe the position of a colour on a scale from blue to yellow (of secondary importance in the acute setting) [24,25]. As this technique was also used in both initial trials, baseline values (before initiation of radiation treatment) for each patient and for both breast halves separately were available (there were no relevant differences in baseline measurements between breast halves in both patient groups). The clinician who performed the automated measurements was blinded to the intrapatient randomisation (i.e., which breast halve had previously been covered with Hydrofilm).

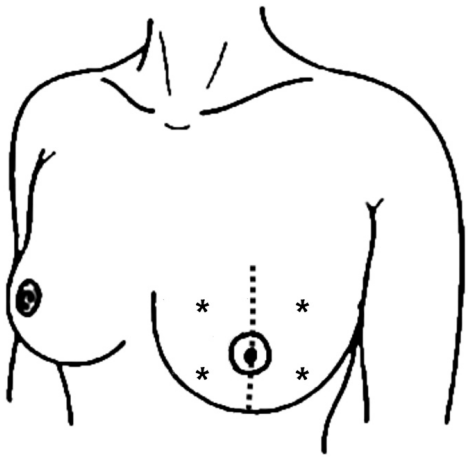

Figure 1. The four stars indicate the location of the spectrophotometric readings and ultrasound measurements at follow-up.

(b) Evaluation of Skin Fibrosis with Ultrasound

To assess the potential impact of Hydrofilm on tissue fibrosis, skin thickness was measured using ultrasound. This method previously proved reliable and valid in the context of late radiation-induced toxicity [26]. All breast examinations were performed in B-mode, using 4–13 MHz ML6-15-D linear array probes on a Voluson E10 (GE Healthcare, Solingen, Germany). Patients were in a supine position, and the axis of the ultrasound probe was held perpendicular to the skin surface, applying minimal pressure. To guarantee proper coupling, a thin layer of transmission gel was used. The thickness of the cutis (epidermis and dermis) and subcutis were measured in each of the breast quadrants (1, 4, 8, and 10 o'clock) (Figure 1). Anatomically, the transition between cutis and subcutis can be determined very precisely, as the epidermal part of the cutis consists mainly of keratinocytes, whereas its dermal part and the subcutis are connective and adipose tissue, reflected by a different image morphology on the ultrasound image. In the case where subcutaneous oedema was present, this was documented and quantified with ultrasound as well. Measurements at follow-up were compared with baseline values (before initiation of radiation treatment). To avoid interobserver variability, all measurements were performed by a single senior breast surgeon with certified expertise in breast ultrasound, who was also blinded to the intrapatient randomisation, to further reduce bias.

2.5. Statistical Analysis

Mean, median, standard deviation (SD), and range were calculated for all applicable clinical data. To compare objective outcomes (spectrophotometry and ultrasound) to baseline values for the same patient, a paired *t*-test was performed. To compare current objective outcomes between Hydrofilm and control halves, the unpaired two-samples *t*-test was used. The statistical significance level was defined as $p < 0.05$. SPSS Statistics version 27 (IBM, Armonk, NY, USA) was used to perform the analyses.

3. Results

3.1. Patient Characteristics

Of 130 patients successfully completing either of the initial trials, 62 (47.7%) consented to the follow-up examination and yielded data for this analysis (Table 1). Median age (range) was 59 (37–81) years, whereas median follow-up time (range) was 58 (37–73) months after WBI. Approximately 98.4% of patients were female, and 95.2% were Caucasian. Further patient and radiation treatment characteristics are presented in Table 2.

Table 1. Overview of patient selection and inclusion.

	Schmeel et al. 2018 (September 2016–September 2017) [12]	**Schmeel et al. 2019 (March 2018–June 2019) [13]**	**Total**
Enrolled	62	80	142
Included	56	74	130
	deceased		−8
	recurrent or metastatic disease		−10
	refusal to participate		−22
	not reached		−28
Included	33	29	62

Table 2. Patient and radiation treatment characteristics (n = 62).

	Median (Range)
Age in years	59 (37–81)
Follow-up time in months	58 (37–73)
	***n* (%)**
Female	61 (98.4)
Caucasian	59 (95.2)
Diabetes mellitus	1 (1.6)
Active smoking	11 (17.7)
Fitzpatrick skin type	
I	11 (17.7)
II	44 (71.0)
III	6 (9.7)
V	1 (1.6)
Fractionation regimen	
50 Gy in 25 fractions	33 (53.2)
40.05 Gy in 15 fractions	29 (46.8)
Sequential boost	31 (50.0)
Hydrofilm halve	
lateral	30 (48.4)
medial	32 (51.6)

3.2. Objective Outcomes

(a) Pigmentation Changes (Spectrophotometry)

Baseline spectrophotometric data (before irradiation) were compared with the means of four ipsilateral measurements at follow-up. A slight decrease in L* value and an increase in a* value (indicating more black and more red, respectively) were observed. These differences, however, were not significant. On the other hand, a significant increase in b* value (indicating more yellow) was observed ($p < 0.001$). Results are summarised in Table 3.

Table 3. Spectrophotometric comparison of baseline breast colour and combined ipsilateral values at follow-up (n = 558 readings).

	Baseline	**Follow-Up**	**Δ**	***p***
Mean L*	69.6	69.3	−0.3	0.191
Mean a*	6.5	6.6	+0.1	0.326
Mean b*	14.1	14.8	+0.7	<0.001

At follow-up, both halves of the irradiated breast (Hydrofilm versus standard of care) were compared. No significant differences in either L*, a*, or b* values were observed. Results are summarised in Table 4.

Table 4. Spectrophotometric comparison of Hydrofilm and control breast halves at follow-up (n = 248 readings).

	Hydrofilm	**Control**	**Δ**	***p***
Mean L*	69.2	69.1	+0.1	0.911
Mean a*	6.6	6.7	−0.1	0.786
Mean b*	14.9	15.0	−0.1	0.811

(b) Skin Fibrosis (Ultrasound)

Baseline ultrasonographic measurements were compared with the means of four ipsilateral measurements at follow-up. Overall, there was a significant increase in skin thickness with a doubling of cutis, subcutis, and subcutaneous oedema dimensions following irradiation. Table 5 summarises these results.

Table 5. Ultrasonographic comparison of baseline breast skin thickness and combined ipsilateral values at follow-up (n = 496 readings).

	Baseline	Follow-Up	Δ	p
Cutis (mm)	1.9	3.8	+1.9	<0.001
Subcutis (mm)	2.7	5.5	+2.8	<0.001
Oedema (mm)	2.3	4.5	+2.2	0.004

At follow-up, both halves of the irradiated breast (Hydrofilm versus standard of care) were compared. No significant differences in either cutis, subcutis, or subcutaneous oedema thickness were observed. Results are summarised in Table 6.

Table 6. Ultrasonographic comparison of Hydrofilm and control breast halves at follow-up (n = 248 measurements).

	Hydrofilm	Control	Δ	p
Cutis (mm)	3.7	3.9	−0.2	0.525
Subcutis (mm)	5.5	5.5	0	0.918
Oedema (mm)	3.8	5.3	−1.5	0.521

4. Discussion

Barrier films such as Hydrofilm prove useful in the prevention of acute RD during WBI for breast cancer. They have been shown to improve clinician- and patient-reported outcomes and subsequent quality of life. An increased interest in this cost-effective prophylactic measure, reflected by a recent surge of publications on this topic, prompts the need for an assessment of the impact of barrier films on late skin toxicities. Here, we report the long-term follow-up of two previously published intrapatient-randomised controlled trials to assess potential differences in pigmentation changes and fibrosis between breast skin compartments that have been treated with Hydrofilm or standard of care and to establish the long-term safety of barrier films.

Overall, a slight difference in skin pigmentation (more yellow tones) and a marked increase in overall skin thickness, reflecting fibrosis, were observed when comparing irradiated breasts to baseline measurements before WBI initiation. These objective results corroborate previous (mainly clinician-reported) findings of increased skin fibrosis following WBI with contemporary radiation techniques [20,21,27].

However, when comparing pigmentation and skin thickness between Hydrofilm and standard of care breast halves, no significant differences were observed. Hydrofilm application during WBI thus does not impact late cutaneous toxicity rates, neither positively nor negatively.

Other barrier films with a similar mechanism of action to Hydrofilm are available and are being used to prevent acute RD in adjuvant WBI. Mepitel® film, a commonly used silicone-based barrier film, results in a similar improvement of both clinician- and patient-reported outcomes [28–30]. Due to its very similar properties and mode of use, we reason that its impact on late toxicity may be similar to that of the here investigated Hydrofilm. The evidence on other barrier films, dressings, and creams, as well as film-forming gels, in the context of acute RD prevention is limited [14]. Furthermore, their impact on late toxicity has not been investigated.

An increasing number of other interventions for acute RD prevention have been or are being investigated, with varying results. Due to insufficient and sometimes even conflicting evidence, a recommendation can currently only be made for a handful of interventions [17]. Of all natural agents, only oral enzymes and olive oil have proved useful so far [31,32]. Since the publication of the Multinational Association of Supportive Care in Cancer (MASCC) guideline, other topical agents such as epigallocatechin-3-gallate have been investigated successfully [33].

Topical corticosteroids (mometasone, betamethasone) are effective in reducing RD-related symptoms such as pain, burning, or itching; however, their widespread and prolonged use remains limited due to the associated side effect profile [34–36]. Care should also be taken if moist desquamation is present, as topical corticosteroids might then delay wound healing or promote infection.

Lastly, medical devices such as photobiomodulation therapy have also proved useful, especially in the context of breast cancer [37]. Other devices for acute RD prevention are currently being investigated [38–40].

Even though many trials have investigated measures to prevent acute RD, none have considered the impact of these interventions on late cutaneous toxicities. Furthermore, there is a general lack of studies exploring preventative or therapeutic interventions for late radiation-induced toxicity. Additional research on these topics is desirable to prevent adverse cosmetic outcomes and improve quality of life of (breast) cancer survivors. Another valuable approach towards reducing acute side effects are advances in radiation treatment techniques and patient positioning [41]. The impact of such developments on late toxicity should also be investigated in the future.

Our study is not without limitations. First, only half of the initial study population could be recruited for this follow-up examination (almost 40% of patients could either not be reached or declined participation), resulting in a relatively small sample size. Therefore, subgroup analyses (e.g., based on fractionation regimen or Fitzpatrick skin type, factors known to influence radiation toxicity) were not performed, and it is currently unknown if certain subgroups might have benefited from Hydrofilm application in terms of late skin toxicity, which should be assessed in future prospective trials. Furthermore, due to the intrapatient-randomised design of both initial trials, an assessment of clinician- and patient-reported late toxicities was not possible, as this requires an evaluation of the entire irradiated breast. If each patient acts as their own control, confounding can be minimised, which omits the need for stratification based on other factors known to influence the RD risk (e.g., breast size, Fitzpatrick skin type, fractionation regimen), which is why this design was chosen in the first place. Furthermore, external factors influencing the development of pigmentation changes and/or skin fibrosis (e.g., skin care routine, sun exposure) can be disregarded due to intrapatient randomisation. The use of validated objective assessment methods in the current trial could also partially bypass this. Long-term follow-up of similar trials with a physical control group who did not receive barrier film will further elucidate this in the future [30].

5. Conclusions

To the best of our knowledge, we provide the first comprehensive assessment with a mature follow-up of the impact of Hydrofilm on late skin toxicity following adjuvant WBI for breast cancer. Even though no improvements in the rate of pigmentation changes or skin fibrosis were observed, the data suggest that Hydrofilm can be safely used in the context of acute RD prevention, without affecting said late radiation-induced side effects. The data thus support the widespread use of barrier films for the prevention of acute RD in WBI.

Author Contributions: L.C.S. conceived the study; C.S.D. and L.C.S. designed the study; material preparation, data collection and analysis were performed by C.S.D., K.L. (Kira Lindner), A.B., A.A. and L.C.S.; the first draft of the manuscript was written by C.S.D.; L.C.S. reviewed and edited, and all remaining authors (K.L. (Kira Lindner), A.B., A.A., K.L. (Katharina Layer), T.A., J.P.L., G.R.S., D.S.,

D.K., C.L., C.K., A.F.) commented, read, and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Research data are available upon reasonable request.

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Conflicts of Interest: There are no relevant financial or non-financial interest to disclose.

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4 Diskussion

Eine Strahlentherapie ist im Verlauf der onkologischen Behandlung bei ca. 50 % der Krebspatienten indiziert (Delaney et al., 2005). Abhängig von der Körperregion, Entität und Intention (d. h. kurativ oder palliativ) mit entsprechender Gesamtdosis variiert die Belastung der Haut als Eintrittsstelle der Photonenstrahlen. Insbesondere bei der kurativen Strahlentherapie im Brust-, Kopf-Hals- oder sonstigen Weichteilbereichen (z. B. Hauttumore, Sarkome) wird die Haut häufig in Mitleidenschaft gezogen, was sich klinisch als Radiodermatitis manifestiert. Die Berücksichtigung von Behandlungs- (z. B. operatives Verfahren, Technik und Fraktionierung der Bestrahlung, parallele Systemtherapien) und Patientencharakteristika (z. B. Ethnizität, BMI, Rauchen) kann dieses Risiko zwar modulieren, insgesamt bleibt die Radiodermatitis dennoch die häufigste Nebenwirkung der perkutanen Strahlentherapie (Böhner et al., 2020; Behroozian et al., 2021a). Was allerdings in der Vergangenheit durch Patienten und andere Gesundheitsdienstleister ebenso (inklusive Strahlentherapeuten) als obligate „Verbrennungen“ gekennzeichnet wurde, ist mittlerweile selten geworden. Heutzutage liegt das Risiko für eine mittelgradige bis schwere Radiodermatitis (d. h. CTCAE Grad ≥ 2) nach einer leitlinienkonformen, hypofraktionierten Ganzbrustbestrahlung noch bei ca. 25 %, was trotz der bereits erzielten Fortschritte allerdings immerhin noch weiteren Raum für Verbesserungen zulässt (Jagsi et al., 2015; Schmeel et al., 2020).

Grundsätzlich kann auf verschiedene Arten versucht werden, die Prävalenz und den Schweregrad der Radiodermatitis weiter zu reduzieren. Eine erste Möglichkeit ist ein sogenannter *top-down approach*, wobei technische Fortschritte in der Strahlentherapie und Medizintechnik eine Verbesserung gestatten, z. B. durch die Anwendung der volumetrisch-modulierten Bogenbestrahlung (VMAT) oder Bestrahlung in Bauchlage bei Patienten mit großem Brustvolumen (Vesprini et al., 2022). Ferner führen neue tumor- und radiobiologische Erkenntnisse bereits zu einer möglichen Verringerung der strahlentherapeutischen Gesamtdosis (z. B. Deeskalation bei Kopf-Hals-Tumoren die mit dem humanen Papillomvirus in Verbindung gebracht werden; aktuell allerdings kontrovers diskutiert) und des bestrahlten Volumens (z. B. Teilbrustbestrahlung bei Mammakarzinomen mit einem insgesamt niedrigen Rezidivrisiko) bei gleicher Effektivität, was bisher jedoch nur bei bestimmten Tumorentitäten bereits etabliert ist (Coles et al., 2017; Rühle et al., 2021). Mit der aktuell vorhandenen technischen Ausstattung

und gegenwärtigen onkologischen Erkenntnissen bleibt allerdings ein Residualrisiko für die Radiodermatitis bestehen. Die zweite Möglichkeit (*bottom-up approach*) versucht dies durch eine Optimierung der Supportivtherapie weiter zu senken. Ein besseres Verständnis der komplexen Pathophysiologie der Radiodermatitis beleuchtet dabei mögliche Startpunkte für ein optimales Nebenwirkungsmanagement. Hier können entweder bereits etablierte Maßnahmen zur Prävention oder Therapie bei anderen Bestrahlungsindikationen oder Tumorentitäten überprüft werden, um die Subgruppen zu definieren, die hiervon am meisten profitieren, oder es können neue Interventionen entwickelt und anschließend getestet werden.

Die Erforschung neuer Bestrahlungstechniken nimmt sehr viel Zeit in Anspruch und außerdem braucht man hierfür entsprechende Mittel und eine ausgiebige technische Expertise, was als deutliche Limitierung dieser Vorgehensweise für eine klinische Abteilung betrachtet werden kann. Somit ist es als Arbeitsgruppe der eigenen Klinik, in der man täglich mit den Patienten in Kontakt kommt, grundsätzlich einfacher, sich auf die Optimierung der Säule der Supportivtherapie zu konzentrieren, solange man die Integration der technischen Fortschritte im klinischen Alltag abwartet, um so einen positiven Einfluss auf die onkologischen Patienten zu haben, die schon heute therapiert werden.

In der ersten Publikation (Dejonckheere et al., 2023a) wurde mit einer kritischen Würdigung der bereits vorhandenen Evidenz hinsichtlich Film- und Folienverbänden angefangen. Mepitel- und Hydrofilm gehören seit mehreren Jahrzehnten zum Standard in der Wundbehandlung (Palfreyman et al., 2010). Diese sterilen Polyurethanfolien können direkt auf eine Wunde aufgebracht werden und schützen sie vor Reibung und Feuchtigkeit, indem sie eine semipermeable mechanische Barriere zwischen der geschädigten Basalschicht der Haut und diesen möglichen zusätzlichen Traumata bilden (Herst, 2014). Feuchte Desquamationen im Rahmen einer Radiodermatitis bei Brustbestrahlung haben eine Prädilektion in denjenigen Bereichen, die besonders anfällig für Friktion sind (z. B. axillär, inframammär). Eine erste Studie aus 2010 untersuchte daher den Einsatz dieser Verbände bei der Behandlung einer Radiodermatitis im Kontext der Brustbestrahlung (Diggelmann et al., 2010). Ab dem Augenblick, wo ein Erythem sichtbar war, wurde ein Schaumverband (Mepilex Lite) auf die Haut aufgetragen, was im Vergleich zur Standardtherapie (eine wasserbasierte Creme) zu einer

signifikanten Verringerung des maximalen Schweregrades führte. Aufgrund dieser vielversprechenden Ergebnisse wurde die Effektivität solcher und ähnlicher Verbände auch als prophylaktische Radiodermatitismaßnahme in anschließenden Studien überprüft.

In der vorgestellten Publikation wurde die internationale Literatur bis März 2023 mit entsprechenden Ein- und Ausschlusskriterien durchsucht und dabei wurden fünf randomisierte Studien identifiziert (Dejonckheere et al., 2023a). Aufgrund des größtenteils übereinstimmenden Designs dieser Studien mit der Erhebung ähnlicher Endpunkte war eine kumulative Auswertung der quantitativen Ergebnisse mittels Metaanalyse möglich, welche den Nutzen dieser Intervention überzeugend bestätigen konnte: eine konsistente Verbesserung der CROs und PROs bei adjuvanter Brustbestrahlung war offensichtlich. Die Ergebnisse schließen sich daher den Empfehlungen der nationalen und internationalen Leitlinien zum Thema radioonkologischer Supportivtherapie an (Behroozian et al., 2023b). Die Schwächen und Limitierungen der einzelnen inkludierten Studien wurden dabei kritisch betrachtet und das jeweilige *risk of bias* eingeschätzt. Über diese fünf Studien hinaus war insbesondere das Fehlen einer Verblindung (aufgrund der sichtbaren Art der Intervention) eine Einschränkung, die bei der Beurteilung der Ergebnisse unbedingt berücksichtigt werden muss.

Im gleichen Zeitraum dieser Publikation der eigenen Arbeitsgruppe erschienen zwei weitere Übersichtsarbeiten zum Einsatz von Film- und Folienverbänden zur Radiodermatitisprophylaxe bei der adjuvanten Bestrahlung des Mammakarzinoms. Das plötzlich erhöhte Interesse für diese Intervention kam am ehesten als Antwort auf die bis dato größte Studie zum Thema zustande, die überdies hochrangig publiziert wurde (Behroozian et al., 2023a). Robijns et al. identifizierten bei deren Literaturrecherche 14 Studien (bis September 2020; es wurden auch Studien zu den sogenannten barriereschichtbildenden Cremes inkludiert, mit allerdings unterschiedlichen Produktspezifikationen), Kraemer et al. inkludierten sechs (Literatur bis März 2023) (Robijns et al., 2023; Kraemer et al., 2023). Obwohl beide Studien zu den gleichen Ergebnissen kamen und den Nutzen von Film- und Folienverbände zur Vorbeugung einer Radiodermatitis bestätigen, sind die Empfehlungen insgesamt schwacher, hauptsächlich aufgrund der weniger strikten Einschlusskriterien für Studien bei der systematischen Überprüfung der Literatur (hinsichtlich Art der untersuchten Interventionen und auch

Studiendesign). Der Mangel an Standardisierung führt hier somit zu inkonsistenten und generell schwachen Empfehlungen.

Die eigene Arbeit diskutiert außerdem als einzige weitere wichtige Aspekte der Intervention, wie z. B. Gesamtkosten, Aufwand der Anwendung sowie subjektive Verträglichkeit und mögliche Nebenwirkungen. Auch die Unterschiede zwischen den beiden inkludierten Folien werden erläutert: Mepitel- und Hydrofilm unterscheiden sich hauptsächlich im Hinblick auf den verwendeten Klebstoff (silikon- bzw. polyacrylatbasiert). Mepitel-Film lässt sich leichter entfernen und ist somit bei Patienten mit einer empfindlicheren Haut gut geeignet, im Gegensatz zum Hydrofilm, der mit seinem stärkeren Klebstoff bei körperlich aktiven Patienten oder solchen, die zu stärkerer Schweißbildung neigen, besser geeignet ist und auch besser in komplexen anatomischen Regionen hält (z. B. bei Frauen mit großem Brustvolumen oder Bestrahlung der regionalen Lymphabflusswege).

Kürzlich wurde auch die Evidenz zu Film- und Folienverbänden bei Bestrahlungen im Kopf-Hals-Bereich mittels einer Metaanalyse gepoolt, wobei drei randomisierte Studien mit Mepitel-Film (Literatur bis März 2023) inkludiert wurden (Lee et al., 2023). Diese Studie wurde durch unsere Arbeitsgruppe mittels *peer review* begutachtet. Die Ergebnisse sind wie bei der Brustbestrahlung durchaus positiv was die maximale Ausprägung der Radiodermatitis und assoziierter Symptomatik anbelangt (d. h. eine Verbesserung der CROs und PROs), aufgrund der etwas komplexeren Anatomie dieser Körperregionen (z. B. mehr Hautfalten, größere Mobilität, Bartwuchs bei Männern) ist die Verträglichkeit des Mepitel-Films bei diesen Patienten im Vergleich jedoch weniger gut. Eine der inkludierten Studien wurde aufgrund dessen sogar vorzeitig abgebrochen, da ca. die Hälfte der Probanden den Filmverband durch Juckreiz bedingt nicht vertragen konnte (Rades et al., 2019). Diese offensichtliche Diskrepanz zwischen Einsatz bei Brust- oder Kopf-Hals-Bestrahlung bestätigt somit die Notwendigkeit der Überprüfung einer Intervention (hier Mepitel-Film) in verschiedenen klinischen Kontexten und es kann nicht a priori eine Wirksamkeit und Extrapolation der Ergebnisse antizipiert werden. Außerdem sollten zukünftige Studien den Nutzen von Film- und Folienverbände zur Radiodermatitisprophylaxe bei Kopf-Hals-Bestrahlungen weiter untersuchen, da die Datenlage bisher insgesamt deutlich limitiert ist.

In der zweiten Arbeit (Dejonckheere et al., 2023b) wird die Wirksamkeit eines innovativen Verfahrens zur möglichen Radiodermatitisprophylaxe zum ersten Mal in einem größeren Kollektiv untersucht. Das NIPP (auch bekannt als Kaltplasma) ist eine flüchtige, aus Umgebungsluft erzeugte reaktive Mischung aus freien Elektronen, Ionen, angeregten Atomen und reaktiven Sauerstoffspezies. Es wurde in der Medizin initial zur Oberflächenreinigung eingesetzt, jedoch wurden die dosisabhängigen und vielversprechenden Wirkungen bei entzündlichen Hautkrankheiten (Psoriasis, Ekzeme, diabetische Ulzera, verschiedene Arten von Dermatitiden) bereits früh erkannt (Gan et al., 2018). Heutzutage gehört das NIPP dementsprechend vor allem zur Ausstattung der Dermatologen, wo es einen bereits etablierten Einsatz bei der Haut- und Wundpflege besitzt. Die stärkste Datenlage besteht zurzeit bei diabetischen Ulzera, eine häufige und oft therapierefraktäre Komplikation dieser metabolen Krankheit. Mehrere randomisierte, placebokontrollierte, verblindete Studien zeigten eine signifikant schnellere Zeit bis zum Wundverschluss nach NIPP-Behandlung, bei außerdem kompletter Abwesenheit von Komplikationen (Mirpour et al., 2020; Stratmann et al., 2020). Im Jahr 2022 wurde sogar zum ersten Mal eine S2k-Leitlinie zum rationalen therapeutischen Einsatz vom NIPP erstellt, die sich aktuell noch hauptsächlich auf Therapie oben genannter chronischer und infizierter Wunden beschränkt (Metelmann, 2022). Einzigartig am NIPP ist die exzellente Verträglichkeit mit Fehlen von unerwünschten Wirkungen (genotoxisch, mutagen oder klinisch). In-vitro Studien, Tierversuche und klinische Studien im Beobachtungszeitraum von mittlerweile acht Jahren konnten bisher keine gravierenden Nebenwirkungen identifizieren, was es zu einem hochinteressanten Thema im Rahmen der onkologischen Supportivtherapie macht (Kluge et al., 2016; Assadian et al., 2019; Boekema et al., 2021).

Die einzigen präklinischen in-vivo Ergebnisse bei Mäusen im Kontext der Radiodermatitis zeigten auch hier eine potenzielle Wirkung des NIPPs, mit einem verzögerten Auftreten und verminderten Schweregrad (Bernhardt et al., 2021). Eine klinische Studie am Menschen war zum damaligen Zeitpunkt allerdings noch nicht durchgeführt worden. Da reaktive Sauerstoffspezies (z. B. O_2^-, O_3, H_2O_2, NO) sowohl bei den durch ionisierende Strahlung verursachten Gewebeschäden eine wichtige Rolle spielen, als auch im Rahmen der NIPP-Therapie an der Gewebereparatur beteiligt sind, war eine Durchführbarkeits- und Dosiseskalationsstudie dieser Kombination gerechtfertigt und sogar obligat, insbesondere um eine potenziell additive oder synergistische Toxizität

durch die NIPP-Applikation im Rahmen der Strahlentherapie ausschließen zu können und zu überprüfen, ob die günstige und dosisabhängige Auswirkung des NIPPs auf die Gewebeheilung überhaupt bestehen bleibt. In einer Phase-1-Studie (30 Patienten) wurden Sicherheit und Durchführbarkeit der Anwendung eines topischen NIPP-Geräts zur Radiodermatitisprävention von der eigenen Arbeitsgruppe zum ersten Mal nachgewiesen (Dejonckheere et al., 2022). Parallel zur Bestrahlung wurde die bestrahlte Brust zusätzlich zur Standardhautpflege mit NIPP behandelt mit verschiedenen Anwendungsschemata (60 Sekunden 2×/Woche, 180 Sekunden 3×/Woche und 120 Sekunden 5×/Woche). Sicherheits- und Durchführbarkeitsmerkmale wurden dabei erfasst sowie auch die Bruttokosten. Keinem der Patienten wurde topische Kortikoide verschrieben und keiner empfand die Behandlung als unangenehm. Bis zu einer Nachbeobachtungszeit von 6 Wochen wurden weder NIPP-bezogene unerwünschte Ereignisse, noch Nebenwirkungen oder Wechselwirkungen mit der Strahlentherapie beobachtet. Im Vergleich mit rezenten Toxizitätsbewertungen in der internationalen Literatur (unter Anwendung der gleichen, modernen hypofraktionierten Ganzbrustbestrahlung) wurden außerdem vielversprechende initiale Ergebnisse beobachtet (Jagsi et al., 2015; Shaitelman et al., 2015; Schmeel et al., 2020).

Als Rationale zur Wirksamkeit wird eine bakterielle Dekolonisierung der Haut diskutiert, was durch eine gleichzeitig publizierte, randomisierte Studie untermauert wird (Kost et al., 2023b). Dabei wurde gezeigt, dass eine bakterielle Dekolonisierung mittels intranasaler Mupirocinsalbe und lokaler Anwendung von Chlorhexidin auf der Haut zu einer signifikanten Verringerung der (verblindeten) Radiodermatitis und feuchten Desquamation führte im Vergleich zur (nicht-definierten) Standardhautpflege. Die PROs (gemessen anhand Skindex-Fragebogen) wurden dabei allerdings nicht beeinflusst. Letztere Studie wurde zwar hochrangig publiziert und von verschiedenen Fachgesellschaften gelobt, unterliegt jedoch zahlreichen methodischen Einschränkungen. So fehlen beispielsweise Angaben zur Standardhautpflege (insbesondere bezüglich der Anwendung topischer Kortikoide), Bestrahlung (Technik, Boost, Bolus) oder zum operativen Verfahren (BET oder Mastektomie) oder Brustvolumen, allesamt Faktoren, die das Risiko einer Radiodermatitis stark beeinflussen können (Böhner et al., 2020; Behroozian et al., 2021a). Chlorhexidin erscheint natürlich attraktiv zur Radiodermatitisprophylaxe, weil der Wirkungsmechanismus sehr plausibel ist: *Staphylococcus aureus*, der bei über 30 % der Menschheit als kommensaler Organismus auf der Haut

vorkommt und ein unabhängiger Risikofaktor für die Entwicklung einer Grad ≥ 2 Radiodermatitis bei der Brustbestrahlung, wird durch Chlorhexidin deaktiviert (Kost et al., 2023b). So wird die Entzündungsreaktion, die durch Mikroben oder mikrobielle Antigene ausgelöst wird und die klinische Ausprägung der Radiodermatitis verstärkt, gebremst. Ferner ist Chlorhexidin einfach anwendbar, allgemein bekannt, günstig und ubiquitär verfügbar, was die Umsetzung dieser Maßnahme in der klinischen Praxis beschleunigt. Die Verträglichkeit war insgesamt gut; Juckreiz durch die supportive Behandlung mit Chlorhexidin wurde nur in 2,5 % (1 Patient) gesehen. Die exakte Rolle des Mikrobioms sowie die longitudinale Dynamik im Kontext der Radiodermatitis werden in einer bereits initiierten Studie der eigenen Arbeitsgruppe weiter untersucht.

Auch das NIPP hat eine hocheffiziente antibakterielle Wirkung, sodass es ähnlich wie Chlorhexidin funktionieren könnte, indem es die bakterielle Belastung des bestrahlten Integuments nebenwirkungsarm verringert und so die lokale Entzündungsreaktion minimiert (Daeschlein et al., 2015; Puligundla et al., 2017). Außerdem besitzt NIPP weitere (theoretische) Wirkungsmechanismen zur Radiodermatitisprophylaxe: so fördert es beispielsweise die Proliferation und Migration von Keratinozyten, Fibroblasten und Endothelzellen und unterstützt dadurch die Heilung des geschädigten Gewebes (Haertel et al., 2014). Die Erhöhung der vaskulären Scherspannung durch eine Beschleunigung der Neovaskularisation fördert die weitere Angiogenese, und der dadurch erhöhte kapillare Blutfluss erhöht außerdem die lokale Nährstoffversorgung und Sauerstoffsättigung des mit NIPP-behandelten Gewebes (Kisch et al., 2016, Duchesne et al., 2019). Transkription und Translation spezifischer DNA-Abschnitte, die an einer effektiven Wundheilung beteiligt sind, werden durch NIPP induziert und Veränderungen in der Lipidstöchiometrie der Hautbarriere sind eine weitere mögliche Auswirkung (Marschewski et al., 2012; Arndt et al., 2013).

Um die generierten Hypothesen in-vivo zu testen und die vorläufigen Ergebnisse der Phase-1-Studie zu bestätigen, wurde daher eine Phase-2-Studie (64 Patienten) durchgeführt, wobei die oben aufgeführten methodologischen Mängel der Arbeit mit Chlorhexidin so gut wie möglich berücksichtigt und vermieden wurden (Dejonckheere et al., 2023b). Um eine möglichst störfaktorfreie Interpretation der Ergebnisse zu gewährleisten, wurde in der Studie eine sogenannte Intrapatienten-Randomisierung vorgenommen, indem die bestrahlten Brusthälften ein und desselben Patienten (medial,

lateral) randomisiert wurden um entweder die Intervention (hier NIPP) oder Placebo (hier ein identisches, aber nicht-funktionelles Gerät, dass kein NIPP erzeugen kann; eine sogenannte *sham* Behandlung) zu erhalten. Da alle Patienten zweimal täglich eine harnstoffhaltige Creme im Bestrahlungsbereich anwendeten (als Standardhautpflege der Institution), wurde letztendlich der additive Effekt des NIPPs (als *add-on* Behandlung) untersucht. Die Anwendung dieser Intrapatienten-Randomisierung hat mehrere Vorteile: abgesehen von der positiven Auswirkung auf die Patientenrekrutierung (alle Patienten erhalten die Intervention), fungiert jeder Patient außerdem als seine eigene Kontrolle, was eine Stratifizierung basierend auf etablierten Risikofaktoren der Radiodermatitis (hier z. B. Hauttyp, Brustvolumen, Bestrahlungsdosis) überflüssig macht und somit *confounding* Faktoren bei der Auswertung größtenteils ausschließt. Dieses attraktive Design wurde bereits erfolgreich bei mehreren Studien zum Thema Radiodermatitisprophylaxe eingesetzt, z. B. bei den Film- und Folienverbände (Herst et al., 2014; Schmeel et al., 2018; Møller et al., 2018; Schmeel et al., 2019).

Was bei dem Design der aktuellen Studie allerdings nicht berücksichtigt wurde (da keine Vorgängerstudien vorhanden waren), ist eine mögliche Diffusion des flüchtigen NIPPs zur Placeboseite, mit entsprechender Wirkung ebendort. Diese Hypothese wird durch die Ergebnisse der Studie unterstützt: zwar wurde eine Verbesserung der CROs, PROs und objektiven Bewertungen (Spektralphotometrie der Haut) der NIPP-Hälften im Vergleich zu den Placebohälften beobachtet, diese war jedoch nicht signifikant unterschiedlich. Ein Vergleich mit einem sehr ähnlichen Kollektiv aus unserer Klinik (Schmeel et al., 2020) in Bezug auf die Prävalenz einer Radiodermatitis (gleiche strikte Einschlusskriterien, gleiches Bestrahlungskonzept, gleiche Standardhautpflege sowie Erhebung der gleichen Endpunkte zu den gleichen Zeitpunkten) konnte jedoch eine hochsignifikante Verbesserung aller Studienzielgrößen nachweisen. Insbesondere das komplette Fehlen von Neben- oder Wechselwirkungen sowie die hohe Akzeptanz (keine der Patienten empfand die NIPP-Behandlung als unangenehm, 97 % würden sie weiterempfehlen und 95 % hätten sich auch außerhalb der Studie mit NIPP behandeln lassen wollen) und den positiven Einfluss auf die verblindeten subjektiven Symptome der Patienten (im Gegensatz zu der Studie mit Chlorhexidin), machen den Einsatz des NIPPs zur Prophylaxe der Radiodermatitis äußerst attraktiv. Um die Wirkung abschließend zu beurteilen ist allerdings eine randomisierte Phase-3-Studie mit einer

physischen Kontrollgruppe erforderlich und bereits unsererseits initiiert (registriert unter DRKS00032560).

Wie es oftmals bei klinischen Studien der Fall ist, führen die erhobenen Ergebnisse zu weiteren Fragestellungen und Hypothesen. So wäre es beispielsweise interessant, NIPP auch bei anderen Tumorentitäten (z. B. Bestrahlung im Kopf-Hals-Bereich) zu überprüfen und auch bei Patienten verschiedener Ethnizitäten (97 % der Probanden in der jetzigen Studie waren kaukasisch, im Gegensatz zu nur 7 % bei der Studie von Kost et al.). Auch die Behandlungszeit des NIPPs könnte in zukünftigen Studien modifiziert werden: es ist nämlich bekannt, dass eine längere Behandlungsdauer mit erhöhter Erzeugung von reaktiven Sauerstoffspezies nicht nur mit einer noch gründlicheren bakteriellen Dekolonisierung einhergeht, sondern auch mit einer gesteigerten Freisetzung entzündungshemmender und regenerativer Signalmoleküle (Sakiyama et al., 2012; Eggers et al., 2022). Eine weitere Dosiseskalation des NIPPs könnte somit zu einem verstärkten Effekt und damit noch besserem Ergebnis führen. Außerdem könnte der Einsatz von NIPP auch zur Prophylaxe und Therapie weiterer strahlentherapieassoziierter Nebenwirkungen im Rahmen klinischer Studien überprüft werden. So behalten Flüssigkeiten, die mit NIPP behandelt wurden, die entsprechenden gewebeheilenden Eigenschaften (sogenanntes *plasma-activated water*), was beispielsweise interessant wäre zur Erzeugung einer NIPP-Mundspüllösung zur Vorbeugung der enoralen Mukositis bei Bestrahlungen im Kopf-Hals-Bereich (Wong et al., 2023). Schließlich könnte die Wirkung des NIPPs auch im Kontext der ungeplanten oder akzidentellen Strahlenexposition überprüft werden, was in einer Übersichtsarbeit diskutiert wird (Dejonckheere et al., 2023d).

In der dritten Arbeit (Dejonckheere et al., 2023c) wurde versucht die methodologischen Stärken der Studien im akuten Kontext auch in der Beurteilung der Spätfolgen nach einer Brustbestrahlung ein- und umzusetzen, da sich verhältnismäßig wenige Studien mit diesem Thema befasst haben (u. a. aufgrund der erforderlichen langen Nachbeobachtungszeit). Dafür wurde ein prospektiv erhobenes, randomisiertes, homogenes Kollektiv der eigenen Klinik (Schmeel et al., 2020) knapp fünf Jahre nach Abschluss der Bestrahlung nachgesorgt. Aufgrund der strengen initialen Ein- und Ausschlusskriterien konnten, abhängig von der damals durchgeführten Fraktionierung (konventionell

oder moderat hypofraktioniert), zwei homogene Gruppen gebildet werden, was die Interpretation und Generalisierbarkeit der neuen Ergebnisse vereinfacht.

Mehrere große Studien untersuchten bereits die Unterschiede in Spättoxizität zwischen beiden Fraktionierungsschemata, bisher jedoch ausschließlich mittels CRO-basierten Bewertungsmethoden. So zeigte eine dänische Studie mit über 1 800 Patienten keine Unterschiede der Brustfibroseraten drei und fünf Jahre nach Bestrahlung, jedoch nach einer etwas längeren Nachbeobachtungszeit von 87 Monaten deutlich mehr Fibrose nach konventioneller Fraktionierung (Offersen et al., 2020). Die Anwendung von nicht-invasiven objektiven Messmethoden (Ultraschallmessung der Brusthaut) in der eigenen Arbeit konnte die Überlegenheit der moderaten Hypofraktionierung bereits nach einer medianen Nachbeobachtungszeit von 57 Monaten nachweisen und ist damit die erste Arbeit, die solche Unterschiede objektiv bestätigt. Die Entwicklung einer Fibrose erscheint somit ein dynamischer Prozess zu sein und Ultraschallmessungen stellen im Vergleich zu den ärztlichen Erhebungen eine sensitivere Bewertungsmethode dieser Spättoxizität dar (nach 57 vs. 87 Monaten oder bereits 2,5 Jahre früher observiert mit Ultraschall). Die Validität dieser Ergebnisse bzw. die Übereinstimmung zwischen CROs und Ultraschall im eigenen Kollektiv wird außerdem unterstützt durch optimierte, verblindete kosmetische Ergebnisratings nach moderater Hypofraktionierung, was den negativen Einfluss der Fibrose auf die Kosmesis nach Brustbestrahlung erneut bestätigt (Immink et al., 2012).

Die ultraschallbasierte Messung der Hautdicke nach Brustbestrahlung wurde bereits in anderen Publikationen untersucht, jedoch wurde hier zum ersten Mal gezeigt, dass mit diesem Protokoll auch klinisch unsichtbare Unterschiede im Submillimeterbereich bereits frühzeitig wahrgenommen werden können (Liu et al., 2010; Landoni et al., 2013). Einflüsse der Bestrahlungsdosis und -Fraktionierung auf das Auftreten der Spättoxizität können somit sensitiver identifiziert werden, was eine mögliche Applikation in zukünftigen Studienprotokollen sinnvoll erscheinen lässt. Auch die Änderungen der Hautpigmentierung, gemessen mittels Spektralphotometrie und verglichen mit den Ausgangswerten vor der ersten Bestrahlung, wurden auf diese Weise zum ersten Mal erfolgreich erfasst.

Verschiedene Items (Juckreiz, Schmerzen, Lymphödem) wurden in der Studie sowohl vom Arzt (CRO) als vom Patienten (PRO) beurteilt, sodass das Maß an Übereinstimmung zwischen beiden berechnet werden kann. Es wurde hier zum ersten Mal bestätigt, dass die vorhandenen Diskrepanzen zwischen CROs und PROs, bekannt aus dem akuten Setting, sich auch bei Erhebungen der Spätfolgen nach Brustbestrahlung (unabhängig von der durchgeführten Fraktionierung) manifestieren, da für die genannten Items nur moderate bis geringe Übereinstimmungen gefunden werden konnten, was den substanziellen Mehrwert der zusätzlichen PRO-Erhebungen neben den gängigen CROs in Studien über Spättoxizität unterstützt.

Die letzte Arbeit (Dejonckheere et al., 2023e) wurde von der ersten (Dejonckheere et al., 2023a) und dritten (Dejonckheere et al., 2023c) Arbeit inspiriert. Dabei wurden die Effekte von Hydrofilm, bekannt aus dem akuten Setting, auf die Spätfolgen nach Ganzbrustbestrahlung zum ersten Mal untersucht. Da die Prognose von Patienten mit Mammakarzinom im Frühstadium heutzutage, wie bereits erwähnt, sehr gut geworden ist und die Zahl an Langzeitüberleber nach Strahlentherapie stetig zunimmt, haben Themen wie Kosmesis, Selbstbild und entsprechende Lebensqualität (sogenanntes *survivorship*) nach einer Krebsbehandlung an Relevanz gewonnen, was die Rationale der durchgeführten Studie unterstützt. Patienten, die in der Vergangenheit an einer von zwei intrapatienten-randomisierten Studien der eigenen Klinik teilgenommen haben (Schmeel et al., 2018; Schmeel et al., 2019), wurden erneut eingeladen für eine objektive Langzeituntersuchung der Brusthaut. Alle Patienten wurden während der Strahlentherapie (im Median ca. fünf Jahre her) mit Hydrofilm versorgt (jeweils nur entweder die mediale oder laterale Brusthälfte) und die zuvor etablierten Messmethoden (Spektralphotometrie zur Beurteilung der Pigmentierung, Ultraschall zur Beurteilung der Hautdicke) wurden erneut eingesetzt. Auch in diesem Kollektiv wurde eine longitudinale Zunahme der Pigmentierung und Kutisdicke beobachtet im Vergleich mit den nicht-bestrahlten Brüsten der gleichen Patienten, Unterschiede zwischen den Brusthälften mit Hydrofilm oder Standardbehandlung ergaben sich jedoch nicht. Die Daten bestätigen somit, dass Hydrofilm die Rate an Spätfolgen nach Ganzbrustbestrahlung nicht erhöht bzw. auch in diesem Zusammenhang ein vernachlässigbarer Boluseffekt hat. Die Ergebnisse unterstützen die generalisierte Anwendung von Hydrofilm zur Prävention der Radiodermatitis weiter. Die größte Schwache dieser Studie ist das relativ kleine Kollektiv von 62 Patienten. Aufgrund der strikten

Einschlusskriterien konnte nur ca. die Hälfte der Patienten erneut eingeschlossen werden, was wohl zu einem sehr homogenen Kollektiv führte. Eine Subgruppenanalyse ist daher zum gegenwärtigen Zeitpunkt nicht möglich. Sinnvoll war allerdings den Vergleich mit den Baseline-Werten der gleichen Patienten, erhoben im Rahmen der initialen Studien. Die Studie stellt eine erste Langzeituntersuchung über den Impakt eines präventiven Ansatzes auf die Spätfolgen dar. Interessant wäre zukünftig noch zu untersuchen, inwiefern Mepitel, ein ähnlicher Filmverband mit allerdings unterschiedlichen Charakteristika, zu den gleichen Ergebnissen führt.

Eine durch unsere Klinik initiierte, multizentrische Umfrage der Strahlentherapiegesellschaft im deutschsprachigen Raum zeigte eine starke Variation der Risikobewertung, Überwachung, nicht-pharmakologischen Prävention und des pharmakologischen Managements der Radiodermatitis zwischen Gesundheitsdienstleistern, die in die Durchführung von Bestrahlungen involviert sind (Layer et al., 2023a; Layer et al., 2023b). Dies ist u. a. darauf zurückzuführen, dass in den verschiedenen Leitlinien (sowohl national als auch international), trotz der umfangreichen Literatur, oft diskrepante Empfehlungen vorhanden sind. Diese finden ihren Ursprung in methodologischen Schwächen der einzelnen Studien und bevorzugen mitunter Eminenz und Erfahrung gegenüber Evidenz. Auch die großen Studien, die sich mit der unterschiedlichen akuten Toxizität zwischen verschiedenen Fraktionierungsschemata befasst haben und deren Ergebnisse für die entsprechende Aufklärung der Patienten im klinischen Alltag angewendet werden, sind leider ebenso nicht frei von diesen Einschränkungen. So erwähnen weder Jagsi et al. (2 309 Patienten) noch Shaitelman et al. (287 Patienten) welche supportiven Maßnahmen, insbesondere die Anwendung topischer Kortikoide und eventuelle Unterschiede zwischen beiden Gruppen, bei den Patienten angewendet wurden, was die Interpretation und Generalisierbarkeit der Ergebnisse beeinträchtigt (Jagsi et al., 2015; Shaitelman et al., 2015). Das übergeordnete Thema der vier hier vorgestellten Arbeiten übersteigt daher die reine Verbesserung der klinischen Endpunkte oder die Darstellung der Überlegenheit bestimmter Fraktionierungsschemata oder präventiver Ansätze. In jeder Studie wird für einen achtsamen Umgang mit dem Studiendesign plädiert, um eine eindeutige Interpretation der Ergebnisse zu gewährleisten. Es wurde dabei großer Wert gelegt auf den Aufbau und die angewendeten Methoden, um zur jeweiligen Schlussfolgerung zu gelangen:

- homogene Kollektive in Bezug auf Patienten- (Behandlungsort, operatives Verfahren) und Behandlungsmerkmale (Dosis und Fraktionierung, begleitende Therapien) durch Anwendung strikter Ein- und Ausschlusskriterien (in der primären Situation und bei der Nachbeobachtung) sowie eine entsprechende Erwähnung dieser Charakteristika in den einzelnen Publikationen, da diese bei der Interpretation der Ergebnisse von großer Bedeutung sind. Dies gilt nicht nur für klinische Studien wo Patienten rekrutiert und inkludiert wurden, sondern auch für die systematische Überprüfung der bereits vorhandenen Literatur und Aufbau einer Metaanalyse (hier zum Thema Film- und Folienverbände);
- Limitierung von bias durch die Anwendung einer einfachen (Studien zur Spättoxizität) oder doppelten (Studie zum NIPP) Verblindung bei der Ergebnisbewertung, insbesondere wenn subjektive CROs erhoben werden;
- Anwendung einer einheitlich definierten Standardhautpflege (hier Thematisierung der Basismaßnahmen bei der Patientenaufklärung sowie Empfehlung einer fünfprozentigen, parfumfreien Harnstofflotion, zweimal täglich ab Beginn der Strahlentherapie) mit schriftlichen und mündlichen Informationen und (mindestens) wöchentlicher Überprüfung der Compliance und des Verzichts auf weitere topische Therapien, die die Ergebnisse beeinflussen können;
- Randomisierung der Patienten zwischen der untersuchten Intervention und einer angemessen definierten inaktiven Placebokontrolle (hier *sham* Behandlung mit einem identischen, aber nicht-funktionellem Gerät). Die Intrapatienten-Randomisierung (z. B. zwischen Brusthälften oder Halsseiten) ist zwar ein interessanter Aufbau für Studien, die prophylaktische oder therapeutische Maßnahmen im Kontext der Radiodermatitis untersuchen (dadurch, dass die Notwendigkeit einer Stratifizierung entfällt und somit das Confounding bei der Ergebnisbewertung gering bleibt); diese ist, wie sich herausgestellt hat, jedoch nicht für jede Intervention geeignet;
- Prädefinition klarer Endpunkte und eindeutige Diskussion der Maßnahmen, die ergriffen wurden bzw. erlaubt waren, um diese entsprechend zu handhaben (insbesondere die Verwendung topischer Kortikoide). Die stetige Anwendung der gleichen Endpunkte vereinfacht außerdem den Vergleich zwischen verschiedenen Interventionen;
- Berücksichtigung und Angabe etablierter Risikofaktoren für die Entwicklung einer Radiodermatitis und entsprechende Stratifizierung der Patienten. Bei der

initiierten Phase-3-Studie mit NIPP, wo eine physische Kontrollgruppe vorhanden ist, wird daher stratifiziert nach den zwei stärksten Risikofaktoren, nämlich Brustvolumen und Bestrahlungsdosis (Boost). Andere Risikofaktoren (z. B. operatives Verfahren, Bestrahlungstechnik- und Fraktionierungsschema) werden bereits beim Einschluss der Patienten homogenisiert;

- korrekte Einbeziehung der Patientenperspektive durch Verwendung einer passenden Befragung von PROs (RISRAS für akute Toxizität, PRO-CTCAE für Spättoxizität). Erstaunlicherweise ergab die oben genannte multizentrische Umfrage (244 Antworten), dass dieses Thema für 84 % der Gesundheitsdienstleister komplett unbekannt ist, was zu einer möglichen Unterbehandlung therapieinduzierter Nebenwirkungen führt (Layer et al., 2023a). Außerdem sind die Diskrepanzen zwischen CROs und PROs in der Bewertung von Nebenwirkungen nicht nur auf die Radiodermatitis oder Brustbestrahlung beschränkt, sondern auch bereits bei Strahlentherapien anderer Tumorentitäten bekannt, wie Prostata-, Analkanal-, Rektum- oder Zervixkarzinom (z. B. Rammant et al., 2018). Eine ähnliche Studie zu diesem Thema wird aktuell von der eigenen Arbeitsgruppe bei zerebraler Bestrahlung (Metastasen und hirneigene Tumoren) geführt, da insbesondere bei diesen Patienten, aufgrund der generell schlechten Prognose, die Lebensqualität und Minimierung therapie-assoziierter Nebenwirkungen äußerst wichtig sind (DRKS00031480);
- Verwendung biophysikalischer Parameter als objektive Endpunkte, um die Robustheit der Daten weiter zu verbessern. Als validierte, nicht-invasive Instrumente wurden die Spektralphotometrie sowie die ultraschallbasierte Messung der Hautdicke eingesetzt, wobei die Praktikabilität im Rahmen klinischer Studien jeweils überzeugend nachgewiesen wurde.

Die oben genannten Vorschläge stammen aus früheren Studien zur Radiodermatitisinterventionen, die in den verschiedenen Leitlinien insgesamt einen hohen Konsensgrad ergaben. Unter Anwendung dieser Maßnahmen erhoffen wir die Evidenz hinsichtlich kutaner Nebenwirkungen und Supportivtherapie, im Kontext der adjuvanten Bestrahlung des Mammakarzinoms und darüber hinaus, zukünftig weiter zu verbessern. Ein transparentes Studiendesign erhöht außerdem die Reproduzierbarkeit, was die Datenlage bestimmter Interventionen (ob supportive Maßnahmen oder Fraktionierungsschemata) stärkt und Empfehlungen bzw. Konsens beschleunigt. So könnte die

exponentielle Zunahme an Veröffentlichungen auch zu einer tatsächlichen Zunahme an präventiven und therapeutischen Optionen mit hohem Evidenzniveau für die Radiodermatitis führen und dementsprechend die Patientenversorgung weiter verbessern.

5 Zusammenfassung

Die akute Radiodermatitis, eine Unterbrechung der Selbsterneuerungsfähigkeit der Epidermis und somit Beeinträchtigung der Hautbarriere, ist die häufigste Nebenwirkung der Strahlentherapie, mit einer besonders hohen Prävalenz bei Brust- und Kopf-Hals-Bestrahlungen. Klinisch ist sie durch Erythem, Überwärmung, Juckreiz, Schmerzen, Ödem, trockene und feuchte Desquamationen gekennzeichnet, und in schweren Fällen (mit Erosionen oder Ulzerationen) kann sogar eine Unterbrechung der Behandlung erforderlich sein, was die Tumorkontrolle beeinträchtigt. Auch wenn meist nur eine geringe Ausprägung vorliegt, die Beschwerden nach Abschluss der Bestrahlung in der Regel selbstlimitierend sind und jüngste Fortschritte der Bestrahlungstechnik (z. B. IMRT), Fraktionierung (z. B. Hypofraktionierung) und Positionierung (z. B. Bestrahlung in Bauchlage bei großem Brustvolumen) das Risiko weiter senken, können auch milde Symptome die Lebensqualität und das Selbstbild erheblich beeinträchtigen, u. a. durch einen negativen Einfluss auf die Kosmesis (sowohl akut als auch chronisch). Trotz laufender Forschungsanstrengungen sind wirksame präventive und therapeutische Optionen begrenzt, und die Behandlungsempfehlungen in den vorhandenen Leitlinien weisen erhebliche Diskrepanzen auf, sodass die Prävention und Behandlung der Radiodermatitis in praxi sehr unterschiedlich gehandhabt wird.

In den Originalarbeiten, die dieser kumulativen Habilitationsschrift zu Grunde liegen, wurde daher versucht, die Evidenz hinsichtlich einer bereits bestehenden und kosteneffektiven Intervention, über die genereller Konsens besteht (die Film- und Folienverbände), kritisch zu prüfen und mittels einer Metaanalyse zu poolen. Hier zeigte sich eine eindeutige Verbesserung der CROs und PROs, was diese Intervention somit zu einer hervorragenden Methode zur Prävention der Radiodermatitis macht. Die Schwächen und Starken der inkludierten Studien wurden berücksichtigt und dahingehend angewendet, um eine neue und innovative Radiodermatitispräventionsmethode zum ersten Mal in einem größeren Kollektiv zu untersuchen. Das NIPP oder Kaltplasma, eine Form des vierten Aggregatzustands, charakterisiert durch freie Elektronen, ist eine nebenwirkungsarme und benutzerfreundliche Methode zur bakteriellen Dekolonisierung der Haut, basierend auf neuesten Erkenntnissen, die das dermale Mikrobiom als potenziellen Risikofaktor der Radiodermatitis aufzeigten. Die Wirksamkeit wurde, nach Bestätigung der Sicherheit und Durchführbarkeit, untersucht und nachgewiesen,

vorbereitend auf eine prospektive, randomisierte, doppelblinde, placebokontrollierte Phase-3-Studie. In den letzten Studien wurden die gleichen methodologischen Stärken im Kontext der Spätfolgen einer Brustbestrahlung angewendet. Die Einflüsse der Bestrahlungsdosis und Fraktionierung auf das Auftreten der Spättoxizität wurden objektiv identifiziert. Außerdem wurde mit den gleichen Methodiken zum ersten Mal gezeigt, dass Hydrofilm im Rahmen der akuten Radiodermatitisprävention sicher eingesetzt werden kann, ohne dass die Rate an Spätnebenwirkungen erhöht wird, was die generelle Anwendung weiter unterstützt.

Das übergeordnete Thema der einzelnen Studien übersteigt die reine Verbesserung der klinischen Endpunkte oder die Darstellung der Überlegenheit bestimmter Fraktionierungsschemata oder präventiver Ansätze. In jeder Studie wird für einen achtsamen Umgang mit dem Studiendesign plädiert, um eine eindeutige Interpretation der Ergebnisse zu gewährleisten, u. a. durch Implementierung von CROs, PROs und objektive Messmethoden. Es wurde großer Wert auf den Aufbau und die angewendeten Methoden gelegt, um jeweils zur Schlussfolgerung zu gelangen, wobei besonders auf ein umfassendes und störfaktorfreies Studiendesign geachtet wurde.

Unter Anwendung dieser Maßnahmen erhoffen wir uns, die Evidenz hinsichtlich kutaner Nebenwirkungen und Supportivtherapie im Kontext der adjuvanten Bestrahlung des Mammakarzinoms und darüber hinaus zukünftig weiter zu verbessern. Ein transparentes Studiendesign erhöht nämlich die Reproduzierbarkeit, was die Datenlage bestimmter Interventionen (ob supportive Maßnahmen oder Fraktionierungsschemata) stärkt und Empfehlungen bzw. Konsens beschleunigt. So könnte die rezent exponentielle Zunahme an Veröffentlichungen auch zu einer tatsächlichen Zunahme an präventiven und therapeutischen Optionen mit hohem Evidenzniveau für die Radiodermatitis führen und dementsprechend die Patientenversorgung weiter verbessern.

6 Darstellung der Überlappung durch geteilte Autorenschaften

Die vorliegende Habilitationsschrift hat vier publizierte Originalarbeiten zur Grundlage, die ich allesamt als Erstautor veröffentlicht habe. Die Studien und Manuskripte sind stets in enger Zusammenarbeit mit der Arbeitsgruppe der eigenen Klinik zustande gekommen, unter Leitung von Herrn Priv.-Doz. Dr. med. Christopher Schmeel.

Eine geteilte Erstautorenschaft liegt bei zwei der Publikationen vor.

Die erste Arbeit wurde geteilt mit Herrn Assoc.-Prof. Dr. Egon Dejonckheere (Fakultät für Psychologie und Pädagogik der Katholischen Universität Löwen, Belgien und Abteilung für Medizinische und Klinische Psychologie, Tilburg Universität, Niederlande). Die Arbeit wurde durch mich initiiert, die Literaturrecherche und die Datengenerierung ebenso. Herr Egon Dejonckheere hat mich bei der statistischen Auswertung sowie der graphischen Gestaltung der Ergebnisse unterstützt. Entsprechend seines Engagements wurde die Autorenschaft geteilt.

Die dritte Arbeit wurde geteilt mit Frau Dr. med. Alina Abramian (Abteilung für Senologie, Klinik für Gynäkologie und Gynäkologische Onkologie, Universitätsklinikum Bonn, Deutschland). Auch hier wurde die Arbeit durch unsere Arbeitsgruppe initiiert (Ethikantrag, Studiendesign, Patientenselektion und -Kontaktierung, Terminorganisation) und das Projekt von mir geleitet. Die Erstellung des Ultraschallprotokolls, die Bewertung des kosmetischen Operationsergebnisses und die Durchführung der Ultraschalluntersuchungen erfolgten seitens Frau Alina Abramians, sodass die Autorenschaft entsprechend ihres Engagements geteilt wurde. Die statistische Analyse und Auswertung sowie die Interpretation der Daten und die Manuskripterstellung erfolgten durch mich.

Eine Überlappung mit anderen Habilitationsschriften ist nicht gegeben.

Bonn, den 1. Mai 2024
Dr. med. Cas Stefaan Jules Victor Dejonckheere

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