Aus der Klinik für Strahlentherapie der Universität zu Lübeck

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# Moderne Methoden bei der Strahlentherapie von Kopf-Hals-Tumoren zur Vermeidung von akuten Nebenwirkungen und zur Verbesserung der Prognose

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# Abkürzungsverzeichnis

| | |
|---|---|
| AF-CB | Accelerated Fractionation with Concomitant Boost |
| AJCC | American Joint Committee on Cancer |
| AUC | Area under the Curve |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CTV | Clinical Target Volume – Klinisches Zielvolumen |
| ECE | Extracapsular Extension |
| ED | Dosis pro Fraktion |
| EGFR | Epidermal Growth Factor Rezeptor |
| EORTC | European Organization for Research and Treatment of Cancer |
| GD | Gesamtdosis |
| GTV | Gross Tumor Volumen |
| HA-RT | Hyper fractionated Accelerated Radiation Therapy |
| HPV | Humans' Papilloma Virus |
| IMRT | Intensity Modulated Radiotherapy - Intensitätsmodulierte Strahlentherapie |
| PTV | Planning Target Volume – Planungs Zielvolumen |
| SEER | the Surveillance, Epidemiology and End Results |
| QLQ-C30 | Core Quality of Life Questionnaire for Oncological Patients |
| QLQ-H&N35 | Core Quality of Life Questionnaire for Oncological Head & Neck Patients |
| VMAT | Volumen Modulated Arc Therapy - Volumenmodulierte Strahlentherapie |

# 1 Einleitung

Lokal fortgeschrittene Kopf-Hals-Karzinome sind eine ernstzunehmende Tumorerkrankung. Im Jahr 2018 zählten Kopf-Hals-Karzinome zu den zehn häufigsten malignen Tumoren weltweit. Etwa 450 000 Patient*innen starben an einem Kopf-Hals-Tumor (1, 2). In ca. 90% der Fälle handelt es sich dabei um Plattenepithelkarzinome. Deutlich seltener kommen Adenokarzinome oder Mischtumore vor. Die Mehrzahl der fortgeschrittenen Plattenepithelkarzinome wird strahlentherapeutisch behandelt. Die Strahlentherapie erfolgt entweder als alleinige (definitive) Therapie oder in der Form einer adjuvanten Strahlentherapie nach Resektion des Primärtumors mit oder ohne Entfernung lokoregionaler Lymphknoten. Wenn die Strahlentherapie als definitives Konzept appliziert wird, erfolgt diese häufig in Kombination mit einer platinhaltigen Chemotherapie als Radiochemotherapie (3). Im Rahmen einer adjuvanten Behandlung wird die Strahlentherapie nur dann durch eine Chemotherapie ergänzt, wenn bestimmte Risikofaktoren vorhanden sind. Derartige Faktoren sind z.B. eine inkomplette Resektion des Tumors sowie eine extrakapsuläre Ausbreitung der Lymphknotenmetastasen (8).

Die perkutane Strahlentherapie lokal fortgeschrittener Plattenepithelkarzinome geht häufig mit relevanten akuten Nebenwirkungen einher, vor allem in Form von Hautreaktionen (Strahlendermatitis). Diese werden durch eine simultane Chemotherapie verstärkt, so dass es häufiger zu erheblichen Nebenwirkungen (Grad ≥3 gemäß „Common Toxicity Criteria for Adverse Events" (CTCAE) Version 4.03) kommt. Je nach Ausprägung der Nebenwirkungen kann es sogar zu einer Reduzierung der geplanten Chemotherapie und einer Unterbrechung der Strahlentherapie kommen. Unterbrechungen der Strahlentherapie von mehr als einer Woche können zu einer Verschlechterung der Therapieergebnisse (lokale Kontrolle, Gesamtüberleben) führen (4, 5).

Um erfolgreich Grad ≥3-Hautreaktionen zu vermeiden, ist es wichtig, die Entwicklung von Grad 2 Nebenwirkungen zu verhindern oder zumindest deren Auftreten zu verzögern. Entsprechend der Literatur kommt es bei bis zu 92% der Patient*innen, die aufgrund eines Kopf-Hals-Tumors eine Strahlentherapie oder Radiochemotherapie erhalten, zu Grad 2-Hautreaktionen (3, 6, 7). Die Nebenwirkungen müssen bei diesen Patient*innen deutlich reduziert werden.

Im ersten Teil dieser Dissertation (Teil A, Publikationen 1-3) werden zwei prospektive Studien präsentiert, die zur Verringerung von Nebenwirkungen, insbesondere der Radiodermatitis, beitragen sollen. Im Rahmen der ersten randomisierten Phase III-Studie wurde ein neuer Folienverband (Mepitel® Film) mit der Standardpflege verglichen. In einer weiteren Phase III Studie wurde die Standardpflege durch eine mobile Applikation (Reminder-App) für die Patient*innen ergänzt und diese Kombination mit der alleinigen Standardpflege verglichen.

Trotz intensiver Supportiv- und Pflegemaßnahmen können viele Patient*innen mit einem Kopf-Hals-Tumor, bei denen eine begleitende Chemotherapie indiziert ist, diese aufgrund von Alter, Komorbidität oder reduziertem Allgemeinzustand nicht erhalten (9, 10). In einer Metaanalyse von 15 Studien führte eine alternative (nicht konventionelle) Fraktionierung im Vergleich zur konventionellen Bestrahlung (5 x 2,0 Gy pro Woche) zu einer signifikant besseren loko-regionalen Kontrolle und einem signifikant besseren Gesamtüberleben (11). Eine besondere Form der alternativen Bestrahlung ist das Concomitant Boost-Regime. Hierbei werden nach initial konventioneller Fraktionierung (zumeist über 3 Wochen) im weiteren Verlauf zwei Fraktionen appliziert (siehe Kapitel 4.2). Auch in Deutschland wurde ein Concomitant Boost-Regime entwickelt (69,9 Gy in 39 Fraktionen über 5,5 Wochen), aber bislang nicht mit der konventionellen Fraktionierung verglichen (12, 13). Im zweiten Teil dieser Dissertation (Teil B, Publikationen 4-6) wird ein solcher Vergleich im Rahmen einer kleinen retrospektiven Studie durchgeführt. In einer weiteren retrospektiven Studie wird das Concomitant Boost-Regime mit einer konventionellen Radiochemotherapie (konventionell fraktionierte Strahlentherapie plus simultane platinbasierte Chemotherapie) verglichen. Ergänzend wird in einer dritten retrospektiven Studie ein Vergleich von akzelerierter Bestrahlung (30 Gy in konventioneller Fraktionierung, anschließend 2 x 1,4 Gy pro Tag bis kumulativ 70,6 Gy) plus simultaner Systemtherapie mit einer konventionellen Radiochemotherapie durchgeführt.

Diese kumulative Dissertation soll dazu beitragen, die Ergebnisse der Strahlentherapie oder Radiochemotherapie von Patient*innen mit einem Kopf-Hals-Tumor durch eine Verringerung von Nebenwirkungen und eine Verbesserung der Behandlungsresultate (loko-regionale Kontrolle, Gesamtüberleben) weiter zu optimieren.

# 2 Teil A (Publikationen 1 – 3)

## 2.1 RAREST-01 – Eine prospektive Phase III-Studie (Publikationen 1 und 2)

### 2.1.1 Hintergrund der RAREST-01 Studie

Mehrere klinische Studien haben eine positive Wirkung von selbstklebenden Verbänden (z.B. Mepilex® Lite) bei der Behandlung von radiogenen Nebenwirkungen der Haut gezeigt (14). Andere selbstklebende Verbände werden erfolgreich bei der Behandlung von Druckulzera (z. B. Mepilex®Sakrum; Mepilex®Heel) und thermalen Hautschäden (z. B. Mepilex®Ag) eingesetzt (15). In Fall von Mepilex®Ag konnten sogar eine Kostenreduktion der Therapie und eine Schmerzlinderung nachgewiesen werden (16). Es stellt sich die Frage, ob man sich diese Eigenschaften auch bei der Strahlentherapie von Kopf-Hals-Tumoren zu Nutze machen kann. Neu entwickelt wurde ein selbstklebender Verband (Mepitel® Film), welcher gemäß Hersteller dünner, weicher und angenehmer auf der Haut zu tragen sein soll als die bisherigen Produkte.

Um das neue Produkt adäquat zu untersuchen und seine Eigenschaften besser einordnen zu können, war es wichtig, eine prospektive Studie zu entwickeln. Für Patient*innen mit einem Kopf-Hals-Tumor ist bisher keine derartige Studie durchgeführt worden. Im Rahmen dieser Dissertation wurde initial ein Studienprotokoll zur Untersuchung von Mepitel® Film als neue Option für den Schutz der Haut vor Grad ≥2-Nebenwirkungen etabliert. Im Rahmen einer randomisierten Phase III-Studie wurde (Mepitel® Film) mit der Standardpflege verglichen.

### 2.1.2 Patient*innen und Methoden der RAREST-01 Studie

Der primäre Endpunkt war die Rate an radiogenen Grad ≥2- Dermatitiden (CTCAE v4.03) bei einer Bestrahlungsdosis von 50,0 Gy. Die Bestrahlungsdosis bis 50,0 Gy wurde als primärer Endpunkt definiert, da die Bestrahlungsvolumina bis 50,0 Gy sehr ähnlich sind. Die Bestrahlungspläne ab 50,0 Gy sind sehr individuell und von mehreren Faktoren abhängig, unter anderem von Tumorlokalisation, Tumorgröße sowie Anzahl und Lokalisation der befallenen Lymphknoten.

Zusätzlich wurden mehrere sekundäre Endpunkte untersucht, unter anderem die Anzahl der Fraktionen bis zur Entwicklung von Grad ≥2- Dermatitiden, Grad ≥3- Dermatitiden, Schmerzen im Bestrahlungsfeld.

Die Studie war als multizentrische Studie konzipiert. Es sollten insgesamt 168 Patient*innen eingeschlossen und in zwei Behandlungsgruppen randomisiert werden. Die Patient*innen der Gruppe A wurden mit Mepitel® Film behandelt, und die der Gruppe B erhielten die Standardpflege, bestehend aus speziellen Cremes (siehe 3.1.2.3). Für die Stratifizierung wurden die Tumorlokalisation (Oropharynx/Mundhöhle vs. Hypopharynx/Larynx), der Therapieansatz (alleinige Bestrahlung vs. Radiochemotherapie) und das teilnehmende Zentrum gewählt. Einschlusskriterien waren Alter ≥ 18 Jahre, konventionelle Fraktionierung mit 5 x 2,0 Gy pro Woche, Vorliegen eines histologisch gesicherten Plattenepithelkarzinoms der Kopf-Hals-Region sowie schriftliche Einwilligung und Geschäftsfähigkeit der Patient*innen.

Als Ausschlusskriterien wurden definiert: N3 (Lymphknoten >6 cm), M1 (Fernmetastasen), Schwangerschaft/Laktation, Behandlung mit einem EGFR-Antikörper und eine zu erwartende „Non- Compliance".

- Strahlentherapie

Die Bestrahlung erfolgte entweder als intensitätsmodulierte (IMRT) oder volumenmodulierte (VMAT) Therapie. Das initiale Bestrahlungsvolumen wurde bis 50,0 Gy (5 x 2,0 Gy pro Woche) bestrahlt und beinhaltete die Region des Primärtumors sowie die zervikalen und supraklavikulären Lymphknotenregionen. Nach vollständiger Resektion von Primärtumor und Lymphknoten erfolgte eine Dosisaufsättigung (Boost) von 10,0 Gy (5 x 2,0 Gy pro Woche) im Bereich des Primärtumors und der befallenen Lymphknoten. Im Falle einer inkompletten (R1) Tumorresektion wurden weitere 6,0 Gy in gleicher Fraktionierung auf die R1-Region appliziert. Bei extrakapsulärer Ausbreitung der Lymphknoten wurde diese Region ebenfalls mit weiteren 6,0 Gy aufgesättigt. Bei Patient*innen, die definitiv therapiert wurden, wurden nach den initialen 50,0 Gy weitere 20,0 Gy in Form von Boost-Bestrahlugen appliziert. Dabei erhielten der Primärtumor und die befallenen Lymphknoten insgesamt 70,0 Gy.

- Chemotherapie

Bei Patient*innen mit einem definitiven Therapiekonzept soll eine begleitende Chemotherapie mit Cisplatin oder mit Carboplatin erfolgen. Cisplatin wurde entweder an den Bestrahlungstagen 1-5 und 21-25 mit täglich 20mg/m$^2$ oder an den Bestrahlungstagen 1-4 und 21-24 mit täglich 25mg/m$^2$ appliziert Für die Chemotherapie mit Carboplatin werden analoge Fraktionierungen (AUC 1,0 an 5 Tagen oder AUC 1,5 an 4 Tagen) gewählt.

- Hautpflege

In Gruppe A (Mepitel® Film) soll am ersten Tag der Bestrahlung mit der Versorgung des Strahlentherapiegebietes begonnen werden. Diese Behandlung wird in gleicher Form bis zum Ende der Studie oder bis zum Auftreten einer Radiodermatitis Grad ≥3 fortgeführt. Bei einer Radiodermatitis Grad ≥3 und/oder bei feuchten Epitheliolysen wird die Hautpflege entsprechend den klinküblichen Standards intensiviert. Eine intensivierte Pflege mit antiseptischen Mitteln und Silikon bzw. Kalziumalginat-Verbänden soll bis zum Abklingen der Grad ≥3-Nebenwirkungenerfolgen.

In Gruppe B (Standardpflege) soll ebenfalls ab dem ersten Tag der Bestrahlung mit der Hautpflege begonnen werden. Diese erfolgt initial mit einer harnstoffhaltigen (2-5%) lipophilen Creme. Im Falle einer Harnstoff-Unverträglichkeit sollten andere fettende Cremes und Mometason-Furoat-Creme benutzt werden. Beim Auftreten einer Radiodermatitis Grad ≥3 und feuchten Epitheliolysen soll in gleicher Weise wie in Gruppe A (Mepitel® Film) vorgegangen werden.

- Datenerhebung und Statistik

Die Radiodermatitis wurde während der gesamten Therapie täglich vor der Bestrahlung von zwei geschulten Personen (Ärzt*innen, MTRAs, spezialisiertes Pflegepersonal) unabhängig voneinander beurteilt und dokumentiert. Bei abweichender Graduierung erfolgte eine weitere Beurteilung durch eine dritte Person. Evaluierung und Dokumentation der Radiodermatitis erfolgten bis zu 3 Wochen nach Ende der Therapie. Alle Daten wurden nach CTCAE v4.03. beurteilt und dokumentiert, ebenso wie alle weiteren relevanten Nebenwirkungen.

Die Lebensqualität (QLQ-C30 Version 3.0 und EORTC QLQ-H&N35) wurde insgesamt viermal erhoben, d.h. vor Beginn der Therapie, in den Wochen 3 und 5 während der Therapie und zuletzt 3 Wochen nach Ende der Therapie. Schmerzen wurden mittels einer visuellen Analogskala, vor Therapiebeginn, täglich während der Therapie und bis zu 3 Wochen nach Ende der Therapie erhoben.

Das primäre Ziel der Studie war es, zu beweisen, dass Mepitel® Film bei Patient*innen mit lokal fortgeschrittenen Kopf-Hals-Tumoren, die eine Radio(chemo)therapie erhalten, dazu geeignet ist, die Rate an Grad ≥2-Radiodermatitiden zu senken und somit eine bessere Alternative zur Standardpflege darstellt. Um eine Signifikanz zu erreichen und unter Berücksichtigung, dass 5% der Patient*innen für die Studie nicht geeignet sein würden, waren insgesamt 168 Patient*innen für die Randomisierung erforderlich (80 Patient*innen pro Gruppe plus jeweils 5%). Basierend auf Daten aus der Literatur war davon auszugehen, dass die Rate an Grad ≥2-Radiodermatitiden in Gruppe B (Standardpflege) 85% betragen wird.

In Gruppe A (Mepitel® Film) wurde eine Rate von 65% erwartet, d.h. eine Verbesserung um 20% als klinisch relevant eingestuft.

- Zwischenanalyse

Um die Verträglichkeit der Behandlung mit Mepitel® Film zu evaluieren, wurde eine Zwischenanalyse nach 57 Patient*innen durchgeführt. Die Rekrutierung wurde pausiert bis die 57 Patient*innen die Therapie beendet hatten. In dem Fall, dass ≥25% der Patient*innen die Therapie mit Mepitel® Film nicht ausreichend vertragen bzw. toleriert haben, sollte die Studie vorzeitig beendet werden.

## 2.1.3 Ergebnisse der RAREST-01 Studie

Zum Zeitpunkt der Zwischenanalyse waren 57 Patient*innen randomisiert (28 in Gruppe A und 29 in Gruppe B). Da in Gruppe A 13 von 28 Patient*innen (46,4%) die Verbände mit Mepitel® Film nicht ausreichend vertragen bzw. toleriert hatten, wurde die Studie vorzeitig beendet.

Von den 28 Patient*innen in Gruppe A haben insgesamt 3 Patient*innen nach jeweils 6,0 Gy, 14,0 Gy und 36,0 Gy ihre Einwilligung für die Studie zurückgezogen. Zwei weitere Patient*innen starben, nachdem jeweils 16,0 Gy und 44,0 Gy appliziert wurden. Für diese 5 Patient*innen konnten somit keine Daten bei einer Dosis von 50,0 Gy erhoben werden. In Gruppe B starb ein Patient, nachdem 36,0 Gy appliziert waren. Somit wurden in dieser Gruppe 28 Patient*innen ausgewertet.

In Gruppe A kam es bei einer Gesamtdosis von 50,0 Gy bei 8 von 23 Patient*innen (34,8%) zu einer Grad 2 Radiodermatitis. In Gruppe B war dies bei 10 von 28 Patient*innen (35,7%) der Fall (p = 1,00). Grad 3-Ddermatitiden traten bis 50,0 Gy nicht auf. Bei 60,0 Gy kam es in Gruppe A bei 15 von 23 Patient*innen (65,2%) zu einer Radiodermatitis Grad ≥2. In Gruppe B war dies bei 16 von 27 Patient*innen (59,3%) der Fall (p = 0,77). Zu einer Grad ≥3-Dermatitis bei 60,0 Gy kam es bei 1 von 23 Patient*innen (4,3%) in Gruppe A sowie bei 3 von 27 Patient*innen (11,1%) in Gruppe B (p = 0,61).

In der Analyse der „Intent-to-Treat Population" betrug die mediane Anzahl von Fraktionen bis zum Auftreten einer Grad 2-Radiodermatitis in Gruppe A 23 Fraktionen (Spannweite: 19 - 25 Fraktionen). In Gruppe B betrug diese ebenfalls 23 Fraktionen (Spannweite: 9 - 25 Fraktionen). Nach 50,0 Gy betrug der Median für die auf der visuellen Analogskala angegebenen Schmerzen im Bestrahlungsfeld in beiden Gruppen 0 (Spannweite: 0 – 7). Nach 60,0 Gy betrug der Median 2,0 (Spannweite: 0 – 6) in Gruppe A bzw. 2,5 (Spannweite: 0 – 8) in Gruppe B. Der Vergleich der Schmerzskala hat einen reinen deskriptiven Wert, da viele Patient*innen bereits eine analgetische Therapie aufgrund einer oralen Mukositis erhalten hatten.

In Gruppe A haben 13 Patient*innen Mepitel® Film nicht toleriert davon fünf aufgrund eines Engegefühls am Hals. Außerdem haftete der Mepitel® Film bei weiteren fünf Patient*innen nicht auf der Haut. Ein Patient starb nach 16,0 Gy aufgrund einer akuten Niereninsuffizienz. Somit verblieben lediglich neun 9 Patient*innen in Gruppe A für die übrig zur Analyse mittels dem Per-Protokoll-Analyse bei 50,0 Gy. Zwischen 50,0 Gy und 60,0 Gy sind weitere zwei Patient*innen (aufgrund von Juckreiz bzw. feuchten Epitheliolysen unter dem Folienverband) ausgeschieden. Sieben Patient*innen konnten somit in der Analyse bei 60,0 Gy ausgewertet werden. In Gruppe B starb ein Patient nach 36,0 Gy aufgrund gastrointestinaler Blutungen. Ein weiterer Patient erhielt Cetuximab statt der

geplanten platinhaltigen Chemotherapie. Somit verblieben 27 Patient*innen für die Per-Protokoll-Analyse. Für einen Patienten wurden keine Daten hinsichtlich der Radiodermatitis bei 60,0 Gy erhoben.

Gemäß der Empfehlung der Ethik-Kommission erfolgte eine Per-Protokoll-Analyse der Daten hinsichtlich der Radiodermatitis. Nach 50,0 Gy hatten 3 von 9 Patient*innen (33,3%) in Gruppe A und 9 von 27 Patient*innen (33,3%) in Gruppe B (p=1,00) eine Radiodermatitis Grad 2. Bei 60,0 Gy waren es 4 von 7 (57,1%) bzw. 15 von 26 (57,7%) Patient*innen (p=1,00). Zu einer Radiodermatitis Grad 3 bei 60,0 Gy kam es bei 1 von 7 (14,3%) bzw. bei 3 von 26 (11,5%) Patient*innen (p=1,00).

## 2.1.4 Diskussion der RAREST-01 Studie

Die Bestrahlung ist eine häufige Behandlungsmethode bei Patient*innen mit lokal fortgeschrittenen Kopf-Hals-Tumoren. Viele dieser Patient*innen erhalten eine begleitende Chemotherapie mit Cisplatin oder Carboplatin (36, 37). Die Strahlentherapie oder Radiochemotherapie kann mit belastenden Nebenwirkungen einhergehen, sehr häufig mit einer Radiodermatitis (3, 17). Ausgeprägte Nebenwirkungen erfordern zum Teil die Unterbrechung der Therapie, was zu einer Verschlechterung der Prognose führen kann (4, 5, 18).

Die multivariate Analyse einer retrospektiven Studie von 153 Patient*innen, die aufgrund eines Kopf-Hals-Tumor bestrahlt wurden, ergab, dass das Gesamtüberleben ohne Unterbrechung der Therapie von mehr als 7 Tagen signifikant besser war (relatives Risiko: 2,59, 95%; Konfidenzintervall: 1,15-5,78; p=0,021). Auch die lokale Kontrolle war signifikant besser (relatives Risiko: 3,32, 95% Konfidenzintervall: 1,26-8,79; p=0,015) (4). In einer SEER Datenbank Analyse von Patient*innen mit Larynxkarzinom ging eine Unterbrechung der Strahlentherapie mit einem um 68% (95% Konfidenzintervall: 42% bis 200%) erhöhten Sterblichkeitsrisiko einher (5).

Um das Risiko für die durch eine Radiodermatitis bedingte Therapieunterbrechung zu reduzieren bzw. diese zu verhindern, ist es wichtig, schon das Auftreten einer Radiodermatitis Grad 2 verzögern bzw. zu vermeiden. Das ist eine Herausforderung für alle Strahlentherapeut*innen, da die bisherigen Studien gezeigt haben, dass trotz

Standardpflege eine Radiodermatitis Grad ≥2 in 86-92% der Fälle auftritt. Demzufolge muss die Hautpflege der Bestrahlungsregion verbessert werden (3, 4, 6).

Die Nutzung eines selbstklebenden, absorbierenden, semipermeablen Folienverbands stellte einen vielversprechenden Ansatz dar. In vorherigen Studien konnte ein solcher Verband die strahlenbedingten Hautreaktionen bei Patientinnen mit Brustkrebs signifikant reduzieren (19). In einer randomisierten Studie mit 74 Brustkrebspatientinnen, die eine Dosis von 50,0 Gy in 25 Fraktionen nach Mastektomie erhielten, konnte durch Mepilex® Lite der Gesamtschweregrad der Radiodermatitis um 41% reduziert werden. Eine weitere Studie mit 88 Patient*innen mit einem Nasopharynx-Karzinom, welche während der Bestrahlung feuchte Epitheliolysen entwickelten, zeigte gegenüber der Standardpflege eine signifikante Verkürzung der Wundheilungsdauer, wenn Patient*innen mit Mepilex® Lite versorgt wurden (median 16 vs. 23 Tage, p=0,009) (20). Eine letzte randomisierte Studie mit 80 Brustkrebspatientinnen zeigte bei der Verwendung von Mepitel® Lite eine Reduktion der Radiodermatitis hinsichtlich aller Schweregrade (44% vs. 100%) (21).

Angesichts dieser vielversprechenden Ergebnisse wurde die RAREST-01 Studie initiiert. Wider Erwarten musste die Studie vorzeitg beendet werden, da in der Zwischenanalyse 46,4% der Patient*innen Mepitel® Film nicht vertragen bzw. toleriert haben. Die Rate an Patient*innen, die den Verband nicht toleriert haben, war deutlich höher als in den vorherigen Studien bei Patientinnen mit Brustkrebs (19). Dieser Unterschied kann möglicher weise durch die Lokalisation der Bestrahlunsgfelder erklärt werden. Ein Folienverband im Kopf-Hals-Bereich scheint störender zu sein als im Thorax-/Brustbereich. Dies gilt insbesondere für ein unangenehmes zervikales Engegefühl. Darüber hinaus können sich Patient*innen durch sichtbare Verbände im Kopf-Hals-Bereich in der Öffentlichkeit stigmatisiert fühlen. Außerdem haftete Mepitel® Film nicht an der Haut mancher Patient*innen, wovon vor allem Männer mit ausgeprägtem Bartwuchs betroffen waren.

Nach Abschluss der RAREST-01 wurde in Neuseeland und China eine Durchführbarkeitsstudie durchgeführt (22), welche den Mepitel® Film und eine Standardpflege mit einer Feuchtigkeitscreme für trockene Haut bei Patient*innen mit einem Kopf-Hals-Tumor verglich. Fast 50% der Patient*innen in China, die den Folienverband trugen, klagten über störenden Juckreiz, 27% beschrieben den Verband als

unangenehm lästig und 9,1% berichteten über ein Engegefühl. 45,6% der Patient*innen in China und 37,5% in Neuseeland gaben an, dass der Verband nicht ordnungsgemäß an der Haut haftete. Von den Patient*innen in Neuseeland klagte niemand über Hautjucken. Die regionalen Unterschiede machen deutlich, wie schwierig es ist, Ergebnisse von Studien aus unterschiedlichen Ländern zu vergleichen.

Die RAREST-01 zeigte keine Überlegenheit von Mepitel® Film gegenüber der Standardpflege. Die Raten an Radiodermatitiden waren sowohl bei 50,0 Gy als auch bei 60,0 Gy nicht signifikant unterschiedlich. Dies galt sowohl für die „Intention-to-Treat Population" als auch für das „Per-Protocol-Set". Möglicherweise war dies durch die geringe Fallzahl aufgrund der vorzeitigen Beendigung der Studie bedingt. Auffällig war, dass die Radiodermatitis Grad ≥2 in beiden Gruppen seltener war als erwartet. Ein Grund für die guten Ergebnisse in Gruppe B könnte darin liegen, dass anders als in anderen Studien eine lipophilen und harnstoffhaltigen Creme verwendet wurde. Außerdem konnte durch die tägliche Visite und das frühe Erkennen von Nebenwirkungen die Standardpflege zeitnah auf Mometason-Creme eskaliert werden. Im Gegensatz zu vorhergehenden Studien, in denen Patient*innen dreimal pro Woche visitiert wurden, wurden die Patient*innen in der RAREST-01 Studie mindestens fünfmal pro Woche befragt und untersucht. Die Standard-Hautpflege wurde von den Patient*innen in der RAREST-01 Studie viermal täglich durchgeführt. Dies erfordert ein hohes Maß an Disziplin und Compliance. Auch die tägliche Begutachtung der Nebenwirkungen und die täglichen Erinnerungen an die Hautpflege durch das Fachpersonal könnte zu einer Verbesserung der Compliance und konsekutiv weniger Nebenwirkungen geführt haben. Es ist davon auszugehen, dass die korrekte und regelmäßige Anwendung der Hautpflege zu einer Verringerung der Inzidenz und des Schweregrads der Radiodermatitis geführt hat. Insgesamt ist die Aussagekraft der Ergebnisse der RAREST-01 Studie aufgrund des vorzeitigen Endes und der geringen Fallzahl eingeschränkt. Weitere prospektive Studien, die den möglichen Stellenwert von Mepitel® Film bei der Vermeidung bzw. Verzögerung radiogener Dermatitiden bei der Strahlentherapie von Kopf-Hals-Tumoren untersuchen, sind erforderlich.

## 2.2 RAREST-02 – Eine weitere prospektive Phase III-Studie (Publikation 3)

Eine mögliche Erklärung für die vergleichsweise niedrige Rate an Hauttoxizität Grad ≥2 im Standard-Arm der RAREST-01 Studie war die tägliche Erinnerung an die regelmäßige

Hautpflege durch Fachpersonal der Klinik. Üblicherweise geschieht dies nur einmal pro Woche. Die täglichen Erinnerungen haben mit hoher Wahrscheinlichkeit zu einer verbesserten Compliance der Patient*innen geführt. Angesichts limitierter personeller Ressourcen im Gesundheitswesen stellt sich die Frage, ob die täglichen Erinnerungen des Personals durch eine mobile Applikation (Reminder-App) ersetzt werden können.

Um diese Frage zu beantworten, wurde die RAREST-02 Studie konzipiert. Diese Studie soll untersuchen, ob die tägliche Nutzung einer Reminder-App in Ergänzung zur Standardpflege bei Patient*innen, die aufgrund eines Plattenepithelkarzinoms der Kopf-Hals-Region zu einer Verringerung von Inzidenz und Schweregrad einer oraler Mukositiden und Radiodermatitiden führt.

Der Aufbau dieser randomisierten Phase III-Studie entspricht in etwa dem der RAREST-01 Studie. Verglichen werden Standardpflege plus Reminder-App (Gruppe A) vs. alleinige Standardpflege (Gruppe B). Primärer Endpunkt ist die Radiodermatitis Grad ≥2 bei 60,0 Gy. Sekundäre Endpunkte beinhalten die Radiodermatitis Grad ≥2 am Ende der Strahlentherapie, die orale Mukositis Grad ≥2 bei 60,0 Gy sowie am Ende der Strahlentherapie, Radiodermatitis und orale Mukositis Grad ≥3 bei 60,0 Gy sowie am Ende der Strahlentherapie, Lebensqualität und Schmerzen im Bereich der Bestrahlungsfelder.

Gemäß Fallzahlberechnungen werden, wie in der RAREST-01 Studie 80 Patient*innen pro Gruppe benötigt. Wiederum wurde davon ausgegangen, dass 5% der Patient*innen für die Analysen nicht geeignet sein werden („Drop-outs"). Somit sollen insgesamt 168 Patient*innen eingeschlossen und randomisiert werden. Der Einsatz der Reminder App wird als klinisch relevant angesehen, wenn die Radiodermatitis Grad ≥2 (primärer Endpunkt) und die orale Radiomukositis Grad ≥2 (sekundärer Endpunkt) um 20% reduziert werden können.

Wenn es tatsächlich gelingt, die Raten an Nebenwirkungen der Strahlentherapie bei der Behandlung von Kopf-Hals-Tumoren durch den Einsatz der Reminder-App signifikant zu verringern, kann diese in Zukunft hilfreich und bedeutungsvoll für diese Patient*innen werden.

# 3 Teil B (Publikationen 4-6)

## 3.1 Hintergrund

Gemäß einer Metaanalyse von 15 Studien konnte gezeigt werden, dass bei Patient*innen mit einem Kopf-Hals-Tumor durch eine alternative Fraktionierung im Vergleich zur Normofraktionierung (5x 2,0 Gy/Woche) eine signifikante Verbesserung der loko-regionalen Kontrolle und des Gesamtüberlebens erreicht werden kann (11).

Eine weitere randomisierte Studie, die im Jahr 2000 publiziert wurde, untersuchte ein Bestrahlungskonzept mit einem sogenannten Concomitant Boost-Konzept, das ebenfalls zu besseren Kurzzeitergebnissen als die konventionell fraktionierte Strahlentherapie führte (23). Langzeitergebnisse dieser Studie wurden 2014 publiziert. Obwohl die Reduktion der kumulativen loko-regionalen Rezidive nach 5 Jahren nicht mehr statistisch signifikant war, zeigte sich ein bemerkenswerter absoluter Vorteil von 6,6% (24). In der initialen Publikation aus dem Jahr 2000 zeigte die Bestrahlung mit einem Concomitant Boost (72,0 Gy in 42 Fraktionen über 6 Wochen) im Vergleich zu der konventionellen Fraktionierung eine erhöhte Spättoxizität (23). Daraufhin wurde ein alternatives Concomitant Boost-Konzept (69,9 Gy in 39 Fraktionen über 5,5 Wochen) in Deutschland entwickelt (12, 13), jedoch bisher nicht mit einer der konventionell fraktionierten Strahlentherapie oder einer konventionellen Radiochemotherapie verglichen.

Im Rahmen von zwei kleinen retrospektiven Studien wurden derartige Vergleiche durchgeführt. Zusätzlich wurden in einer dritten retrospektiven Studie eine akzelerierte Bestrahlung plus simultane Systemtherapie und eine konventionelle Radiochemotherapie miteinander verglichen.

## 3.2 Publikation 4

**Vergleich einer konventionell fraktionierten Bestrahlung mit einer akzelerierten Bestrahlung (Concomitant Boost) bei lokal fortgeschrittenen Kopf-Hals-Tumoren**

Manche Patient*innen mit einem nicht oder nur teilweise resektablen Kopf-Hals-Karzinom sind nicht für eine Chemotherapie geeignet (36, 37). Alternative Therapiekonzepte sind für diese Gruppe erforderlich. Derartige Konzepte sollten effektiver sein als eine alleinige konventionell fraktionierte Bestrahlung.

Diese retrospektive Studie untersuchte Patient*innen mit einem lokal fortgeschrittenen Plattenepithelkarzinom der Kopf-Hals-Region, die eine simultane Chemotherapie zur Strahlentherapie nicht erhalten konnten. Acht Patient*innen erhielten ein intensiveres Bestrahlungskonzept mit einem Concomitant Boost-Regime (Gruppe A). Sie wurden initial über 3 Wochen bis 30,0 Gy konventionell fraktioniert bestrahlt. Im Anschluss wurden morgens 1,8 Gy pro Fraktion (5 Fraktionen / Woche) bis 21,6 Gy auf die gesamte Bestrahlungsregion (Primärtumor plus „Low-Risk"-Lymphabflusswege) appliziert. Nach einer Pause von mindestens 6 Stunden erfolgte eine zweite Fraktion mit 1,5 Gy, zunächst auf den Primärtumor und die „Intermediate Risk"-Region (an 6 Bestrahlungstagen) sowie anschließend auf den Primärtumor und die „High Risk"- Region (an weiteren 6 Bestrahlungstagen). Somit wurden kumulative Dosen von 51,6 Gy („Low-Risk"-Region), 60,6 Gy („Intermediate Risk"-Region) sowie 69,6 Gy (Primärtumor plus „High Risk"-Region) erreicht. Diese acht Patient*innen wurden mit 31 Patient*innen, die konventionell fraktioniert bestrahlt wurden (Gruppe B) und ebenfalls keine Chemotherapie erhielten, verglichen. Beide Gruppen wurden hinsichtlich Tumorlokalisation, Geschlecht, Alter, Allgemeinzustand (Karnofsky-Index) und histologischem Grading abgeglichen.

Nach 2 Jahren betrugen die Raten für das progressionssfreie Überleben 63% in Gruppe A bzw. 41% in Gruppe B aus. Die medianen progressionsfreien Überlebenszeiten lagen bei 36 bzw. 10 Monaten (p = 0,48). Die 2 Jahres-Raten für das Gesamtüberleben betrugen 88% bzw, 37%, die medianen Überlebenszeiten 44 bzw. 14 Monate (p = 0,19).

Die akute Radiodermatitis Grad ≥ 2 war, anders als erwartet, signifikant häufiger (p = 0,040) in Gruppe B. Die weiteren Nebenwirkungen waren in beiden Gruppen nicht signifikant unterschiedlich.

Gemäß dieser kleinen retrospektiven Studie scheint eine akzelerierte Fraktionierung mit einem Concomitant Boost effektiver zu sein als eine konventionelle fraktionierte Bestrahlung und sollte bei Patient*innen, die keine Chemotherapie erhalten können, in Betracht gezogen werden. Diese Studie kann lediglich einen Hinweis liefern. Größere prospektive Studien sind notwendig, um diese Ergebnisse zu bestätigen

## 3.3 Publikation 5

**Akzelerierte Bestrahlung plus Chemotherapie vs. konventionelle Radiochemotherapie (konventionell fraktionierte Bestrahlung plus Standard-Chemotherapie) bei nicht resektablen Kopf-Hals-Tumoren**

Für die meisten resektablen Tumore beinhaltet die Standardtherapie eine operative Resektion des Tumors, gefolgt von einer adjuvanten Bestrahlung. Im Falle von Risikofaktoren, wie z. B einer inkompletten Resektion oder einer extrakapsulären Ausbreitung der Lymphknotenmetastasen, wird eine Radiochemotherapie durchgeführt (3).

Diese retrospektive Studie vergleicht die akzelerierte Bestrahlung mit begleitender Chemotherapie als mögliche Alternative mit einer konventionell fraktionierten Radiochemotherapie. Es wurden die Daten von 95 Patient*innen analysiert. Zehn Patient*innen erhielten eine akzelerierte Bestrahlung mit begleitender Chemotherapie im Rahmen von klinischen Studien zwischen 2010 und 2014 (Gruppe A). Die weiteren 85 Patient*innen erhielten eine konventionelle Radiochemotherapie zwischen 2000 und 2014 und stammen aus einer anonymisierten Datenbank (Gruppe B).

Drei der 10 Patient*innen (Gruppe A) erhielten eine Hyperfraktionierte Akzelerierte Strahlentherapie (HA-RT) kombiniert mit einer wöchentlichen Systemtherapie bestehend aus Cisplatin und Cetuximab. Sie wurden zunächst über 3 Wochen bis 30,0 Gy konventionell fraktioniert bestrahlt. Im Anschluss erhielten sie eine HA-RT über weitere 3 Wochen mit 2 x 1,4 Gy pro Tag. Zwischen den täglichen Fraktionen wurde eine Pause von mindestens 6 Stunden eingehalten. Die kumulative Gesamtdosis betrug 70,6 Gy.

Vier der 10 Patient*innen (Gruppe A) erhielten eine akzelerierte Bestrahlung in Form eines Concomitant Boost-Regimes (Gesamtdosis: 69,6 Gy; siehe Publikation 4) und eine Chemotherapie mit Docetaxel und Cisplatin plus/minus Cetuximab.

Drei weitere Patient*innen (Gruppe A) erhielten ebenfalls HA-RT mit einer anderen Chemotherapie. Es wurde eine begleitende Chemotherapie mit Cisplatin ($20mg/m^2$; d1-4 und d29-32) und Paclitaxel ($20mg/m^2$; d2, d5, d8, d11 und d25, d30, d33, d36) durchgeführt. Es wurden vorerst über 3 Wochen 30,0 Gy in konventioneller Fraktionierung appliziert. Im

Anschluss folgte eine HA-RT über 2,5 Wochen mit 2 x 1,4 Gy pro Tag. Wiederum wurde zwischen den täglichen Fraktionen eine Pause von mindestens 6 Stunden eingehalten. Die kumulative Bestrahlungsdosis betrug 63,6 Gy. Die begleitende Chemotherapie in Gruppe B beinhaltete unterschiedliche Cisplatin-haltige Regime

Beide Gruppen wurden hinsichtlich, Geschlecht, Alter, Tumorstadium, Lymphknotenstatus und histologischem Grading abgeglichen. Der Allgemeinzustand wurde nicht verwendet, da alle Patient*innen einen Karnofsky-Index von mindestens 80% hatten.

Die Art der Therapie hatte keine signifikante Auswirkung auf die loko-regionale Kontrolle (p = 0,98) und das Gesamtüberleben (p = 0,57). Anders sah es bei den Nebenwirkungen aus. In der Gruppe A kamen einige Nebenwirkungen signifikant häufiger vor, wie z.B. eine Mukositis Grad ≥3 (p = 0,041), ein Lymphödeme Grad ≥2 (p = 0,007) und eine Leukopenie Grad ≥ 3 (p = 0,007).

Gemäß den Ergebnissen dieser Studie führte die akzelerierte Bestrahlung mit Chemotherapie nicht zu besseren Ergebnissen als die Standard-Radiochemotherapie, war allerdings mit signifikante mehr Nebenwirkungen assoziiert. Somit sollte die konventionell fraktionierte Radiochemotherapie die Standardbehandlung bleiben. Auch diese Ergebnisse müssen durch prospektive Studien bestätigt werden.

## 3.4 Publikation 6

**Akzelerierte Bestrahlung (Concomitant Boost) vs. konventionelle Radiochemotherapie (konventionell fraktionierte Bestrahlung plus Standard Chemotherapie) als definitive Therapie von lokal fortgeschrittenen Kopf-Hals-Tumoren**

Nachdem eine akzelerierte Bestrahlung (Concomitant Boost) gegenüber einer konventionell fraktionierten Bestrahlung zu besseren Behandlungsergebnissen führte, wird das Concomitant Boost-Regime jetzt mit einer konventionellen Radiochemotherapie verglichen.

Es wurden die Daten von insgesamt 80 Patient*innen mit einem lokal fortgeschrittenen Kopf-Hals-Tumor analysiert. Acht Patient*innen erhielten ein Concomitant Boost-Regime (Gesamtdosis: 69,6 Gy; siehe Publikation 4) über 5,5 Wochen (Gruppe A). Die anderen 72 Patient*innen erhielten eine konventionelle Radiochemotherapie (70,0 Gy in 35 Fraktionen mit einer begleitenden Cisplatin-basierten Chemotherapie) über 7 Wochen und stammen aus einer anonymisierten Datenbank (Gruppe B). Beide Gruppen wurden hinsichtlich, Geschlecht, Alter, Tumorstadium, Lymphknotenstatus, und histologischem Grading abgeglichen.

Es zeigten sich keine signifikanten Unterschiede zwischen beiden Gruppen hinsichtlich der loko-regionalen Kontrolle, des metastasenfreien Überlebens, des Gesamtüberlebens und den radiogenen Nebenwirkungen. Auffällig war allerdings, dass in Gruppe B 38,9% der Patient*innen nicht die vollständige geplante Chemotherapie erhalten konnten. Eine Bestrahlungspause von mehr als 7 Tagen wurde bei 19,3% der Patient*innen in Gruppe B erforderlich. In Gruppe A war bei 0% der Patient*innen eine Pause erforderlich.

Für Patient*innen mit einem lokal fortgeschrittenem Kopf-Hals-Tumor, die keine Chemotherapie erhalten können, ist eine akzelerierte Bestrahlung mit einem Concomitant Boost-Regime eine mögliche Alternative. Dennoch bleibt die konventionelle Radiochemotherapie, wann immer möglich, die Therapie der ersten Wahl.

## 3.5 Diskussion der Publikationen 4-6

## 3.5.1 Allgemeine Diskussion der Publikationen 4-6

Bereits mehrere randomisierte Studien mit Patient*innen mit lokal fortgeschrittenen Kopf-Hals-Tumoren (Stadium III und IV) haben die Vorteile einer kombinierten Radiochemotherapie mit einer konventionellen Fraktionierung (z.B. 70,0 Gy in 35 Fraktionen von 2,0 Gy über 7 Wochen) gegenüber einer alleinigen konventionellen Bestrahlung gezeigt (25-30). Es konnte bei ähnlicher Toxizität unter anderem eine Verbesserung des Gesamtüberlebens, des krankheitsfreien Überlebens und der loko-regionalen Kontrolle erreicht werden. Da viele dieser Patient *innen häufig signifikante Komorbiditäten aufweisen, die eine Narkose/Operation nicht erlauben, wird eine Cisplatin-basierte Radiochemotherapie mit einer konventionellen Fraktionierung empfohlen (31, 36, 37). Allerdings können nicht alle Patient*innen eine Systemtherapie erhalten. Darüber hinaus können Chemotherapie-induzierte Nebenwirkungen zu längeren Therapiepausen (> 7 Tage) führen. In einer multivariaten Analyse einer Studie konnte gezeigt werden, dass Patient*innen, die keine Therapiepausen hatten eine signifikante bessere loko-regionale Kontrolle (Risk Ratio = 3.32, $p = 0.015$) und ein signifikant besseres Gesamtüberleben (Risk Ratio = 2.59, $p = 0.021$) aufwiesen, als Patient*innen, die eine längere Pause hatten (4).

Um die Prognose von Patient*innen mit lokal fortgeschrittenen, teilweise nicht resektablen Kopf-Hals-Tumoren zu verbessern, sind alternative Therapie-Regime notwendig.

Bessere Ergebnisse wurden bereits für unkonventionell fraktionierte Bestrahlungen gezeigt. In einer randomisierten Studie führte eine akzelerierte Fraktionierung mit einem Concomitant Boost (insgesamt 72,0 Gy in 42 Fraktionen über 6 Wochen, d.h. 30 x 1,8 Gy/Tag plus Boost mit 1,5 Gy/Tag 6 Stunden später während der letzten 12 Bestrahlungstage) gegenüber einer konventionell fraktionierten Bestrahlung zu signifikant besseren Ergebnissen hinsichtlich krankheitsfreiem Überlebens und loko-regionaler Kontrolle. Mit einer hyperfraktionierten Bestrahlung (81.6 Gy in 68 Fraktionen, d.h. 2 x 1.2 Gy/Tag an 5 Tagen pro Woche) konnten ähnliche Ergebnisse erzielt werden (11, 23, 24). Die Ergebnisse für die loko-regionale Kontrolle nach 5 Jahren waren nach hyperfraktionierter Bestrahlung 6,5% ($p = 0,05$) und der akzelerierten Fraktionierung mit Concomitant Boost 6,6% ($p = 0,11$) besser als nach der konventionellen Fraktionierung. Außerdem waren beide unkonventionellen Regime signifikant besser in Bezug auf das

krankeitsfreie Überleben. Diese Daten sollten allerdings aufgrund von Unterschieden hinsichtlich der Patientencharakteristika mit Vorsicht interpretiert werden. Dennoch ist die kürzere Therapiedauer ein potenzieller Vorteil der akzelerierten Fraktionierung mit Concomitant Boost. Für Zentren mit hohem Patientenaufkommen oder Wartelisten könnte dieses Regime eine Alternative darstellen.

Dennoch ist der Stellenwert der akzelerierten Fraktionierung mit Concomitant Boost bei der Behandlung von Kopf-Hals-Tumoren bisher nicht hinreichend geklärt. Gemäß zweier Metaanalysen können hyperfraktionierte Regime eine fehlende Chemotherapie nicht ausreichend kompensieren (32, 33). In einer randomisierten Phase III Studie von 2016 konnte allerdings gezeigt werden, dass Patient*innen mit Oropharynxkarzinomen, die eine akzelerierte Fraktionierung mit Concomitant Boost (67,5 Gy in 40 Fraktionen über 5 Wochen) erhalten haben, eine bessere Compliance, ein günstigeres Nebenwirkungsprofil und eine höhere Lebensqualität hatten, als Patient*innen, die mit einer Standard-Radiochemotherapie (66,0 Gy in 33 Fraktionen über 6,5 Wochen plus Cisplatin 100mg/m$^2$ an Tag 1, 22 und 43) behandelt wurden (34). Darüber hinaus waren in einer randomisierten Studie, die im Jahr 2020 publiziert wurde, die Ansprechraten und das krankheitsfreie Überleben für die akzelerierte Fraktionierung mit einem Concomitant Boost und für eine konventionelle Radiochemotherapie nicht signifikant unterschiedlich (35).

## 3.5.2 Diskussion von Publikation 4

In dieser Studie zeigten sich nach akzelerierter Fraktionierung mit Concomitant Boost gegenüber der konventionell fraktionierten Bestrahlung deutlich bessere Ergebnisse hinsichtlich Gesamtüberleben (median 44 *vs.* 14 Monate) und progressionsfreiem Überleben (median 36 *vs.* 10 Monate). Allerdings waren diese Unterschiede nicht signifikant, was am ehesten auf die insgesamt geringe Fallzahl (N=39) zurückzuführen war. Bemerkenswert ist ferner, dass die akzelerierte Fraktionierung mit Concomitant Boost nicht mit einer erhöhten Toxizität einherging. Die geringe Fallzahl sollte bei der Interpretation der Ergebnisse mit einbezogen werden. Weitere Einschränkungen der Studie sind unter anderem das retrospektive Design, die unterschiedlich langen Nachbeobachtungszeiträume, der häufig nicht vorhandene HPV-Status und die unterschiedlichen Behandlungszeiträume. Zusammengefasst scheint die akzelerierte Fraktionierung mit Concomitant Boost ein vielversprechendes Regime und bei nicht

metastasierten Stadium-IV-Kopf-Hals-Tumoren der konventionell fraktionierten Bestrahlung überlegen zu sein. Demzufolge sollte dieses Regime für Patient*innen, die keine Chemotherapie erhalten können, erwogen werden.

### 3.5.3  Diskussion von Publikation 5

Mehrere Machbarkeitsstudien haben bereits unkonventionell fraktionierte Bestrahlungen wie eine hyperfraktioniert-akzelerierte Strahlentherapie oder eine akzelerierte Fraktionierung mit einem Concomitant Boost mit einer begleitenden Chemo-/Immuntherapie (z.B. Carboplatin, Cisplatin oder Cetuximab) untersucht (38-40). Obwohl die meisten dieser Regime von den jeweiligen Autor*innen als machbar eingestuft wurden, waren sie mit einer hohen Toxizität assoziiert. Gemäß den Ergebnissen der vorliegenden retrospektiven Studie konnte durch eine akzelerierte Bestrahlung plus Chemotherapie keine Verbesserung der Behandlungsergebnisse (loko-regionale Kontrolle, Gesamtüberleben) im Vergleich zu einer konventionell fraktionierten Radiochemotherapie erreicht werden. Die Ergebnisse einer akzelerierten Bestrahlung plus Chemotherapie schienen sogar schlechter zu sein, als die der Standardtherapie. Darüber hinaus konnten signifikant mehr akute und späte Toxizitäten in dieser Gruppe festgestellt werden. Unter Berücksichtigung dieser Ergebnisse und der Limitationen dieser Studie sollte die konventionell fraktionierte Radiochemotherapie die Standardtherapie bleiben. Selbstverständlich müssen diese Ergebnisse in prospektiven, randomisierten Studien überprüft werden.

### 3.5.4  Diskussion von Publikation 6

Gemäß den Ergebnissen dieser Studie ist eine akzelerierte Fraktionierung mit Concomitant Boost der konventionell fraktionierten Radiochemotherapie hinsichtlich loko-regionaler Kontrolle, metastasenfreiem Überleben, Gesamtüberleben und Toxizität nicht signifikant unterlegen. Im Gegensatz zum Therapieregime fanden sich signifikante Assoziationen zwischen den Behandlungsergebnissen und der Lokalisation und dem Stadium des Tumors sowie dem Allgemeinzustand. Diese Prognosefaktoren wurden bereits in vorherigen Studien identifiziert (41-44), was für eine Konsistenz unserer Daten spricht. Allerdings sind Einschränkungen wie z.B. das retrospektive Design, die geringe Anzahl an Patient*innen in Gruppe A und die fehlenden Informationen über den HPV-Status zu beachten. Es zeigte

sich ferner, dass eine zeitnahe und sorgfältige Überprüfung der Patient*innen hinsichtlich der Eignung für eine aggressive Therapie wichtig ist. Hierdurch wird der Anteil an Patient*innen, die eine komplette Radiochemotherapie ohne relevante Pausen erhalten können, wahrscheinlich steigen. Zusammengefasst konnte trotz Limitationen dieser Studie gezeigt werden, dass eine akzelerierte Fraktionierung mit Concomitant Boost eine sinnvolle Alternative für die Behandlung von nicht resektablen Kopf-Hals-Tumoren darstellt. Auch diese Ergebnisse müssen in prospektiven Studien überprüft werden. Bis dahin sollte die konventionelle Radiochemotherapie die Therapie der ersten Wahl bleiben.

# 4 Zusammenfassung

Teil A: Eine Strahlentherapie im Kopf-Hals-Bereich geht zumeist mit relevanter Akuttoxizität einher. Häufige Nebenwirkungen sind die Strahlendermatitis und die Mukositis der Mundschleimhaut (4, 5). Diese Nebenwirkungen werden durch eine simultane Chemotherapie verstärkt. Um schwere (Grad 3) Nebenwirkungen zu vermeiden, sollten nach Möglichkeit bereits Grad 2-Nebenwirkungen vermieden oder zumindest deutlich verzögert werden (3, 6, 7). Ein neuer Ansatz zur Vermeidung von Hautreaktionen ist der transparente Folienverband Mepitel® Film.

Im Rahmen einer randomisierten Phase III-Studie (RAREST-01) wurde geprüft, ob Mepitel® Film der Standardbehandlung bei der Strahlentherapie von Kopf-Hals-Tumoren hinsichtlich der Vermeidung einer Strahlendermatitis Grad ≥2 überlegen ist. Die Studie wurde nach einer Zwischenanalyse (nach 57 von geplanten 168 Patient*innen) vorzeitig beendet, da 13 von 28 Patient*innen den Folienverband nicht tolerierten. Die Raten bezüglich der Strahlendermatitis Grad ≥2 nach 50,0 Gy betrugen 34,8% im Mepitel®-Arm sowie 35,7% im Standard-Arm. Nach 60,0 Gy betrugen die Raten 65,2% sowie 59,3%. Demzufolge schien Mepitel® Film der Standardpflege nicht überlegen zu sein. [Publikationen 1 und 2].

Allerdings war die Strahlendermatitis in beiden Gruppen, d.h. auch im Standard-Arm, seltener als im Standard-Arm erwartet. Eine mögliche Erklärung hierfür könnte sein, dass die Behandlung im Rahmen einer Studie zu einer besseren Compliance hinsichtlich der Hautpflege führte. Die Patient*innen wurden täglich von mindestens zwei Mitarbeiter*innen der Klinik gesehen und hinsichtlich möglicher Symptome befragt. Unter Routinebedingungen erfolgen Untersuchung und Befragung etwa einmal pro Woche durch eine Person.

Angesichts limitierter personeller Ressourcen stellte sich die Frage, ob die täglichen Visiten durch eine mobile Applikation (Reminder-App), die die Betroffenen viermal täglich an die Hautpflege erinnert, ersetzt werden können. Dies wird derzeit in einer weiteren Phase III Studie untersucht. [Publikation 3]

Teil B: Wie erwähnt, führt eine simultane Chemotherapie im Rahmen einer definitiven Behandlung von Kopf-Hals-Tumoren zu einer erhöhten Akuttoxizität. Einige Patient*innen können daher keine Chemotherapie erhalten (9, 10). Dann sind Alternativen gefragt, die

der alleinigen konventionellen Strahlentherapie (66,0-70,0 Gy in 33-35 Fraktionen) überlegen sind. Dies kann durch eine unkonventionelle Fraktionierung erreicht werden, z.B. durch eine akzelerierte Strahlentherapie mit einem sogenannten Concomitant Boost (23, 24). Auch in Deutschland wurde ein Concomitant Boost-Regime entwickelt (12, 13). Allerdings wurde dieses Konzept bislang nicht mit einer konventionellen Bestrahlung verglichen. Unklar ist auch, wie dieses Therapie-Regime im Vergleich zu einer konventionellen Radiochemotherapie abschneidet und ob es sinnvoll mit einer Chemotherapie kombiniert werden kann.

Ziel von drei retrospektiven Studien war es, einen Beitrag zur Klärung dieser Fragen zu leisten. In einer Studie wurde das Concomitant Boost-Regime mit einer konventionellen Bestrahlung verglichen. Die Strahlentherapie mit Concomitant Boost führte zu nicht signifikant besserem progressionsfreiem Überleben (median 36 vs. 10 Monate) und Gesamtüberleben (median 44 vs. 14 Monate). [Publikation 4] In einer zweiten Studie wurde das Concomitant Boost-Konzept mit einer konventionellen Radiochemotherapie verglichen. Behandlungsergebnisse und Toxizität waren nicht signifikant unterschiedlich. Somit kann das Concomitant Boost-Konzept eine sinnvolle Alternative für Patient*innen, die keine Chemotherapie erhalten können, sein. [Publikation 5] In einer dritten Studie (N=95) wurde das Concomitant Boost-Regime plus Chemotherapie mit einer konventionellen Radiochemotherapie verglichen. Die Ergebnisse hinsichtlich loko-regionaler Kontrolle und Gesamtüberleben waren vergleichbar. Allerdings war das Regime Concomitant Boost plus Chemotherapie mit signifikant mehr Nebenwirkungen assoziiert, so dass man hier von Abstand nehmen sollte. [Publikation 6]

Selbstverständlich muss bei der Interpretation der Ergebnisse dieser drei Studien das retrospektive Design verbunden mit dem Risiko eines Selektions-Bias berücksichtigt werden.

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8.  Narvaez CA, Doemer C, Idel C, Setter C, Olbrich D, Ujmajuridze Z, Carl JH and Rades D., Radiotherapy related skin toxicity (RAREST-01): Mepitel® film versus standard care in patients with locally advanced head-and-neck cancer. BMC Cancer. 18:197; 2018.

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# 6 Publikationen

**Publikation 1:** <u>Narvaez CA[1]</u>, Doemer C[1], Idel C[2], Setter C[3], Olbrich D[4], Ujmajuridze Z[5], Carl JH[5] and Rades D.[1*], Radiotherapy related skin toxicity (RAREST-01): Mepitel® film versus standard care in patients with locally advanced head-and-neck cancer. BMC Cancer. 2018 Feb 17;18(1):197. doi: 10.1186/s12885-018-4119-x. PMID: 29454311; PMCID: PMC5816351. **[Impact Factor = 4,430]**

**Publikation 2:** Rades D[1], <u>Narvaez CA[2]</u>, Splettstößer L[2], Dömer C[2], Setter C[3], Idel C[4], Ribbat-Idel J[5], Perner S[6] et al. Bartscht T[7], Olbrich D[8], Schild SE[9], Carl J[10]. A randomized trial (RAREST-01) comparing Mepitel® Film and standard care for prevention of radiation dermatitis in patients irradiated for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN). Radiother Oncol. 2019 Oct;139:79-82. doi: 10.1016/j.radonc.2019.07.023. Epub 2019 Aug 17. PMID: 31431372. **[Impact Factor = 6,280]**

**Publikation 3:** Rades D.[1*], <u>Narvaez CA[1]</u>, Doemer C[1], Janssen S[2], Olbrich D[3], Tvilsted S[4], Conde-Moreno AJ[5] and Cacicedo J[6]. Radiotherapy-related skin toxicity (RAREST-02): A randomized trial testing the effect of a mobile application reminding head-and-neck cancer patients to perform skin care (reminder app) on radiation dermatitis. Trials. 2020 May 25;21(1):424. doi: 10.1186/s13063-020-04307-0. PMID: 32450921; PMCID: PMC7249413. **[Impact Factor = 2,279]**

**Publikation 4:** <u>Narvaez CA[1]</u>, Schild SE[2], Rades D[3]. Comparison of Conventional Fractionation and Accelerated Fractionation With Concomitant Boost for Radiotherapy of Non-metastatic Stage IV Head-and-Neck Cancer. In Vivo. 2021 Jan-Feb;35(1):411-415. doi: 10.21873/invivo.12272. PMID: 33402490; PMCID: PMC7880725. **[Impact Factor = 2,155]**

**Publikation 5:** <u>Narvaez CA[1]</u>, Schild SE[2], Janssen S[1,3], Schroeder U[4], Bruchhage KL[4], Hakim SG[5], Rades D[6]. Accelerated Fractionation With Concomitant Boost vs. Conventional Radio-chemotherapy for Definitive Treatment of Locally Advanced Squamous Cell Carcinoma of the Head-and-Neck (SCCHN). Anticancer Res. 2021 Jan;41(1):477-484. doi: 10.21873/anticanres.14798. PMID: 33419846. **[Impact Factor = 2,480]**

**Publikation 6:** Rades D[1], <u>Narvaez CA[2]</u>, Janssen S[2,3], Schröder U[4], Bruchhage KL[4], Hakim SG[5], Bartscht T[6], Schild SE[7]. Accelerated Fractionation Plus Chemotherapy Versus Conventionally Fractionated Radiochemotherapy for Unresectable Head-and-Neck Cancer. Anticancer Res. 2021 Feb;41(2):877-884. doi: 10.21873/anticanres.14840. PMID: 33517293. **[Impact Factor = 2,480]**

# 7 Danksagungen

# 8  Lebenslauf /Persönliche Daten

| | |
|---|---|
| Name: | Carlos Andrés Narváez-Wolf |
| Geburtsort: | León, Nicaragua |
| Geburtstag: | 13.06.1989 |
| Staatsangehörigkeit: | nicaraguanisch / deutsch |
| Familienstand: | verheiratet |

## Schulausbildung:

| | |
|---|---|
| 1995 - 2006 | Nicaraguanisches Nationalabitur |
| 2006 – 2007 | internationales Abitur an der Deutschen Schule Managua |

## Studium:

| | |
|---|---|
| 01/2008 – 09/2008 | Humanmedizin an der „Universidad Nacional Autónoma de Nicaragua" |
| 10/2008 – 06/2015 | Humanmedizin an der „Universität zu Lübeck" |
| 04/2011 | 1. Staatsexamen |
| 04/2014 | 2. Staatsexamen |
| 06/2015 | 3. Staatsexamen und Approbation |
| Seit 2017 | Dissertation in der Klinik für Strahlentherapie bei Prof. Dr. Rades |
| Thema: | „Moderne Methoden bei der Strahlentherapie von Kopf-Hals-Tumoren zur Vermeidung von akuten Nebenwirkungen und zur Verbesserung der Prognose" |

| 04/2015 | Wahltertial Radiologie im PJ am UKSH Lübeck |
| 09/2012 | Famulatur Neuroradiologie am UKSH Lübeck |
| 03/2012 | Famulatur Radiologie im Vinzenzkrankenhaus Hannover |
| 02/2012 | Famulatur Strahlentherapie am UKSH Lübeck |

## Berufliche Laufbahn:

| Seit 10/2015 | Ausbildung zum Facharzt für Strahlentherapie am UKSH Lübeck |
| 07/2016 | Grundkurs im Strahlenschutz |
| 03/2017 | Spezialkurs im Strahlenschutz – Teletherapie – |
| 03/2017 | Spezialkurs im Strahlenschutz – Brachytherapie – |
| 05/2017 | Grundlagenkurs für Prüfer bei klinischen Prüfungen nach dem AMG/MPG |

## Wissenschaftliche Publikationen:

| 02/2018 | Radiotherapy related skin toxicity (RAREST-01): Mepitel® film versus standard care in patients with locally advanced head-and-neck cancer. |
| 08/2019 | A randomized trial (RAREST-01) comparing Mepitel® Film and standard care for prevention of radiation dermatitis in patients irradiated for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN). |
| 05/2020 | Radiotherapy-related skin toxicity (RAREST-02): A randomized trial testing the effect of a mobile application reminding head-and-neck cancer patients to perform skin care (reminder app) on radiation dermatitis |

01/2021     Comparison of Conventional Fractionation and Accelerated Fractionation with Concomitant Boost for Radiotherapy of Non-metastatic Stage IV Head-and-Neck Cancer

01/2021     Accelerated Fractionation with Concomitant Boost vs. Conventional Radio-chemotherapy for Definitive Treatment of Locally Advanced Squamous Cell Carcinoma of the Head-and-Neck (SCCHN).

02/2021     Accelerated Fractionation Plus Chemotherapy Versus Conventionally Fractionated Radiochemotherapy for Unresectable Head-and-Neck Cancer.
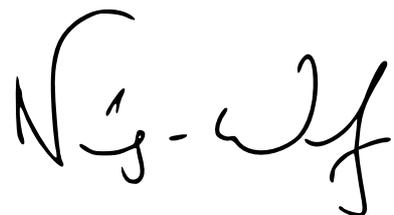
## Sprachen:

Spanisch:         Muttersprache

Deutsch:          Fließend

Englisch:         Gut

## Hobbys/ Interessen:

Schwimmen, Triathlon

Mitgründer des „Enrique Schmidt Stipendiums" für mittellose Studierenden in „La Paz Centro", Nicaragua. www.puentenica.de

Carlos Andrés Narváez-Wolf

Lübeck, 26. Februar 2022

# 9 Eidesstattliche Versicherung

„Ich, Carlos Andrés Narváez-Wolf, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Moderne Methoden bei der Strahlentherapie von Kopf-Hals-Tumoren zur Vermeidung von akuten Nebenwirkungen und zur Verbesserung der Prognose" selbständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autor*innen beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)" des ICMJE -*www.icmje.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden Erklärung angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bzw Co-Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

## 9.1 Anteilserklärung an den erfolgten Publikationen

Carlos Andrés Narváez-Wolf hatte folgenden Anteil an den folgenden Publikationen:

**Publikation 1:** Narvaez CA[1], Doemer C[1], Idel C[2], Setter C[3], Olbrich D[4], Ujmajuridze Z[5], Carl JH[5] and Rades D.[1*], Radiotherapy related skin toxicity (RAREST-01): Mepitel® film versus standard care in patients with locally advanced head-and-neck cancer. BMC Cancer. 2018 Feb 17;18(1):197. doi: 10.1186/s12885-018-4119-x. PMID: 29454311; PMCID: PMC5816351.

**Publikation 2:** Rades D[1], Narvaez CA[2], Splettstößer L[2], Dömer C[2], Setter C[3], Idel C[4], Ribbat-Idel J[5], Perner S[6] et al. Bartscht T[7], Olbrich D[8], Schild SE[9], Carl J[10]. A randomized trial (RAREST-01) comparing Mepitel® Film and standard care for prevention of radiation dermatitis in patients irradiated for locally advanced squamous cell

carcinoma of the head-and-neck (SCCHN). Radiother Oncol. 2019 Oct;139:79-82. doi: 10.1016/j.radonc.2019.07.023. Epub 2019 Aug 17. PMID: 31431372.

**Publikation 3:** Rades D.[1*], <u>Narvaez CA[1]</u>, Doemer C[1], Janssen S[2], Olbrich D[3], Tvilsted S[4], Conde-Moreno AJ[5] and Cacicedo J[6]. Radiotherapy-related skin toxicity (RAREST-02): A randomized trial testing the effect of a mobile application reminding head-and-neck cancer patients to perform skin care (reminder app) on radiation dermatitis. Trials. 2020 May 25;21(1):424. doi: 10.1186/s13063-020-04307-0. PMID: 32450921; PMCID: PMC7249413.

**Publikation 4:** <u>Narvaez CA[1]</u>, Schild SE[2], Rades D[3]. Comparison of Conventional Fractionation and Accelerated Fractionation With Concomitant Boost for Radiotherapy of Non-metastatic Stage IV Head-and-Neck Cancer. In Vivo. 2021 Jan-Feb;35(1):411-415. doi: 10.21873/invivo.12272. PMID: 33402490; PMCID: PMC7880725.

**Publikation 5:** <u>Narvaez CA[1]</u>, Schild SE[2], Janssen S[1,3], Schroeder U[4], Bruchhage KL[4], Hakim SG[5], Rades D[6]. Accelerated Fractionation With Concomitant Boost vs. Conventional Radio-chemotherapy for Definitive Treatment of Locally Advanced Squamous Cell Carcinoma of the Head-and-Neck (SCCHN). Anticancer Res. 2021 Jan;41(1):477-484. doi: 10.21873/anticanres.14798. PMID: 33419846.

**Publikation 6:** Rades D[1], <u>Narvaez CA[2]</u>, Janssen S[2,3], Schröder U[4], Bruchhage KL[4], Hakim SG[5], Bartscht T[6], Schild SE[7]. Accelerated Fractionation Plus Chemotherapy Versus Conventionally Fractionated Radiochemotherapy for Unresectable Head-and-Neck Cancer. Anticancer Res. 2021 Feb;41(2):877-884. doi: 10.21873/anticanres.14840. PMID: 33517293.

Unterschrift des Doktoranden

Unterschrift und Stempel des

betreuenden Hochschullehrer

# Anhang

**UNIVERSITÄT ZU LÜBECK**

Ethik-Kommission
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Herrn
Prof. Dr. med. Rades
Klinik für Strahlentherapie

Im Hause

Aktenzeichen: 16-124
Datum: 24. Juni 2016

**Sitzung der Ethik-Kommission am 02. Juni 2016**
**Antragsteller: Herr Prof. Rades**
**Titel: Strahlentherapie-bedingte Hautreaktionen: Mepitel Film im Vergleich zur Standardbehandlung bei Patienten mit lokal fortgeschrittenem Kopf-Hals-Tumor (RAREST-01)**

Sehr geehrter Herr Prof. Rades,

vielen Dank für Ihr Schreiben vom 21. Juni sowie die Email vom 24.06.2016, in denen Sie den gegebenen Hinweisen nachkommen und folgende überarbeitete Unterlagen vorlegen.

- Studienprotokoll Version 2.0 vom 21.06.2016

- Patienteninformation Version 3 vom 24.06.2016

Die Kommission hat gegen die Durchführung der Studie **keine Bedenken**.

Bei Änderung des Studiendesigns sollte der Antrag erneut vorgelegt werden.
Über alle schwerwiegenden oder unerwarteten und unerwünschten Ereignisse, die während der Studie auftreten, ist die Kommission umgehend zu benachrichtigen.
Die Deklaration von Helsinki in der aktuellen Fassung fordert in § 35 dazu auf, jedes medizinische Forschungsvorhaben mit Menschen zu registrieren. Daher empfiehlt die Kommission grundsätzlich die Studienregistrierung in einem öffentlichen Register (z.B. unter www.drks.de). Die ärztliche und juristische Verantwortung des Studienleiters und der an der Studie teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethikkommission durch unsere Stellungnahme unberührt.

Mit freundlichem Gruß

Prof. Dr. med. Alexander Katalinic
Vorsitzender

UNIVERSITÄT ZU LÜBECK

**Ethik-Kommission**
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**Aktenzeichen: 19-302**
Datum: 08. Oktober 2019

**Sitzung der Ethik-Kommission am 05. September 2019**
**Antragsteller : Herr Prof. Dr. Rades**
**Radiotherapy Related Skin Toxicity: A Reminder App to Reduce Radiation Dermatitis Rates in Patients with Head-and-Neck-Cancer- (RAREST-02)**

Sehr geehrter Herr Prof. Rades,

vielen Dank für Ihr Schreiben vom 30. September 2019, in dem Sie den Hinweisen aus unserer Sitzung vom 05. September 2019 nachkommen.

Folgende Unterlagen lagen vor:

- Ihr Anschreiben vom 30. September 2019

- Patienteninformation und Einwilligung in der Version 2 vom 30. September 2019

- Prüfplan in der Version 2 vom 30. September 2019.

Die Kommission hat gegen die Durchführung der Studie keine Bedenken.

Bei Änderung des Studiendesigns sollte der Antrag erneut vorgelegt werden.
Über alle schwerwiegenden oder unerwarteten und unerwünschten Ereignisse, die während der Studie auftreten, ist die Kommission umgehend zu benachrichtigen.
Die Deklaration von Helsinki in der aktuellen Fassung fordert in § 35 dazu auf, jedes medizinische Forschungsvorhaben mit Menschen zu registrieren. Daher empfiehlt die Kommission grundsätzlich die Studienregistrierung in einem öffentlichen Register (z.B. unter www.drks.de).
Die ärztliche und juristische Verantwortung des Studienleiters und der an der Studie teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethikkommission durch unsere Stellungnahme unberührt.
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Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

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**Aktenzeichen**: 20-454
**Datum**: 20. November 2020 DS

**Verkürztes Verfahren - Anzeige**

**Titel: Akzelerierte Strahlentherapie mit Concomitant Boost bei der Behandlung lokal fortgeschrittener Kopf-Hals-Tumore
Hier: Ihre E-Mail vom 17. November 2020**
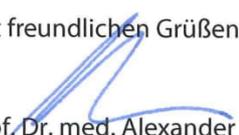

Sehr geehrter Herr Rades,

mit Ihrer o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Folgende Unterlagen lagen vor:

- Studienprotokoll Version 1.0 vom 16.11.2020

Die Ethik-Kommission nimmt das Vorhaben zustimmend zur Kenntnis.

Mit freundlichen Grüßen


Prof. Dr. med. Alexander Katalinic
Vorsitzender

Publikationen

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# Radiotherapy related skin toxicity (RAREST-01): Mepitel® film versus standard care in patients with locally advanced head-and-neck cancer

Carlos Narvaez[1], Claudia Doemer[1], Christian Idel[2], Cornelia Setter[3], Denise Olbrich[4], Zaza Ujmajuridze[5], Jesper Hansen Carl[5] and Dirk Rades[1*]

## Abstract

**Background:** The aim of the present trial is to investigate a new option of skin protection in order to reduce the rate of grade ≥ 2 skin toxicity in patients receiving radiotherapy alone or radiochemotherapy for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN).

**Methods / Design:** This is a randomized, active-controlled, parallel-group multi-center trial that compares the following treatments of radiation dermatitis in patients with head-and-neck cancer: Mepitel® Film (Arm A) vs. standard care (Arm B). The primary aim of this trial is to investigate the rate of patients experiencing grade ≥ 2 radiation dermatitis (according to Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03) until 50 Gy of radiotherapy. Evaluation until 50 Gy of radiotherapy has been selected as the primary endpoint, since up to 50 Gy, the irradiated volume includes the primary tumor and the bilateral cervical and supraclavicular lymph nodes, and, therefore, is similar in all patients. After 50 Gy, irradiated volumes are very individual, depending on location and size of the primary tumor, involvement of lymph nodes, and the treatment approach (definitive vs. adjuvant). In addition, the following endpoints will be evaluated: Time to grade 2 radiation dermatitis until 50 Gy of radiotherapy, rate of patients experiencing grade ≥ 2 radiation dermatitis during radio(chemo)therapy, rate of patients experiencing grade ≥ 3 skin toxicity during radio(chemo)therapy, adverse events, quality of life, and dermatitis-related pain. Administration of Mepitel® Film will be considered to be clinically relevant, if the rate of grade ≥ 2 radiation dermatitis can be reduced from 85% to 65%.

**Discussion:** If administration of Mepitel® Film instead of standard care will be able to significantly reduce the rate of grade ≥ 2 radiation dermatitis, it could become the new standard of skin care in patients irradiated for SCCHN.

**Trial registration:** clinicaltrials.gov NCT03047174. Registered on 26th of January, 2017. First patient included on 9th of May, 2017.

**Keywords:** Head-and-neck cancer, Radio(chemo)therapy, Radiation dermatitis, Mepitel® film, Standard care

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## Background

Locally advanced squamous head-and-neck cancer is a serious malignant disease. In about 90% of head-and-neck cancers, the histology is squamous cell carcinoma (SCCHN). The vast majority of patients with locally advanced SCCHN receive radiotherapy, either as a part of a definitive treatment approach, or as an adjuvant treatment following surgery. If radiotherapy is administered as definitive treatment, it is usually combined with concurrent cisplatin-based chemotherapy [1]. In an adjuvant situation, chemotherapy will be added to radiotherapy in case of risk factors, namely microscopically or macroscopically incomplete resection or in case of extra-capsular spread of lymph nodes metastases.

Radiotherapy of locally advanced SCCHN may be associated with severe acute toxicities including skin reaction such as erythema or desquamation. Skin toxicity is enhanced if concurrent chemotherapy is administered. If the skin toxicity becomes severe (grade ≥ 3 according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03), it may lead to a reduction of the planned chemotherapy dose and to interruptions of radiotherapy. Interruptions of radiotherapy have been reported to be associated with poorer treatment outcomes in patients with SCCHN [2, 3].

In order to successfully avoid grade ≥ 3 skin toxicity, it appears mandatory to avoid or at least postpone the development of grade 2 skin toxicity. In previous studies of patients receiving radiotherapy or radio(chemo)therapy for locally advanced head-and-neck cancer, rates of grade ≥ 2 skin toxicity ranging between 86% and 92% have been reported, although the standard procedures of skin care and protection had been applied [1, 4, 5]. These figures demonstrate that the results of standard care need to be improved.

A few years ago, the results of a systematic inpatient controlled clinical trial were published that had investigated the use of an absorbent, self-adhesive dressing (Mepilex® Lite) for skin protection in patients irradiated for breast cancer [6]. According to this study the dressings were able to significantly reduce the radiation-related skin erythema. Similar dressings (Mepilex® Border Sacrum and Mepilex® Heel dressings) have been demonstrated in a randomized trial to be effective also in the prevention of sacral and heel pressure ulcers in trauma and critically ill patients [7]. In another randomized trial a silver-containing soft silicone foam dressing (Mepilex® Ag dressing) was as effective in the treatment of partial-thickness thermal burns when compared to the standard care (silver sulfadiazine) [8]. In addition, the group of patients treated with the Mepilex® Ag dressing demonstrated decreased pain and lower costs associated with treatment. More recently, a new dressing (Mepitel® Film) has been developed, which is thinner, softer and more comfortable than previous dressings.

The rationale for the present study is to investigate a new option of skin protection in order to reduce the rate of grade ≥ 2 skin toxicity in patients receiving radiotherapy alone or radiochemotherapy for locally advanced SCCHN.

## Methods / Design

### Endpoints of the study

The primary aim of this randomized multi-center trial is to investigate the rate of patients experiencing grade ≥ 2 radiation dermatitis (CTCAE v4.03) until 50 Gy of radiotherapy. Evaluation until 50 Gy of radiotherapy has been selected as the primary endpoint, since up to 50 Gy, the irradiated volume includes the primary tumor and the bilateral cervical and supraclavicular lymph nodes, and, therefore, is similar in all patients. After 50 Gy, irradiated volumes are very individual, depending on location and size of the primary tumor, involvement of lymph nodes, and the treatment approach (definitive vs. adjuvant).

In addition, the following endpoints will be evaluated:

1. Time to grade 2 radiation dermatitis until 50 Gy of radiotherapy
2. Rate of patients experiencing grade ≥ 2 radiation dermatitis during radio(chemo)therapy
3. Rate of patients experiencing grade ≥ 3 skin toxicity during radio(chemo)therapy
4. Adverse Events
5. Quality of life: Evaluation prior to radiotherapy, at the end of radiotherapy weeks 3 + 5, and at 3 weeks following radiotherapy
6. Pain: Evaluation prior to radiotherapy, at the end of radiotherapy weeks 3 + 5, and at 1 and 3 weeks following radiotherapy

### Study design

This is a randomized, active-controlled, parallel-group trial, which will compare the following treatments of radiation related skin toxicity in patients with head-and-neck cancer:
Mepitel® Film (Arm A) vs. Standard Care (Arm B).

The recruitment of all 168 patients should be completed within 24 months. The follow-up period will be 3 weeks. Stratification will be done using the following factors:

1. Tumor site: oropharynx/oral cavity vs. hypopharynx/larynx
2. Treatment approach: radiochemotherapy vs. radiotherapy alone
3. Participating site

### Inclusion criteria

1. Histologically proven locally advanced squamous cell carcinoma of the head-and-neck (SCCHN)

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2. Conventionally fractionated (5 × 2 Gy per week) definitive or adjuvant radio(chemo)therapy
3. Age ≥ 18 years
4. Written informed consent
5. Capacity of the patient to contract

## Exclusion criteria

1. N3 stage (lymph nodes > 6 cm)
2. Distant metastases (M1)
3. Pregnancy, Lactation
4. Treatment with EGFR-antibodies (either given or planned)
5. Expected non-compliance

## Treatment
### Radiotherapy

Radiotherapy is administered using conventional fractionation (5 × 2.0 Gy per week). The initial target volume includes the region of the primary tumor plus bilateral cervical and supraclavicular lymph nodes up to 50 Gy. Patients treated with adjuvant radiotherapy following complete resection of the primary tumor and the involved lymph nodes receive a radiation boost of 10 Gy (5 × 2.0 Gy per week) to the regions of the primary tumor and the involved lymph nodes. In case of a microscopically incomplete resection, the boost dose to the primary tumor region is 16 Gy. In case of extra-capsular spread (ECS) of lymph nodes, the lymph nodes showing ECS receive an additional boost of 6 Gy (i.e. a cumulative boost dose of 16 Gy). Patients receiving definitive radiotherapy, receive a boost of 10 Gy (5 × 2.0 Gy per week) to the primary tumor, the involved lymph nodes, and the lymph node levels adjacent to the involved lymph nodes. An additional boost of another 10 Gy (5 × 2.0 Gy per week) is administered to the primary tumor and the involved lymph nodes. Treatment should be performed as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) radiotherapy.

### Chemotherapy

In patients who receive definitive radiotherapy, concomitant chemotherapy with cisplatin is administered. The cumulative cisplatin dose at the end of the fifth week of radiotherapy (50 Gy) should be 200 mg/m2. This cumulative dose may either be achieved with 20 mg/m2 given with radiotherapy fractions 1–5 and 21–25, 25 mg/m2 given with radiotherapy fractions 1–4 and 21–24, or weekly doses of 40/m2.

### Skin care

**Arm a (Mepitel® film)** Starting on the first day of radiotherapy, Mepitel® Film will be applied. Skin care will be continued until the end of the study period or until a patient experiences grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis. In case of grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis, antiseptic agents will be used daily followed by administration of silicon or calcium alginate bandage until moist desquamation disappears and radiaton dermatitis improves to grade 2.

**Arm B (standard care)** Standard skin care will be applied starting on radiotherapy day 1 including fatty cream with 2–5% urea (fatty cream alone, if patients do not tolerate urea) and mometasone furoate cream. The treatment will be continued until the end of the study period or until a patient experiences grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis. In case of grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis, the same skin care regimen is used as in Arm A.

## Assessments

The following parameters will be recorded at the start of the trial: Medical history, physical examination, complications from head-and-neck surgery, age, gender, performance status, site of primary tumor, tumor stage, histology, HPV-status, histologic grading, surgery of primary tumor, extent of resection, neck dissection, complications of surgery, chemotherapy planned, skin status of the head-and-neck region, and quality of life.

The following parameters will be assessed continuously throughout the course of the trial:

1. Radiation dermatitis: Radiation dermatitis will be assessed by two independent observers (specially trained nurses, technicians, or physicians) prior to radio(chemo)therapy, daily during radio(chemo)therapy and up to three weeks following radio(chemotherapy) according to CTCAE v4.03. If the graduation of radiation dermatitis varies between the two observers, skin toxicity will be assessed by an additional observer. Observers are required to be very experienced in rating skin reactions and will additionally undergo a particular briefing prior to the start of this study.
2. Adverse Events: Adverse events, other than radiation dermatitis will be assessed on an ongoing basis according to CTCAE v4.03.
3. Quality of life: Quality of life will be assessed prior to radio(chemo)therapy, at the end of radiotherapy weeks 3 and 5, and at three weeks following radio(chemo)therapy using EORTC QLQ-C30 Version 3.0 and EORTC QLQ-H&N35.
4. Pain: Dermatitis-related pain is assessed with a visual analogue scale (self-assessment: from 0 = No pain; 1 = Mild pain to 10 = Very severe pain) prior to, daily during and up to three weeks following radio(chemotherapy). Pain scores will be correlated with grade of skin reactions.

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## Sample size calculation

The primary goal of this randomized trial is to demonstrate that Mepitel® Film is superior to Standard Care with respect to prevent grade 2 radiation dermatitis in patients receiving radio(chemo)therapy up to 50 Gy for locally advanced SCCHN. The null hypothesis of equal rates of grade ≥ 2 skin toxicity is tested against the two-sided alternative hypothesis of different rates. Based on this hypothesis system, the sample size required for this trial is calculated taking into account the following assumptions:

- A Chi-square Test will be applied
- The two-sided significance level is set to 5%
- In patients treated with radio(chemo)therapy for locally advanced SCCHN, previous studies have suggested rates of grade ≥ 2 skin toxicity of 86–92% if standard skin care was administered.
- Based on these data, a rate of grade ≥ 2 skin toxicity of 85% can be assumed in the reference group ("worst-case"), i.e. in patients receiving standard care for skin toxicity.
- Administration of Mepitel® Film will be considered to be clinically relevant, if the rate of grade ≥ 2 skin toxicity can be reduced to 65%.
- The power to yield statistical significance if the difference in rates is in fact 20 percentage points is set to 80%.

Based on these assumptions, 80 patients are required per study arm within the full analysis set. Taking into account that 5% of patients will not qualify for the set, a total of 168 patients should be randomized.

The rates of patients experiencing grade ≥ 2 radiation dermatitis in patients receiving radio(chemo)therapy up to 50 Gy will be statistically compared using the Cochran-Mantel-Haenszel Chi-square test on a two-sided significance level of 5%. This test is the natural non-parametric extension of the Chi-square test for testing the treatment effect, while adjusting for the effects of the stratification variables used for randomization. For further assessment of the robustness of the results, a logistic regression model for grade ≥ 2 radiation dermatitis will be applied including the parameters used for stratification. In addition, a model including also additional patient characteristics will be fitted. The confirmatory evaluation will be performed within the Full Analysis Set, the Per Protocol Set serves for further sensitivity analyses.

## Discussion

Radiotherapy is the most frequently administered treatment modality in patients with locally advanced SCCHN. A considerable number of these patients receive concurrent chemotherapy, generally including cisplatin or carboplatin [1]. Many of these patients, particularly those receiving radio-chemotherapy, experience severe acute side effects including radiation dermatitis. Severe skin reactions may require an interruption of the radiotherapy series, which can lead to a worsening of the patients' prognoses. On multivariate analyses of a retrospective study of 153 patients irradiated for SCCHN, better overall survival was significantly associated with no interruptions of radiotherapy longer than one week (relative risk: 2.59, 95% confidence interval: 1.15–5.78, $p$ = 0.021) [2]. So was local control (relative risk: 3.32, 95% confidence interval: 1.26–8.79, $p$ = 0.015). In a SEER database analysis, patients irradiated for larynx cancer with an interruption of their radiotherapy had a 68% (95% confidence interval: 41% to 200%) increased risk of death than those patients without an interruption. Patients with head-and-neck cancers at other sites showed similar associations. However, due to the relatively small numbers of patients, the difference between patients who did and who did experience interruptions of radiotherapy did not reach significance [3]. To avoid such interruptions of radiotherapy due to radiation dermatitis, it is reasonable to avoid or at least significantly postpone grade 2 skin reactions. This appears a challenge for radiation oncologists, since in previous studies grade ≥ 2 radiation dermatitis occurred in 86% to 92% of patients, despite administration of standard skin care procedures from the first day of radiotherapy [1, 4, 5]. Therefore, skin care in patients irradiated for SCCHN needs to be improved, particularly to avoid interruptions of radiotherapy and a subsequent impairment of the patient's prognoses in terms of local control and overall survival [2, 3]. The use of an absorbent, self-adhesive dressing represents a promising approach. According to a systematic inpatient controlled clinical, such dressings can significantly decrease radiation-related erythema of the skin in breast cancer patients [6]. Promising results have also been reported for the prevention of sacral and heel pressure ulcers in trauma and critically ill patients and the treatment of partial-thickness thermal burns [7, 8]. More recently, a new dressing named Mepitel® Film was developed that is thinner and softer than previous dressings and, therefore, appears more comfortable for the patients than the previous dressings. The randomized RAREST-01 compares this new dressing to standard procedures of skin care in patients with locally advanced SCCHN receiving radiotherapy or radiochemotherapy. If Mepitel® Film can significantly reduce the rate of grade ≥ 2 radiation dermatitis in patients irradiated for locally advanced SCCHN it would have the potential to become the new standard of skin care in this group of patients.

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## Authors' contributions
CN, CD, CI, CS, DO, ZU, JHC, and DR participated in the generation of the study protocol of the RAREST-01 trial. CN and DR drafted the manuscript, which has been reviewed by the other authors. The final version of the manuscript has been approved by the authors.

## Ethics approval and consent to participate
The study has been approved by the ethics committee of the University of Lübeck (reference number: AZ 16–124). The study is conducted in accordance with the principles laid out in the Declaration of Helsinki and in accordance with the principles of Good Clinical Practice (ICH-GCP E6). Patients are included after giving written informed consent.

## Consent for publication
Not applicable.

## Competing interests
D.R. is an associate editor for BMC Cancer. Otherwise, the authors declare that they have no competing interest related to the study presented here.

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Short Communication

# A randomized trial (RAREST-01) comparing Mepitel® Film and standard care for prevention of radiation dermatitis in patients irradiated for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN)

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## ARTICLE INFO

## ABSTRACT

Mepitel® Film (MEP) and standard care (STD) were compared for radiation dermatitis in SCCHN patients. This trial was stopped prematurely since13/28 patients did not tolerate MEP. Grade ≥2 dermatitis: 34.8% (MEP) vs. 35.7% (STD) at 50 Gy, 65.2% vs. 59.3% at 60 Gy. MEP was unsatisfactorily tolerated and appeared not superior (NCT03047174).

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Most patients with locally advanced SCCHN receive radiotherapy, which can be associated with significant toxicity including radiation dermatitis [1,2]. Grade 3 radiation dermatitis [8] may force physicians to interrupt radiation treatment, which can impair the patients' prognoses [3–5]. To avoid grade ≥3 radiation dermatitis, grade 2 dermatitis [3] should be avoided or postponed.

In previous studies of radio(chemo)therapy for locally advanced head-and-neck cancer, grade ≥2 dermatitis was observed in 86–92% of patients, despite standard skin care [1,6,7]. A randomized trial showed promising results with Mepilex® Lite, a self-adhesive dressing, in patients with moist dermatitis during radiochemotherapy for nasopharynx cancer [8].

In a randomized trial, prophylactic use of Mepitel® Film, a more recently developed dressing, reduced the severity of skin reactions in breast cancer patients [9]. The present RAREST-01 trial compared Mepitel® Film to standard skin care for prevention of grade ≥2 radiation dermatitis in patients with locally advanced SCCHN [10].

## Patients and methods

This randomized, active-controlled, parallel-group multicenter trial compared Mepitel® Film (MEP) and standard skin care (STD) for prevention of moderate and severe radiation dermatitis in patients receiving radio(chemo)therapy for locally advanced SCCHN [10]. It was approved by local ethics committees (leading committee: University of Lübeck, reference AZ 16–124), conducted in accordance with the Declaration of Helsinki and registered at clinicaltrials.gov (NCT03047174). Criteria for inclusion and exclusion have been reported before [10].

Patients were stratified according to center, tumor site (oropharynx/oral cavity vs. hypopharynx/larynx) and treatment (radiotherapy vs. radiochemotherapy). In addition, several characteristics were assessed (Table 1).

### Radiotherapy and radiochemotherapy

Radiotherapy was performed as conventionally fractionated (5x2.0 Gy/week) volume modulated arc therapy (VMAT). Target volume up to 50 Gy included primary tumor region and bilateral cervical and supraclavicular lymph nodes. Sequential boosts were

**Table 1**
Patient characteristics of the treatment group (Mepitel® Film, *n* = 28) and the reference group (standard skin care, *n* = 29).

| | Mepitel® Film N patients (%) | Standard skin care N patients (%) |
|---|---|---|
| *Age* | | |
| ≤62 years | 15 (53.6) | 14 (48.3) |
| ≥63 years | 13 (46.4) | 15 (51.7) |
| *Gender* | | |
| Female | 6 (21.4) | 5 (17.2) |
| Male | 22 (78.6) | 24 (82.8) |
| *Tumor site (all sites)* | | |
| Oropharynx | 13 (46.4) | 11 (37.9) |
| Oral cavity | 4 (14.3) | 6 (20.7) |
| Hypopharynx | 5 (17.9) | 7 (24.1) |
| Larynx | 6 (21.4) | 5 (17.2) |
| *Tumor site (stratification)* | | |
| Oropharynx/oral cavity | 17 (60.7) | 17 (58.6) |
| Hypopharynx/larynx | 11 (39.3) | 12 (41.4) |
| *Tumor stage (AJCC)* | | |
| Stage II | 3 (10.7) | 2 (6.9) |
| Stage III | 7 (25.0) | 7 (24.1) |
| Stage IV | 18 (64.3) | 20 (69.0) |
| *Histologic grading* | | |
| G 1–2 | 17 (60.7) | 16 (55.2) |
| G 3 | 9 (32.1) | 12 (41.4) |
| Gx | 2 (7.1) | 1 (3.4) |
| *HPV status* | | |
| Negative | 18 (64.3) | 16 (55.2) |
| Positive | 8 (28.6) | 10 (34.5) |
| Unknown | 2 (7.1) | 3 (10.3) |
| *Treatment regimen (stratification)* | | |
| Radiotherapy alone | 6 (21.4) | 7 (24.1) |
| Radiochemotherapy | 22 (78.6) | 22 (75.9) |
| *Chemotherapy given (at least one course)* | | |
| Cisplatin | 15 (71.4) | 14 (66.7) |
| Carboplatin | 6 (28.6) | 5 (23.8) |
| Mitomycin C + 5-Fluorouracil | 0 (0.0) | 2 (9.5) |
| *Surgery performed* | | |
| No | 13 (46.4) | 15 (51.7) |
| Yes | 15 (53.6) | 14 (48.3) |
| *Extent of resection* | | |
| R0 | 11 (73.3) | 13 (92.9) |
| R1 | 3 (20.0) | 0 (0.0) |
| Rx | 1 (6.7) | 1 (7.1) |
| *Neck dissection performed* | | |
| No | 1 (6.7) | 0 (0.0) |
| Unilateral | 9 (60.0) | 10 (71.4) |
| Bilateral | 5 (33.3) | 4 (28.6) |
| *Contributing center (stratification)* | | |
| University of Luebeck | 26 (49.1) | 27 (50.9) |
| Christian-Albrechts University Kiel | 2 (50.0) | 2 (50.0) |

assigned depending on treatment approach, extent of resection and extra-capsular extension of lymph node metastasis [10].

Clinical (CTV) and planning (PTV) target volumes were retracted from the skin by 2 mm. For patients included in this study, no bolus was used. In contrast to other organs at risk, the skin was not included in the optimization process of VMAT. In patients receiving concurrent chemotherapy, cisplatin was the first choice (2 courses of 20 mg/m2/d1–5 or 25 mg/m2/d1–4). In case of impaired renal function, two courses of carboplatin (AUC 5–6) or mitomycin C (10 mg/m2/d1) plus 5-fluorouracil (1000 mg/m2/d1–5) were allowed. Carboplatin was given for the second course, if renal function decreased during or after cisplatin.

### Skin care

In the treatment group, Mepitel® Film (MEP) was started on the first day of radiotherapy and continued until grade ≥2 moist desquamation or grade ≥3 radiation dermatitis occurred, otherwise until one week following radiotherapy. Grade ≥2 moist desquamation and grade ≥3 radiation dermatitis were treated with antiseptic agents followed by silicon or calcium alginate bandage until moist desquamation disappeared and/or radiation dermatitis improved to grade 2. MEP was changed twice per week. Since the film was transparent, the fact that it was not changed daily had no impact on the assessment of radiation dermatitis including desquamation.

In the reference group, standard skin care (STD) was started on the first day of radiotherapy including fatty cream with 2–5% urea (fatty cream alone if patients did not tolerate urea) and mometasone furoate cream. STD was continued until grade ≥2 moist desquamation or grade ≥3 radiation dermatitis occurred or until one week following radiotherapy. For these reactions, the same treatments were administered as in the treatment group.

### Endpoints and assessments

Primary endpoint was grade ≥2 radiation dermatitis (CTCAE v4.03, [3]) at 50 Gy. Secondary endpoints included grade ≥2 dermatitis at 60 Gy, number of fractions up to 50 Gy till grade ≥2 dermatitis, and pain at irradiated skin.

Radiation dermatitis and pain at irradiated skin (self-rating scale from 0 to 10) were assessed from the first day of radiotherapy, prior to each radiation fraction, and up to three weeks following radiotherapy [3].

### Statistical considerations

Primary goal was to demonstrate superiority of MEP over STD in preventing grade 2 radiation dermatitis at 50 Gy. Details regarding sample size calculations have been reported previously [10]. Eighty patients were required for each group. Assuming that 5% of patients would not qualify for the analyses, 168 patients were planned to be randomized.

### Interim analysis

To evaluate the tolerance of the Mepitel® Film treatment, an interim analysis was conducted after 57 patients. Recruitment was put on hold until these patients completed the study. If ≥25% of the patients did not tolerate Mepitel® Film, the study was to be terminated. In this case, comparisons regarding radiation dermatitis were performed according to the intent-to-treat principle and additionally in the per-protocol-set. Comparisons for grade ≥2 and grade ≥3 radiation dermatitis were performed with the Fisher's exact test on a two-sided significance level of 5%.

### Results

At the time of the interim analysis, 57 patients were randomized (28 MEP, 29 STD). Since in the MEP-group, 13 of 28 patients (46.4%) did not tolerate the dressing, the trial was stopped prematurely. At this time, both groups were well balanced for stratification factors and additional characteristics (Table 1). Of the 28 patients of the MEP-group, 3 patients withdrew their consent to participate in the study after 6 Gy, 14 Gy and 36 Gy, respectively, and 2 patients died after 16 Gy and 44 Gy, respectively. Since for these patients, data at 50 Gy were missing, 23 patients remained for intention-to-treat analyses. In the STD-group, one patient died after 36 Gy, and 28 patients could be analyzed.

At 50 Gy, grade 2 radiation dermatitis was observed in 8/23 patients (34.8%) in the MEP-group and 10/28 patients (35.7%) in the STD-group (*p* = 1.00). Grade 3 radiation dermatitis was not observed ≤50 Gy. At 60 Gy, grade ≥2 dermatitis rates were 65.2%

(15/23 patients) in the MEP-group vs. 59.3% (16/27) in the STD-group ($p = 0.77$), and grade $\geq 3$ dermatitis rates were 4.3% (1/23) and 11.1% (3/27), respectively ($p = 0.61$).

Thirteen patients did not tolerate the dressing due to discomfort/distress ($n = 8$) or feeling of tightness ($n = 5$). In additional 5 patients (17.9%), MEP did not adhere properly to the skin. One patient died after 16 Gy (acute renal failure). Thus, 9 patients of the MEP-group were eligible for per-protocol-analyses at 50 Gy. Between 50 and 60 Gy, additional 2 patients (1 itching, 1 moist desquamation during change of dressing) refused to wear the dressing any longer; 7 patients remained for analyses at 60 Gy. In the STD-group, one patient died after 36 Gy (gastrointestinal bleeding), one patient received cetuximab instead of planned chemotherapy. Thus, 27 patients remained for per-protocol-analyses. For one patient, grade of radiation dermatitis was not available at 60 Gy. According to recommendations of the ethics committee, analyses regarding radiation dermatitis were performed in the per-protocol-set. At 50 Gy, grade 2 radiation dermatitis was observed in 3/9 patients (33.3%) in the MEP-group and 9/27 patients (33.3%) in the STD-group ($p = 1.00$). At 60 Gy, grade $\geq 2$ dermatitis rates were 57.1% (4/7) vs. 57.7% (15/26), respectively ($p = 1.00$), and grade 3 radiation dermatitis rates were 14.3% (1/7) and 11.5% (3/26), respectively ($p = 1.00$).

In the intent-to-treat population, grade 2 dermatitis $\leq 50$ Gy occurred after median 23 (19–25) fractions in the MEP-group and 23 (9–25) fractions in the STD-group. Median pain scores at the irradiated skin were 0.0 (0–7) in the MEP-group vs. 0.0 (0–7) in the STD-group at 50 Gy, and 2.0 (0–6) vs. 2.5 (0–8) at 60 Gy. The comparison of the pain scores is descriptive, since many patients received already analgesics due to oral mucositis prior to radiation dermatitis.

## Discussion

To improve the results of radio(chemo)therapy for SCCHN, considerable research has been carried out [11–21]. Prognoses of patients can be improved, if interruptions of radiotherapy, mainly caused by adverse events, are avoided [4,5].

Semi-permeable dressings were investigated to prevent and treat radiation dermatitis [8,9,22,23].

In a randomized trial of 74 breast cancer patients receiving mainly 50 Gy in 25 fractions following mastectomy, Mepilex® Lite did not significantly reduce the incidence of moist desquamation (19% vs. 15%, $p = 0.55$) [23]. However, overall severity of radiation dermatitis was reduced by 41%.

Another randomized trial of 88 patients with nasopharynx cancer, who developed moist dermatitis during radiochemotherapy, compared wound care and wound cleansing with ($n = 43$) vs. without ($n = 45$) Mepilex® Lite [8].Addition of Mepilex® Lite was associated with significantly shorter time to wound-healing (median 16 vs. 23 days, $p = 0.009$).

Another randomized intra-patient controlled trial of 80 breast cancer patients compared prophylactic skin care with a Mepitel® Film to aqueous cream [9]. Patients received radiotherapy following breast-conserving surgery ($n = 46$) or mastectomy ($n = 34$), mainly with 50 Gy in 25 fractions ($n = 37$) or 40 Gy in 15 fractions ($n = 36$). A boost was administered in 28 patients. Mepitel® Film reduced the rate of any grade of radiation dermatitis (44% vs. 100%).

Considering these promising results, we assumed that Mepitel® Film would reduce radiation dermatitis in patients with locally advanced SCCHN and initiated the RAREST-01 trial [10]. Since in the interim analysis, 46.4% of patients did not tolerate Mepitel® Film, the trial was terminated. The proportion of patients not tolerating the dressing was unexpectedly high compared to breast can-

cer trials, where the majority of patients [preferred Mepilex® Lite or Mepitel® Film over cream [9,23]. This difference can be explained by cancer site. Wearing a dressing in the head-and-neck region appears more burdensome, particularly regarding feeling of tightness, than at breast or chest. Distress due to feeling stigmatized is more likely if a dressing is attached to the head-and-neck region and obvious to the public. In our trial the dressing did not adhere properly to the skin in some patients, which may cause distress and is more likely in men with beards.

After completion of the RAREST-01 trial, a feasibility-study comparing Mepitel® Film to a moisturizing cream for dry skin, in patients with head-and-neck cancer was published [24]. Patients in New Zealand received 60–66 Gy in 30 fractions, patients in China 74 Gy in 37 fractions. If radiochemotherapy was indicated, weekly cisplatin (40 mg/m2) was used in New Zealand, weekly nedaplatin (25 mg/m2) in China. Of 11 Chinese patients, almost 50% found the dressing very itchy, 3 (27.3%) rated the dressing as uncomfortable and one patient (9.1%) reported a feeling of tightness. Five of 11 Chinese patients (45.6%) and 6 of 16 patients (37.5%) from New Zealand stated that the dressing did not adhere properly to the skin. No patient from New Zealand complained about itching. The regional differences demonstrate that it is difficult to compare results from different countries.

The RAREST-01 trial did not show superiority of Mepitel® Film over standard care regarding prevention of radiation dermatitis. Comparisons between trials investigating semi-permeable dressings for radiation dermatitis must be made with caution, since they differed with respect to primary tumor type, type of randomization, primary endpoints, and assessment of radiation dermatitis [8,9,22–24].

In the RAREST-01 trial, dermatitis rates between MEP-group and STD-group were not significantly different at 50 Gy and 60 Gy, neither in the intention-to-treat population nor the per-protocol-set. This may be partially explained by the small number of patients remaining after early termination of the trial. Rates of grade $\geq 2$ radiation dermatitis were lower than expected in both groups. One reason for the favorable results in the STD-group may the use of a combination of fatty cream plus/minus urea and mometasone furoate cream, which might be more effective than aqueous and moisturizing creams used in previous studies. In contrast to previous trials, where patients were seen three times a week, patients of the RAREST-01 trial were seen at least five times per week. Moreover, standard skin care was performed 4 times per day compared to twice daily. Performing skin care 4 times a day requires a high level of discipline and compliance from the patients. Daily reminders regarding skin care by staff-members may have improved patients' compliance. Proper daily skin care would likely have led to decreased incidence and severity of radiation dermatitis.

In summary, many patients did not tolerate Mepitel® Film, which led to premature termination of this trial. In patients remaining for analyses, MEP appeared not superior to STD in preventing grade $\geq 2$ radiation dermatitis. Due to the small number of remaining patients, the validity of this conclusion is limited. The question whether selected patients may benefit from the dressing, must be answered in additional trials.

## Role of the funding source

**Declaration of Competing Interest**

The authors declare no conflicts of interest related to this study.

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**Open Access**

# Radiotherapy-related skin toxicity (RAREST-02): A randomized trial testing the effect of a mobile application reminding head-and-neck cancer patients to perform skin care (reminder app) on radiation dermatitis

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## Abstract

**Background:** Radiotherapy of head-and-neck cancer can be associated with significant toxicities including dermatitis and oral mucositis. Severe toxicities may require interruptions of the radiation treatment associated with impairment of the patients' prognoses. This study will investigate whether the addition of a reminder app to standard care can reduce dermatitis and oral mucositis rates during radiotherapy in these patients.

**Methods:** This randomized trial compares standard care supported by a reminder app (Arm A) to standard care alone (Arm B) with respect to grade ≥ 2 radiation dermatitis and oral mucositis at 60 Gy of radiotherapy, the minimum planned dose for patients receiving definitive or adjuvant radiotherapy for locally advanced head- and-neck cancer. Moreover, radiation-induced dermatitis and oral mucositis grade ≥ 3 at 60 Gy and both grade ≥ 2 and grade ≥ 3 at the end of radiation treatment (EOT) will be evaluated, as well as quality of life and pain. According to sample size calculations, 80 patients are required per arm within the full analysis set. Taking into account that 5% of patients will not qualify for full analysis set, 168 patients should be randomized. The impact of the reminder app will be considered clinically relevant, if the rates of grade ≥ 2 radiation dermatitis (primary endpoint) and oral mucositis (secondary endpoint) can be reduced by 20%.

**Discussion:** If the addition of a reminder app to standard care will lead to a significant reduction of radiation dermatitis and oral mucositis, it could become a helpful tool for patients with head-and-neck cancer during radiotherapy.

**Trial registration:** clinicaltrials.gov (NCT04110977). Registered on September 27, 2019. First patient is planned to be included in December 2019.

**Keywords:** head-and-neck cancer, radiotherapy, radiation dermatitis, oral mucositis, reminder app

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## Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

| | |
|---|---|
| Title {1} | **Radiotherapy-related skin toxicity (RAREST-02): A randomized trial testing a reminder app to reduce radiation dermatitis in patients with head-and-neck cancer** |
| Trial registration {2a and 2b}. | NCT04110977, clinicaltrials.gov |
| Protocol version {3} | 09-30-2019, version 2.0 |
| Funding {4} | As part of the project NorDigHealth, the RAREST-02 trial was funded by the European Regional Development Fund through the Interreg Deutschland-Danmark program, reference: 087–1.1-18. |
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| Name and contact information for the trial sponsor {5b} | **Sponsor:** University Hospital Schleswig-Holstein (UKSH), Campus Lübeck Ratzeburger Allee 160, 23,538 Lübeck, Germany **Coordinating Investigator (contact)** Prof. Dr. Dirk Rades Department of Radiation Oncology University of Lübeck Ratzeburger Allee 160 23,538 Lübeck, Germany. Tel.: + 49-(0)451–500-45,400 Fax: + 49-(0)451–500-45,404 Email: Rades.Dirk@gmx.net |
| Role of sponsor {5c} | The sponsor and the funding body have no role in the design of the study, in collection, analysis and interpretation of the data and in the writing of the manuscript. |

## Introduction

### Background and rationale {6a}

Many patients with squamous cell carcinoma of the head and neck (SCCHN), particularly those patients with locally advanced disease, receive radiotherapy. If radiotherapy is administered as definitive treatment (i.e., without preceding surgery), it is generally combined with chemotherapy [1]. In an adjuvant situation (i.e., following surgery), concurrent chemotherapy will be administered if risk factors (incomplete resection and/or extracapsular [ECS] spread of lymph nodes metastases) exist. Radiotherapy of SCCHN can be associated with significant toxicities including dermatitis and oral mucositis. Severe toxicities may require interruptions of the radiotherapy series that can impair the prognoses of these patients [2, 3]. To avoid severe (grade ≥ 3) radiation toxicities, it is important to avoid or postpone grade 2 toxicities. Grade ≥ 2 dermatitis and grade ≥ 2 mucositis rates were very high in previous studies (86–92% and 86–100%, respectively) and require improvement [4–6]. In the previous RAREST-01 trial that compared the dressing Mepitel® Film to standard skin care in patients irradiated for head-and-neck cancer, dermatitis rates were lower than expected in both groups [7, 8]. In the RAREST-01 trial, standard skin care was supposed to be performed four times daily, which required a high level of discipline from the patients. Daily reminders by medical staff members regarding the importance of skin care likely improved the patients' compliance resulting in less radiation dermatitis. It may be questioned whether the daily reminders by staff members can be replaced by a mobile application (a reminder app).

### Objectives {7}

This study aims to show that standard skin care supported by a reminder app is superior to standard skin care alone regarding the avoidance of grade ≥ 2 dermatitis up to 60 Gy in patients irradiated for locally advanced head-and-neck cancers. The null hypothesis of equal grade ≥ 2 dermatitis rates in both groups is tested against the two-sided alternative hypothesis of different dermatitis rates.

### Trial design {8}

This is a randomized, active-controlled, parallel-group trial, which will primarily compare two treatments of radiation dermatitis in patients with head-and-neck cancer: standard care supported by a reminder app (Arm A) versus standard care alone (Arm B).

## Methods: participants, interventions and outcomes

### Study setting {9}

The study will be performed in Germany (one university hospital, one private practice) and Spain (two university hospitals). Study sites can be obtained at clinicaltrials. gov.

### Eligibility criteria {10}

Inclusion criteria

1. Histologically proven locally advanced SCCHN
2. Indication for radiotherapy or radio-chemotherapy
3. Possession of and ability to use a smartphone
4. Age ≥ 18 years
5. Written informed consent
6. Capacity of the patient to contract

Exclusion criteria

1. Nasopharynx cancer
2. Pregnancy, lactation
3. Treatment with epidermal growth factor receptor antibodies (given or planned)
4. Expected noncompliance

Radiation dermatitis and oral mucositis will be assessed by two independent observers (specially trained nurses, technicians, or physicians) weekly during the period of radiotherapy, at 60 Gy and at end of treatment (EOT). If the graduation varies between the two observers, toxicities will be assessed by an additional observer. Observers are required to be very experienced in rating toxicities and will additionally undergo a particular briefing prior to the start of this study.

### Who will take informed consent? {26a}

Informed consent will be taken by specially trained physicians registered as investigators for this trial.

### Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

## Interventions

### Explanation for the choice of comparators {6b}

In a previous trial, daily reminders by medical staff members regarding the importance of skin care likely improved the patients' compliance resulting in less radiation dermatitis [7, 8]. It may be questioned whether the daily reminders by staff members can be replaced by a mobile application (reminder app).

### Intervention description {11a}

#### Standard skin care

In both the experimental (A) and the control arm (B), standard skin care is to be performed by the patient from the beginning of radiotherapy. Standard skin care may vary at the participating centers. At the University of Lübeck, it includes fatty cream with 2–5% urea (fatty cream alone, if patients do not tolerate urea) and mometasone furoate cream. The treatment will be continued until 1 week after EOT or until a patient experiences grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis.

#### Standard mouth care

In both arms, standard mouth care is to be performed by the patient from the beginning of radiotherapy to prevent or at least postpone radiation-induced oral mucositis. At the University of Lübeck, it initially consists of an antibacterial mouth rinse to be used four times a day. If the patient experiences pain, lidocaine hydrochloride + plus dexpanthenole solution will be added. Alternatively, benzdyamine hydrochloride solution may be used. In case of an oral edema/swelling, hydrocortisone acetate may be used.

#### Reminder app

The patients in the experimental arm (Arm A) are supported by a reminder app ("CareReminder"), which has been developed by the professional company Nextlabel OHG from Lübeck, Germany. This app will remind the patients four times a day to perform skin and mouth care. Instructions are given how to perform it properly. The patients may postpone each required care procedure for up to 2 hours. Finally, the patients are asked to state for each procedure whether or not they performed it. To increase the patients' motivation, they will earn points for each successfully performed procedure.

### Criteria for discontinuing or modifying allocated interventions {11b}

In case of grade ≥ 2 moist desquamation or grade ≥ 3 radiation dermatitis, each day antiseptic agents will be administered for wound cleansing followed by administration of silicon or calcium alginate bandage. This treatment will be continued until moist desquamation radiation disappears and radiation dermatitis improves to grade 2. If local anesthetics (lidocaine, benzdyamine) are not sufficient in reducing pain due to oral mucositis, systemic analgesics are given, usually metamizole and if required morphine derivatives.

### Strategies to improve adherence to interventions {11c}

Not applicable.

**Relevant concomitant care permitted or prohibited during the trial {11d}**

If required, any type of concomitant care and interventions are permitted during the trial for treatment of other radiotherapy- or radio-chemotherapy-related toxicities and comorbidities not related to radiotherapy or radio-chemotherapy.

**Provisions for post-trial care {30}**

Following EOT (i.e., end of study), the patients receive the standard follow-up program for patients with head-and-neck cancer. Harm from trial participation is not expected, since all participating patients receive the same anticancer treatment as they would have received if not participating.

**Outcomes {12}**

Primary endpoint is the rate of grade $\geq 2$ radiation dermatitis Common Terminology Criteria for Adverse Events (CTCAE v5.0) at 60 Gy of radiotherapy, the minimum planned total dose for all patients receiving definitive or adjuvant radiotherapy for locally advanced head and neck cancer. In addition, the following endpoints will be evaluated:

1. Radiation dermatitis grade $\geq 2$ at EOT
2. Radiation dermatitis grade $\geq 3$ at 60 Gy and at EOT
3. Radiation-induced oral mucositis grade $\geq 2$ at 60 Gy and at EOT
4. Radiation-induced oral mucositis grade $\geq 3$ at 60 Gy and at EOT
5. Quality of life
6. Pain

**Participant timeline {13}**

A total of approximately four contributing centers are planning to participate, which aim to include an average of 21 patients per year. The recruitment of all 168 patients should be completed within 24 months. The treatment period will be 6–7 weeks. This equals a total running time for the trial of 26 months.

**Sample size {14}**

This study aims to show that standard skin care supported by a reminder app is superior to standard skin care alone regarding the avoidance of grade $\geq 2$ dermatitis up to 60 Gy in patients irradiated for locally advanced head-and-neck cancers.

The null hypothesis of equal grade $\geq 2$ dermatitis rates in both groups is tested against the two-sided alternative hypothesis of unequal dermatitis rates. The calculation of the sample size considered the following assumptions:

- Application of a chi-square test

- Two-sided significance level of 5%
- Rates of grade $\geq 2$ dermatitis of 86–92% with standard care alone according to previous studies
- Assumption of a grade $\geq 2$ dermatitis rate of 85% in the standard care alone group ("worst-case")
- Clinical importance of the impact of the reminder app = reduction of grade $\geq 2$ dermatitis by 20%
- Statistical power of 80%

When considering these assumptions, 80 patients are needed per arm within the full analysis set. Assuming that 5% of the recruited patients will not qualify for the full analysis set, 168 patients need to be randomized.

**Recruitment {15}**

A total of approximately four contributing centers are planning to participate, which aim to include an average of 21 patients per year. The recruitment of all 168 patients should be completed within 24 months.

## Assignment of interventions: allocation
**Sequence generation {16a}**

The patients will be assigned two code numbers: the number of the contributing center plus a patient identity number, continuously ascending, starting with 001.

After registration, patients will be randomized in a 1:1 ratio to receive either standard care supported by a reminder app (Arm A) or standard care (Arm B) for treatment of radiation-related skin toxicity.

A stratified block randomization will be performed. Stratification will be done using the following prognostic factors:

1. Tumor site: oropharynx/oral cavity versus hypopharynx/larynx.
2. Treatment approach: radio-chemotherapy versus radiotherapy alone.
3. Participating site.

The randomization will be performed centrally at the 'Zentrum für Klinische Studien' (ZKS) at the University of Lübeck, Germany via fax. The proceeding is based on standard operating procedures (SOPs) of the ZKS. The fax document has to be completed and finally be signed and dated by the investigator. Once the randomization is allocated to the patient it cannot be changed.

**Concealment mechanism {16b}**

Not applicable.

**Implementation {16c}**

Generation of the allocation sequence, enrollment of participants and assignment of participants to

interventions will be performed by specially trained physicians registered as investigators for this trial.

## Assignment of interventions: blinding

**Who will be blinded {17a}**
Data analysts and statisticians will be blinded.

**Procedure for unblinding if needed {17b}**
Not applicable.

## Data collection and management

**Plans for assessment and collection of outcomes {18a}**
The following parameters will be recorded prior to radiotherapy: Demographics, medical history, concomitant diseases, physical examination, performance status, primary tumor site, stage and histology, upfront surgery, planned chemotherapy, status of skin and oral mucosa, pain, and quality of life.

The following parameters will be assessed throughout the course of the trial:

1. Radiation dermatitis: assessed by two observers weekly during radiotherapy, at 60 Gy and at EOT according to CTCAE v5.0 [9]. If graduation varies, a third observer will be involved.
2. Oral mucositis: assessed by two observers weekly during radiotherapy, at 60 Gy and at EOT according to RTOG criteria [10–13]. If graduation varies, a third observer will be involved.
3. Quality of life: assessed prior to radiotherapy, at 60 Gy and at EOT with European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 Version 3.0 and EORTC QLQ-H&N35.
4. Pain (within radiation fields): assessed prior to radiotherapy, weekly during radiotherapy, at 60 Gy and at EOT with a visual analog scale (from 0 = no to 10 = maximum pain).
5. Other adverse events will be assessed on an ongoing basis according to CTCAE v5.0 [9].

The timeline of the study procedures including the assessments is given in Fig. 1.

**Plans to promote participant retention and complete follow-up {18b}**
The last day of radiotherapy (EOT) is also the end of the follow-up period. Patients are seen at least 5 days per week by medical staff members. Thus, it is unlikely that patients will be lost to follow-up. If patients withdraw their consent to participate in the trial or die during the course of radiotherapy, the data available until this point in time will be used for analyses.

## Data management {19}
**Patient identification list**
All data relating to patients will be recorded in a pseudonymous way. Each patient will be identifiable only by the unique patient number, date of birth and sex. A patient identification list will only be kept in the relevant trial centers and will not be forwarded to the sponsor.

**Documentation sheet**
Data collection will be done using the data documentation sheets.

The data documentation sheets must be filled in using a ballpoint pen. Fountain pens or pencils may not be used. Corrections must be made as follows: cross the error out once with a straight line, enter the correct information next to it and note the date and/or reason for correction. Comments must be made if data fields cannot be filled in because of missing information.

The sheets should be filled in as soon as possible and should be submitted to the checker for review, signed, dated and forwarded to the trial management. All data will be pseudonymized before they are forwarded for analysis. The data will be handled according to the General Data Protection Regulation (GDPR). The data will be brought into one database and analyzed in accordance with a predefined statistical analysis plan. At this stage, subgroup analyses are not planned. At each interim analysis, the need for subgroup analyses will be re-evaluated.

**Storage of trial documents**
The originals of all key trial documents, including the documentation sheets, will be kept at the trial headquarters (i.e., the sponsor responsible for the trial) for a minimum of 10 years after the final report.

The principal investigator/head of the trial center will keep all administrative documents (written correspondence with the ethics committee, regulatory authorities, trial management, trial headquarters), patient identification list, signed informed consent forms, copies of the documentation sheets and general trial documentation (protocol, amendments) for the abovementioned period. Original patient data (patient files) must also be kept for the length of time stipulated for the trial centers, but not for less than 10 years.

## Confidentiality {27}
Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical trial will be stored on electronic data storage devices and treated with utmost confidentiality. Organization measures have been taken in order to prevent the data from being communicated to

| TIMEPOINT** | STUDY PERIOD | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enrolment | Allocation Baseline | Post-allocation | | | | | | | Close-out |
| | Month -1 of Month 0 | Month -1 of Month 0 | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | End of RT* |
| **ENROLMENT:** | | | | | | | | | | |
| **Eligibility screen** | X | | | | | | | | | |
| **Informed consent** | X | | | | | | | | | |
| **Allocation** | | X | | | | | | | | |
| **INTERVENTIONS:** | | | | | | | | | | |
| *Radiotherapy* | | | ◆——————————————————◆ | | | | | | | |
| *Reminder app (arm A only)* | | | X | X | X | X | X | X | X | |
| **ASSESSMENTS:** | | | | | | | | | | |
| *Demographics, medical history, medication, physical examination, performance status, tumor stage, pathology, upfront surgery, planned treatment* | | X | | | | | | | | |
| *Dermatitis, oral mucositis* | | X | X | X | X | X | X | X | X | X |
| *Quality of life* | | X | | | | | X | | | X |
| *Adverse events, other toxicities* | | | X | X | X | X | X | X | X | X |
| *Pain* | | X | X | X | X | X | X | X | X | X |
| *Treatment given as planned?* | | | X | X | X | X | X | X | X | X |
| *Satisfaction with the app* | | | | | | | | X | | |

*RT=radiotherapy

**Fig. 1** Schedule of enrolment, interventions and assessments. *RT* radiotherapy

unauthorized persons. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase and their full name will not be used.

**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}**

Not applicable.

## Statistical methods

### Statistical methods for primary and secondary outcomes {20a}

All data recorded in the case report forms describing the study population, toxicity and quality of life will be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages. Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Number of patients with protocol deviations during the study and listings describing the deviations will be provided. In general, chi-square tests will be used to compare percentages in a two-by-two contingency table, replaced by Fisher exact test if the expected frequency in at least one cell of the associated table is less than five. Stratified two-by-two contingency tables will be analyzed using Cochran-Mantel-Haenszel tests. Logistic regression models serve as multivariable methods for binary endpoint data. Comparison of ordinal

variables between treatment arms will be performed using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with small number of categories and/or sparse data within categories. Any shift in location of quantitative variables between study groups will be performed with the Wilcoxon-Mann-Whitney tests as well. Time-to-event data will be analyzed by Kaplan-Meier methods, when merely non-informative censoring occurs. For statistical comparison, the log rank-test will be provided supplemented by multivariate Cox proportional hazards models. The data analysis will be performed according to the statistical analysis plan, and which will be finalized prior to database lock and prior to any statistical analysis.

### Interim analyses {21b}

After termination of the radiation treatment of one third (N = 56) and two thirds (N = 112), respectively, of the patients, interim analyses will be performed. Recruitment will be put on hold until the 56 and 112 patients, respectively, have completed their radiation treatment. In case of a dissatisfaction rate > 25%, the reminder app needs to be modified and adapted. In case of a dissatisfaction rate > 50%, the study will be terminated prematurely.

### Methods for additional analyses (e.g., subgroup analyses) {20b}

Not applicable.

### Methods in analysis to handle protocol nonadherence and any statistical methods to handle missing data {20c}

The full analysis set includes all randomized patients who have started either therapy with Arm A or with Arm B. The full analysis set will be analyzed according to the intent-to-treat principle, i.e., patients will be analyzed in their initial group of randomization.

The per protocol set will comprise all patients of the full analysis set and will exclude patients if any of the following criteria are met:

- Administration of less than 60 Gy if the reason for discontinuation was any other than death or unacceptable toxicity
- Delay of radiotherapy for more than 7 days prior to reaching 60 Gy

All patients in the per protocol set will be analyzed within their group of actual treatment received.

### Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not applicable.

## Oversight and monitoring

### Composition of the coordinating center and trial steering committee {5d}

Not applicable.

### Composition of the data monitoring committee, its role and reporting structure {21a}

A data monitoring committee is not needed, since all patients participating in this trial receive the same anticancer treatment, the same number and type of visits, and the same treatment for radiation dermatitis, oral mucositis and other toxicities as they would have received if not participating in the trial.

### Adverse event reporting and harms {22}

*Assessment and documentation of adverse events*

The severity of adverse events should be assessed using the national (CTCAE, version 5.0 [9]. Oral mucositis will be assessed according to the criteria of the Radiation Therapy Oncology Group (RTOG) [10–13].

Otherwise, the 5-point scale below will be used to describe an adverse event.

Scale:  1 = mild,  2 = moderate,  3 = severe,  4 = life-threatening and 5 = fatal.

The following scale should be used to describe the likelihood that the event was caused by the trial treatment:

1 = certain/definite,  2 = probable,  3 = possible,  4 = unlikely, 5 = not related, 6 = not assessable.

*Reporting of serious adverse events and unexpected adverse events*

Serious adverse events and unexpected adverse events must be reported within 24 hours after their detection/onset by fax to the coordinating investigator.

### Frequency and plans for auditing trial conduct {23}

The ZKS Lübeck will conduct clinical on-site monitoring at the German sites according to Good Clinical Practice (GCP) and written SOPs to ensure the patients' rights and safety as well as the reliability of trial results. For initiation, trial sites will be visited on-site by a clinical research associate of the ZKS Lübeck. During the trial, sites will be visited at regular intervals depending on the rate of recruiting and data quality. Informed consent and defined key data will be checked of all patients. The medical file of each patient will be screened for adverse and serious adverse events. Patients' questionnaires will be checked for their existence. According to SOPs, all trial-specific monitoring activities will be defined before starting the trial and documented in writing (monitoring manual). The sites in other countries will be monitored according to the corresponding national regulations. No regular audits are planned. However, to ensure correct

execution of the study, audits may be conducted if necessary. As the current study is not linked to any German pharmaceutical or medicinal product act, no inspections of higher federal authorities are scheduled.

### Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Amendments to the study protocol may only be implemented if approved again by the ethics committee responsible. Only the coordinating principal investigator may carry out such changes. However, all co-investigators should contact the coordinating principal investigator if modifications seem to be necessary. In case of changes to the study protocol, all investigators will be informed after ethics committee approval and the notice will have to be confirmed.

### Dissemination plans {31a}

The coordinating principal investigator will work toward comprehensive internal and external dissemination of project results and knowledge. Coordinating principal investigators, biostatisticians, and reference centers will create a report according to the CONSORT statement regardless of regular or abnormal study termination. The scientific results will be published in international, peer-reviewed journals of the highest possible quality. In addition, results will be presented at major medical congresses and symposia.

Due to methodological and statistical aspects, results will be published only after study database closure. All reports and publications related to the study need to be coordinated with the biostatistician to avoid misinterpretation of statistical results. Conclusions need to be statistically secured and require approval of the statistician. The local centers are entitled to use the recorded data for additional scientific exploitation under their own name, but not before the main results have been published. There are no exceptions to this rule. Any sub-publication requires approval by the coordinating principal investigator. For publications of any kind the study acronym RAREST-02 will be used.

### Discussion

Many patients who receive radiotherapy or radio-chemotherapy for locally advanced SCCHN experience radiation-related acute toxicities including dermatitis and oral mucositis. If these toxicities become severe, an interruption of the radiotherapy treatment may be required. Interruptions of 1 week or longer were reported to impair the patient's prognosis. In a retrospective study of patients irradiated for SCCHN, local control ($p = 0.015$) and survival ($p = 0.021$) were significantly worse with such an interruption of the radiation treatment [2].

To avoid toxicity-related interruptions of radiotherapy, it is reasonable to avoid or at least postpone grade 2 reactions. This accounts for both radiation dermatitis and radiation-related oral mucositis. In previous studies of radio-(chemo)-therapy for SCCHN, rates of grade $\geq 2$ radiation dermatitis and grade $\geq 2$ oral mucositis were reported to range from 86% to 92% and from 86% to 100%, respectively, although the patients had received standard skin and mouth care [1, 4–6].

Since the administration of an absorbent, self-adhesive dressing appeared a promising approach to reduce radiation dermatitis, we performed a randomized trial (RAREST-01) that compared the new dressing Mepitel® Film to standard skin care with respect to radiation dermatitis rates [7, 8]. However, almost half of the patients did not tolerate the dressing, and the trial had to be stopped prematurely. In those patients already included, the new dressing appeared to be not superior to standard skin care. Surprisingly, the radiation dermatitis rates were lower than expected in both groups. One possible explanation for this unexpected finding could be that the patients were reminded daily by staff members to perform their skin care, which generally required a high level of discipline and compliance. Improved compliance of patients resulting in a proper performance of daily skin care might have led to a lower incidence and severity of radiation dermatitis. One question is whether the daily reminders by the staff members can also be successfully done by a specific reminder app. Therefore, in this trial the effect of a reminder app on radiation dermatitis rates and, additionally, on oral mucositis rates is being investigated. If the addition of such a reminder app to standard care leads to less radiation dermatitis and oral mucositis, it could become a helpful tool for patients irradiated for head-and-neck cancers.

### Trial status

Protocol version 2.0 from 09-30-2019, recruitment is planned to start in December 2019 and will be completed within 24 months.

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# Comparison of Conventional Fractionation and Accelerated Fractionation With Concomitant Boost for Radiotherapy of Non-metastatic Stage IV Head-and-Neck Cancer

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**Abstract.** *Background/Aim: Some patients with unresectable or incompletely resected head-and-neck cancer (SCCHN) cannot tolerate radiochemotherapy. Alternatives are needed that are more effective than conventional radiotherapy alone. Patients and Methods: This retrospective study investigated patients irradiated for non-metastatic stage IV SCCHN who could not receive concurrent chemotherapy. Eight patients received accelerated radiotherapy with concomitant boost (group A) and 31 patients conventionally fractionated radiotherapy (group B). Groups were matched for tumor site, gender, age, performance score and histologic grade. Results: Two-year PFS-rates were 63% in group A vs. 41% in group B, and median PFS-times were 36 vs. 10 months (p=0.48). Two-year OS-rates were 88% vs. 37%, and median OS-times were 44 vs. 14 months (p=0.19). Grade ≥2 radiation dermatitis was significantly (p=0.040) more common in group B; other toxicities were similar. Conclusion: Accelerated fractionation with concomitant boost appeared superior to conventional fractionation and can be considered for patients with stage IV SCCHN not suitable for radiochemotherapy. Larger studies are needed to confirm these findings.*

In 2018, head-and-neck cancers were amongst the ten most common primary tumor types worldwide and was estimated to account for approximately 450,000 deaths (1, 2). Many patients with locally advanced squamous cell carcinoma of

This article is freely accessible online.

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the head-and-neck (SCCHN) have poor prognoses, particularly if surgical resection of the primary tumor and the loco-regional lymph nodes was not possible or incomplete (3, 4). Several randomized trials and a meta-analysis demonstrated significantly better outcomes after definitive radio-chemotherapy for SCCHN when compared to radiotherapy alone (5-7). Patients receiving only an incomplete resection also benefited from concurrent chemotherapy (5). However, since the addition of chemotherapy increases acute toxicity, a considerable number of patients with SCCHN cannot receive it (8, 9). For these patients, altered fractionated radiotherapy with a reduced overall treatment time can be a reasonable alternative. According to a meta-analysis of 15 trials of patients with SCCHN, altered fractionation regimens resulted in significantly improved loco-regional control and overall survival (OS) when compared to conventional fractionation (5×2.0 Gy per week) (10). One type of altered fractionation is accelerated radiotherapy with concomitant boost. In 2000, a randomized trial showed that accelerated radiotherapy with concomitant boost resulted in better outcomes than conventional fractionation (11). Long-term results of this trial were published in 2014 (12). Although not statistically significant, 5-year reduction in cumulative loco-regional failure was still remarkable for accelerated radiotherapy with concomitant boost (absolute benefit of 6.6%) compared to conventional fractionation. In the initial publication of Fu *et al.*, accelerated fractionation with concomitant boost (72 Gy in 42 fractions over 6 weeks) resulted in higher late toxicity than conventional fractionation (11). In 2001, an alternative concomitant boost regimen (69.9 Gy in 39 fractions over 5.5 weeks) was reported from Germany but not compared to conventional fractionation (13, 14). Therefore, the present study was performed to compare accelerated radiotherapy with concomitant boost to conventional fractionation for non-metastatic stage IV SCCHN in patients unable to receive chemotherapy.

## Patients and Methods

This retrospective study compared two dose-fractionation regimens of radiotherapy for non-metastatic stage IV SCCHN. The 7th edition of the staging manual of American Joint Committee on Cancer (AJCC) was used, because the human papilloma virus (HPV)-status was not available for most patients included in the study but is required for the classification of oropharynx cancer when using the 8th edition (15, 16). The study was approved by the local Ethics Committee (University of Lübeck, 20-454). Eight selected patients received accelerated radiotherapy with concomitant boost (group A) between 2011 and 2019, and 31 patients were treated with conventionally fractionated radiotherapy (control group B) between 2000 and 2014. Both groups were matched for tumor site (oropharynx *vs.* hypopharynx or larynx), gender (female *vs.* male), age (≤60 *vs.* >60 years), Karnofsky performance score (60-70 *vs.* 80-100) and histologic grade (grade 1-2 *vs.* 3). The distributions of the characteristics used for matching are summarized in Table I. Fifteen patients received definitive radiotherapy (7 in group A and 8 in group B, respectively), and 24 patients (1 in group A and 23 in group B, respectively) adjuvant radiotherapy following incomplete resection of SCCHN. Two patients of group A had received induction chemotherapy with docetaxel. No patient included in this study was considered suitable for concurrent chemotherapy in addition to radiotherapy.

In both groups, radiotherapy was performed on five consecutive days per week (Monday to Friday). In group A, radiotherapy was initially administered to the primary tumor region and loco-regional lymph nodes (high, intermediate and low risk areas) with 2.0 Gy per fraction up to 30.0 Gy (3 weeks). Afterwards, the same treatment volumes received 1.8 Gy per fraction in the morning for 12 days (cumulative dose=51.6 Gy). After an interval of at least 6 h, 1.5 Gy per fraction was given on the same day to the primary tumor region and high/intermediate risk lymph node areas for 6 days (first concomitant boost, cumulative dose=60.6 Gy), and to the primary tumor region and high-risk lymph node areas for another 6 days (second concomitant boost, cumulative dose=69.6 Gy). The overall treatment time in group A was 5.5 weeks (13, 14).

Patients of group B received 2.0 Gy per fraction up to 50.0 Gy (5 weeks) to the primary tumor region and the loco-regional lymph nodes (including high, intermediate and low risk areas), followed by a boost of 10 Gy (5×2.0 Gy, 1 week) to the primary tumor region and high/intermediate risk lymph node areas (cumulative dose=60.0 Gy). A second boost of 6 or 10 Gy (5×2.0 Gy, 3 days or 1 week) was given to the primary tumor region and the high-risk lymph node areas (cumulative dose=66.0-70.0 Gy), resulting in an overall treatment time of 6.5 to 7 weeks.

Both groups were compared with respect to progression-free survival (PFS), which was defined as lack of both loco-regional recurrence and distant metastasis, and overall survival (OS). Both endpoints were referenced from the last day of radiotherapy. Calculations of PFS and OS were performed using the Kaplan-Meier method and the Wilcoxon test. In addition, both groups were compared for acute (oral mucositis, radiation dermatitis) and late (cervical/submental lymph edema, xerostomia) toxicities. These comparisons were performed with the Fisher's exact test. The comparisons with respect to the distribution of the characteristics used for matching were also performed with the Fisher's exact test. For all statistical tests used in this study, *p*-values <0.05 were considered significant and *p*-values <0.20 were considered showing a trend.

Table I. *Comparison of the treatment groups A (accelerated fractionation with concomitant boost) and B (conventional fractionation) with respect to patient characteristics used for matching of the groups. The p-values were obtained from the Fisher's exact test.*

| Characteristic | Group A No. of patients (%) | Group B No. of patients (%) | *p*-Value |
|---|---|---|---|
| Main site of cancer | | | |
| Oropharynx | 3 (37.5) | 14 (45) | >0.99 |
| Hypopharynx or larynx | 5 (62.5) | 17 (55) | |
| Gender | | | |
| Female | 2 (25) | 8 (26) | >0.99 |
| Male | 6 (75) | 23 (74) | |
| Age at radiotherapy | | | |
| ≤60 Years | 2 (25) | 10 (32) | >0.99 |
| >60 Years | 6 (75) | 21 (68) | |
| Performance score | | | |
| KPS 60-70 | 4 (50) | 18 (58) | 0.71 |
| KPS 80-100 | 4 (50) | 13 (42) | |
| Histologic grade | | | |
| Grade 1-2 | 6 (75) | 20 (65) | 0.69 |
| Grade 3 | 2 (25) | 11 (35) | |

KPS: Karnofsky performance score.

## Results

Median follow-up times were 13 months (range=2-57 months) in the entire cohort, 21.5 months (7-50 months) in group A and 13 months (range=2-57 months) in group B. When considering only patients who were alive at the last contact, the median follow-up times were 18 months (range=6-51 months), 12 months (10-30 months) and 24 months (range=6-51 months), respectively.

The PFS-rates at 1 year, 2 years and 3 years following radiotherapy were 63%, 63% and 42%, respectively, in group A, and 46%, 41% and 41%, respectively, in group B (*p*=0.48, Table II). Median PFS-times were 36 months in group A and 10 months in group B. In group A, progression of disease during the follow-up after radiotherapy occurred in five patients. First site of failure was loco-regional recurrence in four patients and distant metastasis in one patient. In group B, 18 patients experienced progression of their disease during the period of follow-up. First site of failure was loco-regional recurrence in nine patients, distant metastasis in eight patients and both (concurrent loco-regional recurrence plus distant metastasis) in one patient.

Death was recorded for four patients of group A and 18 patients of group B. The OS-rates at 1 year, 2 years and 3 years following radiotherapy were 88%, 88% and 88%, respectively, in group A compared to 69%, 37% and 37%, respectively, in group B (*p*=0.19, Table II). The median OS-times were 44 months in group A and 14 months in group B.

Table II. *Comparison of the treatment groups A (accelerated fractionation with a concomitant boost) and B (standard fractionation) with respect to treatment outcomes in terms of progression-free survival and overall survival. The p-values were obtained from the Wilcoxon test.*

| Outcome | Group A (%) | Group B (%) | *p*-Value |
|---|---|---|---|
| Progression-free survival | | | |
| At 1 Year | 63 | 46 | 0.48 |
| At 2 Years | 63 | 41 | |
| At 3 Years | 42 | 41 | |
| Overall survival | | | |
| At 1 Year | 88 | 69 | 0.19 |
| At 2 Years | 88 | 37 | |
| At 3 Years | 88 | 37 | |

Table III. *Comparison of the treatment groups A (accelerated fractionation with a concomitant boost) and B (standard fractionation) with respect to grade ≥2 toxicities. The p-values were obtained from the Fisher's exact test.*

| Toxicity | Group A No. of patients (%) | Group B No. of patients (%) | *p*-Value |
|---|---|---|---|
| Grade ≥2 oral mucositis | 8 (100) | 27 (87) | 0.56 |
| Grade ≥2 radiation dermatitis | 4 (50) | 27 (87) | **0.040** |
| Grade ≥2 lymph edema | 2 (25) | 8 (26) | >0.99 |
| Grade ≥2 xerostomia | 4 (50) | 13 (42) | 0.71 |

Statistically significant *p*-values are shown in bold.

When comparing both groups for grade ≥2 toxicities, radiation dermatitis was significantly ($p=0.040$) more common in group B (Table III). The frequencies of the other investigated toxicities were not significantly different. In group A, all patients received the cumulative dose of 69.6 Gy as planned. In group B, two patients could not receive the second boost due to acute radiation-related toxicity, and the cumulative dose in these patients was 60.0 Gy.

## Discussion

Since outcome of patients with locally advanced SCCHN require improvement, many preclinical and clinical studies have been conducted during recent years (17-22). The prognoses of patients with SCCHN are particularly poor, if unresectable or incompletely resected. Many of these patients receive platin-based radiochemotherapy. In a randomized trial of 100 patients with stage III or IV SCCHN, treatment was 66-72 Gy (doses per fraction=1.8-2.0 Gy) of radiotherapy alone or the same regimen plus concurrent chemotherapy with cisplatin and 5-fluorouracil (5-FU) (5). Salvage surgery was planned for persistent loco-regional or recurrent disease. Five-year loco-regional control rates were 51% and 62%, respectively ($p=0.04$), but 5-year OS rates were not significantly different. In another randomized trial of 226 patients with stage III or IV oropharynx cancer, patients received conventionally fractionated radiotherapy with 70 Gy in 35 fractions alone or 70 Gy/35 fractions plus concurrent carboplatin/5-FU (6). The addition of chemotherapy resulted in significantly improved disease-free survival ($p=0.01$) and loco-regional control ($p=0.002$) and almost significantly improved OS ($p=0.05$) at 5 years without significantly increasing toxicity. In another randomized trial of patients with locally advanced larynx cancer, concurrent radiochemotherapy resulted in a significantly higher rate of larynx preservation (23). A meta-analysis of 93 randomized trials demonstrated a significant benefit in 5-year survival for concurrent radiochemotherapy when compared to radiotherapy alone (7). An additional analysis of 87 randomized trials showed such a benefit for different tumor sites including oral cavity, oropharynx, hypopharynx and larynx (24). Moreover, concurrent chemotherapy (cisplatin) when added to radiotherapy led to improved loco-regional control and disease-free survival after incomplete resection of SCCHN (4, 8, 25). Chemotherapy increased the rates of grade ≥3 acute toxicities. In the trial of Bernier *et al*., these rates were 41% with *vs*. 21% without concurrent chemotherapy ($p<0.001$), and in the trial of Cooper *et al*. 77% (including 1.8% treatment-related deaths) *vs*. 34% ($p<0.001$) (8, 9). Thus, a considerable number of patients cannot tolerate the addition of chemotherapy.

For these patients, alternative strategies are required that result in more favorable outcomes than conventionally fractionated radiotherapy alone. Such options include unconventional fractionation of radiotherapy. In 2000, a randomized trial demonstrated that hyperfractionation (2×1.2 Gy per day up to 81.6 Gy/68 fractions) and accelerated fractionation with concomitant boost (72 Gy in 42 fractions over 6 weeks) were superior to conventional fractionation (70 Gy in 35 fractions) with respect to loco-regional control and disease-free survival but not OS (11). In 2006, a meta-analysis found similar results with respect to loco-regional control (10). Moreover, a survival benefit was observed, which was more prominent after hyperfractionation than after accelerated fractionation with concomitant boost (8% *vs*. 2% absolute benefit at 5 years). However, the authors stated that this difference should be interpreted with caution, since the patient characteristics were different in the two groups (10). An advantage of the concomitant boost regimen is the lower number of fractions, particularly for institutions with a high patient load and or limited capacity at the linear accelerators. After publication of the trial of Fu *et al*. (11), other concomitant boost concepts have also been developed (13, 14,

26-28). In Germany, Staar *et al.* introduced the regimen, which was also used in the present study (13). According to the results of our study, accelerated fractionation with concomitant boost showed a trend for improved OS and was associated with non-significantly better PFS compared to conventional fractionation without significantly increasing acute and late toxicity. Although statistical significance was not achieved for PFS and OS, the median times were considerably different, i.e. 30 *vs.* 10 months for PFS and 44 *vs.* 14 months for OS, respectively. The fact that these differences were not significant can be explained by the small sample size of this study, particularly in the concomitant boost group. This limitation must be considered when interpreting the results. The same applies to other limitations including the retrospective study design, different lengths of follow-up, non-consideration of the HPV-status, different proportions of patients receiving upfront incomplete resection, and the different treatment periods, during which systemic treatments for recurrent and metastatic SCCHN improved, which likely had an impact on OS. Moreover, two meta-analyses suggested that radiotherapy with accelerated fractionation alone cannot fully compensate the lack of concurrent chemotherapy for treatment of locally advanced SCCHN (29, 30).

In summary, accelerated fractionation with concomitant boost provided promising results and appeared superior to conventional fractionation for non-metastatic stage IV SCCHN. This type of fractionation can be considered for selected patients who are not suitable for concurrent radiochemotherapy.

## Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

## Authors' Contributions

The study was designed by C.N. and D.R. Data were collected by C.N. and D.R. and analyzed by S.E.S. and D.R. The article was drafted by D.R. and S.E.S. and approved by all Authors.

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# Accelerated Fractionation Plus Chemotherapy *Versus* Conventionally Fractionated Radiochemotherapy for Unresectable Head-and-Neck Cancer

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**Abstract.** *Background/Aim: Prognosis of patients with unresectable squamous cell carcinomas of the head and neck requires improvement. This retrospective study compared accelerated radiotherapy plus chemotherapy to conventional radiochemotherapy. Patients and Methods: Patients received definitive treatment with accelerated radiotherapy plus chemotherapy (group A, n=10) or conventional cisplatin-based radiochemotherapy (group B, n=85). Groups were matched for several patient and tumor characteristics and compared for locoregional control (LRC), overall survival (OS) and toxicities. Additionally, accelerated radiotherapy plus chemotherapy and chemotherapy regimens in group B were compared for LRC and OS. Results: Treatment type had no significant impact on LRC (p=0.98) and OS (p=0.57). In group A, toxicities occurred more often, including grade ≥3 mucositis (p=0.041), grade ≥2 lymphedema (p=0.007) and grade ≥3 leucopenia (p=0.007). Best 2-year LRC (p=0.39) and OS (p=0.015) was achieved with 20 mg/m² cisplatin days 1-5 every 4 weeks; accelerated radiochemotherapy resulted in second-worst outcomes. Conclusion: Given the limitations of this study, accelerated radiotherapy plus chemotherapy*

*provided no significant benefit but increased toxicity compared to conventional radiochemotherapy.*

In both developing and developed countries, squamous cell carcinomas of the head and neck (HNSCC) are common malignant tumors (1-3). For most resectable tumors, the standard treatment includes surgery followed by adjuvant radiotherapy or, if risk factors exist such as incomplete resection and extracapsular spread of lymph node metastases, by radiochemotherapy (4).

Unfortunately, many patients present with locally advanced tumors that are unresectable and require definitive radiochemotherapy (2, 3). According to randomized trials and meta-analyses, outcomes of definitive radiotherapy are considerably improved with the addition of concurrent (mainly cisplatin-based) chemotherapy (5-8). However, since the addition of chemotherapy results in increased acute toxicities, some patients are not suitable for combined treatment and receive radiotherapy alone (9-11). According to a meta-analysis, unconventionally fractionated radiotherapy with reduced overall treatment times resulted in improved locoregional control (LRC) and overall survival (OS) compared to conventionally fractionated radiotherapy (2.0 Gy per fraction on 5 days per week) (12). Types of unconventionally fractionated radiotherapy include hyperfractionated accelerated radiotherapy (HA-RT) and accelerated fractionation with concomitant boost (AF-CB) (12, 13).

In order to further improve the outcomes of patients with unresectable HNSCC, several studies investigated the option of combining accelerated radiotherapy and chemotherapy. In some studies, feasibility of HA-RT or AF-CB plus chemotherapy was shown (14-17). Moreover, a few randomized trials demonstrated that the addition of chemotherapy to accelerated radiotherapy

resulted in better outcomes than accelerated radiotherapy alone (18-20). Another important question is whether accelerated radiotherapy plus chemotherapy is superior to standard conventional radiochemotherapy. According to two randomized trials, accelerated radiotherapy plus chemotherapy did not result in improved outcomes (21, 22). One trial compared AF-CB (70 Gy in 40 fractions over 6 weeks) plus two 5-day courses of carboplatin/5-fluorouracil (5-FU) to conventionally fractionated radiotherapy (70 Gy in 35 fractions over 7 weeks) plus three 4-day courses of carboplatin/5-FU (21). The other trial compared AF-CB (72 Gy in 42 fractions over 6 weeks) plus two courses of 100 mg/m$^2$ of cisplatin on day 1 to conventionally fractionated radiotherapy (70 Gy in 35 fractions over 7 weeks) plus three courses of 100 mg/m$^2$ of cisplatin on day 1 (22). Several other concepts of AF-CB or HA-RT plus chemotherapy exist that have not yet been compared to conventional radiochemotherapy. In this study, patients receiving accelerated radiotherapy plus chemotherapy within previous trials were matched to patients receiving conventionally fractionated cisplatin-based chemotherapy and compared for treatment outcomes and toxicities.

## Patients and Methods

The data of 95 patients with histologically proven unresectable non-metastatic stage IV SCCHN were retrospective analyzed. Staging was performed according to the 7th edition of the American Joint Committee on Cancer manual, since for classification according to the eighth edition, the human papilloma virus status is mandatory for tumors of the oropharynx but was not available for the majority of patients of the present study (23, 24). The study received approval from the local Ethics Committee (University of Lübeck, reference 20-454).

Ten patients received definitive treatment with accelerated fractionation plus chemotherapy within clinical trials between 2010 and 2014 (group A). They were matched and compared to 85 patients from an anonymized database treated with conventionally fractionated radiochemotherapy between 2000 and 2014 (group B).

*Group A.* In group A, three patients received HA-RT that started with 30 Gy (2.0 Gy per fraction on 5 days per week) over 3 weeks, followed by a hyperfractionated-accelerated part with two daily fractions of 1.4 Gy (inter-fraction interval ≥6 h) over another 3 weeks, resulting in a cumulative dose of 70.6 Gy in 44 fractions over 6 weeks (17, 25). Radiotherapy was combined with concurrent cisplatin (40 mg/m$^2$ weekly) and cetuximab (400 mg/m$^2$ loading dose 1 week prior to radiotherapy, followed by 250 mg/m$^2$ weekly).

Four patients were assigned to induction chemotherapy with three courses of docetaxel (75 mg/m$^2$) and cisplatin (75 mg/m$^2$) with (n=3) or without (n=1) cetuximab (loading dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ for a total of 16 weeks during induction and radiotherapy periods) (26). In these four patients, radiotherapy was performed as AF-CB. Radiation of 30 Gy (2.0 Gy per fraction on 5 days per week) over 3 weeks was followed by additional 21.6 Gy (1.8 Gy per fraction) to the same areas over 2.5 weeks (12 treatment days) plus two consecutive boost doses (1.5 Gy per fraction) given the same days (*i.e.* 6 + 6 treatment days) after an interval of ≥6 h, resulting in a cumulative dose of 69.6 Gy in 39 fractions over 5.5 weeks.

Three patients received HA-RT starting with 30 Gy (2.0 Gy per fraction on 5 days per week) over 3 weeks, followed by hyperfractionated-accelerated radiotherapy including two daily fractions of 1.4 Gy (interval ≥6 h) over another 2.5 weeks, resulting in a cumulative dose of 63.6 Gy in 39 fractions over 5.5 weeks (27). Radiotherapy was combined with concurrent cisplatin (20 mg/m$^2$ on days 1-4 and 29-32) and paclitaxel (20 mg/m$^2$ on days 2, 5, 8, 11 and 25, 30, 33, 36).

*Group B.* In group B, 85 patients were assigned to conventionally fractionated radiotherapy with concurrent cisplatin-based chemotherapy. Radiotherapy started with 50 Gy (2.0 Gy per fraction on 5 consecutive days per week) over 5 weeks to the primary tumor and regional lymph nodes, followed by boost doses to primary tumor and high/intermediate-risk lymph node areas, resulting in a cumulative dose of 70 Gy in 35 fractions over 7 weeks. Concurrent chemotherapy regimens included 30 mg/m$^2$ of cisplatin on day 1 every week (n=21), 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks (n=17), 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks (n=24) and 20 mg/m$^2$ of cisplatin on days 1-5 plus 600 or 1000 mg/m$^2$ of 5-FU on days 1-5 every 4 weeks (n=23).

*Endpoints and statistical considerations.* Groups A and B were matched for tumor site (oropharynx *versus* hypopharynx *versus* larynx), gender, age at radiotherapy (≤55 *versus* >55 years), primary tumor category (T2-3 *versus* T4), lymph node category (N0-2a *versus* N2b-2c) and histological grade (G1-2 *versus* G3). Matching for Karnofsky performance score was not performed, since all patients had a score of 80-100. Distributions of the patient characteristics between groups A and B were compared using Fisher's exact test (Table I).

The groups were compared for the endpoints LRC and OS, which were referenced from the last day of radiotherapy. For the corresponding univariate analyses, the Kaplan–Meier method and the log-rank test were used. Characteristics that achieved significance ($p<0.05$) on univariate analyses were included in a multivariate analysis (Cox regression analysis).

Groups A and B were also compared for radiation-related toxicities (acute: oral mucositis and dermatitis; late: cervical lymph edema and xerostomia), chemotherapy-related toxicities (leucopenia, thrombopenia, anemia and reduced renal function), toxicity-related interruptions of radiotherapy longer than 1 week and toxicity-related impossibility to administer the complete chemotherapy as planned (Fisher's exact test). Again, *p*-values less than 0.05 indicated significance. In addition, accelerated fractionation plus chemotherapy (group A) and the different chemotherapy regimens used in group B were compared for LRC and OS.

## Results

Median follow-up periods were 19 months (range=0-112 months) for the entire cohort, 16.5 months (range=0-112 months) for group A and 19 months (range=0-70 months) for group B. On univariate analysis, better LRC was significantly associated with favorable tumor sites (oropharynx or larynx, $p=0.008$) and female gender ($p=0.016$) (Table II). For the type of treatment, no significant association was found with LRC ($p=0.98$). In the Cox regression analysis, female gender maintained significance

Table I. *Characteristics of patients treated with accelerated fractionation plus chemotherapy (group A) and conventionally fractionated radiochemotherapy (group B). p-Values of the comparisons between both groups were obtained from Fisher's exact test.*

| Characteristic | Group A N (%) | Group B N (%) | *p*-Value |
|---|---|---|---|
| Tumor site | | | |
| Oropharynx | 5 (50) | 46 (54) | >0.99* |
| Hypopharynx | 2 (20) | 18 (21) | |
| Larynx | 3 (30) | 21 (25) | |
| Gender | | | |
| Female | 3 (30) | 14 (19.4) | 0.72 |
| Male | 7 (70) | 58 (80.6) | |
| Age at radiotherapy | | | |
| ≤55 Years | 2 (20) | 20 (27.8) | 0.72 |
| >55 Years | 8 (80) | 52 (72.2) | |
| T-Category | | | |
| 2-3 | 3 (30) | 22 (30.6) | >0.99 |
| 4 | 7 (70) | 50 (69.4) | |
| N-Category | | | |
| 0-2a | 4 (40) | 18 (25.0) | >0.99 |
| 2b-2c | 6 (60) | 54 (75.0) | |
| Histological grade | | | |
| 1-2 | 6 (60) | 53 (73.6) | >0.99 |
| 3 | 4 (40) | 19 (26.4) | |

*For calculation of the *p*-value, hypopharynx and larynx were combined.

Table II. *Comparison of locoregional control in patients according to treatment [(accelerated fractionation plus chemotherapy (group A) versus conventionally fractionated radiochemotherapy (group B)] and patient characteristics (univariate analyses). p-Values were obtained from log-rank test.*

| Characteristic | 1 Year (%) | 2 Years (%) | *p*-Value |
|---|---|---|---|
| Treatment group | | | |
| Group A | 89 | 53 | 0.98 |
| Group B | 74 | 69 | |
| Tumor site | | | |
| Oropharynx | 80 | 72 | **0.008** |
| Hypopharynx | 47 | 40 | |
| Larynx | 87 | 80 | |
| Gender | | | |
| Female | 100 | 89 | **0.016** |
| Male | 66 | 59 | |
| Age at radiotherapy | | | |
| ≤55 Years | 64 | 64 | 0.24 |
| >55 Years | 80 | 69 | |
| T-Category | | | |
| 2-3 | 80 | 75 | 0.69 |
| 4 | 74 | 65 | |
| N-Category | | | |
| 0-2a | 82 | 68 | 0.49 |
| 2b-2c | 70 | 67 | |
| Histological grade | | | |
| 1-2 | 74 | 64 | 0.58 |
| 3 | 78 | 74 | |

Significant *p*-values are given in bold.

[risk ratio (RR)=3.42, 95% confidence interval (CI)=1.32-11.64, *p*=0.023)], whereas favorable tumor sites were not significant (RR=1.06, 95% CI=0.71-1.66, *p*=0.77).

On univariate analysis, improved OS was significantly associated with favorable tumor sites (*p*<0.001) and female gender (*p*=0.012) (Table III). No significant difference regarding OS was found between treatment groups A and B (*p*=0.57); however, OS appeared numerically better in group B (65% *versus* 40% at 2 years). In the Cox regression analysis, female gender was significant (RR=2.68, 95% CI=1.27-6.59, *p*=0.008), whereas favorable tumor sites were not significant (RR=1.09, 95% CI=0.77-1.59, *p*=0.63).

The comparisons of groups A and B with respect to treatment-related toxicities showed that the treatment in group A (accelerated fractionation plus chemotherapy) was associated with significantly higher rates of grade ≥3 oral mucositis (*p*=0.041), grade ≥2 cervical lymph edema (*p*=0.007), grade ≥3 leucopenia (*p*=0.007), grade ≥2 thrombopenia (*p*=0.002), grade ≥3 thrombopenia (*p*=0.029) and grade ≥2 anemia (*p*=0.013). Moreover, trends were found for increased toxicity in group A with respect to grade ≥2 radiation dermatitis (*p*=0.20), grade ≥3 cervical lymphedema (*p*=0.14) and grade ≥1 reduced renal function

(*p*=0.12). The rates of all investigated toxicities are summarized in Table IV. In group A, all patients received the planned total radiation doses. In two patients (2%) of group B, radiotherapy was discontinued prior to 70 Gy because of treatment-related toxicity, and six patients (7%) received less than 70 Gy due to other reasons. Data regarding interruptions of radiotherapy longer than 1 week and completion of planned chemotherapy were available for all patients of group A and 64 patients of group B. Interruptions of radiotherapy longer than 1 week became necessary for one patient (10%) of group A and 10 patients (16%) of group B (*p*>0.99). Chemotherapy was not given as planned to four patients (40%) of group A and 17 patients (27%) of group B (*p*=0.46).

When comparing accelerated fractionation plus chemotherapy (group A) and the different chemotherapy regimens used in group B, the best 2-year LRC rates were achieved with 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks followed by 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks and 20 mg/m$^2$ of cisplatin on days 1-5 plus 5-FU every 4 weeks. OS rates at 2 years were most favorable with 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks followed by 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks. The

Table III. *Comparison of overall survival in patients according to treatment [(accelerated fractionation plus chemotherapy (group A) versus conventionally fractionated radiochemotherapy (group B)] and patient characteristics (univariate analyses). p-Values were obtained from log-rank test.*

| Characteristic | 1 Year (%) | 2 Years (%) | p-Value |
|---|---|---|---|
| Treatment group | | | |
| Group A | 50 | 40 | 0.57 |
| Group B | 80 | 65 | |
| Tumor site | | | |
| Oropharynx | 80 | 70 | **<0.001** |
| Hypopharynx | 55 | 27 | |
| Larynx | 88 | 75 | |
| Gender | | | |
| Female | 96 | 85 | **0.012** |
| Male | 70 | 54 | |
| Age at radiotherapy | | | |
| ≤55 Years | 70 | 56 | 0.30 |
| >55 Years | 79 | 64 | |
| T-Category | | | |
| 2-3 | 80 | 71 | 0.33 |
| 4 | 75 | 58 | |
| N-Category | | | |
| 0-2a | 79 | 64 | 0.84 |
| 2b-2c | 75 | 60 | |
| Histological grade | | | |
| 1-2 | 80 | 62 | 0.93 |
| 3 | 72 | 62 | |

Significant p-values are given in bold.

Table IV. *Comparison of grade ≥2 toxicities in patients treated with accelerated fractionation plus chemotherapy (group A) and conventionally fractionated radiochemotherapy (group B). p-Values were obtained from Fisher's exact test.*

| Toxicity | Group A N (%) | Group B N (%) | p-Value |
|---|---|---|---|
| Oral mucositis | | | |
| ≥2 | 10 (100) | 79 (93) | >0.99 |
| ≥3 | 9 (90) | 46 (54) | **0.041** |
| Radiation dermatitis | | | |
| ≥2 | 10 (100) | 67 (79) | 0.20 |
| ≥3 | 3 (30) | 22 (26) | 0.72 |
| Cervical lymph edema* | | | |
| ≥2 | 7 (70) | 15 (24) | **0.007** |
| ≥3 | 1 (10) | 0 (0) | 0.14 |
| Xerostomia* | | | |
| ≥2 | 6 (60) | 49 (64) | >0.99 |
| ≥3 | 0 (0) | 3 (4) | >0.99 |
| Leucopenia | | | |
| ≥2 | 6 (60) | 41 (48) | 0.52 |
| ≥3 | 6 (60) | 15 (18) | **0.007** |
| Thrombopenia | | | |
| ≥2 | 4 (40) | 3 (4) | **0.002** |
| ≥3 | 2 (20) | 1 (1) | **0.029** |
| Anemia | | | |
| ≥2 | 8 (80) | 30 (35) | **0.013** |
| ≥3 | 0 (0) | 8 (9) | 0.59 |
| Reduced renal function* | | | |
| ≥1 | 5 (50) | 15 (23) | 0.12 |
| ≥2 | 2 (20) | 8 (13) | 0.62 |

*In group B, data regarding cervical lymph edema were available for 62 patients, xerostomia for 77 patients, and reduced renal function for 64 patients. Significant p-values are given in bold.

comparisons of all five treatment regimens with respect to LRC and OS are shown in Table V. The difference between the chemotherapy regimens regarding OS was significant in both the univariate ($p$=0.015) and the multivariate analysis (RR=1.30, 95% CI=1.10-1.56, $p$=0.002).

In group A, 1-year OS rates were 67% after HA-RT plus concurrent weekly cisplatin and cetuximab, 50% after induction chemotherapy with docetaxel/cisplatin followed by AF-CB with or without induction/concurrent cetuximab, and 33% after HA-RT plus concurrent paclitaxel/cisplatin, and 2-year OS rates were 33%, 50% and 33%, respectively ($p$=0.88). One-year LRC rates were 100%, 67% and 100%, respectively ($p$=0.43). Two-year LRC rates were not compared, since two or fewer patients were alive in each group.

The most feasible regimen was 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks; no patients (0%) required an interruption of radiotherapy longer than 1 week (compared to 10-30% in patients receiving one of the other four regimens) and 20 patients (83%) received their complete chemotherapy as planned (compared to 56-74%).

## Discussion

Conventional cisplatin-based radiochemotherapy is considered the standard treatment for unresectable HNSCC (7, 8). However, a considerable number of patients cannot tolerate the addition of chemotherapy to radiotherapy, which significantly increases toxicity (9, 10, 28). This also applies to other systemic therapies (20, 29, 30). In patients unable to receive radiochemotherapy, improved outcomes were shown for unconventional fractionation such as HA-RT and AF-CB (12, 13, 31). When considering the superior results of unconventional compared to conventional fractionation, the idea was created to combine HA-RT or AF-CB with systemic agents.

In 2005, a feasibility study was reported that included 84 patients with locally advanced HNSCC (14). Seventy-six patients were evaluable and 65 patients treated per protocol receiving AF-CB with 72 Gy in 42 fractions over 6 weeks (30×1.8 Gy/day plus a concomitant boost of 1.5 Gy given the same day for the last 12 days) plus 100 mg/m$^2$ cisplatin on days 1 and 22. Three patients (4%) died due to toxicity;

Table V. *Additional analysis: Comparison of accelerated fractionation plus chemotherapy (group A) and the different chemotherapy regimens included in the radiochemotherapy group (group B) with respect to locoregional control and overall survival. p-Values were obtained from log-rank test.*

| Endpoint | Type of chemotherapy | 1 Year (%) | 2 Years (%) | *p*-Value |
|---|---|---|---|---|
| Locoregional control | Accelerated fractionation + chemotherapy (n=10) | 89 | 53 | 0.39 |
| | Cisplatin 30 mg/m$^2$, every week (n=21) | 64 | 51 | |
| | Cisplatin 100 mg/m$^2$, every 3 weeks (n=17) | 76 | 76 | |
| | Cisplatin 5×20 mg/m$^2$, every 4 weeks (n=24) | 83 | 83 | |
| | Cisplatin 5×20 mg/m$^2$ + 5-FU, every 4 weeks (n=23) | 73 | 64 | |
| Overall survival | Accelerated fractionation + chemotherapy (n=10) | 50 | 40 | **0.015** |
| | Cisplatin 30 mg/m$^2$, every week (n=21) | 62 | 38 | |
| | Cisplatin 100 mg/m$^2$, every 3 weeks (n=17) | 88 | 80 | |
| | Cisplatin 5×20 mg/m$^2$, every 4 weeks (n=24) | 92 | 87 | |
| | Cisplatin 5×20 mg/m$^2$ + 5-FU, every 4 weeks (n=23) | 78 | 53 | |

5-FU: 5-Fluorouracil. Significant *p*-values are given in bold.

additional 19 patients (25%) experienced grade 4 and 49 patients (64%) grade 3 acute toxicities. Despite the high toxicity, the authors rated this regimen as feasible. In another study, 40 consecutive patients received post-operative radiotherapy with 66 Gy over 5.5 weeks (2.0 Gy per fraction on 5 days per week plus 2.0 Gy as concomitant boost on day 5) plus 100 mg/m$^2$ cisplatin on days 1, 22 and 43 (16). Grade 3 oral mucositis occurred in 25%, grade 3 dermatitis in 13%, grade ≥3 anemia in 6%, grade ≥3 leucopenia in 13% and grade 3 nephrotoxicity in 3% of patients. Grade ≥2 xerostomia and grade ≥2 lymph edema occurred in 25% and 3% of patients, respectively. The authors described their regimen as "easily feasible with acceptable morbidity" (16). In 2010, a phase I study investigated the feasibility of HA-RT with 70.6 Gy in 44 fractions over 6 weeks (30 Gy in 15 fractions over 3 weeks, followed by two 1.4 Gy fractions per day over 3 weeks) plus weekly cetuximab and cisplatin (17). Cisplatin-doses were escalated between 20 and 40 mg/m$^2$. Grade ≥3 oral mucositis occurred in 56%, grade ≥3 dermatitis in 38% and ≥3 neutropenia in 25% of patients. These authors also considered their regimen feasible.

In addition to feasibility studies, randomized trials compared HA-RT or AF-CB plus chemotherapy to HA-RT or AF-CB alone. In 2000, Dobrowsky and Naude compared conventional fractionation (70 Gy/35 fractions) alone, HA-RT (55.3 Gy in 33 fractions over 17 consecutive days) alone and HA-RT plus mitomycin C (20 mg/m$^2$ on day 5) (18). The addition of mitomycin C resulted in significantly improved LRC and OS compared to conventional radiotherapy and HA-RT alone. Another randomized trial compared AF-CB (69.6 Gy in 30 fractions over 5.5 weeks) plus chemotherapy (two courses of 20 mg/m$^2$ of carboplatin on days 1-5 and 600 mg/m$^2$ of 5-FU on days 1-5) to AF-CB alone (19). Two-year LRC (51% *versus* 45%, *p*=0.14) and OS (48% *versus* 39%,

*p*=0.11) rates were non-significantly better after AF-CB plus chemotherapy. In patients with oropharyngeal cancer, 1-year local control (60% *versus* 40%, *p*=0.009) and 1-year OS (68% *versus* 57%, *p*=0.047) were significantly better in the AF-CB plus chemotherapy group (19).

In 2005, a randomized trial compared dose-escalated HA-RT with 77.6 Gy in 52 fractions over 6 weeks (8×2.0 Gy over 1.5 weeks followed by two 1.4-Gy fractions per day over 4.5 weeks) to HA-RT with 70.6 Gy in 44 fractions over 6 weeks (15×2.0 Gy over 3 weeks followed by two 1.4 Gy-fractions per day over 4.5 weeks) plus mitomycin C (10 mg/m$^2$ on days 5 and 36) and 5-FU (600 mg/m$^2$ on days 1-5) (20). HA-RT plus chemotherapy resulted in better LRC (49.9% *versus* 37.4%, *p*=0.001) and OS (28.6% *versus* 23.7%, *p*=0.023) at 5 years.

These promising results led to two randomized trials comparing accelerated radiotherapy plus chemotherapy to conventional radiochemotherapy (21, 22). One trial compared AF-CB (70 Gy in 40 fractions over 6 weeks) plus carboplatin/5-FU to conventional fractionation (70 Gy in 35 fractions over 7 weeks) plus carboplatin/5-FU (21). AF-CB plus chemotherapy did not result in better progression-free survival than conventional radiochemotherapy (hazard ratio=1.02, 95% CI=0.84-1.23, *p*=0.88) (21). In the other trial, AF-CB with 72 Gy in 42 fractions over 6 weeks plus two courses of 100 mg/m$^2$ of cisplatin on day 1 was compared to conventional fractionation (70 Gy/35 fractions) plus three courses of the same cisplatin-dose (22). No significant differences were found for locoregional failure (hazard ratio=1.08, 95% CI=0.84-1.38, *p*=0.78) and OS (hazard ratio=0.96, 95% CI=0.79-1.18, *p*=0.37).

Other accelerated radiotherapy plus chemotherapy concepts have been developed and not yet compared to conventional radiochemotherapy. In the present study,

outcomes of patients receiving one of three regimens of accelerated radiotherapy plus chemotherapy were compared to patients receiving conventional radiochemotherapy (25-27). Groups were matched for several patient and tumor characteristics to reduce the risk of hidden selection biases. However, due to the retrospective nature of this study, this risk cannot be entirely excluded. In addition to the design, other limitations of the study exist including the small number of patients in group A, differences in treatment times and length of follow-up, and non-consideration of the human papilloma virus status; the latter was demonstrated to be a significant prognostic factor for OS in patients with HNSCC, particularly for those with oropharyngeal cancer (32-34).

According to the findings of the current study, accelerated radiotherapy plus chemotherapy did not result in better LRC and OS than conventional radiochemotherapy. Outcomes after accelerated radiotherapy plus chemotherapy appeared even worse when compared to conventional radiochemotherapy with 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks or 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks (Table V). Moreover, accelerated radiotherapy plus chemotherapy was associated with significantly increased acute and late toxicities (Table IV). When considering the results of the two previous randomized trials and the present study, conventional radiochemotherapy should remain the standard treatment for unresectable HNSCC (21, 22). For conventional radiochemotherapy, 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks appeared preferable, since this regimen was associated with the best LRC and OS rates at 2 years and was better tolerated than the other cisplatin-based regimens investigated in this study. These findings agree with previous studies suggesting that 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks resulted in significantly better OS than weekly cisplatin (RR=1.17, *p*=0.011) and cisplatin plus 5-FU (RR=1.35, *p*=0.006) and in non-significantly better OS than 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks (80% *versus* 68% at 3 years, *p*=0.14) (35-37). Moreover, in the previous studies, 20 mg/m$^2$ on days 1-5 of cisplatin every 4 weeks was associated with fewer adverse events than cisplatin plus 5-FU and 100 mg/m$^2$ of cisplatin on day 1 every 3 weeks (35, 36).

In summary, given the limitations of this study, accelerated radiotherapy plus chemotherapy provided no significant benefit but increased toxicity compared to conventional radiochemotherapy. More favorable results were achieved with 20 mg/m$^2$ of cisplatin on days 1-5 every 4 weeks. Conventional radiochemotherapy should remain the standard treatment for unresectable locally advanced HNSCC. These findings need to be confirmed in randomized clinical trials.

## Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

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# Accelerated Fractionation With Concomitant Boost *vs.* Conventional Radio-chemotherapy for Definitive Treatment of Locally Advanced Squamous Cell Carcinoma of the Head-and-Neck (SCCHN)

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**Abstract.** *Background/Aim: Patients with unresectable head-and-neck cancer (SCCHN) unable to tolerate radio-chemotherapy may receive unconventionally fractionated radiotherapy. This retrospective study compared both treatments. Patients and Methods: Eight patients unsuitable for chemotherapy were assigned to accelerated fractionation with concomitant boost (AF-CB, 69.6 Gy/39 fractions) over 5.5 weeks (group A) and 72 patients to cisplatin-based radio-chemotherapy (70 Gy/35 fractions) over 7 weeks (group B). Groups were matched (cancer site, gender, age, performance score, T-/N-stage, histologic grade) and compared for loco-regional control (LRC), metastases-free survival (MFS), overall survival (OS) and toxicities. Results: LRC, MFS, OS and radiation-related toxicities were not significantly different between groups A and B. Improved outcomes were associated with favorable cancer site, better performance score and T3-stage. In group B, toxicity led to reduction/discontinuation of chemotherapy in 38.9% and interruptions of radiotherapy >7 days in 19.3% of patients. Conclusion: AF-CB appeared a reasonable alternative for patients who cannot safely receive radio-chemotherapy for unresectable SCCHN.*

Head-and-neck cancers represented the 7th most common malignancy worldwide in 2018 (1, 2). The vast majority of

these cancers were squamous cell carcinomas (SCCHN). Locally advanced tumors may be unresectable and require definitive radiotherapy. The outcomes after definitive radiotherapy were significantly improved with the addition of concurrent (mainly platin-based) chemotherapy. In 2000, a randomized trial compared 66-72 Gy of radiotherapy alone to 66-72 Gy of radiotherapy with concurrent cisplatin and 5-fluorouracil (5-FU) for unresectable locally advanced SCCHN (3). The combined treatment resulted in significantly better loco-regional control (LRC). In 2004, another randomized trial compared 70 Gy in 35 fractions alone to the same regimen plus concurrent carboplatin/5-FU for definitive treatment of locally advanced oropharynx cancer (4). In this trial, concurrent radio-chemotherapy was associated with significantly improved disease-free survival (DFS) and LRC and almost significantly improved overall survival (OS) when compared to radiotherapy alone. These results were confirmed in a large meta-analysis that included 93 randomized trials and demonstrated significantly better OS for concurrent radio-chemotherapy compared to radiation alone (5).

Unfortunately, the addition of chemotherapy to radiotherapy significantly increased grade ≥3 acute toxicities (6, 7). Thus, a considerable number of patients, particularly patients with significant co-morbidities and elderly patients, are unable to withstand concurrent radio-chemotherapy. Moreover, increased toxicity caused by the addition of chemotherapy may require interruptions of the radiotherapy, which can significantly impair the patients' prognoses (8). Patients who are unsuitable for chemotherapy or other systemic agents are treated with radiotherapy alone. Treatment outcomes can be improved with unconventionally fractionated radiotherapy over less treatment time. According to a meta-analysis, unconventional fractionation was significantly superior to conventional fractionation (daily

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fractions of 2.0 Gy on five consecutive days per week) with respect to LRC and OS (9).

The term "unconventional fractionation" summarizes several altered dose-fractionation regimens including accelerated fractionation with concomitant boost (AF-CB) (9, 10). According to a randomized trial, AF-CB (72 Gy in 42 fractions over 6 weeks) resulted in more favorable outcomes than conventional fractionation (10). However, in this trial, AF-CB was associated with significantly increased late toxicity. Since the publication of the trial, other AF-CB programs were developed (11-14). One of these programs consisted of 69.9 Gy in 39 fractions given over 5.5 weeks (11). To our knowledge, this AF-CB program has not yet been compared to conventionally fractionated radio-chemotherapy. Therefore, the current study was initiated, which compared AF-CB to conventionally fractionated (70 Gy in 35 fractions) cisplatin-based radio-chemotherapy for definitive treatment of unresectable locally advanced SCCHN.

## Patients and Methods

Eighty patients with histologically proven locally advanced unresectable SCCHN were included in this retrospective study, which was approved by the Ethics Committee at the University of Lübeck (20-454). Patients had non-metastatic stage IV disease; TNM-stages included T3 N2 M0 (n=25), T4 N0 M0 (n=8), T4 N1 M0 (n=12) and T4 N2 M0 (n=35) (15, 16). Patients with T1- or T2-tumors were not included to increase the homogeneity of the study population. The 7th edition of the American Joint Committee on Cancer staging manual was applied, since the status of human papilloma virus was not available for most patients, but is necessary for the staging of oropharynx cancers in the 8th edition (17).

Eight patients unable to receive radio-chemotherapy due to comorbidity were treated with accelerated radiotherapy including concomitant boost between 2011 and 2019 (group A). Initially, 30 Gy (15 daily fractions of 2.0 Gy over 3 weeks) were given to the primary tumor and regional lymph nodes including low-risk areas. After 30 Gy, the same volumes received additional 21.6 Gy with 1.8 Gy per fraction in the morning for 2.5 weeks (=12 treatment days). After an interval of ≥6 hours, which allowed the normal tissue to recover, 1.5 Gy were administered on the same days. The dose of 1.5 Gy was given to the primary tumor and high/intermediate-risk lymph node areas for 6 days (first concomitant boost, cumulative dose=60.6 Gy), and to the primary tumor and high-risk lymph node areas for another 6 days (second concomitant boost, cumulative dose=69.6 Gy). The treatment time including both concomitant boosts was 5.5 weeks (11, 18).

The other 72 patients (from an existing database) had been assigned to conventionally fractionated radiotherapy with concurrent cisplatin-based chemotherapy between 2000 and 2014 (group B). Initially, 50 Gy (daily fractions of 2.0 Gy over 5 weeks) were given to the primary tumor and regional lymph nodes including low-risk areas. Afterwards, a boost of 10 Gy (2.0 Gy per fraction, once daily) was administered to the primary tumor and high/intermediate-risk lymph node areas (cumulative dose=60 Gy), followed by a second boost of 10 Gy to the primary tumor and high-risk lymph node areas (cumulative dose=70 Gy). Thus, the treatment time in group B was 7 weeks. Concurrent cisplatin-based chemotherapy included either

Table I. *Comparison of the two treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radiochemotherapy) regarding characteristics used for matching. p-Values were calculated with the Fisher's exact test. p-Values <0.05 were considered significant, p-values <0.10 indicated a trend.*

| Characteristic | Group A (n=8) N patients (%) | Group B (n=72) N patients (%) | *p*-Value |
|---|---|---|---|
| Tumor site | | | |
| Oropharynx | 3 (37.5) | 29 (40.3) | >0.99* |
| Hypopharynx | 3 (37.5) | 24 (33.3) | |
| Larynx | 2 (25.0) | 19 (26.4) | |
| Gender | | | |
| Female | 2 (25.0) | 14 (19.4) | 0.66 |
| Male | 6 (75.0) | 58 (80.6) | |
| Age at radiotherapy | | | |
| ≤55 Years | 2 (25.0) | 20 (27.8) | >0.99 |
| >55 Years | 6 (75.0) | 52 (72.2) | |
| Performance status | | | |
| KPS 60-70 | 5 (62.5) | 19 (26.4) | **0.049** |
| KPS 80-100 | 3 (37.5) | 53 (73.6) | |
| T-stage | | | |
| T3 | 3 (37.5) | 22 (30.6) | 0.70 |
| T4 | 5 (62.5) | 50 (69.4) | |
| N-stage | | | |
| N0-1 | 2 (25.0) | 18 (25.0) | >0.99 |
| N2 | 6 (75.0) | 54 (75.0) | |
| Histologic grade | | | |
| G1-2 | 6 (75.0) | 53 (73.6) | >0.99 |
| G3 | 2 (25.0) | 19 (26.4) | |

KPS: Karnofsky performance score. *For calculation of the *p*-value, hypopharynx and larynx were combined. Statistically significant *p*-values are given in bold.

weekly administration of 30 mg/m$^2$/d of cisplatin (n=15), 100 mg/m$^2$ of cisplatin every 3 weeks (n=14), 20 mg/m$^2$/d1-5 of cisplatin every 4 weeks (n=29), 20 mg/m$^2$/d1-5 of cisplatin plus 600 mg/m$^2$/d1-5 of 5-fluorouracil (5-FU) every 4 weeks (n=12) or 20 g/m$^2$/d1-5 of cisplatin plus 1000 mg/m$^2$/d1-5 of 5-FU every 4 weeks (n=2).

Both groups were matched for tumor site (oropharynx *vs.* hypopharynx *vs.* larynx), gender, age at radiotherapy (≤55 *vs.* >55 years), primary tumor stage (T3 *vs.* T4), stage of regional lymph nodes (N0-1 *vs.* N2) and histologic grade (G1-2 *vs.* G3). Matching for Karnofsky performance score (KPS 60-70 *vs.* 80-100) was not possible, since the KPS was significantly worse in the AF-CB group. The distributions of the parameters are shown in Table I (comparisons performed with Fisher's exact test).

The groups were compared for LRC, metastases-free survival (MFS) and OS, calculated from the last day of radiotherapy. Univariate analyses for these endpoints were performed with the Kaplan–Meier method and the log-rank test. Characteristics found to be significant (*p*<0.05) or indicated a trend (*p*<0.10) were additionally evaluated for independence using a Cox proportional hazard model (multivariate analysis). Moreover, treatment groups A and B were compared for acute (oral mucositis, radiation dermatitis) and late (regional lymph edema, xerostomia) radiation-related toxicities using the Fisher's exact test. Again, *p*-values <0.05 were considered significant and *p*-values <0.10 indicated a trend.

Table II. *Univariate analyses of loco-regional control up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

| Characteristic | 1 Year | 2 Years | 3 Years | *p*-Value |
|---|---|---|---|---|
| Treatment group | | | | |
| Group A | 83 | 83 | 56 | 0.85 |
| Group B | 72 | 64 | 64 | |
| Tumor site | | | | |
| Oropharynx | 80 | 71 | 71 | **0.034** |
| Hypopharynx | 53 | 47 | 47 | |
| Larynx | 85 | 79 | 67 | |
| Gender | | | | |
| Female | 87 | 75 | 75 | 0.26 |
| Male | 69 | 63 | 59 | |
| Age at radiotherapy | | | | |
| ≤55 Years | 63 | 63 | 63 | 0.43 |
| >55 Years | 76 | 67 | 62 | |
| Performance status | | | | |
| KPS 60-70 | 62 | 51 | 38 | 0.078 |
| KPS 80-100 | 77 | 72 | 72 | |
| T-stage | | | | |
| T3 | 77 | 67 | 67 | 0.64 |
| T4 | 71 | 65 | 60 | |
| N-stage | | | | |
| N0-1 | 69 | 54 | 54 | 0.39 |
| N2 | 74 | 70 | 64 | |
| Histologic grade | | | | |
| G1-2 | 74 | 66 | 62 | 0.91 |
| G3 | 69 | 63 | 63 | |

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

Table III. *Univariate analyses of metastases-free survival up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

| Characteristic | 1 Year | 2 Years | 3 Years | *p*-Value |
|---|---|---|---|---|
| Treatment group | | | | |
| Group A | 75 | 75 | 75 | 0.88 |
| Group B | 83 | 75 | 62 | |
| Tumor site | | | | |
| Oropharynx | 84 | 80 | 56 | 0.23 |
| Hypopharynx | 69 | 63 | 63 | |
| Larynx | 95 | 81 | 81 | |
| Gender | | | | |
| Female | 75 | 75 | 75 | 0.82 |
| Male | 84 | 75 | 64 | |
| Age at radiotherapy | | | | |
| ≤55 Years | 79 | 73 | 73 | 0.92 |
| >55 Years | 84 | 76 | 64 | |
| Performance status | | | | |
| KPS 60-70 | 62 | 49 | 49 | **0.005** |
| KPS 80-100 | 92 | 87 | 71 | |
| T-stage | | | | |
| T3 | 92 | 85 | 85 | 0.070 |
| T4 | 78 | 70 | 56 | |
| N-stage | | | | |
| N0-1 | 94 | 86 | 74 | 0.24 |
| N2 | 79 | 71 | 62 | |
| Histologic grade | | | | |
| G1-2 | 87 | 79 | 65 | 0.27 |
| G3 | 69 | 62 | 62 | |

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

## Results

Median follow-up periods were 18.5 months (range=0-70 months) in the entire cohort, 21.5 months (range=2-50 months) in group A and 18.5 months (range=0-70 months) in group B, respectively. On univariate analyses, improved LRC was significantly associated with favorable cancer sites (oropharynx or larynx, *p*=0.034), and a trend was found for KPS 80-100 (*p*=0.078) (Table II). The difference between group A and group B was not significant (*p*=0.85, Figure 1). In the subsequent multivariate analysis, KPS showed a trend [hazard ratio (HR)=1.97, 95% confidence interval (CI)=0.89-4.25, *p*=0.093)]; cancer site was not significant (HR=1.10, 95%CI=0.70-1.71, *p*=0.68).

Better MFS was significantly associated with KPS 80-100 (*p*=0.005) on univariate analyses and lower T-stage (T3) showed a trend (*p*=0.070) (Table III). MFS of treatment groups A and B was not significantly different (*p*=0.88, Figure 2). In the multivariate analysis of MFS, KPS was significant (HR=3.13, 95%CI=1.29-7.75, *p*=0.012); a trend was found for T-stage (HR=2.79, 95%CI=0.93-11.99, *p*=0.068).

Median OS-times were 44 months in the entire cohort, 42.5 months in group A and 50 months in group B, respectively. On univariate analyses (Table IV), improved OS was significantly associated with favorable cancer sites (oropharynx or larynx, *p*=0.015), and KPS 80-100 showed a trend (*p*=0.073). No significant association was found for the type of treatment (*p*=0.47, Figure 3). In the multivariate analysis of OS, KPS showed a trend (HR=1.83, 95%CI=0.91-3.58, *p*=0.089), cancer site was not significant (HR=1.01, 95%CI=0.67-1.49, *p*=0.96).

The comparisons of the treatment groups A and B for grade ≥2 and grade ≥3 radiation-related toxicities did not reveal any significant differences (Table V). In group A, one patient did not receive the planned total dose of 69.6 Gy due to acute toxicity. In group B, four patients received less than 70 Gy because of acute treatment-associated toxicity, and in three patients, radiotherapy was limited to 66 Gy due to other reasons.

Data regarding interruptions of radiotherapy >7 days were available for all patients of group A and 57 patients of group B, respectively. Interruptions >7 days were required in 0
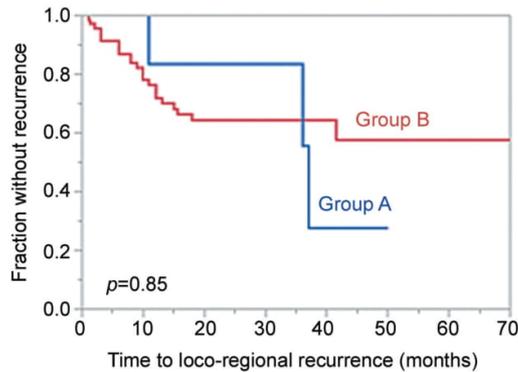
Figure 1. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to loco-regional control. The p-value was obtained from the log-rank test.*
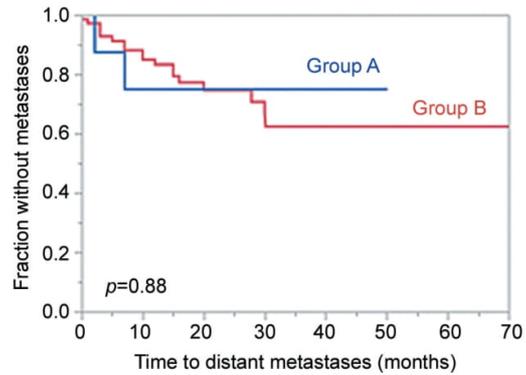


Figure 2. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to metastases-free survival. The p-value was obtained from the log-rank test.*

patients (0%) of group A and 11 patients (19.3%) of group B, respectively ($p$=0.33). Chemotherapy could not be given as planned in 28 patients (38.9%) of group B. Toxicities leading to reduction or discontinuation of chemotherapy included impairment in renal function (n=12), severe oral mucositis (n=8), grade 3 nausea/vomiting (n=5), pneumonia (n=3) and other infections (n=2). Chemotherapy was reduced/discontinued in 8/15 patients (53.3%) receiving 30 mg/m$^2$/d of cisplatin weekly, in 10/14 patients (71.4%) receiving 100 mg/m$^2$ of cisplatin every 3 weeks, in 6/29 patients (30.7%) receiving 20 mg/m$^2$/d1-5 of cisplatin every 4 weeks, in 3/12 patients (25.0%) receiving 20 mg/m$^2$ of cisplatin plus 600 mg/m$^2$ of 5-FU on days 1-5 every 4 weeks, and in 1/2 patients (50.0%) receiving 20 g/m$^2$ of cisplatin plus 1000 mg/m$^2$ of 5-FU on days 1-5 every 4 weeks, respectively.

## Discussion

The prognoses of patients with locally advanced or metastatic SCCHN require improvement. A considerable number of studies were performed during recent years to contribute to this goal (19-24). Patients with locally advanced disease usually receive resection of the primary tumor and dissection of the regional lymph nodes followed by adjuvant radiotherapy or, in case of risk factors, radio-chemotherapy (6, 7, 25). Many patients cannot receive surgery, because the tumor is considered unresectable and/or they have significant co-morbidities. For unresectable SCCHN, cisplatin-based concurrent radio-chemotherapy with conventional fractionation (70 Gy in 35 fractions of 2.0 Gy over 7 weeks) is widely
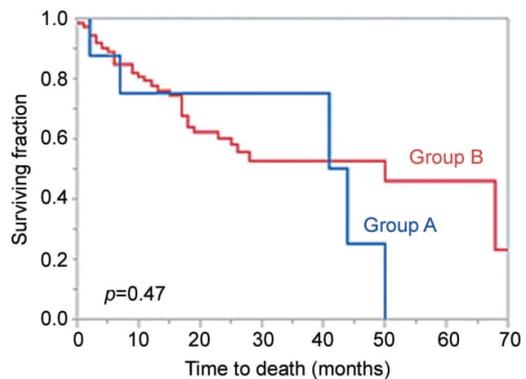


Figure 3. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to overall survival. The p-value was obtained from the log-rank test.*

considered the standard treatment (3-5). However, due to co-morbidities including decreased renal function, peripheral neuropathy and hearing loss, a considerable number of patients cannot safely receive standard cisplatin-based chemotherapy. Other potential options of systemic therapy include carboplatin, mitomycin C plus 5-FU and epidermal growth factor receptor (EGFR) antibodies such as cetuximab (26-28). Since also these agents can be associated with significant side effects, the majority of patients unsuitable for cisplatin-based chemotherapy cannot receive other systemic treatments.

Table IV. *Univariate analyses of overall survival up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

| Characteristic | 1 Year | 2 Years | 3 Years | *p*-Value |
|---|---|---|---|---|
| Treatment group | | | | |
| Group A | 75 | 75 | 75 | 0.47 |
| Group B | 78 | 60 | 53 | |
| Tumor site | | | | |
| Oropharynx | 84 | 68 | 56 | **0.015** |
| Hypopharynx | 59 | 37 | 37 | |
| Larynx | 90 | 84 | 76 | |
| Gender | | | | |
| Female | 81 | 74 | 55 | 0.69 |
| Male | 77 | 60 | 55 | |
| Age at radiotherapy | | | | |
| ≤55 Years | 73 | 55 | 55 | 0.35 |
| >55 Years | 79 | 64 | 56 | |
| Performance status | | | | |
| KPS 60-70 | 71 | 46 | 40 | 0.073 |
| KPS 80-100 | 80 | 67 | 61 | |
| T-stage | | | | |
| T3 | 84 | 64 | 64 | 0.33 |
| T4 | 75 | 60 | 51 | |
| N-stage | | | | |
| N0-1 | 80 | 56 | 42 | 0.40 |
| N2 | 77 | 63 | 61 | |
| Histologic grade | | | | |
| G1-2 | 83 | 63 | 57 | 0.48 |
| G3 | 62 | 56 | 49 | |

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

Table V. *Comparison of the two treatment groups A (accelerated fractionation with a concomitant boost) and B (standard fractionation) with respect to radiation-related toxicities. The p-values were obtained from the Fisher's exact test.*

| Toxicity | Group A N patients (%) | Group B N patients (%) | *p*-Value |
|---|---|---|---|
| Grade ≥2 oral mucositis | 8 (100) | 68 (94.4) | >0.99 |
| Grade ≥3 oral mucositis | 4 (50.0) | 41 (56.9) | 0.72 |
| Grade ≥2 radiation dermatitis | 5 (62.5) | 58 (80.6) | 0.36 |
| Grade ≥3 radiation dermatitis | 1 (12.5) | 21 (29.2) | 0.43 |
| Grade ≥2 lymph edema | 2 (25.0) | 15 (27.3)* | >0.99 |
| Grade ≥3 lymph edema | 1 (12.5) | 1 (1.8)* | 0.24 |
| Grade ≥2 xerostomia | 5 (62.5) | 46 (63.9) | >0.99 |
| Grade ≥3 xerostomia | 1 (12.5) | 6 (8.3) | 0.54 |

*Data regarding lymph edema were available only for 55 patients in group B.

Moreover, all systemic treatment increases the toxicity of the mandatory radiotherapy. This may lead to interruptions of the radiation treatment of more than 7 days, which has been shown to have a negative impact on the patients' prognoses. In the multivariate analysis of a study in patients with non-metastatic stage IV SCCHN, lack of interruptions of radiotherapy >7 days was associated with improved LRC (risk ratio=3.32, *p*=0.015) and OS (risk ratio=2.59, *p*=0.021) (8).

For these patients, alternative treatment options are required that improve LRC and OS compared to conventionally fractionated radiotherapy alone. Improved outcomes were demonstrated for unconventional fractionated radiotherapy. In a randomized trial, hyper-fractionated radiotherapy (81.6 Gy in 68 fractions, *i.e.* 2×1.2 Gy per day on 5 days per week) and AF-CB (72 Gy in 42 fractions over 6 weeks, *i.e.* 30×1.8 Gy/day to a large field plus a concomitant boost of 1.5 Gy/day given 6 hours after the dose to the large field for the last 12 treatment days) resulted in significantly better LRC and DFS compared to conventional radiotherapy (70 Gy in 35 fractions) (10). The results of this

trial were updated in 2014 (29). The absolute reduction in cumulative loco-regional failure at 5 years compared to conventional fractionation was 6.5% for hyper-fractionated radiotherapy and 6.6% for AF-CB, respectively. When considering the patients censored for loco-regional control at 5 years, *p*-values were 0.05 for hyper-fractionation and 0.11 for AF-CB, respectively. Both hyper-fractionation and AF-CB were significantly superior to conventional fractionation with respect to DFS (29). When considering the patients censored for DFS at 5 years, *p*-values were 0.01 for hyper-fractionation and 0.05 for AF-CB, respectively. In addition, a meta-analysis of 15 trials demonstrated a benefit with respect to LRC for AF-CB (9). This meta-analysis also observed a survival benefit for unconventionally fractionated radiotherapy. The absolute benefit at 5 years was larger for hyper-fractionated radiotherapy than for AF-CB (8% *vs*. 2%). According to the authors of this meta-analysis, this difference should be interpreted with caution because of variation in patient characteristics between the treatment groups (9). A potential advantage of AF-CB compared to hyper-fractionation is the lower number of fractions (29-42 *vs*. 60-68 fractions). This can be particularly important for institutions with waiting lists due to high patient load or limited capacities at their linear accelerators.

After the trial of Fu *et al*. (10), additional AF-CB programs were reported that achieved promising results (11-14). The AF-CB program used in the current study was presented in a German trial in 2001 (11). The value of AF-CB has not yet been finally clarified. According to two meta-analyses, radiotherapy with accelerated fractionation such as AF-CB alone cannot entirely compensate for the lack of concurrent chemotherapy (30, 31). In a randomized phase III trial of 216 patients with oropharynx cancer, AF-CB (67.5 Gy in 40 fractions over 5 weeks) provided better compliance,

toxicity profile and quality of life with similar disease control when compared to concurrent radio-chemotherapy including 66 Gy in 33 fractions over 6.5 weeks plus cisplatin $100mg/m^2$ on days 1, 22 and 43 (32). Moreover, in a recent randomized trial published in 2020, response rates and DFS were not significantly different for AF-CB and concurrent conventionally fractionated radio-chemotherapy (33). Thus, more studies comparing AF-CB and radio-chemotherapy for locally advanced SCCHN are warranted.

To our knowledge, the AF-CB included in the present study has not yet been compared to standard concurrent radio-chemotherapy with conventional fractionation. To allow better comparability of both treatments, the patients were matched for cancer site, gender, age, primary tumor stage, stage of regional lymph nodes and histologic grade. Matching for KPS was not possible, since KPS was significantly worse in group A. Patients receiving AF-CB were specifically unsuitable for chemotherapy due to significant co-morbidities that also impact KPS.

According to the results of this study, AF-CB was not significantly inferior to conventionally fractionated concurrent radio-chemotherapy with respect to LRC, MFS, OS and radiation-related toxicities. In contrast to the type of treatment, improved outcomes were associated with favorable cancer site (oropharynx or larynx), KPS of 80-100 and T3-stage (compared to T4-stage). These prognostic factors were also identified in previous studies demonstrating consistency of these findings to other studies (34-37). Limitations of this study include its retrospective design, the small sample size in group A, the lack of data regarding the status of the human papilloma virus, and the different treatment periods between the two treatment groups. In 15 patients (20.8%) of group B, chemotherapy consisted of weekly administration of 30 $mg/m^2$/d of cisplatin. In two previous studies and a meta-analysis, weekly cisplatin appeared less effective than 100 $mg/m^2$ of cisplatin every 3 weeks and 20 $mg/m^2$/d1-5 of cisplatin every 4 weeks (38-40). Thus, the results after radio-chemotherapy might have been more favorable without patients receiving weekly cisplatin. Moreover, 38.9% of patients in group B did not receive their chemotherapy as planned due to acute toxicity. This demonstrates the importance of proper selection of patients for concurrent radio-chemotherapy. When patients with unresectable SCCHN undergo a careful selection process prior to treatment, the proportion of patients receiving the complete radio-chemotherapy as planned would likely increase. Concurrent radio-chemotherapy will remain the treatment-of-choice for the majority of patients with unresectable SCCHN.

In summary, given the limitations of this study, AF-CB produced promising results and is a reasonable alternative for the treatment of unresectable SCCHN in patients who cannot receive radio-chemotherapy. Confirmation of the results with a larger prospective trial including the AF-CB program used in the present study is warranted.

## Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

## Authors' Contributions

The study was designed by all Authors. The data of the new patients were collected by C.A.N. The analyses of the data used for this study were performed by S.E.S. and D.R. The article was drafted by D.R. and S.E.S. and approved by all Authors.

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