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Prognosefaktoren und Prognose-Scores – Ein Beitrag zur Personalisierung der Strahlentherapie von fortgeschrittenen Kopf-Hals-Tumoren

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Abkürzungsverzeichnis

BSC	Best-Supportive-Care (bestmögliche unterstützende Behandlung)
cSCC	cutaneous Squamous-Cell Carcinoma (kutanes Plattenepithelkarzinom)
ECOG-PS	Eastern Cooperative Oncology Group Performance Score
EQD2	Equivalent Dose in 2 Gy Fractions (Äquivalenzdosis)
Gy	Gray
HR	Hazard Ratio
KPS	Karnofsky Performance Score (Karnofsky-Index)
LPFS	Local Progression Free Survival (lokales progressionsfreies Überleben)
MSCC	Metastatic Spinal Cord Compression (metastatisch bedingte Rückenmarkskompression)
OS	Overall Survival (Gesamtüberleben)
RR	Risk Ratio (Risikoverhältnis)
SCC	Squamous Cell Carcinoma (Plattenepithelkarzinom)
SCCHN	Squamous Cell Carcinoma oft the Head and Neck (Plattenepithelkarzinom der Kopf-Hals-Region)
VMAT	Volumetric Modulateted Arc Therapy
WBI	Whole-Brain Irradiation (Ganzhirnbestrahlung)

I Einleitung

Das Plattenepithelkarzinom der Kopf-Hals-Region (SCCHN) ist mit einer weltweiten Inzidenz von mehr als 500.000 neuen Fällen pro Jahr eine der häufigsten Tumorerkrankungen (10, 20, 60). Die kurative Standardbehandlung fortgeschrittener, nicht (fern-)metastasierter SCCHN besteht in der chirurgischen Resektion, gefolgt von Strahlentherapie oder Radiochemotherapie. Mehr als 60 % der Patient*innen mit einem SCCHN werden in einem lokal fortgeschrittenen Stadium diagnostiziert, was durch große Tumore mit lokaler Invasion des umgebenden Gewebes und/oder Nachweis von lokalen Lymphknotenmetastasen charakterisiert ist (10). In diesen Tumorstadien besteht neben einem erhöhten Rezidivrisiko auch eine erhöhte Gefahr von Fernmetastasen, wodurch sich eine insgesamt schlechte Prognose ergibt (5-Jahres Gesamtüberleben < 50 %) (10).

Ähnlich niedrige 5-Jahres-Überlebensraten ergeben sich für Patient*innen mit SCC der Nasennebenhöhlen, einer Erkrankung, die mit lediglich 3-5 % der Tumorerkrankungen im Kopf-Hals-Bereich zu den seltenen Tumoren zählt (33, 62). Hier beträgt die 5-Jahres-Überlebensrate etwa 50 %, 30 % und 15 % für lokale, lokoregionale und metastasierte Erkrankungsstadien (2, 62).

Beim nicht-melanozytären Hautkrebs macht das kutane Plattenepithelkarzinom (cSCC) mit 20 % dieser Karzinome nur einen vergleichsweisen kleinen Anteil aus (21, 73, 76). Ungefähr 70-80 % dieser cSCC treten in der Kopf-Hals-Region auf, und die Inzidenz dieser Tumore nimmt zu (21, 67, 72).

Die Mehrzahl der Patient*innen mit SCCHN sind für eine kurative Behandlung geeignet (10, 36). Wenn eine Resektion nicht sicher möglich ist, erhalten die Patient*innen im Allgemeinen eine kurativ intendierte Radio-Chemotherapie (5, 20, 36). Da diese Behandlung häufig mit erheblicher Toxizität verbunden ist, verträgt eine beträchtliche Anzahl von Patient*innen die aggressive Behandlung nicht und erhält stattdessen eine palliative Strahlentherapie (5, 10, 20, 32, 36, 55, 60).

Dies gilt insbesondere für Patient*innen mit einer metastasierten Erkrankung, lokal oder regional weit fortgeschrittenen Tumoren und für Patient*innen mit erheblichen Komorbiditäten, schlechtem Allgemeinzustand oder fortgeschrittenem Alter (20, 60). Für die palliative Bestrahlung stehen verschiedene Dosis-Fraktionierungsschemata zur Verfügung, darunter auch ultrakurze Konzepte wie

Quad Shot (14 Gy in 4 Fraktionen über nur 2 Tage), Kurzzeit-Schemata wie zum Beispiel 20-24 Gy Gesamtdosis in täglichen Fraktionen von 4,0 Gy, verabreicht fünfmal pro Woche, intermediäre Therapien mit 36-39 Gy Gesamtdosis in täglichen Fraktionen von 3,0 Gy, und länger dauernde Therapien mit 50-60 Gy in täglichen Fraktionen von 2,0-2,5 Gy (10, 12, 20). Insgesamt wird eine Strahlentherapie mit einer höheren biologisch effektiven Dosis (Äquivalenzdosis in 2-Gy Fraktionen, EQD2) voraussichtlich zu einer längeren Krankheitskontrolle führen, demgegenüber aber auch mit erheblicher akuter Toxizität verbunden sein. Zudem steigt das Risiko radiogener Spätfolgen mit der Dosis pro Fraktion an.

Bei der Auswahl eines palliativen Dosis-Fraktionierungsschemas für lokal fortgeschrittene SCCHN sollte deshalb die Überlebensprognose der Patient*innen berücksichtigt werden. Ähnlich wie in anderen palliativen Situationen, wie z. B. bei Hirn- oder Knochenmetastasen, sollten Patient*innen mit schlechter Überlebensprognose idealerweise ein kurzes Regime erhalten (54, 64)

Dies gilt auch für Patient*innen mit zerebralen Metastasen von Kopf-Hals-Tumoren, die allgemein eine schlechte Prognose haben (63). Viele systemisch verabreichte Medikamente passieren die Blut-Hirn-Schranke nur schlecht und sind zur Therapie von Hirnmetastasen nicht sehr wirksam (11, 15, 28). Auch deshalb stellt die Strahlentherapie die häufigste Behandlungsmethode für zerebrale Metastasen von Kopf-Hals-Tumoren dar. Hierbei kommen auch lokale Techniken wie Radiochirurgie und fraktionierte, stereotaktische Strahlentherapie bei einer begrenzten Anzahl von zerebralen Läsionen zum Einsatz (43, 45, 47, 68). Da mehrheitlich bereits multiple Hirnmetastasen vorliegen, erfolgt zumeist eine Ganzhirnbestrahlung (WBI = Whole-Brain Irradiation). (68). Bei ausgewählten Patient*innen kann die WBI mit einer lokalen Strahlentherapie oder einer neurochirurgischen Resektion kombiniert werden (49, 56). Frühere Studien deuten darauf hin, dass Patient*innen mit schlechter Überlebensprognose eher für ein kürzeres WBI-Regime geeignet sind (z. B. 5 × 4 Gy). Demgegenüber können Patient*innen mit sehr günstiger Überlebensprognose von längeren Bestrahlungskonzepten mit niedrigeren Dosen pro Fraktion im Hinblick auf das Gesamtüberleben und weniger Spätfolgen profitieren (13, 48, 51, 61). In der Regel werden diese Schemata mit einer Fraktion pro Tag und fünf Fraktionen pro Woche verabreicht. Sie beinhalten kürzere Konzepte, die eine Woche dauern und längere, die bis zu vier Wochen in Anspruch nehmen (z.B. 10 × 3 Gy und 20 × 2 Gy in 2-4 Wochen) (42, 48).

Auch bei der metastatisch bedingten Rückenmarkskompression (MSCC) ist die Auswahl des geeigneten palliativen Dosis-Fraktionierungsschemas von Bedeutung. Die MSCC geht im Allgemeinen mit neurologischen Funktionsstörungen, hauptsächlich mit motorischen Defiziten, einher (37, 38). Für diese Patient*innen ist die Aufrechterhaltung oder Wiedererlangung der Mobilität ein sehr wichtiges Ziel.

Festzuhalten bleibt, dass für Patient*innen mit sehr eingeschränkter Prognose das Behandlungsschema kurz und mit der geringstmöglichen Belastung für die Betroffenen verbunden sein sollte. Im Gegensatz dazu steht bei Patient*innen mit einer besseren Überlebensprognose die Vermeidung von Spättoxizität und das Erreichen einer längerfristigen lokalen Krankheitskontrolle im Vordergrund. Dementsprechend sollten für diese Patient*innen länger andauernde Strahlentherapieregime mit niedrigeren Dosen pro Fraktion und höheren Gesamtdosen bevorzugt werden.

Hierbei stellt sich dem Behandelnden die Frage, welche Instrumente bereits vor Behandlungsbeginn die Entscheidung für ein individuelles Therapieregime erleichtern können.

Vordringliches Ziel der Arbeiten im Rahmen der kumulativen Dissertation war neben der Identifikation prognostischer Faktoren die Entwicklung eines Prognose-Scores, um zur Personalisierung der Behandlung von Patient*innen mit einem fortgeschrittenen SCCHN beizutragen.

II Prognosefaktoren nach palliativer Strahlentherapie bei lokal fortgeschrittenem Plattenepithelkarzinom im Kopf-Hals-Bereich

II.1 Prognosefaktoren für das Überleben nach palliativer Strahlentherapie lokal fortgeschrittener Plattenepithelkarzinome der Kopf-Hals-Region (Publikation 1)

Patient*innen mit einem fortgeschrittenen Plattenepithelkarzinom der Kopf-Hals-Region (SCCHN) erhalten eine palliative Strahlentherapie. Das Ziel dieser Studie war die Identifizierung prognostischer Faktoren für das Überleben, um eine personalisierte Behandlung für Patient*innen mit fortgeschrittenem SCCHN zu ermöglichen.

Bei 92 Patient*innen wurden 14 Faktoren hinsichtlich möglicher Assoziation mit dem Überleben retrospektiv analysiert: Alter, Geschlecht, Allgemeinzustand, Hämoglobinwert vor der Bestrahlung, Tumorlokalisation und -stadium, histologischer Grad, p16-Status, EQD2, Vollständigkeit der Strahlentherapie, vorausgehende Operation und systemische Therapie.

Die univariaten Analysen erfolgten mit der Kaplan-Meier-Methode und dem Log-Rank-Test. P-Werte < 0,12 wurden als Trend gewertet. Faktoren, die Signifikanz erreichten ($p < 0,05$), wurden zusätzlich multivariat analysiert (Cox Proportional-Hazard Model).

In der univariaten Analyse war das Überleben signifikant mit einem Hämoglobinwert ≥ 12 g/dl ($p = 0,003$) (Abbildung 1), einer EQD2 > 42,3 Gy ($p = 0,003$) und der Vollständigkeit der Strahlentherapie ($p < 0,001$) (Tabelle 1) assoziiert.

In der multivariaten Analyse blieben die Hämoglobinwerte signifikant ($p = 0,024$). Trends ergaben sich für die EQD2 ($p = 0,057$) und die Vollständigkeit der Strahlentherapie ($p = 0,093$).

Es wurden prognostische Faktoren für das Überleben identifiziert, die eine Personalisierung der Behandlung erleichtern können. Die Tatsache, dass ein höherer EQD2 und die Vollständigkeit einer Strahlentherapie mit einem verbesserten Gesamtüberleben verbunden waren, zeigt die Bedeutung einer sorgfältigen Überwachung und Betreuung dieser Patient*innen während der Strahlentherapie.

Tabelle 1: Univariate Analysen in Bezug auf das Überleben. Die p-Werte wurden mit dem Log-Rank-Test berechnet.

Faktor	**Überleben nach 6 Monaten**	**Überleben nach 12 Monaten**	**p-Wert**
Alter			
≤ 68 Jahre	41	24	0.72
≥ 69 Jahre	39	16	
Geschlecht			
Weilblich	42	17	0.83
Männlich	40	21	
ECOG-PS			
0-2	43	24	0.11
3	32	11	
Prä-RT Hämoglobinwert			
< 12 g/dl	26	12	
≥ 12 g/dl	57	41	**0.003**
Lokalisation des Haupttumors			
Oropharynx	48	25	0.11
Hypopharynx	23	7	
Larynx	44	22	
Mundhöhle/Mundboden	42	28	
Tumor Stadium			
T2-3	46	27	0.58
T4	38	18	
Lymphknoten Stadium			
N0-2b	41	18	0.65
N2c-3	40	23	
Metastasen Stadium			
M0	46	25	0.20
M1	29	10	
Histologischer Grad			
G1-2	43	18	0.69
G3	38	26	
p-16 Status			
Negativ	37	20	0.24
Positiv	68	23	
RT Dosis (EQD2)			
≤ 42.3 Gy	29	16	**0.003**
> 42.3 Gy	54	27	
RT abgeschlossen			
Nein	20	8	**< 0.001**
Ja	52	28	
Vorgezogene Operation			
Nein	41	21	0.76
Ja	39	24	
Systemische Therapie			
Nein	39	20	0.65
Unvollständig	38	13	
Vollständig	50	40	

ECOG-PS: Eastern Cooperative Oncology Group performance score, RT: Radiotherapie, EQD2: equivalent Dose in 2 Gy-fractions. Signifikante p-Werte sind hervorgehoben.

II.2 Ein neuer Überlebens-Score für Patient*innen mit einem lokal fortgeschrittenen Kopf-Hals-Tumor nach palliativer Bestrahlung (Publikation 2)

Für Patient*innen mit einem fortgeschrittenen Plattenepithelkarzinom der Kopf-Halsregion (SCCHN), die eine palliative Bestrahlung erhielten, wurde ein Überlebensscore entwickelt, um die Personalisierung der Behandlung zu unterstützen.

In diese retrospektive Studie wurden 78 Patient*innen aus der vorherigen Studie eingeschlossen (65), die eine palliative Bestrahlung bei fortgeschrittenem SCCHN erhalten hatten und bei denen die Daten bezüglich des ECOG Performance Scores, der Hämoglobinwerte vor der Bestrahlung und der Tumorlokalisation vollständig waren. Sowohl in univariaten als auch in multivariaten Analysen waren Hämoglobinwerte ≥ 12 g/dl vor Beginn der Strahlentherapie (gegenüber < 12 g/dl) mit einem signifikant besseren Überleben assoziiert. Darüber hinaus fanden sich in univariaten Analysen Trends für ECOG-PS 0-2 (vs. 3) und eine günstige Tumorlokalisation (Oropharynx, Larynx oder Mundhöhle/Mundboden vs. Hypopharynx). Diese drei Faktoren (Tabelle 2) gingen in den neuen Überlebens-Score ein.

Tabelle 2: Verteilung der drei Faktoren, die für den Überlebens-Score verwendet wurden.

Faktor	**N Patient*innen (%)**
Eastern Cooperative Oncology Group Performance Score	
0-2	61 (78)
3	17 (22)
Hämoglobinwert vor Bestrahlung	
< 12 g/dl	45 (58)
≥ 12 g/dl	33 (42)
Lokalisation des Haupttumors	
Oropharynx	42 (54)
Hypopharynx	18 (23)
Larynx	8 (10)
Mundhöhle/Mundboden	10 (13)

Die 6-Monats-Überlebensraten der drei Faktoren wurden durch 10 geteilt (Tabelle 3). Für jede*n Patient*in wurden die drei resultierenden Punktwerte addiert (Gesamtpunktwert). Basierend auf den Gesamtpunktwerten für die einzelnen Patient*innen wurden prognostische Gruppen erstellt.

Tabelle 3: Sechs-Monats-Überlebensraten der drei Prognosefaktoren (Publikation 1) und die entsprechenden Punktwerte.

Faktor	**Überlebensrate nach 6 Monaten (%)**	**Punktwert**
ECOG Performance Score		
0-2	43	4
3	32	3
Hämoglobinwert vor Bestrahlung		
< 12 g/dl	26	3
≥ 12 g/dl	57	6
Lokalisation des Haupttumors		
Oropharynx	48	5
Hypopharynx	23	2
Larynx	44	4
Mundhöhle/Mundboden	42	4

Die Gesamtpunktwerte lagen zwischen 8 und 15. Basierend auf den 6-Monats-Überlebensraten wurden drei Gruppen gebildet: 8-9 (n = 15), 11-13 (n = 36) und 14-15 (n = 27) Punkte. Die entsprechenden 6-Monats-Überlebensraten betrugen 13 %, 28 % und 63 %, die medianen Überlebenszeiten 1, 2 und 11 Monate (p = 0,001).

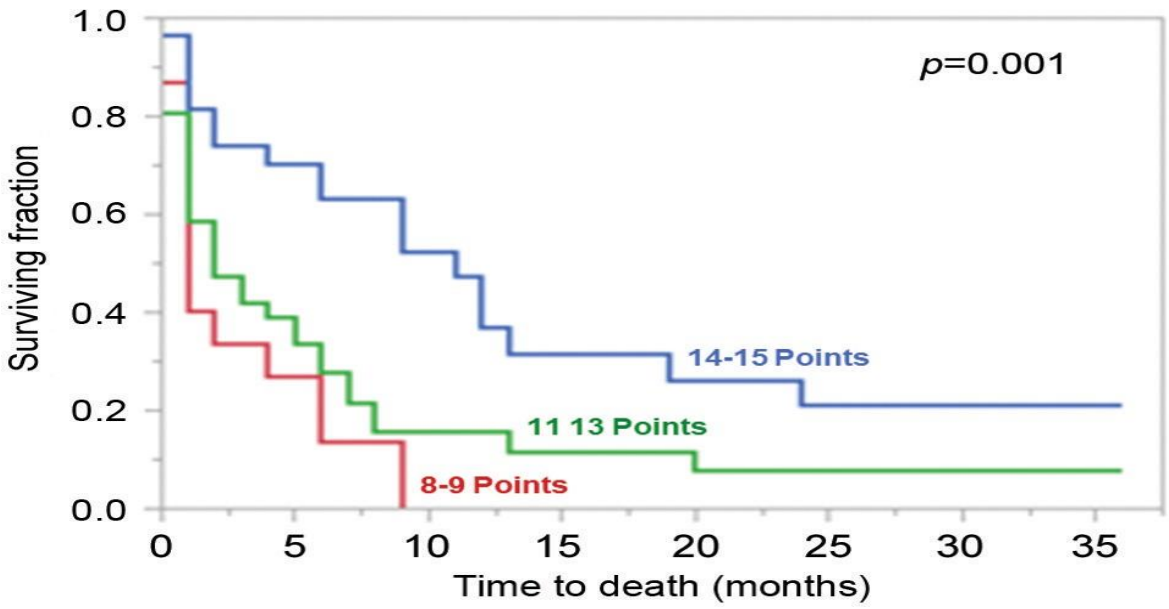

Abbildung 1: Kaplan–Meier Kurven für das Überleben in den drei Prognosegruppen: 8-9, 11-13 und 14-15 Punkte. Der p-Wert wurde mit dem Log-Rank-Test berechnet.

Es wurde ein neuer Überlebens-Score entwickelt, der bei der Personalisierung palliativer Behandlungen von Patient*innen mit fortgeschrittenem SCCHN hilfreich sein kann.

II.3 Der Karnofsky Performance Score - ein unabhängiger Prognosefaktor für das Gesamtüberleben nach palliativer Bestrahlung von Nasennebenhöhlentumoren (Publikation 3)

Tumore der Nasennebenhöhlen sind selten und werden oft erst in fortgeschrittenen Stadien diagnostiziert. Einige Patient*innen können keine kurative Therapie erhalten und werden mit palliativer Bestrahlung behandelt. Ziel war es, prognostische Faktoren für das Überleben zu identifizieren, um auch für diese Gruppe personalisierte Behandlung zu erleichtern.

12 Patient*innen, die eine palliative Strahlentherapie bei lokal fortgeschrittenem Nasennebenhöhlentumor erhielten, wurden retrospektiv hinsichtlich des Gesamtüberlebens untersucht. Folgende 10 Faktoren wurden ausgewertet: Alter, Geschlecht, Karnofsky Performance Score (KPS), Hämoglobinwert vor Beginn der Strahlentherapie, Tumorlokalisation, Lymphknotenbefall, Histologie, EQD2, Vollständigkeit der Strahlentherapie und simultane Chemotherapie.

Die univariaten Analysen erfolgten mit der Kaplan-Meier Methode und dem Log-Rank-Test. Faktoren, die in der univariaten Analyse Signifikanz ($p < 0,05$) oder einen Trend ($p < 0,10$) aufwiesen, wurden multivariat auf ihre Unabhängigkeit untersucht (Cox Proportional-Hazard Model).

In der univariaten Analyse waren ein KPS ≥ 70 ($p < 0,001$) und der planmäßige Abschluss der Strahlentherapie ($p < 0,001$) signifikant mit einem besseren Überleben verbunden. Simultane Chemotherapie wies einen Trend ($p = 0,097$) auf. In der multivariaten Analyse war der KPS ≥ 70 signifikant ($p = 0,025$), für den planmäßigen Abschluss der Strahlentherapie ergab sich ein Trend ($p = 0,080$).

Zusammenfassend erwies sich der KPS als ein unabhängiger Prognosefaktor für das Überleben nach palliativer Bestrahlung von Tumoren der Nasennebenhöhlen. Zudem bedürfen die Patient*innen einer sorgfältigen Überwachung und Kontrolle der Nebenwirkungen, da ein planmäßiger Abschluss der Strahlentherapie für die Prognose von Bedeutung ist.

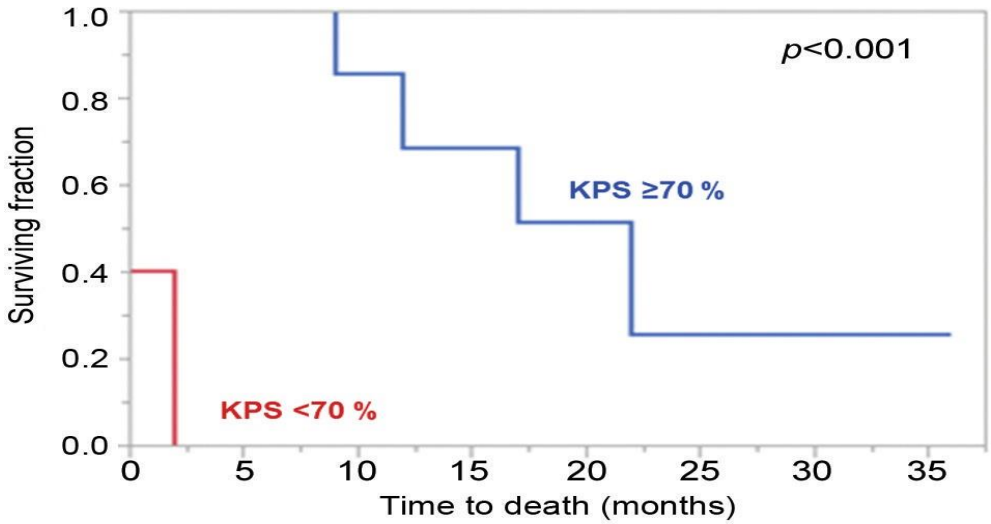

Abbildung 2: Kaplan–Meier Kurven für das Überleben von Patient*innen mit einem Karnofsky Performance Score (KPS) ≥ 70 % versus < 70 %. Der p-Wert wurde mit dem Log-Rank-Test berechnet.

Tabelle 4: Univariate Analysen für das Überleben. P-Werte wurden mit dem Log-Rank-Test berechnet.

Faktor	**Überleben nach 6 Monaten**	**Überleben nach 12 Monaten**	**p-Wert**
Alter			
≤ 76 Jahre	50	33	> 0.99
≥ 79 Jahre	67	44	
Geschlecht			
Weiblich	80	53	0.71
Männlich	43	29	
Karnofsky Performance Score			
< 70	0	0	**< 0.001**
≥ 70	100	69	
Hämoglobinwert vor Bestrahlung			
< 12 g/dl	50	50	0.53
≥ 12 g/dl	100	75	
Lokalisation des Haupttumors			
Nasenhöhle	75	38	0.73
Nasennebenhöhle	50	38	
Lymphknotenbeteiligung			
Nein	57	38	0.69
Ja	60	40	
Histologie			
SCC	43	43	0.54
Andere	80	30	
RT Dosis (EQD2)			
≤ 39.0 Gy	50	33	0.20
> 41.7 Gy	67	50	
RT planmäßig beendet			
Nein	0	0	**< 0.001**
Ja	78	53	
Begleitende Chemotherapie			
Nein	44	30	0.097
Ja	100	67	
Gesamte Kohorte	58	40	

RT: Radiotherapie; SCC: squamous cell carcinoma; EQD2: equivalent dose in 2 Gy-fractions. Signifikante p-Werte sind hervorgehoben.

II.4 Prognosefaktoren nach palliativer Strahlentherapie kutaner Plattenepithelkarzinome der Kopf-Hals-Region (Publikation 4)

Das kutane Plattenepithelkarzinom (cSCC) ist eine häufige Form von Hautkrebs. Die meisten Läsionen werden in einem frühen Stadium entdeckt und erfolgreich mit Resektion plus/minus zusätzlicher Strahlentherapie oder auch alleiniger Strahlentherapie behandelt. Patient*innen mit lokal fortgeschrittener oder metastasierter Erkrankung haben eine schlechtere Prognose. Eine Option für die palliative Behandlung ist systemische Therapie oder eine personalisierte Strahlentherapie. Bei der Auswahl eines Bestrahlungsschemas sollte unter anderem die Überlebensprognose der Patient*innen berücksichtigen werden. Ziel der vorliegenden Studie war es, prognostische Faktoren für das Überleben nach einer palliativen Strahlentherapie von cSCC des Kopf-Hals-Bereichs zu ermitteln.

Dafür wurden 10 Faktoren (Alter, Geschlecht, Tumorlokalisation, histologischer Grad, Stadium des Primärtumors, Lymphknotenbefall, Fernmetastasierung, vorausgegangene Operation, Strahlendosis und planmäßiger Abschluss der Strahlentherapie) bei 12 Patient*innen analysiert. Für die univariaten Analysen wurden die Kaplan-Meier-Methode und der Log-Rank-Test verwendet. Faktoren, die in der univariaten Analyse entweder Signifikanz ($p < 0,05$) oder einen Trend ($p < 0,10$) zeigten, wurden zusätzlich multivariat analysiert (Cox-Regression), wobei p-Werte < 0,05 als signifikant und p-Werte < 0,12 als Hinweis auf einen Trend gewertet wurden.

In der univariaten Analyse war ein besseres Überleben signifikant mit einem niedrigeren histologischen Grad (bessere Differenzierung des Tumors) ($p = 0,022$), Nichtvorhandensein von Fernmetastasen ($p = 0,040$) und dem planmäßigen Abschluss der Strahlentherapie ($p = 0,014$) verbunden. In der multivariaten Analyse zeigten der niedrigere histologische Grad (Risk Ratio = 6,05, $p = 0,100$) sowie der planmäßige Abschluss der Strahlentherapie (Risk Ratio = 4,87, $p = 0,115$) einen Trend.

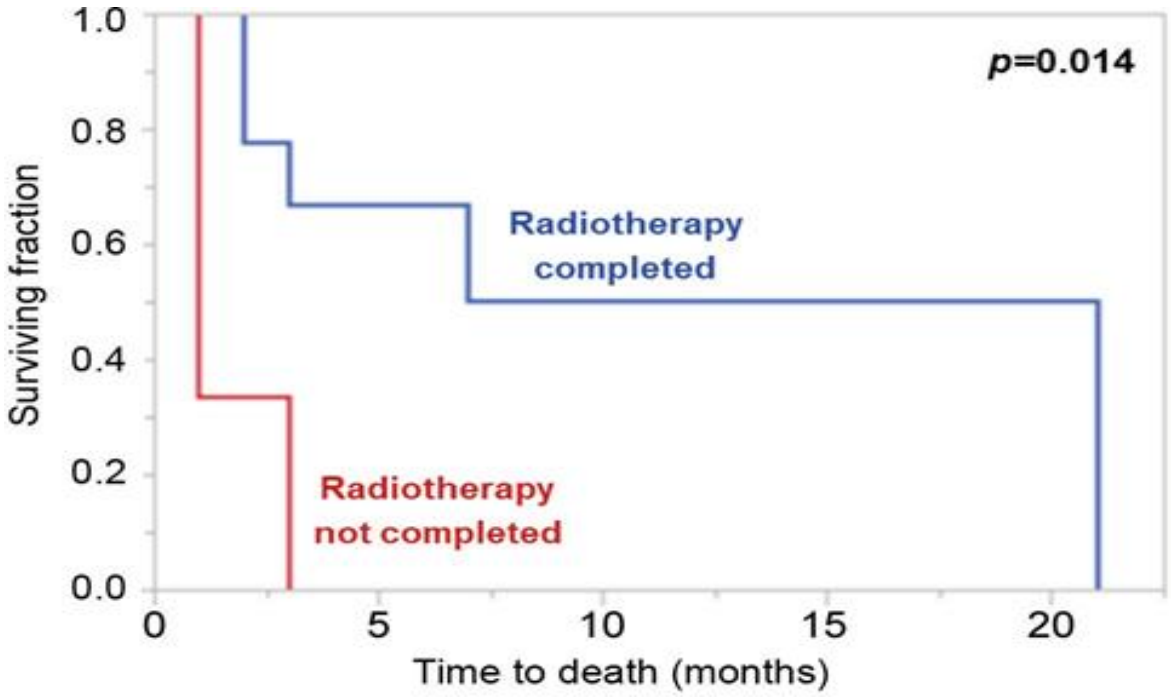

Abbildung 3: Kaplan-Meier Kurven für das Gesamtüberleben: Patient*innen mit planmäßigem Abschluss der Bestrahlung verglichen mit denen, die keine vollständige Bestrahlung erhielten. Der p-Wert wurde mit dem Log-Rank-Test berechnet.

Anhand dieser Arbeit konnten weitere Prognosefaktoren für das Überleben identifiziert werden, die bei der Auswahl individueller Behandlungen helfen können. Zudem wurde erneut der Stellenwert einer optimalen unterstützenden Behandlung der Patient*innen während der Therapie betont, da der planmäßige Abschluss der Strahlentherapie mit einem besseren Überleben verbunden war.

III Prognosefaktoren nach palliativer Strahlentherapie metastasierter Tumore der Kopf-Hals-Region

III.1 Ein Score zur Vorhersage intrazerebraler Rezidive oder neuer zerebraler Metastasen nach Ganzhirnbestrahlung bei Patient*innen mit Kopf-Hals-Tumoren (Publikation 5)

Patient*innen mit metastasierten Kopf-Hals-Tumoren benötigen individuelle Therapien, deren Anwendung durch Prognose-Scores erleichtert wird. Entwickelt wurde ein neues Instrument zur Abschätzung des Risikos von Rezidiven oder neuer zerebraler Metastasen nach einer Ganzhirnbestrahlung (WBI).

Alter, Geschlecht, ECOG-PS, Tumorlokalisation, Anzahl zerebraler Läsionen, Vorliegen extrazerebraler Metastasen sowie die Zeit zwischen Tumordiagnose und Beginn der Behandlung der zerebralen Metastasen wurden in Bezug auf die intrazerebrale Kontrolle bei 23 Patient*innen ausgewertet.

Tabelle 5: Intrazerebrale Kontrollraten 6 Monate nach Ganzhirnbestrahlung (WBI).

Faktor	**Intrazerebrale Kontrolle nach 6 Monaten (%)**	**p-Wert**
Alter		
≤ 64 Jahre	53	
≥ 65 Jahre	48	0.676
Geschlecht		
Weilblich	56	
männlich	51	0.796
ECOG Performance Score		
0-2	69	
3	26	0.093
Lokalisation des Haupttumors		
Nasopharynx	0	
Oropharynx	100	
Larynx	80	
Andere	0	**0.014**
Anzahl zerebraler Läsionen		
1-2	45	
≥ 3	67	0.878
Extrazerebrale Metastasen		
Nein	74	
Ja	0	0.069
Zeit zwischen Tumordiagnose und Behandlung zerebraler Metastasen		
≤ 24 Monate	29	
> 24 Monate	67	0.053

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group. Signifikante p-Werte sind hervorgehoben.

Für die statistischen Analysen wurden die Kaplan-Meier-Methode und der Log-Rank-Test verwendet (25). Die Merkmale, die eine Signifikanz ($p < 0,05$) oder

einen Trend ($p < 0,07$) in Bezug auf die intrazerebrale Kontrolle zeigten, wurden für die Entwicklung des Prognose-Scores verwendet. Eine bessere intrazerebrale Kontrolle war signifikant mit der Tumorlokalisation (Oropharynx- und Larynxkarzinom) assoziiert ($p = 0.014$). Das Nichtvorhandensein extrazerebraler Metastasen ($p = 0,069$) und eine längere Zeit zwischen der Tumordiagnose und dem Beginn der Behandlung zerebraler Metastasen ($p = 0,053$) zeigten Trends. Für jeden dieser drei Faktoren wurde ein separater Punktwert erstellt, indem die intrazerebrale 6-Monats-Kontrollrate (in %) durch 10 geteilt wurde. Der Score eines Patienten/einer Patientin wurde durch Addition der einzelnen Punktwerte ermittelt. Drei prognostische Gruppen wurden gebildet: 3-11, 13-18 und 20-24 Punkte. Die intrazerebralen Kontrollraten nach sechs Monaten betrugen 0 %, 50 % sowie 100 % ($p = 0,003$).

Mit dem Ergebnis dieser Arbeit wurde ein neues Instrument zur Vorhersage der intrazerebralen Kontrolle nach WBI entwickelt, welches zur Personalisierung der Behandlung von Patient*innen mit zerebralen Metastasen von Kopf-Hals-Tumoren beitragen kann.

III.2 Vorhersage der Gehfähigkeit von Patient*innen nach palliativer Bestrahlung bei metastatisch bedingter Rückenmarkskompression (MSCC) von Kopf-Hals-Tumoren (Publikation 6)

Eine personalisierte Behandlung kann die Therapieergebnisse der Patient*innen verbessern und wird durch Scoring-Systeme erleichtert. Ziel dieser Studie war die Entwicklung eines Instruments zur Abschätzung der Gehfähigkeit nach Strahlentherapie bei metastatisch bedingter Rückenmarkskompression (MSCC).

Insgesamt wurden bei 60 Patient*innen neben dem Fraktionierungsschema auch 10 Faktoren zur Abschätzung der Gehfähigkeit nach Abschluss der Bestrahlung analysiert (Chi-Quadrat-Test).

Faktoren, die Signifikanz ($p < 0,05$) erreichten, wurden für das Scoring-System verwendet. Dies wurde entwickelt, um die Wahrscheinlichkeit der Gehfähigkeit 1 Monat nach der Bestrahlung abschätzen zu können. Für jeden Faktor, der Signifikanz erreichte, wurde ein Punktwert berechnet, indem die Rate gehfähiger Patient*innen (in %) durch 10 geteilt wurde. Der individuelle Gesamtpunktwert für jeden Patienten/jede Patientin ergab sich aus der Summe der einzelnen Punktwerte.

Eine Entwicklungszeit der motorischen Defizite > 7 Tage ($p = 0,011$), Gehfähigkeit vor Strahlentherapie ($p < 0,001$) und ein ECOG-PS von 1-2 ($p < 0,001$) waren signifikant mit der Gehfähigkeit nach Abschluss der Behandlung assoziiert (Tabelle 6). Die Punktwerte der Patient*innen betrugen 7, 12, 15, 20, 22 und 27 Punkte. Es wurden drei Gruppen gebildet (7-12, 15- 20 und 22-27 Punkte); der Anteil gehfähiger Patient*innen betrug 11 %, 62 % bzw. 96 % ($p < 0,001$).

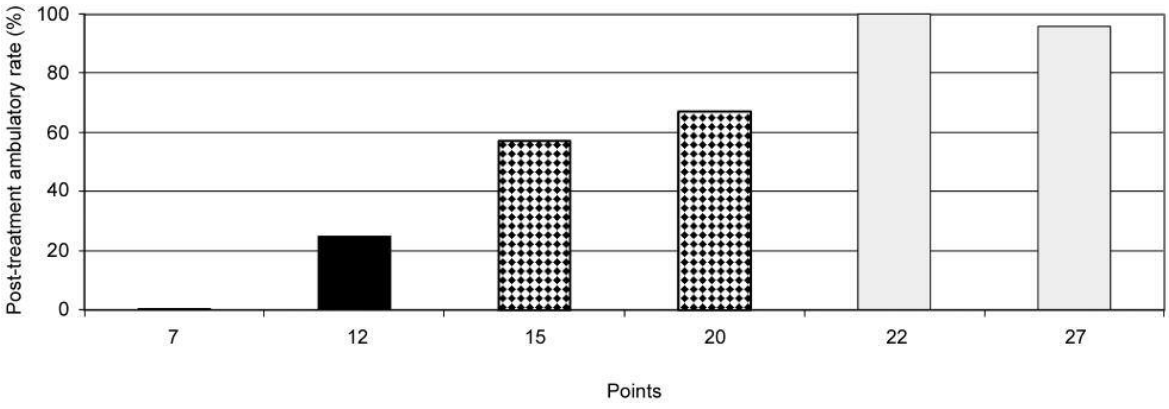

Abbildung 4: Rate gehfähiger Patient*innen (%) nach Bestrahlung bezogen auf die Punktwerte (Points).

Tabelle 6: Gehfähigkeit nach der Bestrahlung.

Faktor	Anzahl der Patient*innen (%)		p-Wert
	Gehfähig	Nicht gehfähig	
Alter			
≤ 59 Jahre	22 (67)	11 (33)	
≥ 60 Jahre	15 (56)	12 (44)	0.844
Intervall zwischen Tumordiagnose und Bestrahlung der MSCC			
≤ 15 Monate	12 (48)	13 (52)	
> 15 Monate	25 (71)	10 (29)	0.340
Viszerale Metastasen			
Nein	23 (74)	8 (26)	
Ja	14 (48)	15 (52)	0.231
Andere Knochenmetastasen			
Nein	19 (70)	8 (30)	
Ja	18 (55)	15 (45)	0.650
Lokalisation des Haupttumors			
Nasopharynx	6 (75)	2 (25)	
Oropharynx	9 (56)	7 (44)	
Hypopharynx	7 (78)	2 (22)	
Larynx	6 (55)	5 (45)	
Andere Lokalisation	9 (56)	7 (44)	0.987
Geschlecht			
Weiblich	6 (67)	3 (33)	
Männlich	31 (61)	20 (39)	0.987
Zeit bis zur Entwicklung motorischer Defizite			
1-7 Tage	7 (33)	14 (67)	
> 7 Tage	30 (77)	9 (23)	**0.011**
Gehfähigkeit vor Bestrahlung			
Nicht gehfähig	2 (11)	17 (89)	
Gehfähig	35 (85)	6 (15)	**< 0.001**
Anzahl betroffener Wirbelkörper			
1-2	17 (61)	11 (39)	
≥ 3	20 (63)	12 (37)	0.999
ECOG Performance Status			
1-2	27 (96)	1 (4)	
3-4	10 (31)	22 (69)	**< 0.001**
Fraktionierung			
Kurzzeitbestrahlung (1 x 8 Gy, 5 x 4 Gy)	6 (34)	8 (57)	
10 x 3 Gy	15 (60)	10 (40)	
Langzeitbestrahlung (Gesamtdosis > 30 Gy)	16 (76)	5 (24)	0.566

MSCC: Metastatic spinal cord compression; ECOG: Eastern Cooperative Oncology Group. Signifikante p-Werte sind hervorgehoben.

Dieses Bewertungssystem hilft bei der Vorhersage der Gehfähigkeit nach Abschluss der Strahlentherapie bei MSCC von Kopf-Hals-Tumoren.

III.3 RAMSES-01: Strahlentherapie bei metastatisch bedingter Rückenmarkskompression mit erhöhter Dosis: Eine prospektive, multizentrische Studie (Publikation 7)

Patient*innen mit metastatisch bedingter Rückenmarkskompression (MSCC) und günstiger Überlebensprognose können möglicherweise von Bestrahlungsdosen von mehr als 30 Gy in 10 Fraktionen in Bezug auf ein verbessertes lokales progressionsfreies Überleben (LPFS) sowie das Gesamtüberleben (OS) profitieren.

Diese prospektive Studie untersucht hauptsächlich das LPFS nach Präzisionsstrahlentherapie (VMAT) mit 18 × 2,33 Gy über 3,5 Wochen oder 15 × 2,633 Gy über 3 Wochen. LPFS ist definiert als Verbesserung oder Status idem der motorischen Defizite während der Strahlentherapie und kein Rezidiv der MSCC im Bestrahlungsfeld im Verlauf.

Diese Therapieregime entsprechen einer Äquivalentdosis von 43,1 Gy bzw. 41,6 Gy und sind damit etwa 33 % bzw. 28 % höher als bei 30 Gy in 10 Fraktionen (EQD2 = 32,5 Gy).

Primärer Endpunkt ist das LPFS 12 Monate nach Bestrahlung. Zu den sekundären Endpunkten gehören der Effekt der Strahlentherapie auf die motorische Funktion, Gehfähigkeit, Sensibilität, Sphinkterdysfunktion, LPFS zu weiteren Nachbeobachtungszeitpunkten, Gesamtüberleben, Schmerzlinderung, der Lebensqualität (Distress) sowie Toxizität.

Nachuntersuchungen erfolgen direkt nach Ende der Strahlentherapie sowie 1, 3, 6, 9 und 12 Monate nach deren Abschluss. Für den prospektiven Teil der Studie werden insgesamt 65 Patient*innen benötigt. Diese werden mit einer historischen Kontrollgruppe von mindestens 235 Patient*innen verglichen, die eine konventionelle Therapie mit 10 × 3 Gy über 2 Wochen erhielten.

Wenn die Präzisionsstrahlentherapie mit 18 × 2,33 Gy oder 15 × 2,633 Gy zu einem signifikant besseren LPFS führt als die konventionelle Strahlentherapie mit 10 × 3 Gy, sollte dieses Regime für Patient*innen mit MSCC und günstiger Überlebensprognose in Betracht gezogen werden.

IV Diskussion

IV.1 Palliative Strahlentherapie von lokal und lokoregional fortgeschrittenen Tumoren der Kopf-Hals-Region (Publikationen 1-4)

Eine beträchtliche Anzahl von Patient*innen mit fortgeschrittenem SCCHN kommen für intensive multimodale Therapiekonzepte nicht in Frage und erhalten dementsprechend die Empfehlung für eine palliative Strahlentherapie. In dieser Situation ist die Auswahl des optimalen Therapieregimes zur Erhaltung der Lebensqualität unter bestmöglicher Kontrolle des Tumorgeschehens eine große Herausforderung. Die Wahl der geeigneten Behandlung sollte in jedem Fall die Prognose der Erkrankung und die Wünsche der Patient*innen berücksichtigen.

Die Überlebensprognosen von Patient*innen mit fortgeschrittenem SCCHN weisen deutliche Unterscheide auf. In den Übersichtsartikeln von Iqbal et al. und Grewal et al. lag die mediane Überlebenszeit lediglich zwischen 3 und 17 Monaten (20, 60). Abhängig von der verbleibenden Lebenszeit der Patient*innen werden unterschiedliche Bestrahlungsregime bevorzugt. Bei sehr eingeschränkter Prognose sollte das Behandlungsschema kurz und mit der geringstmöglichen Belastung für die Betroffenen verbunden sein. Patient*innen mit besserer Überlebensprognose können von länger andauernden Bestrahlungsregimen mit niedrigeren Dosen pro Fraktion und höheren Gesamtdosen profitieren, da hierdurch eine geringere Spättoxizität und eine verbesserte Krankheitskontrolle zu erwarten ist. Dieses Konzept der Personalisierung der Behandlung ist wegweisend, um optimale individuelle Behandlungserfolge für Patient*innen mit SCCHN im lokal fortgeschrittenen oder im metastasierten Stadium, die für eine palliative Bestrahlung vorgesehen sind, zu erlangen.

Es ist wichtig, die verbleibende Lebenszeit der Patient*innen bereits vor Beginn der Behandlung so genau wie möglich abschätzen zu können. Derartige Vorhersagen können durch prognostische Faktoren oder, besser noch, durch prognostische Scores erleichtert werden.

Die erste Studie im Rahmen dieser Dissertation wurde durchgeführt, um Prognosefaktoren für das Überleben von Patient*innen zu identifizieren, die bei fortgeschrittenem SCCHN mit palliativer Strahlentherapie behandelt wurden. Es zeigte sich, dass eine bessere Überlebensprognose signifikant mit einem Hämoglobinwert ≥ 12 g/dl vor Beginn der Strahlentherapie, einer EQD2 > 42,3 Gy und dem planmäßigen Abschluss der Strahlentherapie assoziiert war.

Die Bedeutung des Hämoglobinwerts vor der Strahlentherapie wurde bereits in Studien über Patient*innen mit SCCHN berichtet, die eine kurative Behandlung erhielten. In einer retrospektiven Studie mit 148 Patient*innen mit SCCHN waren Hämoglobinwerte ≥ 12 g/dl vor der Bestrahlung signifikant mit besseren Behandlungsergebnissen assoziiert (41).

In einer anderen retrospektiven Studie mit 153 Patient*innen, die eine Radiochemotherapie im Stadium IV bei SCCHN erhielten, waren in den multivariaten Analysen sowohl eine bessere lokoregionale Kontrolle ($p < 0,001$) als auch ein besseres Überleben ($p = 0,048$) signifikant mit einem Hämoglobinwert ≥ 12 g/dl vor Strahlentherapie verbunden (55).

Ähnliche Ergebnisse wurden in zwei weiteren retrospektiven Studien mit 275 Patient*innen beziehungsweise 225 Patient*innen gefunden, die mit kurativer Absicht bei lokal fortgeschrittenem SCCHN bestrahlt wurden (53, 59). Eine mögliche Erklärung für diese Ergebnisse ist, dass ein niedrigerer Hämoglobinspiegel ein Surrogatmarker für eine weiter fortgeschrittene Erkrankung sein könnte. Ein zweiter Grund könnte die Tatsache sein, dass die verringerte Sauerstofftransportkapazität bei niedrigeren Hämoglobinwerten einen negativen Effekt auf die Sauerstoffversorgung des Tumors hat. Sauerstoff ist wichtig für die Wirksamkeit der Strahlentherapie, die weitgehend von der Induktion von zytotoxischen freien Sauerstoffradikalen abhängt, welche die Tumor-DNA zerstören (4, 70).

Der Einfluss der Strahlendosis auf die Prognose von Patient*innen, die eine palliative Strahlentherapie bei fortgeschrittenem SCCHN erhalten, wurde ebenfalls bereits beobachtet. Um eine bessere Vergleichbarkeit der verschiedenen Dosis-Fraktionierungsschemata zu ermöglichen, werden die Dosen oft als EQD2 angegeben. Die EQD2 berücksichtigt neben der Gesamtdosis auch die Dosis pro Fraktion und basiert auf dem linear-quadratischen Modell. Der alpha/beta-Wert steht dabei für das Verhältnis jener Dosis, bei der die Zellvernichtung durch die lineare und die quadratische Komponente gleich ist. Der alpha/beta-Wert für die Tumorzellvernichtung wird bei der überwiegenden Mehrheit der malignen Tumore mit 10 (Gy) angegeben. Stevens et al. verglichen sechs Dosis-Fraktionierungsschemata in einer retrospektiven Kohorte von 148 Patient*innen mit Kopf-Hals-Tumoren einschließlich SCCHN, adenoid-zystischem Karzinom und undifferenziertem Karzinom der Nasopharynx (66). Das längste mediane Überleben wurde mit einer Gesamtdosis von 70 Gy in 35 Fraktionen erreicht (13 Monate)

gefolgt von 60 Gy in 25 oder 30 Fraktionen (8,9 bzw. 8,5 Monate), 30 Gy in 10 Fraktionen (5,9 Monate), 50 Gy in 20 Fraktionen (5,7 Monate) und 24 Gy in 3 Fraktionen (3,3 Monate).

In einer weiteren retrospektiven Studie von 110 Patient*innen mit inoperablem SCCHN wurde die Strahlentherapie in 2,5 Gy-Fraktionen verabreicht (1). Gesamtdosen von mehr als 40 Gy waren mit einem signifikant besseren progressionsfreien Überleben assoziiert ($p = 0,012$).

In einer kürzlich durchgeführten retrospektiven Studie mit 106 Patient*innen mit unheilbarem Kopf-Hals-Tumor war das mediane Überleben nach 36 Gy in 6 zweiwöchentlichen Fraktionen (EQD2 = 48 Gy) deutlich länger als nach ≤ 30 Gy/EQD2 ≤ 40 Gy (medianes Überleben 26,4 vs. 9,5 Monate, $p = 0,01$) (19). Die Bedeutung eines planmäßigen Abschlusses der Strahlentherapie für die Überlebensprognose wurde ebenfalls in vorherigen Arbeiten berichtet (1, 18, 19). Bisher verfügbare Daten über Auswirkungen des Allgemeinzustands auf das Überleben von Patient*innen mit Kopf-Hals-Tumoren, welche eine palliative Strahlentherapie erhielten, sind widersprüchlich. In der retrospektiven Studie von Laursen et al. (n = 77) war ein ECOG-PS von 0-2 (im Vergleich zu 3-4) mit einer signifikant längeren medianen Überlebenszeit (5,9 vs. 1,5 Monate, $p = 0,007$) assoziiert (27). Darüber hinaus fanden Lok et al. (n = 75) in ihrer retrospektiven Studie, dass ein Karnofsky-Index ≥ 70 ein unabhängiger Prädiktor für ein besseres Überleben ($p = 0,001$) war (28). Im Gegensatz dazu zeigte der ECOG-PS (0-1 vs. 2-3) keinen Zusammenhang mit dem Überleben ($p = 0,85$) in der retrospektiven Studie von Garcia-Anaya et al. (19).

Ähnlich verhält es sich mit dem Zusammenhang zwischen günstiger Tumorlokalisation und verbessertem Überleben. In Studien, die sich auf die palliative Strahlentherapie von SCCHN konzentrierten, konnte diesbezüglich bisher keine eindeutige Verbindung hergestellt werden. Allerdings zeigte eine Studie, die eine kurative Behandlung von lokal fortgeschrittenen Tumoren untersuchte, eben diesen Zusammenhang (58). Ein Trend zeigte sich auch in der vorliegenden Arbeit. Darüber hinaus fanden weitere Studien mit Patient*innen, die eine kurative Behandlung von SCCHN erhielten, eine Verbindung zwischen günstiger Tumorlage und lokoregionaler Kontrolle oder metastasenfreiem Überleben (23, 46, 57).

In Anbetracht der Ergebnisse der aktuellen sowie vorheriger Studien haben Patient*innen mit Risikofaktoren wie einem Hämoglobinwert von weniger als 12 g/dl

vor Beginn der Strahlentherapie, einem schlechten Allgemeinzustand (ECOG-PS ≥ 3) und Tumoren des Hypopharynx eine vergleichsweise schlechte Überlebensprognose und scheinen somit Kandidaten für eine kurzzeitige Strahlentherapie mit höheren Dosen pro Fraktion oder sogar einem "Quad-Shot"-Schema zu sein (12). Im Vergleich dazu haben Patient*innen mit einem Hämoglobinwert von ≥ 12 g/dl vor Beginn der Strahlentherapie, einem günstigeren Allgemeinzustand (ECOG-PS von 0-2) und einem Tumor, der hauptsächlich im Oropharynx, Larynx oder der Mundhöhle/dem Mundboden liegt eine bessere Überlebensprognose und kommen für eine länger dauernde Bestrahlung mit höheren Gesamtdosen und niedrigeren Dosen pro Fraktion in Frage.

Zu beachten bleibt, dass die überwiegende Mehrheit der Studien mit Patient*innen, welche eine palliative Bestrahlung bei fortgeschrittenem SCCHN erhielten, die vorliegende Studie eingeschlossen, retrospektiver Natur waren. Dieser Aspekt, einschließlich des Risikos eines versteckten Selektionsbias, muss bei der Interpretation der Ergebnisse dieser Studien berücksichtigt werden. Darüber hinaus wiesen die vorhandenen prospektiven Studien geringe Fallzahlen auf, was zu einer geringeren statistischen Aussagekraft führt.

Ziel der zweiten Arbeit war es, basierend auf den Erkenntnissen der vorherigen Studie, einen neuen Überlebens-Score für Patient*innen mit fortgeschrittenem SCCHN, die eine palliative lokale oder lokoregionale Bestrahlung erhalten, zu entwickeln.

Überlebens-Scores für die palliative Bestrahlung von Patient*innen mit SCCHN liegen bereits für das metastasierte Stadium vor (40, 52).

In die vorliegende retrospektive Studie wurden 78 Patient*innen eingeschlossen, die eine palliative Bestrahlung für SCCHN erhalten hatten. Die vorherige Studie zeigte den signifikanten Zusammenhang von Hämoglobinwerte ≥ 12 g/dl vor Beginn der Strahlentherapie (gegenüber < 12 g/dl) mit einem besseren Überleben (65). Darüber hinaus fanden sich in den univariaten Analysen entsprechend Trends für einen ECOG-PS 0-2 (vs. 3) und eine günstige Tumorlokalisation (Oropharynx, Larynx oder Mundhöhle/Mundboden vs. Hypopharynx). Diese drei Faktoren wurden für die Entwicklung des Überlebens-Scores verwendet.

Patient*innen, die 8-9 Punkte erreichten, hatten die schlechteste Überlebensprognose mit einer 6-Monats-Überlebensrate von nur 13 % und einer medianen Überlebenszeit von lediglich einem Monat. Diese Patient*innen könnten

Kandidat*innen für eine ultrakurze Therapie wie z.B. Quad-Shot sein oder sogar für eine Best-Supportive-Care Behandlung (BSC) in Frage kommen.
Patient*innen, die 11-13 Punkte erreichten, hatten eine bessere, aber immer noch vergleichsweise schlechte Überlebensprognose. Die mediane Überlebenszeit betrug nur 2 Monate, die 6-Monats-Überlebensrate 28 %. Diese Gruppe scheint für eine Kurzzeittherapie mit einer Gesamtdosis von 20-24 Gy (5 × 4,0 Gy pro Woche) oder für ein intermediäres Behandlungsschema mit einer Dosis von 36-39 Gy (5 × 3,0 Gy pro Woche) geeignet zu sein. Patient*innen, die 14-15 Punkte erreichten, hatten die beste Überlebensprognose mit einer 6-Monats-Überlebensrate von 63 % und einer medianen Überlebenszeit von 11 Monaten. Für diese Gruppe ist die regionale Kontrolle ihrer Krankheit über eine längere Zeit von größerer Bedeutung. Zudem wird die Mehrheit dieser Patient*innen lange genug leben, um strahlenbedingte Langzeitnebenwirkungen zu erleben, welche mit der Lebenszeit zunehmen.
Dieser neue Überlebens-Score kann zu einer personalisierten Behandlung beitragen. Bei der Anwendung dieses Scores sollte man allerdings bedenken, dass er auf der Grundlage retrospektiver Daten entwickelt wurde. Das Risiko eines Selektionsbias ist somit nicht ausgeschlossen. Außerdem waren zwei der Faktoren, die in das Punktesystem einbezogen wurden, nicht signifikant, sondern zeigten in der vorangegangenen Studie lediglich einen Trend (65).

Mit dem Karnofsky Index konnte ein weiterer unabhängiger Prognosefaktor für das Überleben in der dritten Studie dieser Dissertation herausgearbeitet werden. Anhand von 12 Patient*innen, die mit einer palliativen Strahlentherapie bei fortgeschrittenem Nasennebenhöhlenkarzinom behandelt wurden, zeigte sich eine signifikant bessere Überlebensrate bei einem KPS ≥ 70. Insgesamt gibt es bislang nur sehr wenige Studien, die sich mit der palliativen Behandlung von fortgeschrittenem Nasennebenhöhlentumoren befassen.
Jang et al. berichteten über eine Serie von 42 Patient*innen, die mit definitiver Strahlentherapie oder Radiochemotherapie bei T3-4 N0 SCC der Nasenhöhle und der Kieferhöhle behandelt wurden (24). Die Ergebnisse beim Kieferhöhlenkarzinom waren mit einer 5-Jahres-Überlebensrate von 34 % und lokalen Kontrollraten von 29 % schlecht. Die entsprechenden Raten bei Tumoren der Nasenhöhle lagen bei 50 % bzw. 52 %. In einer früheren Studie von Hoppe et al., mit 39 Patient*innen, die eine Strahlentherapie (n = 4) oder eine Radiochemotherapie (n = 35) bei

inoperablem Karzinom der Nasennebenhöhlen erhielten, betrug die 5-Jahres-Überlebensrate nur 15 % (22). In beiden Studien war eine niedrigere biologisch effektive Strahlendosis der einzige Faktor, der signifikant mit einem schlechteren Gesamtüberleben assoziiert war (22, 24). Da die Bestrahlungsdosis kein prätherapeutischer Faktor ist, kann diese nicht bei der Auswahl des optimalen Dosis- Fraktionierungsschemas helfen.

Patient*innen mit einem KPS < 70 scheinen dementsprechend gute Kandidaten für ein Kurzzeitprogramm mit einer höheren Dosis pro Fraktion (Hypofraktionierung) wie zum Beispiel 6 × 4 Gy oder sogar eine Best-Supportive-Care Behandlung zu sein, da alle Patient*innen dieser Studie innerhalb von 2 Monaten verstarben. Das Überleben von Patient*innen mit einem KPS ≥ 70 war deutlich besser. 67 % dieser Betroffenen überlebten 1 Jahr oder länger. Daher erzielen diese Patient*innen in Bezug auf eine bessere Krankheitskontrolle und weniger Spättoxizität voraussichtlich durch eine konventionell fraktionierte Strahlentherapie mit höherer Gesamtdosis (60-70 Gy) ein besseres Ergebnis. Außerdem sollten die Patient*innen der letztgenannten Gruppe gegebenenfalls eine gleichzeitige Chemotherapie erhalten, die in der vorliegenden Studie einen Trend zu einem besseren Überleben zeigte und in einer früheren Studie von Choi et al. an 21 Patient*innen mit lokal fortgeschrittenen Tumoren der Nasennebenhöhlen und der Nasopharynx eine verbesserte lokale Tumorkontrolle aufwies (9).

Bei der Interpretation der Ergebnisse der vorliegenden Studie (und der früheren Studien) sollte man wiederum das retrospektive Design bedenken. Es werden prospektive Studien benötigt, welche aber angesichts der Seltenheit von Nasennebenhöhlentumoren in absehbarer Zeit nicht zu erwarten sind.

Ein wegweisendes Ergebnis der vorliegenden Studie ist die Tatsache, dass der planmäßige Abschluss der Strahlentherapie wichtig für die Überlebensprognose der Patient*innen ist. Dieser Aspekt wurde bereits zuvor für die palliative Strahlentherapie bei Kopf-Hals-Tumoren berichtet. In der retrospektiven Studie von Gamez et al. (n = 21) erhielten die Patient*innen drei Zyklen eines ultrakurzen Bestrahlungsschemas („Quad Shot"), das aus 2 × 3,7 Gy pro Tag über 2 Tage bestand, alle drei Wochen für insgesamt drei Zyklen verabreicht und durch Carboplatin oder Cetuximab ergänzt wurde (18). Eine größere Anzahl an abgeschlossenen Zyklen war signifikant mit einem besseren Überleben verbunden

(p = 0,03). Außerdem wurde in der retrospektiven Studie von Garcia-Anaya et al. (n = 106) eine palliative Strahlentherapie mit 30-36 Gy geplant, die in 5-6 zweiwöchentlichen Fraktionen von jeweils 6 Gy verabreicht wurde (19). Patient*innen, die 30 Gy oder weniger erhielten, hatten ein signifikant schlechteres medianes Überleben als Patient*innen, die mehr als 30 Gy erhielten (9,5 vs. 26,4 Monate, p = 0,01). Diese Daten zeigen, dass eine engmaschige Überwachung und unterstützende Behandlung der Patient*innen, die eine palliative Bestrahlung maligner Tumore im Kopf-Hals-Bereich erhalten, sehr wichtig ist. Hierdurch haben die Patient*innen eine höhere Chance, die Strahlentherapie planmäßig abzuschließen, was das Gesamtüberleben zu verbessern scheint.

Um Entscheidungsprozesse weiter zu erleichtern, gewinnen auch die prognostischen Faktoren der vierten Studie an Bedeutung. Ziel war die Identifizierung solcher Faktoren in einer Kohorte von Patient*innen mit cSCC, die mit einer definitiven oder adjuvanten palliativen Strahlentherapie behandelt wurden. Die Studienlage insbesondere für Patient*innen, die eine palliative Strahlentherapie bei lokal fortgeschrittenem und metastasiertem cSCC erhielten, ist sehr begrenzt. Im Jahr 2015 berichteten Ferro et al. über eine Phase-II-Studie an 31 Patient*innen mit nicht-melanozytärem Hautkrebs im Frühstadium, von denen 14 Patient*innen 80 Jahre oder älter waren (17). Die Patient*innen wurden mit 30 Gy in 5 Fraktionen an sechs aufeinanderfolgenden Tagen behandelt. 30 Patient*innen erreichten ein komplettes Ansprechen der Therapie nach einer medianen Nachbeobachtungszeit von 30 Monaten. Die lokale Kontrollrate nach 2 Jahren betrug 93,2 %. Langzeitnebenwirkungen überstiegen nicht Grad 1, und die kosmetischen Ergebnisse waren überwiegend gut oder ausgezeichnet (17).

In Anbetracht des Spektrums verfügbarer Schemata der hypofraktionierten Strahlentherapie für ältere Patient*innen mit cSCC oder für die palliative Behandlung von fortgeschrittenem cSCC besteht eine Herausforderung für die behandelnden Ärzt*innen in der Auswahl des optimalen Schemas für einzelne Patient*innen. In der vorliegenden Studie waren ein niedrigerer histologischer Grad und Nichtvorhandensein von Fernmetastasen in univariaten Analysen signifikant mit einem besseren Überleben verbunden. Außerdem zeigte der histologische Grad in der multivariaten Analyse einen Trend. Der prädiktive Wert der Differenzierung des Tumors für die Behandlungsergebnisse und die Prognose der Patient*innen wurde zuvor in mehreren Studien und Übersichtsartikeln beschrieben (3, 8, 26, 34, 67, 72).

Die prognostische Rolle von Fernmetastasen wurde bisher nicht explizit beschrieben, am ehesten bedingt durch das seltene Auftreten von Fernmetastasen bei Patient*innen mit cSCC. Allerdings wurde berichtet, dass ein fortgeschrittenes Primär- und ein fortgeschrittenes Nodalstadium einen negativen Einfluss auf die Prognose haben (16, 21, 26, 67, 71, 72, 74, 75). Ein weiterer Faktor, der mit einer schlechteren Prognose einhergeht, ist die extrakapsuläre Ausbreitung von Lymphknotenmetastasen, worüber in mehreren Studien und Übersichtsartikeln berichtet wurde (31, 69, 71, 72, 75, 74). In der vorliegenden Studie zeigte die extrakapsuläre Ausbreitung keinen signifikanten Zusammenhang mit dem Überleben. Dies lässt sich auf die geringe Anzahl von Patient*innen mit Lymphknotenbefall (n = 6) beziehungsweise extrakapsulärer Ausbreitung (n = 2) zurückführen. In Anbetracht der Ergebnisse der vorliegenden Studie und der Daten aus der Literatur haben Patient*innen mit Risikofaktoren wie hochgradigem (G3) cSCC, Vorhandensein von Fernmetastasen und extrakapsulärer Ausbreitung von Lymphknotenmetastasen eine vergleichsweise schlechte Prognose und scheinen Kandidaten für eine kurzzeitige Bestrahlung zu sein. Im Gegensatz dazu haben Patient*innen mit Tumoren niedrigen oder mittleren Grades (G1-2), Tumoren ohne Fernmetastasen und ohne extrakapsuläre Ausbreitung von Lymphknotenmetastasen eine günstigere Prognose. Diese Erkrankten sind besser für längere Bestrahlungskonzepte mit höherer biologisch wirksamer Gesamtdosis und niedrigerer Dosis pro Fraktion geeignet. Wenn man überlegt, diesen Empfehlungen zu folgen, müssen die geringe Stichprobengröße und das retrospektive Design der Studie berücksichtigt werden. Zudem waren der histologische Grad und die Fernmetastasierung in der multivariaten Analyse nicht signifikant und daher keine unabhängigen Prognosefaktoren.

Zusätzlich war der planmäßige Abschluss der Strahlentherapie in der univariaten Analyse signifikant mit einem besseren Überleben verbunden und zeigte in der multivariaten Analyse einen Trend. Die Bedeutung eines planmäßigen Abschlusses der Strahlentherapie für das Überleben wurde bereits für die palliative Bestrahlung von nicht-kutanen Kopf-Hals-Tumoren berichtet (19). Daher sind eine engmaschige Überwachung und eine optimale unterstützende Begleitung während der Strahlentherapie wichtig.

IV.2 Palliative Strahlentherapie von fernmetastasierten Tumoren der Kopf-Hals-Region (Publikationen 4-6)

Die primäre Behandlung von lokal fortgeschrittenen Kopf-Hals-Tumoren konnte durch moderne strahlentherapeutische Ansätze und die Kombination mit einer Chemotherapie oder Immuntherapie verbessert werden (6, 7, 59). Auch deshalb leben immer mehr dieser Patient*innen länger. Hierdurch nimmt die Zahl der Patient*innen, die ein metastasiertes Stadium erleben, zu.

In der ersten Arbeit dieses Abschnitts wurde ein zusätzliches prognostisches Instrument entwickelt, das eine Abschätzung der intrazerebralen Kontrollrate 6 Monate nach einer WBI ermöglicht. Patient*innen mit zerebralen Metastasen eines Kopf-Hals-Tumors sind selten und machen nur etwa 1 % aller Patient*innen mit Hirnmetastasen aus (63). Die Prognose dieser Betroffenen muss verbessert werden, was möglicherweise durch individuelle Behandlungsansätze erreicht werden kann. Die Auswahl eines geeigneten Dosis-Fraktionierungsschemas ist ein Beispiel solch einer Individualisierung. In einer früheren Studie wurde ein Instrument vorgestellt, mit dem sich die Überlebenszeiten einzelner Patient*innen mit zerebralen Metastasen von Kopf-Hals-Tumoren vorhersagen lassen (40). Für Patient*innen mit mittlerer Überlebens-Prognose ist die Auswahl des optimalen WBI-Regimes mitunter schwierig. Um eine angemessene Behandlungsentscheidung treffen zu können, wären zusätzliche Informationen, wie beispielsweise das Risiko intrazerebraler Rezidive, erforderlich.

Daher wurde in der vorliegenden Studie ein zusätzliches prognostisches Instrument entwickelt, das eine Abschätzung der intrazerebralen Kontrollrate 6 Monate nach einer WBI ermöglicht. Basierend auf den Faktoren Art des Primärtumors, extrazerebrale Metastasierung und Zeit zwischen Diagnose des Kopf-Hals-Tumors und der Behandlung zerebraler Metastasen wurden drei Gruppen gebildet. Die Raten für die intrazerebrale Kontrolle nach 6 Monaten betrugen 0 % für 3-11 Punkte, 50 % für 13-18 Punkte und 100 % für 20-24 Punkte. Da eine höhere Dosis einer WBI eine effizientere Abtötung der Tumorzellen erwarten lässt, würden Patient*innen der Gruppe mit 3-11 Punkten sowie viele Patient*innen mit 13-18 Punkten in Abhängigkeit von ihrer Überlebensprognose wahrscheinlich von länger andauernden WBI-Programmen mit einer höheren EQD2 und möglichen besseren intrazerebralen 6-Monats-Kontrollrate profitieren.

Weitgreifende Einschränkungen der Lebensqualität der Patient*innen können auch durch eine metastatisch bedingte Rückenmarkskompression (MSCC) verursacht sein. Die alleinige Strahlentherapie ist die häufigste Behandlung für MSCC (37, 38). Im Jahr 2005 zeigte allerdings eine 101 Patient*innen umfassende randomisierte Studie, dass ausgewählte Patient*innen von einer zusätzlichen vorgeschalteten Operation (Dekompression) hinsichtlich Gehfähigkeit und dem Überleben profitieren können (35). Im Allgemeinen werden diese Kriterien von 10-15 % der Patient*innen mit MSCC erfüllt. Ausgesprochen hilfreich wäre es, das Ansprechen vor Beginn der Behandlung vorhersagen zu können. Aus Sicht der Patient*innen ist die Gehfähigkeit ein wichtiges Kriterium für die Lebensqualität. Somit ist entscheidend, vor Einleitung einer Behandlung zu wissen, ob die Gehfähigkeit der Patient*innen durch alleinige Strahlentherapie erreicht werden kann oder eine vorausgehende Operation erforderlich ist.

Daher wurde die vorliegende Studie durchgeführt, um einen entsprechenden Score speziell für MSCC bei Kopf-Hals-Tumoren zu entwickeln. Basierend auf drei Faktoren, Entwicklungszeit motorischer Defizite vor Strahlentherapie, Gehfähigkeit vor der Behandlung sowie dem ECOG-PS, wurden drei prognostische Gruppen gebildet. Gehfähigkeit nach Radiotherapie lag bei 11 % (Gruppe A), 62 % (Gruppe B) sowie 96 % (Gruppe C) der Patient*innen vor. Die Betroffenen der Gruppe A würden wahrscheinlich von einer vorgeschalteten Operation (Dekompression) profitieren. Auch bei Patient*innen der Gruppe B kann eine vorausgehende Operation in Betracht gezogen werden. In Gruppe C waren 1, 3 und 6 Monate nach der Strahlentherapie 96 %, 100 % bzw. 100 % der Patient*innen gehfähig. Angesichts dieser sehr hohen Raten scheinen diese Patient*innen mit einer alleinigen Strahlentherapie ausreichend behandelt zu sein.

Wenn man diesen Vorschlägen folgt, muss der retrospektive Charakter der Daten, die zur Erstellung des Scores verwendet wurden, berücksichtigt werden. Da jedoch Patient*innen mit MSCC bei Kopf-Hals-Tumoren selten sind, sind in naher Zukunft prospektive Studien nicht zu erwarten.

Insgesamt zeigt sich jedoch ein zunehmender Einsatz von vorangehender Operation zur Dekompression zusätzlich zur Strahlentherapie, auch wenn die Mehrheit der Patient*innen mit MSCC nach wie vor mittels alleiniger Strahlentherapie behandelt wird (35, 37, 38, 44). In einer prospektiven, nicht-randomisierten Studie von Patient*innen mit MSCC und diversen Primärtumoren

lagen die 1-Jahres lokalen Kontrollraten bei 81 % nach Langzeit- und 61 % nach Kurz-Strahlentherapie (p = 0,005) (50). Patient*innen mit günstiger Prognose haben ein höheres Risiko für ein Rezidiv eines MSCC im bestrahlten Bereich, da das Risiko eines solchen Rezidivs mit der Lebenszeit zunimmt.

Die hier entwickelte prospektive Studie untersucht hauptsächlich das LPFS nach Präzisionsstrahlentherapie mit 18 × 2,33 Gy über 3,5 Wochen oder 15 × 2,633 Gy über 3 Wochen. In einer retrospektiven Matched-Pair-Studie waren Bestrahlungsdosen von 37,5-40,0 Gy mit einem besseren LPFS assoziiert als 30 Gy (Rades, Panzner). Eine wichtige Frage ist, ob die Ergebnisse der Strahlentherapie günstiger Überlebensprognose mit Dosen über 40 Gy hinaus weiter verbessert werden können. Für viele dieser Patient*innen ist eine Entlastungsoperation nicht möglich. Außerdem besteht im Falle eines Rezidivs im ehemaligen Bestrahlungsfeld durch eine zweite Bestrahlung das Risiko einer Überschreitung der Toleranzdosis des Rückenmarks, was zu einer radiogenen Myelopathie mit schweren neurologischen Defiziten führen kann (14, 30).

Auch die Erhöhung der Strahlendosis zur Verbesserung des LPFS ist durch die Toleranzdosis des Rückenmarks begrenzt (54, 64). In einer früheren Studie zur Präzisionsstrahlentherapie bei MSCC konnte die maximale Dosis für das Rückenmark auf 101,5 % reduziert werden (39). Die gleiche Einschränkung gilt auch für die vorliegende RAMSES-01-Studie. Dies ermöglicht die sichere Verabreichung einer höheren Strahlendosis als 40 Gy (EQD2 = 43,1 Gy). Die in der RAMSES-01-Studie verabreichte Dosis erhöht die EQD2 in Bezug auf die Tumorzellabtötung um 33 % bzw. 28 % verglichen mit 10 × 3 Gy, dem weltweit am häufigsten verwendeten Langzeitregime für MSCC. Wenn sich dieser neue Ansatz der Präzisionsstrahlentherapie gegenüber der konventionellen Strahlentherapie mit 10 × 3 Gy in Bezug auf das LPFS als überlegen erweist, sollte dieses Schema für Patient*innen mit MSCC und günstiger Überlebensprognose nachdrücklich berücksichtigt werden.

V Zusammenfassung und Ausblick

Im Rahmen dieser kumulativen Dissertation bestanden die Ziele der Studien vornehmlich in der Identifikation von Prognosefaktoren und der Entwicklung von Prognose-Scores, um zur Personalisierung der Therapie von Patient*innen mit einem fortgeschrittenen SCCHN und geplanter palliativer Strahlentherapie beizutragen. Die Datenerhebung erfolgte retrospektiv und schloss Patient*innen ein, die zwischen 2000 und 2020 aufgrund eines fortgeschrittenen SCCHN in palliativer Absicht bestrahlt wurden.

Die vorliegenden Ergebnisse und Erkenntnisse, die anhand dieser Arbeiten gewonnen wurden, leisten einen entscheidenden Beitrag zur Verbesserung individueller Therapiekonzepte. Auf der einen Seite ließen sich bestehende Zusammenhänge in den vorliegenden Studien bestätigen, auf der anderen Seite wurden neue Möglichkeiten geschaffen, palliative Therapiekonzepte zu optimieren. So ließ sich der Stellenwert einzelner Prognosefaktoren wie dem Hämoglobinwert vor Beginn einer Bestrahlung, der Tumorlokalisation, Vollständigkeit der Strahlentherapie oder auch dem ECOG-PS verifizieren. Letzterer zeigte sich neben der Abschätzung für das Überleben bei SCCHN im fortgeschrittenen Stadium vor allem zur Vorhersage der Gehfähigkeit von Patient*innen nach Bestrahlung bei MSCC hilfreich.

Ergänzend wurde mit dem Karnofsky-Index für Patient*innen mit Tumoren der Nasennebenhöhlen ein unabhängiger Prognosefaktor identifiziert. Dieser trägt ebenso wie die übrigen Faktoren zur Erleichterung der Therapieentscheidung in Abhängigkeit von der Überlebensprognose bei und kann darüber hinaus zur Stratifizierung künftiger Studien eingesetzt werden.

Darüber hinaus unterstützt der neu entwickelte Überlebens-Score, welcher drei prognostische Gruppen umfasst, die signifikant unterschiedliche Überlebensraten und mediane Überlebenszeiten aufweisen, Ärzt*innen dabei, ein optimales personalisiertes Behandlungskonzept bei Patient*innen mit SCCHN und geplanter palliativer Bestrahlung zu entwickeln.

Großen Stellenwert für Patient*innen mit eingeschränkter Überlebensprognose hat eine möglichst hohe Lebensqualität für die verbleibende Lebenszeit, sodass die Gesamtbehandlungszeit so kurz und die Therapie so schonend wie möglich gestaltet werden sollte.

Zur Optimierung personalisierter Behandlungen wurde neben den retrospektiven Studien auch eine prospektive multizentrische Studie (RAMSES-01) auf den Weg gebracht. In dieser Studie wird die Strahlentherapie mit einer erhöhten Gesamtdosis bei metastatisch bedingter Rückenmarkskompression untersucht. Die ersten Ergebnisse dieser Studie deuten auf ein besseres lokales progressionsfreies Überleben bei insgesamt guter Verträglichkeit der Bestrahlung hin.

Die vorliegenden Ergebnisse sollen den Weg für größere prospektive Studien ebnen, welche für Patient*innen mit fortgeschrittenem SCCHN und einer geplanten palliativen Behandlung bisher kaum vorhanden sind.

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VII Anhang

VII.1 Publikationsverzeichnis

Staackmann C, Ribbat-ldel J, Perner S, ldel C, Bruchhage KL, Hakim SG, Schild SE, Rades D (2021) Palliative Local Radiotherapy for Advanced Squamous Cell Carcinoma of the Head-and-Neck: Prognostic Factors of Survival. Anticancer Research 41 (6), 3205-3210

Rades D, **Staackmann C**, Ribbat-ldel J, Perner S, ldel C, Bruchhage KL, Hakim SG, Schild SE (2021) A New Survival Score for Patients Scheduled for Palliative Irradiation of Locally Advanced Carcinoma of the Head-and-Neck. Anticancer Research 41 (6), 3055-3058

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Rades D, Hansen 0, Jensen LH, Dziggel L, **Staackmann C**, Doemer C, Cacicedo J, Conde-Moreno AJ, Segedin B, Ciervide-Jurio R, Rubio-Rodriguez C, Perez- Romasanta LA, Alvarez-Gracia A, Dennis K, Ferrer-Albiach C, Navarra-Martin A, Lopez-Campos F, Jankarashvili N, Janssen S, Olbrich D, Holländer NH (2019) Radiotherapy for metastatic spinal cord compression with increased radiation doses (RAMSES-01): a prospective multicenter study. BMC Cancer 29;19 (1) 1163

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Palliative Local Radiotherapy for Advanced Squamous Cell Carcinoma of the Head-and-Neck: Prognostic Factors of Survival

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Abstract. *Background/Aim: A considerable number of patients with advanced head-and-neck cancer (SCCHN) receive palliative radiotherapy. This study aimed to identify prognostic factors for survival to facilitate personalized treatment for these patients. Patients and Methods: Ninety-two patients receiving palliative radiotherapy for SCCHN were retrospectively analyzed. Fourteen characteristics were evaluated for survival including age, gender, performance score, pre-radiotherapy hemoglobin, tumor site and stage, histologic grade, p16-status, equivalent dose in 2 Gy-fractions (EQD2), completion of radiotherapy, upfront surgery and systemic therapy. Results: On univariate analysis, improved survival was significantly associated with pre-radiotherapy hemoglobin ≥12 g/dl (p=0.003), EQD2 >42.3 Gy (p=0.003) and completion of radiotherapy (p<0.001). In the multivariate analysis, hemoglobin levels remained significant (p=0.024). Trends were found for EQD2 (p=0.057) and completion of radiotherapy (p=0.093). Conclusion: Prognostic factors for survival were identified that can facilitate treatment personalization. The fact that higher EQD2 and completion of radiotherapy were associated with improved survival demonstrates the importance of close monitoring and care of these patients during radiotherapy.*

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Key Words: Advanced head-and-neck cancer, palliative radiotherapy, survival, prognostic factors, treatment personalization.

Squamous cell carcinoma of the head and neck (SCCHN) represents one of the most common cancer types worldwide with an incidence of more than 500,000 new cases per year (1-3). Standard curative treatment for advanced non-metastatic disease consists of surgical resection followed by radiotherapy or radio-chemotherapy. If a resection is not safely possible, the patients are generally treated with curative radio-chemotherapy alone (3-5). Since curative treatment for SCCHN is generally associated with significant toxicity, a considerable number of patients cannot tolerate such aggressive treatment and receives palliative radiotherapy instead (1-7). When distant metastases are present at the time of first diagnosis, local treatment is palliative. Most patients assigned to palliative local radiotherapy require personalized treatment accounting for their remaining lifetime. Many different radiation programs are available for palliative local radiotherapy of SCCHN with total doses ranging from 20 to 60 Gy and overall treatment times ranging from 1 to 6 weeks (1, 2). Additionally, ultra-short programs such as "quad shot" (2×3.5 Gy per day over 2 days, total dose=14 Gy) are employed (8). Similar to other palliative cases in radiation oncology such as brain or bone metastases, patients with a poor estimated survival should ideally receive a radiation program which is short and not cumbersome (9, 10). On the contrary, in patients with better survival prognoses, avoidance of late toxicity and achievement of longer-term local disease control become more important and longer-course radiotherapy programs with lower doses per fraction and higher total doses appear preferable. This study aimed to identify prognostic factors for survival in patients with SCCHN receiving palliative local radiotherapy to facilitate the process of treatment personalization.

Patients and Methods

Ninety-two patients who received palliative local radiotherapy for advanced SCCHN between 2000 and 2020 with Eastern Cooperative Oncology Group performance scores (ECOG-PS) of 0-3 were included in this retrospective study (11), which was approved by the Ethics Committee of the University of Lübeck (no. 18-130A). Staging was performed in accordance with the 7th edition of the American Joint Committee on Cancer (AJCC) manual, since the human papilloma virus (HPV) status, which is mandatory for oropharynx cancer for classification according to the 8th edition, was not available in 14% of the patients (12-16).

The patients were treated with palliative radiotherapy with planned total doses ranging between 20 and 60 Gy and doses per fraction between 2.0 and 4.0 Gy. Six of the patients in whom radiotherapy was not completed as planned received a total dose of less than 20 Gy. Using both total dose and dose per fraction, the equivalent dose in 2 Gy-fractions (EQD2) was calculated for each patient using an alpha/beta ratio of 10 Gy for tumor control. The median EQD2 delivered was 42.3 Gy (range=2.6-62.5 Gy).

A total of 14 patient and tumor characteristics (Table I) were evaluated for potential associations with survival, which was calculated from the first day of radiotherapy. These characteristics included age (≤68 *vs.* ≥69 years, median age=68 years), gender, ECOG-PS (0-2 *vs.* 3), hemoglobin level prior to radiotherapy (<12 *vs.* ≥12 g/dl), main tumor site (oropharynx *vs.* hypopharynx *vs.* larynx *vs.* oral cavity/floor of mouth), primary tumor stage (T2-3 *vs.* T4), nodal stage (N0-N2b *vs.* N2c-N3), distant metastasis (no=M0 *vs.* yes=M1), histologic grade (G1-2 *vs.* G3), p16-status as surrogate marker for the HPV-status (14) (negative *vs.* positive), EQD2 (≤42.3 *vs.* >42.3 Gy, median=42.3 Gy), completion of radiotherapy as planned (no *vs.* yes), upfront surgery (no *vs.* yes), and additional systemic therapy (no *vs.* incomplete *vs.* completed as planned). Twenty-eight patients received systemic treatment, which included induction chemotherapy with docetaxel, carboplatin and 5-fluorouracil (5-FU) (n=2), paclitaxel, cisplatin and 5-FU (n=2) or docetaxel, cisplatin and 5-FU (n=1). One patient received induction chemotherapy with paclitaxel and cisplatin followed by concurrent paclitaxel. Concurrent systemic therapies in the other 22 patients included paclitaxel with 20-25 mg/m^2/twice per week (n=9), cisplatin with 20mg/m^2/d1-5 or 25 mg/m^2/d1-4 every 4 weeks (n=6), cetuximab (loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly, n=3), carboplatin (n=2), paclitaxel followed by cetuximab (n=1) and cisplatin/5-FU (n=1).

Univariate analyses of survival were performed using the Kaplan-Meier method and the log-rank test. *p*-Values <0.12 were considered indicating a trend. Characteristics achieving significance ($p<0.05$) were additionally included in a multivariate analysis performed with the Cox proportional hazards model.

Table I. *Distribution of patient and tumor characteristics.*

Characteristic	N patients	Proportion (%)
Age		
≤68 Years	48	52
≥69 Years	44	48
Gender		
Female	20	22
Male	72	78
ECOG-PS		
0-2	70	76
3	22	24
Pre-RT hemoglobin level		
<12 g/dl	40	43
≥12 g/dl	31	34
Unknown	21	23
Main tumor site		
Oropharynx	47	51
Hypopharynx	22	24
Larynx	11	12
Oral Cavity/FoM	12	13
T-stage		
T2-3	32	35
T4	60	65
N-stage		
N0-2b	41	45
N2c-3	51	55
M-stage		
M0	62	67
M1	28	30
Unknown	2	2
Histologic grade		
G1-2	50	54
G3	38	41
Unknown	4	4
p16-status		
Negative	66	72
Positive	13	14
Unknown	13	14
RT dose (EQD2)		
≤42.3 Gy	50	54
>42.3 Gy	42	46
RT completed		
No	34	37
Yes	58	63
Upfront surgery		
No	75	82
Yes	17	18
Systemic therapy		
No	64	70
Incomplete	16	17
Complete	12	13

ECOG-PS: Eastern Cooperative Oncology Group performance score, RT: radiotherapy, FoM: floor of mouth, EQD2: equivalent dose in 2 Gy-fractions.

Results

The median follow-up was 4 months (range=0-36 months) in the entire cohort and 8 months (2-36 months) in the patients who were alive at the last contact. Median survival in the entire cohort was 4 months. On univariate analysis, improved survival was significantly associated with hemoglobin levels prior to radiotherapy ≥12 g/dl (Figure 1, $p=0.003$), an EQD2 >42.3 Gy (Figure 2, $p=0.003$) and completion of radiotherapy as planned (Figure 3, $p<0.001$). In addition, trends were found for an ECOG-PS of 0-2 ($p=0.11$) and tumor site other than hypopharynx ($p=0.11$). The results of the complete univariate analyses are summarized in Table II.

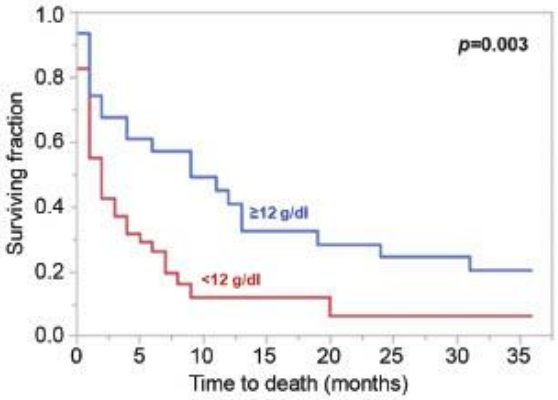

Figure 1. *Kaplan-Meier curves for survival comparing pre-radiotherapy hemoglobin levels of ≥12 g/dl to levels of <12 g/dl.*

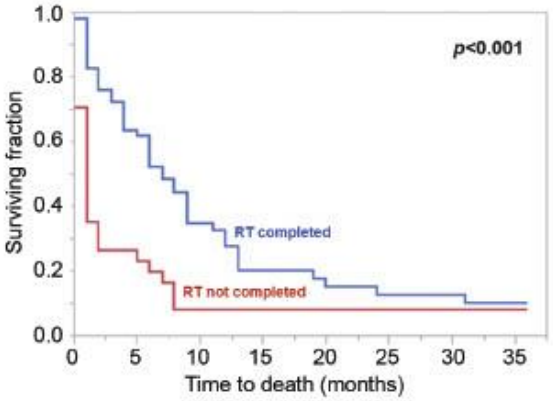

Figure 3. *Kaplan-Meier curves for survival comparing completion of radiotherapy (RT) as planned to non-completion of RT.*

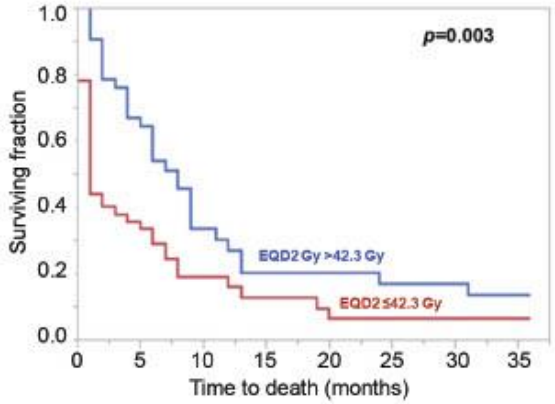

Figure 2. *Kaplan-Meier curves for survival comparing equivalent doses in 2 Gy-fractions (EQD2) of >42.3 Gy to doses ≤42.3 Gy.*

In the subsequent multivariate analysis, pre-radiotherapy hemoglobin levels remained significant [hazard ratio (HR)=1.92, 95% confidence interval (CI)=1.09-3.47, p=0.024]. Trends were found for EQD2 (HR=1.70, 95% CI=0.98-2.98, p=0.057) and completion of radiotherapy (HR=1.65, 95% CI=0.92-2.91, p=0.093).

Discussion

A considerable number of patients with advanced SCCHN are not candidates for an intensive multi-modality treatment and receive palliative radiotherapy alone. The survival prognoses of these patients vary considerably. In the review articles of Iqbal *et al.* and of Grewal *et al.*, median survival times ranged between 3 and 17 months (2, 3). Depending on the patients' remaining lifespan, different radiation programs are considered preferable. For patients with very limited prognoses, the treatment regimen should be short and associated with least possible stress for the patients. Patients with better survival prognoses may benefit from longer-course programs with lower doses per fraction and higher total doses in terms of less late toxicity and improved disease control. Thus, it is important to estimate a patient's expected survival duration as precisely as possible prior to assigning a personalized treatment. The knowledge of prognostic factors facilitates estimation of an individual patient's prognosis.

This study was performed to identify predictors of survival in a cohort of patients treated with palliative radiotherapy for advanced SCCHN. A better survival prognosis was significantly associated with pre-radiotherapy hemoglobin levels ≥12 g/dl, an EQD2 >42.3 Gy, and completion of the radiotherapy course as planned. In addition, trends were found for better a performance score and favorable tumor sites. The importance of pre-radiotherapy hemoglobin was already reported in studies of patients with SCCHN receiving curative treatment. In a retrospective study of 148 patients with SCCHN, pre-radiotherapy hemoglobin levels ≥12 g/dl were significantly associated with treatment outcomes on univariate analyses and with metastases-free survival in the multivariate analysis (p<0.001) (17). In another retrospective study of 153 patients receiving radio chemotherapy for stage IV SCCHN, improved loco-regional control (risk ratio=4.12, p<0.001) and survival (risk ratio=1.88, p=0.048) were significantly associated with pre-radiotherapy hemoglobin levels ≥12 g/dl in the multivariate analyses (6). Similar results were found in two additional retrospective studies of 275 and

Table II. *Univariate analyses of survival (p-values calculated with the log-rank test.*

Characteristic	At 6 months	At 12 months	*p*-Value
Age			
≤68 Years	41	24	0.72
≥69 Years	39	16	
Gender			
Female	42	17	0.83
Male	40	21	
ECOG-PS			
0-2	43	24	0.11
3	32	11	
Pre-RT hemoglobin level			
<12 g/dl	26	12	**0.003**
≥12 g/dl	57	41	
Main tumor site			
Oropharynx	48	25	0.11
Hypopharynx	23	7	
Larynx	44	22	
Oral Cavity/FoM	42	28	
T-stage			
T2-3	46	27	0.58
T4	38	18	
N-stage			
N0-2b	41	18	0.65
N2c-3	40	23	
M-stage			
M0	46	25	0.20
M1	29	10	
Histologic grade			
G1-2	43	18	0.69
G3	38	26	
p16-status			
Negative	37	20	0.24
Positive	68	23	
RT dose (EQD2)			
≤42.3 Gy	29	16	**0.003**
>42.3 Gy	54	27	
RT completed			
No	20	8	**<0.001**
Yes	52	28	
Upfront surgery			
No	41	21	0.76
Yes	39	24	
Systemic therapy			
No	39	20	0.65
Incomplete	38	13	
Complete	50	40	

ECOG-PS: Eastern Cooperative Oncology Group performance score, RT: radiotherapy, FoM: floor of mouth, EQD2: equivalent dose in 2 Gy-fractions. Significant *p*-values are given in bold.

225 patients, respectively, irradiated with curative intention for locally advanced SCCHN (18, 19). One possible explanation for these findings is that a lower hemoglobin level may be a surrogate marker for more advanced disease. A second reason could be the fact that reduced oxygen-carrier capacity in case of lower hemoglobin levels has a negative impact on tumor oxygenation. Oxygen is important for the efficacy of radiation therapy that widely depends on the induction of cytotoxic oxygen free radicals that go on to fragment tumor DNA (20, 21).

The impact of the radiation dose on the prognosis of patients receiving palliative radiotherapy for advanced SCCHN was also previously observed. Stevens *et al.* compared six dose-fractionation regimens in a retrospective cohort of 148 patients with head-and-neck cancer including SCCHN, adenoid-cystic carcinoma and undifferentiated carcinoma of the nasopharynx (22). The longest median survival was achieved with 70 Gy in 35 fractions (13 months) followed by 60 Gy in 25 or 30 fractions (8.9 and 8.5 months, respectively), 30 Gy in 10 fractions (5.9 months), 50 Gy in 20 fractions (5.7 months) and 24 Gy in 3 fractions (3.3 months). In another retrospective study of 110 patients with unresectable SCCHN, radiotherapy was administered with 2.5 Gy-fractions (23). Total doses >40 Gy were associated with significantly (p=0.012) better progression-free survival than doses of 40 Gy (EQD2=41.7 Gy). In a recent retrospective study of 106 patients with incurable head-and-neck cancer, median survival was significantly longer in patients receiving 36 Gy in 6 bi-weekly fractions (EQD2=48 Gy) than in patients receiving ≤30 Gy/EQD2≤40 Gy (median survival 26.4 *vs.* 9.5 months, p=0.01) (24). Moreover, in a prospective trial that was prematurely closed due to slow accrual after enrollment of 34 patients, 50 Gy in 16 fractions/4 fractions per week (EQD2=54.7 Gy) was associated with longer median survival than 36 Gy in 6 bi-weekly fractions (25). In contrast, a randomized trial of 90 patients did not find a significant difference between the three investigated radiation regimens (26). Patients received either 14.8 Gy in 4 fractions ("quad shot"; EQD2=21.5 Gy if there was no recovery of tumor cells between the two daily fractions), 50 Gy in 16 fractions (EQD2=54.7 Gy) or 20 Gy in 5 fractions (EQD2=23.3 Gy). Median survival times were 11.5, 10.5 and 11.0 months, respectively, and 1-year survival rates 40%, 37% and 33%, respectively. The importance of completion of the planned radiotherapy course for the survival prognosis has also been reported (23, 24, 27). Similar to the current study, completion of radiotherapy was associated with the administered radiation dose, since not completing the treatment results in a lower total dose.

In the present study, better ECOG-PS showed a trend toward improved survival. The data available so far regarding the impact of the performance status on survival of head-and-neck cancer patients receiving palliative radiotherapy are conflicting. In the retrospective study of Laursen *et al.* (n=77), an ECOG-PS of 0-2 (compared to 3-4) was associated with a significantly longer median survival (5.9 vs.1.5 months, p=0.007) (28). In addition, Lok *et al.* (n=75) found in their retrospective study that a Karnofsky performance score of ≥70

was an independent predictor of improved survival (p=0.001) (29). In contrast, ECOG-PS (0-1 *vs*. 2-3) showed no association with survival (p=0.85) in the retrospective study of Garcia-Anaya *et al*. (24). An association between favorable tumor site and improved survival was not reported in studies focusing on palliative radiotherapy of SCCHN but in a study investigating curative treatment for locally advanced tumors (30). Moreover, other studies of patients receiving curative treatment for SCCHN found associations between favorable tumor site and loco-regional control or metastases-free survival (31-33).

Thus, considering the results of the current study and of previous studies, patients with risk factors such as pre-radiotherapy hemoglobin levels of less than 12 g/dl, a poor performance status (ECOG-PS of ≥3) and cancer of the hypopharynx have comparably poor survival prognoses and appear candidates for short-course radiotherapy with higher doses per fraction or even a "quad shot" regimen. Compared to these patients, those patients with pre-radiotherapy hemoglobin levels of ≥12 g/dl, a more favorable performance status (ECOG-PS of 0-2) and cancer mainly located in the oropharynx, larynx or oral cavity/floor of mouth have better survival prognoses can be considered candidates for longer-course radiation with higher total doses and lower doses per fraction. However, the vast majority of the studies performed in patients receiving palliative irradiation for advanced SCCHN including the present study, were retrospective in nature. This aspect including the risk of hidden selection biases needs to be considered when interpreting the results of the available studies. Moreover, existing prospective studies were of limited size resulting in low statistical power.

In conclusion, prognostic factors for survival were identified that can facilitate treatment personalization. Patients with pre-radiotherapy anemia, a poor performance status and hypopharynx cancer appear to have comparably poor survival prognoses and may benefit from short-course radiotherapy, *e.g*. a "quad shot" regimen. Patients with normal pre-radiotherapy hemoglobin levels, a better performance status, and cancer at a favorable site may be candidates for longer-course radiotherapy with a higher EQD2, and lower doses per fraction. Moreover, the fact that a higher EQD2 and completion of radiotherapy were associated with improved survival demonstrates the importance of close monitoring and care of these patients during their treatment so they can complete radiotherapy. Larger prospective trials are required to better define the optimal treatment for patients with advanced SCCHN who are not candidates for curative treatment.

Conflicts of Interest

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

Authors' Contributions

The study was designed by all Authors. Data were collected by C.S. and J. R.-I. and analyzed by S.E.S. and D.R. The draft of the article was prepared by D.R. and S.E.S. and the final version approved by all Authors.

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A New Survival Score for Patients Scheduled for Palliative Irradiation of Locally Advanced Carcinoma of the Head-and-Neck

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Abstract. *Background/Aim: Patients with advanced squamous cell carcinoma of the head-and-neck (SCCHN) may be assigned to palliative irradiation. A survival score was developed for this group to support treatment personalization. Patients and Methods: Seventy-eight patients who received palliative irradiation for SCCHN and had complete data regarding performance score, pre-radiotherapy hemoglobin levels, and main tumor site were included in this retrospective study. Six-month survival rates of these factors were divided by 10 (factor scores) and added for each patient (total patient scores). Results: Total patient scores ranged between 8 and 15 points. Three groups were designed based on the 6-month survival rates, namely 8-9 (n=15), 11-13 (n=36), and 14-15 (n=27) points. Six-month survival rates were 13%, 28%, and 63%, and median survival times were 1, 2, and 11 months (p=0.001). Conclusion: A new survival score including three prognostic groups was developed. This new tool can help physicians when designing personalized treatments for patients with SCCHN scheduled for palliative irradiation.*

The majority of patients with squamous cell carcinoma of the head-and-neck (SCCHN) are candidates for a curative treatment approach including surgery and/or radio-(chemo)therapy (1, 2). However, a considerable number of patients are not suitable for such a treatment and are scheduled for palliative irradiation. This applies particularly to patients with metastatic disease, locally or loco-regionally very advanced tumors and to patients with significant co-morbidity, a poor performance status or old age (3, 4). For palliative irradiation, different dose-fractionation schedules are available including ultra-short regimens such as quad shot (14 Gy in 4 fractions over only 2 days), short-course regimens such as 20-24 Gy with daily fractions of 4.0 Gy given five times per week, intermediate-course regimens such as 36-39 Gy with daily fractions of 3.0 Gy, and long-course regimens such as 50-60 Gy with daily fractions of 2.0-2.5 Gy (1, 4, 5). The patient's survival prognosis should be considered when selecting a palliative dose-fractionation regimen for loco-regionally advanced SCCHN. If the prognosis is poor, the patient should not receive a time-consuming regimen but one which is able to relieve existing symptoms and does not take longer than necessary. Patients with longer expected survival can benefit from longer-course regimens in terms of longer disease control and lower probability of late toxicities. Therefore, survival scores are important because they allow estimating the patient's prognosis prior to radiation therapy. Such scores exist for irradiation of metastatic SCCHN (6, 7). The current study was performed to add a new survival score for patients with SCCHN scheduled for palliative local or loco-regional irradiation.

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Key Words: Survival score, palliative irradiation, carcinoma of the head-and-neck, personalized treatment.

Patients and Methods

Seventy-eight patients who were treated with palliative irradiation for advanced SCCHN between 2000 and 2020 and had complete data regarding Eastern Cooperative Oncology Group performance score (ECOG-PS), hemoglobin levels prior to radiotherapy, and primary tumor site were included in this retrospective study. These patients were previously analyzed in a study that investigated ten

pre-radiotherapy factors (age, gender, ECOG-PS, pre-radiotherapy hemoglobin level, primary tumor site and stage, nodal stage, distant metastasis, histologic grade, p16-status) and four treatment-related factors (radiation dose, completion of radiation therapy, upfront surgery, systemic treatment) for associations with survival (8). Of the ten pre-radiotherapy factors, pre-radiotherapy hemoglobin levels of ≥12 g/dl (*vs.* <12 g/dl) showed significant associations with better survival in both univariate and multivariate analyses. Moreover, trends toward better survival were found on univariate analyses for ECOG-PS 0-2 (*vs.* 3) and favorable tumor site (oropharynx, larynx or oral cavity/floor of mouth *vs.* hypopharynx). These three factors (Table I) were included in the survival score developed in the present study approved by the local Ethics Committee (University of Lübeck, 18-130A). In seven patients, additional data regarding pre-radiotherapy hemoglobin levels were collected.

Statistical analyses. The 6-month survival rates of the three factors, pre-radiotherapy hemoglobin level, ECOG-PS, and tumor site were divided by 10 to receive the factor scores (Table II). For each patient, the three factor scores were added to obtain the total patient score. Based on the total patient scores, prognostic groups were designed and compared for survival using the Kaplan–Meier method and the log-rank test. A p-value of <0.05 was regarded as indicating statistical significance. The software used for the statistical analyses was JMP Pro 14.1.0 (SAS Institute Inc., Cary, NC, USA).

Table I. *Distribution of the tree factors used for the survival score.*

Factor	N patients (%)
Eastern Cooperative Oncology Group performance score	
0-2	61 (78)
3	17 (22)
Pre-radiotherapy hemoglobin level	
<12 g/dl	45 (58)
≥12 g/dl	33 (42)
Main tumor site	
Oropharynx	42 (54)
Hypopharynx	18 (23)
Larynx	8 (10)
Oral cavity/Floor of mouth	10 (13)

Table II. *Six-month survival rates of the three prognostic factors (8) and the corresponding factor scores.*

Factor	6-months survival rate (%)	Factor score
Eastern Cooperative Oncology Group performance score		
0-2	43	4
3	32	3
Pre-radiotherapy hemoglobin level		
<12 g/dl	26	3
≥12 g/dl	57	6
Main tumor site		
Oropharynx	48	5
Hypopharynx	23	2
Larynx	44	4
Oral cavity/Floor of mouth	42	4

Results

The total patient scores ranged between 8 and 15 points. No patient had 10 points. The corresponding 6-month survival rates were 0% (0/3) for 8 points, 17% (2/12) for 9 points, 25% (4/16) for 11 points, 29% (5/17) for 12 points, 33% 81/3) for 13 points, 50% (5/10) for 14 points and 79% (12/17) for 15 points, respectively (Figure 1).

Three prognostic groups were designed based on these 6-month survival rates, namely 8-9 points (n=15), 11-13 points (n=36), and 14-15 points (n=27). The corresponding 6-month survival rates were 13%, 28%, and 63%, respectively, and the 12-month survival rates were 0%, 15%, and 37%, respectively (Figure 2, p=0.001). The median survival times were 1 month, 2 months, and 11 months, respectively.

Discussion

The concept of treatment personalization is important to achieve optimal individual outcomes for patients with advanced-stage SCCHN who are scheduled for palliative irradiation. Personalized treatment regimens should be based on several factors including the patient's survival prognosis. Therefore, it is desirable to be able to estimate an individual patient's remaining lifespan as precisely as possible before initiation of treatment. Such an estimation can be considerably facilitated with the availability of prognostic factors or, even better, prognostic scores. Survival scores for palliative irradiation of patients with SCCHN are already available for those with metastatic disease. In 2015, a survival score was developed for patients with brain metastases from SCCHN (6). This tool included three prognostic groups with 6-month survival rates of 0%, 50%, and 100%, respectively. In the same year, a survival score for patients with SCCHN and patients with metastatic spinal cord compression was reported (7). This score included four groups with 6-month survival rates of 0%, 27%, 71%, and 100%, respectively.

The present study was conducted to provide an additional survival score for patients with advanced SCCHN receiving local or loco-regional irradiation with palliative intent. The methodology used in this study was similar to the methodology of the two scores for metastatic SCCHN (6, 7). The new score developed in the current study is based on prognostic factors significantly associated with survival or at least showing a trend. It consists of three groups with significantly different 6-month survival rates.

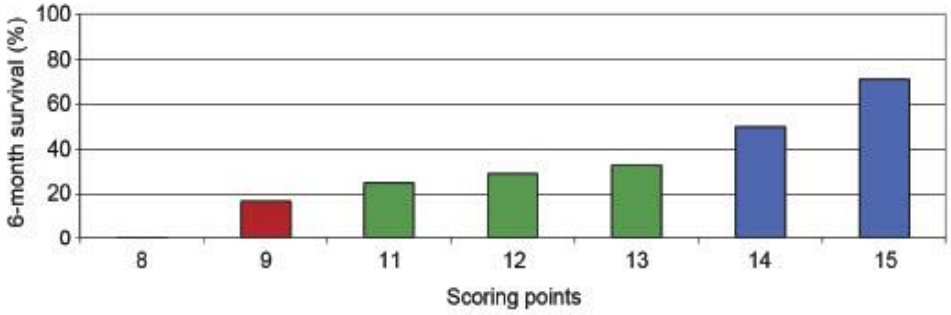

Figure 1. *Six-month survival rates of the total patient scores that ranged between 8 and 15 points.*

Patients achieving 8-9 points had the poorest survival prognoses with a 6-month survival rate of only 13% and a median survival time of only 1 month. These patients may be considered candidates for an ultra-short regimen such as quad shot or for best supportive care alone. Patients who achieved 11-13 points had better but still poor survival prognoses. The median survival time was only 2 months, and the 6-month survival rate was 28%. These patients appear good candidates for a short-course regimen with a total dose of 20-24 Gy (5×4.0 Gy per week) or an intermediate-course regimen with a dose of 36-39 Gy (5×3.0 Gy per week). Patients achieving 14-15 points had the most favorable survival prognoses with a 6-month survival rate of 63% and a median survival time of 11 months. For these patients, loco-regional control of their disease for a longer time is more important. Moreover, the majority of these patients will live long enough to experience late radiation-related toxicities. The risk of experiencing such toxicities increases with time. However, when applying this new score, one should be aware that it has been developed from retrospective data. Thus, a risk of a hidden selection bias exists. Moreover, two of the factors included in the scoring system were not significant but showed only a trend in the preceding study (8).

In summary, a new survival score including three prognostic groups with significantly different survival rates and median survival times was developed. This new tool can help physicians who wish to assign a personalized treatment to a patient with SCCHN scheduled for palliative irradiation.

Conflicts of Interest

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

Authors' Contributions

All Authors participated in the design of the study. C.S. collected the data that were analyzed by S.E.S. and D.R. The article drafted by D.R. and S.E.S. was reviewed and finally approved by all Authors.

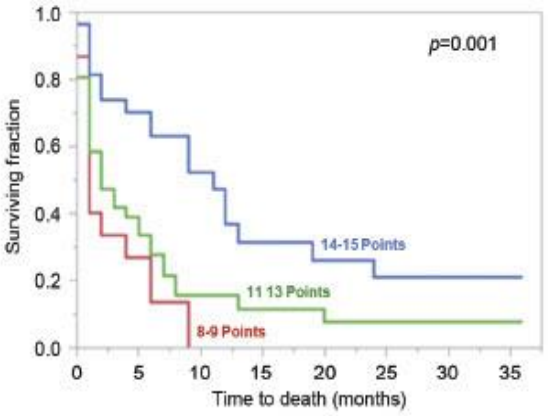

Figure 2. *Kaplan–Meier curves for survival of the three prognostic groups: 8-9 points, 11-13 points, and 14-15 points. The p-value was calculated using the log-rank test.*

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Karnofsky Performance Score – An Independent Prognostic Factor of Survival After Palliative Irradiation for Sino-nasal Cancer

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Abstract. *Background/Aim: Sino-nasal cancer is rare and often diagnosed at advanced stages. Some patients cannot receive curative treatment and are treated with palliative irradiation. We aimed to identify prognostic factors for survival to facilitate treatment personalization for this group. Patients and Methods: Twelve patients treated with palliative radiotherapy for locally advanced sino-nasal cancer were retrospectively analyzed for survival. Ten characteristics were evaluated including age, gender, Karnofsky performance score (KPS), pre-radiotherapy hemoglobin, tumor site, lymph node involvement, histology, equivalent dose in 2 Gy-fractions, completion of radiotherapy and concurrent chemotherapy. Results: On univariate analysis, KPS ≥70 ($p<0.001$) and completion of radiotherapy ($p<0.001$) were significantly associated with better survival. Chemotherapy showed a trend ($p=0.097$). In the multivariate analysis, KPS ≥70 was significant ($p=0.025$), and completion of radiotherapy showed a trend ($p=0.080$). Conclusion: KPS is an independent predictor of survival for palliative irradiation of sino-nasal cancer. Patients require close monitoring and care for side effects, since completion of radiotherapy is important for survival.*

Cancers of the nasal cavity and the paranasal sinuses (sino-nasal cancers) are very rare and account for only 3-5% of head-and-neck cancers and less than 0.5% of all types of cancer (1, 2). The most common site involved is the maxillary sinus (60-70%) followed by the nasal cavity (20-30%) and the ethmoid sinus (10-15%) (2). Tumors in the sphenoid and frontal sinuses account for only 1-2%. The most common type of histology is squamous cell carcinoma (SCC), which represents more than 80% of sino-nasal cancers (2). Sino-nasal cancers can by asymptomatic for a considerable time due to the airspace and the cavities in the corresponding regions (2).

The 5-year survival rates of patients with SCC of the paranasal sinuses were reported to be approximately 50%, 30% and 15% for local, loco-regional and metastatic disease, respectively (2, 3). For adeno-carcinomas, 5-year disease-specific survival rates of 78-95% and a 5-year survival rate of 95% were reported, and for adenoid-cystic carcinomas of the sino-nasal tract 5-year survival rates of 64-86% (4-7).

Locally advanced resectable tumors are generally treated with surgery followed by radiotherapy or (mainly cisplatin-based) chemoradiation (1). Treatment for unresectable tumors generally consists of definitive radiotherapy or chemoradiation. Recommended total radiation doses are 66-70 Gy (doses per fraction of 1.8-2.0 Gy) for definitive treatment and, depending on the extent of resection, 50-66 Gy for adjuvant treatment with at least 60 Gy to the residual tumor and lymph nodes with extracapsular spread (1, 8).

Some patients cannot tolerate high radiation doses, chemoradiation or surgery. This applies particularly to very elderly and frail patients. Moreover, in palliative cases, the major focus of the treatment lies on symptom control and prevention of complications rather than on prolongation of survival. Particularly patients in a palliative situation can benefit from treatment personalization. In patients with a very limited remaining lifespan, the treatment program should not be long or burdensome. These patients likely benefit from hypo-fractionated radiotherapy with doses per fraction mainly ranging between 2.5 and 4.0 Gy. For patients who are in a situation considered palliative but still have a comparably favorable survival prognosis, late radiation-related toxicity and longer-term control of their disease gain importance. Better disease control can be achieved with

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Key Words: Sino-nasal cancer, palliative radiotherapy, survival, performance score, personalized treatment.

higher total doses, and a reduction of late sequelae with the use of conventional doses per fraction (1-8-2.0 Gy).

These considerations demonstrate that it is important to be able to estimate a patient's survival prognosis prior to treatment. This study was performed to identify independent prognostic factors for survival in patients with locally advanced sino-nasal cancer who require palliative irradiation. These factors can assist physicians during the process of selecting the best personalized treatment for such a patient.

Patients and Methods

Twelve patients treated with palliative radiotherapy for locally advanced cancer of the nasal cavity or paranasal sinus between 2000 and 2019 were retrospectively analyzed for survival. The study was approved by the Ethics Committee of the University of Lübeck (reference 18-130A). Eleven patients had primary tumor stage T4, and one very elderly patient with a poor performance status had a T3-tumor plus lymph node involvement. Surgery was not performed in 10 patients, and two patients received debulking. Histologies included squamous cell carcinoma (SCC, n=7), adenocarcinoma (n=2), solid undifferentiated carcinoma (n=2), and adenoid-cystic carcinoma (n=1).

Nine patients completed their radiotherapy as planned with total doses ranging between 30 and 55 Gy and doses per fraction between 2.0 and 3.0 Gy. All patients who did not complete radiotherapy received total doses <20 Gy. The equivalent doses in 2 Gy-fractions (EQD2) with respect to tumor control (alpha/beta ratio=10 Gy) ranged between 2 Gy and 57.3 Gy. The EQD2 was ≤39.0 Gy in six patients and ≥41.7 Gy in the other six patients. Thus, the median EQD2 was 40.35 Gy. Three patients received concurrent chemotherapy with paclitaxel (20-25 mg/m^2/twice per week, n=2) or cisplatin (20 mg/m^2/d1-5, n=1).

Ten characteristics were evaluated for associations with survival, which was referenced from the start of palliative irradiation (Table I). Characteristics included age (≤76 *vs.* ≥79 years, no patient was 77 or 78 years of age), gender, Karnofsky performance score (KPS <70 *vs.* ≥70), pre-radiotherapy hemoglobin levels (<12 *vs.* ≥12 g/dl), tumor site (nasal cavity *vs.* paranasal sinus), lymph node involvement (no *vs.* yes), type of histology (SCC *vs.* other histology), EQD2 (≤39.0 *vs.* ≥41.7 Gy), completion of planned radiotherapy (no *vs.* yes) and concurrent chemotherapy (no *vs.* yes).

Univariate analyses were performed with the Kaplan–Meier method and supplemented by the log-rank test. Characteristics that achieved significance in the univariate analysis ($p<0.05$) or showed a trend ($p<0.10$) were additionally analyzed for independence in a multivariate analysis (Cox proportional hazards model).

Results

The median follow-up was 9 months (range=0-36 months) in the whole series and 18 months (range=9-36 months) in those three patients alive at the time of the last follow-up. The median survival time was 10.5 months. On univariate analysis, a KPS ≥70 (Figure 1, $p<0.001$) and completion of the planned radiotherapy ($p<0.001$) were significantly associated with better survival. In addition, concurrent chemotherapy showed a trend ($p=0.097$). The results of the entire univariate analyses are shown in Table II.

Table I. *Patient and tumor characteristics evaluated for associations with survival.*

Characteristic	No. of patients	Proportion (%)
Age		
≤76 Years	6	50
≥79 Years	6	50
Gender		
Female	5	42
Male	7	58
Karnofsky performance score		
<70	5	42
≥70	7	58
Pre-RT hemoglobin level		
<12 g/dl	4	33
≥12 g/dl	4	33
Unknown	4	33
Tumor site		
Nasal cavity	4	33
Paranasal sinus	8	67
Lymph node involvement		
No	7	58
Yes	5	42
Histology		
SCC	7	58
Other	5	42
RT dose (EQD2)		
≤39.0 Gy	6	50
≥41.7 Gy	6	50
Completion of RT		
No	3	25
Yes	9	75
Concurrent chemotherapy		
No	9	75
Yes	3	25

RT: Radiotherapy; SCC: squamous cell carcinoma; EQD2: equivalent dose in 2 Gy-fractions.

In the multivariate analysis, KPS ≥70 was significant ($p=0.025$), and completion of radiotherapy showed a trend ($p=0.080$). Administration of concurrent chemotherapy was not significant in the multivariate analyses ($p=0.39$).

Discussion

Some patients with locally advanced sino-nasal cancer cannot withstand multi-modality treatment and receive palliative radiotherapy. Several dose-fractionation regimens are available for palliative irradiation of sino-nasal cancer with overall treatment times ranging between a few days and several weeks. A challenge for the treating radiation oncologists is the selection of the optimal personalized regimen, which should always consider the individual's survival prognosis. If the prognosis is poor, the dose-

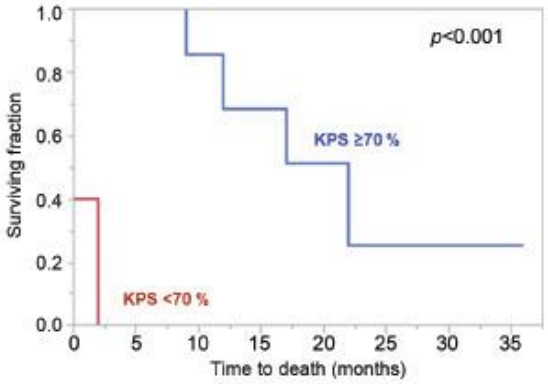

Figure 1. *Kaplan–Meier curves for survival comparing patients with a Karnofsky performance score (KPS) of ≥70% and patients with a KPS of <70%. The p-Value was obtained using the log-rank test.*

Table II. *Univariate analyses of survival (p-values obtained using the log-rank test).*

Characteristic	At 6 months	At 12 months	*p*-Value
Age			
≤76 Years	50	33	>0.99
≥79 Years	67	44	
Gender			
Female	80	53	0.71
Male	43	29	
Karnofsky performance score			
<70	0	0	**<0.001**
≥70	100	69	
Pre-RT hemoglobin level			
<12 g/dl	50	50	0.53
≥12 g/dl	100	75	
Tumor site			
Nasal cavity	75	38	0.73
Paranasal sinus	50	38	
Lymph node involvement			
No	57	38	0.69
Yes	60	40	
Histology			
SCC	43	43	0.54
Other	80	30	
RT dose (EQD2)			
≤39.0 Gy	50	33	0.20
≥41.7 Gy	67	50	
Completion of RT			
No	0	0	**<0.001**
Yes	78	53	
Concurrent chemotherapy			
No	44	30	0.097
Yes	100	67	
Entire cohort	58	40	

RT: Radiotherapy; SCC: squamous cell carcinoma; EQD2: equivalent dose in 2 Gy-fractions. Significant *p*-Values are given in bold.

fractionation regimen should be short, avoiding patients spending more time than necessary receiving palliative radiotherapy. In contrast, a patient with more favorable survival prognosis (despite a palliative situation) appears better treated with a radiation program including a higher EDD2 and conventional doses per fraction (1.8-2.0 Gy). To provide the best individual radiation treatment, it is important to be able to judge the patient's remaining lifetime. This process can be improved with the availability of significant (ideally independent) prognostic factors. However, very few studies have focused on the palliative treatment of advanced sino-nasal cancers. Farber *et al*. evaluated different palliative treatment approaches in 380 patients with a sino-nasal malignancy from a national cancer database and found that palliative surgery was associated with the best outcomes regarding 1-year and median survival when compared to other treatment modalities (9). However, most of the patients were younger than 70 years and more likely to tolerate surgery compared to the present study, where 67% of the patients were older than 70 years. Jang *et al*. reported a series of 42 patients treated with definitive radiotherapy or chemoradiation for T3-4 N0 SCC of the nasal cavity and maxillary sinus (10). Outcomes were poor for cancer of the maxillary sinus with a 5-year survival rate of 34% and a local control rate of 29%. The corresponding rates for patients with cancer of the nasal cavity were 50% and 52%, respectively. In an earlier study of Hoppe *et al*., which included 39 patients receiving radiotherapy (n=4) or chemoradiation (n=35) for unresectable carcinoma of paranasal sinus, the 5-year survival rate was only 15% (11). In both studies, a lower biologically effective radiation dose was the only factor significantly associated with worse survival (10, 11). Since the radiation dose was not a pre-treatment factor, it cannot support radiation oncologists when selecting the optimal dose-fractionation regimen for an individual patient. Moreover, the choice of doses given may have reflected the physician's bias to offer higher doses to healthier appearing patients.

The present study was performed to identify additional specific pre-treatment predictors of survival, for patients treated with palliative radiotherapy for advanced sino-nasal cancer. Improved survival was significantly associated with the pre-treatment factor KPS ≥70, and the treatment-related factor completion of the radiotherapy course. In addition, a trend toward better survival was found for concurrent chemotherapy. In the multivariate analysis, KPS maintained significance and is, therefore, an independent predictor of survival. This factor can guide physicians when choosing a personalized radiation regimen. Patients with a KPS <70

appear good candidates for a short-course program with a higher dose per fraction (hypo-fractionation) such as 6×4 Gy or even for best supportive care alone, since all patients died within 2 months. The survival of patients with a KPS ≥70 was much better, 67% of the patients survived for 1 year or longer. Therefore, these patients likely benefit from conventionally fractionated radiotherapy with higher total doses (60-70 Gy) in terms of better disease control and less late toxicity. Moreover, patients of the latter group should probably receive concurrent chemotherapy, which showed a trend toward better survival in the present study and led to improved local tumor control in a previous study of Choi *et al*. of 21 patients with locally advanced tumors of the paranasal sinus and the nasopharynx (12).

Another important finding of the present study is the fact that completion of the radiotherapy course is important for the patient's survival prognosis. This aspect has been previously reported for palliative radiotherapy for head-and-neck cancers in general. In the retrospective study of Gamez *et al*. (n=21), patients were planned to receive three cycles of an ultra-short regimen called "quad shot" that consisted of 2×3.7 Gy per day for 2 days, given every three weeks to a total of three cycles supplemented by carboplatin or cetuximab (13). A greater number of completed cycles was significantly associated with better survival (p=0.03). Moreover, in the retrospective study of Garcia-Anaya *et al*. (n=106), palliative radiotherapy was planned to be 30-36 Gy, given in 5-6 bi-weekly fractions of 6 Gy (14). Patients who received 30 Gy or less had a significantly worse median survival than patients who received more than 30 Gy (9.5 *vs*. 26.4 months, p=0.01). These data demonstrate that it is very important to provide close monitoring and supportive care for patients receiving palliative irradiation for malignant tumors in the head-and-neck region including sino-nasal cancers. This affords them a better opportunity of completing radiotherapy, which appears to improve survival.

When interpreting the findings of the present study (and of previous studies), one should be aware of the retrospective design, which always bears the risk of hidden selection biases. Prospective trials are needed. However, regarding the rarity of patients with sino-nasal cancers, in particular patients assigned to palliative irradiation, such trials are difficult to perform and not expected soon.

In conclusion, KPS proved to be an independent predictor of survival for patients who received palliative irradiation for sino-nasal cancer. Patients with a KPS <70 appear suitable candidates for a short course of radiotherapy or best supportive care alone, and patients with a KPS ≥70 appear to benefit from dose-fractionation regimens similar to those used for curative treatment probably combined with concurrent chemotherapy. Patients receiving palliative irradiation for sino-nasal cancer need close monitoring and optimal supportive care, since survival depends on the completion of the radiotherapy course as planned.

Conflicts of Interest

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

Authors' Contributions

The study was designed by all Authors. Data were collected by C.S. and analyzed by S.E.S. and D.R. The draft of the article was prepared by D.R. and S.E.S., and the final version was approved by all three Authors.

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Palliative Radiotherapy for Cutaneous Squamous Cell Carcinoma of the Head-and-Neck Region

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Abstract. *Background/Aim: Cutaneous squamous cell carcinoma (cSCC) is a common type of skin cancer. Options for palliative treatment include systemic agents and radiotherapy. Selection of a radiation regimen should consider the patient's survival prognosis. This study aimed to identify prognostic factors of survival after palliative radiotherapy for cSCC of the head-and-neck. Patients and Methods: Ten factors were analyzed for survival in 12 patients including age, gender, tumor site, histological grade, primary tumor stage, lymph node involvement, distant metastases, upfront surgery, radiation dose and completion of radiotherapy. Results: On univariate analysis, improved survival was significantly associated with lower histological grade (better differentiation) (p=0.022), no distant metastases (p=0.040) and completion of radiotherapy (p=0.014). In the multivariate analysis, lower histological grade (risk ratio=6.05, p=0.100) and completion of radiotherapy (risk ratio=4.87, p=0.115) showed trends. Conclusion: Predictors of survival were identified that can help design individual treatments. Patients require optimal supportive care as completion of radiotherapy was associated with better survival.*

Non-melanoma skin cancer is the most frequently diagnosed malignant disease (1-3). The most common of these tumors are basal cell carcinomas comprising 70-80% of cases (2, 3). Cutaneous squamous cell carcinomas (cSCC) represent the second most common type of non-melanoma skin cancer and account for 20% of these malignancies (2-4). Approximately 70-80% of cSCC occur in the head-and-neck region, and the incidence of these tumors is increasing (4-6).

The vast majority of cSCC can be cured with surgery and/or radiotherapy. Radiotherapy alone is generally used for unresectable lesions or if a patient is unsuitable for surgery due to significant co-morbidities, a poor performance status or very advanced age (2-4, 7). In most cases, radiotherapy alone is administered with curative intent, and longer-course programs are used. For radiotherapy alone (definitive treatment), total doses of 45-50 Gy with doses per fraction of 2.5 to 3.0 Gy are recommended for smaller lesions (<2 cm), and total doses of 60 to 66 Gy (2.0 Gy per fraction) or 50 to 60 Gy (2.5 Gy per fraction) for larger lesions according to the European interdisciplinary guideline on invasive cSCC (7). However, frail or very elderly patients may be unable to tolerate curative treatment and receive a shorter course of radiotherapy with higher doses per fraction (hypo-fractionation). This applies particularly to patients with locally advanced disease and loco-regional or distant metastases, who have worse prognoses than patients with early-stage disease (4, 8). In some patients with locally advanced or metastatic disease, the intent of treatment is palliative with a major focus on relief of symptoms and prevention of complications such as ulceration, bleeding and infiltration of adjacent structures. Several hypo-fractionated radiotherapy programs are available for palliative radiotherapy of cSCC ranging from single large fractions of 12-20 Gy to longer-course irradiation with 50 Gy in 15 fractions over 3 weeks (2, 9-11). Radiotherapy with a higher biologically effective dose (equivalent dose in 2-Gy fractions, EQD2) will likely lead to longer disease control but can be associated with significant acute toxicity.

Moreover, the risk of late radiation-related toxicity increases with the dose per fraction. Therefore, patients with a short survival appear appropriately treated with a short, little stressful treatment regimen. Whereas patients with a longer expected survival likely benefit from a longer-course regimen with a higher EQD2 and a lower dose per fraction (*e.g.* 2.0 Gy).

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Key Words: Cutaneous squamous cell carcinoma, head-and-neck region, palliative radiotherapy, survival, prognostic factors.

Thus, when assigning optimally personalized radiation to a patient requiring palliative radiotherapy for cSCC, it is important to be able to judge the patient's remaining lifetime precisely. Therefore, the major goal of the present study is the identification of prognostic factors for survival in patients receiving palliative radiotherapy for cSCC.

Patients and Methods

The data of 12 patients who received palliative radiotherapy for cSCC of the head-and-neck region between 2009 and 2019 were retrospectively evaluated. The study received approval from the Ethics Committee of the University of Lübeck (18-130A). Eleven patients (92%) were older than 76 years, and 5 patients (42%) were even older than 86 years. In three patients (33%) distant metastases were present at the time of palliative radiotherapy including bone metastases in two patients and lung metastases in one patient. Ten patients (83%) received upfront loco-regional resection, which was microscopically complete (R0) in four patients. Systemic treatment was not given.

Nine patients completed radiotherapy as planned. In these patients, the median total dose was 45 Gy (range=20 to 55 Gy), and the median dose per fraction 3.0 Gy (range=2.5 to 5.0 Gy). In the other three patients, median total dose and dose per fraction were 39 Gy (range=6-40 Gy) and 2.0 Gy (range=2.0 to 3.0 Gy), respectively. In the entire cohort, the equivalent doses in 2 Gy-fractions (EQD2, alpha/beta ratio=10 Gy for tumor control) ranged between 6.0 and 57.3 Gy (median EQD2=42.25 Gy).

A total of 10 potential prognostic factors were analyzed with respect to survival, which was calculated from administration of the first radiation fraction. Investigated factors included age (<80 *vs.* ≥80 years, median age=79.5 years), gender (female *vs.* male), main tumor site (cheek *vs.* ear *vs.* forehead or temple), histological grade (G1-2 *vs.* G3), primary tumor stage (T1-3 *vs.* T4), lymph node involvement (no *vs.* yes), distant metastases (no *vs.* other histology), upfront surgery (no *vs.* yes), EQD2 (≤42.25.0 *vs.* >42.25 Gy) and completion of radiotherapy as planned (no *vs.* yes). The distributions of these factors are shown in Table I.

For univariate analyses, the Kaplan-Meier method and the log-rank test were used. Those factors that were significant on univariate analysis ($p<0.05$) or showed a trend ($p<0.10$) were additionally included in a Cox regression model (multivariate analysis). In the multivariate analysis, p-values <0.05 were considered significant and p-values <0.12 indicating a trend.

Table I. *Potential prognostic factors that were analyzed with respect to survival.*

Factor	N patients	Proportion (%)
Age		
<80 Years	6	50
≥80 Years	6	50
Gender		
Female	6	50
Male	6	50
Tumor site		
Cheek	5	42
Ear	3	25
Forehead/Temple	4	33
Histological grade		
G1-2	10	83
G3	2	17
Primary tumor stage		
T1-3	7	58
T4	5	42
Lymph node involvement		
No	6	50
Yes	6	50
Distant metastases		
No	9	75
Yes	3	25
Upfront resection		
No	2	17
Yes	10	83
RT dose (EQD2)		
≤42.25 Gy	7	58
>42.25 Gy	5	42
Completion of RT		
No	3	25
Yes	9	75

RT: Radiotherapy, EQD2: equivalent dose in 2 Gy-fractions.

Results

In the entire cohort, the median follow-up period was 3.5 months (range=1 to 21 months). In the four patients who were alive at the last contact, median follow-up period was 5.5 months. On univariate analysis, improved survival was significantly associated with a lower histological grade (G1-2) ($p=0.022$), absence of distant metastases ($p=0.040$), and completion of radiotherapy as planned (Figure 1, $p=0.014$). The results of the univariate analyses are summarized in Table II. Of the six patients with lymph node involvement, two patients had extracapsular spread of the lymph node metastasis. The 3-months survival rates were 25% without and 50% with extracapsular spread, respectively ($p=0.78$, log-rank test).

In the multivariate analysis, lower histological grade (risk ratio=6.05, 95% CI=0.68 to 58.84, $p=0.100$) and completion of radiotherapy (risk ratio=4.87, 95% CI=0.65 to 42.55, $p=0.115$) showed trends; absence of distant metastases was not significant (risk ratio=1.36, 95% CI=0.17 to 9.55, $p=0.75$).

Discussion

Non-melanoma skin cancer represents the most common malignancy worldwide (1-3). Approximately 20% of these tumors are cSCC. Most lesions are detected at an early stage and successfully treated with resection plus/minus adjuvant radiotherapy or radiotherapy alone. However, patients with locally advanced or metastatic disease have worse prognoses. Considerable research has been performed in recent years to better understand the pathophysiology of cSCC and improve treatment (12-14).

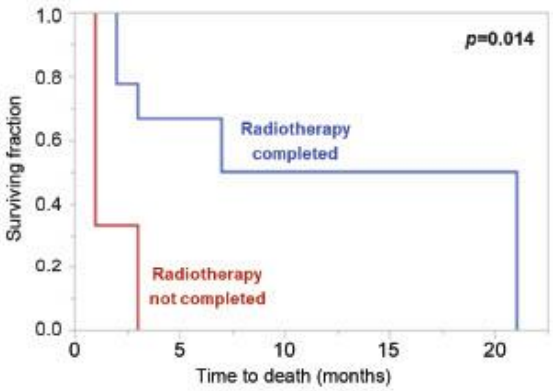

Figure 1. *Kaplan-Meier curves for survival comparing patients in whom radiotherapy was completed as planned ti those patienst in whom radiotherapy was not completed. The p-value was calculated with the log-rank test.*

Table II. *Univariate analyses of survival (p-values from the log-rank test).*

Characteristic	At 3 Months	At 6 Months	At 12 Months	*p*-Value
Age				
<80 Years	33	n.a.	n.a.	0.20
≥80 Years	67	67	50	
Gender				
Female	67	67	50	0.27
Male	33	n.a.	n.a.	
Tumor site				
Cheek	60	60	n.a.	0.92
Ear	33	n.a.	n.a.	
Forehead/Temple	50	50	50	
Histological grade				
G1-2	60	60	45	**0.022**
G3	0	0	0	
Primary tumor stage				
T1-3	57	57	38	0.76
T4	40	40	40	
Lymph node involvement				
No	67	67	50	0.39
Yes	33	n.a.	n.a.	
Distant metastases				
No	67	67	50	**0.040**
Yes	0	0	0	
Upfront resection				
No	100	100	100	0.15
Yes	40	40	27	
RT dose (EQD2)				
≤42.25 Gy	43	43	43	0.95
>42.25 Gy	60	60	30	
Completion of RT				
No	0	0	0	**0.014**
Yes	67	67	50	
Entire cohort	50	50	38	

RT: Radiotherapy, EQD2: Equivalent dose in 2 Gy-fractions, n.a.: Not available. Significant *p*-values are given in bold.

Unresectable lesions are generally treated with curative radiotherapy alone, which includes high total and biologically effective doses and generally takes several weeks. However, some patients, particularly if they are very old or frail, cannot tolerate longer-course radiation programs with high doses and receive shorter-course hypo-fractionated irradiation instead. Moreover, hypo-fractionated regimens are also used to treat patients with locally advanced or metastatic disease. For a considerable number of these patients, the intent is palliative. For palliative radiotherapy of cSCC, several dose-fractionation regimens have been used ranging from single-fraction treatment to multi-fraction regimens lasting three weeks or longer.

When aiming to tailor the radiation treatment to a patient's individual situation, several aspects need to be considered such as the patient's treatment preferences, social situation, travel distance to radiotherapy, age, co-morbidity, and performance status. Another important aspect is the patient's remaining lifespan. If this is very short, the radiation program should be less stressful and time consuming. Considering the limited prognosis, the patients should spend as little as possible of their short remaining lifetime receiving treatment for their cSCC. On the other hand, if the survival prognosis is comparably favorable, longer-term disease control and prevention of late radiation toxicities become more important, and the patients could benefit from a course of radiotherapy with higher total and biologically effective doses but lower dose per fraction. Thus, it is important to accurately estimate an individual patient's survival prognosis prior to assigning a personalized treatment regimen. To facilitate the decision-making process, prognostic factors would be helpful. The present study aimed to identify such factors in a cohort of patients with cSCC treated with definitive or adjuvant palliative radiotherapy.

Until now, very few studies have been performed particularly in patients receiving palliative radiotherapy for locally advanced and metastatic cSCC. In 2003, Veness and Richards stated in their review article that large uncurable lesions often painful and complicated by bleeding and superinfection can be treated with single-fraction radiotherapy using high doses of 12-20 Gy (11). These large fractions were well tolerated and associated with little acute toxicity. For elderly patients with moderate co-morbidity and a good performance status, dose-fractionation regimens of 35 Gy in 5-7 fractions and 40 Gy in 10 fractions were considered appropriate (11). In 2010, Barnes *et al*. presented a retrospective study of 28 patients who received a total of 31 courses of palliative irradiation with 8 Gy for basal cell

carcinoma (five courses) or cSCC (26 courses) (9). After a median follow-up of 17 weeks, the overall response rate was 58.1%, and relief of cSCC-related symptoms was achieved in 61.3% of the cases. Severe late toxicity was not observed. In addition to palliative treatment, short-course hypofractionated radiotherapy was found effective in elderly patients. In 2015, Ferro *et al.* reported a phase II study of 31 patients with early-stage non-melanoma skin cancer, of whom 14 patients were 80 years or older (10). Patients were treated with 30 Gy in 5 fractions over six consecutive days. Thirty patients experienced a complete response after a median follow-up period of 30 months, and the 2-year actuarial local control rate was 93.2%. Late toxicities did not exceed grade 1, and cosmetic outcomes were mainly good or excellent (10). In a systematic review of Gunaratne and Veness, total doses of 30-40 Gy with 1-3 fractions of 5-7 Gy per week resulted in excellent local control and tolerable toxicity (15). In 2018, Fogarty *et al.* presented a split-course regimen, which consisted of 5×5 Gy over one week followed by an 8-week break and another course of 5×5 Gy if complete response was not yet achieved (16). Fourteen patients with a total of 22 lesions (15 cSCC, 5 basal cell carcinomas, 2 melanomas) were treated with this regimen. Overall response at 2 months after completion of the second course of 5×5 Gy was 100%, and toxicity was acceptable.

Considering the range of available regimens of hypofractionated radiotherapy for elderly patients with cSCC or for palliative treatment of advanced cSCC, one challenge for the treating physicians is the selection of the optimal regimen for an individual patient. As mentioned above, personalized treatment concepts should consider the patient's survival prognosis, which can be estimated with the help of pre-treatment prognostic factors. In the present study, lower histological grade (better differentiation of the tumor) and absence of distant metastasis were significantly associated with improved survival on univariate analyses. Moreover, a trend was observed for the histological grade in the multivariate analysis. The predictive value of the differentiation of the tumor for treatment outcomes and the patients' prognoses was previously described in several studies and review articles (5, 6, 8, 17-19). These previous results demonstrate consistency of the findings of the present study. The prognostic role of distant metastases was not explicitly described before, most likely because this is rare in patients with cSCC. However, advanced primary and nodal stage were previously reported to have a negative impact on the patients' prognoses (4, 6, 18, 20-23). Another factor associated with worse prognoses is extracapsular spread of lymph node metastasis, which was reported in several studies and review articles (6, 20, 22-25). In the present study, extracapsular spread showed no significant association with survival. However, this was most likely due to the small numbers of patients with lymph node involvement (n=6) and patients with extracapsular spread of the lymph node metastasis (n=2). Considering the findings of the present study and the data from the literature, patients with risk factors such as high-grade (G3) cSCC, presence of distant metastasis and extracapsular spread of lymph node metastasis have comparably poor prognoses and appear candidates for a short course of radiotherapy. On the contrary, patients with low or intermediate grade (G1-2) tumors without distant metastasis and without extracapsular spread of lymph node metastasis have more favorable prognoses and appear better treated with longer-course radiation programs including higher total and biologically effective doses and lower doses per fraction. However, when considering to follow these recommendations, the small sample size and the retrospective design of the present study, similar to most reported studies, are significant limitations. Moreover, histological grade and distant metastases were not significant in the multivariate analysis and, therefore, not independent predictors of survival. Considering the limitations of this study, there is a risk of misjudgment of a patient's remaining lifespan. This may lead to over- or undertreatment with respect to the patient's well-being or survival. Larger studies, for example pooled analyses, are required to predict a patient's survival prognosis more properly and to provide optimal personalized treatment.

In addition to the two pre-treatment factors, lower histological grade and absence of distant metastasis, completion of the radiotherapy as planned was significantly associated with better survival on univariate analysis and showed a trend in the multivariate analysis. This importance of the completion of the radiotherapy course for survival aspect was previously reported for palliative irradiation of non-cutaneous head-and-neck cancer (26). Thus, close monitoring and optimal supportive care during radiotherapy is important for patients receiving palliative irradiation for advanced cSCC.

In summary, prognostic factors of survival were identified that can help physicians when choosing individual treatment regimens for patients with advanced cSCC who require palliation. For these patients, optimal care during the course of radiotherapy is crucial, since completion of radiotherapy as planned was associated with better survival.

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 were collected by C.S. and analyzed by S.E.S. and D.R. The article was written and approved by all Authors.

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A Tool to Predict the Probability of Intracerebral Recurrence or New Cerebral Metastases After Whole-brain Irradiation in Patients with Head-and-Neck Cancer

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Abstract. *Background/Aim: Patients with metastatic head-and-neck cancer require individual therapies facilitated by prognostic tools. A tool to estimate the risk of recurrent or new cerebral metastases following whole-brain irradiation (WBI) is presented. Patients and Methods: Age, gender, performance status, cancer site, number of cerebral lesions, extracerebral metastases, and time between cancer diagnosis and treatment of cerebral metastases were evaluated for intracerebral control in 23 patients. For characteristics showing a trend ($p<0.07$), points for these characteristics were created by dividing 6-month intracerebral control rates by 10. Patient scores were obtained by adding these points. Results: Better intracerebral control was significantly associated with oropharyngeal and laryngeal cancer ($p=0.014$). Absence of extra-cerebral metastases ($p=0.069$) and longer time between cancer diagnosis and treatment of cerebral metastases ($p=0.053$) showed trends. Three groups were identified, namely with 3-11, 13-18 and 20-24 points. Six-month intracerebral control rates were 0%, 50% and 100% ($p=0.003$), respectively, for these groups. Conclusion: A new tool was created to predict intracerebral control following WBI and should contribute to personalization of treatment for patients with cerebral metastases of head-and-neck cancer.*

Patients with cerebral metastases from head-and-neck cancer generally have poor prognoses (1). Many systemic anticancer drugs pass through the blood–brain barrier poorly and are not as effective for brain metastases (2-4). Thus, radiotherapy is the most common treatment modality for cerebral metastases from head-and-neck cancer. Radiotherapy options include local techniques, such as radiosurgery and fractionated stereotactic radiotherapy (5). However, local techniques are reasonable in patients with a limited number of cerebral lesions (5-8). Therefore, the most frequently administered type of radiotherapy in patients with metastases from head-and-neck cancer is whole-brain irradiation (WBI) (5). WBI may be combined with local radiotherapy or upfront neurosurgical resection in selected cases, particularly in patients with very few lesions (9, 10). For WBI, a variety of dose-fractionation regimens are in use worldwide, also depending on national preferences and standards (5). Usually these regimens are administered with one fraction per day and five fractions per week. They include shorter programs that take one week (*e.g.* 5×4 Gy) and longer programs that take up to four weeks (*e.g.* 10×3 Gy and 20×2 Gy) (11, 12). When aiming to select for the optimal WBI program for an individual patient, many factors should be considered, including the patient's social situation, distance to the Radiation Oncology Department, personal treatment preferences, and the patient's remaining lifespan. A prognostic score to estimate the survival prognosis of patients irradiated for cerebral metastases from head-and-neck cancer is already available (13). Previous studies suggested that patients with a very limited prognosis are better candidates for a less time-consuming shorter WBI program, whereas those with a very favorable survival prognosis can benefit from longer programs with lower doses per fraction, in terms of better survival and fewer neurocognitive deficits (11, 14-16). However, the appropriate regimen for patients with an intermediate survival prognosis is often unclear. For these patients, another aspect becomes more important, namely the ability of WBI to provide long-term intracerebral control, *i.e.* freedom from new and progression of treated cerebral metastases. The biologically-

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effective dose, which can be given as equivalent dose in 2-Gy-fractions (EQD2), of a WBI program depends on both total dose and dose per fraction (17). In general, longer WBI programs are associated with higher EQD2. For example, the EQD2 of 5×4 Gy, 10×3 Gy and 20×2 Gy are 23.3 Gy, 32.5 Gy and 40.0 Gy, respectively. In radiation oncology, a higher EQD2 generally means a greater efficacy with respect to tumor cell kill and local (intracerebral) control, which has been described for the treatment of primary head-and-neck cancer and for cerebral metastases from other solid tumors (18-23). However, a higher EQD2 often also means a higher risk of radiation-related toxicities. Prior to radiotherapy, it would be advantageous to identify those patients with cerebral metastases from head-and-neck cancer and an intermediate survival prognosis who may benefit from WBI with a higher EQD2 with respect to long-term intracerebral control. The present study aimed to provide a prognostic tool to do so by predicting the risk of developing recurrent or new cerebral metastases following WBI in patients with cerebral metastases from head-and-neck cancer.

Patients and Methods

Twenty-three patients who had received WBI alone (n=19), WBI with upfront resection or WBI with boost with upfront resection for cerebral metastases from head-and-neck cancer between 1995 and 2015 were included in this retrospective study. Dose-fractionation of WBI regimens included 5×4 Gy in 1 week (n=4), 10×3 Gy in 2 weeks (n=11) and longer-course regimens with doses >30 Gy given over 3-4 weeks (n=8). Seven pre-treatment characteristics were evaluated with respect to intracerebral control. Intracerebral control was defined as lack of progression of treated lesions and freedom from new cerebral metastases. These characteristics included age (≤64 *vs.* ≥65 years, median age: 65 years), gender, Eastern Cooperative Oncology Group (ECOG) performance score (0-1 *vs.* 2-3, median performance score: 2), site of origin of head-and-neck cancer (nasopharynx *vs.* oropharynx *vs.* larynx *vs.* other sites), number of cerebral lesions (1-2 *vs.* ≥3, median: 3 lesions), extra-cerebral metastases (no *vs.* yes) and time between diagnosis of head-and-neck cancer and treatment of cerebral metastases (≤24 *vs.* >24 months, median time: 24 months). Distributions of the characteristics are shown in Table I. For statistical analyses, the Kaplan–Meier method and log-rank test were used (24). Those characteristics that showed significance ($p<0.05$) or a trend ($p<0.07$) with respect to intracerebral control were used to design the prognostic tool. For each of these characteristics, a separate score was created by dividing the 6-month intracerebral control rate (as a percentage) by 10. The prognostic score for each patient was then obtained by summing the scores for each characteristic.

Results

Better intracerebral control was significantly associated with oropharyngeal and laryngeal cancer ($p=0.014$). In addition, absence of extra-cerebral metastases ($p=0.069$) and longer time (*i.e.* >24 months) between diagnosis of head-and-neck cancer and treatment of cerebral metastases ($p=0.053$) showed trends for better intracerebral control (Table II). These three characteristics were used to design the prognostic tool to estimate the 6-month probability of intracerebral control, as described in the Patients and Methods section (Table III). The prognostic scores for individual patients ranged between 3 and 24 points and were 3, 7, 10, 11, 13, 14, 15, 17, 18, 20, 22 or 24 points, respectively. Based on these scores, three prognostic groups were formed, namely 3-11 points, 13-18 points and 20-24 points. The 6-month intracerebral control rates were 0% (median control of 4 months), 50% (median control of 9.5 months) and 100% (median control not reached), respectively ($p=0.003$).

Table I. *Distribution of patient characteristics.*

	Number of patients (%)
Age at the time of treament	
≤64 Years	11 (48)
≥65 Years	12 (52)
Gender	
Female	5 (22)
Male	18 (78)
ECOG performance score	
0-1	11 (48)
2-3	12 (52)
Site of primary tumor	
Nasopharynx	2 (9)
Oropharynx	5 (22)
Larynx	8 (35)
Other	8 (35)
Number of cerebral lesions	
1-2	10 (43)
≥3	13 (57)
Extracerebral metastases	
No	11 (48)
Yes	12 (52)
Time between cancer diagnosis and treatment of cerebral metastases	
≤24 Months	12 (52)
>24 Months	11 (48)

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group.

Discussion

The primary treatment of locally advanced head-and-neck cancer can be improved due to modern radiotherapeutic approaches and combination with chemotherapy and immunotherapy (25-27). Therefore, more patients live longer, which generally translates into an increased risk of experiencing metastatic disease correlating with a patient's lifespan. Patients presenting with cerebral metastases of head-and-neck cancer are still rare and account for only about 1% of patients with metastatic disease affecting the brain (1).

Table II. *Intracerebral control rates 6 months following whole-brain irradiation.*

	Intracerebral control at 6 months (%)	*p*-Value
Age at time of treament		
≤64 Years	53	
≥65 Years	48	0.676
Gender		
Female	56	
Male	51	0.796
ECOG performance score		
0-1	69	
2-3	26	0.093
Site of primary tumor		
Nasopharynx	0	
Oropharynx	100	
Larynx	80	
Other	0	**0.014**
Number of cerebral lesions		
1-2	45	
≥3	67	0.878
Extracerebral metastases		
No	74	
Yes	0	0.069
Time between cancer diagnosis and treatment of cerebral metastases		
≤24 months	29	
>24 months	67	0.053

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group. Significant *p*-values are shown in bold type.

Table III. *Points assigned for the characteristics included in the prognostic tool derived by dividing the percentage 6-month intracerebral control rate by 10.*

Characteristic	Intracerebral control at 6 months (%)	Points
Site of primary tumor		
Nasopharynx	0	0
Oropharynx	100	10
Larynx	80	8
Other	0	0
Extra-cerebral metastases		
No	74	7
Yes	0	0
Time between cancer diagnosis and treatment of cerebral metastases		
≤24 Months	29	3
>24 Months	67	7

The prognoses of these patients require improvement that may be achieved with individualized treatment approaches. For patients assigned to receiving WBI for their cerebral metastases, individualization would include the selection of the appropriate dose-fractionation schedule. In a previous study, an instrument was presented that can help predict the survival times of individual patients with cerebral metastases from head-and-neck cancer (13). That scoring instrument was based on performance status, and number of cerebral lesions and extracranial metastases, and included three prognostic groups with 6-month survival rates of 0% (0-1 point), 50% (2 points) and 100% (3 points). In a larger retrospective study of 442 patients with cerebral metastases from different solid tumors and mainly poor survival prognoses, 5×4Gy in 1 week was not inferior to 10×3 Gy in 2 weeks regarding intracerebral control (p=0.07), survival (p=0.29) and acute toxicity; 5×4 Gy was recommended particularly for patients with a poor survival prognosis (11). This would apply to the 0-1 point group by the survival score previously created for patients with cerebral metastases form head-and-neck cancer (13). On the other hand, patients with a very favorable survival prognosis were reported to benefit from longer-course WBI programs with lower doses per fraction in terms of improved intracerebral control and survival with fewer neurocognitive deficits (14-16). Therefore, patients of the group with 3 points by the previously created survival score would appear to be good candidates for a longer-course WBI program (13). However, for patients of the intermediate group (2 points) by that survival score, the optimal WBI program is more difficult to select. To make an appropriate treatment decision, additional information would be required including the risk of an intracerebral failure.

Therefore, in the present study, an additional prognostic tool was developed that allows estimation of the intracerebral control rates at 6 months following WBI. Based on three pre-treatment characteristics, namely site of origin of head-and-neck cancer, extracerebral metastases and time between diagnosis of head-and-neck cancer and treatment of cerebral metastases, three groups were identified with significantly different 6-month intracerebral control probabilities. These rates were 0% for 3-11 points, 50% for 13-18 points and 100% for 20-24 points, respectively. Because a higher dose of WBI can be expected to result in more efficient tumor-cell kill, patients of the group with 3-11 points and the 13-18 points with an intermediate survival prognosis may benefit from longer-course WBI programs with a higher EQD2 in order to achieve a better 6-month intracerebral control. In conclusion, a new tool was created that can help predict the intracerebral control probability 6 months following WBI and can, therefore, contribute to the personalization of the treatment for patients with cerebral metastases from head-and-neck cancer.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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Predicting the Ambulatory Status of Patients Irradiated for Metastatic Spinal Cord Compression (MSCC) from Head-and-neck Cancer

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Abstract. *Background/Aim: Personalized cancer care can improve patient outcomes and is facilitated by scoring systems. This study aimed to create an instrument to estimate ambulatory status after radiotherapy for metastatic spinal cord compression (MSCC) from head-and-neck cancer. Patients and Methods: In 60 patients, fractionation regimen plus 10 pre-treatment factors were analyzed for post-treatment ambulatory status. Significant factors were used for the scoring system by dividing the ambulatory rate (in %) by 10. Patients' scores were received by adding the factor scores. Results: Time developing motor deficits >7 days (p=0.011), being ambulatory prior to radiotherapy (p<0.001) and ECOG performance score 1-2 (p<0.001) showed significant associations with post-treatment ambulatory status. Patients' scores were 7, 12, 15, 20, 22 and 27 points. Three groups were designed (7-12, 15-20 and 22-27 points) with post-treatment ambulatory rates of 11%, 62% and 96% (p<0.001). Conclusion: This scoring system helps predict ambulatory status after radiotherapy for MSCC from head-and-neck cancer.*

Metastatic spinal cord compression (MSCC) is generally associated with neurologic dysfunction mainly with motor deficits (1, 2). For these patients, maintaining or regaining the ability to walk, either with or without aid, is a very important endpoint. This may be achieved with radiotherapy alone, which still is the most frequent treatment for MSCC (3-5). In case of inadequate response to radiotherapy patients may not be able to walk after treatment and might have done better with upfront decompressive surgery plus stabilization (6, 7). However, upfront surgery has been reported to be associated with severe complications in more than 10% of the patients and is generally reserved for selected patients with a good performance status and a relatively favorable survival prognosis (6-8). In order to assign the most appropriate treatment protocol to a patient with MSCC, it would be helpful to be able to estimate the patient's ambulatory status following radiotherapy alone. Since MSCC is considered an oncologic emergency and, therefore, treatment decisions have to be made fast, a simple scoring system would be of great value for clinicians that helps predict post-treatment ambulatory status following radiotherapy alone (1, 2).

It has been previously stated that it is reasonable to identify predictive factors and develop scoring systems specifically for single tumor entities associated with MSCC due to differences, for example, with respect to tumor biologies, patterns of metastatic spread and survival prognoses (9-15). Therefore, the present study aims to create a scoring system that supports clinicians to estimate the post-treatment ambulatory status of patients irradiated for MSCC, particularly for those patients with MSCC from head-and-neck cancer.

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Key Words: Metastatic spinal cord compression, head-and-neck cancer, radiotherapy, post-treatment ambulatory status, scoring system.

Patients and Methods

Sixty patients who had been treated with radiotherapy alone for motor deficits due to MSCC from head-and-neck cancer between 1997 and 2015 were retrospectively evaluated for ambulatory status at 1 month following irradiation. The fractionation regimen (short-course radiotherapy (1×8 Gy or 5×4 Gy) *vs.* 10×3 Gy *vs.* longer-course radiotherapy with total doses >30 Gy (15×2.5 Gy or 20×2 Gy)) plus 10 pre-treatment factors were analyzed. The pre-treatment factors included age (≤59 years *vs.* ≥60 years, median 59 years), interval between first diagnosis of head-and-neck cancer and radiotherapy of MSCC (≤15 months *vs.* >15 months (4, 16)), visceral metastasis (no *vs.* yes), other bone metastasis (no *vs.* yes), cancer site (nasopharynx *vs.* oropharynx *vs.* hypopharynx *vs.* larynx *vs.* other

sites), gender, time developing motor deficits (1-7 days *vs.* >7 days (17)), ambulatory status prior to radiotherapy (not ambulatory *vs.* ambulatory), number of vertebrae affected by MSCC, (1-2 *vs.* ≥3, median 3), and performance score according to the Eastern Cooperative Oncology Group (ECOG) (1-2 *vs.* 3-4, median 3). Distributions of all 11 factors are summarized in Table I.

The statistical analyses regarding the post-treatment ambulatory status were performed with the Chi-square test. Factors that achieved significance ($p<0.05$) were used for the scoring system developed to estimate the probability of being ambulatory at 1 month following irradiation. For each significant factor, a factor score was calculated by dividing the ambulatory rate in percent by 10. The individual score for each patient was received by adding the factor scores.

Table I. *Distributions of the evaluated factors.*

	Number of patients (%)
Age at the time of irradiation	
≤59 years	33 (55)
≥60 years	27 (45)
Interval between cancer diagnosis and radiotherapy of MSCC	
≤15 months	25 (42)
>15 months	35 (58)
Visceral metastasis	
No	31 (52)
Yes	29 (48)
Other bone metastasis	
No	27 (45)
Yes	33 (55)
Cancer site	
Nasopharynx	8 (13)
Oropharynx	16 (27)
Hypopharynx	9 (15)
Larynx	11 (18)
Other sites	16 (27)
Gender	
Female	9 (15)
Male	51 (85)
Time developing motor deficits	
1-7 days	21 (35)
>7 days	39 (65)
Pre-treatment ambulatory status	
Not ambulatory	19 (32)
Ambulatory	41 (68)
Number of affected vertebrae	
1-2	28 (47)
≥3	32 (53)
ECOG performance score	
1-2	28 (47)
3-4	32 (53)
Fractionation regimen	
Short-course radiotherapy (1×8 Gy, 5×4 Gy)	14 (23)
10×3 Gy	25 (42)
Longer-course radiotherapy (total doses >30 Gy)	21 (35)

MSCC: Metastatic spinal cord compression; ECOG: Eastern Cooperative Oncology Group.

Results

Three of the investigated factors showed a significant positive association with the post-treatment ambulatory status, namely time developing motor deficits of >7 days ($p=0.011$), being ambulatory prior to radiotherapy ($p<0.001$), and an ECOG performance score 1-2 ($p<0.001$). The post-treatment ambulatory rates of all investigated factors are summarized in Table II. The post-treatment ambulatory rates of the three significant factors were used to develop the scoring system (Table III). The individual scores for the 60 patients were 7 points, 12 points, 15 points, 20 points, 22 points and 27 points, respectively (Figure 1). Three prognostic groups were designed, namely 7-12 points (group A), 15-20 points (group B) and 22-27 points (group C), respectively. The corresponding post-treatment ambulatory rates at 1 month following radiotherapy were 11% for group A, 62% for group B and 96% for group C, respectively ($p<0.001$). The p-values for the comparisons of groups A *vs.* B and B *vs.* C were 0.027 and 0.034, respectively. In group C, ambulatory rates at 3 months and at 6 months following radiotherapy were 100% (24 of 24 patients) and 100% (20 of 20 patients), respectively.

Discussion

The survival prognosis of patients with locally advanced head-and-neck cancer has been improved due to novel treatment approaches including surgery, radiotherapy and systemic therapies (18-20). Since the risk of developing distant metastasis increases with lifetime, the number of patients presenting with metastatic disease such as MSCC is growing. Radiotherapy alone is the most common treatment for MSCC (1, 2). In 2005, a randomized trial of 101 patients that compared radiotherapy alone to radiotherapy plus upfront decompressive surgery showed that selected patients (MSCC from a solid tumor, Karnofsky performance score of 70 or greater, survival prognosis of 3 months or longer, involvement of only one spinal segment by MSCC and paraplegia lasting for not longer than 48 h) could benefit from the addition of surgery with respect to post-treatment ambulatory status and survival (6). In general, these criteria are met by 10-15% of patients with MSCC. Insufficient response to radiotherapy is considered another good indication for decompressive surgery plus stabilization (1, 2). Therefore, it would be helpful to be able to predict the response prior to the start of treatment. From the patient's point of view, post-treatment ambulatory status is a major key point with respect to their quality of life. From the physician's point of view, it is very important to know prior to assigning a treatment to a patient whether the ability to walk can be

Table II. *Post-treatment ambulatory status.*

	Number of patients (%)		
	Ambulatory	Not ambulatory	*p*-Value
Age at the time of irradiation			
≤59 years	22 (67)	11 (33)	
≥60 years	15 (56)	12 (44)	0.844
Interval between cancer diagnosis and radiotherapy of MSCC			
≤15 months	12 (48)	13 (52)	
>15 months	25 (71)	10 (29)	0.340
Visceral metastasis			
No	23 (74)	8 (26)	
Yes	14 (48)	15 (52)	0.231
Other bone metastasis			
No	19 (70)	8 (30)	
Yes	18 (55)	15 (45)	0.650
Cancer site			
Nasopharynx	6 (75)	2 (25)	
Oropharynx	9 (56)	7 (44)	
Hypopharynx	7 (78)	2 (22)	
Larynx	6 (55)	5 (45)	
Other sites	9 (56)	7 (44)	0.987
Gender			
Female	6 (67)	3 (33)	
Male	31 (61)	20 (39)	0.987
Time developing motor deficits			
1-7 days	7 (33)	14 (67)	
>7 days	30 (77)	9 (23)	**0.011**
Pre-treatment ambulatory status			
Not ambulatory	2 (11)	17 (89)	
Ambulatory	35 (85)	6 (15)	**<0.001**
Number of affected vertebrae			
1-2	17 (61)	11 (39)	
≥3	20 (63)	12 (37)	0.999
ECOG performance score			
1-2	27 (96)	1 (4)	
3-4	10 (31)	22 (69)	**<0.001**
Fractionation regimen			
Short-course radiotherapy (1×8 Gy, 5×4 Gy)	6 (43)	8 (57)	
10×3 Gy	15 (60)	10 (40)	
Longer-course radiotherapy (total doses >30 Gy)	16 (76)	5 (24)	0.566

MSCC: Metastatic spinal cord compression; ECOG: Eastern Cooperative Oncology Group; bold *p*-values: significant values.

achieved with radiotherapy alone or upfront surgery is required. This information can be provided with the help of a scoring system predicting the probability to be ambulatory following radiotherapy alone. Two systems have already been developed for patients with MSCC in general, but not for specific tumor entities (4, 21). Therefore, the present study has been conducted in order to develop such a scoring system particularly for MSCC from head-and-neck cancer. Based on three predictive factors, time developing motor deficits prior to radiotherapy, pre-treatment ambulatory status and ECOG performance score, three prognostic groups were designed with significantly different post-treatment ambulatory rates of 11% (group A), 62% (group B) and 96% (groups C), respectively. Patients of group A have a low probability of being ambulatory following radiotherapy alone and would likely benefit from the addition of upfront decompressive surgery, particularly if they meet the criteria of the randomized trial of Patchell *et al*. (6). The post-treatment ambulatory rate of group B patients is also not optimal. Thus, for these patients, upfront surgery may be considered. In group C, the post-treatment ambulatory rates at 1, 3 and 6 months following radiotherapy were extremely high with

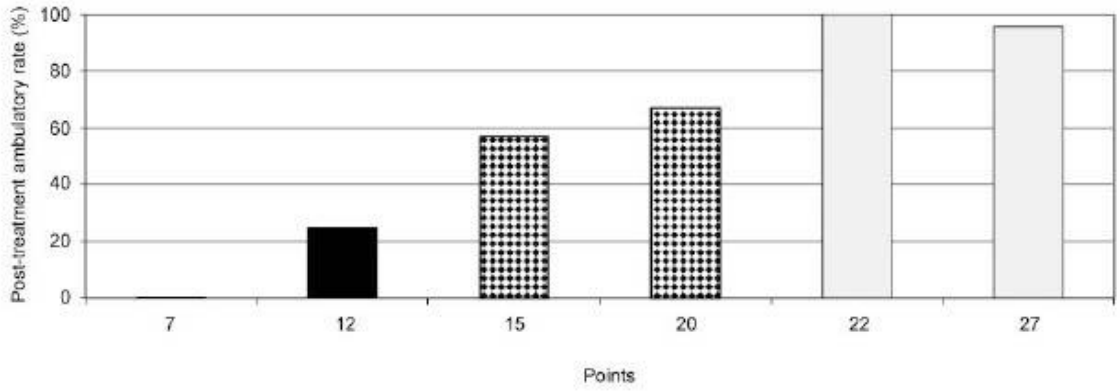

Figure 1. *Post-treatment ambulatory rates related to the scoring points.*

Table III. *Points for the factors included in the scoring system received by dividing post-treatment ambulatory rates (on %) by 10.*

	Post-treatment ambulatory rate (%)	Points
Time developing motor deficits		
1-7 days	33	3
>7 days	77	8
Pre-treatment ambulatory status		
Not ambulatory	11	1
Ambulatory	85	9
ECOG performance score		
1-2	96	10
3-4	31	3

ECOG: Eastern Cooperative Oncology Group.

96%, 100% and 100%, respectively. Therefore, these patients appear well treated with radiotherapy alone and may not require upfront surgery. When following these suggestions, the retrospective nature of the data used to create the scoring system should be taken into consideration. Retrospective data are always associated with a risk of hidden selection biases. However, due to the fact that patients with MSCC from head-and-neck cancer are rare, prospective studies focusing on this group of patients will be very unlikely in the near future.

In this study, three predictive factors were identified regarding the ambulatory status after radiotherapy for MSCC from head-and-neck cancer. Based on these factors, a scoring system including three prognostic groups was developed. This system can help predict the probability of being ambulatory after radiotherapy alone and identify patients who could benefit from upfront decompressive surgery in this particular group of cancer patients.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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STUDY PROTOCOL Open Access

Radiotherapy for metastatic spinal cord compression with increased radiation doses (RAMSES-01): a prospective multicenter study

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Abstract

Background: Patients with metastatic spinal cord compression (MSCC) and favorable survival prognoses can benefit from radiation doses greater than 30Gy in 10 fractions in terms of improved local progression-free survival (LPFS) and overall survival (OS).

Methods/design: This prospective study mainly investigates LPFS after precision radiotherapy (volumetric modulated arc therapy or stereotactic body radiotherapy) with 18 × 2.33Gy in 3.5 weeks. LPFS is defined as freedom from progression of motor deficits during radiotherapy and an in-field recurrence of MSCC following radiotherapy. The maximum relative dose allowed to the spinal cord is 101.5% of the prescribed dose, resulting in an equivalent dose in 2Gy-fractions (EQD2) for radiation myelopathy is 45.5Gy, which is below the tolerance dose of 50Gy according to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC). The EQD2 of this regimen for tumor cell kill is 43.1Gy, which is 33% higher than for 30Gy in 10 fractions (EQD2 = 32.5Gy). Primary endpoint is LPFS at 12 months after radiotherapy. Secondary endpoints include the effect of 18 × 2.33Gy on motor function, ambulatory status, sensory function, sphincter dysfunction, LPFS at other follow-up times, overall survival, pain relief, relief of distress and toxicity. Follow-up visits for all endpoints will be performed directly and at 1, 3, 6, 9 and 12 months after radiotherapy. A total of 65 patients are required for the prospective part of the study. These patients will be compared to a historical control group of at least 235 patients receiving conventional radiotherapy with 10x3Gy in 2 weeks.

Discussion: If precision radiotherapy with 18 × 2.33Gy results in significantly better LPFS than 10x3Gy of conventional radiotherapy, this regimen should be strongly considered for patients with MSCC and favorable survival prognoses.

Trial registration: Clinicaltrials.gov NCT04043156. Registered 30-07-2019.

Keywords: Metastatic spinal cord compression, Favorable survival prognosis, Precision radiotherapy, Increased radiation dose, Local progression-free survival

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Background

A considerable number of patients irradiated for metastatic spinal cord compression (MSCC) have a favorable survival prognosis with 6-month and 12-month survival rates of > 80 and > 70%, respectively [1, 2]. These patients are easily identified using validated prognostic tools [1, 2] and can live long enough to develop a recurrence of MSCC in the irradiated part of the spine. In case of such an in-field recurrence, many patients are not suitable for surgery [3, 4]. Moreover, safe administration of a second course of radiotherapy is often taking into account the risk of radiation myelopathy [5]. Longer-course radiotherapy programs (2–4 weeks) can result in better local control and local progression-free survival (LPFS) than short-course programs [6, 7]. In a retrospective matched-pair study, local control and LPFS were further improved with doses beyond the most commonly used longer-course regimen 30Gy in 10 fractions (10x3Gy) [8]. Increase of the dose for MSCC is limited by the radiation tolerance of the spinal cord [9, 10]. With precision radiotherapy techniques such as volumetric modulated arc therapy (VMAT) and stereotactic body radiotherapy (SBRT), radiation doses can be further increased than with conventional radiotherapy [11].

In the RAMSES-01 study, precision radiotherapy with 18 × 2.33Gy in 3.5 weeks is investigated. The equivalent dose in 2Gy-fractions (EQD2) of this regimen for tumor cell kill is 43.1Gy, which is 33% higher than for 30Gy in 10 fractions (32.5Gy) [12, 13]. The EQD2 of 18 × 2.33Gy for radiation myelopathy is 45.5Gy, which is below the tolerance dose of the spinal cord of 50Gy according to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [9]. The EQD2 of 18 × 2.33Gy for damage to the vertebral bone is 45.1Gy, which is below the tolerance dose of bone of 52Gy [9, 10]. Thus, precision radiotherapy with 18 × 2.33Gy can be considered safe.

This study includes two parts, a single-arm trial of patients receiving 18 × 2.33Gy and a comparison of this cohort to a historical control group treated with 10x3Gy. It aims to show that 18 × 2.33Gy of precision radiotherapy results in significantly better LPFS than 10x3Gy of conventional RT. If such superiority is shown, 18 × 2.33Gy could be recommended for patients with favorable survival prognoses.

Methods/design

Endpoints of the study

The primary endpoint is the 12-month LPFS following 18 × 2.33Gy of VMAT (preferred) or SBRT (possible for a single vertebra) in patients with favorable survival prognoses according to a validated score [1, 2]. This survival score is used by many physicians worldwide when aiming to assign the appropriate radiation regimen to a patient with MSCC.

Study design

The first part of this study represents a single-arm trial and evaluates the effect of precision radiotherapy with 18 × 2.33Gy given over 3.5 weeks on LPFS. Sixty-five patients (62 patients + 5% for drop-outs) are supposed to be recruited within 21 months. The characteristics to be recorded to allow a comparison with the historical control group include age, gender, primary tumor type, interval between tumor diagnosis and MSCC, number of vertebrae affected by MSCC, additional bone or visceral metastases, time developing motor deficits, pre-radiotherapy ambulatory status, and performance status according to the Eastern Cooperative Oncology Group (ECOG) [7]. Propensity score techniques will be applied to reduce confounding due to differences between the historical control group and prospective trial data [14]. The inclusion and exclusion criteria are almost identical to those of a previous trial investigating 5x5Gy of precision radiotherapy of MSCC [11]. Only the inclusion criteria are supplemented by favorable survival prognosis (defined as 36–45 points on a survival score) [1, 2].

Treatment

Radiotherapy is administered with VMAT (or SBRT) with 2.33Gy per fraction up to 42.0Gy in 3.5 weeks. This regimen represents an EQD2 of 43.1Gy for tumor cell kill, which means an increase of the radiation dose by 33% compared to 10x3Gy in 2 weeks (EQD2 = 32.5Gy). The EQD2 for radiation myelopathy is 45.5Gy for 100% of the prescribed dose [12, 13]. An EQD2 of <50Gy is considered safe and estimated to be associated with a risk of radiation-related myelopathy of < 0.2% [9]. Treatment should be started as soon as possible, i.e. within 48 h after first presentation to a radiation oncologist.

The planning target volume (PTV) should include the involved vertebrae plus 1 cm above and below. The PTV should be covered by the 95%-isodose. The spinal cord should not receive more than 101.5% of the prescribed dose (EQD2 = 46.6Gy for radiation myelopathy, $\alpha/\beta = 2$Gy). This maximum dose is estimated to be associated with a risk of radiation-related myelopathy of < 0.2% [9]. Both the EQD2 of the prescribed dose (45.1Gy) and the EQD2 of the maximum dose (46.1Gy, $\alpha/\beta = 2.5$Gy) are below the tolerance dose of bone of 52Gy [9, 11]. The mean doses (EQD2) for esophagus, heart and lung must be <34Gy, <26Gy and ≤ 7Gy [9]. The patients should receive concomitant corticosteroids during radiotherapy [15, 16].

Assessments

The following endpoints will be prospectively assessed by the participating physicians directly and at 1, 3, 6, 9 and 12 months after radiotherapy and recorded in a case report form (CRF): Motor function, ability to walk, sensory function, sphincter dysfunction, LPFS, overall

survival (OS), pain relief, relief of distress, and toxicity. If a recurrence of MSCC is clinically suspected (deterioration of motor function following improvement or no change of motor function during radiotherapy), MRI will be performed. For MRI, rates of sensitivity, specificity and diagnostic accuracy regarding the detection of MSCC of 93, 97, and 95%, respectively, were reported [16, 17]. In case of an out-field recurrence of MSCC, the patient will be censored for LPFS. Assessment directly after radiotherapy will result in a difference of one and a half week between the prospective cohort and the historical control group. However, this way of assessment was selected, since the primary endpoint LPFS included no progression of motor deficits during radiotherapy (=immediate response), which would ideally be assessed directly after the end of radiotherapy. Motor function will be evaluated with a 5-point scale [11, 18]. Sensory function will be assessed as absent, impaired or normal, sphincter dysfunction as yes or no [19]. For assessment of pain, a numeric self-assessment scale will be used (0–10 points) [20]. Distress will be evaluated with the distress thermometer (0–10 points [21, 22]. For assessment of toxicity, the Common Terminology Criteria for Adverse Events version 4.03 will be used [23].

Comparisons with the historical control group

The patients receiving 18 × 2.33Gy will be compared to historical control group of patients with a favorable survival prognosis treated with 10x3Gy of conventional radiotherapy from an anonymized database. Patients of the control group must fulfil the same inclusion and exclusion criteria as the patients of the prospective part of the study. It is estimated that 235 patients will qualify for the control group. To reduce the risk of hidden selection biases, a propensity score approach including 10 potential prognostic factors will be used for comparisons between the prospective cohort and the historical control group [7, 11].

Sample size calculation

The primary aim is to evaluate the LPFS at 12 months after 18 × 2.33Gy using VMAT or SBRT and to show superiority to 10x3Gy of conventional radiotherapy.

With respect to tumor cell kill, the EQD2 of 18 × 2.33Gy is considerably higher (+ 33%) than the EQD2 of 10x3Gy (43.1Gy vs. 32.5Gy). In a previous study, the 12-month LPFS rate was 84% with 10x3Gy in 2 weeks [8]. An increase by 12.5 percentage points is considered clinically important. Sixty-two eligible patients are required for estimation of the 12-month LPFS with appropriate precision. The statistical power should be at least 80%. Assuming that 5% of the patients will not be eligible for the efficacy analysis, a total of 65 patients should be recruited for the prospective trial.

For the comparison of the prospective trial and the historical cohort group, propensity score methods will be used to reduce confounding due to differences between the two data sets. Assuming that this comparison is performed with a simple Pearson-Chi-Square test (two-sided significance level = 5%), the power will be 77.9%, if the data of 62 prospectively treated patients and the data of 235 patients serving as historical control group can be used. Since the historical control database is constantly growing, the power will likely be 80% or higher at the time of the final analyses.

Data management

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 gender. A patient identification list will only be kept in the relevant study centers and will not be forwarded to the sponsor. Data collection will be done using the paper-based case report forms. These forms should be filled in as soon as possible and be submitted to the checker for review, signed, dated and forwarded to the study management via fax or secure email.

The originals of all key study documents, including the documentation sheets, will be kept at the study headquarters for a minimum of 10 years after the final report. The principal investigator/head of the study center will keep all administrative documents (written correspondence with the ethics committee, regulatory authorities, study management, study headquarters), the patient identification list, the signed informed consent forms, copies of the documentation sheets and the general study documentation (protocol, amendments) for the above mentioned period. Original patient data (patient files) must also be kept for the length of time stipulated for the study centres, but not for less than 10 years. The site principle investigators are responsible for the day-to-day organization and the data management at their sites.

Discussion

Despite an increasing use of upfront decompressive surgery in addition to radiotherapy, the majority of patients with MSCC still receive radiotherapy alone [3, 4, 15, 16]. Short-course radiotherapy programs such as 5x4Gy within 1 week are not inferior to longer-course programs such as 10x3Gy with respect to the effect on motor function and ambulatory status [24, 25]. However, longer-course programs result in better local control of MSCC and LPFS, particularly in patients with favorable survival prognoses [6, 7, 24]. In a prospective non-randomized trial of patients with MSCC and poor to favorable survival prognoses, the 1-year local control rates were 81% after longer-course and 61% after short-course

radiotherapy ($p = 0.005$) [6]. Patients with favorable prognoses are at a higher risk to experience an in-field recurrence of MSCC, since the risk of such a recurrence increases with survival time. Moreover, a retrospective study of patients with favorable survival prognoses (according to a survival score that has been validated in a prospective cohort of patients) suggested that these patients can benefit from radiation doses beyond 30Gy in 10 fractions [1, 2, 8]. In that study, 191 patients receiving 30Gy in 10 fractions were matched to 191 patients treated with 37.5Gy in 15 fractions or 40Gy in 20 fractions [8]. In order to reduce the risk of a hidden selection bias, the patients were matched 1:1 for 10 characteristics including age, gender, tumor type, performance status, number of involved vertebrae, visceral metastases, other bone metastases, interval from tumor diagnosis to radiotherapy, ambulatory status, and time developing motor deficits. Patients receiving 37.5Gy or 40Gy did achieve better outcomes in terms of local control of MSCC (92% vs. 71% at 2 years, $p = 0.012$), LPFS (90% vs. 68%, $p = 0.013$) and OS (68% vs. 53%, $p = 0.032$).

One important question is whether outcomes of radiotherapy for MSCC in patients with favorable survival prognoses can be further increased with radiation doses beyond 40Gy. LPFS is an important endpoint, since a lack of response to radiotherapy and an in-field recurrence of MSCC associated with neurologic deficits must be considered serious for the patients. For many of these patients, decompressive surgery is not possible. Moreover, in case of an in-field recurrence, a second radiation course may lead to exceedence of the tolerance dose of the spinal cord resulting in radiation myelopathy with severe neurologic deficits [9, 10]. The effect of radiotherapy on motor function was not selected as primary endpoint, since a previous retrospective study in patients with MSCC and favorable survival prognoses suggested a benefit of higher radiation doses regarding LPFS but not regarding post-treatment motor function [8]. Moreover, the previous randomized trials of radiotherapy for MSCC that were not limited to patients with favorable prognoses did not show a benefit for higher doses with respect to improvement of motor function, which is particularly important for patients with poor or intermediate survival prognoses who likely will not live long enough to experience a local recurrence of MSCC [25–29].

Increasing the radiation dose in order to improve LPFS is also limited due to the tolerance dose of the spinal cord [9, 10]. With conventional radiotherapy, the maximum dose to the spinal cord is always higher than 100% (frequently about 105%) of the prescribed dose, which accounts for both total dose and dose per fraction, resulting in a significantly higher EQD2 for myelopathy. In a previous trial of precision radiotherapy for MSCC, the maximum dose to the spinal cord could be reduced to 101.5% [11]. The same constraint is used for the present RAMSES-01 trial. This allows safe administration of a radiation dose higher than 40Gy (EQD2 = 43.1Gy). The dose administered in the RAMSES-01 trial represents an increase of the EQD2 for tumor cell kill by 33% when compared to 10x3Gy, the most commonly used longer-course program for MSCC worldwide. In a previous prospective study of precision radiotherapy for MSCC, radiation treatment could be delivered within 24 h [11]. Thus, the use of precision radiotherapy did not delay treatment.

A higher EQD2 can also be administered with single-fraction SBRT. However, the tolerance doses of spinal cord and vertebral bone must be taken into account to avoid neurologic deficits and vertebral fractures [30, 31]. The updated ASTRO evidence-based guideline recommends that SBRT for MSCC should be limited to clinical trials [32]. Since single-fraction SBRT with ≥20Gy has been identified as a significant risk factor for vertebral fractures, fractionated precision radiotherapy (SBRT or VMAT) is considered a preferable option [33, 34].

If this new approach of precision radiotherapy with 18 × 2.33Gy proves to be superior to 10x3Gy of conventional radiotherapy for LPFS, this regimen should be strongly considered for patients with MSCC and favorable survival prognoses.

Abbreviations

CT: Computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EQD2: Equivalent dose in 2Gy-fractions; LPFS: Local progression-free survival; MRI: Magnetic resonance imaging; MSCC: Metastatic spinal cord compression; OS: Overall survival; PTV: Planning target volume; QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic; SBRT: Stereotactic body radiotherapy; VMAT: Volumetric modulated arc therapy

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Authors' contributions

DR, OH, LHJ, LD, CS, CD, JC, AJC-M, BS, RC-J, CR-R, LAP-R, AA-G, KD, CF-A, AN-M, FL-C, NJ, SJ, DO and NHH participated in the generation of the study protocol of the RAMSES-01 trial. D.R. drafted the manuscript, which has been reviewed by all other authors. The final version of the manuscript has been approved by all authors.

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Availability of data and materials

The study has been registered at clinicaltrials.gov (identifier: NCT04043156), where data regarding the study are available as well.

Ethics approval and consent to participate

The study has been approved by the ethics committee of the University of Lübeck (reference number: AZ 18–360). 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. Patients are included after giving written informed consent.

Consent for publication
Not applicable.

Competing interests
D.R. and S.J. are associate editors of BMC Cancer. Otherwise, the authors declare that they have no competing interests related to the study presented here.

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Publisher's Note

VII.2 Voten der Ethik-Kommission

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Ethik-Kommission

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Aktenzeichen: 18-130A
Datum: 14. Mai 2018

Prognosefaktoren bei der palliativen Strahlentherapie von Kopf-Hals-Tumoren in der primären und metastasierten Situation
Ihr Schreiben vom 07. Mai 2018

Sehr geehrter Herr Prof. Rades,

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

Es werden ausschließlich anonymisierte Daten verarbeitet.

Die Ethik-Kommission nimmt das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis. Eine Behandlung im normalen Antragsverfahren wird nicht für notwendig erachtet.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

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Aktenzeichen: 18-360
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Sitzung der Ethik-Kommission am 03. Januar 2019
Antragsteller: Herr Prof. Dr. Rades
Titel: Hochpräzisions-Strahlentherapie mit erhöhter Dosis bei motorischen Defiziten aufgrund metastatisch bedingter Rückenmarkskompression

Sehr geehrter Herr Prof. Rades,
vielen Dank für Ihr Schreiben vom 14. März 2019, in dem Sie den Hinweisen aus unserer Sitzung vom 03. Januar 2019 nachkommen.

Folgende Unterlagen lagen vor:

- Ihr Anschreiben vom 14. März 2019
- Basisformular vom 14. März 2019 und Studienprotokoll in der Version 2.0 vom 13. März 2019
- Synopsis in der Version 2.0 vom 13. März 2019
- Aufklärung in der Version 2.0 vom 13. März 2019 und Einwilligigung
- Distress Management in der Version 2.2013
- Änderungshistorie.

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.
Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum / diese Bewertung ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.

Mit freundlichem Gruß

Prof. Dr. med. Alexander Katalinic
Vorsitzender

VIII Danksagung

Mein herzlicher Dank gilt Herrn Prof. Dr. med. Dirk Rades für die Überlassung des Themas, die intensive Betreuung, sein Engagement, fördernde Kritik und die stets harmonische Zusammenarbeit.

Auch gilt mein ausgesprochener Dank Herrn Prof. Dr. med. Steven E. Schild für die immerwährende Unterstützung bei der statistischen Auswertung.

Den Mitarbeiter*innen unserer Klinik möchte ich für grenzenlose Aufmunterung, Bereitstellung von Nervennahrung und ein immerzu offenes Ohr danken.

Nicht zuletzt danke ich meiner Familie, vor allem meinen Eltern und meiner Schwester, meiner über alles geliebten Partnerin Anna Katharina Olbrisch sowie meinen Freunden, hier im Besonderen Jaspar Witteler, für die Unterstützung und allen voran die Geduld während der Entstehung dieser Arbeit.

Zu guter Letzt gehört meinem Sohn Felix ein Dank für die Entbehrung von gemeinsamer Zeit während der finalen Phase dieses Werks.

IX Curriculum Vitae

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Berufs- und Schulausbildung

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08/05 – 08/07	Bachelorstudiengang der Biologie und Chemie mit medizinischer Ausrichtung an der University of North Carolina at Pembroke, USA
08/94 – 06/03	Fördegymnasium Flensburg Erwerb der „Allgemeinen Hochschulreife“
08/90 – 06/94	Grundschule Friedheim in Flensburg

Veröffentlichte Publikationen

Becker L S, Gebauer J, Küchler J, ***Staackmann C****, Schacht H, Lauten M, Jensen-Kondering U, Schramm P, Langer T, Neumann A* (2021) Are Radiation-induced Cavernomas Clinically Relevant Findings? Results from Long-term Follow-up with Brain Magnetic Resonance Imaging of Childhood Cancer Survivors. Radiol Oncol 55(3): 274-283

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