Aus der Klinik für Strahlentherapie
der Universität zu Lübeck
Direktor: Prof. Dr. med. J. Dunst

_____

Vergleich verschiedener Radiochemotherapie-Regime

beim lokal fortgeschrittenen Plattenepithelkarzinom

der Kopf-Hals-Region

Inauguraldissertation

zur Erlangung der Doktorwürde

der Universität zu Lübeck

- Aus der Sektion Medizin -

Vorgelegt von Daniel Seidl aus Siegen

Lübeck 2021

1. Berichterstatter: Prof. Dr. med. Dirk Rades

2. Berichterstatterin/Berichterstatter: Prof. Dr. med. Armin Steffen

Tag der mündlichen Prüfung: 14.12.2021

Zum Druck genehmigt. Lübeck, den 14.12.2021

Promotionskommission der Sektion Medizin

I. Abkürzungsverzeichnis

5-FU: 5 - Fluorouracil

Abb.: Abbildung

CI: Confidence Interval, Konfidenzintervall

Cis: Cisplatin

CPS: Combined positive score

CTCAE: Common Terminology Criteria for Adverse Events

ECOG: Eastern Cooperative Oncology Group

EGFR: Epidermal Growth Factor Receptor, Epidermaler Wachstumsfaktor-Rezeptor

Gy: Gray

Hb: Hemoglobin, Hämoglobin

HPV: Human Papilloma Virus, humanes Papillomavirus

HR: Hazard Ratio

IMRT: Intensitätmodulierte Radiotherapie/Strahlentherapie

LRC: Loco-Regional Control, loko-regionale Kontrolle

MFS: Metastases-Free Survival, metastasenfreies Überleben

OS: Overall Survival, Gesamtüberleben

PD-1: Programmed cell death protein1

PD-L1: Programmed cell death-ligand 1

VMAT: Volumetric Modulated Arc Therapy

II. Einleitung und Fragestellung

Pro Jahr erkranken in Deutschland circa 20 Männer und 5 Frauen pro 100.000 Einwohner*innen an einem Plattenepithelkarzinom der Kopf-Hals-Region, womit diese Entität insgesamt zu den zehn häufigsten malignen Tumorerkrankungen gehört.

Wesentliche Risikofaktoren für die Entstehung dieser Tumoren sind Rauchen und der regelmäßige Konsum von (hochprozentigem) Alkohol. Zudem konnte in den letzten Jahren ein direkter Zusammenhang mit einer Infektion durch Hochrisikostämme des humanen Papillomavirus (HPV) festgestellt werden [1]. Die Tumoren werden häufig erst in einem fortgeschrittenen Stadium diagnostiziert. In den letzten 15 Jahren konnte die Prognose aufgrund moderner Behandlungsmethoden zwar verbessert werden, bleibt im Allgemeinen jedoch weiter unbefriedigend [2, 3]. Moderne Behandlungsmethoden beinhalten Hochpräzisionstechniken bei der Bestrahlung, neue systemische Substanzen und weniger invasive Operationstechniken [4, 5, 6].

Die Standardtherapie besteht dabei aus der operativen Resektion des Primärtumors und der regionalen Lymphknoten gefolgt von einer Strahlentherapie oder Radiochemotherapie bei entsprechenden Risikofaktoren. Bei Inoperabilität erfolgt in der Regel eine definitive Radiochemotherapie. Bei der kombinierten Radiochemotherapie ist die simultane Behandlung der sequenziellen Therapie überlegen [7-13]. Sowohl in der adjuvanten, als auch bei der definitiven Therapie ist die am häufigsten verwendete Substanz Cisplatin, entweder als Monotherapie oder als Bestandteil einer Kombinationstherapie [14-18, 20-22]. Die simultane Radiochemotherapie mit drei Zyklen Cisplatin 100 mg/m² stellt hierbei einen weit verbreiteten Standard dar, obwohl es bis heute keine Phase 3 Studie mit einer adäquaten statistischen Aussagekraft zum Vergleich

unterschiedlicher Cisplatin Dosierungen und Sequenzen gibt. Lediglich ein Vorteil gegenüber einer reinen Strahlentherapie konnte dokumentiert werden [7, 8].

Dieses Therapieregime ist häufig, auch in Anbetracht der Begleiterkrankungen vieler Patient*innen, mit einer hohen Toxizität verbunden [19]. Mögliche Nebenwirkungen sind unter anderem Einschränkungen der Nierenfunktion, Minderung des Hörvermögens und eine Polyneuropathie.

Individuelle Therapiekonzepte sollten nach Möglichkeit das Alter, Komorbiditäten und die persönliche Situation der Patient*innen berücksichtigen. Auch sollte ein individueller Therapieansatz unter Berücksichtigung des erwarteten Ergebnisses hinsichtlich der loko-regionalen Kontrolle, des metastasenfreien Überlebens und des Gesamtüberlebens gewählt werden [23]. Hierbei können Prognosefaktoren sehr hilfreich sein.

In dieser Arbeit wurden mögliche Prognosefaktoren für die Behandlungsergebnisse nach einer simultanen Radiochemotherapie lokal fortgeschrittener Kopf-Hals-Tumoren untersucht. Des Weiteren wurden verschiedene Cisplatin-haltige Regime hinsichtlich der loko-regionalen Kontrolle, des metastasenfreien Überlebens, des Gesamtüberlebens und relevanter Nebenwirkungen miteinander verglichen. Das wesentliche Ziel der vorliegenden Arbeit war es, das am besten geeignete Regime zu identifizieren und somit zur Verbesserung der Behandlung und der Prognose von Patient*innen mit einem lokal fortgeschrittenen Kopf-Hals-Tumor beizutragen.

III. Material und Methoden

a. Patient*innen

In die im Rahmen dieser Arbeit durchgeführten multizentrischen Studien wurden Patient*innen eingeschlossen, welche an einem histologisch gesicherten Plattenepithelkarzinom der Kopf-Hals-Region (Mundhöhle/Mundboden, Oropharynx, Hypopharynx und Larynx) erkrankten und im Zeitraum von 1999 bis 2014 eine definitive Radiochemotherapie oder eine Operation gefolgt von einer Radiochemotherapie erhielten. Je nach Studie wurden hierbei zwischen 122 und 329 Patient*innen eingeschlossen und retrospektiv analysiert. Die Patientencharakteristika für die einzelnen Studien werden detailliert in den Tabellen 1-7 zusammengefasst.

b. Bestrahlungstechniken

Die Bestrahlung erfolgte entweder im Rahmen einer adjuvanten Radio(-chemo)therapie bei Vorliegen entsprechender Risikofaktoren (unvollständige Resektion und/oder Lymphknotenmetastasen mit Kapseldurchbruch) oder als definitive Radiochemotherapie. Die Bestrahlung erfolgte konventionell fraktioniert mit 2 Gy pro Tag an fünf aufeinander folgenden Tagen pro Woche. Die Gesamtdosis im Bereich des Primärtumors betrug in der Regel 66-70 Gy bei definitiver Therapie oder adjuvant nach makroskopisch unvollständiger Resektion (R2), 66 Gy nach mikroskopisch unvollständiger Resektion (R1) sowie 60 Gy nach mikroskopisch vollständiger Resektion (R0). Bei definitiver Therapie erhielten befallene Lymphknoten 66-70 Gy. Postoperativ wurden 66 Gy bei Kapseldurchbruch sowie 60 Gy bei erhaltener Lymphknotenkapsel appliziert. Nicht involvierte Lymphknotenregionen des Halsbereiches wurden mit 50-60 Gy behandelt. Die Strahlentherapie erfolgte mit 6-10 MeV Photonen eines Linearbeschleunigers, entweder

als dreidimensional konformale Bestrahlung, als intensitätsmodulierte Radiotherapie (IMRT) oder als volumenmodulierte Rotations-Bestrahlung (VMAT).

c. Chemotherapie

Die Patient*innen in den, im Rahmen dieser Arbeit, durchgeführten Studien wurden mit Cisplatin als Monotherapeutikum oder in Kombination mit 5-Fluorouracil behandelt. Hierbei wurden entweder drei Zyklen mit 100 mg/m² Cisplatin an den Bestrahlungstagen 1, 22 und 43, eine wöchentliche Behandlung mit 30-40 mg/m² Cisplatin, zwei Zyklen mit 20 mg/m² Cisplatin an den Bestrahlungstagen 1-5 und 29-33 oder zwei Zyklen mit 20 mg/m² Cisplatin ergänzt durch 600 bzw. 1000 mg/m² 5-FU, ebenfalls an den Bestrahlungstagen 1-5 und 29-33, appliziert.

d. Weitere potentielle Prognosefaktoren

Bis zu elf Prognosefaktoren wurden hinsichtlich einer möglichen Assoziation mit der loko-regionalen Kontrolle, dem metastasen-freien Überleben und dem Gesamtüberleben in den einzelnen Studien analysiert. Diese Charakteristika beinhalteten das T-Stadium (T1/2 versus T3/4), das N-Stadium (N0-2a versus N2b-3), das histologische Grading (G1/2 versus G3), das Alter der Patient*innen (≤ 57 versus > 57 Jahre), das Geschlecht (weiblich versus männlich), den Allgemeinzustand in Form des Eastern Cooperative Oncology Group (ECOG) Performance Scores (0-1 versus 2), bzw. Karnofsky Performance-Index (≤ 70 % versus ≥ 80 %) die Tumorlokalisation (Mundhöhle/Mundboden versus Oropharynx versus Hypopharynx versus Larynx), den Hämoglobinwert vor Radiochemotherapie (< 12g/dl versus ≥ 12g/dl), eine vorgeschaltete Operation (ja versus nein), die Bestrahlungstechnik (3D-konformal versus IMRT/VMAT) sowie die kumulative Cisplatindosis (< 180 mg/m² versus ≥ 180 mg/m²).

e. Statistische Methoden

Die untersuchten Endpunkte waren die loko-regionale Kontrolle, das metastasen-freie Überleben und das Gesamtüberleben. Die entsprechenden univariaten Analysen erfolgten mit der Kaplan-Meier Methode und dem log-rank Test. Die Ergebnisse wurden als signifikant betrachtet, wenn der p-Wert <0,05 war. Prognostische Faktoren, die signifikant oder nahezu signifikant (p<0,07) in der univariaten Analyse waren, wurden zusätzlich in eine multivariate Analyse eingeschlossen. Die multivariaten Analysen erfolgten mit dem Cox Proportional Hazards Model. Nebenwirkungen wurden nach den Common Terminology Criteria of Adverse Events (CTCAE) 4.0 [24] graduiert und die Vergleiche zwischen den Patientengruppen mit dem Chi-Quadrat-Test durchgeführt.

IV. Ergebnisse

a. Prognosefaktoren nach definitiver Radiochemotherapie lokal fortgeschrittener Tumoren der Kopf-Hals Region (Studie 1)

Daniel Seidl, Stefan Janssen, Primoz Strojan, Amira Bajrovic, Steven E. Schild, Dirk Rades: Prognostic Factors after Definitive Radio(Chemo)Therapy of Locally Advanced Head-and-Neck Cancer. Anticancer Res 36, 2526-2526 (2016) [Impact Factor = 1.994]

In dieser Studie wurden zehn mögliche Prognosefaktoren in einer Serie von 275 Patient*innen retrospektiv hinsichtlich ihrer Bedeutung für die loko-regionale Kontrolle und das Gesamtüberleben untersucht.

Die Raten für die loko-regionale Kontrolle in der kompletten Serie nach 1, 3 und 5 Jahren betrugen 73 %, 60 % und 58 %. In der univariaten Analyse war die loko-regionale Kontrolle positiv assoziiert mit einem Hämoglobin-Wert von 12-14 g/dl vor Radiochemotherapie (p=0,003), niedrigem T-Stadium (p=0,029), niedrigem N-Stadium (p=0,020) und weiblichem Geschlecht (p=0,009; Tabelle 1). In der multivariaten Analyse waren der Hämoglobin-Wert vor Radiochemotherapie (p=0,040), das T-Stadium (p=0,010), das N-Stadium (p=0,042) und das Geschlecht (p=0,006) signifikant (Tabelle 8). Die Überlebensraten nach 1, 3 und 5 Jahren waren 76 %, 50 % und 36 %. In der univariaten Analyse war ein besseres Gesamtüberleben mit einem Hämoglobin-Wert von 12-14 g/dl bzw. > 14 g/dl (p=0,019), niedrigem N-Stadium (p<0,001), einem Karnofsky-Index von ≥ 80 % (p<0,001), weiblichem Geschlecht (p=0,045), einer Chemotherapie mit 3 Zyklen Cisplatin 100 mg/m² oder 2 Zyklen Cisplatin 5x20 mg/m² (p=0,009) und einer Tumorlokalisation im Larynx oder Oropharynxbereich (p<0,001) assoziiert (Tabelle 9). In der multivariaten Analyse für das Gesamtüberleben waren der Hämoglobin-Wert vor Radiochemotherapie (p=0,020), das N-Stadium (p<0,001), der Karnofsky-Index (p<0,001),

das Geschlecht (p=0,024) und die Art der simultanen Chemotherapie (p<0,001) signifikant (Tabelle 10).

b. Bedeutung von simultaner Chemotherapie und Strahlendosis nach mikroskopisch unvollständiger Resektion lokal fortgeschrittener Kopf-Hals-Tumoren (Studie 2)

Daniel Seidl, Stefan Janssen, Primo Strojan, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild, Dirk Rades: Importance of Chemotherapy and Radiation Dose After Microscopically Incomplete Resection of Stage III/IV Head-and-Neck Cancer. Anticancer Res 36, 2487-2491 (2016) [Impact Factor = 1.994]

In dieser Studie wurden retrospektiv Daten von 122 Patient*innen ausgewertet, die eine alleinige Bestrahlung (n=45) oder eine simultane Cisplatin-basierte Radiochemotherapie (n=77) nach R1-Resektion erhielten. In der gesamten Kohorte betrugen die Raten für die loko-regionale Kontrolle 3 bzw. 4 Jahre nach Therapie 73 % bzw. 66 %. Lediglich die simultane Chemotherapie war signifikant in der univariaten Analyse (Tabelle 2). In der multivariaten Analyse blieb die simultane Chemotherapie ebenfalls signifikant (p=0,048). In der univariaten Analyse waren ein niedriges N-Stadium (p=0,006), ein niedriges histologisches Grading (p=0,021) und ein Hämoglobinwert vor Radiochemotherapie ≥ 12 g/dl (p=0,002) signifikant mit einem besseren Überleben assoziiert (Tabelle 11). Zusätzlich zeigten ein niedriges T-Stadium (p=0,053) und eine Bestrahlungsdosis von 66-70 Gy (p=0,076) einen Trend. In der multivariaten Analyse waren das T-Stadium (p=0,018), das N-Stadium (p=0,011), Hämoglobin vor Radiochemotherapie (p=0,003) und die Bestrahlungsdosis (p=0,021) signifikant (Tabelle 12).

c. Vergleich von Cisplatin 100 mg/m² alle drei Wochen mit wöchentlichen Cisplatin-Gaben von 30-40 mg/m² bei der definitiven Radiochemotherapie lokal fortgeschrittener Kopf-Hals-Tumoren (Studie 3)

Dirk Rades, Daniel Seidl, Stefan Janssen, Amira Bajrovic, Katarina Karner, Primoz Strojan, Steven E. Schild: Comparison of weekly administration of cisplatin versus three courses of cisplatin 100 mg/m² for definitive radiochemotherapy of locally advanced head-and-neck cancers. BMC Cancer 16:437 (2016) [Impact Factor = 3.150]

In dieser retrospektiven Studie wurden 133 Patient*innen eingeschlossen, die aufgrund eines inoperablen Plattenepithelkarzinoms der Kopf-Hals-Region definitiv mit einer kombinierten Radiochemotherapie behandelt wurden. 75 Patient*innen erhielten
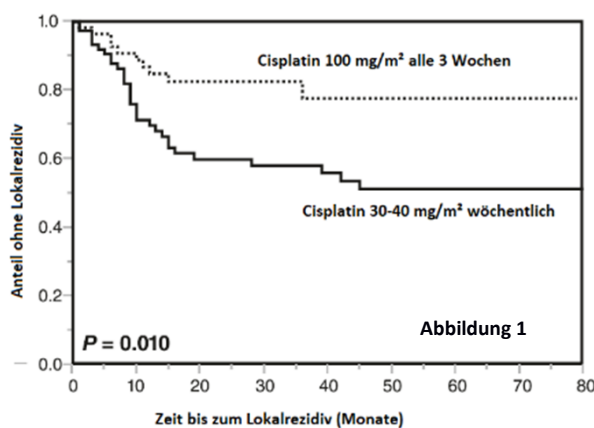
wöchentlich 30-40 mg/m² Cisplatin und 58 Patient*innen 100 mg/m² Cisplatin an den Tagen 1, 22 und 43 der Strahlentherapie. In der univariaten Analyse war Cisplatin 100 mg/m² alle 3 Wochen signifikant mit einer besseren

loko-regionalen Kontrolle assoziiert (p=0,010; Abb. 1, Tabelle 13). Auch in der multivariaten Analyse war das Radiochemotherapie-Regime signifikant (p=0,008; Tabelle 14). In der univariaten Analyse war ein besseres Gesamtüberleben mit einer

günstigen Tumorlokalisation (Oropharynx und Larynx; p<0,001), Cisplatin 100 mg/m², (p=0,024; Abb. 2) und einem ECOG Performance Score von 0-1 (p=0,006) assoziiert; das weibliche Geschlecht zeigte
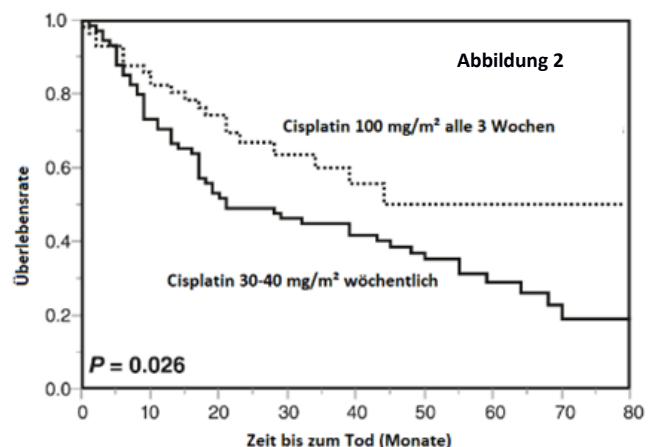
einen Trend (p=0,050; Tabelle 15). In der multivariaten Analyse waren die Art der Chemotherapie (p=0,023), der ECOG Performance Score (p=0,029) und das Geschlecht (p=0,026) signifikant (Tabelle 14). Allerdings ging das Regime Cisplatin 100 mg/m² alle 3 Wochen mit signifikant höheren Raten an Grad ≥ 3 Hämotoxizität (p=0,004), Grad ≥ 2 Niereninsuffizienz (p=0,004) und Pneumonien/Septitiden (p=0,033) einher (Tabelle 16). Die geplante Chemotherapie konnte in 63 % der Fälle (47/75) bei der wöchentlichen Gabe und in 50 % der Fälle (29/58) in der Cisplatin 100 mg/m² Gruppe vollständig appliziert werden (p=0,34).

d. Radiochemotherapie lokal fortgeschrittener Plattenepithelkarzinome der Kopf-Hals-Region (LA-SCCHN): Vergleich von hochdosiertem Cisplatin alle drei Wochen versus Cisplatin 5x20 mg/m² plus 5-FU alle vier Wochen (Studie 4)

Dirk Rades, Primoz Strojan, Daniel Seidl, Stefan Janssen, Amira Bajrovic, N. Kazic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Radiochemotherapy for locally advanced squamous cell carcinoma of the head and neck: Higher-dose cisplatin every 3 weeks versus cisplatin/5-fluorouracil every 4 weeks. J Craniomaxillofac Surg 44, 1436-1440 (2016) [Impact Factor = 1.766]

In diese Studie wurden 329 Patient*innen eingeschlossen. Von diesen wurden 131 mit Cisplatin 100 mg/m²/d1 alle 3 Wochen (Gruppe A) und 198 Patient*innen mit Cisplatin 20 mg/m²/d1-5 + 5-FU/d1-5 alle 4 Wochen (Gruppe B) therapiert (Tabelle 4). Die beiden Therapieregime wurden hinsichtlich loko-regionaler Kontrolle, Gesamtüberleben und Nebenwirkungen verglichen.

Die Art der Chemotherapie war hierbei nicht signifikant mit der loko-regionalen Kontrolle assoziiert (p=0,36; Tabelle 17). Ebenfalls hatte sie keinen signifikanten Einfluss auf das Gesamtüberleben (p=0,64; Tabelle 18). Die Inzidenz der meisten Nebenwirkungen war in

beiden Gruppen nicht signifikant unterschiedlich (Tabelle 19). Ausnahme war die Niereninsuffizienz, welche in Gruppe A signifikant häufiger auftrat (p=0,008).

e. Bedeutung von 5-Fluorouracil zusätzlich zu Cisplatin bei der Radiochemotherapie lokal fortgeschrittener Kopf-Hals-Tumoren (Studie 5)

Dirk Rades, Daniel Seidl Stefan Janssen, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Do we need 5-FU in addition to cisplatin for chemoradiation of loacally advanced head-and-neck cancer? Oral Oncol 57, 40-45 (2016) [Impact Factor = 3.979]

In dieser Studie wurden 142 Patient*innen, die eine definitive Radiochemotherapie mit Cisplatin als Monotherapie erhielten, retrospektiv mit 170 Patient*innen verglichen, bei denen die simultane Chemotherapie aus einer Kombination von Cisplatin und 5-FU bestand. In der Cisplatin-Gruppe konnte bei 27 Patient*innen (19 %) aufgrund akuter Nebenwirkungen die geplante Dosis nicht vollständig verabreicht werden. In der Cisplatin + 5-FU Gruppe waren es hingegen 46 Patient*innen (27 %; p=0,18). Eine Unterbrechung der Bestrahlung von mehr als einer Woche war bei 20 (14 %) bzw. 39 Patient*innen (23 %) notwendig (p=0,09). Hinsichtlich der loko-regionalen Kontrolle gab es in der univariaten Analyse keinen signifikanten Unterschied zwischen beiden Gruppen (p=0,71; Tabelle 20). In der multivariaten Analyse war die Cisplatin-Monotherapie signifikant mit einem besseren Überleben assoziiert (p=0,006). Das MFS war in der Cisplatin Gruppe nicht signifikant unterschiedlich zur Cisplatin + 5-FU Gruppe (p=0,37, Tabelle 21). Die Häufigkeit der meisten akuten Nebenwirkungen war nicht signifikant unterschiedlich in beiden Gruppen (Tabelle 22). Ausnahme war die Rate an Pneumonien/Septitiden, die in der Cisplatin + 5-FU Gruppe höher war (p=0,034). Ein Trend für vermehrt auftretende Übelkeit und Erbrechen Grad ≥ 2 (p=0,08) fand sich ebenfalls in der Cisplatin + 5-FU Gruppe. Chronische Nebenwirkungen Grad ≥ 2 wie

Xerostomie, Hautreaktionen und subkutane Fibrose waren häufiger nach Cisplatin + 5-FU als nach Cisplatin-Monotherapie (Tabelle 22).

f. Radiochemotherapie lokal fortgeschrittener Plattenepithelkarzinome der Kopf-Hals Region: Ist Cisplatin 20 mg/m² an fünf Tagen alle vier Wochen eine Alternative zu Cisplatin 100 mg/m² alle drei Wochen? (Studie 6)

Dirk Rades, Daniel Seidl, Stefan Janssen, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, K. Karner, Primoz Strojan, Steven E. Schild: Chemoradiation of locally advanced squamous cell carcinoma of the head-and-neck (LASCCHN): Is 20 mg/m² cisplatin on five days every four weeks an alternative to 100 mg/m² cisplatin every three weeks? Oral Oncol 59, 67-72 (2016) [Impact Factor = 3.979]

In dieser Studie wurde retrospektiv Cisplatin 100 mg/m²/d1 alle drei Wochen (Gruppe A) und Cisplatin 20 mg/m²/d1-5 alle vier Wochen (Gruppe B) im Rahmen einer kombinierten Radiochemotherapie verglichen.

Insgesamt wurden 230 Patient*innen eingeschlossen, 126 in Gruppe A und 104 in Gruppe B. Hierbei zeigte sich in der univariaten Analyse kein signifikanter Unterschied hinsichtlich der loko-regionalen Kontrolle (p=0,53; Tabelle 23). Das Therapie-Regime hatte ebenfalls keinen signifikanten Einfluss auf das metastasenfreie Überleben (p=0,67; Tabelle 24) und das Gesamtüberleben (p=0,14; Tabelle 25). In den Gruppen A und B wurde bei 66 (52 %) bzw. 16 Patient*innen (15 %) nicht die volle Dosis der Chemotherapie aufgrund von relevanten Nebenwirkungen appliziert (p<0,001).

Eine Radiochemotherapie mit Cisplatin 100 mg/m² alle drei Wochen war mit einer signifikant höheren Rate an Nebenwirkungen assoziiert: Pneumonie/Sepsis (p=0,003), Grad ≥ 2 Übelkeit/Erbrechen (p<0,001), Grad ≥ 2 Xerostomie (p=0,002) und Grad ≥ 2

Ototoxizität (p=0,048). Ein Trend zeigte sich hinsichtlich Grad ≥ 3 Hämatotoxizität (p=0,052; Tabelle 26).

g. Vergleich zweier niedrig dosierter Cisplatin-Regime bei der Therapie lokal fortgeschrittener Tumoren der Kopf-Hals-Region (Studie 7)

Dirk Rades, Daniel Seidl, Stefan Janssen, Primoz Strojan, Katarina Karner, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Comparing two lower-dose cisplatin programs for radiochemotherapy of locally advanced head-and-neck cancers. Eur Arch Otorhinolaryngol 274, 1021-1027 (2017) [Impact Factor = 1,809]

In dieser retrospektiven Studie wurden 170 Patient*innen eingeschlossen, die eine simultane Radiochemotherapie mit Cisplatin als Monotherapeutikum erhielten. Gruppe A (n=85) wurde mit zwei Zyklen Cisplatin 20 mg/m² an fünf aufeinanderfolgenden Tagen alle vier Wochen behandelt, Gruppe B erhielt wöchentlich Cisplatin 30-40 mg/m². Die Raten für die loko-regionale Kontrolle nach 3 Jahren waren 74 % bzw. 63 % (p=0,12; Tabelle 27). Die 3-Jahres Überlebensraten betrugen 73 % und 49 % (p=0,011; Tabelle 28). In der multivariaten Analyse war das Gesamtüberleben signifikant mit der Art der Chemotherapie (p=0,002) und zusätzlich mit dem ECOG Performance Score (p<0,001) assoziiert. In den Gruppen A und B erhielten 10 (12 %) bzw. 24 Patient*innen (28 %) keine kumulative Cisplatin-Dosis von ≥ 180 mg/m² (p=0,016). Akut- und Spättoxizität waren nicht signifikant unterschiedlich (Tabelle 29).

Eine Subgruppenanalyse ergab, dass bei definitiver Radiochemotherapie das Cisplatin-Regime in Gruppe A dem Regime in Gruppe B für die LRC (p=0,040) und das OS (p=0,005) überlegen war, nicht jedoch in der adjuvanten Situation (Tabellen 30, 31).

V. Diskussion

Zur optimalen individuellen Therapieplanung ist, neben der patientenspezifischen Situation, das Wissen um die Prognose wichtig. Um diese abschätzen zu können, ist die Identifikation unabhängiger Prognosefaktoren notwendig. Diesbezüglich wurden in vorangegangen Arbeiten bereits klinische und präklinische Marker identifiziert [23, 25].

In der vorliegenden Arbeit wurden klinische Prädiktoren für die loko-regionale Kontrolle und das Gesamtüberleben bei der definitiven und der adjuvanten Radiochemotherapie retrospektiv evaluiert. Der Schwerpunkt lag hierbei in der Bedeutung der simultanen Chemotherapie zusätzlich zur Bestrahlung bei entsprechenden Risikofaktoren sowie dem Vergleich verschiedener Cisplatin-basierter Therapieregime.

Unabhängige prognostische Faktoren:

Je nach Studie erwiesen sich in den multivariaten Analysen für die loko-regionale Kontrolle ein prätherapeutischer Hb-Wert von ≥ 12 g/dl, ein T-Stadium von 1-2, ein N-Stadium von 0-2a, ein Grading von 1-2, ein ECOG-Performance Score von 0-1 (bzw. ein Karnofsky-Index > 80 %), die Gesamtstrahlendosis, eine kumulierte Cisplatindosis von ≥ 180 mg/m² sowie das weibliche Geschlecht als unabhängige günstige Prognosefaktoren. In den multivariaten Analysen für das OS waren ein Hb-Wert ≥ 12 g/dl, ein T-Stadium von 1-2, ein N-Stadium von 0-2a, ein Grading von 1-2, der ECOG-Status 0-1, die Strahlendosis, eine kumulierte Cisplatindosis von ≥ 180 mg/m² sowie das weibliche Geschlecht signifikant. Diese Ergebnisse stimmen überwiegend mit denen vorheriger Studien überein, was für eine Beständigkeit der Resultate dieser Arbeit spricht [20, 23, 25].

Hinsichtlich der prognostischen Rolle des Hämoglobin-Wertes vor einer Radiochemotherapie gibt es in der Literatur zwei Interpretationen. Ein niedriger Wert gilt zum einen als Surrogatmarker für eine fortgeschrittene Erkrankung. Zum anderen geht

ein niedriger Hämoglobinwert mit einer schlechteren Oxygenierung des Tumors einher, wodurch die Wirkung der Strahlentherapie, die auf der Induktion von Sauerstoffradikalen basiert, beeinträchtigt wird [26-29].

Radiochemotherapie:

Generell sollten Patient*innen im klinischen Stadium III/IV eine adjuvante Bestrahlung erhalten [11-18]. In Folge zweier randomisierter Studien und deren Reanalysen hat sich in der Situation einer R1-Resektion die adjuvante kombinierte Radiochemotherapie als Standard etabliert [11-13]. Allerdings wird das am besten geeignete Chemotherapie-Regime immer noch kontrovers diskutiert. In o.g. randomisierten Studien wurde ein aggressives Schema mit Cisplatin 100 mg/m² an den Tagen 1, 22 und 43 gewählt. Dieses Regime entspricht in vielen Ländern, insbesondere in den USA, dem Standard. Hierbei treten jedoch beachtliche Nebenwirkungen auf. In der RTOG 88-24 Studie kam es bei 20 % der Patient*innen zu schwerwiegenden und in 12 % zu lebensbedrohlichen Nebenwirkungen bei der adjuvanten Radiochemotherapie mit 60 Gy und drei Kursen Cisplatin 100 mg/m² [35]. Aufgrund der sehr hohen Toxizitätsraten werden in anderen Zentren, vor allem in Europa, andere Regime verwendet.

Ein Ansatz ist die Reduktion der kumulativen Cisplatindosis von 300 mg/m² auf 160-200 mg/m² unter Hinzunahme von 5-Fluorouracil [15, 20, 36-38]. In einer retrospektiven Studie von 128 Patient*innen trat zum Beispiel eine Niereninsuffizienz Grad 2-3 signifikant seltener unter der fraktionierten Gabe von Cisplatin (20 mg/m²/d1-5 in der ersten und fünften Woche) plus 5-FU als unter Cisplatin 100 mg/m² alle drei Wochen auf (18 % versus 1 %, p=0,001) [20, 37]. Ein signifikanter Nachteil hinsichtlich loko-regionaler Kontrolle (66 % versus 72 %, p=0,32) und Gesamtüberleben (56 % vs. 68 %, p=0,82) nach 2 Jahren zeigte sich nicht.

In einer weiteren retrospektiven Studie, in der vier verschiedene Cisplatin-basierte Chemotherapie-Regime miteinander verglichen wurden, war eine Grad 3 Nierentoxizität in 8 % der Fälle bei Patient*innen, die 3 Kurse mit Cisplatin 100 mg/m² erhielten, zu verzeichnen, während diese unter 20 mg/m² Cisplatin plus 5-FU 600 mg/m² nur bei 1 % bzw. unter 20 mg/m² Cisplatin plus 5-FU 1000 mg/m² nur bei 2 % der Patient*innen auftrat. Nach 3 Jahren betrugen die Raten für die loko-regionale Kontrolle 67 %, 60 % und 72 % und die Überlebens-Raten 60 %, 50 % und 63 % [37]. In einer randomisierten Studie von Rodriguez et al. mit 69 Patient*innen trat eine relevante Nierentoxizität bei 26 % der Patient*innen in der Cisplatin 100 mg/m² Gruppe auf, während es 3 % in der Gruppe mit Cisplatin 20 mg/m² plus 5-FU 600 mg/m² waren (p=0,003) [38]. Im Gegensatz dazu traten eine Grad ≥ 2 Radiodermatitis (43 % versus 68 %, p=0,038) und eine Grad ≥ 3 Neutropenie (34 % versus 65 %, p=0,012) häufiger in der Cisplatin + 5-FU-Gruppe auf. Auch in dieser Studie waren die 3-Jahres Raten für die loko-regionale Kontrolle in beiden Gruppen ähnlich (96 % versus 94 %, p=0,52). Allerdings war das Gesamtüberleben nach hochdosierter Cisplatin-Monotherapie signifikant besser (97 % versus 85 %, p=0,013).

Die vorliegenden Studien legen nahe, dass Cisplatin 100 mg/m² alle drei Wochen mit einer höheren Rate an renaler Toxizität einhergeht als die Kombination bestehend aus niedriger dosiertem Cisplatin und 5-FU. Hinsichtlich weiterer Nebenwirkungen ist die Datenlage hingegen nicht eindeutig. Aus diesem Grund wurden in dieser Arbeit die Daten von 329 Patient*innen zusammengetragen und analysiert, um weitere Vergleiche zwischen diesen Regimen zu ermöglichen. Beide Optionen zeigten sich dabei als gleichwertig hinsichtlich der loko-regionalen Kontrolle und des Gesamtüberlebens. Neben diesen Ergebnissen wurde in der zweiten Studie dieser Arbeit gezeigt, dass eine kombinierte Radiochemotherapie, unabhängig davon ob Cisplatin 100 mg/m² oder Cisplatin + 5-FU verabreicht wurde, einer alleinigen Bestrahlung überlegen ist.

Die Behandlungsergebnisse waren denen zweier randomisierter Studien zur adjuvanten Therapie R1-resezierter Plattenepithelkarzinome der Kopf-Hals-Region gleichwertig [11, 12]. Bezüglich der inkonsistenten Ergebnisse im Vergleich zu der Studie von Rodriguez et al. können verschiedene Ursachen zugrunde liegen. Es handelt es sich bei der vorliegenden Arbeit um eine retrospektive Analyse, welche eine Verzerrung (Bias) beinhalten kann. Es könnte möglicherweise eine unterschiedliche Verteilung HPV positiver Tumoren vorliegen; der HPV-Status lag in dieser Arbeit nur bei wenigen Patient*innen vor. In einer vorangegangenen Studie aus Lübeck waren allerdings 14 % der Tumoren HPV-positiv und damit ein geringerer Anteil als in der randomisierten Studie von Rodriguez et al. (33 %) [34, 38]. Im Gegenzug beinhaltete die randomisierte Studie eine kleine Population von lediglich 69 Patient*innen, bei denen in der Cisplatin Monotherapie-Gruppe vermehrt günstige Patienteneigenschaften vorhanden waren. Aufgrund der vorliegenden Daten sind beide Therapieregime ähnlich effektiv. Die Rate der meisten Nebenwirkungen ist nicht signifikant unterschiedlich, ausgenommen die renale Toxizität. Aus diesem Grund bedarf es bei der Therapie mit Cisplatin 100 mg/m² alle 3 Wochen eines engmaschigen Monitorings der Nierenfunktion. Patient*innen mit einer eingeschränkten Nierenfunktion sollten ein niedriger dosiertes Cisplatin-Regime oder eine Chemotherapie mit anderen Substanzen erhalten.

Es stellt sich ferner die Frage, ob die zusätzliche Gabe von 5-FU einen Vorteil bietet. Diesbezüglich existieren nur wenige vergleichende Studien. In einer vorherigen retrospektiven Arbeit wurde Cisplatin als Monotherapeutikum (zwei Zyklen mit 20 mg/m² an fünf aufeinander folgenden Tagen der Woche eins und fünf der Radiochemotherapie) mit Cisplatin 20 mg/m² plus 5-Fluorouracil (zwei Zyklen mit je 600 mg/m² an fünf aufeinander folgenden Tagen) bei 128 Patient*innen mit einem inoperablen, lokal fortgeschrittenen Plattenepithelkarzinom der Kopf-Hals-Region verglichen. Die Ergebnisse

hinsichtlich der loko-regionalen Kontrolle, des metastasenfreien Überlebens und des Gesamtüberlebens unterschieden sich nicht signifikant [22]. Jedoch entwickelten in der Cisplatin plus 5-FU Gruppe signifikant mehr Patient*innen eine orale Mukositis (p=0,027) und eine radiogene Dermatitis (p=0,001).

Allgemein haben sich als Alternativen zu Cisplatin 100 mg/m² alle drei Wochen von den niedriger dosierten bzw. fraktionierten Cisplatin-Regime zwei Konzepte etabliert. Neben Cisplatin 20 mg/m² an fünf aufeinander folgenden Tagen der Wochen eins und fünf besteht die Möglichkeit einer wöchentlichen Gabe von Cisplatin 30-40 mg/m². In der vorliegenden Arbeit wurden beide Regime direkt miteinander und auch mit Cisplatin 100 mg/m² alle 3 Wochen verglichen. Die wöchentliche Gabe von Cisplatin 30-40 mg/m² [20, 39-43] ist insbesondere für Patient*innen geeignet, die während der Therapie nicht stationär behandelt werden möchten. Aktuell ist noch offen, ob eine wöchentliche Gabe so effektiv wie die Standardtherapie mit Cisplatin 100 mg/m² alle drei Wochen ist. Verfügbare Studien zeigten inkonsistente Ergebnisse. In einer retrospektiven Studie mit 94 Patient*innen war das Regime mit Cisplatin 100 mg/m² mit einem signifikant besseren Gesamtüberleben (p=0,041) bei gleichem progressionsfreiem Überleben (p=0,47) vergesellschaftet [40]. Jedoch waren Patient*innen in der „Weekly"-Gruppe signifikant älter (p=0,001), was möglicherweise eine Verzerrung (Bias) zur Folge hatte. Eine jüngere Studie zeigte ein längeres progressionsfreies Überleben und ein längeres Gesamtüberleben in der Cisplatin 100 mg/m² Gruppe. Die Raten nach 5 Jahren für das progressionsfreie Überleben und das Gesamtüberleben waren 56 % versus 44 % sowie 62 % versus 53 %. Die Ergebnisse waren in der univariaten Analyse signifikant, jedoch nicht in der multivariaten Analyse [41].

Eine weitere retrospektive Studie verglich 100 mg/m² Cisplatin alle drei Wochen mit Cisplatin 30 mg/m² weekly im Rahmen einer adjuvanten simultanen Radiochemotherapie.

Die 3-Jahres Raten lagen bei 71 % bzw. 74 % (p=0,95) für die loko-regionale Kontrolle sowie bei 84 % bzw. 75 % für das Gesamtüberleben (p=0,30) [42].

Zusätzlich zu diesen retrospektiven Studien wurde eine randomisierte Studie durchgeführt, welche 100 mg/m² Cisplatin alle drei Wochen mit Cisplatin weekly 40 mg/m² verglich [43]. Die 1-Jahres Raten betrugen 71 % bzw. 60 % für die loko-regionale Kontrolle (p=0,81) sowie 79 % bzw. 72 % für das Gesamtüberleben (p=0,98). Die Anzahl von 50 auswertbaren Patient*innen war jedoch zu gering für eine valide Aussage. Außerdem beschränkte sich die Studie auf Patient*innen mit Tumoren der Mundhöhle und kann somit nicht auf die Gesamtheit der Plattenepithelkarzinome der Kopf-Hals-Region übertragen werden.

Insgesamt ist die Gabe von 100 mg/m² Cisplatin alle 3 Wochen mit besserer lokoregionaler Kontrolle und besserem Gesamtüberleben assoziiert. Hinsichtlich schwerwiegender Nebenwirkungen ist die Datenlage uneinheitlich. Ho et al. zeigten, dass 100 mg/m² Cisplatin dreiwöchentlich schlechter vertragen wurde als die wöchentliche Gabe von Cisplatin 40 mg/m² [39]. Im Gegensatz hierzu beschrieben Tsan et al. eine signifikant höhere Rate an Grad ≥ 3 Mukositiden (75 % versus 39 %, p=0,012) und Grad ≥ 3 Gesamttoxizität (92 % versus 81 %, p=0,02) in der Cisplatin 40 mg/m² weekly Gruppe [43]. In der Studie von Espeli et al. kam es signifikant häufiger zu einer Niereninsuffizienz in der Cisplatin 100 mg/m² Gruppe (p=0,04) [40]. In der bisher größten Studie war Cisplatin 100 mg/m² mit einer signifikant höheren Rate an Nebenwirkungen als die wöchentliche Applikation von 40 mg/m² assoziiert [41]. Die Raten an Grad 3/4 Mukositiden lagen dabei bei 34 % bzw. 12 % (p<0,001) und die Raten an Grad 3/4 Dermatitiden bei 7 % und 1 % (p=0,014). Zudem war eine Abnahme der Kreatinin-Clearance deutlicher in der 100 mg/m² Gruppe (p<0,001) [41]. Auch in der aktuellen Arbeit waren einige akute Nebenwirkungen in der 100 mg/m² Gruppe signifikant häufiger

(Tabelle 16). Diese Ergebnisse machen deutlich, dass Patient*innen in der Cisplatin 100 mg/m² Gruppe ein intensiveres Monitoring sowie eine zeitige supportive Behandlung benötigen.

Auch im Vergleich zwischen Cisplatin 20 mg/m² an fünf aufeinanderfolgenden Tagen der Woche eins und fünf zu Cisplatin 100 mg/m² alle drei Wochen war eine signifikant niedrigere Rate an Nebenwirkungen wie Pneumonie/Sepsis, Grad ≥ 2 Übelkeit/Erbrechen, Grad ≥ 2 Nephrotoxizität und Grad ≥ 2 Xerostomie auffällig. Zudem zeigte sich hinsichtlich Hämatotoxizität Grad ≥ 3 und Ototoxizität Grad ≥ 2 ein Trend. Eine kumulative Cisplatindosis ≥ 200 mg/m² wurde in der Cisplatin 5x20 mg/m² Gruppe häufiger erreicht als in der Cisplatin 100 mg/m² Gruppe, was auf die geringeren Nebenwirkungen zurückzuführen ist. Hinsichtlich der Endpunkte loko-regionale Kontrolle, metastasenfreies Überleben und Gesamtüberleben ergab sich kein signifikanter Nachteil durch den Einsatz von 5x20 mg/m² alle 4 Wochen im Vergleich zu 100 mg/m² alle 3 Wochen (Tabellen 23-25). In der Gruppe der Patient*innen, die eine definitive Radiochemotherapie erhielten, war die loko-regionale Kontrolle in der Cisplatin 5x20 mg/m² Gruppe sogar signifikant besser.

Im Rahmen dieser Arbeit wurden zudem die Radiochemotherapie mit 2 Kursen Cisplatin 20 mg/m²/d1-5 mit der wöchentlichen Gabe von 30-40 mg/m² direkt verglichen. Das Regime Cisplatin 20 mg/m²/d1-5 war mit einem signifikant besseren Gesamtüberleben nach 3 Jahren assoziiert. Allerdings war auch hier der Vorteil auf Patient*innen beschränkt, die eine definitive Radiochemotherapie erhielten (Tabelle 30, 31). Es erhielten signifikant weniger Patient*innen der „weekly"-Gruppe eine kumulative Cisplatin-Dosis von 180 mg/m², was einer wöchentlichen Dosis von 30 mg/m² für sechs Wochen entspräche. Dieser Unterschied kann zu einem gewissen Maße dadurch erklärt werden, dass die Patient*innen der Cisplatin 20 mg/m² Gruppe ihre Chemotherapie unter

stationären Bedingungen und die „Weekly"-Gruppe diese ambulant erhielten. Patient*innen der letztgenannten Gruppe wiesen dabei möglicherweise eine geringere Compliance auf. Betrachtet man das Patientenkollektiv, worunter zumeist starke Raucher und Alkoholiker sind, bedarf es einer hohen Motivation, die geplanten sechs bis sieben ambulanten Termine zusätzlich zur laufenden Bestrahlung wahrzunehmen. Außerdem sind supportive Maßnahmen für stationäre Patient*innen aufgrund infrastruktureller Gegebenheiten tendenziell leichter verfügbar.

Insgesamt muss bei der Interpretation der Ergebnisse der Studien dieser Arbeit dem retrospektiven Design mit dem Risiko für Selektionsbias Rechnung getragen werden. Eine weitere Limitation dieser Arbeit ist die mögliche unterschiedliche Verteilung von HPV-positiven Tumoren, da der HPV-Status bei vielen Patient*innen nicht zur Verfügung stand und aus diesem Grund nicht in die Auswertung einfloss. In vorangegangenen Berichten aus Slowenien und Norddeutschland konnte HPV-Positivität bei 20 % bzw. 15 % der Patient*innen mit einem Oropharynxkarzinom nachgewiesen werden [34, 44]. Prospektive, randomisierte Studien sind wünschenswert.

In dieser Arbeit wurde der Stellenwert einer simultanen Radiochemotherapie bei R1-resezierten Tumoren der Kopf-Hals-Region untermauert. Hinsichtlich der Strahlendosis zeigte die absolute Strahlendosis in der adjuvanten Situation (70 versus 60-66 Gy) keinen signifikanten Einfluss auf die loko-regionale Kontrolle und das Gesamtüberleben, so dass eine Gesamtdosis von 66 Gy nach R1-Resektion ausreichend erscheint.

Im Fall einer definitiven simultanen Radiochemotherapie besteht das weltweit häufigste Regime aus 3 Kursen 100 mg/m² Cisplatin im Abstand von je 3 Wochen. Wie bereits im Vorfeld diskutiert und demonstriert, handelt es sich hierbei um ein Therapiekonzept mit einer sehr hohen Toxizität. Trotz der nachgewiesenen Effektivität limitieren folgenschwere Nebenwirkungen den Therapieerfolg, so dass alternative Regime gefragt

sind. In dieser Arbeit wurden 2 Kurse Cisplatin 20 mg/m²/d1-5 mit und ohne 5-FU sowie die wöchentliche Gabe von 30-40 mg/m² (entsprechend 6-7 Gaben) untersucht und mit 3 Kursen 100 mg/m² Cisplatin verglichen. Die wöchentliche Cisplatin-Gabe war dem Regime mit 3 Kursen von 100 mg/m² hinsichtlich loko-regionaler Kontrolle und Gesamtüberleben signifikant unterlegen, wies allerdings eine geringere Toxizität auf. Eine mögliche Erklärung für die schlechtere loko-regionale Kontrolle und das schlechtere Gesamtüberleben ist, dass die Compliance der Patient*innen bei 6-7 gegenüber 3 ambulanten Terminen trotz geringerer Toxizität schlechter ist, was zu einer niedrigeren kumulativen Cisplatindosis führen kann. Ein weiteres alternatives Cisplatin-Regime besteht aus 2 Kursen Cisplatin 20 mg/m²/d1-5 im Abstand von 4 Wochen in Kombination mit 5-FU. Dieses Regime war 3 Kursen 100 mg/m² Cisplatin hinsichtlich loko-regionaler Kontrolle und Gesamtüberleben nicht unterlegen. Allerdings war die Toxizität bis auf eine geringere Rate an Niereninsuffizienzen ähnlich hoch. Weiter wurde gezeigt, dass bei 2 Kursen Cisplatin 20 mg/m²/d1-5 die Hinzunahme von 5-FU in unterschiedlichen Dosierungen lediglich die Toxizität erhöht, ohne die Wirksamkeit zu verbessern. Im Vergleich von drei Kursen 100 mg/m² Cisplatin mit zwei Kursen Cisplatin 20 mg/m²/d1-5 ohne 5-FU war das letztgenannte Regime deutlich besser verträglich und hinsichtlich loko-regionaler Kontrolle, metastasenfreien Überleben und Gesamtüberleben nicht unterlegen. Beim Vergleich mit der wöchentlichen Gabe von 30-40 mg/m² Cisplatin führte das Regime mit 2 Kursen Cisplatin 20 mg/m²/d1-5 ohne 5-FU zu einem signifikant besseren Gesamtüberleben.

Somit ist das Regime bestehend aus 2 Kursen Cisplatin 20 mg/m²/d1-5 unter Berücksichtigung von Wirksamkeit und Toxizität von jenen, in dieser Arbeit untersuchten Regimen bei der Radiochemotherapie von Kopf-Hals-Tumoren zu empfehlen. Die

Ergebnisse sollten idealerweise in prospektiven randomisierten Studien überprüft werden.

VI. Ausblick

Cisplatin ist, unabhängig davon, in welcher Kombination oder Dosierung durchgeführt, der zentrale Bestandteil der derzeitigen Radiochemotherapie des lokal fortgeschrittenen Plattenepithelkarzinoms der Kopf-Hals-Region. Gerade in Bezug auf das Patientengut besteht hier jedoch eine relevante Einschränkung der Therapieoption(en). Neben dem Alter vieler Patient*innen ist vor allem eine eingeschränkte Nierenfunktion ein limitierender Faktor, zum Teil auch eine absolute Kontraindikation zur Durchführung einer Cisplatingabe. Als Alternative steht hierbei der monoklonale Antikörper gegen den epithelialen Wachstumsfaktor (EGFR) Cetuximab zur Verfügung, wobei die Effektivität der Therapie im Vergleich zur Cisplatintherapie geringer ausfällt [45].

Neben dem EGFR Antikörper wird in der aktuellen Leitlinie zur Therapie des Mundhöhlenkarzinoms [46] der PD-1 Antikörper Nivolumab im Rahmen der Rezidivtherapie als Option beschrieben. Neben diesen sind weitere Immuncheckpointinhibitoren gegen PD-1 bzw. PD-L1 mit unterschiedlichen Indikationen erhältlich. Hierhingehend gilt es die Ergebnisse laufender bzw. geplanter Studien zur Erstlinientherapie des fortgeschrittenen Plattenepithelkarzinoms der Kopf-Hals-Region abzuwarten. Diese könnten in naher Zukunft die Therapiemöglichkeiten unter gewissen Voraussetzungen, wie dem PD-L1-Status oder combined positive score (CPS), erweitern.

VII. Literaturverzeichnis

1. Wentzensen N, von Knebel Doeberitz M: Viral carcinogenesis of head and neck tumors. Pathologe 25, 21-30 (2004)

2. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L; EUROCARE Working Group: Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer 51, 2130-2143 (2015)

3. Siegel RL, Miller KD and Jemal A: Cancer statistics: CA Cancer J Clin 65, 5-29 (2015)

4. Eder-Czembirek C, Erovic BM, Czembirek C, Brunner M, Selzer E, Pötter R, Thurnher D: Betulinic acid a radiosensitizer in head and neck squamous cell carcinoma cell lines. Strahlenther Onkol 186, 143-148 (2010)

5. Fan S, Liang FY, Chen WL, Yang ZH, Huang XM, Wang YY, Lin ZY, Zhang DM, Zhou B, Chen WX, Chai Q, Wang HJ, Pan CB, Liang QX, Yu X, Dias-Ribeiro E, Feng YH, Li JS: Minimally Invasive Selective Neck Dissection: A Prospective Study of Endoscopically Assisted Dissection via a Small Submandibular Approach in cT1-2 N0. Oral Squamous Cell Carcinoma. Ann Surg Oncol 21, 3876-3881 (2014)

6. Jacob V, Bayer W, Astner ST, Busch R, Kneschaurek P: A planning comparison of dynamic IMRT for different collimator leaf thicknesses with helical tomotherapy and RapidArc for prostate and head and neck tumors. Strahlenther Onkol 186, 502-510 (2010)

7. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G.: Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 22, 69-76 (2004)

8. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N.: Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in

locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 43, 29-37 (1997)

9. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, Vaskovic Z, Tadic L.: Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 18, 1458-1464 (2000)

10. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group: Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92, 4-14 (2009)

11. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M.: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350, 1945-1952 (2004)

12. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK.: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350, 1937-1944 (2004)

13. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al.: Defining risk levels in locally advanced head and neck cancer: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) RTOG (#9501). Head Neck 27, 843-50 (2005)

14. Adelstein DJ, Saxton JP, Lavertu P, Tuason L, Wood BG, Wanamaker JR, et al.: A phase III radnomized trial comparing concurrent chemotherapy and radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. Head Neck 19, 567-75 (1997)

15. Fietkau R, Lautenschläger C, Sauer R, Dunst J, Becker A, Baumann M, et al.: Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: results of a German phase III trial ARO 96-3.: J Clin Oncol 24, 5507-5507 (2006)

16. Huguenin P, Glanzmann C, Taussky D, Lütolf UM, Schmid S, Moe K.: Hyperfractionated radiotherapy and simultaneous cisplatin for stage III and IV carcinomas of the head and neck. Long term results including functional outcome. Strahlenther Onkol 174, 397-402 (1998)

17. Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al.: Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 22, 4665-73 (2004)

18. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, Schuller DE, Forastiere AA.: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21, 92-98 (2003)

19. de Castro G Jr, Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, Federico MH.: High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 264, 1475-1482 (2007)

20. Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, et al. Comparison of four cisplatin based radiochemotherapy regimes for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 80, 1037-44 (2011)

21. Driessen CM, de Boer JP, Gelderblom H, Rasch CR, de Jong MA, Verbist BM, et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study): a randomized phase II study. Eur J Cancer 52, 77-84 (2016)

22. Tribius S, Kronemann S, Kilic Y, Schroeder U, Hakim S, Schild SE, et al. Radiochemotherapy including cisplatin alone versus cisplatin + 5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol 185, 675-81 (2009)

23. Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE, Schmidt R.: Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol 43, 535-543 (2007)

24. National Institutes of Health/National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; 2009 <https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf >

25. Rades D, Seibold ND, Gebhard MP, Noack F, Schild SE, Thorns C.: Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma oft he head and neck (SCCHN) Strahlenther Onkol.187, 626-632 (2011)

26. Becker A, Stadler P, Lavey RS, Hänsgen G, Kuhnt T, Lautenschläger C, Feldmann HJ, Molls M, Dunst J: Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys 46, 459-466 (2000)

27. Vaupel P, Kelleher DK and Höckel M: Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. Semin Oncol 28 (2 Suppl 8), 29-35 (2001)

28. Vaupel P, Mayer A and Höckel M: Impact of hemoglobin levels on tumor oxygenation: the higher, the better? Strahlenther Onkol 182, 63-71 (2006)

29. Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE, Dunst J: Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys 70, 1108-1114 (2008)

30. Rades D, Seibold ND, Gebhard MP, Noack F, Bruchhage KL, Schild SE: Fibroblast growth factor 2 is of prognostic value for patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 190, 68-74 (2014)

31. Rades D, Seibold ND, Schild SE, Bruchhage KL, Gebhard MP, Noack F: Androgen receptor expression: Prognostic value in locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 189, 849-855 (2013)

32. Seibold ND, Schild SE, Bruchhage KL, Gebhard MP, Noack F, Rades D. Prognostic impact of VEGF and FLT-1 receptor expression in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 189, 639-646 (2013)

33. Seibold ND, Schild SE, Gebhard MP, Noack F, Schröder U, Rades D: Prognosis of patients with locally advanced squamous cell carcinoma of the head and neck. Impact of tumor cell expression of EPO and EPO-R. Strahlenther Onkol 189, 559-565 (2013)

34. Rades D, Seibold ND, Hoffmann A, Gebhard MP, Noack F, Thorns C, Schild SE: Impact of the HPV-positivity definition on the prognostic value of HPV status in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 189, 856-860 (2013)

35. Al-Sarraf M, Pajak TF, Byhardt RW, Beitler JJ, Salter M, Cooper JS: Postoperativ radiotherapy with concurrent cisplatin appears to improve locoregional control of advanced, resectable head an neck cancers: RTOG 88-24. Int J Radiat Oncol Biol Phys 37, 777-782 (1997)

36. Adelstein DJ, Saxton JP, Rybicki LA, Esclamado RM, Wood BG, Strome M., et al.: Multiagent concurrent chemoradiotherapy for locoregionally advanced squamous cell head and neck cancer: mature results from a single institution. J Clin Oncol 24, 1064-1071 (2006)

37. Rades D, Fehlauer F, Sheikh-Sarraf M, Kazic N, Basic H, Poorter R, et al.: Toxicity of two cisplatin-based radiochemotherapy regimes for the treatment of patients with stage III/IV head and neck cancer. Head Neck 30, 235-241 (2008)

38. Rodriguez CP, Adelstein DJ, Rybicki LA, Savvides P, Saxton JP, Koyfman SA, et al: Randomized phase III study of 2 cisplatin-based chemoradiation regimes in locally advanced head and neck squamous cell carcinoma: impact of changing disease epidemiology on contemporary trial desing. Head Neck 37, 1583-1589 (2015)

39. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck

cancer: a retrospective comparison New Cross Hospital Wolverhampton, UK. Acta Oncol 47, 1513-1518 (2008)

40. Espel V, Zucca E, Ghielmini M, Ghielmini M, Giannini O, Salatino A, Martucci F, Richetti A: Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol 48, 266-271 (2012)

41. Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupart M, Ramade A, Zrounba P, Ceruse P, Pommier P: Radiotherapy potentiation with weekly cisplatin compared to standart every 3 weeks cisplatin chemotherapy for locally advanced head and neck squamous cell carcinoma. Drug Des Devel Ther. 9, 6203-10 (2015)

42. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, Olsen KD, Kasperbauer JL, Price DL, Garces YI, Ma DJ, Neben-Wittich MA, Molina JR, Garcia JJ, Price KA: Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncol. 50, 311-8 (2014)

43. Tsan DL, Lin CY, Kang SF, Fan KH, Liao CT, Chen IH, Lee LY, Wang HM, Chang JT. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol. 7, 215 (2012)

44. Strojan P, Zadnik V, Sifrer R, Lanisnik B, Didanovic V, Jereb S, Poljak M, Kocjan BJ, Gale N. Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983-2009: role of human papillomavirus infection. Eur Arch Otorhinolaryngol. 272, 3805-14 (2015)

45. Maura L Gillison, Andy M Trotti, Jonathan Harris, Avraham Eisbruch, Paul M Harari, David J Adelstein, Richard C K Jordan, Weiqiang Zhao, Erich M Sturgis, Barbara Burtness, John A Ridge, Jolie Ringash, James Galvin, Min Yao, Shlomo A Koyfman, Dukagjin M Blakaj, Mohammed A Razaq, A Dimitrios Colevas, Jonathan J Beitler, Christopger U Jones, Neal E Dunlap, Samantha A Seaward, Sharon Spencer, Thomas J Galloway, Jack Phan, James J Dignam, Quynh Thu Le. Radiohterapy Plus Cetuximab or Cisplatin in Human Papillomavirus-Positive Oropharyngeal Cancer (NRG Oncology

RTOG 1016): A Randomised, Multicentre, Non-Inferiority Trial. Lancet 393, 40-50 (2019)

46. https://www.leitlinienprogramm-onkologie.de/leitlinien/mundhoehlenkarzinom

VIII. Anhang

a. Tabellen

Tabelle 1 (Studie 1)
Patientencharakteristika und univariate Analyse verschiedener Prognosefaktoren in Bezug auf die LRC

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	Nach 5 Jahren (%)	*p*-Wert
Hämoglobin vor Radiochemotherapie				
< 12 g/dl (n=94)	61	48	48	
12-14 g/dl (n=109)	83	69	69	
> 14 g/dl (n=72)	73	61	54	**0.003**
T-Stadium				
T1/T2 (n=38)	95	72	72	
T3/T4 (n=237)	69	58	56	**0.029**
N-Stadium				
N0/N1/N2a (n=116)	81	67	63	
N2b/N2c/N3 (n=159)	67	54	54	**0.020**
Karnofsky Index				
≤ 70 (n=66)	65	52	52	
≥ 80 (n=209)	75	63	60	0.055
Geschlecht				
weiblich (n=56)	91	72	72	
männlich (n=219)	68	57	54	**0.009**
Alter				
≤ 57 Jahre (n=141)	72	57	57	
≥ 58 Jahre (n=134)	73	62	58	0.59
Simultane Chemotherapie				
Keine (n=14)	75	47	n/a	
Cisplatin weekly (n=70)	65	53	49	
Cisplatin 100 mg/m² (n=47)	87	72	72	
Cisplatin 20 mg/m² (n=72)	71	61	61	
Cisplatin 20 mg/m² + 5-FU (n=72)	73	56	56	0.15
Tumorlokalisation*				
Oropharynx (n=135)	75	62	60	
Hypopharynx (n=41)	54	50	50	
Larynx (n=57)	78	66	62	
Mundhöhle/-boden (n=39)	72	53	53	0.21
Histologischer Grad				
G1/G2 (n=165)	73	62	58	
G3 (n=110)	72	58	58	0.89
Totale Strahlendosis				
60-66 Gy (n=38)	75	63	63	
70 Gy (n=237)	73	59	57	0.92

n/a = not available / nicht verfügbar, *bei drei Patienten nicht eindeutig definiert

Tabelle 2 (Studie 2)
Patientencharakteristika und LRC nach R1-Resektion +/- adjuvanter Radiochemotherapie
nach 3 und 4 Jahren (univariate Analyse)

	Nach 3 Jahren (%)	Nach 4 Jahren (%)	*p*-Wert
Alter			
≤ 60 Jahre (n=72)	73	73	
> 60 Jahre (n=50)	72	55	0.90
Geschlecht			
weiblich (n=29)	70	70	
männlich (n=93)	74	65	0.84
Karnofsky-Index			
80-100 (n=80)	73	65	
≤ 70	74	74	0.75
Tumorlokalisation			

Oropharynx (n=60)	78	74	
Hypopharynx (n=20)	69	69	
Larynx (n=25)	80	0	
Mundhöhle/-boden (n=17)	46	n/a	0.15
T-Stadium			
T1/T2 (n=48)	79	73	
T3/T4 (n=74)	70	60	0.17
N-Stadium			
N0-1 (n=43)	75	68	
N2-3 (n=79)	73	67	0.46
Histologischer Grad			
G1/G2 (n=71)	80	74	
G3 (n=51)	63	54	0.19
Hämoglobin vor Radiochemotherapie			
<12 g/dl (n=49)	71	71	
≥12 g/dl (n=73)	75	66	0.49
Bestrahlungsdosis			
60-64 Gy (n=15)	32	n/a	
66 Gy (n=97)	77	69	
70 Gy (n=10)	80	n/a	0.18
Simultane Chemotherapie			
Keine (n=45)	61	33	
Cisplatin (n=44)	83	83	
Cisplatin/5-FU (n=33)	77	77	**0.010**

n/a = not available / nicht verfügbar

Tabelle 3 (Studie 3)
Patientencharakteristika in den Radiochemotherapiegruppen
(Cisplatin 100 mg/m² alle drei Wochen bzw. 30-40 mg/m² weekly; Chi-Quadrat-Test)

	Cisplatin weekly n Patienten (%)	Cisplatin 100 mg/m² n Patienten (%)	p-Wert
Alter			
≤ 56 Jahre (n=67)	37 (49)	30 (52)	
≥ 57 Jahre (n=66)	38 (51)	28 (48)	0.92
Geschlecht			
weiblich (n=29)	15 (20)	14 (24)	
männlich (n=104)	60 (80)	44 (76)	0.86
ECOG-Status			
0-1 (n=115)	64 (85)	51 (88)	
2 (n=18)	11 (15)	7 (12)	0.92
Tumorlokalisation			
Oropharynx (n=69)	36 (48)	33 (57)	
Hypopharynx (n=19)	12 (16)	7 (12)	
Larynx (n=30)	19 (25)	11 (19)	
Mundhöhle/-boden (n=15)	8 (11)	7 (12)	0.88
T-Stadium			
T1/T2 (n=16)	9 (12)	7 (12)	
T3/T4 (n=117)	66 (88)	51 (88)	0.99
N-Stadium			
N0-2a (n=66)	39 (52)	27 (47)	
N2b-3 (n=67)	36 (48)	31 (53)	0.75
Histologischer Grad			
G1/G2 (n=85)	49 (65)	36 (62)	
G3 (n=48)	26 (35)	22 (38)	0.89
Kumulative Cisplatin-Dosis			
≤ 200 mg/m² (n=85)	51 (68)	34 (59)	
> 200 mg/m² (n=48)	24 (32)	24 (41)	0.50

Nach Bonferroni Korrektur für multiple Tests (8 Tests) wurde ein p-Wert <0.006 als signifikant betrachtet

Tabelle 4 (Studie 4)

Patientencharakteristika der Gruppe A (100 mg/m² Cisplatin alle drei Wochen) und Gruppe B (20 mg/m² Cisplatin plus 600/1000 mg/m² 5-FU an fünf Tagen alle 4 Wochen

	Gruppe A (n=131) n Patienten (%)	Gruppe B (n=198) n Patienten (%)	*p*-Wert
Alter			
≤ 57 Jahre (n=178)	72 (55)	106 (54)	
≥ 58 Jahre (n=151)	59 (45)	92 (46)	0.87
Geschlecht			
Weiblich (n=67)	30 (23)	37 (19)	
Männlich (n=262)	101 (77)	161 (81)	0.68
Performance-Status			
ECOG 0-1 (n=289)	119 (91)	170 (86)	
ECOG 2 (n=40)	12 (9)	28 (14)	0.64
Tumorlokalisation			
Oropharynx (n=167)	69 (53)	98 (49)	
Hypopharynx (n=53)	23 (18)	30 (15)	
Larynx (n=66)	25 (19)	41 (21)	
Mundhöhle, -boden (n=43)	14 (11)	29 (15)	0.90
T-Stadium			
T1/T2 (n=129)	49 (37)	80 (40)	
T3/T4 (n=200)	82 (63)	118 (60)	0.73
N-Stadium			
N0-2a (n=118)	50 (38)	68 (34)	
N2b-3 (n=211)	81 (62)	130 (66)	0.67
Histologischer Grad			
G1-G2 (n=183)	76 (58)	107 (54)	
G3 (n=146)	55 (42)	91 (46)	0.64
Upfront-Operation			
Nein (n=105)	44 (34)	61 (31)	
Ja (n=224)	87 (66)	137 (69)	0.76
Hämoglobin vor Chemotherapie			
< 12 g/dl (n=107)	39 (30)	68 (34)	
≥ 12 g/dl (n=222)	92 (70)	130 (66)	0.62

Tabelle 5 (Studie 5)

Patientenmerkmale der zwei Gruppen: (Chi-Quadrat-Test)
Cisplatin (n=142) und Cisplatin + 5-FU (n=170)

	Cisplatin n Patienten (%)	Cisplatin + 5-FU n Patienten (%)	*p*-Wert
T-Stadium			
T1-2 (n=103)	47 (33)	56 (33)	
T3-4 (n=209)	95 (67)	114 (67)	0.99
N-Stadium			
N0-1 (n=66)	26 (18)	40 (24)	
N2-3 (n=246)	116 (82)	130 (76)	0.65
ECOG Score			
0-1 (n=224)	86 (61)	138 (81)	
2 (n=88)	56 (39)	32 (19)	
Geschlecht			
weiblich (n=61)	27 (19)	34 (20)	
männlich (n=251)	115 (81	136 (80)	0.92
Alter			
≤ 57 Jahre (n=165)	75 (53)	90 (53)	
≥ 58 Jahre (n=147)	67 (47)	80 (47)	0.99
Tumorlokalisation			
Oropharynx (n=147)	74 (52)	73 (43)	

Hypopharynx (n=46)	18 (13)	28 (16)	
Larynx (n=58)	23 (16)	35 (21)	
Mundhöhle/-boden (n=61)	27 (19)	34 (20)	0.72
Histologischer Grad			
G1/G2 (n=151)	72 (51)	79 (46)	
G3 (n=161)	70 (49)	91 (54)	0.65
Vorherige Operation			
Nein (n=148)	73 (51)	75 (44)	
Ja (n=164)	69 (49)	95 (56)	0.42
Bestrahlungstechnik			
3D konform (n=246)	111 (78)	135 (79)	
IMRT/VMAT (n=66)	31 (22)	35 (21)	0.91
Hämoglobin vor Radiochemotherapie			
< 12 g/dl (n=109)	49 (35)	60 (35)	
≥ 12 g/dl (n=203)	93 (65)	110 (65)	0.94

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.005 als signifikant betrachtet

Tabelle 6 (Studie 6)

Patientencharakteristika in der Gruppe A (Cisplatin 100 mg/m² alle drei Wochen)und
Gruppe B (Cisplatin 20 mg/m² an fünf Tagen alle vier Wochen)

	Gruppe A n Patienten (%)	Gruppe B n Patienten (%)	*p*-Wert
T-Stadium			
T1/T2 (n=85)	44 (35)	41 (39)	
T3/T4 (n=145)	82 (65)	63 (61)	0.37
N-Stadium			
N0-1 (n=55)	44 (35)	41 (39)	
N2-3 (n=175)	82 (65)	63 (61)	0.66
Performance-Status			
ECOG 0-1 (n=197)	112 (89)	85 (82)	
ECOG 2 (n=33)	14 (11)	19 (18)	0.56
Geschlecht			
Weiblich (n=53)	31 (25)	22 (21)	
Männlich (n=177)	95 (75)	82 (79)	0.76
Alter			
≤ 56 Jahre (n=124)	71 (56)	53 (51)	
≥ 57 Jahre (n=106)	55 (44)	51 (49)	0.58
Tumorlokalisation			
Oropharynx (n=130)	72 (57)	958 (56)	
Hypopharynx (n=31)	17 (13)	14 (13)	
Larynx (n=39)	23 (18)	16 (15)	
Mundhöhle (n=30)	14 (11)	16 (15)	0.92
Histologischer Grad			
G1-G2 (n=134)	76 (60)	58 (56)	
G3 (n=96)	50 (40)	46 (44)	0.65
Upfront-Operation			
Nein (n=98)	53 (42)	45 (43)	
Ja (n=132)	73 (58)	59 (57)	0.90
Bestrahlungstechnik			
3D Conformal (n=187)	106 (84)	81 (78)	
IMRT/VMAT (n=43)	20 (16)	23 (22)	0.60
Hämoglobin vor Chemotherapie			
< 12 g/dl (n=72)	37 (29)	35 (34)	
≥ 12 g/dl (n=158)	89 (71)	69 (66)	0.70
Kumulative Cisplatin-Dosis			
<200 mg/m² (n=61)	45 (36)	16 (15)	
≥ 200 mg/m² (n=169)	81 (64)	88 (85)	0.07

Nach Bonferroni Korrektur für multiple Tests (n=11) wurde ein *p*-Wert <0.0045 als signifikant betrachtet

Tabelle 7 (Studie 7)

Patientencharakteristika Gruppe A (Cisplatin 20 mg/m² an 5 Tagen alle 4 Wochen, n = 85)
und Gruppe B (Cisplatin 30-40 mg/m² wöchentlich, n = 85)

	Gruppe A, *n* Patienten (%)	Gruppe B, *n* Patienten (%)
Alter		
≤ 57 Jahre (n = 86)	43 (51)	43 (51)
≥ 58 Jahre (n = 84)	42 (49)	42 (49)
Geschlecht		
Weiblich (n = 34)	17 (20)	17 (20)
Männlich (n = 136)	68 (80)	68 (80)
ECOG Performance Score		
0-1 (n = 128)	64 (75)	64 (75)
2 (n = 42)	21 (25)	21 (25)
Tumorlokalisation		
Oropharynx (n = 86)	43 (51)	43 (51)
Hypopharynx (n= 28)	14 (16)	14 (16)
Larynx (n = 32)	16 (19)	16 (19)
Mundhöhle (n = 24)	12 (14)	12 (14)
T-Kategorie		
T1-2 (n = 34)	17 (20)	17 (20)
T3-4 (n = 136)	68 (80)	68 (80)
N-Kategorie		
N0-2a (n = 78)	39 (46)	39 (46)
N2b-3 (n = 92)	46 (54)	46 (54)
Vorherige Operation		
Nein (n = 120)	60 (71)	60 (71)
Ja (n = 50)	25 (29)	25 (29)
Hämoglobin vor Radiochemotherapie		
< 12 g/dl (n = 48)	24 (28)	24 (28)
≥ 12 g/dl (n = 122)	61 (72)	61 (72)
Bestrahlungstechnik		
3D konform (n = 126)	63 (74)	63 (74)
IMRT (n = 44)	22 (26)	22 (26)

Tabelle 8 (Studie 1)

Multivariate Analyse verschiedener Prognosefaktoren auf die LRC

	Relatives Risiko	95 % Konfidenzintervall	*p*-Wert
Hämoglobin vor Radiochemotherapie	1.33	1.01-1.77	**0.040**
T-Stadium	1.53	1.10-2.30	**0.010**
N-Stadium	1.54	1.02-2.38	**0.042**
Geschlecht	2.24	1.24-4.46	**0.006**

Tabelle 9 (Studie 1)

Univariate Analyse verschiedener Prognosefaktoren auf das OS

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	Nach 5 Jahren (%)	*p*-Wert
Hämoglobin vor Radiochemotherapie				
<12 g/dl (n=94)	64	41	35	
12-14 g/dl (n=109)	84	54	39	
> 14 g/dl (n=72)	81	57	37	**0.019**
T-Stadium				
T1/T2 (n=38)	84	67	43	
T3/T4 (n=237)	75	47	35	0.13
N-Stadium				
N0/N1/N2a (n=116)	85	63	46	
N2b/N2c/N3 (n=159)	70	40	28	**<0.001**
Karnofsky Index				
≤ 70 (n=66)	62	25	25	

≥ 80 (n=209)	81	58	51	**<0.001**
Geschlecht				
weiblich (n=56)	84	66	40	
männlich (n=219)	74	46	35	0.045
Alter				
≤ 57 Jahre (n=141)	77	51	33	
≥ 58 Jahre (n=134)	76	49	39	0.98
Simultane Chemotherapie				
Keine (n=14)	64	21	n/a	
Cisplatin weekly (n=70)	70	46	31	
Cisplatin 100 mg/m² (n=47)	87	67	45	
Cisplatin 20 mg/m² (n=72)	79	62	48	
Cisplatin 20 mg/m² + 5-FU (n=72)	75	34	34	**0.009**
Tumorlokalisation*				
Oropharynx (n=135)	76	52	38	
Hypopharynx (n=41)	61	33	13	
Larynx (n=57)	88	61	48	
Mundhöhle/-boden (n=39)	74	42	34	**<0.001**
Histologischer Grad				
G1/G2 (n=165)	81	49	39	
G3 (n=110)	70	52	32	0.38
Totale Strahlendosis				
60-66 Gy (n=38)	66	40	40	
70 Gy (n=237)	78	52	35	0.38

n/a = not available / nicht verfügbar, *bei drei Patienten nicht eindeutig definiert

Tabelle 10 (Studie 1)
Multivariate Analyse verschiedener Prognosefaktoren auf das OS

	Relatives Risiko	95 % Konfidenzintervall	*p*-Wert
Hämoglobin vor Radiochemotherapie	1.32	1.04-1.68	**0.020**
N-Stadium	2.02	1.39-2.98	**<0.001**
Karnofsky-Index	2.05	1.39-3.01	**<0.001**
Geschlecht	1.67	1.07-2.74	**0.024**
Art der Chemotherapie	1.22	1.12-1.34	**<0.001**
Tumorlokalisation	1.04	0.91-1.17	0.57

Tabelle 11 (Studie 2)
OS nach R1-Resektion +/- adjuvanter Radiochemotherapie
(univariate Analyse)

	Nach 3 Jahren (%)	Nach 4 Jahren (%)	*p*-Wert
Alter			
≤ 60 Jahre (n=72)	60	57	
> 60 Jahre (n=50)	55	50	0.81
Geschlecht			
weiblich (n=29)	65	65	
männlich (n=93)	57	51	0.33
Karnofsky-Index			
80-100 (n=80)	62	5	
≤ 70	50	50	0.25
Tumorlokalisation			
Oropharynx (n=60)	64	60	
Hypopharynx (n=20)	36	36	
Larynx (n=25)	67	56	
Mundhöhle/-boden (n=17)	41	n/a	0.11
T-Stadium			
T1/T2 (n=48)	72	64	
T3/T4 (n=74)	47	47	0.053
N-Stadium			

N0-1 (n=43)	76	65	
N2-3 (n=79)	48	48	**0.006**
Histologischer Grad			
G1/G2 (n=71)	66	60	
G3 (n=51)	48	38	**0.021**
Hämoglobin vor Radiochemotherapie			
< 12 g/dl (n=49)	42	42	
≥ 12 g/dl (n=73)	69	62	**0.002**
Bestrahlungsdosis			
60-64 Gy (n=15)	25	0	
66 Gy (n=97)	61	59	
70 Gy (n=10)	70	n/a	0.076
Simultane Chemotherapie			
Keine (n=45)	51	44	
Cisplatin (n=44)	65	61	
Cisplatin/5-FU (n=33)	57	57	0.21

n/a = not available / nicht verfügbar

Tabelle 12 (Studie 2)
OS nach R1-Resektion +/- adjuvanter Radiochemotherapie
Multivariate Analyse (Cox Regression)

	Relatives Risiko	95 % Konfidenzintervall	*p*-Wert
T-Stadium (T1/2 vs. T3/4)	1.44	1.06-1.99	**0.018**
N-Stadium (N0/1 vs. N2/3)	2.50	1.23-5.51	**0.011**
Histologischer Grad (G1/2 vs. G3	1.31	0.97-1.78	0.078
Hämoglobin vor Radiochemotherapie (<12 g/dl vs. ≥ 12 g/dl)	2.56	1.38-4.78	**0.003**
Strahlendosis (70 Gy vs. 66 Gy vs. 60-64 Gy)	2.49	1.15-5.15	**0.021**
Simultane Chemotherapie (Keine vs. Cisplatin vs. Cisplatin/5-FU)	1.44	0.99-2.12	0.055

Tabelle 13 (Studie 3)
Univariate Analyse der LRC
(Cisplatin 100 mg/m² alle drei Wochen bzw. 30-40 mg/m² weekly)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	*p*-Wert
Radiochemotherpie-Regime			
Cisplatin weekly (n=75)	70	58	
Cisplatin 100 mg/m² (n=58)	85	78	**0.010**
Alter			
≤ 56 Jahre (n=67)	78	65	
≥ 57 Jahre (n=66)	74	68	0.72
Geschlecht			
weiblich (n=29)	92	87	
männlich (n=104)	72	61	**0.010**
ECOG-Status			
0-1 (n=115)	78	69	
2 (n=18)	66	49	0.14
Tumorlokalisation			
Oropharynx (n=69)	83	74	
Hypopharynx (n=19)	47	47	
Larynx (n=30)	79	67	
Mundhöhle/-boden (n=15)	75	56	0.047
T-Stadium			
T1/T2 (n=16)	93	76	
T3/T4 (n=117)	74	65	0.28
N-Stadium			
N0-2a (n=66)	76	68	

N2b-3 (n=67)	76	65	0.93
Histologischer Grad			
G1/G2 (n=85)	77	69	
G3 (n=48)	75	63	0.65
Kumulative Cisplatin-Dosis			
≤ 200 mg/m² (n=85)	70	62	
> 200 mg/m² (n=48)	86	74	0.09

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.006 als signifikant betrachtet

Tabelle 14 (Studie 3)
Ergebnisse der multivariaten Analyse der LRC, MFS und des OS
(Cisplatin 100 mg/m² alle drei Wochen bzw. 30-40 mg/m² weekly)

	Hazard Ratio	95 % Konfidenzintervall	*p*-Wert
Lokoregionale Kontrolle			
Radiochemotherapieregime: (Cisplatin weekly vs. Cisplatin 100 mg/m²)	1.57	1.12-2.31	**0.008**
Geschlecht (Weiblich vs. Männlich)	4.37	1.58-18.11	**0.003**
Tumorlokalisation (Oropharynx/Larynx vs. andere)	1.18	0.94-1.45	0.16
Metastasenfreies Überleben			
ECOG-Status (0-1 vs. 2)	5.63	2.19-14.11	**<0.001**
N-Stadium (N0-2a vs. N2b-3)	2.02	0.09-4.84	0.09
Histologischer Grad (G1-2 vs. G3)	1.81	1.26-2.66	**0.002**
Tumorlokalisation (Oropharynx/Larynx vs. andere)	1.15	0.88-1.50	0.30
Gesamtüberleben			
Radiochemotherapieregime: (Cisplatin weekly vs. Cisplatin 100 mg/m²)	1.33	1.04-1.73	**0.023**
Geschlecht (Weiblich vs. Männlich)	1.98	1.08-3.96	**0.026**
ECOG-Status (0-1 vs. 2)	2.15	1.09-3.99	**0.029**
Tumorlokalisation (Oropharynx/Larynx vs. andere)	1.09	0.92-1.30	0.32

Tabelle 15 (Studie 3)
Univariate Analyse des Gesamtüberlebens (OS)
(Cisplatin 100 mg/m² alle drei Wochen bzw. 30-40 mg/m² weekly)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	*p*-Wert
Radiochemotherapie-Regime			
Cisplatin weekly (n=75)	71	45	
Cisplatin 100 mg/m² (n=58)	83	60	0.026
Alter			
≤ 56 Jahre (n=67)	77	54	
≥ 57 Jahre (n=66)	74	49	0.50
Geschlecht			
weiblich (n=29)	89	70	
männlich (n=104)	72	47	0.050
ECOG-Status			
0-1 (n=115)	78	56	

2 (n=18)	61	14	0.006
Tumorlokalisation			
Oropharynx (n=69)	78	61	
Hypopharynx (n=19)	53	21	
Larynx (n=30)	83	59	
Mundhöhle/-boden (n=15)	80	29	**<0.001**
T-Stadium			
T1/T2 (n=16)	81	63	
T3/T4 (n=117)	75	50	0.85
N-Stadium			
N0-2a (n=66)	79	60	
N2b-3 (n=67)	73	42	0.14
Histologischer Grad			
G1/G2 (n=85)	78	52	
G3 (n=48)	73	51	0.47
Kumulative Cisplatin-Dosis			
≤ 200 mg/m² (n=85)	69	46	
> 200 mg/m² (n=48)	87	61	0.13

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.006 als signifikant betrachtet

Tabelle 16 (Studie 3)
Akut- und Spättoxizitäten: Cisplatin 100 mg/m² alle drei Wochen bzw. 30-40 mg/m² weekly

	Cisplatin weekly n Patienten (%)	Cisplatin 100 mg/m² n Patienten (%)	*p*-Wert
Orale Mukositis			
Grad ≥ 2	70 (93)	55 (95)	0.95
Hautreaktionen			
Grad ≥ 2	48 (64)	48 (83)	0.25
Hämatotoxizität			
Grad ≥ 3	7 (9)	19 (33)	**0.004**
Nephrotoxizität			
Grad ≥ 2	2 (3)	12 (21)	**0.004**
Pneumonie/Sepsis			
Grad ≥ 3	1 (1)	7 (12)	0.033
Xerstomie[a]			
Grad ≥ 2	28/60 (47)	34/58 (59)	0.44
Subkutane Fibrose[a]			
Grad ≥ 2	27/72 (38)	28/51 (55)	0.20

[a] nicht bei allen Patienten verfügbar
Nach Bonferroni Korrektur für multiple Tests (7 Tests) wurde ein *p*-Wert <0.007 als signifikant betrachtet

Tabelle 17 (Studie 4)
Vergleich der Chemotherapie-Regime und neun Prognosefaktoren hinsichtlich der LRC (univariate Analyse)
(Cisplatin 100 m/m² alle drei Wochen versus 5x20 mg/m² plus 5-FU alle 4 Wochen)

	Nach einem Jahr (%)	Nach drei Jahren (%)	Nach fünf Jahren (%)	*p*-Wert
Radiochemotherapiegruppen				
Gruppe A (n=131)	89	79	77	
Gruppe B (n=198)	85	77	77	0.36
Alter				
≤ 57 Jahre (n=178)	87	76	76	
≥ 58 Jahre (n=151)	87	80	78	0.43
Geschlecht				
Weiblich (n=67)	94	80	80	
Männlich (n=262)	85	77	76	0.32
Performance-Status				
ECOG 0-1 (n=289)	88	81	80	
ECOG 2 (n=40)	75	41	41	**<0.001**

	Nach einem Jahr (%)	Nach drei Jahren (%)	Nach fünf Jahren (%)	p-Wert
Tumorlokalisation				
Oropharynx (n=167)	89	79	79	
Hypopharynx (n=53)	76	70	63	
Larynx (n=66)	91	83	83	
Mundhöhle, -boden (n=43)	85	76	76	0.16
T-Stadium				
T1/T2 (n=129)	95	84	82	
T3/T4 (n=200)	82	74	74	**0.012**
N-Stadium				
N0-2a (n=118)	92	85	82	
N2b-3 (n=211)	84	73	73	**0.026**
Histologischer Grad				
G1-G2 (n=183)	90	85	83	
G3 (n=146)	83	69	69	**0.006**
Upfront-Operation				
Nein (n=105)	79	63	63	
Ja (n=224)	91	83	82	**<0.001**
Hb vor Chemotherapie				
< 12 g/dl (n=107)	76	65	65	
≥ 12 g/dl (n=222)	92	84	82	**<0.001**

Tabelle 18 (Studie 4)

Vergleich der Chemotherapie-Regime und neun Prognosefaktoren hinsichtlich des OS (univariate Analyse) (Cisplatin 100 m/m² alle drei Wochen versus 5x20 mg/m² plus 5-FU alle 4 Wochen)

	Nach einem Jahr (%)	Nach drei Jahren (%)	Nach fünf Jahren (%)	p-Wert
Radiochemotherapiegruppen				
Gruppe A (n=131)	88	67	57	
Gruppe B (n=198)	85	65	57	0.64
Alter				
≤ 57 Jahre (n=178)	87	68	58	
≥ 58 Jahre (n=151)	85	63	55	0.73
Geschlecht				
Weiblich (n=67)	91	76	53	
Männlich (n=262)	85	63	58	0.59
Performance-Status				
ECOG 0-1 (n=289)	89	73	64	
ECOG 2 (n=40)	65	11	5	**<0.001**
Tumorlokalisation				
Oropharynx (n=167)	85	71	60	
Hypopharynx (n=53)	75	49	45	
Larynx (n=66)	95	64	54	
Mundhöhle, -boden (n=43)	88	72	72	0.047
T-Stadium				
T1/T2 (n=129)	90	78	65	
T3/T4 (n=200)	83	56	52	**0.003**
N-Stadium				
N0-2a (n=118)	95	75	62	
N2b-3 (n=211)	81	60	53	**0.003**
Histologischer Grad				
G1-G2 (n=183)	91	71	65	
G3 (n=146)	80	59	47	**0.002**
Upfront-Operation				
Nein (n=105)	78	47	38	
Ja (n=224)	90	72	63	**<0.001**
Hb vor Chemotherapie				
< 12 g/dl (n=107)	71	46	43	
≥ 12 g/dl (n=222)	93	75	64	**<0.001**

Tabelle 19 (Studie 4)

Vergleich akuter und chronischer Nebenwirkungen der Chemotherapie-Regime
(Cisplatin 100 m/m² alle drei Wochen versus 5x20 mg/m² plus 5-FU alle 4 Wochen)

	Gruppe A n Patienten (%)	Gruppe B n Patienten (%)	*p*-Wert
Orale Mukositis			
Grad ≥ 2	122 (93)	164 (83)	0.36
Dermatitis			
Grad ≥ 2	102 (78)	166 (84)	0.60
Hämatotoxizität			
Grad ≥ 3	29 (22)	40 (20)	0.81
Nephrotoxizität			
Grad ≥ 2	17 (13)	8 (4)	**0.008**
Pneumonie/Sepsis			
Grad ≥ 3	8 (6)	10 (5)	0.91
Xerostomie			
Grad ≥ 2	68 (52)	79 (40)	0.13
Subkutane Fibrose			
Grad ≥ 2	63[a] (51)	68[b] (36)	0.10

a von 129 Patienten, b von 188 Patienten

Tabelle 20 (Studie 5)

LRC: Vergleich Cisplatin +/- 5-FU (univariate Analyse)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	Nach 5 Jahren (%)	*p*-Wert
Chemotherapie-Regime				
Cisplatin (n=142)	81	69	69	
Cisplatin + 5-FU (n=270)	82	68	68	0.71
T-Stadium				
T1-2 (n=103)	95	79	79	
T3-4 (n=209)	75	64	64	**<0.001**
N-Stadium				
N0-1 (n=66)	92	79	79	
N2-3 (n=246)	78	66	66	0.010
ECOG Score				
0-1 (n=224)	84	74	74	
2 (n=88)	75	51	n/a	0.005
Geschlecht				
weiblich (n=61)	92	75	75	
männlich (n=251)	79	67	67	0.14
Alter				
≤ 57 Jahre (n=165)	81	64	64	
≥ 58 Jahre (n=147)	82	75	75	0.28
Tumorlokalisation				
Oropharynx (n=147)	82	73	73	
Hypopharynx (n=46)	79	72	n/a	
Larynx (n=58)	82	63	63	
Mundhöhle/-boden (n=61)	83	66	66	0.87
Histologischer Grad				
G1/G2 (n=151)	85	77	77	
G3 (n=161)	78	61	61	0.033
Vorherige Operation				
Nein (n=148)	72	61	61	
Ja (n=164)	90	75	75	**0.002**
Bestrahlungstechnik				
3D konform (n=246)	81	67	67	
IMRT/VMAT (n=66)	85	73	73	0.32
Hämoglobin vor Radiochemotherapie				

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	Nach 5 Jahren (%)	p-Wert
< 12 g/dl (n=109)	70	57	57	
≥ 12 g/dl (n=203)	88	75	75	**<0.001**
Vollständige Chemotherapie				
Nein (n=73)	71	47	47	
Ja (n=239)	84	74	74	**<0.001**
Bestrahlungspause > 1 Woche				
Nein (n=253)	86	77	77	
Ja (n=59)	59	30	30	**<0.001**

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.0038 als signifikant betrachtet

n/a = not available / nicht verfügbar

Tabelle 21 (Studie 5)

Vergleich Cisplatin +/- 5-FU hinsichtlich des MFS (univariate Analyse)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	Nach 5 Jahren (%)	*p*-Wert
Chemotherapie-Regime				
Cisplatin (n=142)	85	76	72	
Cisplatin + 5-FU (n=270)	87	69	62	0.37
T-Stadium				
T1-2 (n=103)	96	82	75	
T3-4 (n=209)	82	68	65	**0.003**
N-Stadium				
N0-1 (n=66)	97	82	73	
N2-3 (n=246)	83	70	65	0.019
ECOG Score				
0-1 (n=224)	91	77	71	
2 (n=88)	74	61	n/a	**<0.001**
Geschlecht				
weiblich (n=61)	88	75	75	
männlich (n=251)	86	72	65	0.61
Alter				
≤ 57 Jahre (n=165)	88	75	66	
≥ 58 Jahre (n=147)	85	70	70	0.21
Tumorlokalisation				
Oropharynx (n=147)	90	80	71	
Hypopharynx (n=46)	64	55	n/a	
Larynx (n=58)	98	70	70	
Mundhöhle/-boden (n=61)	83	78	70	**<0.001**
Histologischer Grad				
G1/G2 (n=151)	90	74	62	
G3 (n=161)	83	71	68	0.19
Vorherige Operation				
Nein (n=148)	80	64	60	
Ja (n=164)	92	80	73	**0.004**
Bestrahlungstechnik				
3D konform (n=246)	86	72	66	
IMRT/VMAT (n=66)	88	74	74	0.45
Hämoglobin vor Radiochemotherapie				
< 12 g/dl (n=109)	78	64	64	
≥ 12 g/dl (n=203)	90	77	69	0.019
Vollständige Chemotherapie				
Nein (n=73)	79	66	66	
Ja (n=239)	89	75	68	0.020
Bestrahlungspause > 1 Woche				
Nein (n=253)	88	77	70	
Ja (n=59)	77	52	52	**0.002**

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.0038 als signifikant betrachtet

n/a = not available / nicht verfügbar

Tabelle 22 (Studie 5)

Akut- und Spättoxizitäten: Vergleich Cisplatin (n=142) und Cisplatin + 5-FU (n=170)

	Cisplatin n Patienten (%)	Cisplatin + 5-FU n Patienten (%)	*p*-Wert
Orale Mukositis			
Grad ≥ 2	122 (86)	161 (95)	0.56
Akute Hautreaktionen			
Grad ≥ 2	109 (77)	160 (94)	0.11
Hämatotoxizität			
Grad ≥ 3	25 (18)	38 (22)	0.42
Übelkeit/Erbrechen			
Grad ≥ 2	31 (22)	56 (33)	0.08
Nephrotoxizität			
Grad ≥ 2	6 (4)	9 (5)	0.92
Pneumonie/Sepsis			
Grad ≥ 3	1 (<1)	10 (6)	0.034
Xerstomie			
Grad ≥ 2	40 (29)	78 (48)	0.009
Späte Hautreaktionen			
Grad 2	16 (12)	35 (22)	0.046
Zervikale Lymphödeme			
Grad 2	24 (17)	42 (26)	0.13
Subkutane Fibrose			
Grad ≥ 2	31 (22)	66 (41)	0.006

Nach Bonferroni Korrektur für multiple Tests wurde ein *p*-Wert <0.005 als signifikant betrachtet

Tabelle 23 (Studie 6)

Univariate Analyse der Lokoregionären Kontrolle (LRC)
(Cisplatin 100 mg/m² alle drei Wochen versus Cisplatin 5x20 mg/m² alle vier Wochen)

	Nach einem Jahr (%)	Nach drei Jahren (%)	*p*-Wert
Chemotherapie-Regime			
Gruppe A (n=126)	89	79	
Gruppe B (n=104)	87	74	0.53
T-Stadium			
T1/T2 (n=85)	96	82	
T3/T4 (n=145)	84	74	0.058
N-Stadium			
N0-1 (n=55)	88	75	
N2-3 (n=175)	88	77	0.89
Performance-Status			
ECOG 0-1 (n=197)	88	77	
ECOG 2 (n=33)	90	80	0.80
Geschlecht			
Weiblich (n=53)	96	79	
Männlich (n=177)	86	76	0.22
Alter			
≤ 56 Jahre (n=124)	87	73	
≥ 57 Jahre (n=106)	90	81	0.33
Tumorlokalisation			
Oropharynx (n=130)	92	82	
Hypopharynx (n=31)	73	62	
Larynx (n=39)	90	72	
Mundhöhle (n=30)	86	73	0.029
Histologischer Grad			
G1-G2 (n=134)	87	82	
G3 (n=96)	90	70	0.45
Upfront-Operation			
Nein (n=98)	83	71	

	Nach einem Jahr (%)	Nach drei Jahren (%)	p-Wert
Ja (n=132)	92	81	0.11
Bestrahlungstechnik			
3D Conformal (n=187)	89	77	
IMRT/VMAT (n=43)	85	79	0.65
Hämoglobin vor Chemotherapie			
< 12 g/dl (n=72)	74	60	
≥ 12 g/dl (n=158)	95	84	**<0.001**
Kumulative Cisplatin-Dosis			
< 200 mg/m² (n=61)	86	70	
≥ 200 mg/m² (n=169)	89	79	0.23

Nach Bonferroni Korrektur für multiple Tests (n=12) wurde ein *p*-Wert <0.0042 als signifikant betrachtet

Tabelle 24 (Studie 6)
Univariate Analyse des metastasenfreien Überlebens (MFS)
(Cisplatin 100 mg/m² alle drei Wochen versus Cisplatin 5x20 mg/m² alle vier Wochen)

	Nach einem Jahr (%)	Nach drei Jahren (%)	p-Wert
Chemotherapie-Regime			
Gruppe A (n=126)	87	77	
Gruppe B (n=104)	89	79	0.67
T-Stadium			
T1/T2 (n=85)	93	83	
T3/T4 (n=145)	85	76	0.08
N-Stadium			
N0-1 (n=55)	91	83	
N2-3 (n=175)	87	77	0.78
Performance-Status			
ECOG 0-1 (n=197)	89	81	
ECOG 2 (n=33)	81	43	0.014
Geschlecht			
Weiblich (n=53)	92	83	
Männlich (n=177)	87	77	0.17
Alter			
≤ 56 Jahre (n=124)	90	83	
≥ 57 Jahre (n=106)	86	73	0.18
Tumorlokalisation			
Oropharynx (n=130)	91	85	
Hypopharynx (n=31)	69	54	
Larynx (n=39)	92	68	
Mundhöhle (n=30)	86	86	**0.002**
Histologischer Grad			
G1-G2 (n=134)	88	80	
G3 (n=96)	88	76	0.52
Upfront-Operation			
Nein (n=98)	84	75	
Ja (n=132)	91	81	0.11
Bestrahlungstechnik			
3D Conformal (n=187)	86	80	
IMRT/VMAT (n=43)	85	61	0.36
Hämoglobin vor Chemotherapie			
< 12 g/dl (n=72)	81	65	
≥ 12 g/dl (n=158)	91	83	0.032
Kumulative Cisplatin-Dosis			
< 200 mg/m² (n=61)	86	77	
≥ 200 mg/m² (n=169)	89	78	0.75

Nach Bonferroni Korrektur für multiple Tests (n=12) wurde ein *p*-Wert <0.0042 als signifikant betrachtet

Tabelle 25 (Studie 6)
Univariate Analyse des OS
(Cisplatin 100 mg/m² alle drei Wochen versus Cisplatin 5x20 mg/m² alle vier Wochen)

	Nach einem Jahr (%)	Nach drei Jahren (%)	*p*-Wert
Chemotherapie-Regime			
Gruppe A (n=126)	87	68	
Gruppe B (n=104)	91	80	0.14
T-Stadium			
T1/T2 (n=85)	89	78	
T3/T4 (n=145)	89	70	0.22
N-Stadium			
N0-1 (n=55)	93	75	
N2-3 (n=175)	88	72	0.94
Performance-Status			
ECOG 0-1 (n=197)	91	77	
ECOG 2 (n=33)	79	22	**0.004**
Geschlecht			
Weiblich (n=53)	96	88	
Männlich (n=177)	87	69	0.23
Alter			
≤ 56 Jahre (n=124)	90	76	
≥ 57 Jahre (n=106)	89	68	0.99
Tumorlokalisation			
Oropharynx (n=130)	89	78	
Hypopharynx (n=31)	77	46	
Larynx (n=39)	95	74	
Mundhöhle (n=30)	93	70	0.022
Histologischer Grad			
G1-G2 (n=134)	89	72	
G3 (n=96)	90	75	0.86
Upfront-Operation			
Nein (n=98)	87	73	
Ja (n=132)	91	73	0.26
Bestrahlungstechnik			
3D Conformal (n=187)	89	72	
IMRT/VMAT (n=43)	88	79	0.95
Hämoglobin vor Chemotherapie			
< 12 g/dl (n=72)	81	62	
≥ 12 g/dl (n=158)	93	78	**<0.001**
Kumulative Cisplatin-Dosis			
< 200 mg/m² (n=61)	82	61	
≥ 200 mg/m² (n=169)	92	78	0.11

Nach Bonferroni Korrektur für multiple Tests (n=12) wurde ein *p*-Wert <0.0042 als signifikant betrachtet

Tabelle 26 (Studie 6)
Vergleich akuter und chronischer Nebenwirkungen der Chemotherapie-Regime
(Cisplatin 100 mg/m² alle drei Wochen versus Cisplatin 5x20 mg/m² alle vier Wochen)

	Gruppe A n Patienten (%)	Gruppe B n Patienten (%)	*p*-Wert
Orale Mukositis			
Grad ≥ 2	117 (93)	86 (83)	0.41
Dermatitis			
Grad ≥ 2	98 (78)	80 (77)	0.94
Hämatotoxizität			
Grad ≥ 3	33 (26)	15 (14)	0.052
Pneumonie/Sepsis			
Grad ≥ 3	9 (12)	1 (1)	**0.003**
Übelkeit/Erbrechen			

Grad ≥ 2	40 (51)*	22 (21)	**<0.001**
Ototoxizität			
Grad ≥ 2	5 (6)*	1 (1)	0.048
Nephrotoxizität			
Grad ≥ 2	22 (17)	5 (5)	**0.005**
Xerostomie			
Grad ≥ 2	70 (57)**	31 (30)	**0.002**

Nach Bonferroni Korrektur für multiple Tests (n=8) wurde ein *p*-Wert <0.0063 als signifikant betrachtet
* Daten von 78 vorliegenden **Daten von 122 Patienten vorliegend

Tabelle 27 (Studie 7)
Univariate Analyse der LRC (Cisplatin 5x20 mg/m² versus Cisplatin 30-40 mg/m² wöchentlich)

	1-Jahres LRC (%)	3 Jahres-LRC (%)	*p*
Art der Chemotherapie			
Gruppe A (n = 85)	83	69	0.12
Gruppe B (n = 85)	74	63	
Alter			
≤ 57 Jahre (n = 86)	77	63	0.63
≥ 58 Jahre (n = 84)	80	71	
Geschlecht			
Weiblich (n = 34)	91	79	0.07
Männlich (n = 136)	75	74	
ECOG Performance Score			
0-1 (n = 128)	80	68	0.37
2 (n = 42)	71	62	
Tumorlokalisation			
Oropharynx (n = 86)	84	75	0.08
Hypopharynx (n= 28)	60	54	
Larynx (n = 32)	73	57	
Mundhöhle (n = 24)	85	63	
T-Kategorie			
T1-2 (n = 34)	97	79	0.030
T3-4 (n = 136)	74	64	
N-Kategorie			
N0-2a (n = 78)	79	68	0.89
N2b-3 (n = 92)	78	66	
Vorherige Operation			
Nein (n = 120)	73	61	0.011
Ja (n = 50)	91	81	
Hämoglobin vor Radiochemotherapie			
< 12 g/dl (n = 48)	64	58	0.08
≥ 12 g/dl (n = 122)	84	71	
Bestrahlungstechnik			
3D konform (n = 126)	77	66	0.41
IMRT (n = 44)	83	71	
Kumulative Cisplatindosis			
< 180 mg/m²	79	64	0.37
≥ 180 mg/m²	78	68	

Tabelle 28 (Studie 7)
Univariate Analyse des OS (Cisplatin 5x20 mg/m² versus Cisplatin 30-40 mg/m² wöchentlich)

	Nach einem Jahr (%)	Nach drei Jahren (%)	*p*
Art der Chemotherapie			
Gruppe A (n = 85)	93	73	0.011
Gruppe B (n = 85)	91	49	
Alter			
≤ 57 Jahre (n = 86)	94	58	0.37
≥ 58 Jahre (n = 84)	90	62	

Geschlecht			
Weiblich (n = 34)	91	72	0.66
Männlich (n = 136)	92	58	
ECOG Performance Score			
0-1 (n = 128)	94	67	**< 0.001**
2 (n = 42)	85	38	
Tumorlokalisation			
Oropharynx (n = 86)	95	63	0.07
Hypopharynx (n= 28)	81	57	
Larynx (n = 32)	97	61	
Mundhöhle (n = 24)	88	54	
T-Kategorie			
T1-2 (n = 34)	89	79	0.41
T3-4 (n = 136)	92	56	
N-Kategorie			
N0-2a (n = 78)	94	62	0.29
N2b-3 (n = 92)	90	58	
Vorherige Operation			
Nein (n = 120)	90	56	0.11
Ja (n = 50)	96	73	
Hämoglobin vor Radiochemotherapie			
< 12 g/dl (n = 48)	87	57	0.50
≥ 12 g/dl (n = 122)	94	61	
Bestrahlungstechnik			
3D konform (n = 126)	93	59	0.57
IMRT (n = 44)	88	62	
Kumulative Cisplatindosis			
< 180 mg/m²	71	55	0.14
≥ 180 mg/m²	83	63	

Tabelle 29 (Studie 7)
Vergleich der Toxizität in den Gruppen A und B
(Cisplatin 5x20 mg/m² versus Cisplatin 30-40 mg/m² wöchentlich)

	Gruppe A, n Patienten (%)	Gruppe B, n Patienten (%)	*p*-Wert
Orale Mukositis			
Grad ≥ 2	74 (87)	73 (86)	0.93
Dermatitis			
Grad ≥ 2	66 (78)	53 (62)	0.23
Hämatotoxizität			
Grad ≥ 2	68 (80)	65 (76)	0.79
Nephrotoxizität			
Grad ≥ 2	4 (5)	4 (5)	1.00
Xerostomie			
Grad ≥ 2	27 (32)	34 (47)[a]	0.37
Subkutane Fibrose			
Grad ≥ 2	18 (21)	28 (36)[b]	0.07

[a] Daten von 72 Patienten verfügbar
[b] Daten von 77 Patienten verfügbar

Tabelle 30 (Studie 7)
Ergebnisse der Subgruppenanalyse der 120 Patienten mit definitiver Radiochemotherapie
(Cisplatin 5x20 mg/m² versus Cisplatin 30-40 mg/m² wöchentlich)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	*p*-Wert
Lokoregionale Kontrolle			
Gruppe A (n = 60)	79	68	**0.040**
Gruppe B (n = 60)	70	53	
Überleben			
Gruppe A (n = 60)	87	70	**0.005**

Gruppe B (n = 60)	67	43	

Tabelle 31 (Studie 7)
Ergebnisse der Subgruppenanalyse der 50 Patienten mit adjuvanter Radiochemotherapie
(Cisplatin 5x20 mg/m² versus Cisplatin 30-40 mg/m² wöchentlich)

	Nach 1 Jahr (%)	Nach 3 Jahren (%)	p-Wert
Lokoregionale Kontrolle			
Gruppe A (n = 25)	92	72	0.29
Gruppe B (n = 25)	90	90	
Überleben			
Gruppe A (n = 25)	96	80	0.19
Gruppe B (n = 25)	84	70	

b. Publikationsverzeichnis

Daniel Seidl, Stefan Janssen, Primoz Strojan, Amira Bajrovic, Steven E. Schild, Dirk Rades: Prognostic Factors after Definitive Radio(Chemo)Therapy of Locally Advanced Head-and-Neck Cancer. Anticancer Res 36, 2526-2526 (2016)

Daniel Seidl, Stefan Janssen, Primo Strojan, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild, Dirk Rades: Importance of Chemotherapy and Radiation Dose After Microscopically Incomplete Resection of Stage III/IV Head-and-Neck Cancer. Anticancer Res 36, 2487-2491 (2016)

Dirk Rades, **Daniel Seidl**, Stefan Janssen, Amira Bajrovic, Katarina Karner, Primoz Strojan, Steven E. Schild: Comparison of weekly administration of cisplatin versus three courses of cisplatin 100 mg/m² for definitive radiochemotherapy of locally advanced head-and-neck cancers. BMC Cancer 16:437 (2016)

Dirk Rades, Primoz Strojan, **Daniel Seidl**, Stefan Janssen, Amira Bajrovic, N. Kazic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Radiochemotherapy for locally advanced squamous cell carcinoma of the head and neck: Higher-dose cisplatin every 3 weeks versus cisplatin/5-fluorouracil every 4 weeks. J Craniomaxillofac Surg 44, 1436-1440 (2016)

Dirk Rades, **Daniel Seidl** Stefan Janssen, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Do we need 5-FU in addition to cisplatin for chemoradiation of loacally advanced head-and-neck cancer? Oral Oncol 57, 40-45 (2016)

Dirk Rades, **Daniel Seidl**, Stefan Janssen, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, Katarina Karner, Primoz Strojan, Steven E. Schild: Chemoradiation of locally advanced squamous cell carcinoma of the head-and-neck (LASCCHN): Is 20 mg/m² cisplatin on five days every four weeks an alternative to 100 mg/m² cisplatin every three weeks? Oral Oncol 59, 67-72 (2016)

Dirk Rades, **Daniel Seidl**, Stefan Janssen, Primoz Strojan, Katarina Karner, Amira Bajrovic, Samer G. Hakim, Barbara Wollenberg, Steven E. Schild: Comparing two lower-dose cisplatin programs for radiochemotherapy of locally advanced head-and-neck cancers. Eur Arch Otorhinolaryngol 274, 1021-1027 (2017)

Prognostic Factors After Definitive Radio(Chemo)Therapy of Locally Advanced Head and Neck Cancer

DANIEL SEIDL[1], STEFAN JANSSEN[1,2], PRIMOZ STROJAN[3], AMIRA BAJROVIC[4],
STEVEN E. SCHILD[5] and DIRK RADES[1]

[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;
[2]Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;
[3]Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia;
[4]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany;
[5]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Aim: To identify predictors of locoregional control (LRC) and overall survival (OS) after definitive radio(chemo)therapy for squamous cell carcinoma of the head and neck (SCCHN). Patients and Methods: Two hundred and seventy-five patients were evaluated; 261 patients received radiochemotherapy with 30-40 mg/m^2 of cisplatin weekly, three courses of cisplatin 100 mg/m^2, two courses of cisplatin 5x20 mg/m^2 or two courses of cisplatin 5×20 mg/m^{2}plus 5-fluorouracil. Ten characteristics were analyzed: Pre-radiotherapy hemoglobin, T-/N-category, Karnofsky performance-score (KPS), gender, age, chemotherapy type, tumor site, grading and radiation dose. Results: On multivariate analyses, hemoglobin 12-14 g/dl (p=0.040), lower T-category (p=0.010), lower N-category (p=0.042) and female gender (p=0.006) were predictive of LRC. Hemoglobin >12 g/dl (p=0.020), lower N-category (p<0.001), KPS ≥80 (p<0.001), female gender (p=0.024) and cisplatin 100 mg/m^2 or 5×20 mg/m^2 (p<0.001) were predictors of improved OS. Conclusion: Predictors of LRC and OS were identified that can improve personalization of treatment. Since chemotherapy type was associated with OS, studies comparing different regimens are warranted.*

The most common treatments for locally advanced squamous cell carcinoma of the head and neck (SCCHN) include surgical resection followed by radio(chemo)therapy and definitive radio(chemo)therapy (1). The preference of treatment approaches depends on local expertise, national and institutional standards. Often, patients receiving definitive radio(chemo)therapy have large unresectable primary tumors, extensive lymphadenopathy, poorer performance and higher comorbidity than patients considered suitable for resection. Therefore, many patients treated with definitive radio(chemo)therapy for locally advanced SCCHN have a poor prognosis, requiring further research. In addition to modern radiation techniques and novel anticancer drugs, the use of more individualized treatment approaches can lead to better outcomes after definitive radio(chemo) therapy for patients with SCCHN (2-4). Besides age, comorbidity, personal situation and treatment preference, individualized therapeutic approaches should take into account the expected outcomes of treatment, such as locoregional control (LRC) and overall survival (OS). Both LRC and OS can be estimated with profound knowledge of independent prognostic factors. Furthermore, the most appropriate radiation dose and type of concurrent chemotherapy are critical to understand. This study analyzed the prognostic role of radiation dose, different dosing regimens of cisplatin-based chemotherapy and additional potential prognostic factors on LRC and OS in patients receiving definitive radio(chemo)therapy for locally advanced SCCHN.

Patients and Methods

Two hundred and seventy-five patients who received definitive radio(chemo)therapy for locally advanced SCCHN were evaluated for LRC and OS in this retrospective study. Irradiation was performed as conventionally fractionated (2.0 Gy per weekday) three-dimensional conformal radiotherapy. Total radiation doses administered to the primary tumor and the involved lymph nodes ranged between 60 Gy and 70 Gy. Doses given to non-involved intermediate-risk and high-risk lymph nodes were 50 Gy and 60 Gy, respectively. All but 14 patients received simultaneous chemotherapy in addition to radiotherapy, either with cisplatin weekly (30-40 mg/m^2 each week),

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: rades.dirk@gmx.net

three courses of cisplatin 100 mg/m^2 (days 1, 22 and 43), two courses of cisplatin 20 mg/m^2 (days 1-5 and 29-33) or two courses of cisplatin 20 mg/m^2 supplemented by 600/1,000 mg/m^2 5-fluorouracil (5-FU) (days 1-5 and 29-33).

Ten characteristics were analyzed for potential associations with LRC and OS, including pre-radiotherapy hemoglobin level (<12 g/dl *versus* 12-14 g/dl *vs.* >14 g/dl), T-category (T1/T2 *versus* T3/T4), N-category (N0/N1/N2a *vs.* N2b/N2c/N3), Karnofsky performance-score (≤70 *versus* ≥80), gender, age (≤57 years *versus* ≥58 years, median age=57 years), type of chemotherapy (none *versus* cisplatin weekly *versus* cisplatin 100 mg/m^2 *versus* cisplatin 20 mg/m^2 *versus* cisplatin 20 mg/m^2 plus 5-FU), primary tumor site (oropharynx *versus* hypopharynx *versus* larynx *versus* oral cavity/floor of mouth), histologic grading (G1/G2 *versus* G3) and total radiation dose (60-66 Gy *versus* 70 Gy).

The Kaplan-Meier method plus the log-rank test were applied for univariate analyses of LRC and OS (5). Characteristics showing a significant association ($p<0.05$) with LRC or OS were also included in a multivariate analysis performed with the Cox proportional hazards model.

Results

The LRC rates in the entire series were 73%, 60% and 58%, respectively, after 1, 3 and 5 years following irradiation. On univariate analyses, LRC was positively associated with a pre-radiotherapy hemoglobin level of 12-14 g/dl ($p=0.003$), lower T-category ($p=0.029$), lower N-category ($p=0.020$) and female gender ($p=0.009$). Results of the univariate analyses of LRC are shown in Table I. On the multivariate analysis, pre-radiotherapy hemoglobin level ($p=0.040$), T-category ($p=0.010$), N-category ($p=0.042$) and gender ($p=0.006$) proved to be independent predictors of LRC (Table II).

OS rates after 1, 3 and 5 years were 76%, 50% and 36%, respectively. In the univariate analyses, OS was positively associated with pre-radiotherapy hemoglobin levels of 12-14 g/dl and >14 g/dl ($p=0.019$), lower N-category ($p<0.001$), a KPS of ≥80 ($p<0.001$), female gender ($p=0.045$), chemotherapy with three courses of cisplatin 100 mg/m^2 or two courses of cisplatin 20 mg/m^2 ($p=0.009$) and larynx or oropharynx cancer ($p<0.001$). The results of the univariate analyses of OS are summarized in Table III. In the multivariate analysis of OS, pre-radiotherapy hemoglobin level ($p=0.020$), N-category ($p<0.001$), KPS ($p<0.001$), gender ($p=0.024$) and type of simultaneous chemotherapy ($p<0.001$) were significant predictors, whereas the primary tumor site did not achieve significance ($p=0.57$). The complete results of multivariate analyses of OS are shown in Table IV.

Discussion

The prognoses of patients with SCCHN presenting with distant metastases or locally advanced unresectable disease are generally poor and require improvement (1-3, 6-8). For locally advanced disease, modern techniques of head-and-neck surgery and radiotherapy have already led to improved outcomes, which may be further enhanced with new chemotherapy approaches (9, 10). The application of personalized treatment programs may also result in better outcomes. Such programs should consider an individual patient's specific situation, including his prognosis. Therefore, the identification of prognostic factors is important. In this study, several potential predictors for LRC and OS were analyzed. In the multivariate analysis of LRC, pre-radiotherapy hemoglobin levels of 12-14 g/dl, lower T-category, lower N-category and female gender were independent prognostic factors. In the multivariate analysis of

Table I. *Univariate analysis of locoregional control.*

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p-Value
Pre-radiotherapy hemoglobin level				
<12 g/dl (n=94)	61	48	48	
12-14 g/dl (n=109)	83	69	69	
>14 g/dl (n=72)	73	61	54	0.003
T-category				
T1/T2 (n=38)	95	72	72	
T3/T4 (n=237)	69	58	56	0.029
N-category				
N0/N1/N2a (n=116)	81	67	63	
N2b/N2c//N3 (n=159)	67	54	54	0.020
Karnofsky performance-score				
≤70 (n=66)	65	52	52	
≥80 (n=209)	75	63	60	0.055
Gender				
Female (n=56)	91	72	72	
Male (n=219)	68	57	54	0.009
Age				
≤57 years (n=141)	72	57	57	
≥58 years (n=134)	73	62	58	0.59
Simultaneous chemotherapy				
No chemotherapy (n=14)	75	47	n/a	
Cisplatin weekly (n=70)	65	53	49	
Cisplatin 100 mg/m^2 (n=47)	87	72	72	
Cisplatin 20 mg/m^2 (n=72)	71	61	61	
Cisplatin 20 mg/m^2 + 5-FU (n=72)	73	56	56	0.15
Primary tumor site*				
Oropharynx (n=135)	75	62	60	
Hypopharynx (n=41)	54	50	50	
Larynx (n=57)	78	66	62	
Oral cavity/Floor of mouth (n=39)	72	53	53	0.21
Histologic grading				
G1/G2 (n=165)	73	62	58	
G3 (n=110)	72	58	58	0.89
Total radiation dose				
60-66 Gy (n=38)	75	63	63	
70 Gy (n=237)	73	59	57	0.92

n/a=Not available, *not clearly defined in 3 patients.

Table II. *Multivariate analysis of locoregional control.*

	Risk ratio	95% confidence interval	*p*-Value
Pre-radiotherapy hemoglobin level	1.33	1.01-1.77	0.040
T-category	1.53	1.10-2.30	0.010
N-category	1.54	1.02-2.38	0.042
Gender	2.24	1.24-4.46	0.006

Table III. *Univariate analysis of survival.*

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p-Value
Pre-radiotherapy hemoglobin level				
<12 g/dl (n=94)	64	41	35	
12-14 g/dl (n=109)	84	54	39	
>14 g/dl (n=72)	81	57	37	0.019
T-category				
T1/T2 (n=38)	84	67	43	
T3/T4 (n=237)	75	47	35	0.13
N-category				
N0/N1/N2a (n=116)	85	63	46	
N2b/N2c//N3 (n=159)	70	40	28	<0.001
Karnofsky performance-score				
≤70 (n=66)	62	25	25	
≥80 (n=209)	81	58	41	<0.001
Gender				
Female (n=56)	84	66	40	
Male (n=219)	74	46	35	0.045
Age				
≤57 years (n=141)	77	51	33	
≥58 years (n=134)	76	49	39	0.98
Simultaneous chemotherapy				
No chemotherapy (n=14)	64	21	n/a	
Cisplatin weekly (n=70)	70	46	31	
Cisplatin 100 mg/m^2 (n=47)	87	67	45	
Cisplatin 20 mg/m^2 (n=72)	79	62	48	
Cisplatin 20 mg/m^2 + 5-FU (n=72)	75	34	34	0.009
Primary tumor site*				
Oropharynx (n=135)	76	52	38	
Hypopharynx (n=41)	61	33	13	
Larynx (n=57)	88	61	48	
Oral cavity/Floor of mouth (n=39)	74	42	34	<0.001
Histologic grading				
G1/G2 (n=165)	81	49	39	
G3 (n=110)	70	52	32	0.38
Total radiation dose				
60-66 Gy (n=38)	66	40	40	
70 Gy (n=237)	78	52	35	0.38

n/a=Not available, *not clearly defined in 3 patients.

OS, pre-radiotherapy hemoglobin levels of >12 g/dl, lower N-category, KPS ≥80, female gender and the type of the concurrent chemotherapy were independent predictors. These results widely agree with those of previous studies of treatment of SCCHN demonstrating consistency of the results of this study (11-13). An impact of the tumor stage on outcomes was already shown for patients with locally advanced SCCHN. The prognostic role of the pre-radiotherapy hemoglobin was also reported before, for which two interpretations exist. The hemoglobin level may be a surrogate marker for more advanced underlying disease. However, it has also been suggested that hemoglobin levels are important for tumor oxygenation, which is important for the efficacy of radiation therapy (14, 15). The effect of irradiation widely depends on the induction of oxygen free radicals that lead to damage of the tumor cell DNA and, subsequently, the tumor cell itself. It is well-recognized that anemia, which is associated with a reduced oxygen-carrier capacity, has a detrimental effect on tumor cell oxygenation (14). In addition, it has been suggested that high concentrations of hemoglobin may also have a negative impact on tumor cell oxygenation due to a reduced perfusion of the small capillaries (16). Hemoglobin levels of 12-14 g/dl or 13-15 g/dl have been considered optimal for tumor oxygenation. Indeed, in the present study, hemoglobin levels of 12-14 g/dl were associated with a better LRC than levels >14 g/dl and <12 g/dl. This result supports the idea of an optimal range of hemoglobin levels in the light of tumor cell oxygenation. With respect to OS, both hemoglobin levels of 12-14 g/dl and >14 g/dl were superior to levels <12 g/dl, while the OS rates for 12-14 g/dl and >14 g/dl were similar. Thus, in addition to the aspect of tumor cell oxygenation, the hemoglobin level may also be a surrogate marker for advanced disease.

In the present study, the radiochemotherapy protocols, including three courses of 100 mg/m^2 cisplatin (on days 1, 22 and 43) or two courses of 20 mg/m^2 cisplatin (on days 1-5 and 29-33), resulted in better OS than the protocols that included weekly administration of cisplatin or cisplatin plus 5-FU. However, the retrospective design of the current study must be taken into account when using these findings to recommend a chemotherapy regimen. Additional (matched-

pair) studies should be performed directly comparing two radiochemotherapy programs.

In contrast to other significant predictors, the total radiation dose (70 Gy *vs*. 60-66 Gy) had no significant impact on LRC or OS. This finding may be due to the relatively small number of patients (n=38) who received doses of 60-66 Gy. However, it may also be true that a total dose of 66 Gy is sufficient for definitive radio(chemo)therapy of advanced SCCHN when administered with chemotherapy. A randomized trial comparing 66 Gy to 70 Gy for definitive treatment of SCCHN is recommended.

In conclusion, this study demonstrated the prognostic significance of the pre-radiotherapy hemoglobin levels for

Table IV. *Multivariate analysis of survival.*

	Risk ratio	95% confidence interval	*p*-Value
Pre-radiotherapy hemoglobin level	1.32	1.04-1.68	0.020
N-category	2.02	1.39-2.98	<0.001
Karnofsky performance score	2.05	1.39-3.01	<0.001
Gender	1.67	1.07-2.74	0.024
Type of simultaneous chemotherapy	1.22	1.12-1.34	<0.001
Primary tumor site	1.04	0.91-1.17	0.57

definitive treatment of SCCHN. Furthermore, concurrent chemotherapy is mandatory to achieve optimal results. Cisplatin alone with three courses of 100 mg/m^2 (on days 1, 22 and 43) or two courses of 20 mg/m^2 (on days 1-5 and 29-33) appear most effective. However, further studies are required to identify the optimal chemotherapy program. A total radiation dose of 70 Gy may not be superior to lower doses, which needs to be properly investigated in a future randomized trial. These findings, regarding prognostic factors, can aid treatment recommendations and stratification of groups when designing prospective trials.

Conflicts of Interest

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

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin *65*: 5-29, 2015.

2 Song JH, Jeong BK, Choi HS, Jeong H, Kang MH, Kang JH, Kim JP, Park JJ, Woo SH, Jang HS, Choi BO and Kang KM: Comparison of failure patterns between conventional and intensity-modulated radiotherapy for stage III and IV head and neck squamous cell carcinoma. Anticancer Res *35*: 6833-6840, 2015.

3 Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE and Schmidt R: Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol *43*: 535-543, 2007.

4 Chen LY, Huang CC, Tsou YA, Bau DT and Tsai MH: Prognostic factor of severe complications in patients with hypopharyngeal cancer with primary concurrent chemoradiotherapy. Anticancer Res *35*: 1735-1741, 2015.

5 Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

6 Rades D, Schild SE, Karstens JH and Hakim SG: Predicting survival of patients with metastatic epidural spinal cord compression from cancer of the head-and-neck. Anticancer Res *35*: 385-388, 2015.

7 Rades D, Dziggel L, Hakim SG, Rudat V, Janssen S, Trang NT, Khoa MT and Bartscht T: Predicting survival after irradiation for brain metastases from head and neck cancer. In Vivo *29*: 525-528, 2015.

8 Tribius S, Kronemann S, Kilic Y, Schroeder U, Hakim S, Schild SE and Rades D: Radiochemotherapy including cisplatin alone *versus* cisplatin + 5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol *185*: 675-681, 2009.

9 Franco P, Potenza I, Schena M, Riva G, Pecorari G, Demo PG, Fasolis M, Moretto F, Garzaro M, Di Muzio J, Melano M, Airoldi M, Ragona R, Rampino M and Ricardi U: Induction chemotherapy and sequential concomitant chemo-radiation in locally advanced head and neck cancers: How induction-phase intensity and treatment breaks may impact on clinical outcomes. Anticancer Res *35*: 6247-6254, 2015.

10 Fujimoto Y, Kato S, Itoh Y, Naganawa S and Nakashima T: A phase I study of concurrent chemoradiotherapy using oral s-1 for head and neck cancer. Anticancer Res *34*: 209-213, 2014.

11 Rades D, Seibold ND, Gebhard MP, Noack F, Schild SE and Thorns C: Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma of the head and neck (SCCHN). Strahlenther Onkol *187*: 626-632, 2011.

12 Leemans CR, Tiwari R, Nauta JJ, van der Waal I and Snow GB: Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer *71*: 452-456, 1993.

13 Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE and Dunst J: Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys *80*: 1037-1044, 2011.

14 Vaupel P, Kelleher DK and Höckel M: Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. Semin Oncol *28(2 Suppl 8)*: 29-35, 2001.

15 Becker A, Stadler P, Lavay RS, Hänsgen G, Kuhnt T, Lautenschläger C, Feldmann HJ, Molls M and Dunst J: Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys *46*: 459-466, 2000.

16 Vaupel P, Mayer A and Höckel M: Impact of hemoglobin levels on tumor oxygenation: the higher, the better? Strahlenther Onkol *182*: 63-71, 2006.

Importance of Chemotherapy and Radiation Dose After Microscopically Incomplete Resection of Stage III/IV Head and Neck Cancer

DANIEL SEIDL[1], STEFAN JANSSEN[1,2], PRIMOZ STROJAN[3], SAMER G. HAKIM[4], BARBARA WOLLENBERG[5], STEVEN E. SCHILD[6] and DIRK RADES[1]

*Departments of [1]Radiation Oncology, [4]Oral and Maxillofacial Surgery and Oto-Rhino-Laryngology and
[5]Head and Neck Surgery, University of Lübeck, Lübeck, Germany;
[2]Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;
[3]Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia;
[6]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Aim: To investigate the importance of chemotherapy and radiation dose after R1 resection of squamous cell carcinoma of the head-and-neck (SCCHN). Patients and Methods: One hundred and twenty-two patients receiving radiotherapy alone or with concurrent chemotherapy [cisplatin or cisplatin/5-fluorouracil (5-FU)] were retrospectively analyzed. Results: On multivariate analysis, chemotherapy was significantly associated with improved locoregional control (p=0.048). Three-year locoregional control rates were 61% for those treated without chemotherapy, 83% for those treated with cisplatin and 77% for those treated with cisplatin/5-FU. Radiation doses of 66 and 70 Gy were non-significantly superior to 60-64 Gy (p=0.18). On multivariate analysis, chemotherapy showed a trend for improving survival (p=0.055). Three-year OS rates were 51% for those without chemotherapy, 65% for those treated with cisplatin and 57% for those treated with cisplatin/5-FU. Radiation doses of 66 Gy (3-year survival=61%) and 70 Gy (70%) were superior to 60-64 Gy (25%) (p=0.021). Conclusion: Concurrent chemotherapy and a radiation dose of 66 Gy resulted in better outcomes. Cisplatin and cisplatin/5-FU were similarly effective. Radiation doses >66 Gy appear not to be necessary.*

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: rades.dirk@gmx.net

Patients with locally advanced (stage III/IV) squamous cell carcinoma of the head and neck region (SCCHN) have a comparably poor prognosis (1). Many patients undergo resection of the primary tumor and regional lymph nodes followed by radiotherapy or radiochemotherapy (2). Microscopically incomplete resection (R1 resection) is considered a risk factor for worse treatment outcomes (3). A re-analysis of two randomized trials suggested that patients in whom an R1 resection was performed benefited from the addition of chemotherapy to postoperative irradiation (4). Despite these randomized trials, two questions remain unanswered. One question relates to the chemotherapy regimen. Both randomized trials used an aggressive regimen consisting of 100 mg/m^2 cisplatin alone given on days 1, 22 and 43 during the radiation course (5, 6). However, many centers worldwide use 5-fluorouracil (5-FU) in addition to cisplatin. The question is whether patients undergoing R1 resection would also benefit from cisplatin/5-FU. Another question relates to the most appropriate radiation dose. In one of the two randomized trials, all patients received 66 Gy (4), and in the other trial, 60 Gy or 66 Gy (5). Some centers also use 70 Gy. The present study investigated chemotherapy and compared no chemotherapy, cisplatin alone and cisplatin plus 5-FU. Additionally, three radiation dose levels were compared with respect to locoregional control and survival after R1 resection of non-metastatic stage III/IV SCCHN.

Patients and Methods

Data of 122 patients who received radiotherapy alone (n=45) or in combination with concurrent cisplatin-based chemotherapy (n=77) following R1 resection of locally advanced SCCHN were retrospectively analyzed for locoregional control and survival. Patients received radiotherapy of 2.0 Gy once daily on five days per week. Total doses ranged from 60-70 Gy (median dose=66 Gy) to

the R1-resected former primary tumor. Higher-risk and intermediate-risk lymph nodes received 60 Gy and 50 Gy, respectively. When concurrent chemotherapy was administered, it included cisplatin alone (30-40 mg/m^2 weekly, 20 mg/m^2 on days 1-5+29-33, or 100 mg/m^2 on days 1, 22 and 43) or cisplatin (20 mg/m^2 on days 1-5+29-33) plus 600/1000 mg/m^2 5-FU on days 1-5 and 29-33.

The impact of the following potential prognostic factors on locoregional control and survival was evaluated: Age (≤60 vs. >60 years), gender, pre-radiotherapy Karnofsky performance score (80-100 vs. ≤70), site of SCCHN (oropharynx vs. hypopharynx vs. larynx vs. oral cavity/floor of mouth), T-stage (T1/T2 vs. T3/T4), N-stage (N0/N1 vs. N2/N3), histological grade (G1/G2 vs. G3), pre-radiotherapy hemoglobin (<12 vs. ≤12 g/dl), radiotherapy dose (60-64 Gy vs. 66 Gy vs. 70 Gy) and concurrent chemotherapy (none vs. cisplatin alone vs. cisplatin/5-FU).

The univariate analyses of locoregional control and survival were performed using the Kaplan–Meier analysis supplemented by the log-rank test. Potential prognostic factors achieving significance ($p<0.05$) or a trend ($p<0.08$) on univariate analyses were additionally evaluated in a multivariate manner with the Cox regression model.

Results

Patients were followed up until death or for a median of 28 months (range=5-76 months) in those alive at the last follow-up. For the entire cohort, the locoregional control rates at 3 and 4 years were 73% and 66%, respectively. Of all investigated factors, only chemotherapy was found to have a significant association with locoregional control (Table I). The 3- and 4-year rates were 61% and 33%, respectively, for patients who did not receive chemotherapy; 83% and 83% respectively, after radiochemotherapy with cisplatin alone; and 77% and 77%, respectively, after radiochemotherapy with cisplatin/5-FU ($p=0.010$, Figure 1). On the Cox regression analysis, the addition of chemotherapy to radiotherapy was also significant (risk ratio=1.64, 95% confidence interval=1.01-2.77; $p=0.048$).

The 3- and 4-year survival rates for the whole patient cohort were 58% and 54%, respectively. On univariate analyses, lower N-stage ($p=0.006$), lower histological grade (i.e. better differentiated tumors) ($p=0.021$) and pre-radiotherapy hemoglobin levels of ≥12 g/dl ($p=0.002$) were significantly associated with improved survival (Table II). In addition, lower T-stage ($p=0.053$) and RT doses of 66 Gy or 70 Gy ($p=0.076$) showed a trend for association with better survival. These five factors plus chemotherapy were included in the Cox regression analysis. In that analysis, T-stage ($p=0.018$), N-stage ($p=0.011$), pre-radiotherapy hemoglobin level ($p=0.003$) and the radiotherapy dose ($p=0.021$) achieved significance. Histological grade ($p=0.078$) and chemotherapy ($p=0.055$) showed a trend. The complete results of the Cox regression analysis are summarized in Table III.

Table I. *Locoregional control rates at 3 and 4 years (univariate analysis).*

	At 3 years (%)	At 4 years (%)	p-Value
Age			
≤60 years (n=72)	73	73	
>60 years (n=50)	72	55	0.90
Gender			
Female (n=29)	70	70	
Male (n=93)	74	65	0.84
Karnofsky performance score			
80-100 (n=80)	73	65	
≤70 (n=42)	74	74	0.75
Tumor site			
Oropharynx (n=60)	78	74	
Hypopharynx (n=20)	69	69	
Larynx (n=25)	80	0	
Oral cavity/floor of mouth (n=17)	46	n/a	0.15
T-Stage			
T1/T2 (n=48)	79	73	
T3/T4 (n=74)	70	60	0.17
N-Stage			
N0/N1 (n=43)	75	68	
N2/N3 (n=79)	73	67	0.46
Histological grade			
G1/G2 (n=71)	80	74	
G3 (n=51)	63	54	0.19
Pre-radiotherapy hemoglobin			
<12 g/dl (n=49)	71	71	
≥12 g/dl (n=73)	75	66	0.49
Radiotherapy dose			
60-64 Gy (n=15)	32	n/a	
66 Gy (n=97)	77	69	
70 Gy (n=10)	80	n/a	0.18
Concurrent chemotherapy			
None (n=45)	61	33	
Cisplatin alone (n=44)	83	83	
Cisplatin/5-FU (n=33)	77	77	0.010

n/a: Not available.

Discussion

Patients with metastatic SCCHN have a very poor prognosis (7, 8). Patients with locally advanced non-metastatic disease have a better expected outcome (1). In many patients with resectable stage III/IV SCCHN, the final pathological evaluation reveals that the tumor has not been removed completely microscopically. The question is whether a second surgery should be performed. A re-resection is often not possible or refused by patients. There is general agreement that patients undergoing resection of stage III/IV tumors should receive postoperative radiotherapy (3, 9). Since two randomized trials and their re-analysis demonstrated 10 years ago that patients in whom only R1 resection was performed benefited from the addition of concurrent chemotherapy, this
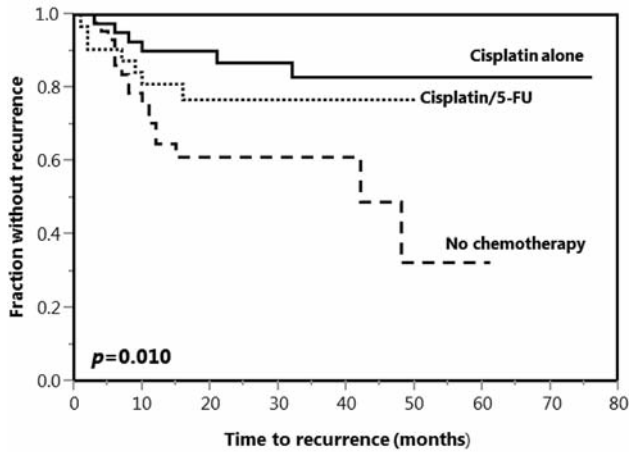
Figure 1. *Locoregional control of the groups with no chemotherapy treated with cisplatin alone and treated with cisplatin/5-fluorouracil (5-FU).*

Table II. *Survival rates at 3 and 4 years (univariate analysis).*

	At 3 years (%)	At 4 years (%)	p-Value
Age			
≤60 years (n=72)	60	57	
>60 years (n=50)	55	50	0.81
Gender			
Female (n=29)	65	65	
Male (n=93)	57	51	0.33
Karnofsky performance score			
80-100 (n=80)	62	5	
≤70 (n=42)	50	50	0.25
Tumor site			
Oropharynx (n=60)	64	60	
Hypopharynx (n=20)	36	36	
Larynx (n=25)	67	56	
Oral cavity/floor of mouth (n=17)	41	n/a	0.11
T-Stage			
T1/T2 (n=48)	72	64	
T3/T4 (n=74)	47	47	0.053
N-Stage			
N0/N1 (n=43)	76	65	
N2/N3 (n=79)	48	48	0.006
Histological grade			
G1/G2 (n=71)	66	60	
G3 (n=51)	48	38	0.021
Pre-radiotherapy hemoglobin			
<12 g/dl (n=49)	42	42	
≥12 g/dl (n=73)	69	62	0.002
Radiotherapy dose			
60-64 Gy (n=15)	25	0	
66 Gy (n=97)	61	59	
70 Gy (n=10)	70	n/a	0.076
Concurrent chemotherapy			
None (n=45)	51	44	
Cisplatin alone (n=44)	65	61	
Cisplatin/5-FU (n=33)	57	57	0.21

n/a: Not available.

approach became the standard procedure in many centers worldwide (4-6). However, radiochemotherapy after R1 resection is not performed everywhere. When concurrent chemotherapy is administered, the most appropriate chemotherapy protocol is still controversial. In the two randomized trials, an aggressive protocol with three courses of 100 mg/m^2 of cisplatin was used. This regimen is the standard in many countries, including the United States. Since this regimen is fairly toxic and the patients require substantial supportive care, other centers, particularly in Europe, have explored alternatives. One alternative is a regimen including two courses of 20 mg/m2 cisplatin given for five days in the first and fifth week of radiotherapy (10). This regimen has been shown to be much better tolerated than three courses of 100 mg/m^2 of cisplatin (11). However, since the cumulative cisplatin dose of two courses of 20 mg/m^2 cisplatin is only two-thirds that of three times 100 mg/m^2, many centers added two courses of 5-FU (either 600 or 1,000 mg/m^2) over five days in the first and fifth week of radiotherapy to cisplatin at 20 mg/m^2. To our knowledge, it has not yet been shown that after R1 resection, patients benefit from radiochemotherapy with cisplatin/5-FU.

In this study, radiochemotherapy either with cisplatin alone or cisplatin/5-FU was superior to radiotherapy alone. Cisplatin/5-FU resulted in similar locoregional control and survival rates as different cisplatin alone regimens. Moreover, the outcomes were similar to those found in the two previous randomized trials using high-dose cisplatin (three courses of 100 mg/m^2). In order to better define the optimal chemotherapy regimen for radiochemotherapy of R1-resected SCCHN, additional studies directly comparing these regimens are warranted. Novel approaches including induction chemotherapy and 5-FU pro-drugs may be reasonable (12, 13).

Another important question addresses the most appropriate total radiation dose. One of the previous randomized trials used 66 Gy for all patients, the other trial either 60 Gy or 66 Gy. In the latter trial, a separate analysis of the separate dose groups was not performed. Thus, the optimal dose is unclear. Is 60 Gy sufficient or should the dose be 66 Gy or even greater? In the present study, 66 Gy was clearly superior to 60-64 Gy, as was a dose of 70 Gy. However, an escalation of the radiation dose beyond 66 Gy did not appear to further improve outcomes significantly. Thus, 66 Gy appears to be appropriate.

In addition to concurrent chemotherapy and the radiation dose, T-stage, N-stage and pre-radiotherapy hemoglobin were significantly associated with survival. Histological grade showed a trend towards such an association. These findings agree with previously reported

Table III. *Multivariate analysis (Cox regression model) of survival.*

Variable	Risk ratio	95% Confidence interval	*p*-Value
T-Stage (T1/T2 *vs*. T3/T4)	1.44	1.06-1.99	0.018
N-Stage (N0/N1 *vs*. N2/N3)	2.50	1.23-5.51	0.011
Histological grade (G1/G2 *vs*. G3)	1.31	0.97-1.78	0.078
Pre-radiotherapy hemoglobin (≥12 g/dl *vs*. <12 g/dl)	2.56	1.38-4.78	0.003
Radiotherapy dose (70 Gy *vs*. 66 Gy *vs*. 60-64 Gy)	2.49	1.15-5.15	0.021
Concurrent chemotherapy (Cisplatin alone *vs*. Cisplatin/5-FU *vs*. none)	1.44	0.99-2.12	0.055

data, which reveals some consistency of the results of the present study (14-17). However, its retrospective nature should be taken into account when interpreting the data. Prospective randomized trials focusing on R1-resected SCCHN are desirable but may not be practical, since R1 resection is less common due to improved surgical procedures and standards.

In conclusion, this study supported the importance of concurrent chemotherapy when added to radiotherapy for R1-resected SCCHN. Cisplatin alone and cisplatin/5-FU appeared to be similarly efficacious. The optimal chemotherapy regimen needs to be defined. 66 Gy appears to be an appropriate radiation dose.

Conflicts of Interest

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

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin *65*: 5-29, 2015.
2 Chen LY, Huang CC, Tsou YA, Bau DT and Tsai MH: Prognostic factor of severe complications in patients with hypopharyngeal cancer with primary concurrent chemoradio-therapy. Anticancer Res *35*: 1735-1741, 2015.
3 Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE and Schmidt R: Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol *43*: 535-543, 2007.
4 Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK and Lefèbvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck *27*: 843-850, 2005.
5 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A and van Glabbeke M: Postoperative irradiation with or without concomitant

6 Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N and Fu KK: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med *350*: 1937-1944, 2015.
7 Rades D, Schild SE, Karstens JH and Hakim SG: Predicting survival of patients with metastatic epidural spinal cord compression from cancer of the head-and-neck. Anticancer Res *35*: 385-388, 2015.
8 Rades D, Dziggel L, Hakim SG, Rudat V, Janssen S, Trang NT, Khoa MT and Bartscht T: Predicting survival after irradiation for brain metastases from head and neck cancer. In Vivo *29*: 525-528, 2015.
9 Song JH, Jeong BK, Choi HS, Jeong H, Kang MH, Kang JH, Kim JP, Park JJ, Woo SH, Jang HS, Choi BO and Kang KM: Comparison of failure patterns between conventional and intensity-modulated radiotherapy for stage III and IV head and neck squamous cell carcinoma. Anticancer Res *35*: 6833-6840, 2015.
10 Tribius S, Kronemann S, Kilic Y, Schroeder U, Hakim S, Schild SE and Rades D: Radiochemotherapy including cisplatin alone versus cisplatin + 5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol *185*: 675-681, 2009.
11 Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE and Dunst J: Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys *80*: 1037-1044, 2011.
12 Franco P, Potenza I, Schena M, Riva G, Pecorari G, Demo PG, Fasolis M, Moretto F, Garzaro M, Di Muzio J, Melano M, Airoldi M, Ragona R, Rampino M and Ricardi U: Induction chemotherapy and sequential concomitant chemo-radiation in locally advanced head and neck cancers: How induction-phase intensity and treatment breaks may impact on clinical outcomes. Anticancer Res *35*: 6247-6254, 2015.
13 Fujimoto Y, Kato S, Itoh Y, Naganawa S and Nakashima T: A phase I study of concurrent chemoradiotherapy using oral s-1 for head and neck cancer. Anticancer Res *34*: 209-213, 2014.
14 Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE and Dunst J: Locally advanced stage IV squamous cell carcinoma of

the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys *70*: 1108-1114, 2008.

15 Rades D, Seibold ND, Gebhard MP, Noack F, Schild SE and Thorns C: Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma of the head and neck (SCCHN). Strahlenther Onkol *187*: 626-632, 2011.

16 Vaupel P, Kelleher DK and Höckel M: Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. Semin Oncol *28(2 Suppl 8)*: 29-35, 2001.

17 Noble AR, Greskovich JF, Han J, Reddy CA, Nwizu TI, Khan MF, Scharpf J, Adelstein DJ, Burkey BB and Koyfman SA: Risk factors associated with disease recurrence in patients with stage III/IV squamous cell carcinoma of the oral cavity treated with surgery and postoperative radiotherapy. Anticancer Res *36*: 785-792, 2016.

BMC Cancer

Comparison of weekly administration of cisplatin versus three courses of cisplatin 100 mg/m^2 for definitive radiochemotherapy of locally advanced head-and-neck cancers

Dirk Rades[1*], Daniel Seidl[1], Stefan Janssen[1,2], Amira Bajrovic[3], Katarina Karner[4], Primoz Strojan[4] and Steven E Schild[5]

Abstract

Background: To compare definitive radiochemotherapy with weekly administration of 30–40 mg/m^2 of cisplatin to 100 mg/m^2 of cisplatin on days 1, 22 and 43 for outcomes and toxicity in patients with squamous cell carcinoma of the head-and-neck.

Methods: Seventy-five patients receiving radiochemotherapy with weekly cisplatin (30–40 mg/m^2) were compared to 58 patients receiving radiochemotherapy with 100 mg/m^2 cisplatin on days 1, 22 and 43. Radiochemotherapy regimen plus seven characteristics (age, gender, performance score, tumor site, T-/N-category, histologic grading) were evaluated for locoregional control (LRC), metastases-free survival (MFS) and overall survival (OS). Radiochemotherapy groups were compared for toxicity.

Results: On multivariate analysis, improved LRC was associated with cisplatin 100 mg/m^2 (hazard ratio [HR] 1.57; $p = 0.008$) and female gender (HR 4.37; $p = 0.003$). Radiochemotherapy regimen was not significantly associated with MFS on univariate analysis ($p = 0.66$). On multivariate analysis, better MFS was associated with ECOG performance score 0–1 (HR 5.63; $p < 0.001$) and histological grade 1–2 (HR 1.81; $p = 0.002$). On multivariate analysis, improved OS was associated with cisplatin 100 mg/m^2 (HR 1.33; $p = 0.023$), ECOG performance score 0–1 (HR 2.15; $p = 0.029$) and female gender (HR 1.98; $p = 0.026$). Cisplatin 100 mg/m^2 was associated with higher rates of grade ≥3 hematotoxicity ($p = 0.004$), grade ≥2 renal failure ($p = 0.004$) and pneumonia/sepsis ($p = 0.033$).

Conclusions: Radiochemotherapy with 100 mg/m^2 of cisplatin every 3 weeks resulted in better LRC and OS than weekly doses of 30–40 mg/m^2. Given the limitations of a retrospective study, 100 mg/m^2 of cisplatin appears preferable. Since this regimen was associated with considerable acute toxicity, patients require close monitoring.

Keywords: Head-and-neck cancer, Definitive treatment, Radiochemotherapy, Cisplatin, Outcomes, Adverse events

---

* Correspondence: Rades.Dirk@gmx.net
[1]Department of Radiation Oncology, University of Lubeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany
Full list of author information is available at the end of the article

Rades *et al. BMC Cancer* (2016) 16:437

Page 2 of 8

Background

Many patients with locally advanced squamous cell carcinoma of the head-and-neck (SCCHN) are not candidates for surgical resection and receive definitive radiotherapy. After randomized trials had demonstrated that radiochemotherapy was superior to radiotherapy alone for definitive treatment of SCCHN, radiochemotherapy became the standard treatment for these patients [1–3]. According to a large meta-analysis, concurrent administration of radiochemotherapy resulted in significantly better outcomes than sequential approaches [4]. This meta-analysis included patients who received radiochemotherapy with cisplatin alone or various poly-chemotherapy regimens, including combined cisplatin-based regimens, but did not show significantly superiority of a particular regimen. Thus, the most appropriate chemotherapy given concurrently with radiation therapy for locally advanced SCCHN requires further clarification.

In two randomized trials comparing radiochemotherapy and radiotherapy alone after surgery for SCCHN in patients with risk factors, radiochemotherapy with 100 mg/m^2 of concurrent cisplatin given on days 1, 22 and 43 was significantly superior to radiotherapy alone with respect to treatment outcomes [5, 6]. In definitive radiotherapy setting, the same cisplatin regimen was also tested in phase III randomized fashion [7, 8]. Guided by these trials, radiochemotherapy with three courses 100 mg/m^2 of cisplatin became the preferred regimen for both definitive and postoperative in many institutions. However, other centers are concerned about this regimen, since it was reported to be very toxic [9]. Therefore, other cisplatin-regimens have been introduced to the radiochemotherapy of SCCHN. One of these alternative regimens is weekly administration of 30–40 mg/m^2 of cisplatin. In 2008, a retrospective study showed that weekly administration of 33–40 mg/m^2 of cisplatin was better tolerated than 80–100 mg/m^2 of cisplatin given every 3 weeks [10].

Three retrospective studies and one randomized study of 50 eligible patients had compared higher-dose cisplatin (100 mg/m^2 on days 1, 22 and 43) to weekly administration of 30 or 40 mg/m^2 of cisplatin for non-nasopharyngeal SCCHN [11–14]. However, these studies produced inconsistent results with respect to treatment outcomes. One retrospective study suggested that 100 mg/m^2 of cisplatin resulted in better overall survival (OS) and similar progression-free survival (PFS) compared to weekly cisplatin [11]. In another retrospective study of patients receiving definitive (30 %) or adjuvant (70 %) radiochemotherapy, 100 mg/m^2 of cisplatin resulted in significantly better PFS and OS on univariate analyses but not on multivariate analyses [12]. In the other two studies, outcomes were not significantly different with 100 mg/m^2 of cisplatin given every 3 weeks or weekly administration of cisplatin [13, 14]. Of the latter two studies, the small prospective

trial was limited to patients with cancer of the oral cavity, and the retrospective study was performed in patients receiving postoperative radiochemotherapy ($N = 104$). Taking into account the available data from the literature, it becomes obvious that more studies comparing 100 mg/m^2 of cisplatin every 3 weeks to weekly administration of 30 or 40 mg/m^2 are required, particularly in patients receiving definitive radiochemotherapy for SCCHN. Therefore, the present study included only SCCHN patients receiving definitive radiochemotherapy. It aimed to contribute to the question whether weekly cisplatin is a reasonable and less toxic alternative to 100 mg/m^2 of cisplatin given every 3 weeks.

Methods

A total of 133 patients treated with definitive radiochemotherapy for histologically confirmed locally advanced unresectable SCCHN between 2003 and 2014 were included in this retrospective study, which was approved by the local ethics committee (University of Lübeck). Seventy-five patients had received weekly cisplatin doses of 30–40 mg/m^2 and were compared to 58 patients treated with 100 mg/m^2 of cisplatin given on days 1, 22 and 43. Patients receiving Cisplatin weekly were mainly from Ljubljana, and those receiving100 mg/m2 of cisplatin on days 1, 22 and 43 were mainly from Northern Germany. Chemotherapy regimens were selected according to interdisciplinary treatment protocols preferred at the contributing institutions at the time the patients were treated. Both groups were not significantly different regarding the distribution of patient characteristics including age, gender, Eastern Cooperative Oncology Group (ECOG) performance score, primary tumor site, T-category, N-category, histologic grading and cumulative cisplatin dose (Table 1). Cancer of the oral cavity was also included in this study although response to radiochemotherapy is often not satisfactory for these tumors, since it represents a common site of SCCHN. The proportion of patients with cancer of the oral cavity was similar in both groups (11 versus 12 %, Table 1).

Definitive radiotherapy was performed with 6–10 MV photon beams from a linear accelerator as three-dimensional conformal radiotherapy after computed tomography-based treatment planning. Patients treated with intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) were not included. The planned total radiation dose administered to the primary tumor and the involved lymph nodes was 70 Gy given in 2-Gy fractions on 5 days per week (conventional fractionation). Total doses to lymph nodes were 50–60 Gy. Concurrent cisplatin was given as bolus infusion of 30–40 mg/m^2 once a week or as bolus infusion of 100 mg/m^2 on days 1, 22 and 43. All patients received prophylactic hydration and antiemetic agents and were monitored for

Rades *et al. BMC Cancer* (2016) 16:437

Page 3 of 8

Table 1 Comparison of the distributions of patient characteristics in the radiochemotherapy groups (30–40 mg/m2 of cisplatin weekly vs. 100 mg/m^2 of cisplatin on days 1, 22 and 43; Chi-square test)

	Cisplatin weekly N patients (%)	Cisplatin 100 mg/m^2 N patients (%)	P
Age			
≤56 years (N = 67)	37 (49)	30 (52)	
≥ 57 years (N = 66)	38 (51)	28 (48)	0.92
Gender			
Female (N = 29)	15 (20)	14 (24)	
Male (N = 104)	60 (80)	44 (76)	0.86
ECOG Performance score			
0–1 (N = 115)	64 (85)	51 (88)	
2 (N = 18)	11 (15)	7 (12)	0.92
Primary tumor site			
Oropharynx (N = 69)	36 (48)	33 (57)	
Hypopharynx (N = 19)	12 (16)	7 (12)	
Larynx (N = 30)	19 (25)	11 (19)	
Oral cavity/Floor of mouth (N = 15)	8 (11)	7 (12)	0.88
T-category			
T1-2 (N = 16)	9 (12)	7 (12)	
T3-4 (N = 117)	66 (88)	51 (88)	0.99
N-category			
N0-2a (N = 66)	39 (52)	27 (47)	
N2b-3 (N = 67)	36 (48)	31 (53)	0.75
Histologic grading			
G 1–2 (N = 85)	49 (65)	36 (62)	
G3 (N = 48)	26 (35)	22 (38)	0.89
Cumulative cisplatin dose			
≤200 mg/m^2 (N = 85)	51 (68)	34 (59)	
>200 mg/m^2 (N = 48)	24 (32)	24 (41)	0.50

After Bonferroni correction for multiple tests (8 tests), *p*-values of <0.006 were considered significant

potential toxicity (clinical examination, blood samples) at least weekly.

The radiochemotherapy regimen and eight additional characteristics (Table 1) were evaluated with respect to LRC, MFS and OS. The HPV-status was available only in a few patients and, therefore, not analyzed. Radiochemotherapy regimens were additionally compared for acute and late adverse events (Common Terminology Criteria of Adverse Events (CTCAE) version 4.0) [15]. The follow-up schedule included visits every 3 months for 2 years, every 6 months during the third year, and every 12 months thereafter. Additional visits were performed when toxicity-related symptoms occurred or progressive disease was suspected.

LRC, MFS and OS were referenced form the last day of radiotherapy and calculated with the Kaplan-Meier-

method [16]. The corresponding Kaplan-Meier curves were compared using the log-rank test. Those characteristics found to be significant (*p* < 0.006 after Bonferroni correction for multiple tests representing an alpha level of 0.05) or showed a trend (*p* < 0.055) on univariate analyses were subsequently analyzed in a multivariate manner with the Cox proportional hazards model. In the multivariate analyses, *p*-values of <0.05 were considered significant. For comparisons of the radiochemotherapy groups for acute and late adverse events, the Chi-square test was used.

Results

Median follow up times were 21 months (range: 0–80 months) in the entire cohort and 38 months (range: 4–80 months) in those patients being alive at their last follow up visit.

On univariate analyses, cisplatin 100 mg/m^2 (Fig. 1, *p* = 0.010), female gender (*p* = 0.010) and favorable (oropharynx or larynx) primary tumor site (*p* = 0.047) showed a trend towards improved LRC (Table 2). In the multivariate analysis of LRC, radiochemotherapy regimen (*p* = 0.008) and gender (*p* = 0.003) were significant, whereas primary tumor site (*p* = 0.16) did not achieve significance (Table 5).

In the entire cohort, MFS rates at 1 and 3 years were 86 and 71 %, respectively. On univariate analysis, improved MFS was associated with ECOG performance score 0–1 (*p* < 0.001), favorable (oropharynx or larynx) primary tumor site (*p* = 0.002), N-category 0–2a (*p* = 0.001) and histological grade 1–2 (*p* = 0.003) (Table 3). The radiochemotherapy regimen was not significantly associated with MFS (*p* = 0.66). On multivariate analysis of MFS, ECOG performance score (*p* < 0.001) and histological grading (*p* = 0.002) achieved significance, whereas N-category (*p* = 0.09) and primary tumor site (*p* = 0.30) were not significant (Table 5).

In the entire cohort, median survival time was 39 months, and the OS rates at 1 and 3 years were 76 and 51 %, respectively. In the univariate analyses, better OS was significantly associated with favorable (oropharynx or larynx) primary tumor site (*p* < 0.001). Cisplatin 100 mg/m^2 (Fig. 1, *p* = 0.024), ECOG performance score 0–1 (*p* = 0.006) and female gender showed a trend (*p* = 0.050) (Table 4). On multivariate analysis of OS, radiochemotherapy regimen (*p* = 0.023), ECOG performance score (*p* = 0.029) and gender (*p* = 0.026) achieved significance, whereas primary tumor site (*p* = 0.32) did not (Table 5).

The comparison of both radiotherapy groups for acute and late adverse events revealed that 100 mg/m^2 of cisplatin was associated with significantly higher rates of grade ≥3 hematotoxicity (*p* = 0.004), grade ≥2 renal failure (*p* = 0.004), and pneumonia/sepsis showed a trend (*p* = 0.033) (Table 6). The rates of grade ≥2 oral mucositis (*p* = 0.95), grade ≥2 skin toxicity (*p* = 0.25), grade ≥2
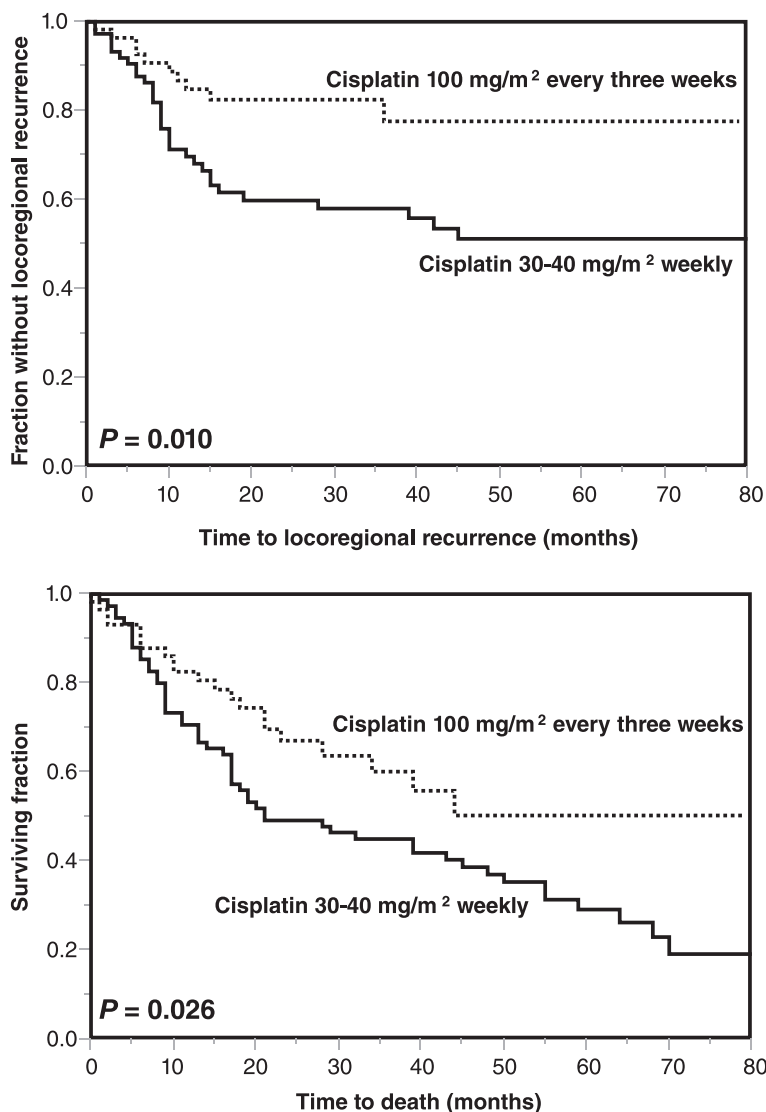
Rades *et al. BMC Cancer* (2016) 16:437

Page 4 of 8

Fig. 1 Comparison of the radiochemotherapy groups (30–40 mg/m^2 of cisplatin weekly vs. 100 mg/m^2 of cisplatin every 3 weeks) for locoregional control (*top*) and overall survival (*bottom*)

xerostomia ($p = 0.44$) and grade ≥2 subcutaneous fibrosis ($p = 0.20$) were not significantly different in both groups. The complete planned chemotherapy could be administered in 63 % (47/75) of patients in the cisplatin weekly group and in 50 % (29/58) of patients in the cisplatin 100 mg/m^2 group, respectively ($p = 0.34$). A total radiation dose of 70 Gy could be administered in 92 % (69/75) and 95 % (55/58) of patients, respectively ($p = 0.87$). Death during radio-chemotherapy occurred in 4 % (3/75) and 2 % (1/58) of patients, respectively ($p = 0.48$).

Discussion

Definitive radiochemotherapy is one of the most common treatment approaches for locally advanced SCCHN. In order to achieve the best possible outcomes, irradiation and chemotherapy should be administered concurrently [4]. The most important agent for definitive radiochemotherapy of SCCHN is cisplatin either given alone or as part of combined chemotherapy regimens. The most commonly used of these regimens worldwide is 100 mg/m^2 of cisplatin alone given every 3 weeks, i.e. on days 1, 22 and 43. This regimen can be associated with high rates of severe adverse events [9]. Therefore, alternative cisplatin regimens became relatively popular for radiochemotherapy of SCCHN, such as two courses of 20 mg/m^2 cisplatin on five consecutive days or weekly administration of 30–40 mg/m^2 [10–14, 17, 18]. The latter regimen is particularly used for patients who do not wish to stay in hospital during chemotherapy.

It is not yet clear whether weekly administration of 30–40 mg/m^2 cisplatin is as effective as the "standard"

Rades *et al. BMC Cancer* (2016) 16:437

Page 5 of 8

Table 2 Univariate analysis of locoregional control (LRC)

	At 1 year (%)	At 3 years (%)	P
Radiochemotherapy regimen			
Cisplatin weekly (N = 75)	70	58	
Cisplatin 100 mg/m^2 (N = 58)	85	78	0.010
Age			
≤56 years (N = 67)	78	65	
≥57 years (N = 66)	74	68	0.72
Gender			
Female (N = 29)	92	87	
Male (N = 104)	72	61	0.010
ECOG Performance score			
0–1 (N = 115)	78	69	
2 (N = 18)	66	49	0.14
Primary tumor site			
Oropharynx (N = 69)	83	74	
Hypopharynx (N = 19)	47	47	
Larynx (N = 30)	79	67	
Oral cavity/Floor of mouth (N = 15)	75	56	0.047
T-category			
T1–2 (N = 16)	93	76	
T3–4 (N = 117)	74	65	0.28
N-category			
N0-2a (N = 66)	76	68	
N2b-3 (N = 67)	76	65	0.93
Histologic grading			
G 1–2 (N = 85)	77	69	
G3 (N = 48)	75	63	0.65
Cumulative cisplatin dose			
≤200 mg/m^2 (N = 85)	70	62	
>200 mg/m^2 (N = 48)	86	74	0.09

After Bonferroni correction for multiple tests, *p*-values of <0.006 were considered significant

Table 3 Univariate analysis of metastases-free survival (MFS)

	At 1 year (%)	At 3 years (%)	P
Radiochemotherapy regimen			
Cisplatin weekly (N = 75)	89	68	
Cisplatin 100 mg/m^2 (N = 58)	83	76	0.66
Age			
≤56 years (N = 67)	85	71	
≥57 years (N = 66)	88	72	0.30
Gender			
Female (N = 29)	79	69	
Male (N = 104)	89	72	0.59
ECOG Performance score			
0–1 (N = 115)	92	79	
2 (N = 18)	52	25	**<0.001**
Primary tumor site			
Oropharynx (N = 69)	89	78	
Hypopharynx (N = 19)	71	61	
Larynx (N = 30)	100	77	
Oral cavity/Floor of mouth (N = 15)	62	44	**0.002**
T-category			
T1–2 (N = 16)	93	85	
T3–4 (N = 117)	85	69	0.93
N-category			
N0-2a (N = 66)	97	81	
N2b-3 (N = 67)	76	62	**0.001**
Histologic grading			
G 1–2 (N = 85)	95	76	
G3 (N = 48)	72	63	**0.003**
Cumulative cisplatin dose			
≤200 mg/m^2 (N = 85)	87	71	
>200 mg/m^2 (N = 48)	86	73	0.69

After Bonferroni correction for multiple tests, *p*-values of <0.006 were considered significant
Bold values represent significant *p*-values

regimen 100 mg/m^2 of cisplatin given every 3 weeks. The available studies performed in patients with non-nasopharyngeal SCCHN produced inconsistent results. In a retrospective study of 94 patients, 100 mg/m^2 of cisplatin resulted in better OS ($p = 0.041$) and similar PFS ($p = 0.47$) [11]. However, patients in the cisplatin-weekly group were significantly older ($p = 0.001$), which likely have introduced a bias. A more recent retrospective study suggested that 100 mg/m^2 cisplatin every 3 weeks resulted in better PFS and OS than weekly administration of 40 mg/m^2 cisplatin [12]. The 5-year PFS rates were 56 and 44 %, respectively, and the 5-year OS rates 62 and 53 %, respectively. Both differences achieved significance in the univariate analyses but not in the multivariate analyses. In that study, 30 % of patients received definitive radiochemotherapy and 70 %

radiochemotherapy following surgery or induction chemotherapy. The heterogeneity of treatment regimens may have confounded the results. Another retrospective study compared 100 mg/m^2 cisplatin every 3 weeks to weekly administration of 30 mg/m^2 cisplatin in a more homogeneously treated cohort of patients, who all received radiochemotherapy following surgery [13]. Three-year LRC rates were 71 and 74 %, respectively ($p = 0.95$), and 3-year OS rates 84 and 75 %, respectively ($p = 0.30$). In addition to these retrospective studies, one randomized trial was performed that compared 100 mg/m^2 cisplatin every 3 weeks to 40 mg/m^2 cisplatin weekly [14]. The 1-year LRC rates were 71 and 60 %, respectively ($p = 0.81$), and 1-year OS rates were 79 and 72 %, respectively ($p = 0.98$). The sample size of 50

Rades *et al. BMC Cancer* (2016) 16:437

Page 6 of 8

Table 4 Univariate analysis of overall survival (OS)

	At 1 year (%)	At 3 years (%)	P
Radiochemotherapy regimen			
Cisplatin weekly (N = 75)	71	45	
Cisplatin 100 mg/m² (N = 58)	83	60	0.026
Age			
≤56 years (N = 67)	77	54	
≥57 years (N = 66)	74	49	0.50
Gender			
Female (N = 29)	89	70	
Male (N = 104)	72	47	0.050
ECOG Performance score			
0–1 (N = 115)	78	56	
2 (N = 18)	61	14	0.006
Primary tumor site			
Oropharynx (N = 69)	78	61	
Hypopharynx (N = 19)	53	21	
Larynx (N = 30)	83	59	
Oral cavity/Floor of mouth (N = 15)	80	29	**<0.001**
T-category			
T1–2 (N = 16)	81	63	
T3–4 (N = 117)	75	50	0.85
N-category			
N0-2a (N = 66)	79	60	
N2b-3 (N = 67)	73	42	0.14
Histologic grading			
G 1–2 (N = 85)	78	52	
G3 (N = 48)	73	51	0.47
Cumulative cisplatin dose			
≤ 200 mg/m² (N = 85)	69	46	
> 200 mg/m² (N = 48)	87	61	0.13

After Bonferroni correction for multiple tests, *p*-values of <0.006 were considered significant
Bold values represent significant *p*-values

Table 5 Results of the multivariate analyses of locoregional control, metastases-free survival and overall survival

	Hazard ratio	95 %-confidence interval	P
Locoregional control			
Radiochemotherapy regimen			
(Cisplatin 100 mg/m2 vs. Cisplatin weekly)	1.57	1.12–2.31	**0.008**
Gender			
(female vs. male)	4.37	1.58–18.11	**0.003**
Primary tumor site			
(oropharynx or larynx vs. others)	1.18	0.94–1.45	0.16
Metastases-free survival			
ECOG performance score			
(0–1 vs. 2)	5.63	2.19–14.11	**<0.001**
N-category			
(N0-2a vs. N2b-3)	2.02	0.90–4.84	0.09
Histological grading			
(G1–2 vs. G3)	1.81	1.26–2.66	**0.002**
Primary tumor site			
(oropharynx or larynx vs. others)	1.15	0.88–1.50	0.30
Overall survival			
Radiochemotherapy regimen			
(Cisplatin 100 mg/m2 vs. Cisplatin weekly)	1.33	1.04–1.73	**0.023**
Gender			
(female vs. male)	1.98	1.08–3.96	**0.026**
ECOG performance score			
(0–1 vs. 2)	2.15	1.09–3.99	**0.029**
Primary tumor site			
(oropharynx or larynx vs. others)	1.09	0.92–1.30	0.32

Bold values represent significant *p*-values

eligible patients was too small to achieve an adequate statistical power. Furthermore, the trial was limited to patients with cancer of the oral cavity and may not be generalized to other sites of SCCHN.

Thus, more studies comparing 30–40 mg/m² weekly to 100 mg/m² given every 3 weeks for radiochemotherapy of SCCHN would be helpful, ideally in form of a randomized trial with an adequate statistical power. However, such a trial will likely be difficult to perform, since most centers wish to keep on using their preferred radiochemotherapy regimen. Therefore, the present retrospective study was initiated to provide additional information to answer this important question. It included only patients, who had received definitive radiochemotherapy, to avoid a potential

selection bias caused by different types of treatment. However, when interpreting the results of this study one has to keep in mind that this study is retrospective in nature. Retrospective studies always bear the risk of including hidden selection biases.

There could have been different proportions of HPV-positive tumors in both radiochemotherapy groups. The HPV-status was not available in most patients and, therefore, not included in the analyses. In previous reports from Slovenia and Northern Germany, 20 and 15 % respectively of oropharynx cancers were HPV-positive [19, 20]. Further limitations of this study included the facts that the radiochemotherapy groups were not compared for treating institution, that patients receiving IMRT or VMAT were not included and that both radiochemotherapy groups were

Rades *et al. BMC Cancer* (2016) 16:437

Page 7 of 8

Table 6 Comparison of the radiochemotherapy groups (30–40 mg/m2 of cisplatin weekly vs. 100 mg/m^2 of cisplatin on days 1, 22 and 43) for acute and late adverse events

	Cisplatin weekly N patients (%)	Cisplatin 100 mg/m^2 N patients (%)	P
Oral mucositis			
Grade ≥2	70 (93)	55 (95)	0.95
Skin reactions			
Grade ≥2	48 (64)	48 (83)	0.25
Hematotoxicity			
Grade ≥3	7 (9)	19 (33)	**0.004**
Renal failure			
Grade ≥2	2 (3)	12 (21)	**0.004**
Pneumonia/Sepsis			
Grade ≥3	1 (1)	7 (12)	0.033
Xerostomia[a]			
Grade ≥2	28/60 (47)	34/58 (59)	0.44
Subcutaneous fibrosis[a]			
Grade ≥2	27/72 (38)	28/51 (55)	0.20

[a]not available in all patients
After Bonferroni correction for multiple tests (7 tests), p-values of <0.007 were considered significant
Bold values represent significant p-values

compared for patient characteristics with the Chi-square test instead of using propensity score matching.

According to the results of the present study, 100 mg/m^2 cisplatin given every 3 weeks led to better LRC and OS than weekly administration of 30–40 mg/m^2 cisplatin. Summarizing the results of both studies with respect to treatment outcomes, 100 mg/m^2 cisplatin appears preferable to weekly administration of 30–40 mg/m^2 cisplatin for definitive radiochemotherapy of SCCHN. However, one question is whether improved outcomes are impaired by more serious adverse events? Ho et al. reported that 100 mg/m^2 cisplatin was less tolerated than weekly administration of 40 mg/m^2 cisplatin [10]. In contrast, *Tsan* et al. observed a higher rate of grade ≥3 oral mucositis (75 versus 39 %, $p = 0.012$) and a higher rate of grade ≥3 overall toxicity (92 versus 81 %, $p = 0.02$) in the 40 mg/m^2 cisplatin-weekly group [14]. In the study of *Espeli* et al., 100 mg/m^2 cisplatin resulted in more renal failures ($p = 0.04$) [11]. In the largest study so far (Fayette et al.), 100 mg/m^2 cisplatin was associated with significantly more adverse events than weekly administration of 40 mg/m^2 cisplatin [12]. The rates of grade 3/4 mucositis were 34 and 12 %, respectively ($p < 0.001$), and the rates of grade 3/4 dermatitis were 7 and 1 %, respectively ($p = 0.014$). Decrease of creatinine clearance was also more pronounced in the 100 mg/m^2 cisplatin group ($p < 0.001$). Also in the present study, some of the acute adverse events were significantly more frequent in the 100 mg/m^2 cisplatin group (Table 5). These findings demonstrate that patients receiving definitive radiochemotherapy with 100 mg/m^2

cisplatin on days 1, 22 and 42 require intensive monitoring (clinical examination, bone marrow function, renal function) and timely supportive care. If they are able to withstand this intensive radiochemotherapy regimen, they can benefit in terms of LRC and OS. I may be questioned why more patients treated with 100 mg/m^2 cisplatin received a cumulative dose >200 mg/m^2 than in the weekly cisplatin group, although 100 mg/m^2 cisplatin was associated with more acute toxicity? This finding can to a certain extent be explained by the reduced compliance of some patients. In the cisplatin weekly group, the weekly cisplatin dose was 30 mg/m^2 in 71 of 75 patients. If such a patient refused the last administration of cisplatin, the cumulative dose was only 180 mg/m^2. Of the 71 patients receiving weekly cisplatin doses of 30 mg/m^2, nine patients (13 %) received a cumulative dose of only 180 mg/m^2 without developing a grade 3 acute toxicity.

Conclusions

Definitive radiochemotherapy with 100 mg/m^2 of cisplatin given on days 1, 22 and 43 resulted in better LRC and OS than weekly doses of 30–40 mg/m^2. Thus, 100 mg/m^2 of cisplatin appears preferable for definitive radiochemotherapy of locally advanced SCCHN. However, one should be aware that the regimen including 100 mg/m^2 of cisplatin given every 3 weeks is associated with considerable acute toxicity. Patients receiving this regimen need close monitoring and timely supportive care.

Rades *et al. BMC Cancer* (2016) 16:437

Page 8 of 8

Author details
[1]Department of Radiation Oncology, University of Lubeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. [2]Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany. [3]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany. [4]Department of Radiotherapy, Institute of Oncology Ljubljana, Ljubljana, Slovenia. [5]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA.

References
1. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2004;22:69–76.
2. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol. 1997;43:29–37.
3. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, Vaskovic Z, Tadic L. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol. 2000;18:1458–64.
4. Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4–14.
5. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350:1945–52.
6. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350:1937–44.
7. Adelstein DJ, Li Y, Adams GL, Wagner Jr H, Kish JA, Ensley JF, Schuller DE, Forastiere AA. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003;21:92–8.
8. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, Glisson B, Trotti A, Ridge JA, Chao C, Peters G, Lee DJ, Leaf A, Ensley J, Cooper J. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091–8.
9. de Castro Jr G, Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, Federico MH. High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2007;264:1475–82.
10. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol. 2008;47:1513–8.
11. Espeli V, Zucca E, Ghielmini M, Ghielmini M, Giannini O, Salatino A, Martucci F, Richetti A. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol. 2012;48:266–71.
12. Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupart M, Ramade A, Zrounba P, Ceruse P, Pommier P. Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. Drug Des Devel Ther. 2015;9:6203–10.
13. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, Olsen KD, Kasperbauer JL, Price DL, Garces YI, Ma DJ, Neben-Wittich MA, Molina JR, Garcia JJ, Price KA. Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncol. 2014;50:311–8.
14. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, Chen IH, Lee LY, Wang HM, Chang JT. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol. 2012;7:215.
15. National Institutes of Health/National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, 2009. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
16. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457–81.
17. Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, Pestalozzi B, Schmid S, Thöni A, Ozsahin M, Bernier J, Töpfer M, Kann R, Meier UR, Thum P, Bieri S, Notter M, Lombriser N, Glanzmann C. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol. 2004;22:4665–73.
18. Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE, Dunst J. Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2011;80:1037–44.
19. Strojan P, Zadnik V, Šifrer R, Lanišnik B, Didanović V, Jereb S, Poljak M, Kocjan BJ, Gale N. Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983–2009: role of human papillomavirus infection. Eur Arch Otorhinolaryngol. 2015;272:3805–14.
20. Rades D, Seibold ND, Hoffmann A, Gebhard MP, Noack F, Thorns C, Schild SE. Impact of the HPV-positivity definition on the prognostic value of HPV status in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol. 2013;189:856–60.

Radiochemotherapy for locally advanced squamous cell carcinoma of the head and neck: Higher-dose cisplatin every 3 weeks versus cisplatin/5-fluorouracil every 4 weeks

Dirk Rades [a, *], Primoz Strojan [b], Daniel Seidl [a], Stefan Janssen [a, c], Amira Bajrovic [d],
Nadja Kazic [e], Samer G. Hakim [f], Barbara Wollenberg [g], Steven E. Schild [h]

[a] Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[b] Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia
[c] Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany
[d] Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany
[e] Oncology Clinic, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[f] Department of Oral and Maxillofacial Surgery, University of Lübeck, Lübeck, Germany
[g] Department of Oto-Rhino-Laryngology and Head and Neck Surgery, University of Lübeck, Lübeck, Germany
[h] Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA

ARTICLE INFO

ABSTRACT

Many patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) receive cisplatin-based radiochemotherapy. The optimal regimen is still unclear when considering both efficacy and feasibility. This study compared two regimens for locoregional control (LRC), overall survival (OS), and adverse events. Data of 329 patients with LASCCHN receiving definitive or postoperative radiochemotherapy were retrospectively analyzed. A total of 131 patients received 100 mg/m^2 cisplatin on days 1, 22, and 43 (group A), and 198 patients received 20 mg/m^2 cisplatin plus 600/1000 mg/m^2 5-FU on days 1—5 and days 29—33 (group B). Radiochemotherapy regimens plus nine factors were compared for LRC and OS, and radiochemotherapy regimens additionally for adverse events. On univariate analysis, chemotherapy type was not associated with LRC ($p = 0.36$). On multivariate analysis, performance score ($p = 0.039$), N-category ($p = 0.007$), histologic grade ($p = 0.007$), upfront surgery ($p = 0.030$), and pre-radiochemotherapy hemoglobin levels ($p < 0.001$) were associated with LRC. On univariate analysis, chemotherapy type had no impact on OS ($p = 0.64$). On multivariate analysis, performance score ($p < 0.001$), T-category ($p = 0.025$), N-category ($p < 0.001$), histologic grade, and hemoglobin levels ($p < 0.001$) were associated with OS. Renal failure occurred significantly more often in group A ($p = 0.008$). Otherwise, adverse events were not significantly different. Thus, both radiochemotherapy regimens appeared similarly effective for LASCCHN. Patients receiving 100 mg/m^2 of cisplatin require close monitoring of their renal function.

© 2016 European Association for Cranio-Maxillo-Facial Surgery. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Many patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) are treated with radio-chemotherapy. Randomized trials have demonstrated that radiochemotherapy is superior to radiotherapy alone for definitive treatment and postoperative treatment in patients with specific risk factors (Bernier et al., 2004; Cooper et al., 2004; Denis et al., 2004; Jeremic et al., 1997, 2000). Risk factors included incomplete tumor resection and extracapsular extension of lymph nodes (Kwon et al., 2015). In a metaanalysis of 16,485 patients receiving definitive treatment for SCCHN, concurrent radiochemotherapy resulted in significantly better outcomes than chemotherapy followed by radiotherapy (Pignon et al., 2009). Most patients in that metaanalysis received cisplatin alone or in combination with 5-

fluorouracil (5-FU). No particular radiochemotherapy regimen was found to be superior to others.

Two randomized trials that compared radiochemotherapy to radiotherapy alone for postoperative treatment of LASCCHN with risk factors demonstrated the combined approach including 100 mg/m^2 of cisplatin on days 1, 22, and 43 to be significantly superior to irradiation alone (Bernier et al., 2004; Cooper et al., 2004). Radiochemotherapy with 100 mg/m^2 of cisplatin every 3 weeks became the most common regimen for LASCCHN. Because this regimen can be very toxic, many centers use alternative cisplatin-based approaches (De Castro et al., 2007). The second most common radiochemotherapy regimen for LASCCHN is cisplatin plus 5-FU, in which cisplatin is generally administered in a fractionated way, i.e., with two courses of 12–20 mg/m^2 of cisplatin on 4–5 consecutive days. 5-FU (daily doses of 600–1000 mg/m^2) is given on the same days (Adelstein et al., 2006; Fietkau et al., 2006; Rades et al., 2011; Su et al., 2011; Zaboli et al., 2012; Rodriguez et al., 2015).

Only very few studies are available that compared radiochemotherapy with 100 mg/m^2 of cisplatin every 3 weeks to cisplatin plus 5-FU for LASCCHN. In 2008, a retrospective study of 128 patients suggested that the combined approach was better tolerated (Rades et al., 2008a). Recently, a small randomized trial compared 100 mg/m^2 of cisplatin (days 1, 22, and 43) to 20 mg/m^2 of cisplatin plus 600 mg/m^2 of 5-FU given (on 4 days in radiotherapy weeks 1 and 4) (Rodriguez et al., 2015). In that trial, 3-year locoregional control (LRC) was not significantly different, whereas overall survival (OS) was better in patients receiving 100 mg/m^2 of cisplatin every 3 weeks. Since this trial included only 69 patients, larger studies comparing 100 mg/m^2 of cisplatin to cisplatin plus/5-FU are required. A larger randomized trial with an appropriate statistical power is not expected soon. We initiated this retrospective study of 329 patients to aid in identifying the appropriate radiochemotherapy regimen for LASCCHN.

2. Material and methods

A total of 329 patients who received definitive or postoperative concurrent radiochemotherapy for LASCCHN between May 1999 and December 2014 were included in this study. Of these patients, 131 received 100 mg/m^2 of cisplatin every 3 weeks (group A), and 198 patients 20 mg/m^2 of cisplatin every 4 weeks supplemented with 5-FU (group B). The selection of the type of chemotherapy depended on the preferences of the contributing centers at the time when the patients included in this study were treated. Thus, each cohort of patients from a contributing center represented a consecutive series. The radiochemotherapy groups and nine additional factors were retrospectively compared for treatment outcomes in terms of LRC and OS. Additional factors included age, gender, Eastern Cooperative Oncology Group (ECOG) performance score, tumor site, T-category, N-category, histological grade, upfront surgery, and pre-radiochemotherapy hemoglobin levels. The distributions of these factors in the radiochemotherapy groups are summarized in Table 1. The two radiochemotherapy groups were additionally compared for adverse events in terms of oral mucositis, dermatitis, hematotoxicity, renal toxicity, pneumonia/sepsis, xerostomia, and subcutaneous cervical fibrosis.

Radiotherapy was performed with 6–10 MV photon beams from a linear accelerator after three-dimensional conformal treatment planning. Total doses to the primary tumor and to involved lymph nodes depended on the type treatment (definitive or postoperative) and on the results of upfront surgery (microscopically complete or incomplete resection). Total doses were 66–70 Gy for definitive treatment, 63–66 Gy following microscopically incomplete resection, and 59.4–66.6 Gy after microscopically complete resection, respectively. Total doses to noninvolved lymph nodes

were 59.4–60 Gy to higher-risk and 50–50.4 Gy to intermediate-risk regions, respectively.

In group A, concurrent chemotherapy consisted of 100 mg/m^2 of cisplatin alone given as bolus infusion on days 1, 22, and 43. In group B, patients received 20 mg/m^2 of cisplatin on days 1–5 and 29–33 plus daily doses of 600 or 1000 mg/m^2 of 5-FU administered as continuous infusion over 120 h on days 1–5 and 29–33. Patients in both radiotherapy groups had received prophylactic hydration and antiemetic agents as well as treatment for occurring symptomatic adverse events.

The follow-up schedule included visits every 3 months for 2 years, every 6 months for an additional year and then, yearly. LRC and OS were calculated from the last day of radiochemotherapy. The univariate analyses of LRC and OS rates were performed with the Kaplan–Meier method and the log-rank test (Kaplan and Meier, 1958). If the difference between the compared groups achieved significance (defined as $p < 0.05$) on univariate analyses, the corresponding factors were additionally included in multivariate analyses (Cox regression analysis) to test for independent associations.

Adverse events were graded according to the Common Terminology Criteria of Adverse Events (CTCAE) 4.0 (National Institutes of Health/National Cancer Institute, 2009), and the comparisons of the radiochemotherapy were performed with the χ^2 test.

3. Results

In the entire cohort, LRC rates at 1, 3, and 5 years were 87%, 78%, and 77%, respectively. On univariate analyses, improved LRC was associated with ECOG performance score 0–1 ($p < 0.001$), T-category 1–2 ($p = 0.012$), N-category 0–2a ($p = 0.026$), histologic grade 1–2 ($p = 0.006$), upfront surgery ($p < 0.001$), and pre-

Table 1
Patient characteristics of the radiochemotherapy group A (100 mg/m^2 of cisplatin every 3 weeks) and group B (20 mg/m^2 of cisplatin plus 600/1000 mg/m^2 of 5-FU on 5 consecutive days every 4 weeks).

	Group A (N = 131) N patients (%)	Group B (N = 198) N patients (%)	p value (χ^2 test)
Age			
≤57 years (N = 178)	72 (55)	106 (54)	
≥58 years (N = 151)	59 (45)	92 (46)	0.87
Gender			
Female (N = 67)	30 (23)	37 (19)	
Male (N = 262)	101 (77)	161 (81)	0.68
ECOG performance score			
0–1 (N = 289)	119 (91)	170 (86)	
2 (N = 40)	12 (9)	28 (14)	0.64
Tumor site			
Oropharynx (N = 167)	69 (53)	98 (49)	
Hypopharynx (N = 53)	23 (18)	30 (15)	
Larynx (N = 66)	25 (19)	41 (21)	
Oral cavity/floor of mouth (N = 43)	14 (11)	29 (15)	0.90
T-category			
T1–2 (N = 129)	49 (37)	80 (40)	
T3–4 (N = 200)	82 (63)	118 (60)	0.73
N-category			
N0–2a (N = 118)	50 (38)	68 (34)	
N2b–3 (N = 211)	81 (62)	130 (66)	0.67
Histologic grade			
G 1–2 (N = 183)	76 (58)	107 (54)	
G3 (N = 146)	55 (42)	91 (46)	0.64
Surgery prior to radiochemotherapy			
No (N = 105)	44 (34)	61 (31)	
Yes (N = 224)	87 (66)	137 (69)	0.76
Hemoglobin prior to radiochemotherapy			
<12 g/dl (N = 107)	39 (30)	68 (34)	
≥12 g/dl (N = 222)	92 (70)	130 (66)	0.62

radiochemotherapy hemoglobin levels ≥12 g/dl (p < 0.001) (Table 2). In contrast to these factors, the type of concurrent chemotherapy was not associated with LRC (p = 0.36) (Fig. 1). On multivariate analysis of LRC, ECOG performance score (risk ratio [RR] 2.02; 95% confidence interval [CI] 1.04–3.72; p = 0.039), N-category (RR 2.12; 95% CI 1.22–3.89; p = 0.007), histologic grade (RR 1.41; 95% CI 1.10–1.83; p = 0.007), upfront surgery (RR 1.80; 95% CI 1.06–3.07; p = 0.030), and pre-radiochemotherapy hemoglobin levels (RR 2.42; 95% CI 1.44–4.05; p < 0.001) remained significant, and T-category showed a trend (RR 1.32; 95% CI 0.99–1.79; p = 0.06).

For the entire cohort, the OS rates at 1, 3 and 5 years were 86%, 66% and 57%, respectively. On univariate analyses, improved OS was associated with ECOG performance score 0–1 (p < 0.001), tumor site other than hypopharynx (p = 0.047), T-category 1–2 (p = 0.003), N-category 0–2a (p = 0.003), histologic grade 1–2 (p = 0.002), upfront surgery (p < 0.001), and pre-radiochemotherapy hemoglobin levels ≥12 g/dl (p < 0.001) (Table 3). The type of chemotherapy was not associated with OS (p = 0.64, Fig. 2). On multivariate analysis of OS, ECOG performance score (RR 3.13; 95% CI 1.93–4.94; p < 0.001), T-category (RR 1.29; 95% CI 1.03–1.63; p = 0.025), N-category (RR 2.08; 95% CI 1.35–3.33; p < 0.001), histologic grade (RR 1.35; 95% CI 1.10–1.66; p = 0.003), and pre-radiochemotherapy hemoglobin levels (RR 2.38; 95% CI 1.59–3.57; p < 0.001) maintained significance. Tumor site (RR 1.02; 95% CI 0.88–1.20; p = 0.77) and upfront surgery (RR 1.42; 95% CI 0.92–2.16; p = 0.11) were not significant on multivariate analysis.

The incidence of most adverse events was not significantly different for both radiochemotherapy groups (Table 4). Renal
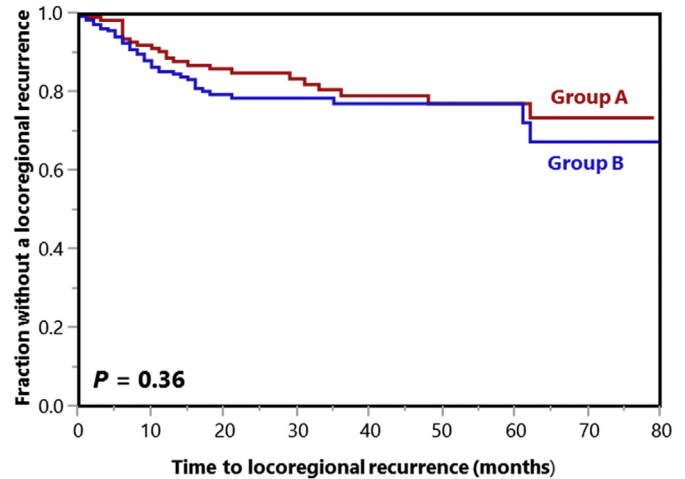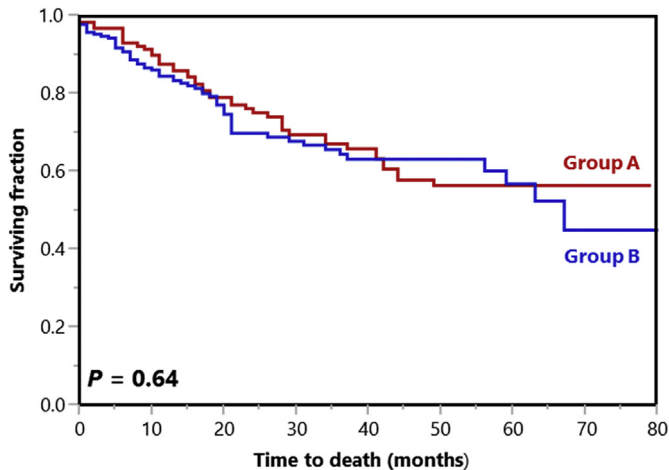

Fig. 1. Comparison of the radiochemotherapy group A (100 mg/m^2 of cisplatin every 3 weeks) and group B (20 mg/m^2 of cisplatin plus 600/1000 mg/m^2 of 5-FU on 5 consecutive days every 4 weeks) with respect to loco-regional control.

failure occurred significantly more often in group A than in group B (p = 0.008).

4. Discussion

Although the multidisciplinary treatment of LASCCHN has progressed during the last two decades, further improvements are desirable (Mercante et al., 2015; Ren et al., 2015; Schlittenbauer

Table 2
Comparison of the radiochemotherapy groups and the additional nine factors with respect to loco-regional control (univariate analysis).

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p value
Radiochemotherapy groups				
Group A (N = 131)	89	79	77	
Group B (N = 198)	85	77	77	0.36
Age				
≤57 years (N = 178)	87	76	76	
≥58 years (N = 151)	87	80	78	0.43
Gender				
Female (N = 67)	94	80	80	
Male (N = 262)	85	77	76	0.32
ECOG performance score				
0–1 (N = 289)	88	81	80	
2 (N = 40)	75	41	41	<0.001
Tumor site				
Oropharynx (N = 167)	89	79	79	
Hypopharynx (N = 53)	76	70	63	
Larynx (N = 66)	91	83	83	
Oral cavity/floor of mouth (N = 43)	85	76	76	0.16
T-category				
T1–2 (N = 129)	95	84	82	
T3–4 (N = 200)	82	74	74	0.012
N-category				
N0–2a (N = 118)	92	85	82	
N2b–3 (N = 211)	84	73	73	0.026
Histologic grade				
G 1–2 (N = 183)	90	85	83	
G3 (N = 146)	83	69	69	0.006
Surgery prior to radiochemotherapy				
No (N = 105)	79	63	63	
Yes (N = 224)	91	83	82	<0.001
Hemoglobin prior to radiochemotherapy				
<12 g/dl (N = 107)	76	65	65	
≥12 g/dl (N = 222)	92	84	82	<0.001

Table 3
Comparison of the radiochemotherapy groups and the additional nine factors with respect to overall survival (univariate analysis).

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p value
Radiochemotherapy groups				
Group A (N = 131)	88	67	57	
Group B (N = 198)	85	65	57	0.64
Age				
≤57 years (N = 178)	87	68	58	
≥58 years (N = 151)	85	63	55	0.73
Gender				
Female (N = 67)	91	76	53	
Male (N = 262)	85	63	58	0.59
ECOG performance score				
0–1 (N = 289)	89	73	64	
2 (N = 40)	65	11	5	<0.001
Tumor site				
Oropharynx (N = 167)	85	71	60	
Hypopharynx (N = 53)	75	49	45	
Larynx (N = 66)	95	64	54	
Oral cavity/Floor of mouth (N = 43)	88	72	72	0.047
T-category				
T1–2 (N = 129)	90	78	65	
T3–4 (N = 200)	83	56	52	0.003
N-category				
N0–2a (N = 118)	95	75	62	
N2b–3 (N = 211)	81	60	53	0.003
Histologic grade				
G 1–2 (N = 183)	91	71	65	
G3 (N = 146)	80	59	47	0.002
Surgery prior to radiochemotherapy				
No (N = 105)	78	47	38	
Yes (N = 224)	90	72	63	<0.001
Hemoglobin prior to radiochemotherapy				
<12 g/dl (N = 107)	71	46	43	
≥12 g/dl (N = 222)	93	75	64	<0.001

Fig. 2. Comparison of the radiochemotherapy group A (100 mg/m^2 of cisplatin every 3 weeks) and group B (20 mg/m^2 of cisplatin plus 600/1000 mg/m^2 of 5-FU on 5 consecutive days every 4 weeks) with respect to overall survival.

Table 4
Comparison of the radiochemotherapy group A (100 mg/m^2 of cisplatin every 3 weeks) and group B (20 mg/m^2 of cisplatin plus 600/1000 mg/m^2 of 5-FU on 5 consecutive days every 4 weeks) with respect to adverse events.

	Group A N patients (%)	Group B N patients (%)	p value
Oral mucositis			
Grade ≥ 2	122 (93)	164 (83)	0.36
Dermatitis			
Grade ≥ 2	102 (78)	166 (84)	0.60
Hematotoxicity			
Grade ≥ 3	29 (22)	40 (20)	0.81
Renal failure			
Grade ≥ 2	17 (13)	8 (4)	0.008
Pneumonia/sepsis			
Grade ≥ 3	8 (6)	10 (5)	0.91
Xerostomia			
Grade ≥ 2	68 (52)	79 (40)	0.13
Subcutaneous cervical fibrosis			
Grade ≥ 2	63[a] (51)	68[b] (36)	0.10

[a] Of 129 patients.
[b] Of 188 patients.

et al., 2015). It is recognized that concurrent radiochemotherapy results in better outcomes than radiotherapy alone for definitive treatment (Pignon et al., 2009). Also, in selected resected patients with risk factors, the addition of concurrent chemotherapy to irradiation improves the prognosis (Bernier et al., 2004; Cooper et al., 2004). It is generally agreed that cisplatin should be part of the regimen, either alone or in combination with other agents, most frequently 5-FU (Pignon et al., 2009). The choice of a chemotherapy regimen should take into account several aspects including efficacy, feasibility, patient preference, and quality of life (Bilal et al., 2015; Mücke et al., 2015). Thus, the most appropriate radiochemotherapy for LASCCHN still requires further clarification. The most common regimen, 100 mg/m^2 of cisplatin on days 1, 22, and 43, was demonstrated to be effective (Bernier et al., 2004; Cooper et al., 2004). However, there is considerable acute toxicity. In the RTOG 88-24 trial, there were 20% severe and 12% life-threatening acute adverse events in patients receiving postoperative radiochemotherapy with 60 Gy plus 100 mg/m^2 of cisplatin on days 1, 22, and 43 (Al-Sarraf et al., 1997). Therefore, physicians have looked for alternative cisplatin-based regimens. One way to reduce renal toxicity was to decrease the cumulative cisplatin dose from 300 mg/m^2 to 160–200 mg/m^2 and add 5-FU to compensate

(Adelstein et al., 2006; Fietkau et al., 2006; Rades et al., 2008a,b; Rodriguez et al., 2015). Furthermore, cisplatin was not given as a single dose of 100 mg/m^2 but in four to five fractions of 20 mg/m^2 on consecutive days. In a retrospective study of 128 patients, grade 2–3 renal failure was significantly more common after 100 mg/m^2 of cisplatin every 3 weeks than after cisplatin/5-FU (18% vs. 1%, p = 0.001) (Rades et al., 2008a,b). Other acute adverse events such as grade 3–4 hematotoxicity (39% vs. 22%, p = 0.049) were also more common. The 2-year LRC (72% vs. 66%, p = 0.32) and 2-year OS (68% vs. 56%, p = 0.82) were not significantly different. In another retrospective study that compared four cisplatin-based radiochemotherapy regimens for LASCCHN, grade 3 renal toxicity rates were 8% with 100 mg/m^2 of cisplatin alone versus 1% with cisplatin plus 600 mg/m^2 of 5-FU and 2% with cisplatin plus 1000 mg/m^2 of 5-FU. Grade 3–4 hematotoxicity rates were 35% versus 19% and 46%, 3-year LRC rates 67% versus 60% and 72%, and 3-year OS rates 60% versus 50% and 63%, respectively (Rades et al., 2011). In a randomized study of 69 patients, significant renal toxicity occurred in 26% of patients after 100 mg/m^2 of cisplatin every 3 weeks and 3% after 20 mg/m^2 of cisplatin plus 600 mg/m^2 of 5-FU given on days 1–4 and days 22–35 (p = 0.007) (Rodriguez et al., 2015). In contrast, grade ≥2 radiation dermatitis (43% vs. 68%, p = 0.038) and grade ≥3 neutropenia (34% vs. 65%, p = 0.012) were more common in the cisplatin/5-FU group. In that trial, 3-year LRC rates were similar after cisplatin alone and cisplatin/5-FU (96% vs. 94%, p = 0.52). However, and most importantly, 3-year OS rates were significantly better in the cisplatin-alone group (97% vs. 85%, p = 0.013).

The available studies suggested that 100 mg/m^2 of cisplatin every 3 weeks was associated with higher rates of renal failure than cisplatin/5-FU. The results with respect to other adverse events were inconclusive. Therefore, we have collected more data and performed an additional analysis comparing both radiochemotherapy regimens in 329 patients. This is the largest study to compare 100 mg/m^2 of cisplatin every 3 weeks to cisplatin/5-FU for radiochemotherapy of LASCCHN so far. Both regimens were similarly effective with respect to LRC, which agrees with the findings of the previous studies (Rades at al., 2008a,b, 2011; Rodriguez et al., 2015). In the present study, OS rates were also similar, which agrees with the findings of the two previous retrospective studies. In contrast, 3-year OS was better after 100 mg/m^2 of cisplatin every 3 weeks than after cisplatin/5-FU in the randomized study (Rodriguez et al., 2015). One can speculate about these different results. The present study was retrospective in nature, which can include hidden biases. For example, there could have been a difference regarding the proportion of HPV-positive tumors between the two groups, since the HPV-status was not available in most patients. In a previous study from Lübeck, 14% of tumors were HPV-positive compared to 33% in the randomized trial (Rades et al., 2013; Rodriguez et al., 2015). Furthermore, the randomized trial included only 69 patients, which is fairly small. Although it was a randomized trial, patients in the cisplatin alone group had more favorable characteristics including higher proportions of HPV-positive tumors (74% vs. 68%), stage III disease (11% vs. 6%) and ECOG performance score 0 (91% vs. 85%), and a lower proportion of active smokers during radiochemotherapy (11% vs. 24%).

Taking into account the available data, both radiochemotherapy regimens compared in this study are effective for LASCCHN. The frequency of most adverse events is likely not significantly different, except renal failure, which occurs more often after radiochemotherapy with 100 mg/m^2 of cisplatin every 3 weeks than with cisplatin/5-FU. Patients receiving 100 mg/m^2 of cisplatin on days 1, 22, and 43 require close monitoring of renal function. Patients with impaired creatinine clearance or a history of renal

disease should not receive this regimen and should be considered for cisplatin/5-FU or regimens without cisplatin.

In contrast to the chemotherapy regimen, improved treatment outcomes in terms of LRC and OS were significantly associated with better performance status, lower T-category, lower N-category, lower histological grade, upfront surgery, and pre-radiochemotherapy hemoglobin levels ≥12 g/dl in this study. These results agree with those of previous studies (Kwong et al., 1997; Leemans et al., 1993; Rades et al., 2008b). Anemia results in decreased tumor oxygenation, resulting in turn in a lower cell kill by radiotherapy, as the subsequent breaks in tumor DNA are mediated by oxygen radicals (Becker et al., 2000).

5. Conclusion

In this study, both radiochemotherapy regimens appeared to be similarly effective for LASCCHN in terms of LRC ands OS. The frequency of most adverse events was also similar. However, renal failure occurred significantly more often in patients receiving 100 mg/m^2 of cisplatin, who require close monitoring of renal function. The results should be confirmed in a randomized trial with an adequate sample size and adequate stratification of known prognostic factors.

Conflict of interest

The authors hereby declare that there is no conflict of interest related to this study.

Role of the funding source

The study was not funded.

References

Adelstein DJ, Saxton JP, Rybicki LA, Esclamado RM, Wood BG, Strome M, et al: Multiagent concurrent chemoradiotherapy for locoregionally advanced squamous cell head and neck cancer: mature results from a single institution. J Clin Oncol 24: 1064–1071, 2006

Al-Sarraf M, Pajak TF, Byhardt RW, Beitler JJ, Salter MM, Cooper JS: Postoperative radiotherapy with concurrent cisplatin appears to improve locoregional control of advanced, resectable head and neck cancers: RTOG 88-24. Int J Radiat Oncol Biol Phys 37: 777–782, 1997

Becker A, Stadler P, Lavay RS, Hänsgen G, Kuhnt T, Lautenschläger C, et al: Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys 46: 459–466, 2000

Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al, European Organization for Research and Treatment of Cancer Trial 22931: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350: 1945–1952, 2004

Bilal S, Doss JG, Cella D, Rogers SN: Quality of life associated factors in head and neck cancer patients in a developing country using the FACT-H&N. J Craniomaxillofac Surg 43: 274–280, 2015

Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al, Radiation Therapy Oncology Group 9501/Intergroup: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350: 1937–1944, 2004

De Castro Jr G, Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, et al: High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 264: 1475–1482, 2007

Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al: Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 22: 69–76, 2004

Fietkau R, Lautenschläger C, Sauer R, Dunst J, Becker A, Baumann M, et al: Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: results of the German phase III trial ARO 96–3. J Clin Oncol 24(Suppl.): 5507, 2006

Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al: Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 18: 1458–1464, 2000

Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N: Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 43: 29–37, 1997

Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481, 1958

Kwon M, Roh JL, Lee J, Cho KJ, Choi SH, Nam SY, et al: Extranodal extension and thickness of metastatic lymph node as a significant prognostic marker of recurrence and survival in head and neck squamous cell carcinoma. J Craniomaxillofac Surg 43: 769–778, 2015

Kwong DL, Sham JS, Chua DT, Choy DT, Au GK, Wu PM: The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 39: 703–710, 1997

Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB: Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 71: 452–456, 1993

Mercante G, Masiello A, Sperduti I, Cristalli G, Pellini R, Spriano G: Quality of life and functional evaluation in patients with tongue base tumors treated exclusively with transoral robotic surgery: a 1-year follow-up study. J Craniomaxillofac Surg 43: 1561–1566, 2015

Mücke T, Koschinski J, Wolff KD, Kanatas A, Mitchell DA, Loeffelbein DJ, et al: Quality of life after different oncologic interventions in head and neck cancer patients. J Craniomaxillofac Surg 43: 1895–1898, 2015

National Institutes of Health/National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf; 2009

Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92: 4–14, 2009

Rades D, Fehlauer F, Sheikh-Sarraf M, Kazic N, Basic H, Poorter R, et al: Toxicity of two cisplatin-based radiochemotherapy regimens for the treatment of patients with stage III/IV head and neck cancer. Head Neck 30: 235–241, 2008a

Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE, et al: Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiochemotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys 70: 1108–1114, 2008b

Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, et al: Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 80: 1037–1044, 2011

Rades D, Seibold ND, Hoffmann A, Gebhard MP, Noack F, Thorns C, et al: Impact of the HPV-positivity definition on the prognostic value of HPV status in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 189: 856–860, 2013

Ren ZH, Wu HJ, Zhang S, Wang K, Gong ZJ, He ZJ, et al: A new surgical strategy for treatment of tongue squamous cell carcinoma based on anatomic study with preliminary clinical evaluation. J Craniomaxillofac Surg 43: 1577–1582, 2015

Rodriguez CP, Adelstein DJ, Rybicki LA, Savvides P, Saxton JP, Koyfman SA, et al: Randomized phase III study of 2 cisplatin-based chemoradiation regimens in locally advanced head and neck squamous cell carcinoma: impact of changing disease epidemiology on contemporary trial design. Head Neck 37: 1583–1589, 2015

Schlittenbauer T, Zeilinger M, Nkenke E, Kreißel S, Wurm MC, Lell M, et al: Positron emission tomography-computed tomography versus positron emission tomography-magnetic resonance imaging for diagnosis of oral squamous cell carcinoma: a pilot study. J Craniomaxillofac Surg 43: 2129–2135, 2015

Su NW, Leu YS, Lee JC, Chen YJ, Chen HW, Liu CJ, et al: Comparison of the efficacy and toxicity of two dose levels of cisplatin/5-fluorouracil as the chemoradiotherapy regimen for the treatment of locally advanced squamous cell carcinoma of the head and neck. Acta Otolaryngol 131: 1333–1340, 2011

Zaboli D, Tan M, Gogineni H, Lake S, Fan K, Zahurak ML, et al: Hyperfractionated radiotherapy with concurrent cisplatin/5-fluorouracil for locoregional advanced head and neck cancer: analysis of 105 consecutive patients. Int J Otolaryngol 2012: 754191, 2012
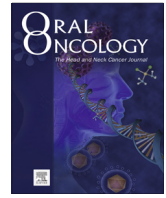
CrossMark

Do we need 5-FU in addition to cisplatin for chemoradiation of locally advanced head-and-neck cancer?

Dirk Rades [a,*], Daniel Seidl [a], Stefan Janssen [a,b], Amira Bajrovic [c], Samer G. Hakim [d], Barbara Wollenberg [e], Steven E. Schild [f]

[a] Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[b] Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany
[c] Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany
[d] Department of Oral and Maxillofacial Surgery, University of Lübeck, Germany
[e] Department of Oto-Rhino-Laryngology and Head and Neck Surgery, University of Lübeck, Germany
[f] Department of Radiation Oncology, Mayo Clinic Scottsdale, Arizona, USA

ARTICLE INFO

SUMMARY

Objectives: To compare chemoradiation with cisplatin alone or cisplatin plus 5-FU for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN).
Materials and methods: The outcomes of 142 patients who received chemoradiation with cisplatin alone for locally advanced SCCHN were retrospectively compared to 170 patients who received cisplatin plus 5-fluorouracil (5-FU). The outcomes compared included loco-regional control (LRC), metastases-free survival (MFS), overall survival (OS) and adverse events.
Results: Although patients who received cisplatin alone had a significantly worse performance status, 81% of these patients completed planned chemotherapy compared to 73% of patients in the cisplatin plus 5-FU group ($p = 0.18$). Radiotherapy breaks >1 week were necessary in 14% and 23% of patients, respectively ($p = 0.09$). The 5-year LRC rates were 69% after cisplatin alone and 68% after cisplatin plus 5-FU ($p = 0.71$). The 5-year MFS rates were 72% and 62%, respectively ($p = 0.37$), and 5-year OS rates were 60% and 45%, respectively ($p = 0.066$). On multivariate analysis, cisplatin alone was significantly associated with improved OS (RR 1.35; 95%-CI 1.09–1.69; $p = 0.006$). Nausea/vomiting, pneumonia/sepsis and late adverse events occurred more common in the cisplatin plus 5-FU group.
Conclusion: Given the limitations of a retrospective study, chemoradiation with cisplatin alone appeared associated with fewer adverse events and better OS than with cisplatin plus 5-FU in patients with locally advanced SCCHN. Thus, 5-FU in addition to cisplatin may be omitted for these patients. A randomized trial is warranted to confirm these findings.

Introduction

The survival of patients with squamous cell carcinoma of the head-and-neck (SCCHN) has improved during the last 15 years [1]. However, many of these patients present with locally advanced or even metastatic disease. The outcome of therapy particular of these patients groups can be further improved. Randomized trials demonstrated that definitive chemoradiation resulted in significantly better treatment outcomes than radiotherapy alone for locally advanced SCCHN [2–4]. In a subsequent large

meta-analysis of 16,485 patients from 2009, simultaneous chemoradiation was superior to chemotherapy followed by irradiation in terms of significantly better loco-regional control (LRC) and overall survival (OS) [5]. According to this meta-analysis, outcomes were not significantly different with cisplatin alone and with cisplatin-based combinations.

Based on these studies, concurrent chemoradiation has become the standard approach for the definitive treatment of unresectable locally advanced SCC of the head-and neck (SCCHN). In that large meta-analysis, the majority of the patients had received chemoradiation with cisplatin and/or 5-fluorouracil (5-FU). Also about 12 years ago, two randomized trials demonstrated that concurrent chemoradiation with three courses of higher-dose cisplatin (100 mg/m^2 on days 1, 22 and 43) resulted in significantly better outcomes than radiotherapy alone following head-and-neck

* Corresponding author at: Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. Tel.: +49 451 500 6661; fax: +49 451 500 3324.
E-mail address: Rades.Dirk@gmx.net (D. Rades).

surgery in patients with specific risk factors (extra-capsular spread of lymph node metastasis and microscopically or macroscopically incomplete resection) [6–8]. Thus, chemoradiation with three courses of higher-dose cisplatin has become the preferred regimen in many centers. However, this regimen can be associated with high or even unacceptable toxicity [9]. Therefore, other cisplatin-based chemoradiation regimens are also common for SCCHN including two courses of fractionated cisplatin (20 mg/m^2) plus 5-fluorouracil (5-FU) given on four consecutive days. This regimen was shown to be tolerable and effective but toxic [10,11]. Thus, 5-FU was omitted in some studies, and fractionated cisplatin (20 mg/m^2) alone was administered on five days [12,13]. This regimen was reported to be well tolerated and highly effective. In a retrospective study that compared different cisplatin-based chemoradiation regimens for SCCHN, fractionated cisplatin (20 mg/m^2) alone was associated with similar outcomes and less acute toxicity than the most common regimen, higher-dose cisplatin (100 mg/m^2 on days 1, 22 and 43) [14]. Grade 3 nausea/vomiting occurred in 6% and 24% of patients, grade 3 nephrotoxicity in 1% and 8% of patients, and grade 3–4 hematologic toxicity in 21% and 35% of patients, respectively.

In order to improve the outcome after chemoradiation of SCCHN, attempts to further intensify chemotherapy have been performed. However, more intense chemotherapy regimens can result in greater toxicity without improving outcomes. For example, in a recent randomized phase II study from the Netherlands, induction chemotherapy with four courses of docetaxel, cisplatin and 5-FU followed by chemoradiation with cisplatin was not feasible [15]. Only 32% of the patients could receive the complete planned cisplatin dose. Thus, cisplatin alone and cisplatin plus 5-FU are the most common regimens used for the chemoradiation of SCCHN. Our previous report suggested that two courses of cisplatin alone (20 mg/m^2 per day on five consecutive days) resulted in similar outcomes with less toxicity when compared to the same cisplatin regimen with 5-FU for unresectable locally advanced SCCHN [16]. However, many centers continue to use cisplatin plus 5-FU for SCCHN. Since that study, cisplatin alone has become the standard for chemoradiation of SCCHN at our institution. We are now able to present an updated study including a larger number of patients with longer follow-up in order to further contribute to the question "does the addition of 5-FU provide better patient outcomes?"

Patients and methods

Data of 142 patients who received chemoradiation with cisplatin alone for locally advanced SCCHN were retrospectively compared to 170 patients who received cisplatin plus (5-FU). The chemoradiation regimens were chosen by interdisciplinary treatment protocols for SCCHN preferred at the three contributing institutions at the time. Patients included in this study were treated between 2003 and 2014. Of the patients of the cisplatin alone group, 123 were treated at institution A and 19 at institution B. Of the patients of the cisplatin plus 5-FU group, 69 were treated at institution A, 81 at institution B. and 20 at institution C. The patient characteristics of both groups are summarized in Table 1. The comparison of both treatment groups with respect to 10 characteristics showed no significant difference in any characteristic. However, patients in the cisplatin alone group had a worse performance status than patients in the cisplatin plus 5-FU group ($p = 0.039$, Chi-square test).

All patients received conventionally fractionated radiotherapy with 1.8–2.0 Gy given once daily, five days per week. Radiotherapy was performed with a linear accelerator, using 3-dimensional conformal irradiation or intensity modulated radiotherapy (IMRT). The IMRT was delivered from stationary beams or as volumetric

Table 1
Patient characteristics of the two compared groups, chemoradiation with cisplatin alone ($N = 142$) vs. chemoradiation with cisplatin plus 5-FU ($N = 170$). p-values were obtained from the Chi-square test.

	Cisplatin alone N patients (%)	Cisplatin + 5-FU N patients (%)	p-value
T-classification			
T1-2 ($N = 103$)	47 (33)	56 (33)	
T3-4 ($N = 209$)	95 (67)	114 (67)	0.99
N-classification			
N0-1 ($N = 66$)	26 (18)	40 (24)	
N2-3 ($N = 246$)	116 (82)	130 (76)	0.65
Performance score			
ECOG 0-1 ($N = 224$)	86 (61)	138 (81)	
ECOG 2 ($N = 88$)	56 (39)	32 (19)	0.039
Gender			
Female ($N = 61$)	27 (19)	34 (20)	
Male ($N = 251$)	115 (81)	136 (80)	0.92
Age			
⩽57 years ($N = 165$)	75 (53)	90 (53)	
⩾58 years ($N = 147$)	67 (47)	80 (47)	0.99
Main tumor site			
Oropharynx ($N = 147$)	74 (52)	73 (43)	
Hypopharynx ($N = 46$)	18 (13)	28 (16)	
Larynx ($N = 58$)	23 (16)	35 (21)	
Oral cavity/floor of mouth ($N = 61$)	27 (19)	34 (20)	0.72
Histologic grading			
G 1-2 ($N = 151$)	72 (51)	79 (46)	
G 3 ($N = 161$)	70 (49)	91 (54)	0.65
Upfront surgery			
No ($N = 148$)	73 (51)	75 (44)	
Yes ($N = 164$)	69 (49)	95 (56)	0.42
Radiation technique			
3D conformal ($N = 246$)	111 (78)	135 (79)	
IMRT/VMAT ($N = 66$)	31 (22)	35 (21)	0.91
Hemoglobin prior to chemoradiation			
<12 g/dl ($N = 109$)	49 (35)	60 (35)	
⩾12 g/dl ($N = 59$)	93 (65)	110 (65)	0.94

After Bonferroni correction for multiple tests, p-values <0.005 were considered significant.

modulated arc therapy (VMAT) (Table 1). The total dose delivered to the primary tumor and to the involved lymph nodes depended on the extent of upfront surgery when performed. Total doses were 66–70 Gy for definitive treatment or after macroscopically incomplete resection and 60–66 Gy after macroscopically complete resection. In all patients, the total dose was 60 Gy to higher-risk lymph nodes and 50 Gy to intermediate-risk lymph nodes.

Simultaneous chemotherapy was administered either with cisplatin alone (bolus infusion of 20 mg/m^2 on radiotherapy days 1–5 and 29–33) or with the same cisplatin regimen plus 5-FU (continuous infusion over 120 h of 600 mg/m^2 or 1000 mg/m^2 on radiotherapy days 1–5 and 29–33). All patients received prophylactic hydration and antiemetic agents.

Both groups were compared for treatment outcomes in terms of LRC, MFS and OS and adverse events (acute and chronic). In addition, the ten characteristics summarized in Table 1 were evaluated for potential associations with LRC, MFS and OS. The HPV-status was not included in the analysis, since it was not available in most patients. Tumor volume was not included, since it tumor volume and T-/N-classification are confounding variables. The follow-up schedule included visits every 3 months during the first and second year, every 6 months during the third year, and every 12 months during the following years. The LRC, MFS and OS

rates were estimated with the Kaplan–Meier-method, and the corresponding curves compared with the log-rank test in the univariate analyses [17]. In cases with a significant difference between the curves or a trend toward a difference in outcome ($p \leqslant 0.08$), additional multivariate analyses (Cox regression analysis) were performed. After Bonferroni correction for multiple tests, p-values of <0.0038 (13 tests) or <0.005 (10 tests) were considered significant representing an alpha-level of 0.05.

Acute and late adverse events were graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0 [18]. The comparisons of the two chemoradiation groups with respect to acute and late adverse events were performed with the Chi-square test.

Results

In the cisplatin alone group, 27 patients (19%) were not able to receive the complete planned chemotherapy due to acute adverse events compared to 46 patients (27%) in the cisplatin plus 5-FU group ($p = 0.18$). Interruptions of the radiation treatment longer than one week were necessary in 20 patients (14%) and 39 patients (23%), respectively ($p = 0.09$).

LRC rates were not significantly different between both treatment groups ($p = 0.71$, Fig. 1) on univariate analysis. In contrast, LRC was significantly associated with T-classification, upfront surgery, pre-chemoradiation hemoglobin levels, completion of chemotherapy and radiotherapy breaks >1 week (Table 2). N-classification, performance score and histologic grading showed a trend. On multivariate analysis of LRC, radiotherapy breaks (risk ratio [RR] 3.17; 95%-confidence interval [CI] 1.73–5.77; $p < 0.001$), pre-chemoradiation hemoglobin levels (RR 1.61; 95%-CI 1.02–2.56; $p = 0.043$), T-classification (RR 1.58; 95%-CI 1.18–2.18; $p = 0.002$), N-classification (RR 2.83; 95%-CI 1.46–6.21; $p = 0.010$), histologic grading (RR 1.35; 95%-CI 1.06–1.72; $p = 0.013$) and surgery (RR 2.11; 95%-CI 1.30–3.48; $p = 0.002$) were significant.
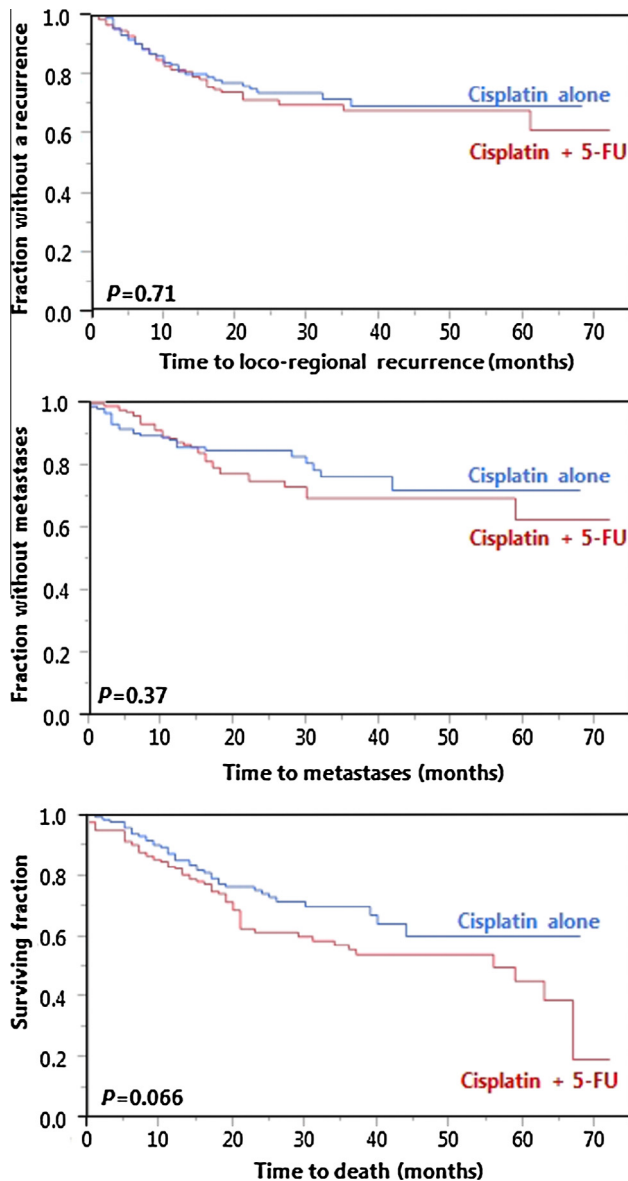

Fig. 1. Comparison of chemoradiation with cisplatin alone and chemoradiation with cisplatin plus 5-FU with respect to loco-regional control (top), metastases-free survival (middle), and overall survival (bottom).

Table 2
Comparison of cisplatin and cisplatin plus 5-FU for loco-regional control (univariate analysis).

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p
Chemotherapy regimen				
Cisplatin alone ($N = 142$)	81	69	69	
Cisplatin + 5-FU ($N = 270$)	82	68	68	0.71
T-classification				
T1-2 ($N = 103$)	95	79	79	
T3-4 ($N = 209$)	75	64	64	**<0.001**
N-classification				
N0-1 ($N = 66$)	92	79	79	
N2-3 ($N = 246$)	78	66	66	0.010
Performance score				
ECOG 0-1 ($N = 224$)	84	74	74	
ECOG 2 ($N = 88$)	75	51	n/a	0.005
Gender				
Female ($N = 61$)	92	75	75	
Male ($N = 251$)	79	67	67	0.14
Age				
$\leqslant$57 years ($N = 165$)	81	64	64	
$\geqslant$58 years ($N = 147$)	82	75	75	0.28
Main tumor site				
Oropharynx ($N = 147$)	82	73	73	
Hypopharynx ($N = 46$)	79	72	n/a	
Larynx ($N = 58$)	82	63	63	
Oral cavity/floor of mouth ($N = 61$)	83	66	66	0.87
Histologic grading				
G 1-2 ($N = 151$)	85	77	77	
G 3 ($N = 161$)	78	61	61	0.033
Upfront surgery				
No ($N = 148$)	72	61	61	
Yes ($N = 164$)	90	75	75	**0.002**
Radiation technique				
3D conformal ($N = 246$)	81	67	67	
IMRT/VMAT ($N = 66$)	85	73	73	0.32
Hemoglobin prior to chemoradiation				
<12 g/dl ($N = 109$)	70	57	57	
$\geqslant$12 g/dl ($N = 59$)	88	75	75	**<0.001**
Completion of chemotherapy				
No ($N = 73$)	71	47	47	
Yes ($N = 239$)	84	74	74	**<0.001**
Radiotherapy breaks >1 week				
No ($N = 253$)	86	77	77	
Yes ($N = 59$)	59	30	30	**<0.001**

After Bonferroni correction for multiple tests, p-values <0.0038 were considered significant.

MFS rates in the cisplatin alone group were not significantly different from the cisplatin plus 5-FU group ($p = 0.37$, Fig. 1). On univariate analyses, MFS was significantly associated with T-classification, performance score, tumor site, upfront surgery and radiotherapy breaks >1 week (Table 3). A trend was observed for N-classification, pre-chemoradiation hemoglobin levels and completion of chemotherapy. On multivariate analysis of MFS, T-classification (RR 1.48; 95%-CI 1.08–2.10; $p = 0.014$), N-classification (RR 2.73; 95%-CI 1.31–6.66; $p = 0.006$), ECOG performance score (RR 1.86; 95%-CI 1.09–3.12; $p = 0.023$) and surgery (RR 1.84; 95%-CI 1.07–3.23; $p = 0.027$) remained significant.

On univariate analysis, cisplatin alone showed a trend for improved OS ($p = 0.066$, Fig. 1). OS was significantly associated with T-classification, performance score, upfront surgery, pre-chemoradiation hemoglobin levels, completion of chemotherapy and radiotherapy breaks (Table 4). N-classification and histologic grading showed a trend. On multivariate analysis, cisplatin alone

was significantly associated with improved OS (RR 1.35; 95%-CI 1.09–1.69; $p = 0.006$). Other significant factors were completion of chemotherapy (RR 1.80; 95%-CI 1.05–3.06; $p = 0.032$), radiotherapy breaks (RR 2.50; 95%-CI 1.46–4.27; $p < 0.001$), hemoglobin levels (RR 1.74; 95%-CI 1.16–2.61; $p = 0.008$), T-classification (RR 1.35; 95%-CI 1.06–1.76; $p = 0.017$), N-classification (RR 2.34; 95%-CI 1.30–4.53; $p = 0.004$), ECOG performance score (RR 2.17; 95%-CI 1.40–3.35; $p < 0.001$) and surgery (RR 2.49; 95%-CI 1.58–3.98; $p < 0.001$).

The incidence of most acute adverse events was not significantly different for either group (Table 5). However, pneumonia and sepsis were significantly more common in the cisplatin plus 5-FU group ($p = 0.034$). A trend was found for more grade $\geqslant 2$ nausea/vomiting ($p = 0.08$) with cisplatin plus 5-FU than with cisplatin alone. Late adverse events grade $\geqslant 2$ including xerostomia, skin toxicity and subcutaneous fibrosis were more common in the cisplatin plus 5-FU than in the cisplatin alone group (Table 5).

Table 3
Comparison of cisplatin and cisplatin plus 5-FU for metastases-free survival (univariate analysis).

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p
Chemotherapy regimen				
Cisplatin alone ($N = 142$)	85	76	72	
Cisplatin + 5-FU ($N = 270$)	87	69	62	0.37
T-classification				
T1-2 ($N = 103$)	96	82	75	
T3-4 ($N = 209$)	82	68	65	**0.003**
N-classification				
N0-1 ($N = 66$)	97	82	73	
N2-3 ($N = 246$)	83	70	65	0.019
Performance score				
ECOG 0-1 ($N = 224$)	91	77	71	
ECOG 2 ($N = 88$)	74	61	n/a	**<0.001**
Gender				
Female ($N = 61$)	88	75	75	
Male ($N = 251$)	86	72	65	0.61
Age				
$\leqslant 57$ years ($N = 165$)	88	75	66	
$\geqslant 58$ years ($N = 147$)	85	70	70	0.21
Main tumor site				
Oropharynx ($N = 147$)	90	80	71	
Hypopharynx ($N = 46$)	64	55	n/a	
Larynx ($N = 58$)	98	70	70	
Oral cavity/floor of mouth ($N = 61$)	83	78	70	**<0.001**
Histologic grading				
G 1-2 ($N = 151$)	90	74	62	
G 3 ($N = 161$)	83	71	68	0.19
Upfront surgery				
No ($N = 148$)	80	64	60	
Yes ($N = 164$)	92	80	73	**0.004**
Radiation technique				
3D conformal ($N = 246$)	86	72	66	
IMRT/VMAT ($N = 66$)	88	74	74	0.45
Hemoglobin prior to chemoradiation				
<12 g/dl ($N = 109$)	78	64	64	
$\geqslant 12$ g/dl ($N = 59$)	90	77	69	0.019
Completion of chemotherapy				
No ($N = 73$)	79	66	66	
Yes ($N = 239$)	89	75	68	0.020
Radiotherapy breaks >1 week				
No ($N = 253$)	88	77	70	
Yes ($N = 59$)	77	52	52	**0.002**

After Bonferroni correction for multiple tests, p-values <0.0038 were considered significant.

Table 4
Comparison of cisplatin and cisplatin plus 5-FU for overall survival (univariate analysis).

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p
Chemotherapy regimen				
Cisplatin alone ($N = 142$)	85	70	60	
Cisplatin + 5-FU ($N = 270$)	82	56	45	0.066
T-classification				
T1-2 ($N = 103$)	90	75	60	
T3-4 ($N = 209$)	80	55	51	**0.002**
N-classification				
N0-1 ($N = 66$)	95	72	48	
N2-3 ($N = 246$)	80	59	52	0.012
Performance score				
ECOG 0-1 ($N = 224$)	88	73	63	
ECOG 2 ($N = 88$)	71	32	0	**<0.001**
Gender				
Female ($N = 61$)	87	72	44	
Male ($N = 251$)	83	60	52	0.34
Age				
$\leqslant 57$ years ($N = 165$)	83	63	52	
$\geqslant 58$ years ($N = 147$)	84	61	47	0.86
Main tumor site				
Oropharynx ($N = 147$)	84	65	51	
Hypopharynx ($N = 46$)	76	52	n/a	
Larynx ($N = 58$)	91	68	58	
Oral cavity/floor of mouth ($N = 61$)	82	59	53	0.20
Histologic grading				
G 1-2 ($N = 151$)	89	65	54	
G 3 ($N = 161$)	78	58	48	0.018
Upfront surgery				
No ($N = 148$)	76	51	44	
Yes ($N = 164$)	91	72	60	**<0.001**
Radiation technique				
3D conformal ($N = 246$)	82	60	50	
IMRT/VMAT ($N = 66$)	89	69	60	0.24
Hemoglobin prior to chemoradiation				
<12 g/dl ($N = 109$)	70	47	44	
$\geqslant 12$ g/dl ($N = 59$)	91	70	56	**<0.001**
Completion of chemotherapy				
No ($N = 73$)	65	41	14	
Yes ($N = 239$)	89	69	63	**<0.001**
Radiotherapy breaks >1 week				
No ($N = 253$)	89	71	62	
Yes ($N = 59$)	59	27	12	**<0.001**

After Bonferroni correction for multiple tests, p-values <0.0038 were considered significant.

Table 5
Comparison of chemoradiation with cisplatin alone ($N = 142$) versus cisplatin plus 5-FU ($N = 170$) with respect to acute and late adverse events.

	Cisplatin alone N patients (%)	Cisplatin + 5-FU N patients (%)	p-value
Oral mucositis			
Grade ⩾ 2	122 (86)	161 (95)	0.56
Skin reactions			
Grade ⩾ 2	109 (77)	160 (94)	0.11
Hematotoxicity			
Grade ⩾ 3	25 (18)	38 (22)	0.42
Nausea/vomiting			
Grade ⩾ 2	31 (22)	56 (33)	0.08
Nephrotoxicity			
Grade ⩾ 2	6 (4)	9 (5)	0.92
Pneumonia/sepsis			
Grade ⩾ 3	1 (<1)	10 (6)	0.034
Xerostomia			
Grade ⩾ 2	40 (29)	78 (48)	0.009
Late skin toxicity			
Grade 2	16 (12)	35 (22)	0.046
Cervical lymph edema			
Grade 2	24 (17)	42 (26)	0.13
Subcutaneous fibrosis			
Grade ⩾ 2	31 (22)	66 (41)	0.006

After Bonferroni correction for multiple tests, p-values <0.005 were considered significant.

Discussion

Many patients with locally advanced SCCHN receive chemoradiation either alone as definitive treatment or following surgery if certain risk factors are present. Concurrent administration of radiotherapy and chemotherapy provides the best results [5,19]. It is widely agreed that cisplatin is the most important and most commonly used chemotherapeutic agent for this indication. Uncertainty exists whether cisplatin alone is the most appropriate regimen or whether it should be supplemented by 5-FU. There are few comparative studies. In a previous retrospective study comparing cisplatin alone (two courses of 20 mg/m^2 on five consecutive days) to cisplatin plus 5-FU (two courses of 600 mg/m^2 on five consecutive days) in 128 patients with stage IV unresectable SCCHN treated between 2000 and 2008, the 2-year rates of LRC, MFS and OS were not significantly different in both groups [16]. However, in the cisplatin plus 5-FU group significantly more patients experienced oral mucositis ($p = 0.027$) and acute skin reactions ($p = 0.001$). In the present study, more acute skin reactions (17% absolute difference with respect to grade ⩾2 events) were found in the cisplatin plus 5-FU group, whereas the absolute differences with respect to grade 2, grade 3 and grade ⩾2 oral mucositis were less than 10%. This may be a result of more advanced treatment planning and increased use of modern techniques such as IMRT and VMAT with better sparing of the normal tissue following the previous study. Furthermore, patients in the cisplatin alone group had a significantly worse performance status compared to those receiving cisplatin plus 5-FU, which may be associated with a reduced immune system and a decreased resistance of the oral mucosa to chemoradiation. In the present study, pneumonia and sepsis as a consequence of chemotherapy-related immunosuppression occurred more often in the cisplatin plus 5-FU than in the cisplatin alone group. This difference was most likely due to the addition of 5-FU and may be an argument against 5-FU. Pneumonia and sepsis were not investigated in the previous study [16]. Xerostomia, late skin toxicity and subcutaneous fibrosis were non-significantly more common after chemoradiation with cisplatin plus 5-FU in the present cohort. In the previous report these late adverse events were also more common in the cisplatin plus 5-FU group. Previous randomized trials comparing chemoradiation to radiotherapy alone for SCCHN did not find increased xerostomia and late skin reactions in the chemoradiation groups [2,6,7]. Thus, the findings of the present study regarding late these toxicities may have been introduced by a hidden selection bias.

Another retrospective study published in 2011 compared several cisplatin-based regimens for the chemoradiation of stage III or IV SCCHN [14]. In that study, the 3-year LRC rates were 72% and 60% after chemoradiation with two courses of cisplatin 20 mg/m^2 plus 5-FU 1000 mg/m^2 on days 1–5 ($N = 49$) and with two courses of cisplatin 20 mg/m^2 plus 5-fluororuracil 600 mg/m^2 on days 1–5 ($N = 102$), respectively. Because cisplatin plus 5-FU has been rarely used for SCCHN in the major contributing center of the present study since the data of that study were available, about two thirds of these patients were included also in the present study. In the previous study, the 3-year MFS rates were 74% and 63%, respectively, and the 3-year OS rates were 63% and 50%, respectively. Thus, the 3-year rates of LRC (69%), MFS (76%) and OS (70%) of the patients receiving cisplatin alone in the present study were similar or better than in the previous report. Given the limitations of a retrospective study, cisplatin plus 5-FU appears not superior to cisplatin alone with respect to treatment outcomes in terms of LRC, MFS and OS. In the present study, late grade 3 adverse events after chemoradiation were rare. Rates of grade 3 xerostomia, late skin toxicity, cervical lymph edema and subcutaneous fibrosis were only 3%, 0%, 0% and 0%, respectively, compared to 9–10%, 5–6%, 4–6% and 4–10%, respectively, in patients who received cisplatin plus 5-FU in the previous study [14].

In addition to cisplatin alone, completion of the planned chemotherapy, no interruptions of radiotherapy longer than one week, lower T-classification, lower N-classification, a better performance status, lower histologic grading, upfront surgery and hemoglobin levels prior to chemoradiation ⩾12 g/dl were independent predictors of treatment outcomes. The findings are consistent with the results of previous studies. The impact of tumor stage and pre-treatment hemoglobin levels on outcomes were previously described [14,16,20,21]. Anemia is associated with decreased tumor oxygenation, which is mandatory for an optimal effect of irradiation which is mediated by cytotoxic free radicals. The negative impact of interruptions of radiotherapy on the patients' prognosis was also previously reported [22,23].

In the current study, the treatment groups were balanced for all but one characteristic (ECOG performance score), which likely would have decreased the risk of a hidden selection bias. However, retrospective studies always bear such a risk, which cannot be completely excluded. This aspect must be taken into account when interpreting this data.

In conclusion, given the limitations of a retrospective study, cisplatin alone appeared associated with better survival and less toxicity. Thus, for chemoradiation of locally advanced unresectable stage IV SCCHN, two courses of fractionated cisplatin alone (20 mg/m^2/day on RT days 1–5 and 29–33) may be preferable to fractionated cisplatin plus 5-FU (600 mg/m^2/day on RT days 1–5 and 29–33). A randomized trial is warranted to confirm these results.

References

[1] Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, Licitra L, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. Eur J Cancer 2015. http://dx.doi.org/10.1016/j.ejca.2015.07.043 [Epub ahead of print].

[2] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.

[3] Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 1997;43:29–37.

[4] Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000;18:1458–64.

[5] Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.

[6] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.

[7] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.

[8] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–50.

[9] de Castro Jr G, Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, et al. High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2007;264:1475–82.

[10] Adelstein DJ, Saxton JP, Lavertu P, Tuason L, Wood BG, Wanamaker JR, et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. Head Neck 1997;19:567–75.

[11] Fietkau R, Lautenschläger C, Sauer R, Dunst J, Becker A, Baumann M, et al. Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: results of the German phase III trial ARO 96-3. J Clin Oncol 2006;24(Suppl). #5507.

[12] Huguenin P, Glanzmann C, Taussky D, Lütolf UM, Schmid S, Moe K. Hyperfractionated radiotherapy and simultaneous cisplatin for stage-III and -IV carcinomas of the head and neck. Long-term results including functional outcome. Strahlenther Onkol 1998;174:397–402.

[13] Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 2004;22:4665–73.

[14] Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, et al. Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2011;80:1037–44.

[15] Driessen CM, de Boer JP, Gelderblom H, Rasch CR, de Jong MA, Verbist BM, et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study) (Dutch Head and Neck Society 08-01): a randomized phase II study. Eur J Cancer 2016;52:77–84.

[16] Tribius S, Kronemann S, Kilic Y, Schroeder U, Hakim S, Schild SE, et al. Radiochemotherapy including cisplatin alone versus cisplatin + 5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol 2009;185:675–81.

[17] Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

[18] National Institutes of Health/National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; 2009 <http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf>.

[19] Marta GN, Riera R, Bossi P, Zhong LP, Licitra L, Macedo CR, et al. Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: systematic review and meta-analysis. Eur J Cancer 2015;51:2596–603.

[20] Becker A, Stadler P, Lavay RS, Hänsgen G, Kuhnt T, Lautenschläger C, et al. Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys 2000;46:459–66.

[21] Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993;71:452–6.

[22] Kwong DL, Sham JS, Chua DT, Choy DT, Au GK, Wu PM. The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1997;39:703–10.

[23] Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE, et al. Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:1108–14.
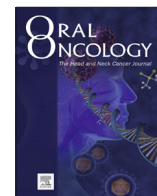
CrossMark

Chemoradiation of locally advanced squamous cell carcinoma of the head-and-neck (LASCCHN): Is 20 mg/m^2 cisplatin on five days every four weeks an alternative to 100 mg/m^2 cisplatin every three weeks?

Dirk Rades [a,*], Daniel Seidl [a], Stefan Janssen [a,b], Amira Bajrovic [c], Samer G. Hakim [d], Barbara Wollenberg [e], Katarina Karner [f], Primoz Strojan [f], Steven E. Schild [g]

[a] Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[b] Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany
[c] Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany
[d] Department of Oral and Maxillofacial Surgery, University of Lübeck, Germany
[e] Department of Oto-Rhino-Laryngology and Head and Neck Surgery, University of Lübeck, Germany
[f] Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia
[g] Department of Radiation Oncology, Mayo Clinic Scottsdale, AZ, USA

ARTICLE INFO

SUMMARY

Objectives: To compare chemoradiation with 100 mg/m^2 cisplatin every three weeks to 20 mg/m^2 on five days every four weeks for locally advanced squamous cell carcinoma of the head-and-neck (LASCCHN).
Materials and methods: In 230 patients receiving chemoradiation for LASCCHN, 100 mg/m^2 cisplatin every three weeks ($N = 126$) and 20 mg/m^2 cisplatin on five days every four weeks ($N = 104$) were retrospectively compared. Chemoradiation plus eleven characteristics (T-/N-classification, performance score, gender, age, tumor site, grading, surgery, radiation technique, pre-chemoradiation hemoglobin, cumulative cisplatin dose) were analyzed for locoregional control (LRC), metastases-free survival (MFS) and overall survival (OS). Chemoradiation groups were compared for adverse events.
Results: On univariate analyses, chemoradiation had no impact on LRC ($p = 0.53$), MFS ($p = 0.67$) and OS ($p = 0.14$). On multivariate analysis of LRC, T-classification ($p = 0.045$) and hemoglobin ($p < 0.001$) were significant. On multivariate analysis of MFS, performance score ($p = 0.028$) was significant. On multivariate analysis of OS, performance score ($p = 0.009$) and hemoglobin levels ($p = 0.002$) achieved significance. Chemoradiation with 100 mg/m^2 cisplatin was associated with more pneumonia/sepsis ($p = 0.003$), grade $\geqslant 2$ nausea/vomiting ($p < 0.001$), grade $\geqslant 2$ nephrotoxicity ($p = 0.005$), grade $\geqslant 2$ xerostomia ($p = 0.002$), grade $\geqslant 3$ hematotoxicity ($p = 0.052$) and grade $\geqslant 2$ ototoxicity ($p = 0.048$).
Concluding statement: 20 mg/m^2 cisplatin on five days every four weeks was associated with fewer adverse events than 100 mg/m^2 cisplatin every three weeks. 100 mg/m^2 cisplatin was not significantly superior to 20 mg/m^2 cisplatin regarding LRC, MFS and OS. Given the limitations of a retrospective study, 20 mg/m^2 cisplatin appeared preferable. The results should be confirmed in a randomized trial.

Introduction

Many patients with locally advanced squamous cell carcinoma of the head-and-neck (LASCCHN) receive chemoradiation, either alone (definitive treatment) or following surgical resection if specific risk factors such as incomplete resection or extracapsular extension of lymph node metastases are identified (adjuvant treatment). Randomized trials demonstrated that chemoradiation was superior to radiotherapy alone for both definitive treatment and adjuvant treatment for patients with risk factors [1–7]. Furthermore, according to an updated large meta-analysis, the concurrent administration of chemoradiation resulted in significantly better outcomes than the sequential approach of chemotherapy and radiotherapy [8]. In this meta-analysis, which included different chemotherapy regimens, no other cytoroxic agents with cisplatin were identified that was superior to other cisplatin-based

* Corresponding author at: Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. Tel.: +49 451 500 6661; fax: +49 451 500 3324.
E-mail address: Rades.Dirk@gmx.net (D. Rades).

regimens. Therefore, the most appropriate chemotherapy combination used for chemoradiation of LASCCHN is yet to be defined.

Because several randomized trials demonstrated that chemoradiation with 100 mg/m^2 cisplatin given every three weeks (i.e. on days 1, 22 and 43) resulted in significantly better outcomes than radiotherapy alone for both definitive and adjuvant treatment, this regimen is the preferred approach at many institutions and can be considered the "standard" approach [1,2,6,7]. However, no phase III trials with an adequate statistical power have been completed so far to compare 100 mg/m^2 cisplatin given every three weeks to other cisplatin-based regimens. Moreover, 100 mg/m^2 cisplatin every three weeks can be associated with a high rate of severe adverse events [9]. Therefore, many centers do not accept this regimen as their "standard" approach for LASCCHN and use other cisplatin-based regimens including lower cisplatin doses per administration. Alternative regimens include daily or weekly administrations of 5–7 mg/m^2 or 30–40 mg/m^2 of cisplatin alone, respectively, and fractionated cisplatin (e.g. 20 mg/m^2 on five days every four weeks) with or without the addition of 5-fluorouracil [4,5,10–16].

Taking into account the current lack of data, randomized phase III trials comparing 100 mg/m^2 cisplatin every three weeks to other cisplatin-based regimens are required to better define the appropriate chemotherapy regimen for chemoradiation of LASCCHN. However, since the vast majority of institutions treating these patients prefer to use their favorite regimen, such trials are unlikely to be available in the near future. To provide additional information to this burning issue and to set the stage for prospective trials, retrospective studies comparing different cisplatin-based chemoradiation regimens for LASCCHN are welcomed. The present retrospective study compared 100 mg/m^2 of cisplatin given every three weeks to 20 mg/m^2 of cisplatin given on five days every four weeks with respect to treatment outcomes in terms of locoregional control (LRC), metastases-free survival (MFS) and overall survival (OS), and with respect to adverse events. The goal of this study was to contribute to answering the question whether 20 mg/m^2 of cisplatin given on five days every four weeks could be an alternative option to the "standard" approach 100 mg/m^2 cisplatin every three weeks?

Patients and methods

A total of 230 patients, who were treated for LASCCHN with one of two cisplatin-based concurrent chemoradiation regimens, were included in this retrospective study, which was approved by the local ethics committee. The most commonly used "standard" chemoradiation (bolus infusions of 100 mg/m^2 cisplatin administered every three weeks (days 1, 22 and 43; group A)) was compared to a more novel regimen (bolus infusions of 20 mg/m^2 cisplatin administered on five days every four weeks (days 1–5 and 29–33; group B)). The patients of both groups received prophylactic hydration and antiemetic agents. The two chemotherapy programs were selected according to multidisciplinary treatment protocols preferred at the contributing institutions during the time patients included in this study were treated (2003–2014).

The patients in both groups had received conventionally fractionated radiotherapy with five fractions of 1.8–2.0 Gy per week, which was delivered with a linear accelerator either as three-dimensional conformal radiotherapy (3DCRT) or as intensity modulated radiotherapy (IMRT). IMRT was administered as IMRT with stationary beams or as volumetric modulated arc therapy (VMAT). Total doses were 66–70 Gy for definitive treatment or after macroscopically incomplete resection and 60–66 Gy following macroscopically complete resection. Total doses to non-involved lymph nodes ranged from 50 to 60 Gy.

The chemoradiation groups were not significantly different with respect to patients-, disease- and treatment-related characteristics according to the comparisons with the Chi-square test (Table 1). Because the HPV (human papilloma virus)-status was available only in a few patients, it was not included in the analysis. The chemoradiation groups and eleven additional characteristics were analyzed for potential associations with treatment outcomes in terms of LRC, MFS and OS. In addition, the chemoradiation groups were compared with respect to acute/subacute adverse events (according to CTCAE version 4.0) [17].

The follow-up schedule after the end of chemoradiation included visits every 2–3 months during the initial two years, every 3–6 months during the third year, and every 6–12 months thereafter. The rates of LRC, MFS and OS were referenced from the last day of chemoradiation and calculated with the Kaplan–Meier-method and the log-rank test for univariate analyses [18]. After Bonferroni correction for multiple tests, p-values of <0.0042 (for 12 tests) were considered significant. $p = 0.0042$ represented an alpha-level of 0.05. When the difference between the Kaplan–Meier curves was significant or showed a trend ($p < 0.06$), the factors were additionally analyzed for independence in a multivariate way (Cox proportional hazards model). For the comparisons of the chemoradiation groups regarding acute and late adverse events,

Table 1
Patient characteristics of the two chemoradiation groups cisplatin 100 mg/m^2 every three weeks (group A, $N = 126$) and cisplatin 20 mg/m^2 on five days every four weeks (group B, $N = 104$).

	Group A N patients (%)	Group B N patients (%)	*p*-value
T-classification			
T1-2 ($N = 85$)	44 (35)	41 (39)	
T3-4 ($N = 145$)	82 (65)	63 (61)	0.37
N-classification			
N0-1 ($N = 55$)	44 (35)	41 (39)	
N2-3 ($N = 175$)	82 (65)	63 (61)	0.66
Performance score			
ECOG 0-1 ($N = 197$)	112 (89)	85 (82)	
ECOG 2 ($N = 33$)	14 (11)	19 (18)	0.56
Gender			
Female ($N = 53$)	31 (25)	22 (21)	
Male ($N = 177$)	95 (75)	82 (79)	0.76
Age			
⩽56 years ($N = 124$)	71 (56)	53 (51)	
⩾57 years ($N = 106$)	55 (44)	51 (49)	0.58
Tumor site			
Oropharynx ($N = 130$)	72 (57)	58 (56)	
Hypopharynx ($N = 31$)	17 (13)	14 (13)	
Larynx ($N = 39$)	23 (18)	16 (15)	
Oral cavity ($N = 30$)	14 (11)	16 (15)	0.92
Histologic grading			
G 1-2 ($N = 134$)	76 (60)	58 (56)	
G 3 ($N = 96$)	50 (40)	46 (44)	0.65
Upfront surgery			
No ($N = 98$)	53 (42)	45 (43)	
Yes ($N = 132$)	73 (58)	59 (57)	0.90
Radiation technique			
3D conformal ($N = 187$)	106 (84)	81 (78)	
IMRT/VMAT ($N = 43$)	20 (16)	23 (22)	0.60
Hemoglobin prior to chemoradiation			
<12 g/dl ($N = 72$)	37 (29)	35 (34)	
⩾12 g/dl ($N = 158$)	89 (71)	69 (66)	0.70
Cumulative cisplatin dose			
<200 mg/m^2 ($N = 61$)	45 (36)	16 (15)	
⩾200 mg/m^2 ($N = 169$)	81 (64)	88 (85)	0.07

After Bonferroni correction for multiple tests ($N = 11$), *p*-values <0.0045 were considered significant.

the Chi-square test was applied. After Bonferroni correction for multiple tests (adverse events), *p*-values of <0.0063 (for 8 tests) were considered significant.

Results

On univariate analysis, the LRC rates were not significantly different in both chemoradiation groups (*p* = 0.53, see Fig. 1). Improved LRC was associated with pre-chemoradiation hemoglobin levels of ⩾12 g/dl (*p* < 0.001). Lower T-classification (*p* = 0.058) and non-hypopharynx tumor site (*p* = 0.029) showed a trend for better LRC (Table 2). In the multivariate analysis of LRC, T-classification (hazard ratio (HR) 1.41; 95%-confidence interval (CI) 1.01–2.04; *p* = 0.045) and pre-chemoradiation hemoglobin

Fig. 1. Comparisons of chemoradiation groups A (100 mg/m² cisplatin given every three weeks) and B (20 mg/m² of cisplatin given on five days every four weeks) for loco-regional control (top), metastases-free survival (middle) and overall survival (bottom). Dotted lines represent the 95%-confidence intervals.

Table 2
Univariate analysis of loco-regional control (LRC).

	At 1 year (%)	At 3 years (%)	*p*
Chemoradiation regimen			
Group A (*N* = 126)	89	79	
Group B (*N* = 104)	87	74	0.53
T-classification			
T1-2 (*N* = 85)	96	82	
T3-4 (*N* = 145)	84	74	0.058
N-classification			
N0-1 (*N* = 55)	88	75	
N2-3 (*N* = 175)	88	77	0.89
Performance score			
ECOG 0-1 (*N* = 197)	88	77	
ECOG 2 (*N* = 33)	90	80	0.80
Gender			
Female (*N* = 53)	96	79	
Male (*N* = 177)	86	76	0.22
Age			
⩽56 years (*N* = 124)	87	73	
⩾57 years (*N* = 106)	90	81	0.33
Tumor site			
Oropharynx (*N* = 130)	92	82	
Hypopharynx (*N* = 31)	73	62	
Larynx (*N* = 39)	90	72	
Oral cavity (*N* = 30)	86	73	0.029
Histologic grading			
G 1-2 (*N* = 134)	87	82	
G 3 (*N* = 96)	90	70	0.45
Upfront surgery			
No (*N* = 98)	83	71	
Yes (*N* = 132)	92	81	0.11
Radiation technique			
3D conformal (*N* = 187)	89	77	
IMRT/VMAT (*N* = 43)	85	79	0.65
Hemoglobin prior to chemoradiation			
< 12 g/dl (*N* = 72)	74	60	
⩾ 12 g/dl (*N* = 158)	95	84	**<0.001**
Cumulative cisplatin dose			
<200 mg/m² (*N* = 61)	86	70	
⩾200 mg/m² (*N* = 169)	89	79	0.23

After Bonferroni correction for multiple tests (*N* = 12), *p*-values < 0.0042 were considered significant.

(HR 3.75; 95%-CI 2.02–7.09; *p* < 0.001) were significantly associated with LRC, whereas tumor site did not achieve significance (HR 1.05; 95%-CI 0.85–1.27; *p* = 0.65).

The chemotherapy regimen had no significant impact on MFS in the univariate analysis (*p* = 0.67, see Fig. 1). Improved MFS was significantly associated with favorable tumor site (*p* = 0.002). ECOG performance score 0–1 (*p* = 0.014) and pre-chemoradiation hemoglobin levels ⩾12 g/dl (*p* = 0.032) showed a trend (Table 3). On multivariate analysis of MFS, the ECOG performance score (HR 2.53; 95%-CI 1.11–5.26; *p* = 0.028) was significant, and pre-chemoradiation hemoglobin levels showed a trend (HR 1.89; 95%-CI 0.98–3.58; *p* = 0.056). The tumor site did not achieve significance on multivariate analysis of MFS (HR 1.08; 95%-CI 0.87–1.33; *p* = 0.46).

In the univariate analysis of OS, the chemotherapy regimen was not significantly associated with outcomes (*p* = 0.14, see Fig. 1). Improved OS was significantly associated with ECOG performance score 0–1 (*p* = 0.004) and pre-chemoradiation hemoglobin levels ⩾12 g/dl (*p* < 0.001); favorable tumor site (*p* = 0.022) showed a trend (Table 4). In the multivariate analysis of OS, ECOG performance score (HR 2.61; 95%-CI 1.30–4.90; *p* = 0.009) and pre-chemoradiation hemoglobin levels (HR 2.34; 95%-CI 1.38–3.91; *p* = 0.002) achieved significance, whereas the tumor site was not significant (HR 1.01; 95%-CI 0.84–1.19; *p* = 0.95).
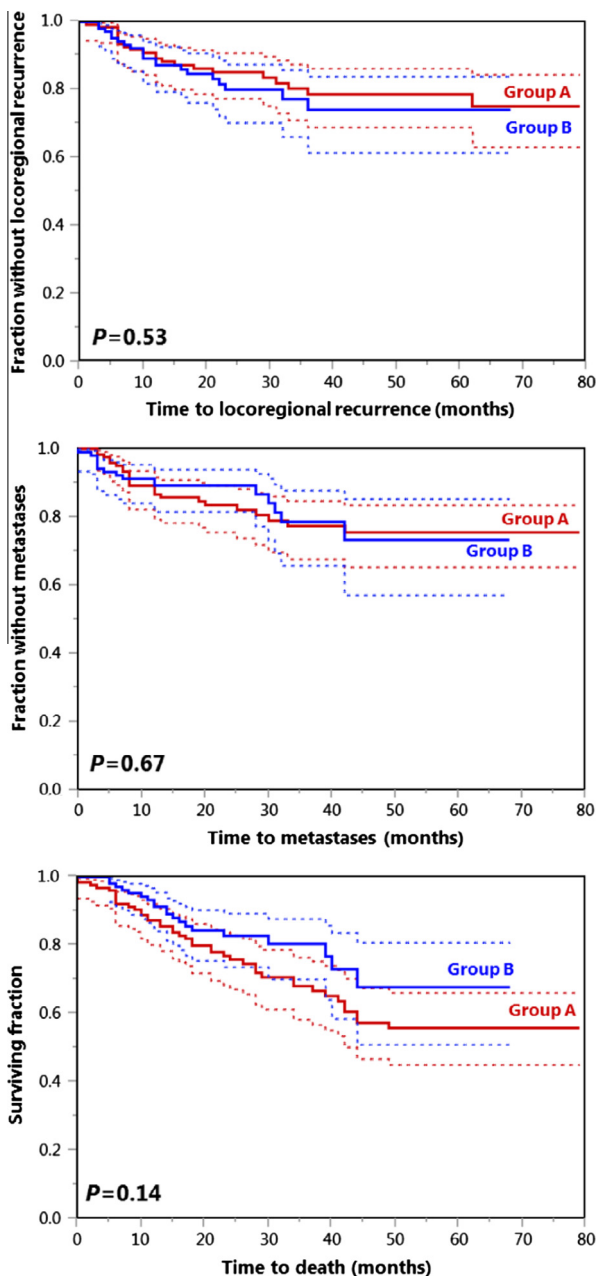
Table 3
Univariate analysis of metastases-free (MFS).

	At 1 year (%)	At 3 years (%)	p
Chemoradiation regimen			
Group A (N = 126)	87	77	
Group B (N = 104)	89	79	0.67
T-classification			
T1-2 (N = 85)	93	83	
T3-4 (N = 145)	85	76	0.08
N-classification			
N0-1 (N = 55)	91	83	
N2-3 (N = 175)	87	77	0.78
Performance score			
ECOG 0-1 (N = 197)	89	81	
ECOG 2 (N = 33)	81	43	0.014
Gender			
Female (N = 53)	92	83	
Male (N = 177)	87	77	0.17
Age			
$\leqslant$ 56 years (N = 124)	90	83	
$\geqslant$ 57 years (N = 106)	86	73	0.18
Tumor site			
Oropharynx (N = 130)	91	85	
Hypopharynx (N = 31)	69	54	
Larynx (N = 39)	92	68	
Oral cavity (N = 30)	86	86	**0.002**
Histologic grading			
G 1-2 (N = 134)	88	80	
G 3 (N = 96)	88	76	0.52
Upfront surgery			
No (N = 98)	84	75	
Yes (N = 132)	91	81	0.11
Radiation technique			
3D conformal (N = 187)	86	80	
IMRT/VMAT (N = 43)	85	61	0.36
Hemoglobin prior to chemoradiation			
< 12 g/dl (N = 72)	81	65	
$\geqslant$ 12 g/dl (N = 158)	91	83	0.032
Cumulative cisplatin dose			
< 200 mg/m^2 (N = 61)	86	77	
$\geqslant$ 200 mg/m^2 (N = 169)	89	78	0.75

After Bonferroni correction for multiple tests (N = 12), p-values < 0.0042 were considered significant.

Table 4
Univariate analysis of overall survival (OS).

	At 1 year (%)	At 3 years (%)	p
Chemoradiation regimen			
Group A (N = 126)	87	68	
Group B (N = 104)	91	80	0.14
T-classification			
T1-2 (N = 85)	89	78	
T3-4 (N = 145)	89	70	0.22
N-classification			
N0-1 (N = 55)	93	75	
N2-3 (N = 175)	88	72	0.94
Performance score			
ECOG 0-1 (N = 197)	91	77	
ECOG 2 (N = 33)	79	22	**0.004**
Gender			
Female (N = 53)	96	88	
Male (N = 177)	87	69	0.23
Age			
$\leqslant$ 56 years (N = 124)	90	76	
$\geqslant$ 57 years (N = 106)	89	68	0.99
Tumor site			
Oropharynx (N = 130)	89	78	
Hypopharynx (N = 31)	77	46	
Larynx (N = 39)	95	74	
Oral cavity (N = 30)	93	70	0.022
Histologic grading			
G 1-2 (N = 134)	89	72	
G 3 (N = 96)	90	75	0.86
Upfront surgery			
No (N = 98)	87	73	
Yes (N = 132)	91	73	0.26
Radiation technique			
3D conformal (N = 187)	89	72	
IMRT/VMAT (N = 43)	88	79	0.95
Hemoglobin prior to chemoradiation			
< 12 g/dl (N = 72)	81	62	
$\geqslant$ 12 g/dl (N = 158)	93	78	**< 0.001**
Cumulative cisplatin dose			
< 200 mg/m^2 (N = 61)	82	61	
$\geqslant$ 200 mg/m^2 (N = 169)	92	78	0.11

After Bonferroni correction for multiple tests (N = 12), p-values < 0.0042 were considered significant.

In the chemoradiation groups A and B, 66 patients (52%) and 16 patients (15%), respectively, did not receive the complete chemotherapy as planned due to treatment-related adverse events ($p < 0.001$). Chemoradiation including cisplatin 100 mg/m^2 given every three weeks was associated with significantly more adverse events in terms of pneumonia/sepsis ($p = 0.003$), grade $\geqslant 2$ nausea/vomiting ($p < 0.001$), grade $\geqslant 2$ nephrotoxicity ($p = 0.005$) and grade $\geqslant 2$ xerostomia ($p = 0.002$). Trends were observed for more grade $\geqslant 3$ hematotoxicity ($p = 0.052$) and grade $\geqslant 2$ ototoxicity ($p = 0.048$). The adverse events observed in both chemoradiation groups are summarized in Table 5.

Discussion

The appropriate chemotherapy regimen for chemoradiation of LASCCHN is still under debate. Although 100 mg/m^2 of cisplatin given every three weeks is the preferred regimen in many centers and considered by many radiation oncologists to be the "standard" approach, a considerable number of centers are hesitant to use this regimen because of its high toxicity [9]. Previous studies that compared 100 mg/m^2 of cisplatin given every three weeks to other cisplatin regimens including lower doses per administration provided inconsistent results with respect to adverse events and efficacy.

In a small randomized study of 50 eligible patients, grade $\geqslant 3$ oral mucositis (75% versus 39%, $p = 0.012$) and grade $\geqslant 3$ overall adverse events (92% versus 81%, $p = 0.02$) were more common with weekly administration of 40 mg/m^2 cisplatin than with 100 mg/m^2 cisplatin every three weeks [14]. In contrast, in a retrospective study of 51 patients, 40 mg/m^2 cisplatin weekly was better tolerated than 100 mg/m^2 of cisplatin given every three weeks [19]. In another retrospective study of 94 patients, 100 mg/m^2 cisplatin every three weeks was associated with more renal failures ($p = 0.04$) [13]. In a larger retrospective study of 262 patients, 100 mg/m^2 cisplatin every three weeks was associated with significantly more adverse events than weekly administration of 40 mg/m^2 cisplatin in terms of grade $\geqslant 3$ mucositis (34% vs.12%, $p < 0.001$), grade $\geqslant 3$ skin reactions (7% vs. 1%, $p = 0.014$) and decrease of creatinine clearance ($p < 0.001$) [10]. Another retrospective study compared four different cisplatin-based chemoradiation regimens for LASCCHN including 100 mg/m^2 cisplatin every three weeks (N = 74), 20 mg/m^2 of cisplatin given on five days every four weeks (N = 86), and two cisplatin/5-fluorouracil regimens (N = 49 and N = 102, respectively) [16]. Grade 3 nausea/vomiting ($p = 0.003$), grade 3 nephrotoxicity ($p = 0.019$) and grade 3–4 hematotoxicity ($p = 0.027$) were more common in the 100 mg/m^2 cisplatin group than in the other three groups. Thus, in all but

Table 5
Comparison of the chemoradiation groups for acute and late adverse events.

	Group A N patients (%)	Group B N patients (%)	p-value
Oral mucositis			
Grade ⩾2	117 (93)	86 (83)	0.41
Dermatitis			
Grade ⩾2	98 (78)	80 (77)	0.94
Hematotoxicity			
Grade ⩾3	33 (26)	15 (14)	0.052
Pneumonia/Sepsis			
Grade ⩾3	9 (12)*	1 (1)	**0.003**
Nausea/vomiting			
Grade ⩾2	40 (51)*	22 (21)	**<0.001**
Ototoxicity			
Grade ⩾2	5 (6)*	1 (1)	0.048
Nephrotoxicity			
Grade ⩾2	22 (17)	5 (5)	**0.005**
Xerostomia			
Grade ⩾2	70 (57)**	31 (30)	**0.002**

After Bonferroni correction for multiple ($N = 8$) tests, p-values < 0.0063 were considered significant.
  * Data of 78 patients available.
  ** Data of 122 patients available.

one of the available studies, 100 mg/m^2 cisplatin every three weeks was more toxic than other cisplatin-based regimens. The results of the present study agree with those findings. In the present study, 100 mg/m^2 every three weeks was associated with significantly greater morbidity in terms of pneumonia/sepsis, grade ⩾2 nausea/vomiting, grade ⩾2 nephrotoxicity and grade ⩾2 xerostomia. Additionally, a trend was found for more grade ⩾3 hematotoxicity and grade ⩾2 ototoxicity.

Therefore, 20 mg/m^2 of cisplatin on five days every four weeks appears preferable to 100 mg/m^2 cisplatin every three weeks, if it was as effective as the more toxic higher-dose regimen. According to the findings from the present study, both chemoradiation regimens were not significantly different with respect to LRC, MFS and OS. These findings agree with those of the previous retrospective study that compared four cisplatin-based chemoradiation regimens [16]. In that study, 100 mg/m^2 cisplatin every three weeks and 20 mg/m^2 of cisplatin on five days every four weeks resulted in 3-year LRC rates of 67% and 59%, respectively, 3-year MFS-rates of 67% and 79%, respectively, and 3-year OS rates of 60% and 71%, respectively. P-values were given only for the comparisons of all four groups and not for a comparison of the two regimens investigated in the present study.

The results of the few studies that compared 100 mg/m^2 of cisplatin every three weeks to weekly administration of 30–40 mg/m^2 of cisplatin for outcomes were inconsistent. One retrospective study suggested that 100 mg/m^2 of cisplatin every three weeks led to better OS but similar progression-free survival (PFS) than weekly cisplatin [13]. In another retrospective study, 100 mg/m^2 of cisplatin was associated with better PFS and OS only in the univariate analyses and not in the multivariate analysis [10]. In the two other studies, treatment outcomes were similar with 100 mg/m^2 of cisplatin given every three weeks and with weekly administration of cisplatin [12,14]. Thus, taking into account the results from the available studies comparing 100 mg/m^2 of cisplatin every three weeks to regimens including lower doses of cisplatin per administration with respect to treatment outcomes, similar outcomes can be achieved with lower-dose cisplatin regimens [10–16]. These results agree with the findings of the present study, which suggests that 20 mg/m^2 of cisplatin on five days every four weeks is as effective as 100 mg/m^2 cisplatin every three

weeks. Therefore, 20 mg/m^2 of cisplatin on five days every four weeks appears preferable taking into account both toxicity and efficacy.

However, all available data were obtained from retrospective studies and a small underpowered randomized study. Retrospective studies are always at risk of bearing a hidden selection bias. This applies also to the present study. Such a bias could have been introduced due different proportions of HPV-positive tumors in the compared groups [20,21]. Only one previous study considered the HPV-status [12]. Another source of bias could be the cumulative cisplatin dose as a trend ($p = 0.07$) of larger proportion of patients that received ⩾200 mg/m^2 of cisplatin were found in group B. The cumulative cisplatin dose in chemoradiation protocols for LASCCHN was reported to positively correlate with survival [22]. The fact that more patients in group B did receive a cumulative cisplatin dose of ⩾200 mg/m^2 may also be a consequence of the lower acute toxicity of 20 mg/m^2 of cisplatin on five days every four weeks, which can be considered an argument for this regimen.

In conclusion, 20 mg/m^2 of cisplatin given on five days every four weeks was associated with significantly fewer adverse events than 100 mg/m^2 cisplatin given every three weeks. 100 mg/m^2 cisplatin was not significantly superior to 20 mg/m^2 cisplatin with respect to LRC, MFS and OS. Thus, given the limitations of a retrospective study, 20 mg/m^2 cisplatin on five days every four weeks appeared preferable to 100 mg/m^2 cisplatin every three weeks. The results should be confirmed in a randomized trial providing maximum prophylactic and supportive measures for the patients, particularly for those receiving 100 mg/m^2 cisplatin.

Conflict of interest statement

None declared.

Acknowledgements

References

[1] Adelstein DJ, Li Y, Adams GL, Wagner Jr H, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–8.
[2] Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–8.
[3] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
[4] Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 1997;43:29–37.
[5] Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000;18:1458–64.
[6] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
[7] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
[8] Pignon JP, le Maître A, Maillard E, Bourhis J. MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[9] de Castro G, Jr SnitcovskyIM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, et al. High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage

IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2007;264:1475–82.

[10] Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupart M, et al. Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. Drug Des Devel Ther 2015;9:6203–10.

[11] Fietkau R, Lautenschläger C, Sauer R, Dunst J, Becker A, Baumann M, et al. Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: Results of the German phase III trial ARO 96–3. J Clin Oncol 2006; 24 (Suppl): #5507.

[12] Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, et al. Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncol 2014;50:311–8.

[13] Espeli V, Zucca E, Ghielmini M, Ghielmini M, Giannini O, Salatino A, et al. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol 2012;48:266–71.

[14] Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, et al. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol 2012;7:215.

[15] Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 2004;22:4665–73.

[16] Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, et al. Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2011;80:1037–44.

[17] National Institutes of Health/National Cancer Institute (2009) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. <http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf>.

[18] Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

[19] Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol 2008;47:1513–8.

[20] Rades D, Seibold ND, Hoffmann A, Gebhard MP, Noack F, Thorns C, et al. Impact of the HPV-positivity definition on the prognostic value of HPV status in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 2013;189:856–60.

[21] Strojan P, Zadnik V, Sifrer R, Lanisnik B, Didanovic V, Jereb S, et al. Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983–2009: role of human papillomavirus infection. Eur Arch Otorhinolaryngol 2015;272:3805–14.

[22] Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz Jr M, Bossi P, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. Head Neck 2016;38(Suppl 1). E2151-8.

CrossMark

HEAD AND NECK

Comparing two lower-dose cisplatin programs for radio-chemotherapy of locally advanced head-and-neck cancers

Dirk Rades[1] · Daniel Seidl[1] · Stefan Janssen[1,2] · Primoz Strojan[3] · Katarina Karner[3] · Amira Bajrovic[4] · Samer G. Hakim[5] · Barbara Wollenberg[6] · Steven E. Schild[7]

Abstract Radio-chemotherapy is a common treatment for locally advanced squamous cell head-and-neck cancers (LA-SCCHN). Cisplatin ($100\ mg/m^2$) every 3 weeks is very common but associated with considerable toxicity. Therefore, cisplatin programs with lower daily doses were introduced. There is a lack of studies comparing lower-dose programs. In this study, 85 patients receiving radio-chemotherapy with $20\ mg/m^2$ cisplatin on 5 days every 4 weeks (group A) were retrospectively compared to 85 patients receiving radio-chemotherapy with $30–40\ mg/m^2$ cisplatin weekly (group B). Groups were matched for nine factors including age, gender, performance score, tumor site, T-/N-category, surgery, hemoglobin before radio-chemotherapy, and radiation technique. One- and 3-year loco-regional control rates were 83 and 69 % in group A versus 74 and 63 % in group B ($p = 0.12$). One- and 3-year survival rates were 93 % and 73 % in group A versus 91 and 49 % in group B ($p = 0.011$). On multivariate analysis, survival was significantly better for group A (HR 1.17; $p = 0.002$). In groups A and B, 12 and 28 % of patients, respectively, did not receive a cumulative cisplatin dose $\geq 180\ mg/m^2$ ($p = 0.016$). Toxicity rates were not significantly different. On subgroup analyses, group A patients had better loco-regional control ($p = 0.040$) and survival ($p = 0.005$) than group B patients after definitive radio-chemotherapy. In patients receiving adjuvant radio-chemotherapy, outcomes were not significantly different. Thus, $20\ mg/m^2$ cisplatin on 5 days every 4 weeks resulted in better loco-regional control and survival in patients receiving definitive radio-chemotherapy and may be preferable for these patients. Confirmation of these results in a randomized trial is warranted.

Keywords LA-SCCHN · Radio-chemotherapy · Lower-dose cisplatin · Loco-regional control · Survival · Toxicity

✉ Dirk Rades
   Rades.Dirk@gmx.net

1 Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

2 Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany

3 Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia

4 Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany

5 Department of Oral and Maxillofacial Surgery, University of Lübeck, Lübeck, Germany

6 Department of Oto-Rhino-Laryngology and Head and Neck Surgery, University of Lübeck, Lübeck, Germany

7 Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA

Introduction

Radio-chemotherapy is a common modality for the treatment of locally advanced squamous cell carcinoma of the head-and-neck (LA-SCCHN). Randomized trials demonstrated that radio-chemotherapy resulted in significantly better survival than radiation therapy alone in patients who did not receive upfront surgery. In postoperative setting, randomized trials confirmed that patients with LA-SCCHN and specific risk factors (incomplete resection and/or extracapsular spread of lymph node metastasis) also benefit from the addition of chemotherapy to irradiation [1–6]. After publication of a large meta-analysis showing concurrent radio-chemotherapy to be superior to any other combinations of radiation therapy and chemotherapy,

concurrent administration of radio-chemotherapy became the standard therapy [7]. Cisplatin, either alone or as part of combined chemotherapy regimens, is now the most frequently used agent for radio-chemotherapy of LA-SCCHN.

Several randomized trials confirmed that radio-chemotherapy including 100 mg/m^2 of cisplatin alone given every 3 weeks was significantly superior to radiation therapy alone in both definitive and adjuvant settings. Consequently, three courses of 100 mg/m^2 cisplatin alone became the most commonly used regimen for the radio-chemotherapy of LA-SCCHN [3–6]. However, this radio-chemotherapy has been associated with considerable acute toxicity and many radiation oncologists are hesitant to use three courses of 100 mg/m^2 cisplatin and prefer regimens with lower cisplatin doses per administration (lower-dose programs) [8–10]. Other cisplatin monotherapy regimens include daily administration of 5–7 mg/m^2, weekly administration of 30–40, and 20 mg/m^2 on 5 days every 4 weeks [1, 2, 9–12]. However, there are only few studies comparing different lower-dose programs of cisplatin alone used in concurrent radio-chemotherapy protocols for LA-SCCHN. In the present study 20 mg/m^2 of cisplatin alone given on 5 days every 4 weeks was compared to weekly administration of 30–40 mg/m^2 of cisplatin alone for loco-regional control, survival, and toxicity.

Patients and methods

In this retrospective study, 170 patients were included who received concurrent radio-chemotherapy with cisplatin alone for LA-SCCHN. Criteria for inclusion in this study were locally advanced cancer of the oropharynx, hypopharynx, larynx or oral cavity requiring radio-chemotherapy as definitive or adjuvant treatment, no distant metastasis, age at least 18 years, no history of another type of cancer, an Eastern Cooperative Oncology Group (ECOG) performance score of ≤2, and no contraindications to receive cisplatin. Patients who did not meet these criteria were excluded from this study. Radiotherapy was delivered as three-dimensional (3D) conformal irradiation or as intensity-modulated radiotherapy (IMRT). IMRT included so-called classic IMRT and volumetric-modulated arc therapy (VMAT). The total radiation doses administered to the primary tumor and the involved lymph nodes were 66–70 Gy in case of definitive radio-chemotherapy or adjuvant radio-chemotherapy following macroscopically incomplete resection and 60–66 Gy in case of adjuvant radio-chemotherapy following macroscopically complete resection. Non-involved lymph node regions in the neck received 50–60 Gy. Regarding concurrent chemotherapy, two regimens with lower-dose cisplatin alone were compared. The regimens were given according to multidisciplinary protocols preferred at contributing institutions between 2003 and 2014, the timeframe that patients in this study were treated.

In group A ($n = 85$), chemotherapy included two courses of 20 mg/m^2 cisplatin alone administered on 5 days every 4 weeks as bolus infusions on days 1–5 and 29–33. In group B ($n = 85$), chemotherapy also consisted of cisplatin alone, which in this group was administered once a week with doses of 30–40 mg/m^2. Cisplatin was also given as bolus infusions, which were, in both groups, supplemented by prophylactic hydration with antiemetic drugs prior to and during its administration.

Both radio-chemotherapy groups were matched with respect to nine factors including age (≤57 vs. ≥58 years, median age 57 years), gender, ECOG performance score (0–1 vs. 2), tumor site (oropharynx vs. hypopharynx vs. larynx vs. oral cavity), T-category (T1–2 vs. T3–4), N-category (N0–2a vs. N2b–3), upfront surgery (no vs. yes), hemoglobin level prior to radio-chemotherapy (<12 vs. ≥12 g/dl), and radiation technique (3D conformal vs. IMRT) (Table 1). These factors were equally distributed in both radio-chemotherapy groups. The HPV (human papilloma virus)-status was not available in the majority of patients and, therefore, not included in the analysis. In those patients receiving upfront surgery, a microscopically complete resection was achieved in 20 of 25 patients (80 %) in group A and in 18 of 25 patients (72 %) in group B, respectively ($p = 0.89$; Chi-square test).

Chemotherapy dose groups, the nine factors used for matching the groups, and the cumulative cisplatin dose (<180 vs. ≥180 mg/m^2) were evaluated for the endpoints loco-regional control and survival (i.e., death of any cause was considered as event). Both endpoints were calculated form the last day of radiation using the Kaplan–Meier method. The corresponding Kaplan–Meier curves of each investigated factor were compared with the log-rank test (univariate analyses) [13]. After Bonferroni correction, p values <0.0045 (11 tests) were considered significant, which represented an alpha-level of 0.05. Factors that achieved significance on log-rank test or showed a trend ($p < 0.05$) were evaluated for independence with the Cox proportional hazards model.

Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [14]. The comparison of the two radio-chemotherapy groups for toxicities was performed with the Chi-square test. After Bonferroni correction for multiple tests (six investigated adverse events), p values <0.0083 represented an alpha-level of 0.05 and were considered significant.

Additional subgroup analyses with respect to loco-regional control and survival were performed for the 120 patients receiving definitive radio-chemotherapy and for those 50 patients receiving adjuvant radio-chemotherapy.

Table 1 Distribution of the factors used for matching the radio-chemotherapy groups A (20 mg/m^2 of cisplatin on 5 days every 4 weeks, $n = 85$) and B (30–40 mg/m^2 of cisplatin weekly, n = 85)

	Group A, N patients (%)	Group B, N patients (%)
Age		
≤57 years ($N = 86$)	43 (51)	43 (51)
≥58 years ($N = 84$)	42 (49)	42 (49)
Gender		
Female ($N = 34$)	17 (20)	17 (20)
Male ($N = 136$)	68 (80)	68 (80)
ECOG performance score		
0–1 ($N = 128$)	64 (75)	64 (75)
2 ($N = 42$)	21 (25)	21 (25)
Tumor site		
Oropharynx ($N = 86$)	43 (51)	43 (51)
Hypopharynx ($N = 28$)	14 (16)	14 (16)
Larynx ($N = 32$)	16 (19)	16 (19)
Oral cavity ($N = 24$)	12 (14)	12 (14)
T-category		
T1–2 ($N = 34$)	17 (20)	17 (20)
T3–4 ($N = 136$)	68 (80)	68 (80)
N-category		
N0–2a ($N = 78$)	39 (46)	39 (46)
N2b–3 ($N = 92$)	46 (54)	46 (54)
Upfront surgery		
No ($N = 120$)	60 (71)	60 (71)
Yes ($N = 50$)	25 (29)	25 (29)
Pre-radiochemotherapy hemoglobin		
<12 g/dl ($N = 48$)	24 (28)	24 (28)
≥12 g/dl ($N = 122$)	61 (72)	61 (72)
Radiation technique		
3D conformal ($N = 126$)	63 (74)	63 (74)
IMRT ($N = 44$)	22 (26)	22 (26)

Results

In the entire cohort, the 1- and 3-year loco-regional control rates were 83 and 69 % in group A, versus 74 and 63 % in group B ($p = 0.12$; Table 2). A trend toward improved loco-regional control was found for lower (T1–2) T-category ($p = 0.030$) and upfront surgery ($p = 0.011$) (Table 2). In the subsequent multivariate analysis, upfront surgery [hazard ratio (HR) 2.24; 95 % confidence interval (CI) 1.04–5.59; $p = 0.037$] achieved significance, whereas T-category (HR 1.42; 95 % CI 0.92–2.45; $p = 0.12$) was not significant.

The 1- and 3-year survival rates were 93 and 73 %, respectively, in group A, versus 91 and 49 %, respectively, in group B ($p = 0.011$; Table 3). On univariate analysis, improved survival was associated with a better (ECOG 0–1) performance status ($p < 0.001$) (Table 3). On multivariate analysis, survival was significantly associated with type of chemotherapy (HR 1.17; 95 % CI 1.06–1.30; $p = 0.002$) and ECOG performance score (HR 3.01; 95 %

CI 1.75–5.05; $p < 0.001$). In groups A and B, 10 patients (12 %) and 24 patients (28 %), respectively, did not receive a cumulative cisplatin dose of ≥180 mg/m^2 ($p = 0.016$). The rates of toxicities in terms of oral mucositis, dermatitis, hematotoxicity, nephrotoxicity, xerostomia, and subcutaneous fibrosis were not significantly different in both groups (Table 4).

The additional subgroup analyses revealed that the cisplatin regimen used in group A was significantly superior to the regimen in group B with respect to loco-regional control ($p = 0.040$) and survival ($p = 0.005$) in patients receiving definitive radio-chemotherapy (Table 5) but not in those patients receiving adjuvant radio-chemotherapy (Table 6).

Discussion

Cisplatin-based regimens are very often used for the radio-chemotherapy of LA-SCCHN, particularly regimens including cisplatin alone. Due to randomized trials

Table 2 Results of the univariate analyses of loco-regional control

	At 1 year (%)	At 3 years (%)	p
Type of chemotherapy			
Group A ($N = 85$)	83	69	0.12
Group B ($N = 85$)	74	63	
Age			
≤57 years ($N = 86$)	77	63	0.63
≥58 years ($N = 84$)	80	71	
Gender			
Female ($N = 34$)	91	79	0.07
Male ($N = 136$)	75	74	
ECOG performance score			
0–1 ($N = 128$)	80	68	0.37
2 ($N = 42$)	71	62	
Tumor site			
Oropharynx ($N = 86$)	84	75	0.08
Hypopharynx ($N = 28$)	60	54	
Larynx ($N = 32$)	73	57	
Oral cavity ($N = 24$)	85	63	
T-category			
T1–2 ($N = 34$)	97	79	0.030
T3–4 ($N = 136$)	74	64	
N-category			
N0–2a ($N = 78$)	79	68	0.89
N2b–3 ($N = 92$)	78	66	
Upfront surgery			
No ($N = 120$)	73	61	0.011
Yes ($N = 50$)	91	81	
Pre-radiochemotherapy hemoglobin			
<12 g/dl ($N = 48$)	64	58	0.08
≥12 g/dl ($N = 122$)	84	71	
Radiation technique			
3D conformal ($N = 126$)	77	66	0.41
IMRT ($N = 44$)	83	71	
Cumulative cisplatin dose			
<180 mg/m^2 ($N = 34$)	79	64	0.37
≥180 mg/m^2 ($N = 136$)	78	68	

demonstrating that 100 mg/m^2 of cisplatin given every 3 weeks resulted in significantly better outcomes than radiation therapy alone, this regimen became the standard approach for LA-SCCHN in many centers. However, this radio-chemotherapy program was associated with high acute toxicity [9]. Thus, taking into account both efficacy and toxicity, the optimal radio-chemotherapy approach for LA-SCCHN requires further clarification.

In an attempt to minimize toxicity but retain the benefits of cisplatin, many centers use doses lower than 100 mg/m^2 per administration. Several studies compared lower-dose programs to 100 mg/m^2 of cisplatin every 3 weeks [9–11, 15–17]. However, there are few studies

comparing exclusively different lower-dose of cisplatin programs. Therefore, this study was initiated to compare 20 mg/m^2 of cisplatin on 5 days every 4 weeks to weekly administration of cisplatin with doses of 30-40 mg/m^2. According to the results of this study, 20 mg/m^2 of cisplatin on 5 days every 4 weeks resulted in significantly better outcomes than weekly administrations. In the entire cohort, the absolute differences of loco-regional control rates at 1 and 3 years were 9 and 6 % in favor of group A (Table 2), but these differences did not achieve significance ($p = 0.12$). However, in the subgroup analysis of patients receiving definitive radio-chemotherapy, the cisplatin regimen used in group A resulted in significantly better loco-regional control than weekly administration of cisplatin (group B). The absolute differences of loco-regional control rates at 1 and 3 years were 9 and 15 % in favor of group A (Table 5). In a retrospective study of 77 patients with locally advanced cancer of the uterine cervix, 20 mg/m^2 of cisplatin alone on 5 days every 3 weeks (inpatient regimen) was compared to weekly administration of 40 mg/m^2 of cisplatin (outpatient regimen) [18]. Progression-free survival at 3 years was significantly better in the 20 mg/m^2 of cisplatin group than in the weekly cisplatin group (90 vs. 76 %, $p = 0.01$). In the multivariate analysis of that study, this finding maintained significance with an HR of 3.46 (96 % CI 1.25–9.58; $p = 0.02$). Acute toxicities were 3.43 times more common in the weekly cisplatin group (95 % CI 1.38–8.52; $p = 0.02$). The cumulative cisplatin doses were not stated. However, it appears quite likely that patients in the 20 mg/m^2 of cisplatin group did receive higher cumulative doses, as it was the case in the present study.

In the present study, radio-chemotherapy with two courses of 20 mg/m^2 cisplatin resulted in significantly better survival rates at 1 and 3 years than radio-chemotherapy with cisplatin administered once a week with doses of 30–40 mg/m^2. However, according to the additional subgroup analyses, the superiority of the regimen used in group A was limited to patients receiving definitive radio-chemotherapy (Tables 5, 6). Therefore, the improved survival appears to be a consequence of the significantly improved loco-regional control in this particular subgroup.

In this study, significantly more patients in group B did not receive a cumulative cisplatin dose of 180 mg/m^2, which represents weekly doses of 30 mg/m^2 given over 6 weeks (concurrently with a total radiation dose of 60 Gy). This appears surprising, since acute toxicity rates were not significantly different between groups A and B. One may speculate about the reason for the difference regarding the cumulative cisplatin doses. Other acute toxicities not assessed in this study such as nausea/vomiting

Table 3 Results of the univariate analyses of survival

	At 1 year (%)	At 3 years (%)	p
Type of chemotherapy			
Group A (N = 85)	93	73	0.011
Group B (N = 85)	91	49	
Age			
≤57 years (N = 86)	94	58	0.37
≥58 years (N = 84)	90	62	
Gender			
Female (N = 34)	91	72	0.66
Male (N = 136)	92	58	
ECOG performance score			
0–1 (N = 128)	94	67	<0.001
2 (N = 42)	85	38	
Tumor site			
Oropharynx (N = 86)	95	63	0.07
Hypopharynx (N = 28)	81	57	
Larynx (N = 32)	97	61	
Oral cavity (N = 24)	88	54	
T-category			
T1–2 (N = 34)	89	79	0.41
T3–4 (N = 136)	92	56	
N-category			
N0–2a (N = 78)	94	62	0.29
N2b–3 (N = 92)	90	58	
Upfront surgery			
No (N = 120)	90	56	0.11
Yes (N = 50)	96	73	
Pre-radiochemotherapy hemoglobin			
<12 g/dl (N = 48)	87	57	0.50
≥12 g/dl (N = 122)	94	61	
Radiation technique			
3D conformal (N = 126)	93	59	0.57
IMRT (N = 44)	88	62	
Cumulative cisplatin dose			
<180 mg/m^2 (N = 34)	71	55	0.14
≥180 mg/m^2 (N = 136)	83	63	

might have been more common in group B. The difference regarding the cumulative cisplatin doses can to a certain extent be explained by the fact that patients in group A received their cisplatin as inpatients, in contrast to group B patients, who received their weekly cisplatin as outpatients. The latter group likely had poorer compliance. It may be difficult to motivate patients with LA-SCCHN, who are often heavy smokers and alcohol consumers to come to an outpatient department or a private practice six to seven times during radiation course. Furthermore, supportive care is more easily provided for inpatients, where the infrastructure of a hospital and multiple disciplines are available "under one roof".

The difference between groups A and B regarding the cumulative cisplatin doses is a source of potential bias [19]. Another source of a hidden bias may be a possible difference regarding the distribution of the human papilloma virus (HPV) status, which was not available in most patients of the present study. The HPV-status was reported to have a significant impact on the prognosis of patients with SCCHN [20, 21]. This must be considered a significant limitation of the present study. In general, retrospective studies like the present one always bear the risk of hidden selection biases. Furthermore, retrospective chart reviews can be affected by a recall bias and difficulties with the abstraction of the data from the charts. This

Table 4 Comparison of both radio-chemotherapy groups for toxicity

	Group A, N patients (%)	Group B, N patients (%)	p value
Oral mucositis			
Grade ≥2	74 (87)	73 (86)	0.93
Dermatitis			
Grade ≥2	66 (78)	53 (62)	0.23
Hematotoxicity			
Grade ≥2	68 (80)	65 (76)	0.79
Nephrotoxicity			
Grade ≥2	4 (5)	4 (5)	1.00
Xerostomia			
Grade ≥2	27 (32)	34 (47)[a]	0.37
Subcutaneous fibrosis			
Grade ≥2	18 (21)	28 (36)[b]	0.07

[a] Data of 72 patients available

[b] Data of 77 patients available

Table 5 Results of the subgroup analyses of the 120 patients receiving definitive radio-chemotherapy

	At 1 year (%)	At 3 years (%)	p
Loco-regional control			
Group A (N = 60)	79	68	0.040
Group B (N = 60)	70	53	
Survival			
Group A (N = 60)	87	70	0.005
Group B (N = 60)	67	43	

Table 6 Results of the subgroup analyses of the 50 patients receiving adjuvant radio-chemotherapy

	At 1 year (%)	At 3 years (%)	p
Loco-regional control			
Group A (N = 25)	92	72	0.29
Group B (N = 25)	90	90	
Survival			
Group A (N = 25)	96	80	0.19
Group B (N = 25)	84	70	

applies particularly to toxicity data, although the CTCAE criteria are standardized [14]. Since patients of both groups were matched 1:1 also with respect to the tumor site, this factor likely did not have a relevant impact on the results of this study. In those patients receiving surgery, data regarding pathological aspects such as perineural invasion, lymphovascular invasion and extracapsular spread of lymph node metastases were not available, which may have led to a selection bias in this subgroup.

Therefore, the results of this study should ideally be confirmed in a prospective randomized trial. However, since institutions treating patients with LA-SCCHN generally prefer specific regimens, it may be difficult to perform such a randomized trial in an appropriately large cohort with a sufficient statistical power.

In conclusion, 20 mg/m^2 cisplatin on 5 days every 4 weeks resulted in significantly better loco-regional control and survival than weekly administration of 30–40 mg/m^2 of cisplatin in patients who received definitive radio-chemotherapy but not in patients receiving adjuvant treatment. The toxicity rates were not significantly different with both regimens. Taking into account the limitations and the retrospective design of this study, 20 mg/m^2 cisplatin on 5 days every 4 weeks may be preferable to weekly administrations for definitive radio-chemotherapy. These results should be verified in a prospective randomized trial.

Compliance with ethical standards

References

1. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N (1997) Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 43:29–37

2. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, Vaskovic Z, Tadic L (2000) Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 18:1458–1464

3. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, Glisson B, Trotti A, Ridge JA, Chao C, Peters G, Lee DJ, Leaf A, Ensley J, Cooper J (2003) Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 349:2091–2098

4. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, Schuller DE, Forastiere AA (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21:92–98

5. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Iralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350:1945–1952

6. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK (2004) Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350:1937–1944

7. Pignon JP, Le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92:4–14

8. de Castro G, Jr Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, Federico MH (2007) High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, non-metastatic stage IV head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 264:1475–1482

9. Ho KF, Swindell R, Brammer CV (2008) Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol 47:1513–1518

10. Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupart M, Ramade A, Zrounba P, Ceruse P, Pommier P (2015) Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. Drug Des Dev Ther 9:6203–6210

11. Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE, Dunst J (2011) Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 80:1037–1044

12. Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, Pestalozzi B, Schmid S, Thöni A, Ozsahin M, Bernier J, Töpfer M, Kann R, Meier UR, Thum P, Bieri S, Notter M, Lombriser N, Glanzmann C (2004) Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 22:4665–4673

13. Kaplan EL, Meier P (1958) Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481

14. National Institutes of Health/National Cancer Institute (2009) Common terminology criteria for adverse events (CTCAE) version 4.0. http://www.evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

15. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, Olsen KD, Kasperbauer JL, Price DL, Garces YI, Ma DJ, Neben-Wittich MA, Molina JR, Garcia JJ, Price KA (2014) Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. Oral Oncol 50:311–318

16. Espeli V, Zucca E, Ghielmini M, Ghielmini M, Giannini O, Salatino A, Richetti A (2012) Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol 48:266–271

17. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, Chen IH, Lee LY, Wang HM, Chang JT (2012) The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol 7:215

18. Einstein MH, Novetsky AP, Garg M, Hailpern SM, Huang GS, Glueck A, Fields AL, Kalnicki S, Goldberg GL (2007) Survival and toxicity differences between 5-day and weekly cisplatin in patients with locally advanced cervical cancer. Cancer 109:48–53

19. Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz M Jr, Bossi P, Worden FP, Langendijk JA, Eisbruch A, Mendenhall WM, Lee AW, Harrison LB, Bradford CR, Smee R, Silver CE, Rinaldo A, Ferlito A (2016) Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. Head Neck 38(Suppl 1):E2151–E2158

20. Rades D, Seibold ND, Hoffmann A, Gebhard MP, Noack F, Thorns C, Schild SE (2013) Impact of the HPV-positivity definition on the prognostic value of HPV status in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol 189:856–860

21. Strojan P, Zadnik V, Šifrer R, Lanišnik B, Didanović V, Jereb S, Poljak M, Kocjan BJ, Gale N (2015) Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983–2009: role of human papillomavirus infection. Eur Arch Otorhinolaryngol 272:3805–3814

c. Ethikantrag

UNIVERSITÄT ZU LÜBECK

Universität zu Lübeck · Ratzeburger Allee 160 · 23538 Lübeck

Herrn
Prof. Dr. med. Dirk Rades
Klinik für Strahlentherapie

im Hause

Ethik-Kommission

Vorsitzender:
Herr Prof. Dr. med. Alexander
Katalinic
Stellv. Vorsitzender:
Herr Prof. Dr. med. Frank Gieseler

Ratzeburger Allee 160
23538 Lübeck

Sachbearbeitung: Frau Janine
Erdmann
Tel.: +49 451 500 46 39
Fax: +49 451 500 30 26
ethikkommission@uni-luebeck.de

Aktenzeichen: 15-354A
Datum: 10. Dezember 2015

**Vergleich verschiedener Therapieregime bei Patienten und Patientinnen,
die aufgrund eines Kopf-Hals-Tumors oder eines Rezidives eine
Radio-Chemotherapie erhalten haben
Ihr Schreiben vom 08. Dezember 2015**

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

IX. Danksagungen

Mein herzlicher Dank gilt Herrn Prof. Dr. med. Dirk Rades für die Überlassung des Themas, die hervorragende Betreuung sowie Zusammenarbeit.

Außerdem danke ich Herrn Prof. Dr. med. Steven E. Schild für die Unterstützung bei der statistischen Auswertung.

Ich danke dem Institut der Klinik für Hals-, Nasen- und Ohrenheilkunde für die Überlassung klinischer Daten.

Mein besonderer Dank gilt meiner Mutter die mich in allem unterstützt, gefördert und in jeglicher Hinsicht die Grundsteine für meinen Weg gelegt hat. Gleiches gilt für meinen leider zu früh verstorbenen Vater.

Außerdem möchte ich mich bei meiner Ehefrau Nina bedanken, die mich in meiner Arbeit immer bestärkt hat und auf die ich mich stets verlassen kann.