Reirradiation with Alternating Docetaxel-Based Chemotherapy for Recurrent Head and Neck Squamous Cell Carcinoma

Update of a Single-Center Prospective Phase II Protocol

Bernhard Berger[1], Claus Belka[2], Martin Weinmann[1], Michael Bamberg[1], Wilfried Budach[3], Thomas Hehr[4]

Purpose: To report follow-up data and results of a dose escalation within a prospective phase II protocol scheduling alternating chemoreirradiation for patients with unresectable locoregional recurrence of head and neck cancer after previous curative-intent radiotherapy.
Patients and Methods: Chemoreirradiation was initially performed in 27 patients by 40.0 Gy split-course reirradiation (re-RT) alternating with three cycles of docetaxel 50 mg/m^2 day 1 and cisplatin 15 mg/m^2 days 2–5 (first cohort). From 2002 onward, 30 consecutively treated patients received a late-course concomitant boost to 49.6 Gy (second cohort). In July 2008, the survival outcome was analyzed separately for both cohorts and the entire collective (n = 57).
Results: The Kaplan-Meier estimates for 1- and 2-year overall survival (OS) were 52% and 24%, respectively (median OS 13.4 months). The median time of locoregional control was 9.6 months, and the actuarial 2-year freedom from distant metastasis rate was 55%. The re-RT dose escalation led to a significant improvement of the median OS (17.4 vs. 9.4 months; p = 0.039). Irrespective of the cohort, severe treatment-related toxicities occurred in about one third of patients.
Conclusion: The treatment results confirm the efficacy and the safety of escalated re-RT doses in this chemoreirradiation protocol.

Key Words: Recurrent head and neck cancer · Reirradiation · Radiochemotherapy · Chemoradiation · Docetaxel

Strahlenther Onkol 2010;186:255–61
DOI 10.1007/s00066-010-2082-9

Dosiseskalierte alternierende Radiochemotherapie für lokoregional rezidivierende HNO-Plattenepithelkarzinome nach vorausgegangener Strahlentherapie. Follow-up einer prospektiven Phase-II-Studie

Ziel: Berichtet werden das Follow-up einer Phase-II-Studie zur alternierenden Reradiochemotherapie lokoregional rezidivierender, inoperabler HNO-Plattenepithelkarzinome sowie die Auswirkungen der in ihrem Rahmen erfolgten Dosiseskalation.
Patienten und Methodik: Das ursprüngliche Therapieprotokoll umfasste drei Zyklen Chemotherapie (Docetaxel 50 mg/m^2 Tag 1, Cisplatin 15 mg/m^2 Tage 2–5) in den Wochen 1, 5 und 7, alternierend mit einer „split-course"-Rebestrahlung bis 40,0 Gy (täglich 2,0 Gy in den Wochen 2 + 3 und 5 + 6). Nach einer Zwischenauswertung im Jahr 2002 (erste Kohorte, n = 27) erhielten weitere 30 Patienten (zweite Kohorte) in Woche 6 einen konkomitanten Boost bis 49,6 Gy. Im Juli 2008 wurden die Studienendpunkte separat für beide Kohorten sowie für das Gesamtkollektiv (n = 57) analysiert.
Ergebnisse: Im Gesamtkollektiv betrugen das 1- und 2-Jahres-Überleben 52% und 24% (medianes Überleben 13,4 Monate). Die mediane lokoregionale Kontrolle lag bei 9,6 Monaten, und nach 2 Jahren waren 55% der Patienten metastasenfrei. Die Dosiseskalation in der zweiten Kohorte führte zu einem signifikant verbesserten Gesamtüberleben (17,4 vs. 9,4 Monate; p = 0,039). Etwa ein Drittel der Patienten erlitt schwere behandlungsassoziierte Toxizitäten, und dies war unabhängig von der Patientenkohorte.
Schlussfolgerung: Die Behandlungsergebnisse bestätigen die Effektivität und Sicherheit einer Dosiseskalation im Rahmen dieses Therapieprotokolls.

Schlüsselwörter: Rezidivierende HNO-Plattenepithelkarzinome · Rebestrahlung · Reradiatio · Radiochemotherapie · Docetaxel

[1]Department of Radiation Oncology, University of Tübingen, Germany,
[2]Department of Radiation Oncology, Ludwig Maximilians University of Munich, Germany,
[3]Department of Radiation Oncology, University Hospital Düsseldorf, Germany,
[4]Department of Radiation Oncology, Marienhospital Stuttgart, Germany.

Received: September 8, 2009; accepted: March 5, 2010
Published Online: April 26, 2010

Introduction

Locoregional recurrence in a previously irradiated area is the main source of treatment failure in advanced head and neck squamous cell cancer (HNSCC). As reported by numerous trials, its incidence is 30–50% 5 years after primary chemoradiation or surgery followed by adjuvant chemoradiation [5, 19]. Treatment options comprise salvage surgery, reirradiation (re-RT, either by external RT or brachytherapy), chemoreirradiation, or chemotherapy alone (including molecular targeted therapies) [1, 6–10, 24]. Aggressive local treatment is mandatory to achieve locoregional control (LRC) that is linked to freedom from distant metastasis (FFDM) and overall survival (OS) [19].

With respect to chemoreirradiation, phase I/II trials have been performed showing considerable variability in patient selection, re-RT doses/performance, and chemotherapy concepts [8, 10]. The best-evaluated treatment protocol schedules split-course hyperfractionated re-RT to 60.0 Gy (1.5 Gy twice daily every other week for four cycles) concurrent to 5-fluorouracil (5-FU) and hydroxyurea (HU; Vokes protocol) [25]. As for radiosensitization, 5-FU/HU chemotherapy subsequently has been intensified by other cytostatics (triple-agent chemotherapy) [15, 17]. The institutional experience on chemoreirradiation has been corroborated by two multicenter trials sponsored by the Radiation Therapy Oncology Group (RTOG) [11, 20]. The RTOG 9610 study yielded a 2-year OS rate of 16.9% in 86 patients treated by concurrent chemoreirradiation according to the Vokes protocol [20]. In the RTOG 9911 trial, 5-FU/HU chemotherapy was replaced by cisplatin and paclitaxel. Compared to the RTOG 9610 study, the final analysis of 105 patients revealed a significantly improved outcome (2-year OS 24.9%) [11].

In 1997, we started a single-center prospective phase I/II protocol on chemoreirradiation that, for the first time, included cisplatin and docetaxel. To guarantee sufficient chemotherapy doses without excess of mucosal toxicity, the concept of treatment alternation was used [13, 14]. The protocol scheduled split-course re-RT to a moderate dose (40.0 Gy) alternating with three cycles of docetaxel and cisplatin. After a median follow-up time of 42 months for patients alive, the first analysis showed promising results (2-year OS 23%) and acceptable toxicities [6]. Thus, to further improve the efficacy, a re-RT dose escalation was introduced in 2002. In addition to follow-up data of the first cohort, we here report on outcome and tolerability of 30 consecutive patients treated according to the modified protocol.

Patients and Methods

Treatment Protocol

Since 1997, 27 patients with locoregional HNSCC recurrence had undergone chemoreirradiation (first cohort) [6]. Treatment consisted of split-course re-RT to 40.0 Gy in standard fractionation (2.0 Gy per fraction for 5 days in weeks 2–3 and 5–6) alternating with three cycles of docetaxel 60 mg/m^2 day 1 and cisplatin 15 mg/m^2 days 2–5 in weeks 1, 4, and 7. Due to grade 3/4 hematologic toxicity, the docetaxel dose was reduced from 60 mg/m^2 to 50 mg/m^2 after the treatment of twelve patients, and this dosage was maintained for all following patients. From September 2002 to July 2007, 30 consecutive patients (second cohort) received a late-course concomitant boost of 9.6 Gy given in 1.6-Gy daily fractions starting after 28.0 Gy. The total re-RT dose was 49.6 Gy.

The eligibility criteria for treatment have been reported previously [6]. In brief, the protocol stipulated nonmetastatic unresectable recurrent or second primary HNSCC in a previously irradiated area occurring ≥ 6 months after definitive or adjuvant RT. The Eastern Cooperative Oncology Group (ECOG) performance status had to be ≤ 1. The recurrence had to be biopsy-proven in a head and neck site overlapping with a previous RT field (≥ 50.0 Gy). Re-RT was performed by conventional three-dimensional conformal RT techniques using linear accelerators with 6-MV photons and 4- to 12-MeV electrons. Five patients received intensity-modulated radiotherapy (IMRT) for re-RT due to the proximity of target volumes to previously irradiated structures at risk. As confirmed by evaluation of the previous RT records, the lifetime spinal cord or brain stem dose was not allowed to exceed 40.0 Gy if the time interval between initial RT and re-RT was < 12 months, 55.0 Gy if the interval was 12–24 months, and 60.0 Gy if the interval was > 24 months [6]. The planning target volume (PTV) generally included the gross tumor volume (GTV) with safety margins of at least 1.0 cm in all directions. In the case of exceeding spinal cord tolerance doses, the PTV was abridged manually, but with the tumor volume generally kept within the 95% isodose. For boosting, the PTV was defined as GTV without safety margins.

After our first report mainly had focused on toxicity and feasibility of the protocol [6], the objective of this follow-up analysis was to specify its therapeutic efficacy. Accordingly, we evaluated the survival outcome (OS) as well as local (LRC) and distant (FFDM) tumor control rates. Secondary endpoints were acute and late toxicity as well as pretreatment and treatment-related prognostic factors. The assessment of the treatment outcome was independently performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [23]. The treatment-related toxicities were scored according to the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) with late toxicity evaluation commencing after 3 months. Informed consent and permission for data abstraction were obtained from all patients, and the treatment protocol was approved by the University of Tübingen Ethics Commission.

Statistical Analysis

Baseline characteristics of the first and second cohort were compared using a two-sided Mann-Whitney U-test for continuous variables and the χ^2-test for categorical variables (p-values ≤ 0.05 considered significant). The survival outcome

Table 1. Patient characteristics at time of recurrence. ECOG: Eastern Cooperative Oncology Group; RT: radiation therapy.

Tabelle 1. Patientencharakteristika zum Zeitpunkt der Rezidivdiagnose. ECOG: Eastern Cooperative Oncology Group; RT: Radiotherapie.

	First cohort (n = 27)	Second cohort (n = 30)	Entire collective (n = 57)
Median age [years (range)]	56 (18–73)	62 (22–73)	58 (18–73)
Gender [n (%)]			
• Male	22 (81)	23 (77)	45 (79)
• Female	5 (19)	7 (23)	12 (21)
ECOG performance status [n (%)]			
• 0	2 (7)	3 (10)	5 (9)
• 1	25 (93)	27 (90)	52 (91)
Index treatment [n (%)]			
• Adjuvant RT	18 (67)	15 (50)	33 (57)
• Adjuvant radiochemotherapy	2 (7)	4 (13)	6 (10)
• Primary RT	2 (7)	3 (10)	5 (9)
• Primary radiochemotherapy	5 (19)	8 (27)	13 (22)
• Median RT dose [Gy (range)]	60.0 (60.0–77.6)	64.0 (50.0–80.0)	64.0 (50.0–80.0)
Primary tumor subsite [n (%)]			
• Nasal cavity/nasopharynx	1 (4)	1 (3)	2 (3)
• Oral cavity	5 (19)	2 (7)	7 (12)
• Oropharynx	15 (56)	19 (63)	34 (59)
• Hypopharynx	5 (19)	4 (13)	9 (16)
• Larynx	1 (4)	3 (10)	4 (7)
• Parapharyngeal/cervical lymph nodes	0	1 (3)	1 (2)
Recurrence type [n (%)]			
• First locoregional recurrence	20 (74)	25 (83)	45 (78)
• Second/third locoregional recurrence	5 (19)	3 (10)	8 (14)
• Second primary tumor	2 (7)	2 (7)	4 (7)
Tumor recurrence subsite [n (%)]			
• Nasal cavity/nasopharynx	0	1 (3)	1 (2)
• Oral cavity	0	2 (7)	2 (3)
• Oropharynx	11 (41)	15 (50)	26 (45)
• Hypopharynx	4 (15)	2 (7)	6 (10)
• Larynx	0	2 (7)	2 (3)
• Parapharyngeal/cervical lymph nodes	12 (44)	8 (27)	20 (35)

was calculated using the Kaplan-Meier method with LRC, FFDM, and OS being assessed from the 1st day of treatment until locoregional recurrence or progress, appearance of distant metastases, and death, respectively. To compare survival data, the Mantel-Cox log-rank test was used (p-values ≤ 0.05 considered significant). Univariate and multivariate analysis using the Cox proportional hazards model was performed to investigate the influence of the following nine covariates: age at re-RT, sex, type of index treatment (primary vs. adjuvant), interval between treatments (≤ vs. > 36 months), PTV volume of recurrence (≤ vs. > median volume), re-RT dose (≤ vs. 49.6 Gy), chemotherapy dose (< 100% vs. full dose), tumor response (complete response [CR] or partial response [PR] vs. less), and salvage treatment after chemoreirradiation (present vs. not present). Statistical evaluations were performed on SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Performance of Chemoreirradiation

Baseline patient demographics are shown in Table 1. An intercohort comparison revealed no statistically significant differences. Chemoreirradiation was performed after a median time interval of 16.3 months (range, 7.5–188.0 months; Table 2). The median cumulative lifetime dose was 109.6 Gy (range, 76.0–129.6 Gy). Toxicity-related early treatment interruptions occurred in five patients; all other patients (91%) received at least 40.0 Gy. Re-RT was applied per protocol to 86% of the patients. With respect to chemotherapy, 27 patients (47%) completed three courses as scheduled; 82% received at least two thirds of the planned chemotherapy dose. Considering any type of treatment modification, the overall adherence to protocol was 46%.

Follow-Up of the First Cohort

Six of 27 patients were alive at the time of first analysis; three of the surviving patients experienced locoregional progression or recurrence and died 11.7, 22.7, and 54.8 months after treatment, respectively. One patient developed a contralateral second primary tumor 57.4 months after re-RT (cumulative dose in the tumor area 82.6 Gy) and underwent chemoreirradiation for a second time (re-re-RT to 40.0 Gy, total lifetime dose 122.6 Gy). He died after 14.3 months of locoregional progression (OS 71.4 months); due to the repeated re-RT, however, he was excluded from further survival analysis. The remaining two living patients of the first cohort were lost to follow-up without evidence of local recurrence 38 and 42 months after treatment. The follow-up of the first cohort did not significantly modify the Kaplan-Meier estimates as reported before [6].

Treatment Results

52 of 57 patients (91%) could be assessed for treatment response. The overall response rate (CR plus PR) was 73%

Table 2. Details of chemoreirradiation. RT: radiation therapy; PTV: planning target volume.

Tabelle 2. Behandlungsdetails der Reradiochemotherapie. RT: Radiotherapie; PTV: Planungszielvolumen.

	First cohort (n = 27)	Second cohort (n = 30)	Entire collective (n = 57)
Median time interval [months (range)]	14.4 (7.5–188.0)	20.7 (8.4–94.0)	16.3 (7.5–188.0)
Resection status before re-RT [n (%)]			
• Unresectable/no surgery	24 (89)	27 (90)	51 (89)
• R2	1 (4)	1 (3)	2 (4)
• R1	2 (7)	2 (7)	4 (7)
Re-RT			
• Re-RT dose (Gy)	40.0 (14.0–50.0)	49.6 (22.0–60.0)	40.0 (14.0–60.0)
• Total lifetime dose (Gy)	100.0 (76.0–120.6)	113.3 (86.0–129.6)	109.6 (76.0–129.6)
• Re-RT dose as planned [n (%)]	24 (89)	25 (83)	49 (86)
• Median PTV [ml (range)]	263.5 (51.0–670.0)	331.5 (64.0–863.0)	294.0 (51.0–863.0)
Chemotherapy [n (%)]			
• Full dose as planned [n (%)]	12 (44)	15 (50)	27 (47)
• ≥ 2/3 dose	21 (78)	26 (87)	47 (82)
• < 2/3 dose	6 (22)	4 (13)	10 (18)
Treatment as planned [n (%)]	12 (44)	14 (47)	26 (46)
Treatment response [n (%)]	(n = 24)	(n = 28)	(n = 52)
• Complete response (CR)	9 (38)	9 (32)	18 (34)
• Partial response (PR)	11 (46)	9 (32)	20 (38)
• Stable disease (SD)	3 (13)	10 (36)	14 (26)
• Progressive disease (PD)	1 (4)	0	1 (2)
• Overall response rate (CR + PR)	20 (83)	18 (64)	38 (72)

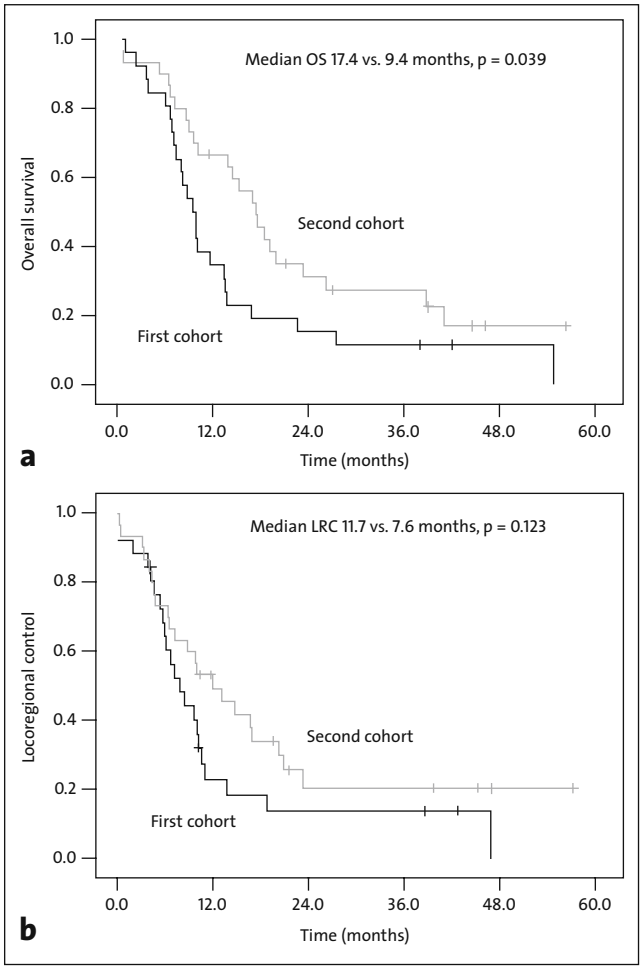
with almost equal portions of patients achieving CR and PR, respectively. At the time of the present analysis, 21 patients of the second cohort (75%) had died; seven patients were alive, of which five were without treatment and evidence of disease. Of the 21 deceased patients, 15 (71%) had died of locoregional tumor progression (six had fatal tumor hemorrhages), three of distant progression, and three patients for unknown or not tumor-related reasons.

On intent-to-treat analysis, the median OS for the entire cohort was 13.4 months (95% confidence interval [CI], 8.8–18.0). The estimated 1- and 2-year OS probability was 52% (standard error [SE], 0.067) and 24% (SE, 0.058), respectively. The median LRC estimate was 9.6 months (95% CI, 7.2–12.0), and the actuarial 1- and 2-year FFDM rates were 74% (SE, 0.066) and 55% (SE, 0.092), respectively. With a median follow-up time of 39 months for patients alive (range, 11.5–65.3 months), the median OS of patients of the second cohort was 17.4 months (95% CI, 13.3–21.5); the corresponding 1- and 2-year OS rates were 67% (SE, 0.086) and 31% (SE, 0.087), respectively. The log-rank comparison of survival data between the first and second cohort revealed significantly better OS values for patients of the second cohort (median OS 17.4 vs. 9.4 months; $p = 0.039$; Figure 1a). The difference between the LRC rates did not reach statistical significance (median LRC 11.7 vs. 7.6 months; $p = 0.123$; Figure 1b), and neither did the FFDM ($p = 0.439$). A comparison of treatment features identified the re-RT dose as being the only differing factor between the two cohorts ($p < 0.001$; Table 2).

Univariate analysis of the covariates mentioned above revealed a statistically significant prognostic impact of the following on LRC and OS: re-RT dose (Figure 2), chemotherapy dose and overall treatment response (PR/CR). A multivariate analysis considering all covariates showed that the overall treatment response was the only residual variable being independently prognostic of OS ($p = 0.039$). By contrast, higher re-RT and chemotherapy doses showed only a trend toward better outcome ($p = 0.153$ and 0.088, respectively).

Treatment-Related Toxicity

Severe acute and late treatment-related toxicities are listed in Table 3. Four patients (7%) experienced acute grade 5 complications. As for acute nonhematologic toxicity, grade 3 dysphagia was the most prevailing effect requiring gastrostomy tubes in four patients (24% of those 17 patients who did not have tube-dependent dysphagia before). Regarding late toxicity, 52 patients could be assessed. 37 patients (71%) were already dependent on tube feedings before re-RT and had no documented impairment of the swallowing function thereafter. Severe chronic dysphagia unambiguously related to re-RT was found in six patients (40% of the 15 patients who did not have severe dysphagia before). Other soft-tissue complications included fibrosis (25%) and chronic lymphedema (15%) with two patients requiring late tracheostomy 3.3 and 7.0 months after re-RT, respectively (7% of those 28 patients who were not tracheostomied before). The median time to any late grade 3/4 toxicity was 4.7 months, and the Kaplan-Meier probability of severe late effects was 38.1% at 13.4 months (median OS; Figure 3). Altogether, 31 of 52 patients (60%) remained without high-grade late toxicity, and there was no significant difference between the two cohorts.



Figures 1a and 1b. Kaplan-Meier curves indicating a) overall survival (OS), and b) locoregional control (LRC) stratified for the first and second cohort. The p-values have been determined by log-rank test.

Abbildungen 1a und 1b. Kaplan-Meier-Kurven für a) das Gesamtüberleben (OS) und b) die lokoregionale Tumorkontrolle (LRC), stratifiziert nach erster und zweiter Kohorte (Log-Rank-Test).

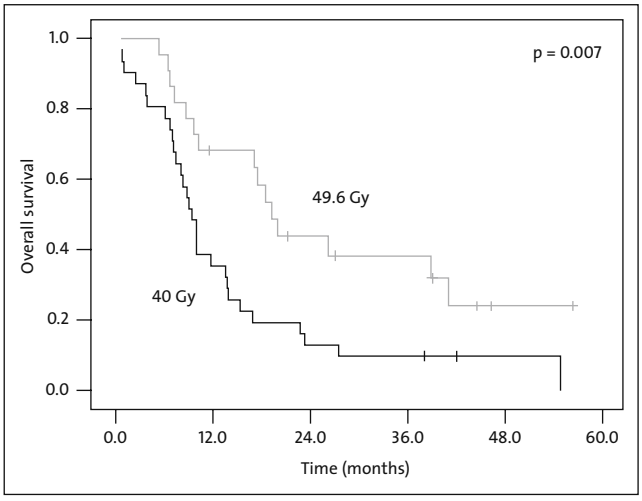


Figure 2. Kaplan-Meier curves indicating overall survival stratified by reirradiation dose. The p-value has been determined by log-rank test.

Abbildung 2. Kaplan-Meier-Kurven für das Gesamtüberleben, stratifiziert nach der Bestrahlungsdosis (Log-Rank-Test).

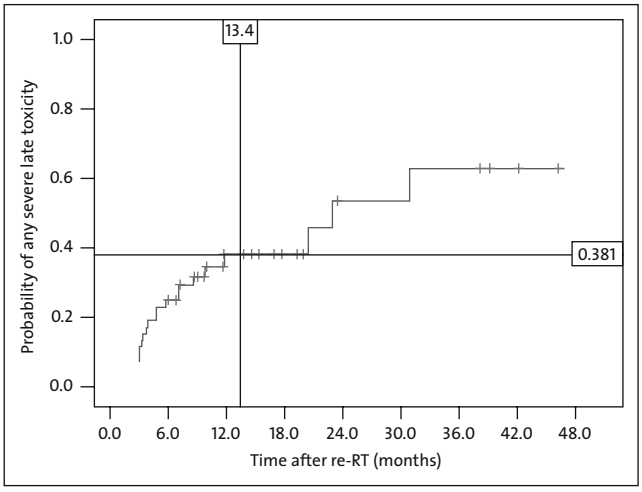


Figure 3. Kaplan-Meier curve indicating the probability of grade 3/4 late toxicities. Severe consequential late effects have been scored to become manifest 3 months after reirradiaton (re-RT).

Abbildung 3. Kaplan-Meier-Kurve für die Wahrscheinlichkeit einer Grad-3/4-Spättoxizität (für konsekutive Spättoxizitäten wurde eine Erstmanifestation nach 3 Monaten angenommen).

Discussion

With 1- and 2-year OS estimates of 52% and 24%, respectively, the follow-up analysis of this treatment protocol has reconfirmed its therapeutic efficacy. Compared to our first report [6], tumor control and survival estimates have been further improved; accordingly, an intercohort comparison showed significantly better OS estimates for patients of the second cohort. Among all covariates, the re-RT dose was the only statistically significant differing factor between the two cohorts ($p < 0.001$). The impact of the re-RT dose is corroborated by contemporary reviews indicating a re-RT dose-response relationship in chemoreirradiation for recurrent HNSCC [12, 18, 22].

Concomitant chemoradiation generally yields better results than a sequential course in primary treatment of HNSCC [5, 19]. In analogy, for relapsing HNSCC chemoreirradiation has been routinely performed concomitantly [3, 4, 11, 15, 17, 18, 20]. However, the concurrent application of both modalities tends to be limited by toxicity rendering periodic treatment breaks and/or hematologic support strategies necessary. To overcome this problem, alternating chemotherapy and RT has been used successfully in primary treatment of HNSCC [14]. In 1997, we introduced this concept for chemoreirradiation of recurrent HNSCC. The alternation of treatment modalities allowed for the full dosage of chemotherapy while re-RT doses were kept on a moderate level. Considering the

Table 3. Acute and late treatment-related toxicity. G-CSF: granulocyte colony-stimulating factor; RBC: red blood cells; RT: radiotherapy.

Tabelle 3. Behandlungsassoziierte Akut- und Spättoxizitäten. G-CSF: Granulozyten-koloniestimulierender Faktor; RBC: Erythrozyten; RT: Radiotherapie.

	First cohort	Second cohort	Entire collective
Acute toxicity [n (%)]	n = 27	n = 30	n = 57
Hematologic			
None	15 (56)	18 (60)	33 (58)
Leucopenia grade 3/4	11 (41)	11 (37)	22 (39)
• G-CSF administration	3 (11)	3 (10)	6 (11)
Anemia grade 3/4	3 (11)	1 (3)	4 (7)
• Packed RBC transfusion (anemia grade 2–4)	9 (33)	6 (20)	15 (26)
• Erythropoietin administration	0	4 (13)	4 (7)
Nonhematologic			
None	18 (67)	19 (63)	37 (65)
Cardiovascular (arrhythmia/general) grade 5	0	2 (7)	2 (4)
Pharyngocutaneous fistula/bleeding grade 5	2 (7)	0	2 (4)
Tumor bleeding requiring surgery	0	1 (3)	1 (2)
Acute dysphagia			
• Preexisting feeding tube dependency[a]	19 (70)	21 (70)	40 (70)
• Mucositis requiring gastrostomy during re-RT [n/n at risk (%)]	2/8 (25)	2/9 (22)	4/17 (24)
Diarrhea grade 3	6 (22)	2 (7)	8 (14)
Lymphedema/swelling			
• Preexisting tracheostomy	9 (33)	13 (43)	22 (39)
• Acute edema requiring tracheostomy [n/n at risk (%)]	0/18	2/17 (12)	2/35 (6)
Colitis grade 4 requiring surgery	1 (4)	0	1 (2)
Late toxicity [n (%)]	n = 24	n = 28	n = 52
None	12 (50)	19 (68)	31 (60)
Chronic dysphagia			
• Long-term feeding tube dependency	21 (88)	22 (79)	43 (83)
– Preexisting feeding tube dependency[a]	18 (75)	19 (68)	37 (71)
– New feeding tube dependency since re-RT [n/n at risk (%)]	2/6 (33)	2/9 (22)	4 /15 (27)
– Chronic dysphagia requiring late gastrostomy [n/n at risk (%)]	1/6 (17)	1/9 (11)	2 /15 (18)
Fibrosis grade 3	7 (29)	6 (21)	13 (25)
Lymphedema grade 3	4 (17)	4 (14)	8 (15)
• Late tracheostomy due to edema/fibrosis [n/n at risk (%)]	1/15 (7)	1/13 (8)	2/28 (7)
Trismus grade 3	0	2 (7)	2 (4)
Late tumor bleeding requiring surgery	1 (4)	1 (4)	2 (4)
Late pharyngocutaneous fistula	0	1 (4)	1 (2)

[a]indicating patients who needed to supplement more than one half of their diet with gastrostomy tube feedings before re-RT

increased use of 5-FU in primary treatment, its standard administration was abandoned in favor of cisplatin and a taxane. For the first time, docetaxel was applied for chemoreirradiation; today, this substance is the best prospectively evaluated taxane in neoadjuvant and definitive treatment of HNSCC [2].

As with all institutional series, our study has some inherent limitations in terms of the small patient collective and potential biases in patient selection and treatment. This may limit the validity of survival data and prognostic factors derived by multivariate analysis. Although statistically limited, our analysis indicates a similar therapeutic efficacy of the present protocol compared to contemporary prospective series on concomitant chemoreirradiation. Apart from the RTOG studies mentioned above [11, 20], the largest patient collective treated concomitantly has been reviewed by a recent meta-analysis [18]. 115 patients had received a median re-RT dose of 64.8 Gy, and more than two thirds had undergone triple-agent concurrent chemotherapy. The median and 3-year OS were 11 months and 22%, respectively. Regarding the patient baseline characteristics, it is worthwhile to note that 43% were surgically resected before. Prior surgery has been shown to be predictive of survival by subgroup analyses [3, 18]. By contrast, the background of the present collective was rather unfavorable: all patients had unresectable disease and a large tumor burden (median PTV 294.0 ml, range, 51.0–863.0 ml). In our series, minor deviations from chemotherapy led to a low overall compliance to protocol (46%); although comparable to that reported by the RTOG 9911 study [11], this rate remains unsatisfactory and highlights the need for improvement of surveillance and support strategies.

It can generally be stated that chemoreirradiation for recurrent HNSCC is linked to substantial treatment-related morbidity and mortality [8, 10]. Concerning late toxicity, the overlapping of changes originating from previous therapeutic procedures with those induced secondarily hampers a reliable toxicity assessment [3, 12, 22]. In the present study, however, the reference to the patient number at risk has allowed for a detailed analysis. Correspondingly, up to 40% of our patients were documented to develop severe late soft-tissue complications (dysphagia, fibrosis, and chronic lymphedema). This incidence is higher

than reported in comparable series (10–30%) [11, 18, 20]; by contrast, however, the majority of those changes was scored to be grade 3, and there were only few life-threatening late complications. On the basis of current toxicity data [3, 11, 12, 18, 20, 22], one might argue that the risks of re-RT outweigh the survival benefit compared to chemotherapy alone [5, 24]. As to functional deficits and quality of life, however, the uncontrolled locoregional tumor growth is likewise problematic. Thus, lacking a systematic assessment of functional aspects, the therapeutic ratio of chemoreirradiation has to be preestimated individually [27]. Future efforts should be aimed at the improvement of tolerability using IMRT [3, 12, 22], innovative re-RT delivery techniques such as helical tomotherapy [16, 21, 26], and optimized support strategies.

Conclusion

The escalation of re-RT doses has been shown to be effective characterizing this alternating chemoreirradiation concept as valuable alternative to split-course concomitant chemoreirradiation protocols.

References

1. Ayukawa F, Shibuya H, Yoshimura R, et al. Curative brachytherapy for recurrent/residual tongue cancer. Strahlenther Onkol 2007;183:133–7.
2. Bernier J, Vrieling C. Docetaxel in the management of patients with head and neck squamous cell carcinoma. Expert Rev Anticancer Ther 2008;8:1023–32.
3. Biagioli MC, Harvey M, Roman E, et al. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:1067–73.
4. De Crevoisier R, Bourhis J, Domenge C, et al. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. J Clin Oncol 1998;16:3556–62.
5. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med 2008;359:1143–54.
6. Hehr T, Classen J, Belka C, et al. Reirradiation alternating with docetaxel and cisplatin in inoperable recurrence of head-and-neck cancer: a prospective phase I/II trial. Int J Radiat Oncol Biol Phys 2005;61:1423–31.
7. Jereczek-Fossa BA, Kowalczyk A, D'Onofrio A, et al. Three-dimensional conformal or stereotactic reirradiation of recurrent, metastatic or new primary tumors. Analysis of 108 patients. Strahlenther Onkol 2008;184:36–40.
8. Kasperts N, Slotman B, Leemans CR, Langendijk JA. A review on re-irradiation for recurrent and second primary head and neck cancer. Oral Oncol 2005;41:225–43.
9. Kolotas C, Tselis N, Sommerlad M, et al. Reirradiation for recurrent neck metastases of head-and-neck tumors using CT-guided interstitial ^{192}Ir HDR brachytherapy. Strahlenther Onkol 2007;183:69–75.
10. Langendijk JA, Bourhis J. Reirradiation in squamous cell head and neck cancer: recent developments and future directions. Curr Opin Oncol 2007;19:202–9.
11. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol 2007;25:4800–5.
12. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;68:731–40.
13. Looney WB, Hopkins HA. Rationale for different chemotherapeutic and radiation therapy strategies in cancer management. Cancer 1991;67:1471–83.
14. Merlano M, Benasso M, Corvò R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. J Natl Cancer Inst 1996;88:583–9.
15. Milano MT, Vokes EE, Salama JK, et al. Twice-daily reirradiation for recurrent and second primary head-and-neck cancer with gemcitabine, paclitaxel, and 5-fluorouracil chemotherapy. Int J Radiat Oncol Biol Phys 2005;61:1096–106.
16. Rades D, Stoehr M, Meyners T, et al. Evaluation of prognostic factors and two radiation techniques in patients treated with surgery followed by radio(chemo)therapy or definitive radio(chemo)therapy for locally advanced head-and-neck cancer. Strahlenther Onkol 2008;184:198–205.
17. Salama JK, Haraf DJ, Stenson K, et al. Phase I study of concomitant chemoradiotherapy with irinotecan, 5-FU, and hydroxyurea for patients with advanced and/or recurrent head and neck cancer. Cancer J 2005;11:140–6.
18. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2006;64:382–91.
19. Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat Clin Pract Oncol 2007;4:156–71.
20. Spencer SA, Harris J, Wheeler RH, et al. RTOG 9610: reirradiation with concurrent hydroxyurea and 5-fluorouracil in patients with squamous cell cancer of the head and neck. Int J Radiat Oncol Biol Phys 2001;51:1299–304.
21. Sterzing F, Schubert K, Sroka-Perez G, et al. Helical tomotherapy. Experiences of the first 150 patients in Heidelberg. Strahlenther Onkol 2008;184:8–14.
22. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer – disease control and morbidity outcomes. Int J Radiat Oncol Biol Phys 2009;73:399–409.
23. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
24. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
25. Vokes EE, Panje WR, Schilsky RL, et al. Hydroxyurea, fluorouracil, and concomitant radiotherapy in poor-prognosis head and neck cancer: a phase I–II study. J Clin Oncol 1989;7:761–8.
26. Voordeckers M, Everaert H, Tournel K, et al. Longitudinal assessment of parotid function in patients receiving tomotherapy for head-and-neck cancer. Strahlenther Onkol 2008;184:400–5.
27. Wong SJ, Machtay M, Li Y. Locally recurrent, previously irradiated head and neck cancer: concurrent re-irradiation and chemotherapy, or chemotherapy alone? J Clin Oncol 2006;24:2653–8.

Address for Correspondence
Dr. Bernhard Berger
Department of Radiation Oncology
University of Tübingen
Hoppe-Seyler-Straße 3
72076 Tübingen
Germany
Phone (+49/7071) 29-85960, Fax -5324
e-mail: Bernhard.Berger@med.uni-tuebingen.de