Cisplatin Versus Carboplatin and Paclitaxel in Radiochemotherapy for Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract. *Background/Aim:* The implementation of a platinum-containing regimen is recommended for definitive and adjuvant therapy of patients with locally advanced head and neck tumour. We compared the conditions for the use of cisplatin or carboplatin/paclitaxel or for changing between these two regimens on a clinic-specific basis. *Patients and Methods:* We evaluated 150 patients with advanced head and neck squamous cell carcinoma who received simultaneous radiochemotherapy at our institution between 2012 and 2017. Chemotherapy with weekly doses of cisplatin (40 mg/m², group 1) or, in cases of impaired renal and/or cardiac function, with weekly doses of carboplatin AUC2 and paclitaxel (45 mg/m², group 2), was performed as a first-choice therapy. If toxicities occurred in group 1, treatment was switched to the carboplatin/paclitaxel regimen (group 3). *Patient- and therapy-related parameters, toxicity and survival data were compared across groups. Results:* We examined 99, 30, and 21 patients in each group who received at least 1 course of chemotherapy. Group 3 patients switched from cisplatin to carboplatin/paclitaxel after a median of 3 courses due to nephrotoxicity (95.2%). The target of at least 5 chemotherapy courses was most frequently achieved by patients in group 1 (69.7%), followed by group 3 (61.9%) and then group 2 (40.0%). Multivariate analysis revealed that patients who switched groups were more likely to be over 60 years old ($p=0.021$), undergo definitive

radiochemotherapy ($p=0.049$) and develop higher nephrotoxicity ($p=0.036$) than group 1 patients. Outcomes did not differ between groups. *Conclusion:* When cisplatin application is contraindicated due to renal- or cardio-toxicity, carboplatin/paclitaxel is an appropriate option.

In definitive and adjuvant radiochemotherapy (RCT) of locally advanced head and neck tumour patients, different chemotherapy (CTx) regimens are applied depending on specific clinical criteria. The guideline recommendation foresees the utilization of a platinum-containing regimen (1, 2), with cisplatin being the most commonly advocated and used at a cumulative dose of at least 200 mg/m² (3, 4). At our institution, we prefer weekly administration of cisplatin 40 mg/m² body surface area (BSA) (5). We observed an increased incidence of renal toxicity following administration of cisplatin, as did other studies (6, 7). Some patients have initially high renal parameters or cardiac comorbidities, disqualifying them for cisplatin use. In these circumstances, a carboplatin-based regimen is administered (8, 9). Carboplatin, with its radiosensitizing properties and lower renal effect than cisplatin, qualifies under National Comprehensive Cancer Network (NCCN) guidelines as an effective alternative for patients for whom cisplatin is not appropriate. Phase II trials of carboplatin-oriented concurrent RCTs have shown complete response rates of 65.0%-70.0%, similar to those seen with cisplatin. Noronha *et al.* concluded that a carboplatin-based RCT is well tolerated by patients who are ineligible for cisplatin and appears to provide superior outcomes than those reported in trials of radiotherapy (RT) alone (10). A combination of carboplatin and paclitaxel has previously been described in the context of head and neck tumours (11-13). In addition, carboplatin acts as a radiosensitizer in other entities, often in conjunction with paclitaxel, as exemplified in the setting of CTx for oesophageal (14, 15) and lung cancer (16). In many cases, initial therapy with cisplatin is accompanied by the occurrence

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of renal toxicity, so changing the cytostatic agent to carboplatin allows for continued chemotherapeutic treatment.

The overall objective of this study was to compare the conditions for using cisplatin or carboplatin/paclitaxel or for changing between the two regimens in a clinic-specific manner. Therefore, we analysed the survival parameters of the two cytostatic regimens, cisplatin *vs.* carboplatin/paclitaxel, and their application criteria. Finally, we examined whether a direct correlation exists between renal toxicity or the Charlson Comorbidity Index (CCI) and cytostatic regimen change.

Patients and Methods

Patients and treatment. For our retrospective observational study comparing cisplatin and carboplatin/paclitaxel, data were collected from patients who underwent simultaneous RCT as part of the multimodal treatment of advanced head and neck squamous cell carcinoma at our institution between May 2012 and December 2017. Patient-related demographical and treatment data were gathered from records and analysed for each group separately as well as for all patients as a whole group. The procedure was performed according to the guidelines of the Ethics Committee and the Data Protection Department of the same institution (Ethics Application Number: 9250_BO_K_2020).

In the case of pre-RCT surgery, resection status (R X/0 *vs.* R 1/2) and time interval between surgery and RT (≤ 6 weeks *vs.* > 6 weeks) were recorded. By default, our RT concept involves the use of intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) with simultaneous integrated boost (SIB) as image-guided radiotherapy (IGRT). In the frame of definitive therapy, doses of 66 (2.2) Gy to the primary tumour, 60 (2.0) Gy to pathologic lymph nodes, and 54 (1.8) Gy to the corresponding lymph node area are common, with the first number representing the total dose and the number in parentheses representing the single dose. However, in adjuvant therapy, 62.4 (2.08) Gy to the tumour region and 54 (1.8) Gy to the corresponding lymph node area are typically applied. Adjuvant radiochemotherapy was indicated for R1 resection or extracapsular extension (ECE), otherwise for large tumours (T4, N3) and optionally at the patient's request. In case of lymph node involvement without ECE, adjuvant radiotherapy represented the treatment of choice. For parallel group comparisons, our patients were divided into 3 groups as follows: patients in group 1 were treated exclusively with cisplatin, with a weekly administration of 40 mg/m² BSA; in group 2, carboplatin AUC2+paclitaxel (45 mg/m² BSA) was initially preferred for treatment due to comorbidities. Group 3 consisted of patients who started with cisplatin and switched to carboplatin/paclitaxel during the course of therapy because of toxicity. We aimed for at least 5 (adjuvant treatment) to 6 (definitive treatment) CTx courses for optimal outcomes. To calculate whether or to what extent the target total dose was achieved, we assumed 5 as the intended number of courses. Only patients with squamous cell carcinoma of the head and neck were included; prior CTx or RT to the head and neck area were exclusion criteria.

CCI was determined with and without taking age into account. In the first step, points are summed for each patient according to their comorbidities (*e.g.*, heart attack, myocardial infarction), with a small score corresponding to a low comorbidity burden and vice

versa (17-20). In addition, points are assigned to different age ranges and can be added to the comorbidity score, thus forming the Age-Adjusted Charlson Comorbidity Index (ACCI) (21-23). The age span of our patients was 33 to 86 years. Panendoscopy, computer tomography of the head and neck as well as bone scan, chest X-ray and ultrasound of the neck nodes and abdomen were all parts of the staging process (24, 25). Tumour stage was determined with the aid of the TNM Classification of Malignant Tumours according to the Union Internationale Contre Le Cancer (UICC) (26). If the date of the initial diagnosis was before January 3, 2017, the 7th edition was utilized; thereafter, the 8th edition was applied. Tumours occupying more than one location were categorized as multilevel tumours.

Toxicity. For nephrotoxicity and haematotoxicity, the nadir values of parameters such as creatinine, leukocytes, haemoglobin and platelets were noted. For toxicity classification, we deliberately chose to apply CTCAE versions 3 and 5, as each categorizes nephrotoxicity and haematotoxicity in its own way consistent with our needs. For haematotoxicity, CTCAE version 3 (27) was followed with separate determinations of leukocytes, platelets and haemoglobin to identify the main cause of haematotoxicity; subsequently, the highest of these three detected grades was adopted as the overall haematotoxicity grade. For one analysis, the occurrence and non-occurrence of haematotoxicity was distinguished (grade 0 *vs.* grade 1-4), and for the other, differentiation was made between grade 1/2 and grade 3/4. To determine the degree of renal toxicity, CTCAE version 5 was consulted, more precisely the sub-item "Investigations." For creatinine levels, toxicity grade assignment was guided by the following normal value limits: for men 59-104 $\mu\text{mol/l}$, for women 45-48 $\mu\text{mol/l}$. Considering male patients, grade 1 corresponded to a creatinine value between 105 and 156 $\mu\text{mol/l}$, whereas grade 2 corresponded to a creatinine value between 157 and 312 $\mu\text{mol/l}$; however, in women, grade 1 was defined by a creatinine value between 85 and 126 $\mu\text{mol/l}$, while grade 2 was between 127 and 252 $\mu\text{mol/l}$. Assessment of renal toxicity distinguished between grade 0 (normal values) and grades 1 or 2.

Ethics approval. This study is compliant with the ethical standards of the committees on human experimentation (institutional and national) and with the Declaration of Helsinki. It was carried out according to the guidelines of the Ethics Committee and the Data Protection Department of the Hannover Medical School (Ethics Application Number: 9250_BO_K_2020). All patients gave their informed consent before participating in the study.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics Version 27. The date of the first therapy day and the last contact or death served as references for calculating follow-up time. Due to small sample sizes, the two-tailed Fisher's exact test (28) was applied to compare patient characteristics plus RCT and toxicity data between groups 1 and 2 and groups 1 and 3. The null hypothesis is that no relationship exists between expected and observed frequencies. The influence of individual factors on the change in cytostatic agents was investigated by means of univariate logistic regression, in which odds ratios were given with a confidence interval of 95%. The independent variables were then compared using multivariate logistic regression. During this process, all parameters not showing a significant correlation with cytostatic

drug change were successively removed from the analysis through backward elimination beginning with the highest p -value. To compare groups 1 and 2 for 3-year survival, binary logistic regression was utilized. Finally, the two-tailed Fisher's exact test was also applied for recurrence and metastasis rates as well as for toxicity comparing each group with the other two. Survival rates were depicted using Kaplan-Meier curves. Overall survival (OS), progression-free survival (PFS) and locoregional control (LRC) were investigated in the different therapy groups, with two of the three groups examined per analysis run. Due to the study's retrospective nature, no distinction could be drawn between tumour- and nontumour-related deaths.

Results

Patient characteristics. As shown in Table I, we enrolled a total of 150 patients who received at least 1 course of CTx in group 1/2/3 with $n=99/30/21$. ACCI scores were higher in groups 2 and 3 than in group 1: almost half of the cisplatin patients, 49 (49.5%), scored <4 , whereas more patients in groups 2 and 3 achieved an ACCI score ≥ 4 , namely, 26 of the carboplatin/paclitaxel (86.7%) and 17 of the regimen change patients (81.0%).

Number of chemotherapy courses and reasons for change or cancellation. The target of at least 5 courses of CTx was achieved most often in group 1 (69.7%) but only by 40.0% in group 2 and 61.9% in the regimen change group. Two of the 99 cisplatin (2.0%) and one of the 30 group 2 patients (3.3%) received only one CTx course – in the latter case because of paclitaxel allergy and in the other two cases at patient request. Overall, 20 patients underwent dose reduction, most of whom were cisplatin patients (Table II). In the majority of cases, the dose was reduced from the 5th course onward due to deteriorated blood values, with 50.0% being the most frequent reduction. Ninety-five percent of patients in group 3 switched regimens as a result of worsened renal parameters.

In univariate analysis, we compared group 1 patients who were continuously treated with cisplatin and group 3 patients who started therapy with cisplatin and subsequently changed to carboplatin/paclitaxel. Such switching, as observed in group 3, was associated with an age of over 60 ($p=0.006$), an ACCI ≥ 4 ($p=0.016$), definitive therapy ($p=0.020$) and nephrotoxicity level 1/2 ($p=0.001$). Multivariate analysis revealed that patients who changed the cytostatic drug were more likely to be over 60 years old ($p=0.021$), undergo definitive therapy ($p=0.049$) and develop a nephrotoxicity grade 1/2 ($p=0.036$) than patients treated with cisplatin only when all other variables were held constant. Elevating the significance level from $p<0.050$ to $p<0.100$ produced the same significance. The results of univariate and multivariate analysis for the comparison of the cisplatin and change groups are summarized in Table III.

Toxicity. Patients treated exclusively with cisplatin (Group 1) were comparatively least likely to reach CTCAE haematotoxicity grade 3/4, with 19 patients (19.2%). In Group 2 and Group 3 14 patients (46.7%) and 8 patients (38.1%), respectively, developed haematotoxicity grade 3/4. Regarding nephrotoxicity, group 1 had two patients (2.0%) that achieved a CTCAE grade 2 toxicity level in the nadir compared with one patient in group 2 (3.3%) and two patients in group 3 (9.5%). Finally, none of the patients showed nephrotoxicity levels of 3/4.

Fisher's exact tests showed a difference in the occurrence of nephrotoxicity grade 1/2 ($p=0.011$), haematotoxicity grade 1-4 ($p=0.015$) or grade 3/4 ($p=0.003$) between the cisplatin arm and the other arms. Furthermore, a dependence was observed between group 2 and the occurrence of grade 3/4 haematotoxicity ($p=0.012$). Compared to groups 1 and 2, the regimen change group displayed a dependence on the incidence of nephrotoxicity grade 1/2 ($p=0.003$). All results of Fisher's exact tests are summarized in Table IV. Beyond switching to carboplatin/paclitaxel, cisplatin-induced toxicity did not lead to relevantly stronger pronounced treatment discontinuation or dose reduction in group 1 patients compared to the other two groups, yet the carboplatin/paclitaxel-only patients accomplished fewer chemotherapy courses compared with the cisplatin-only patients. The change group contained too few patients for statistical analysis, but the majority completed 5 courses or more, as shown in Table II.

Survival. Median follow-up was 41 months for patients in all groups, specifically, 42 in group 1, 41 in group 2 and 36 in group 3. During the follow-up period, a total of 47 patients died, of whom 17 experienced progression of their cancer after therapy termination. No significant difference in OS, PFS or LRC was found among the groups (Figure 1, Figure 2, and Figure 3). Also, a separate evaluation of patients with definitive or adjuvant therapy did not reveal any significant differences in terms of OS, PFS, and LRC when comparing the different groups with each other.

The Kaplan-Meier evaluations demonstrated 3-year OS rates of 73.3% in the cisplatin Group 1, 56.3% in Group 2 and 77.4% in the Change Group. Additionally, 3-year PFS rates of 72.6% in cisplatin patients, 68.9% in group 2 and 81.6% in regimen change patients were observed. The 3-year LRC rates were 83.1% in the cisplatin group compared to 88.3% in Group 2 and 88.7% in the Change Group. The comparison of 3-year survival between the cisplatin and carboplatin/paclitaxel groups in multivariate logistic regression showed no significant difference.

Discussion

This retrospective study compared the preconditions and criteria for using cisplatin or carboplatin/paclitaxel or

Table I. Patient characteristics.

Categories	Total Number	Cisplatin Group 1 n (%)	Carboplatin/ Paclitaxel Group 2 n (%)	Regimen Change Group 3 n (%)	Fisher's Exact <i>p</i> -Value	
					Group 1 vs. Group 2	Group 1 vs. Group 3
Number of patients	n=150	99	30	21		
Age (years)					≤60 vs. >60	
≤60	n=70	58 (58.6)	7 (23.3)	5 (23.8)	0.001	0.007
>60	n=80	41 (41.4)	23 (76.7)	16 (76.2)		
Gender					Female vs. Male	
Female	n=39	27 (27.3)	8 (26.7)	4 (19.0)	1.000	0.586
Male	n=111	72 (72.7)	22 (73.3)	17 (81.0)		
Tumour category					T 0/1/2 vs. T 3/4	
T 0	n=13	9 (9.2)	2 (6.7)	2 (9.5)	0.010	0.327
T 1/2	n=40	33 (33.7)	3 (10.0)	4 (19.0)		
T 3/4	n=96	56 (57.1)	25 (83.3)	15 (71.4)		
Lymph nodes category					N 0/1 vs. N 2/3	
N 0/1	n=45	33 (33.7)	7 (23.3)	5 (23.8)	0.370	0.448
N 2/3	n=104	65 (66.3)	23 (76.7)	16 (76.2)		
Metastases category						
M 0	n=147	98 (100.0)	29 (96.7)	20 (95.2)		
M 1	n=2*	0 (0.0)	1 (3.3)	1 (4.8)		
UICC stage					Stage III vs. Stage IV	
Stage I/II	n=3	2 (2.0)	0 (0.0)	1 (4.8)	1.000	0.193
Stage III	n=23	17 (17.3)	5 (16.7)	1 (4.8)		
Stage IV	n=123	79 (80.6)	25 (83.3)	19 (90.5)		
Tumour site					Multilevel tumour	
Lip, oral cavity	n=34	28 (28.3)	3 (10.0)	3 (14.3)	Yes vs. No	
Oropharynx	n=40	27 (27.3)	9 (30.0)	4 (19.0)	0.240	0.762
Hypopharynx	n=18	6 (6.1)	8 (26.7)	4 (19.0)		
Nasopharynx	n=3	1 (1.0)	0 (0.0)	2 (9.5)		
Larynx	n=18	11 (11.1)	5 (16.7)	2 (9.5)		
Nose, paranasal sinuses	n=1	1 (1.0)	0 (0.0)	0 (0.0)		
Large salivary glands	n=3	2 (2.0)	1 (3.3)	0 (0.0)		
CUP, lymph node metastasis	n=10	6 (6.1)	2 (6.7)	2 (9.5)		
Multilevel tumour	n=23	17 (17.2)	2 (6.7)	4 (19.0)		
Treated tumour is a recurrence					Yes vs. No	
Yes	n=23	18 (18.2)	4 (13.3)	1 (4.8)	0.782	0.190
No	n=127	81 (81.8)	26 (86.7)	20 (95.2)		
CCI						
2	n=104	76 (76.8)	13 (43.3)	15 (71.4)		
3	n=22	15 (15.2)	5 (16.7)	2 (9.5)		
4	n=16	6 (6.1)	7 (23.3)	3 (14.3)		
≥5	n=8	2 (2.0)	5 (16.7)	1 (4.8)		
ACCI						
2	n=17	16 (16.2)	0 (0.0)	1 (4.8)		
3	n=40	33 (33.3)	4 (13.3)	3 (14.3)		
4	n=43	25 (25.3)	6 (20.0)	12 (57.1)		
5	n=22	16 (16.2)	5 (16.7)	1 (4.8)		
6	n=15	7 (7.1)	6 (20.0)	2 (9.5)		
≥7	n=13	2 (2.0)	9 (30.0)	2 (9.5)		
ACCI, Dichotomized					<4 vs. ≥4	
<4	n=57	49 (49.5)	4 (13.3)	4 (19.0)	0.000	0.015
≥4	n=93	50 (50.5)	26 (86.7)	17 (81.0)		
Follow-up median [Range (months)]	41 (1-97)	42 (1-97)	41 (4-74)	36 (5-81)		

*Solitary pulmonary metastasis, questionable or excision performed. CCI: Charlson Comorbidity Index; ACCI: age-adjusted Charlson Comorbidity Index; UICC: Union Internationale Contre le Cancer. Bold *p*-Values indicate statistical significance.

Table II. Radiochemotherapy characteristics and toxicities.

Categories	Total Number	Cisplatin Group 1 n (%)	Carboplatin/ Paclitaxel Group 2 n (%)	Regimen Change Group 3 n (%)	Fisher's Exact p-Value	
					Group 1 vs. Group 2	Group 1 vs. Group 3
Therapy category					Definitive vs. Adjuvant	
Definitive	n=79	42 (42.4)	22 (73.3)	15 (71.4)	0.004	0.018
Adjuvant	n=71	57 (57.6)	8 (26.7)	6 (28.6)		
Extent of resection					R X/0 vs. R 1/2	
R X/0	n=51	41 (78.8)	6 (75.0)	4 (66.7)	1.000	0.608
R 1/2	n=15	11 (21.2)	2 (25.0)	2 (33.3)		
Interval surgery to radiotherapy					≤6 Weeks vs. >6 Weeks	
≤6 Weeks	n=11	7 (12.3)	1 (12.5)	3 (50.0)	1.000	0.048
>6 Weeks	n=60	50 (87.7)	7 (87.5)	3 (50.0)		
Neck dissection before radiotherapy					Yes vs. No	
Yes	n=66	51 (51.5)	9 (30.0)	6 (28.6)	0.059	0.091
No	n=84	48 (48.5)	21 (70.0)	15 (71.4)		
Boost modality						
SIB	n=141	93 (94.9)	28 (100.0)	20 (100.0)		
Sequential boost	n=2	2 (2.0)	0 (0.0)	0 (0.0)		
SIB and sequential Boost	n=3	3 (3.1)	0 (0.0)	0 (0.0)		
RTT median [Range (days)]	43 (9-73)	42 (9-73)	43 (36-53)	43 (39-50)		
RTT >49 Days					Yes vs. No	
Yes	n=11	6 (6.1)	4 (13.3)	1 (4.8)	0.280	1.000
No	n=139	93 (93.9)	26 (86.7)	20 (95.2)		
Total number of chemotherapy courses					<5 vs. ≥5	
1	n=3	2 (2.0)	1 (3.3)	0 (0.0)	0.001	0.157
2	n=4	1 (1.0)	3 (10.0)	0 (0.0)		
3	n=9	4 (4.0)	4 (13.3)	1 (4.8)		
4	n=29	14 (14.1)	8 (26.7)	7 (33.3)		
5	n=81	59 (59.6)	11 (36.7)	11 (52.4)		
6	n=24	19 (19.2)	3 (10.0)	2 (9.5)		
Chemotherapy dose reduction					Yes vs. No	
Yes	n=20	15 (15.2)	3 (10.0)	2 (9.5)	0.564	0.734
No	n=130	84 (84.8)	27 (90.0)	19 (90.5)		
Ordinal number of first dose-reduced course						
3	n=1	0 (0.0)	1 (33.3)	0 (0.0)		
4	n=5	3 (20.0)	0 (0.0)	2 (100.0)		
5	n=11	9 (60.0)	2 (66.7)	0 (0.0)		
6	n=3	3 (20.0)	0 (0.0)	0 (0.0)		
Achieved portion of the target total dose						
20-39%	n=3	2 (2.0)	1 (3.3)	0 (0.0)		
40-59%	n=5	1 (1.0)	4 (13.3)	0 (0.0)		
60-79%	n=12	7 (7.1)	3 (10.0)	2 (9.5)		
80-99%	n=36	20 (20.2)	10 (33.3)	6 (28.6)		
100-119%	n=74	53 (53.5)	9 (30.0)	12 (57.1)		
120%	n=20	16 (16.2)	3 (10.0)	1 (4.8)		
Completion or exceeding of the target total dose					Yes vs. No	
Yes	n=94	69 (69.7)	12 (40.0)	13 (61.9)	0.005	0.606
No	n=56	30 (30.3)	18 (60.0)	8 (38.1)		
CTCAE grading for increased creatinine					Grade 0 vs. Grade 1/2	
Grade 0	n=124	88 (88.9)	24 (80.0)	12 (57.1)	0.225	0.001
Grade 1	n=21	9 (9.1)	5 (16.7)	7 (33.3)		
Grade 2	n=5	2 (2.0)	1 (3.3)	2 (9.5)		
CTCAE haematotoxicity grading					Grade 0/1/2 vs. Grade 3/4	
Grade 0	n=28	24 (24.2)	3 (10.0)	1 (4.8)	0.004	0.083
Grade 1/2	n=81	56 (56.6)	13 (43.3)	12 (57.1)		
Grade 3/4	n=41	19 (19.2)	14 (46.7)	8 (38.1)		
Cause of haematotoxicity grade 3/4						
Leukocytes (Leuc)	n=22	10 (52.6)	8 (57.1)	4 (50.0)		
Haemoglobin (Hb)	n=8	3 (15.8)	4 (28.6)	1 (12.5)		
Thrombocytes (Throm)	n=0	0 (0.0)	0 (0.0)	0 (0.0)		
Combination of Leuc, Hb, Throm	n=11	6 (31.6)	2 (14.3)	3 (37.5)		

SIB: Simultaneous integrated boost; RTT: radiation treatment time; CTCAE: Common Terminology Criteria for Adverse Events. Bold *p*-Values indicate statistical significance.

Table III. (Significant) Influencing factors that led to a change from cisplatin to carboplatin/paclitaxel evaluated in univariate and multivariate logistic regression.

Categories	Regimen change		Exponent (B) Odds Ratio	Confidence interval 95%		<i>p</i> -Value
	Yes n=21	No n=99		Lowest Value	Highest Value	
Univariate logistic regression						
Age						
≤60 <i>vs.</i> >60 years			4.527	1.536	13.342	0.006
Gender						
Female <i>vs.</i> Male			0.627	0.194	2.033	0.437
UICC						
Stage III <i>vs.</i> Stage IV			4.089	0.512	32.663	0.184
Tumour category						
T 0/1/2 <i>vs.</i> T 3/4			1.875	0.671	5.241	0.231
Lymph nodes category						
N 0/1 <i>vs.</i> N 2/3			1.625	0.547	4.823	0.382
Multilevel tumour	17.5%	82.5%				
Yes <i>vs.</i> No			1.135	0.339	3.798	0.837
RCT of a recurrence						
Yes <i>vs.</i> No			0.225	0.028	1.787	0.158
ACCI						
<4 <i>vs.</i> ≥4			4.165	1.308	13.263	0.016
Therapy						
Definitive <i>vs.</i> adjuvant			0.295	0.106	0.823	0.020
Nephrotoxicity						
G 0 <i>vs.</i> G 1/2			6.000	2.063	17.451	0.001
Multivariate logistic regression						
Age						
≤60 <i>vs.</i> >60 years			3.886	1.230	12.276	0.021
Therapy						
Definitive <i>vs.</i> adjuvant	17.5%	82.5%	0.330	0.109	0.997	0.049
Nephrotoxicity						
G 0 <i>vs.</i> G 1/2			3.574	1.085	11.775	0.036

UICC: Union Internationale Contre le Cancer; RCT: radiochemotherapy; ACCI: Age-Adjusted Charlson Comorbidity Index. Bold *p*-Values indicate statistical significance.

Table IV. *p*-Values based on Fisher's exact tests comparing toxicity and outcome parameters in each group versus the two other groups.

Categories		Cisplatin Group 1	Carboplatin/Paclitaxel Group 2	Regimen change Group 3
Nephrotoxicity	G 0 vs. G 1/2	0.011	0.787	0.003
Haematotoxicity	G 0 vs. G 1-4	0.015	0.202	0.127
Haematotoxicity	G 0/1/2 vs. G 3/4	0.003	0.012	0.291
RTT >49 days	Yes vs. No	0.511	0.231	1.000
Recurrence after RCT	Yes vs. No	0.302	0.529	1.000
Metastases after RCT	Yes vs. No	0.803	1.000	0.741

RTT: Radiation treatment time; RCT: radiochemotherapy. Bold *p*-Values indicate statistical significance.

changing between both regimens in definitive or adjuvant RCTs in locally advanced squamous cell head and neck cancer and evaluated toxicity and outcome parameters. The results demonstrated that cisplatin application led to CTx continuation and achievement of the target number of 5

courses more frequently than carboplatin/paclitaxel. Group 2 patients exhibited the most severe comorbidities; therefore, carboplatin/paclitaxel was administered from the start of therapy. In addition, haematotoxicity was highest in patients receiving carboplatin/paclitaxel, and renal toxicity

Figure 1. Kaplan-Meier curves of overall survival for comparison between the cisplatin, carboplatin/paclitaxel, and regimen change group.

Figure 2. Kaplan-Meier curves of progression-free survival for comparison between the cisplatin, carboplatin/paclitaxel, and regimen change group.

was greatest in the Change Group, explaining the change in the cytostatic drug from cisplatin to carboplatin/paclitaxel during therapy. However, none of the three groups differed significantly in OS, PFS, or LRC, which may be attributable to our study's limiting factors, including its retrospective character and small group sizes. To date, few studies have compared the toxicity and outcome of CRT with cisplatin vs. carboplatin-based regimens in locally

advanced head and neck tumour patients. To our knowledge, this is the first study to show data from patients who switched from cisplatin to carboplatin/paclitaxel during the course of therapy.

Noronha *et al.* presented reasons for not using cisplatin, such as low creatinine clearance in 65.07% of cases, sensorineural hearing loss in 28.57%, uncontrolled comorbidities in 4.76% and advanced age in 1.60% of

Figure 3. Kaplan-Meier curves of locoregional control for comparison between the cisplatin, carboplatin/paclitaxel, and regimen change group.

patients. Sixteen of the 63 patients suffered from one or more of the following comorbidities: diabetes, hypertension, past cerebrovascular accident (CVA), asthma, and hepatitis B virus surface antigen (HBsAg) positivity (10). In contrast to our study, the work by Noronha *et al.* did not apply CCI to measure comorbidities, making it difficult to define which patients had more comorbidities. However, the reasons for not utilizing cisplatin confirm what we considered relevant.

Although not concerning head and neck cancer, a study by Birtle *et al.* evaluating the efficacy of systemic platinum-based CTx in patients with upper urinary tract urothelial carcinomas after nephroureterectomy with curative intent in a phase III trial caught our attention. In that study, 6 out of 76 patients changed from planned therapy with gemcitabine-cisplatin to gemcitabine-carboplatin before treatment began, and another 10 patients switched in the second cycle or later: 6 of these cases could be associated with a reduction in glomerular filtration rate (GFR), 2 with suspected renal failure, and 2 more with grade 3 toxicity manifested as joint pain or tinnitus (29). In the study of Chitapanarux *et al.*, leucocytopenia as well as anaemia and renal toxicity were predominant in the cisplatin group, while thrombocytopenia was predominant in the carboplatin group (9). In our cohort, both anaemia and leucocytopenia alone were more prevalent in patients receiving carboplatin/paclitaxel than in those receiving cisplatin. Thrombocytopenia, which always appeared in combination with anaemia and/or leucocytopenia, likewise occurred more frequently in the cisplatin group. Of note, both our analyses and those of Chitapanarux *et al.* indicated an association between cisplatin and renal toxicity that was absent in the

carboplatin/paclitaxel arm. Rades *et al.* also compared cisplatin and carboplatin monotherapy in adjuvant RCTs for locally advanced tumours of the oropharynx and oral cavity. While both regimens led to acute toxicities, including mucositis, nausea/vomiting, haematotoxicity, renal toxicity and skin toxicity, as well as late toxicities, such as xerostomia, neck fibrosis, lymphoedema and skin toxicity, differences between the cisplatin and carboplatin groups were not significant (30). In contrast, our findings reveal a significant association of renal toxicity of any degree with the cisplatin cohort and haematotoxicity with both the cisplatin and carboplatin/paclitaxel cohorts. Based on practical experience in our department, we advocate the use of carboplatin alone when paclitaxel administration is not possible, for example, in case of allergy. However, we do not have our own study results in this regard.

Regarding survival, a randomized study by Homma *et al.* involving 119 patients with squamous cell carcinoma of the head and neck who received weekly carboplatin 100 mg/m² or daily low-dose cisplatin 4 mg/m² each during the first 4 weeks of RT offers some insights. Their conclusion of favouring weekly carboplatin in the frame of concomitant RCT contrasts with those of our study supporting cisplatin as the preferable choice for adjuvant therapy. However, Homma *et al.* noted that the total applied cisplatin dose of 64 mg/m² may have been too low to be effective. They reported 5-year rates for LRC of 56.2% in the carboplatin group and 35.5% in the cisplatin group ($p < 0.05$), with no significant difference in 5-year OS rates, which were 71.4% in the carboplatin group and 66.0% in the cisplatin arm (31). In their work comparing cisplatin and carboplatin in adjuvant RCT for locally advanced tumours of

the oropharynx and oral cavity, Rades *et al.* also determined the 3-year rates for outcome parameters: LRC rates were 85.0% in the cisplatin and 62.0% in the carboplatin cohort ($p=0.004$), while those of OS reached 78.0% in the cisplatin and 51.0% in the carboplatin group ($p=0.001$) (30). Comparing their results with ours, neither LRC nor OS showed any significant differences between the two groups. Of note, the application of the cytostatic drug was not weekly as in our study, but rather consisted of two courses of cisplatin 20 mg/m² on days 1-5 and 29-33 or two courses of carboplatin AUC 1.5 on days 1-5 and 29-33 (30). In this context, it is worth considering another study by Rades *et al.* on definitive radiochemotherapy of locally advanced head and neck cancer, showing that weekly cisplatin 30-40 mg/m² was inferior to 3 courses of cisplatin 100 mg/m² on days 1, 22, and 43 in terms of OS and LRC (32). Yet a further recent 2019 study by Helfenstein *et al.* found that significantly more head and neck tumour patients achieved a cumulative cisplatin dose of ≥ 200 mg/m² in the setting of an RCT when treated with a 3-week regimen compared with weekly dosing. However, a cumulative cisplatin dose ≥ 200 mg/m² was not associated with improved outcome in this study (33). In a nasopharyngeal carcinoma study by Chitapanarux *et al.*, the 3-year OS rates were 77.7% in the cisplatin arm and 79.2% in the carboplatin arm ($p=0.9884$) (9). As in our study, no significance was found ($p=0.094$). However, another team set out to assess outcome parameters in patients with locally advanced nasopharyngeal carcinoma: Luttke *et al.* matched a standard group of 238 patients receiving standard RCT and an intervention group of 242 patients undergoing 3 cycles of induction CTx with gemcitabine and cisplatin followed by concomitant RCT with cisplatin in the IMRT technique. The result was a significantly better relapse-free survival at 3 years of 85.3% in the intervention arm compared with 76.5% in the standard arm. Moreover, improved 3-year OS was observed in the induction CTx group, with 94.6% vs. 90.3% in the standard group. However, the intervention group faced comparatively higher toxicities and side effects, mainly neutropaenia, thrombocytopaenia, anaemia, nausea and vomiting (34). Regarding paclitaxel as an alternative for patients who cannot tolerate standard platinum-based therapies, a recent study by Okada *et al.* is of great value, evaluating the safety and efficacy of the combination of paclitaxel and cetuximab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Overall response and disease control rates of 43% and 79%, respectively, were observed with first-line therapy, while rates of 20% and 90%, respectively, were achieved with second-line and later therapies. With a median PFS of 5.3 months and a median OS of 12.5 months, it was concluded that the aforementioned combination therapy may be appropriate. Adverse events such as neutropenia (grade 3/4) and anemia, which affected 8-13% of the patients studied, were all considered manageable (35). Another study by Sato *et al.*

was devoted to evaluating the efficacy of paclitaxel-based CTx in patients with head and neck cancer. They studied 12 patients who received CTx with paclitaxel before and 10 patients after nivolumab. Thereby it was found that paclitaxel-based CTx had a significantly better overall response rate (ORR) of 70% ($p=0.027$) and time to progression (TTP) of 7.4 months ($p=0.020$) after nivolumab compared with an ORR of 17% and TTP of 4.9 months before nivolumab (36). Regardless of whether cisplatin or carboplatin/paclitaxel was applied, one would expect the achievement of the targeted 5 courses to have a positive effect on survival. In contrast, we found, as did Steinmann *et al.* (5), that the number of courses was not critical. Nonetheless, other studies have found that a cumulative cisplatin dose ≥ 200 mg/m² resulted in a significantly better outcome than a cumulative dose of < 200 mg/m² (3, 4). A randomized trial by Chitapanarux *et al.* evaluated RCTs with cisplatin vs. carboplatin in the management of locally advanced nasopharyngeal carcinoma, treating 101 patients with cisplatin and 105 with carboplatin – in the case of adjuvant therapy combined with 5-fluorouracil. The results showed planned RCT completion in 59.0% of cases in the cisplatin group compared with 73.0% in the carboplatin group (9). In contrast to these findings, our study revealed that 69.7% of cisplatin and only 40.0% of carboplatin/paclitaxel patients finished the scheduled 5 CTx courses. A further trial by Dahlke *et al.* on treatment-related factors, such as total treatment time and radiotherapy time (RTT) in head and neck cancer patients, reported a median RTT of 40 days (37) – in our cohort, the median was 43 days, with 42 days in the cisplatin cohort and 43 days each in the carboplatin/paclitaxel and regimen change group. RT length (RT ≤ 49 days vs. RT > 49 days) was not significant in the univariate logistic regression examining factors affecting the cytostatic drug transition from cisplatin to carboplatin/paclitaxel. Likewise, no dependency was found between RT duration > 49 days and the three groups tested. In another trial, Chiang *et al.* investigated the prognostic impact of missed RT sessions in patients undergoing surgery for oral squamous cell carcinoma. As a result, they found 5-year OS to be 53.0%, 58.1% and 64.5% in the early missed RT, late missed RT and RT-as-planned groups, respectively ($p=0.046$). Early missed RT was independently associated with both poorer OS ($p=0.006$) and the occurrence of distant metastases ($p=0.031$) (38).

Speaking about the management of cancer in the elderly, there are different perspectives as to what is the most appropriate approach. For head and neck cancer patients, both radiotherapy alone (39) and combined radiochemotherapy (40) are feasible strategies. When it comes to esophageal cancer, radiochemotherapy in older patients resulted in outcomes comparable to those of younger patients (41-43). In elderly patients with non-small-cell lung carcinoma (NSCLC), combined radiochemotherapy even resulted in improved survival compared with radiotherapy alone (44, 45).

On all accounts, the indication for irradiation of elderly tumour patients should be made in dependence of general condition and comorbidities; age alone rarely is considered a contraindication for radiotherapy. Thus, also dose reduction, especially with regard to a curative approach, does not seem to be justified solely by reason of age (46).

Limitations. One of the limiting factors is our study's retrospective nature, which may bias our results, particularly in the context of selection bias. An additional constraint could be the follow-up time, which, with a median of 41 months, may still be too short to draw reliable conclusions on survival data. Furthermore, our analysed collective partly consists of small group sizes, especially regarding group 3.

However, another limitation we encountered was the CCI ignoring psychological parameters and diseases, making a holistic evaluation of comorbidities difficult. Nevertheless, the CCI served its most crucial purpose in our study, namely, to make comorbidities measurable and comparable in the three groups. The uneven distribution of age in the groups can also be listed within the limitations. However, the presence of elderly patients in groups 2 and 3 supports the fact that, according to our findings, an age of more than 60 years is significantly associated with a change of cytostatic drug from cisplatin to carboplatin/paclitaxel. In addition, HPV/p16 status was not yet regularly determined in the laboratory during the treatment period of our collective's individuals, and therefore could not be considered in patients with oropharyngeal carcinoma.

Conclusion

Although potentially leading to higher nephrotoxicity levels, cisplatin-oriented combined RCT remains the recommended treatment for definitive and adjuvant RCT of patients with locally advanced head and neck cancer. Even when combined with a switch to carboplatin/paclitaxel during the course of therapy, the use of cisplatin proves to be the superior choice by achieving 5 targeted CTx courses. In summary, therapy initiation with cisplatin is advised if the patient's general condition allows. Patients who change from cisplatin to carboplatin/paclitaxel do not suffer any survival disadvantage in comparison. However, treatment with carboplatin/paclitaxel offers a valid alternative for patients unfit for cisplatin, despite its association with haematotoxicity and a higher likelihood of noncompletion of planned CTx. Because of their retrospective nature, the results should be considered critically and confirmed in a prospective study.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

Authors' Contributions

All Authors contributed to the study conception and design. JW, SV, and HC were significantly involved in writing and revising the manuscript, while DoS played an essential role in the statistical analyses and their interpretation. DS supervised our work from the beginning and made seminal decisions in consultation with the team. All Authors read and approved the final manuscript.

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