# A Multicenter Evaluation of Different Chemotherapy Regimens in Older Adults With Head and Neck Squamous Cell Carcinoma Undergoing Definitive Chemoradiation

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Abstract: PURPOSE: The number of older adults with head-and-neck squamous cell carcinoma (HNSCC) is increasing, and treatment of these patients is challenging. Although cisplatin-based chemotherapy concomitantly with radiotherapy is considered standard regimen for patients with locoregionally advanced HNSCC, there is substantial real-world heterogeneity regarding concomitant chemotherapy in older HNSCC patients. METHODS: The XXX study is an international multicenter cohort study including older (≥65 years) HNSCC patients treated with definitive radiotherapy at 13 academic centers in the United States and Europe. Here, patients with concomitant chemoradiation were analyzed regarding overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier analyses, while Fine-Gray competing risks regressions were performed regarding the incidence of locoregional failures (LRFs) and distant metastases (DMs). RESULTS: Six hundred ninety-seven patients with a median age of 71 years were included in this analysis. Single-agent cisplatin was the most common chemotherapy regimen (n=310; 44%), followed by cisplatin plus 5-fluorouracil (n=137; 20%), carboplatin (n=73; 10%), and mitomycin c plus 5-fluorouracil (n=64; 9%). Carboplatin-based regimens were associated with diminished PFS (HR=1.39 [1.03-1.89], p<0.05) and a higher incidence of LRFs (SHR=1.54 [1.00-2.38], p=.05) compared with single-agent cisplatin, whereas OS (HR=1.15 [0.80-1.65], p=.46) was comparable. There were no oncological differences between single-agent and multi-agent cisplatin regimens (all p>.05). Median cumulative dose of cisplatin was 180 mg/m2 (IQR, 120-200 mg/m2). Cumulative cisplatin doses ≥200 mg/m2 were associated with increased OS (HR=0.71 [0.53-0.95], p=.02), PFS (HR=0.66 [0.51-0.87], p=.003), and lower incidence of LRFs (SHR=0.50 [0.31-0.80], p=.004). Higher cumulative cisplatin doses remained an independent prognostic variable in the multivariate regression analysis for OS (HR=0.996 [0.993-0.999], p=.009). CONCLUSIONS: Single-agent cisplatin can be considered as the standard chemotherapy regimen for older HNSCC patients who can tolerate cisplatin. Cumulative cisplatin doses are prognostically relevant also in older HNSCC patients.

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**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Abstract**

***Purpose***

The number of older adults with head-and-neck squamous cell carcinoma (HNSCC) is increasing, and treatment of these patients is challenging. Although cisplatin-based chemotherapy concomitantly with radiotherapy is considered standard regimen for patients with locoregionally advanced HNSCC, there is substantial real-world heterogeneity regarding concomitant chemotherapy in older HNSCC patients.

***Methods***

The XXX study is an international multicenter cohort study including older (≥65 years) HNSCC patients treated with definitive radiotherapy at 13 academic centers in the United States and Europe. Here, patients with concomitant chemoradiation were analyzed regarding overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier analyses, while Fine-Gray competing risks regressions were performed regarding the incidence of locoregional failures (LRFs) and distant metastases (DMs).

***Results***

Six hundred ninety-seven patients with a median age of 71 years were included in this analysis. Single-agent cisplatin was the most common chemotherapy regimen (n=310; 44%), followed by cisplatin plus 5-fluorouracil (n=137; 20%), carboplatin (n=73; 10%), and mitomycin c plus 5-fluorouracil (n=64; 9%). Carboplatin-based regimens were associated with diminished PFS (HR=1.39 [1.03-1.89], $p$<0.05) and a higher incidence of LRFs (SHR=1.54 [1.00-2.38], $p$=.05) compared with single-agent cisplatin, whereas OS (HR=1.15 [0.80-1.65], $p$=.46) was comparable. There were no oncological differences between single-agent and multi-agent cisplatin regimens (all $p$>.05). Median cumulative dose of cisplatin was 180 mg/m2 (IQR, 120-200 mg/m2). Cumulative cisplatin doses ≥200 mg/m2 were associated with increased OS (HR=0.71 [0.53-0.95], $p$=.02), PFS (HR=0.66 [0.51-0.87], $p$=.003), and

lower incidence of LRFs (SHR=0.50 [0.31-0.80], *p*=.004). Higher cumulative cisplatin doses remained an independent prognostic variable in the multivariate regression analysis for OS (HR=0.996 [0.993-0.999], *p*=.009).

***Conclusions***

Single-agent cisplatin can be considered as the standard chemotherapy regimen for older HNSCC patients who can tolerate cisplatin. Cumulative cisplatin doses are prognostically relevant also in older HNSCC patients.

***Trial Registration***

XXX

***Keywords***

Radiotherapy, chemotherapy, elderly, geriatric, cisplatin, carboplatin, mitomycin, head and neck cancer

## Introduction

Due to the demographic change, the proportion of older adults with head-and-neck squamous cell carcinoma (HNSCC) is estimated to increase in the following decades.[1] Surgical resection followed by risk-adapted adjuvant (chemo)radiation or definitive chemoradiation are the treatment standards for locoregionally advanced HNSCCs (LA-HNSCCs).[2,3] With underrepresentation of older HNSCC patients in clinical trials and several specific characteristics of this population (e.g., increased prevalence of comorbidities, higher vulnerability to treatment-related toxicities, differences in treatment goal prioritization) treatment of these patients is challenging.[4-6] There are particular controversies regarding the usage of concomitant chemotherapy in general, the choice of chemotherapeutic agents and dosage, and the management of patients with contraindications against cisplatin.[7]

Concomitant chemotherapy significantly improves survival in HNSCC patients compared with definitive radiotherapy alone, as reported in the MACH-NC meta-analysis; however, the survival benefit was found to be declining with higher patient age and to be absent in patients aged ≥70 years.[8] Large database analyses based on the Surveillance, Epidemiology, and End Results (SEER) registry, and the National Cancer Database (NCDB) reported conflicting results regarding the value of concomitant chemotherapy in older HNSCC patients.[9,10] A previous international multicenter cohort study reported a significant improvement of OS and PFS with the addition of concomitant chemotherapy in older adults with HNSCC even after adjusting for several potentially confounding variables, whereas there was no such benefit for the addition of concomitant cetuximab.[11]

Although both the NCCN and ESMO guidelines indicate concomitant high-dose cisplatin (100 mg/m2 at days 1, 22 and 43) as treatment standard for definitive chemoradiation, a significant number of treatment centers favor weekly cisplatin regimens with 40 mg/m2 for older HNSCC patients given the reduced toxicity burden for this regimen.[11-14] Oncological equivalence between the three-weekly high-dose cisplatin regimen

and the weekly cisplatin regimen with 40 mg/m2 has been shown for the postoperative situation.[15] Two large randomized trials, the ConCERT trial (CTRI/2018/03/012422) and the NRG-HN009 trial (NCT05050162), are comparing these two cisplatin regimens also for definitive chemoradiation. As reported from the ConCERT data, weekly cisplatin was non-inferior to three-weekly high-dose cisplatin and was better tolerated with less interruptions, hospitalizations and toxicity.[16] Besides the controversies regarding cisplatin dosing, further uncertainty exists whether cisplatin may be replaced by alternative agents such as carboplatin in older HNSCC patients. There is one non-inferiority trial comparing carboplatin with cisplatin concomitantly to radiotherapy for nasopharyngeal carcinoma patients that showed comparable survival rates and fewer toxicities (renal toxicity, leucopenia, and anemia) for carboplatin[17]; however, there is currently no data of randomized phase III trials comparing cisplatin with carboplatin for non-nasopharyngeal HNSCCs. Given the prospective evidence for other regimens, mitomycin c- and taxane-based protocols are also used in the clinical routine.[18-20] However, older HNSCCs were highly underrepresented in these trials: Median age was about 55 years both in the ARO 95-06[18] and IAEA mitomycin c trial[19], and 56 years in the trial regarding carboplatin plus paclitaxel at the University of Maryland trial.[20]

Considering the limited evidence regarding the optimal chemotherapy regimen concomitantly to definitive radiotherapy in older adults with HNSCC, we conducted a comprehensive multicenter cohort analysis to examine the impact of different chemotherapy regimens on overall survival (OS), progression-free survival (PFS), incidence of locoregional failures (LRFs), and incidence of distant metastases (DMs). To the best of our knowledge, this study represents the largest analysis of older adults with HNSCC focusing on the comparison of commonly utilized chemotherapy regimens across various oncological outcome measures including locoregional and distant tumor control. Even though there are conflicting definitions when a patient should be considered as “old” or “elderly”[21], many guidelines still indicate 65 years as the threshold, so that we decided to apply a cutoff of 65 years as inclusion criterion

for our cohort analysis.[22,23] However, given the fact that other guidelines considers 70 years as age threshold for the definition of an older adult[24], and that the MACH-NC meta-analysis reported an absent benefit of concomitant chemotherapy for the group of patients aged 70 years and older[8], we also provide subgroup analyses for patients ≥70 years.

## Materials and methods

### *Study Design*

The present study comprises a subset of patients that were included in an international registry (XXX) consisting of currently 1,100 older adults with LA-HNSCC (**supplementary figure 1**). Patient and treatment data were collected retrospectively from 13 academic centers in the XXX, XXX, XXX, and XXX. The present analysis includes 697 patients aged 65 years and older, diagnosed with LA-HNSCCs of the oral cavity, oropharynx, hypopharynx, or larynx, who received definitive chemoradiation between 2005 and 2019. For an exploratory subgroup analysis, the oncological outcomes of older adults with HNSCC receiving curative radiotherapy alone within the XXX registry (n=242) were compared with the outcomes of the chemoradiation group. Patients who had received induction or adjuvant chemotherapy, had a history of previous head-and-neck carcinomas or radiotherapy in the head-and-neck region, presented with distant metastases at treatment initiation, or had cancers of the nasopharynx, salivary glands, skin, or cancers of an unknown primary were excluded. The study used the 7th Edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system to classify the patients, and the Charlson Comorbidity Index (CCI) was calculated for each patient as reported in the literature, with the primary tumor and patient age not included in the calculation.[25] The Modification of Diet in Renal Disease (MDRD) equation was used to calculate the estimated glomerular filtration rate based on sex, age, serum creatinine concentration and race. The study was approved by the XXX,

and the institutional review boards at each participating center. The study followed the STROBE reporting guideline for cohort studies.

***Statistical Analysis***

Patient and tumor characteristics were presented as median values including interquartile range (IQR) or absolute numbers with percentages, and the different chemotherapy groups were compared using one-way ANOVA (for age, CCI, estimated glomerular filtration rate, and radiotherapy dose) or $\chi^2$-tests (for categorial variables). OS and PFS were calculated using the Kaplan-Meier method. Death, local or locoregional progression, and development of DMs were considered as events for PFS. Endpoints were calculated from the start of radiotherapy until the event or last follow-up date, with patients being censored at the last date of follow-up. Proportional hazards models were used to evaluate both the incidence of LRFs and the incidence of DMs, respectively, with death as competing risk. Multivariate Cox proportional hazards analyses were conducted regarding OS, and Fine-Gray proportional hazards models with death as competing risk were performed for the incidence of LRFs and DMs. For the regression analyses, multiple imputation of missing data was conducted using k-Nearest Neighbor Imputation, in which the five nearest neighbors were computed based on a variation of the Gower distance. All statistical analyses were performed using R version 4.1.3, and *p*-values and 95% confidence intervals were not corrected for multiple comparisons, as the analyses were exploratory in nature. As a result, *p*-values and 95% confidence intervals were not corrected for multiple comparisons and inferences drawn from them may not be reproducible. A *p*-value <.05 was considered as statistically significant for all analyses.

**Results**

***Characteristics of the Study Cohort***

The median age of the analyzed cohort was 71 years (IQR, 68-76), and 482 patients (69.2%) were male (**table 1**). A total of 590 patients (84.6%) had an ECOG performance status of ≤1, and 502 exhibited a Charlson Comorbidity Index of ≤2 (72.0%), indicative of relatively few comorbidities. Tumors were most commonly located in the oropharynx (n=383, 54.9%), followed by hypopharynx (n=111, 15.9%), oral cavity (n=89, 12.9%) and larynx (n=84, 12.1%). Half of the patients exhibited cT4 carcinomas (n=348, 49.9%), and 583 patients (83.6%) had locoregional lymph node metastases at the time of chemoradiation. About one-fifth of the patients (n=151, 22%) presented with HPV-positive oropharyngeal carcinomas. Radiotherapy was administered to a median dose of 70.0 Gy (IQR, 69.3-70.4 Gy), and 633 patients (90.8%) completed the prescribed radiotherapy course. Single-agent cisplatin was the most common chemotherapy regimen (n=310, 44%). Cisplatin plus 5-fluorouracil (n=137, 20%), carboplatin (n=73, 10%), mitomycin c plus 5-fluorouracil (n=64%, 9%), mitomycin c (n=50, 7%), carboplatin plus paclitaxel (n=27, 4%), cisplatin plus paclitaxel (n=13, 2%), and paclitaxel (n=12, 2%) were other regimens that were commonly used in the cohort. Descriptive statistics depending on the type of concomitant systemic treatment are shown in **supplementary table 1**.

Among patients treated with single-agent cisplatin, median cumulative cisplatin dose amounted to 180 mg/m2, and 146 patients (48% of patients with known cumulative cisplatin dose) achieved a cumulative dose of ≥200 mg/m2. Median cumulative cisplatin dose of patients receiving any type of cisplatin-containing regimen (n=451 with known cumulative cisplatin dose) was also 180 mg/m2, and 191 patients (42%) were exposed to cumulative dose of ≥200 mg/m2 (**supplementary table 2**). Patients treated with weekly 30-40 mg/m2 cisplatin (n=157) received a median cumulative dose of 180 mg/m2, and 83 of them (53%) completed ≥5 cycles of weekly cisplatin (**supplementary table 3**). The vast majority of weekly cisplatin regimens consisted of 40 mg/m2 as single dose (n=130, 83%).

***Comparison between cisplatin and other chemotherapy agents***

The median follow-up time was 56 months (95% CI, 50-63 months). A total of 337 deaths (48.4%), 144 LRFs (20.7%) and 76 DMs (10.9%) had occurred at the time of analysis. Median OS and PFS were 53 months (95% CI, 43-63 months) and 33 months (95% CI, 25-41 months), respectively. The 2-year incidence of LRFs and DMs was 19.6% (95% CI, 16.5%-22.7%) and 9.5% (95% CI, 7.2%-11.8%), respectively.

Patients treated with other regimens than single-agent cisplatin exhibited a non-significant trend towards lower OS (HR=1.24; 95% CI, 0.99-1.55; *p*=.06), while PFS (HR=1.16; 95% CI, 0.95-1.42; *p*=.15), incidence of LRFs (SHR=1.11; 95% CI, 0.80-1.55; *p*=.52), and incidence of DMs (SHR=0.65; 95% CI, 0.41-1.02; *p*=.06) were not different (**figure 1**). In patients aged ≥70 years, treatment with single-agent cisplatin translated into improved OS (HR=1.35; 95% CI, 1.03-1.77; *p*=.03), whereas incidence of LRFs was not different (SHR=1.24; 95% CI, 0.81-1.90; *p*=.31) when compared with patients receiving other regimens than single-agent cisplatin (**supplementary figure 2**). Cisplatin-based regimens (including both single-agent cisplatin and multi-agent cisplatin regimens) were associated with superior survival (OS: HR=1.24; 95% CI, 1.00-1.55; *p*=.05; PFS: HR=1.29; 95% CI, 1.05-1.58; *p*=.02) compared with cisplatin-free regimens, while incidence of LRFs (SHR=0.74; 95% CI, 0.54-1.03; *p*=.08) and DMs (SHR=1.38; 95% CI, 0.83-2.29; *p*=.22) was not different (**supplementary figure 3**). However, in the multivariate Cox regression model, neither usage of single-agent cisplatin (**supplementary table 4**) nor usage of cisplatin-based chemotherapy (**supplementary table 5**) was an independent prognostic parameter for OS.

As concomitant carboplatin is often discussed as alternative to cisplatin, we compared single-agent cisplatin with carboplatin-containing regimens (i.e., carboplatin mono, carboplatin plus paclitaxel, carboplatin plus docetaxel, and carboplatin plus 5-fluorouracil) (**figure 2**). Here, carboplatin-consisting regimens were associated with reduced PFS (HR=1.39; 95% CI, 1.03-1.89; $p<0.05$), and a higher incidence of LRFs (SHR=1.54; 95% CI,

1.00-2.38; *p*=.05) compared with single-agent cisplatin, whereas OS (HR=1.15; 95% CI, 0.80-1.65; *p*=.46) and the incidence of DMs (SHR=0.86; 95% CI, 0.43-1.71; *p*=.67) were comparable. These findings were also found in the subgroup of patients aged ≥70 years (**supplementary figure 4**). Patients treated with mitomycin c-containing regimens exhibited significantly lower OS (HR=1.46; 95% CI, 1.10-1.93; *p*=.01); however, neither PFS (HR=1.26; 95% CI, 0.97-1.65; *p*=.09) nor the incidence of LRFs (SHR=0.95; 95% CI, 0.63-1.44; *p*=.81) or DMs (SHR=0.59; 95% CI, 0.29-1.17; *p*=.13) differed between single-agent cisplatin and mitomycin c-based protocols (**figure 2**). Subgroup analyses for mitomycin c-based regimens in the cohort of patients aged 70 years and older are also shown in **supplementary figure 4**.

Addition of further chemotherapeutic agents (e.g., 5-fluorouracil) to single-agent cisplatin did not translate to differences in OS (HR=1.16; 95% CI, 0.88-1.53; *p*=.29), PFS (HR=1.01; 95% CI, 0.78-1.31; *p*=.94), incidence of LRFs (SHR=0.89; 95% CI, 0.57-1.39; *p*=.60), or incidence of DMs (SHR=0.69; 95% CI, 0.42-1.14; *p*=.14) when compared with single-agent cisplatin (**supplementary figure 5, supplementary figure 6**). In general, multi-agent chemotherapy protocols yielded comparable oncological outcomes compared with single-agent protocols (**supplementary figure 7**). Subgroup analyses for patients with HPV-positive and HPV-negative oropharyngeal cancer are shown in **supplementary figures 8-11**. Even though patient numbers were rather small for this subgroup analyses, older adults with HPV-positive oropharyngeal cancer (n=151) treated with single-agent cisplatin exhibited significantly longer OS compared with HPV-positive oropharyngeal cancer patients receiving other regimens than single-agent cisplatin (HR=2.58; 95% CI, 1.25-5.32; *p*=.01). Comparative analyses including the oncological outcomes of patients treated with radiotherapy alone are shown in **supplementary figures 12-13**. **Table 2** summarizes the oncological outcomes at 2 years after chemoradiation depending on the type of concomitant systemic treatment.

***Prognostic value of cumulative cisplatin dose***

As a median cumulative cisplatin dose of at least 200 mg/m2 is considered as a prognostically relevant threshold in the general HNSCC population receiving definitive chemoradiation, we also analyzed this issue in our cohort of older HNSCC patients (**figure 3**). Cumulative doses ≥200 mg/m2 were associated with significantly higher OS (HR=0.71; 95% CI, 0.53-0.95; *p*=.02) and PFS (HR=0.66; 95% CI, 0.51-0.87; *P*=.003), mainly related to the significantly lower incidence of LRFs (SHR=0.50; 95% CI, 0.31-0.80; *p*=.004). The incidence of DMs was not dependent on the cumulative cisplatin dose (SHR=1.06; 95% CI, 0.62-1.81; *p*=.84). A subgroup analysis in which incrementally increased cumulative cisplatin doses (≤100 mg/m2, 101-200 mg/m2, >200 mg/m2) were compared revealed a dose-response relationship: Patients receiving up to 100 mg/m2 exhibited the worst OS and PFS (**supplementary figure 14**). Especially the incidence of LRFs was significantly reduced in patients treated with >200 mg/m2 compared with patients receiving ≤100 mg/m2 (SHR=0.42; 95% CI, 0.19-0.89; *p*=.02). These results were also seen in the subgroup of patients aged 70 years and older (**supplementary figure 15-16**). However, in the multivariate regression analyses, a median cumulative cisplatin dose of at least 200 mg/m2 was not prognostic regarding OS (HR=0.71; 95% CI, 0.47-1.07; *p*=.10) or the incidence of LRFs (SHR=0.69; 95% CI, 0.35-1.35; *p*=.28) (**supplementary table 6-7**). When the cumulative cisplatin dose was entered as continuous variable into the multivariate analyses, it was an independent favorable prognostic variable in terms of OS (HR=0.996; 95% CI, 0.993-0.999; *p*=.009); the association between the cumulative cisplatin dose and the incidence of LRFs missed statistical significance (SHR=0.995; 95% CI, 0.990-1.000; *p*=.06) (**supplementary table 8-9**).

Weekly cisplatin was associated with superior OS (HR=0.64; 95% CI, 0.45-0.92; *p*=.01) and PFS (HR=0.69; 95% CI, 0.51-0.95; *p*=.02) compared with all other single-agent cisplatin regimens (e.g., cisplatin 20 mg/m2 at days 1-5 and 29-33; cisplatin 20 mg/m2 at days 1-5, 22-26, 43-47), while there was no significant difference regarding the incidence of LRFs

(SHR=0.76; 95% CI, 0.46-1.26; *p*=.29) or DMs (SHR=1.86; 95% CI, 0.98-3.50; *p*=.06) (**figure 4**). There was no significant difference in oncological outcomes between patients treated with cisplatin weekly and patients receiving high-dose three-weekly cisplatin (**supplementary figure 17**); however, only few patients (n=9) received high-dose three-weekly cisplatin. Cumulative cisplatin doses did not differ between weekly cisplatin and other single-agent cisplatin regimens (mean 182 mg/m2 [weekly] vs. 172 mg/m2 [other regimens]; *p*=.193) (**supplementary table 10**).

## Discussion

In this international cohort study of 697 older adults with LA-HNSCC undergoing definitive chemoradiation, carboplatin-based regimens were associated with more LRFs and diminished PFS, but OS was similar between cisplatin- and carboplatin-based regimens. Neither single-agent cisplatin nor cisplatin-based regimens were independent parameters regarding OS in the multivariate regression models, and there was no significant benefit in adding additional chemotherapeutic drugs to single-agent cisplatin. A higher cumulative cisplatin dose was found to serve as an independent prognostic parameter for OS.

In line with the results of the MACH-NC meta-analysis showing that multi-agent chemotherapy is not superior to single-agent chemotherapy[26], our data do not support multi-agent cisplatin regimens such as cisplatin plus 5-fluorouracil. A previous retrospective multicenter analysis reported similar oncological outcomes but significantly less toxicities after single-agent cisplatin compared with cisplatin plus 5-fluorouracil.[27] In addition, the toxicity profile of 5-fluorouracil (e.g., cardiotoxicity, diarrhea, mucositis) makes its usage challenging in the older HNSCC population when given in combination with cisplatin.[5,28] A retrospective analysis of LA-HNSCC patients treated with chemoradiation in two Dutch cancer centers found significantly lower chemotherapy completion rates for carboplatin plus 5-fluorouracil than for single-agent three-weekly cisplatin 100 mg/m2.[29] Another

retrospective study observed that rates of late toxicity (defined as presence of percutaneous endoscopic gastrostomy tube or tracheostomy) were higher with carboplatin plus 5-fluorouracil (25%) compared with single-agent cisplatin (8%).[30] Results of other multi-agent cisplatin protocols, e.g., cisplatin plus paclitaxel[31,32] have also shown considerable risks for severe toxicities.

The known prognostic value of cumulative cisplatin dose in the general HNSCC population was validated also in older patients with HNSCCs.[33] To the best of our knowledge, this cohort study is the largest analysis about the prognostic value of cumulative cisplatin dose in older adults with LA-HNSCC. The fact that the cumulative cisplatin dose (when entered as continuous variable) remained an independent prognostic variable concerning OS provides a strong basis to improve supportive care measures (e.g., intravenous hydration protocols, state-of-the art antiemetic treatments) in order to ensure high cumulative cisplatin doses. However, considering the absent prognostic benefit of a cumulative cisplatin of ≥200 mg/m2 in the multivariate regression analysis, the optimal cumulative target dose for the elderly HNSCC population remains a matter of debate. Our real-world data are in accordance with patterns-of-care analyses in which cisplatin weekly is the preferred schedule of cisplatin administration in older patients with LA-HNSCC.[12,34] Given the significantly lower incidence of higher-grade toxicities in low-dose once-a-week compared with high-dose once-every-3-weeks cisplatin administration protocols[15,35], cisplatin 40 mg/m2 weekly may especially be attractive for older patients with HNSCC who exhibit higher hazards for nephrotoxicity and ototoxicity.[36-38]

The fact that carboplatin-based regimens were found to be associated with significantly reduced PFS, mainly mediated by a higher incidence of LRFs, points out that cisplatin should not generally be replaced by carboplatin in the older HNSCC population. However, carboplatin is known to result in fewer renal and vestibulocochlear toxicities than cisplatin and is considered an alternative for HNSCC patients with contraindications against cisplatin. A meta-analysis with three randomized clinical trials, eight retrospective studies and

one matched-pair analysis observed comparable 3-year survival and tumor control rates, although 5-year survival rates were higher for cisplatin.[39] Both the NCCN (as category 1) and the ESMO guidelines (for patients unfit for cisplatin; level of evidence II, grade of recommendation A) indicate carboplatin plus 5-fluoruracil as a possible chemotherapy regimen in HNSCC patients.[40,41] As carboplatin plus 5-fluorouracil was only administered in 5 patients in our cohort, we cannot make any conclusions regarding the efficacy of this protocol in the older HNSCC population. Mean age was about 56 years both in the GORTEC 99-02 trial[42] and in the GORTEC 94-01 trial[43] for the carboplatin plus 5-fluorouracil groups, and no patient was older than 75 years in these studies, making extrapolation of these trial results to older adults with HNSCC challenging. However, in consideration of other retrospective analyses including a large US cohort study in which carboplatin-based regimens were associated with improved outcomes compared with cetuximab [44,45], carboplatin-based regimens are a treatment alternative for patients unfit for cisplatin. Weighing the higher evidence concerning carboplatin plus 5-fluorouracil (compared with single-agent carboplatin) against the higher toxicity rates of the carboplatin combination protocol due to additional toxicities caused by 5-fluorouracil, carboplatin plus 5-fluorouracil should can be considered in older adults with very good performance status but specific contraindications against cisplatin (e.g., renal or hearing impairments).[46] Considering the comparable OS between single-agent cisplatin and carboplatin-based regimens (which mainly consisted of single-agent carboplatin) as well as the existing prospective evidence for single-agent carboplatin [47,48], it could be an alternative for patients with contraindications against cisplatin and moderate performance status, although further prospective evidence is warranted.

A recently published randomized phase III trial has shown improved disease-free survival, locoregional control and overall survival after addition of docetaxel to radiotherapy (either definitive [61%] or adjuvant [39%]) in HNSCC patients unfit for cisplatin, without affecting long-term quality of life.[49] The main strength of this trial is the fact that this was the

first randomized trial in which the addition of concomitant systemic treatment was tested for cisplatin-ineligible patients, which was not the inclusion criteria for the Bonner trial or the carboplatin plus 5-fluorouracil trials.[42,43,50] Thirty-one out of 180 patients (17%) were aged 70 years or older in the docetaxel chemoradiation group. Unfortunately, single-agent docetaxel was only administered in one patient within our cohort, so that we cannot contribute real-world data regarding this regimen's efficacy in the older HNSCC population. However, studies in which single-agent docetaxel was investigated in older adults with non-HNSCC cancers (e.g., breast or prostate cancer) showed acceptable compliance and toxicity rates.[51,52] It would be highly desirable to obtain further real-world data on concomitant docetaxel in older adults with HNSCC treated with state-of-the-art radiotherapy techniques, as only about 20% received intensity-modulated radiotherapy in the DHANUSH trial.

Although our analyses are based on a large international multicenter cohort study and incorporate several oncological endpoints including incidence of LRFs and DMs, there are some limitations mainly due to the retrospective character of data acquisition. First, the prognostic benefit of cumulative cisplatin doses is prone to selection biases, as patients with good performance status and few comorbidities may tolerate more cycles of cisplatin, so that the improved outcomes associated with higher cisplatin doses could be related to the fact that healthier patients were able to receive more cisplatin cycles.[46] However, the fact that higher cumulative cisplatin doses were prognostic also in the multivariate Cox proportional hazards analyses (in which patient age, performance status, comorbidity burden, etc. were included) for OS makes a causative relationship more conceivable. Second, cisplatin ineligibility was not assessed in a standardized manner. No uniformly accepted criteria have been established for cisplatin ineligibility, and there is a strong heterogeneity regarding the definition, e.g., concerning parameters for renal function or performance status, complicating consistent analyses on this issue.[38,53,54] Third, only very few patients were treated with high-dose cisplatin (100 mg/m2 at days 1, 22 and 43), therefore not allowing for conclusive comparative

analyses between high-dose and low-dose weekly cisplatin. Fourth, geriatric screenings were not mandatory for inclusion, and results of a geriatric screening or assessment, if performed, were not collected in our data registry. Last, we did not adjust for multiple testing due to the explorative nature of our analyses. The results should therefore be interpreted cautiously; however, they provide a basis for further prospective studies on this issue.

**Conclusions**

The results obtained from this cohort study of 697 older patients with LA-HNSCC suggest that single-agent cisplatin can be considered standard regimen also for older adults with LA-HNSCC who exhibit a good performance status and no specific contraindications against cisplatin. The fact that patients who received carboplatin-based chemoradiation exhibited comparable survival rates to patients undergoing cisplatin-based chemoradiation makes carboplatin-based regimens an alternative for patients with contraindications to cisplatin, although the observed higher incidence of LRFs should be taken into consideration. Given the favorable prognostic value of higher cumulative cisplatin doses, optimal supportive care measures should be undertaken to ensure high cumulative cisplatin doses. Further efforts are necessary to elaborate on the optimal treatment approach for frail patients and patients with contraindications against cisplatin.

**References**


1. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009;27(17):2758-2765.
2. Bernier J, Cooper JS, Pajak TF, 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(10):843-850.
3. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* 2013;31(7):845-852.
4. McDowell L, Rischin D, Gough K, Henson C. Health-Related Quality of Life, Psychosocial Distress and Unmet Needs in Older Patients With Head and Neck Cancer. *Front Oncol.* 2022;12:834068.
5. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008;26(21):3582-3589.
6. Dickstein DR, Powers AE, Vujovic D, Roof S, Bakst RL. Clinical and Therapeutic Considerations for Older Adults with Head and Neck Cancer. *Clin Interv Aging.* 2023;18:409-422.
7. Porceddu SV, Scotté F, Aapro M, et al. Treating Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck Unsuitable to Receive Cisplatin-Based Therapy. *Front Oncol.* 2019;9:1522.
8. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19805 patients, on behalf of MACH-NC group. *Radiother Oncol.* 2021.

9. VanderWalde NA, Meyer AM, Deal AM, et al. Effectiveness of chemoradiation for head and neck cancer in an older patient population. *Int J Radiat Oncol Biol Phys.* 2014;89(1):30-37.

10. Amini A, Jones BL, McDermott JD, et al. Survival outcomes with concurrent chemoradiation for elderly patients with locally advanced head and neck cancer according to the National Cancer Data Base. *Cancer.* 2016;122(10):1533-1543.

11. Rühle A, Marschner S, Haderlein M, et al. Evaluation of Concomitant Systemic Treatment in Older Adults With Head and Neck Squamous Cell Carcinoma Undergoing Definitive Radiotherapy. *JAMA Network Open.* 2023;6(2):e230090-e230090.

12. Haehl E, Rühle A, Spohn S, et al. Patterns-of-Care Analysis for Radiotherapy of Elderly Head-and-Neck Cancer Patients: A Trinational Survey in Germany, Austria and Switzerland. *Front Oncol.* 2021;11:723716.

13. Kang EJ, Lee YG, Keam B, et al. Characteristics and treatment patterns in older patients with locally advanced head and neck cancer (KCSG HN13-01). *Korean J Intern Med.* 2022;37(1):190-200.

14. Szturz P, Wouters K, Kiyota N, et al. Low-Dose vs. High-Dose Cisplatin: Lessons Learned From 59 Chemoradiotherapy Trials in Head and Neck Cancer. *Frontiers in oncology.* 2019;9:86-86.

15. Kiyota N, Tahara M, Mizusawa J, et al. Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. *Journal of Clinical Oncology.* 2022;40(18):1980-1990.

16. Sharma A, Kumar M, Bhasker S, et al. An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced

head and neck squamous cell carcinoma (ConCERT trial). *Journal of Clinical Oncology.* 2022;40(16_suppl):6004-6004.

17. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer.* 2007;43(9):1399-1406.
18. Budach V, Stromberger C, Poettgen C, et al. Hyperfractionated accelerated radiation therapy (HART) of 70.6 Gy with concurrent 5-FU/Mitomycin C is superior to HART of 77.6 Gy alone in locally advanced head and neck cancer: long-term results of the ARO 95-06 randomized phase III trial. *Int J Radiat Oncol Biol Phys.* 2015;91(5):916-924.
19. Grau C, Prakash Agarwal J, Jabeen K, et al. Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. *Radiother Oncol.* 2003;67(1):17-26.
20. Suntharalingam M, Haas ML, Conley BA, et al. The use of carboplatin and paclitaxel with daily radiotherapy in patients with locally advanced squamous cell carcinomas of the head and neck. *Int J Radiat Oncol Biol Phys.* 2000;47(1):49-56.
21. Ouchi Y, Rakugi H, Arai H, et al. Redefining the elderly as aged 75 years and older: Proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. *Geriatr Gerontol Int.* 2017;17(7):1045-1047.
22. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol.* 2018;36(22):2326-2347.
23. Dale W, Klepin HD, Williams GR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update. *J Clin Oncol.* 2023:Jco2300933.

24. Pallis AG, Fortpied C, Wedding U, et al. EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer.* 2010;46(9):1502-1513.

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

26. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. 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(1):4-14.

27. Rades D, Kronemann S, Meyners T, 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(4):1037-1044.

28. Hsieh MC, Wang CC, Yang CC, et al. Tegafur-Uracil versus 5-Fluorouracil in Combination with Cisplatin and Cetuximab in Elderly Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Propensity Score Matching Analysis. *Biology (Basel).* 2021;10(10).

29. Hanemaaijer SH, Kok IC, Fehrmann RSN, et al. Comparison of Carboplatin With 5-Fluorouracil vs. Cisplatin as Concomitant Chemoradiotherapy for Locally Advanced Head and Neck Squamous Cell Carcinoma. *Front Oncol.* 2020;10:761.

30. Shapiro LQ, Sherman EJ, Riaz N, et al. Efficacy of concurrent cetuximab vs. 5-fluorouracil/carboplatin or high-dose cisplatin with intensity-modulated radiation therapy (IMRT) for locally-advanced head and neck cancer (LAHNSCC). *Oral Oncol.* 2014;50(10):947-955.

31. Kuhnt T, Becker A, Pigorsch S, et al. Aggressive simultaneous radiochemotherapy with cisplatin and paclitaxel in combination with accelerated hyperfractionated radiotherapy in locally advanced head and neck tumors. Results of a phase I-II trial. *Strahlenther Onkol.* 2003;179(10):673-681.

32. Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. *J Clin Oncol.* 2004;22(14):2856-2864.

33. Strojan P, Vermorken JB, Beitler JJ, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: A systematic review. *Head & Neck.* 2016;38(S1):E2151-E2158.

34. Oosting SF, Desideri I, Staelens D, et al. Treatment patterns in older patients with locally advanced head and neck squamous cell carcinoma: Results from an EORTC led survey. *J Geriatr Oncol.* 2021;12(8):1261-1265.

35. Noronha V, Joshi A, Patil VM, et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. *J Clin Oncol.* 2018;36(11):1064-1072.

36. Duan ZY, Liu JQ, Yin P, Li JJ, Cai GY, Chen XM. Impact of aging on the risk of platinum-related renal toxicity: A systematic review and meta-analysis. *Cancer Treat Rev.* 2018;69:243-253.

37. Theunissen EA, Bosma SC, Zuur CL, et al. Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: a systematic review of the literature. *Head Neck.* 2015;37(2):281-292.

38. Ahn MJ, D'Cruz A, Vermorken JB, et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. *Oral Oncol.* 2016;53:10-16.

39. Guan J, Li Q, Zhang Y, et al. A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). *Oncotarget.* 2016;7(6):7110-7119.

40. National Comprehensive Cancer Network. Head and Neck Cancer (Version 2.2023). 2023; https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed June 16, 2023.

41. Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2020;31(11):1462-1475.

42. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *The Lancet Oncology.* 2012;13(2):145-153.

43. Denis F, Garaud P, Bardet E, 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(1):69-76.

44. Sun L, Candelieri-Surette D, Anglin-Foote T, et al. Cetuximab-Based vs Carboplatin-Based Chemoradiotherapy for Patients With Head and Neck Cancer. *JAMA Otolaryngol Head Neck Surg.* 2022;148(11):1022-1028.

45. Barney C, Healy E, Zamora P, et al. Carboplatin versus cetuximab chemoradiation in cisplatin ineligible patients with locally advanced p16 negative head and neck squamous cell carcinoma. *International Journal of Radiation Oncology, Biology, Physics.* 2017;99(2):E322-E323.

46. Szturz P, Cristina V, Herrera Gómez RG, Bourhis J, Simon C, Vermorken JB. Cisplatin Eligibility Issues and Alternative Regimens in Locoregionally Advanced Head and Neck Cancer: Recommendations for Clinical Practice. *Frontiers in Oncology.* 2019;9.

47. 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(1):29-37.

48. Fountzilas G, Ciuleanu E, Dafni U, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. *Med Oncol.* 2004;21(2):95-107.

49. Patil VM, Noronha V, Menon N, et al. Results of Phase III Randomized Trial for Use of Docetaxel as a Radiosensitizer in Patients With Head and Neck Cancer, Unsuitable for Cisplatin-Based Chemoradiation. *J Clin Oncol.* 2023;41(13):2350-2361.

50. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567-578.

51. Hainsworth JD, Burris HA, 3rd, Yardley DA, et al. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol.* 2001;19(15):3500-3505.

52. Italiano A, Ortholan C, Oudard S, et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. *Eur Urol.* 2009;55(6):1368-1375.

53. Falco A, de Oliveira TB, Cacicedo J, et al. Ibero-American Expert Consensus on Squamous Cell Carcinoma of the Head and Neck Treatment in Patients Unable to Receive Cisplatin: Recommendations for Clinical Practice. *Cancer Manag Res.* 2021;13:6689-6703.

54. Alvarado-Muñoz JF, Falco A, Morales AR, et al. Platinum ineligibility in squamous cell carcinoma of the head and neck: consensus from Central America and the Caribbean. *Future Oncology.* 2021;17(15):1963-1971.

**Figure Legends**

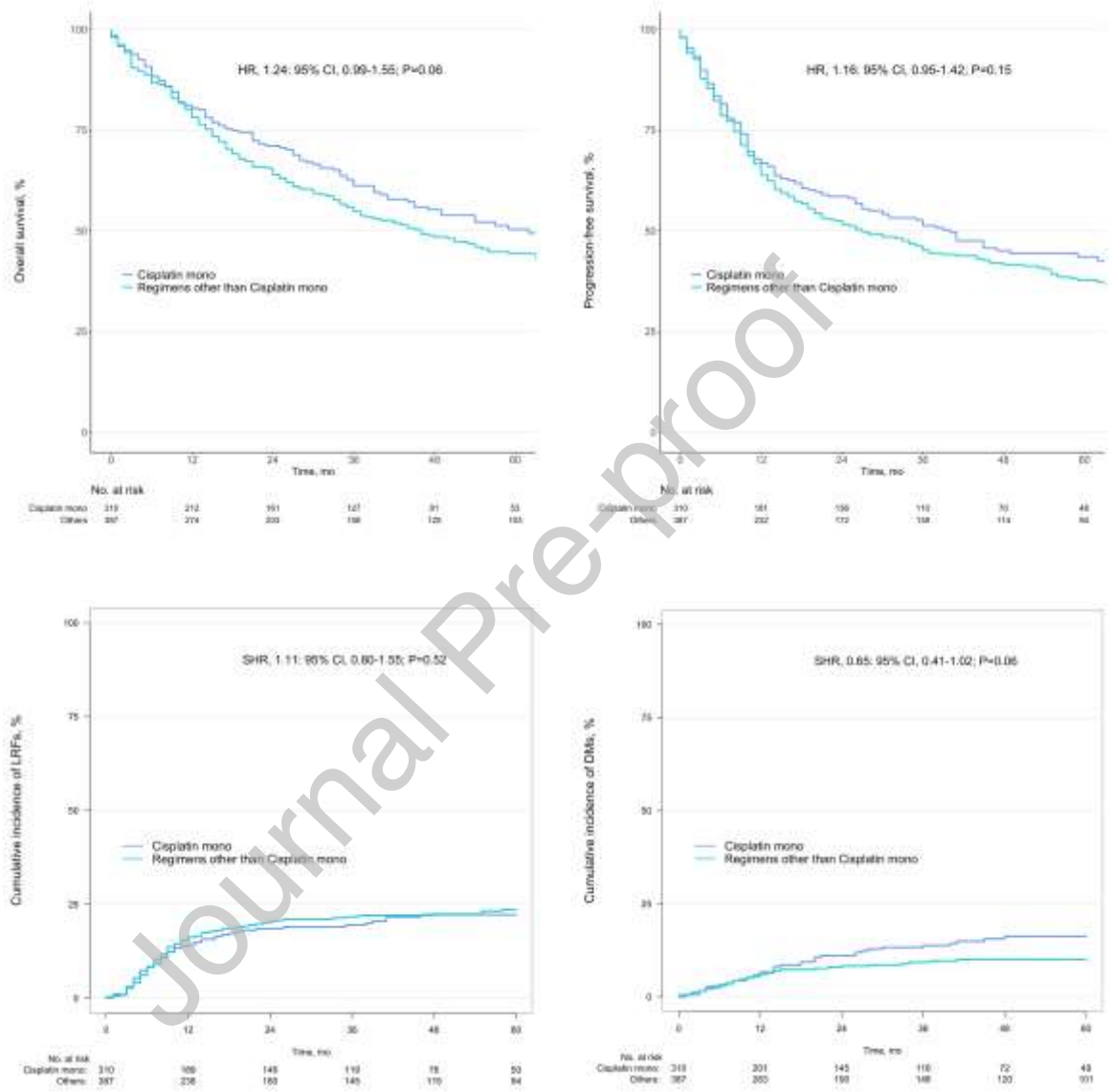


**Figure 1. Overall Survival, Progression-Free Survival, Incidence of Locoregional Failures, and Incidence of Distant Metastases of Older (≥65 Years) Head and Neck Squamous Cell Carcinoma Patients Receiving Either Single-agent Cisplatin or Other Chemotherapy Regimens (Multi-agent Cisplatin Regimens, Carboplatin-Based**

**Regimens, Mitomycin C-Based Regimens, etc.) Concomitantly to Definitive Radiotherapy.** HR, hazard ratio; SHR, subdistribution hazard ratio.

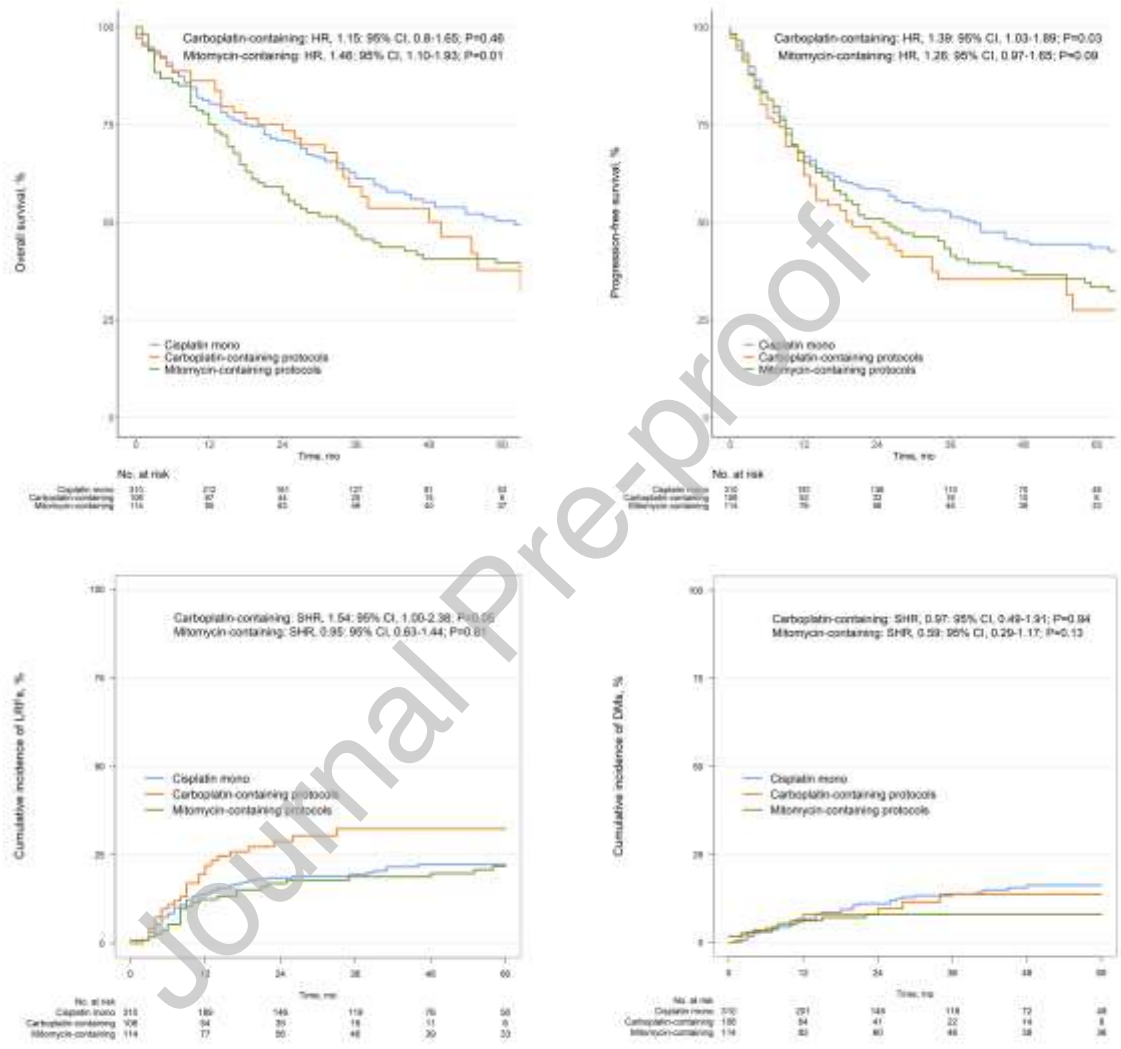


**Figure 2. Overall Survival, Progression-Free Survival, Incidence of Locoregional Failures, and Incidence of Distant Metastases of Older (≥65 Years) Head and Neck Squamous Cell Carcinoma Patients Receiving Single-agent Cisplatin, or Carboplatin-based Regimens, or Mitomycin C-based Regimens Concomitantly to Definitive Radiotherapy.** HR, hazard ratio; SHR, subdistribution hazard ratio.

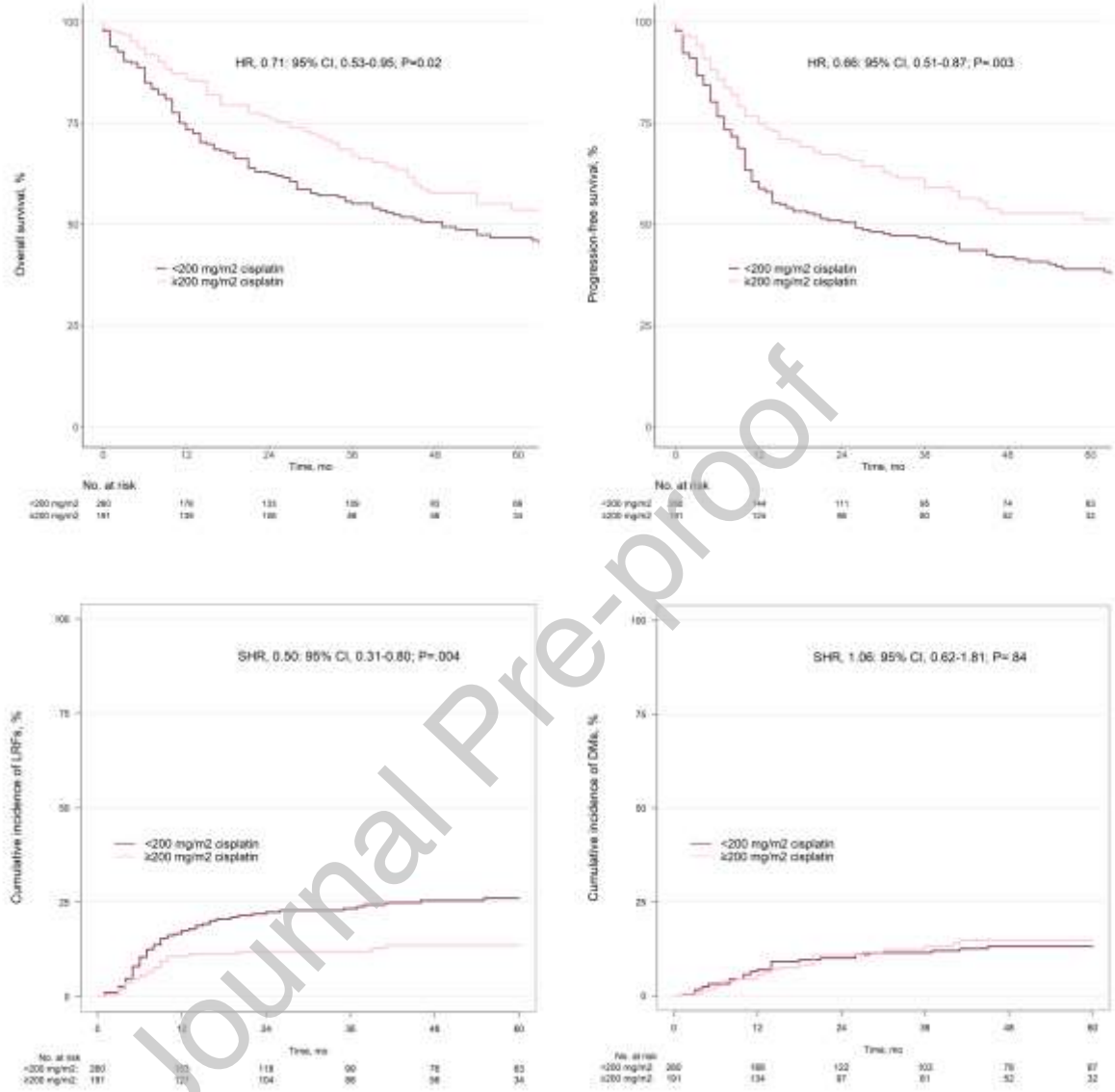


**Figure 3. Overall Survival, Progression-Free Survival, Incidence of Locoregional Failures, and Incidence of Distant Metastases of Older (≥65 Years) Head and Neck Squamous Cell Carcinoma Patients Depending on the Cumulative Cisplatin Dose Administered During Chemoradiation.** HR, hazard ratio; SHR, subdistribution hazard ratio.

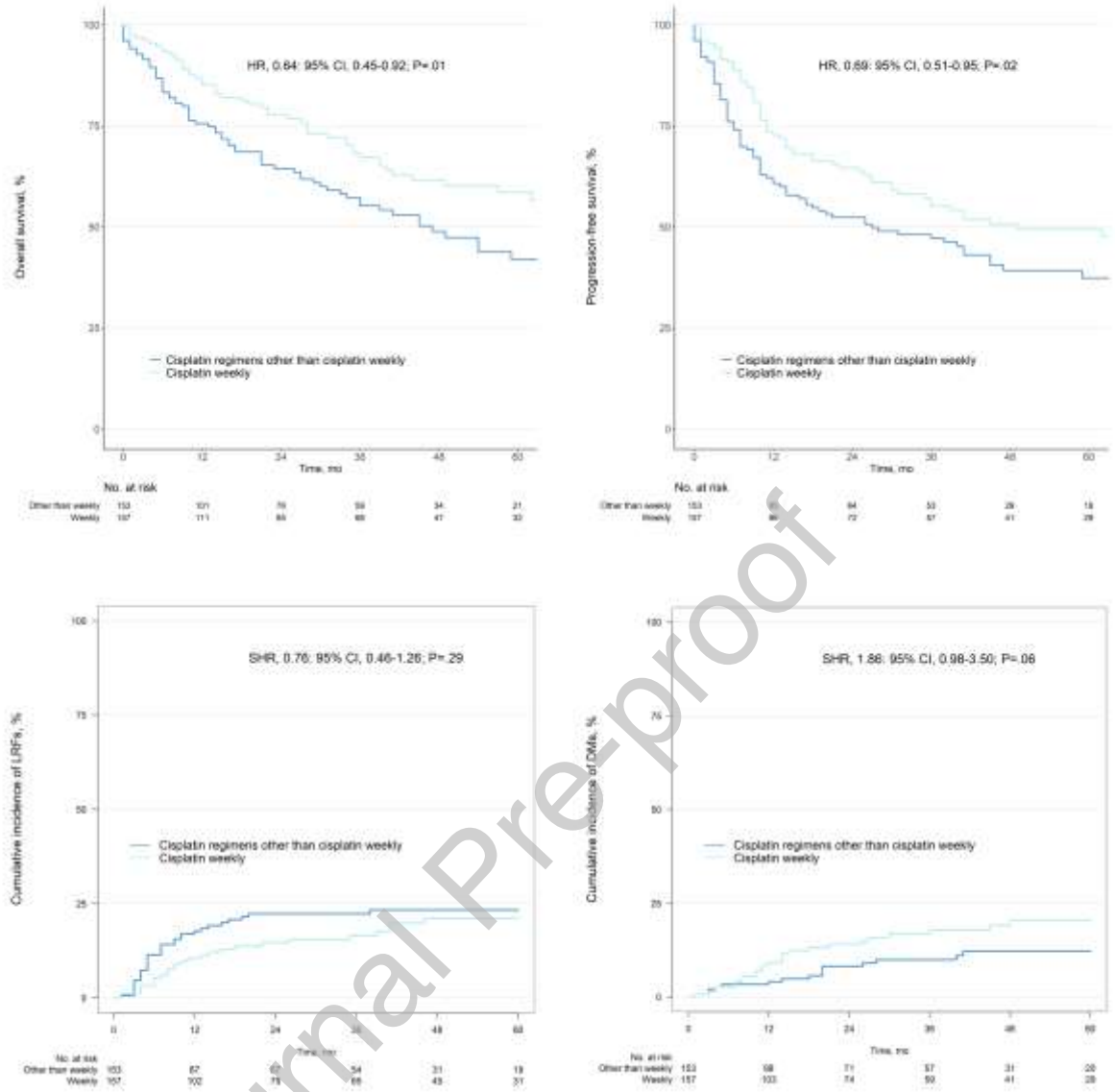


**Figure 4. Overall Survival, Progression-Free Survival, Incidence of Locoregional Failures, and Incidence of Distant Metastases of Older (≥65 Years) Head and Neck Squamous Cell Carcinoma Patients Depending on the Type of Cisplatin Administration.** Cisplatin 30-40 mg/m2 weekly was compared with all other applied single-agent cisplatin regimens (e.g., 100 mg/m2 at days 1, 22, 43; 20 mg/m2 at days 1-5, 29-33; 20 mg/m2 at days 1-5, 22-26, 43-37; 33 mg/m2 at days 1-3, 22-24, 43-45; 6 mg/m2 daily; see supplementary data for details). HR, hazard ratio; SHR, subdistribution hazard ratio.

**Table 1. Baseline Characteristics of Patients 65 Years and Older Who Underwent Definitive Chemoradiation for Locoregionally Advanced Head and Neck Squamous Cell Carcinoma between 2005 and 2019.** CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus. Please note that the initially prescribed chemotherapy regimen was considered for this analysis (e.g., patients treated with cisplatin first and then switched to carboplatin were included in the cisplatin group).

| Characteristic | Number (%) |
|---|---|
| **Age, median (IQR), y** | 71 (68-76) |
| **Sex** | |
| Female | 215 (30.8) |
| Male | 482 (69.2) |
| **ECOG** | |
| 0 | 226 (32.4) |
| 1 | 364 (52.2) |
| ≥2 | 96 (13.8) |
| Missing | 11 (1.6) |
| **CCI, median (IQR)**[a] | 1 (0-3) |
| **Smoking** | |
| Never smoker/limited smoking | 188 (27.0) |
| Smoking >10 pack-years | 393 (56.4) |
| Missing | 116 (16.6) |
| **Localization** | |
| Oral cavity | 89 (12.8) |
| Oropharynx | 383 (54.9) |
| Hypopharynx | 111 (15.9) |
| Larynx | 84 (12.1) |
| Oro-/Hypopharynx | 30 (4.3) |
| **Clinical T stage** | |
| cT1 | 35 (5.0) |
| cT2 | 90 (12.9) |
| cT3 | 224 (32.1) |
| cT4 | 348 (49.9) |
| **Clinical N stage** | |
| cN0 | 114 (16.4) |
| cN1 | 86 (12.3) |
| cN2a | 17 (2.4) |
| cN2b | 147 (21.1) |
| cN2c | 147 (21.1) |
| cN2, not specified | 147 (21.1) |
| cN3 | 39 (5.6) |
| **HPV status of oropharynx carcinomas** | |
| HPV-positive | 151 (39.4) |
| HPV-negative | 75 (19.6) |
| Missing | 157 (41.0) |
| **Radiotherapy dose, median (IQR), Gy** | 70.0 (69.3-70.4) |
| **Radiotherapy completion** | |
| Radiotherapy completed | 633 (90.8) |
| Radiotherapy not completed | 64 (9.2) |
| **Chemotherapy regimen** | |
| Cisplatin | 310 (44.5) |
| Cisplatin + 5-fluorouracil | 137 (19.7) |
| Carboplatin | 73 (10.5) |
| Mitomycin c + 5-fluorouracil | 64 (9.2) |
| Mitomycin c | 50 (7.2) |
| Carboplatin + paclitaxel | 27 (3.9) |
| Cisplatin + paclitaxel | 13 (1.9) |
| Paclitaxel | 12 (1.7) |
| Others | 11 (1.6) |

[a] 695 patients

**Table 2. Summary of Oncological Data for the Analyzed Chemotherapy Regimens in Older Adults who Underwent Definitive Chemoradiation for Locoregionally Advanced Head and Neck Squamous Cell Carcinoma between 2005 and 2019.** 95% confidence intervals are shown in square brackets. DM, distant metastases; LRF, local and/or locoregional failure; OS, overall survival; PFS, progression-free survival.

| Regimen | 2-year OS | 2-year PFS | 2-year incidence of LRFs | 2-year incidence of DMs |
|---|---|---|---|---|
| **Entire cohort (patients aged ≥65 years)** | | | | |
| Single-agent cisplatin | 71.1 [65.8-76.7] | 58.5 [53.0-64.6] | 18.5 [13.9-23.1] | 11.1 [7.3-14.8] |
| Multi-agent cisplatin | 63.2 [55.7-71.6] | 54.5 [46.9-63.2] | 17.3 [11.1-23.5] | 8.4 [3.8-13.0] |
| Cisplatin-based chemotherapy (including single-agent and multi-agent) | 68.3 [63.9-72.9] | 57.1 [52.6-62.0] | 18.1 [14.4-21.8] | 10.1 [7.2-13.0] |
| Single-agent carboplatin | 70.2 [58.5-84.2] | 42.1 [30.8-57.4] | 32.4 [20.3-44.5] | 10.8 [2.4-19.3] |
| Carboplatin-based chemotherapy | 73.4 [64.2-83.9] | 46.0 [36.3-58.3] | 28.8 [19.0-38.6] | 9.7 [3.2-16.1] |
| Mitomycin-based chemotherapy | 57.3 [48.7-67.4] | 50.9 [42.4-61.1] | 16.0 [9.2-22.8] | 8.1 [3.0-13.1] |
| **Subgroup analysis for patients aged ≥70 years** | | | | |
| Single-agent cisplatin | 72.6 [66.4-79.4] | 60.8 [54.2-68.2] | 15.8 [10.6-21.0] | 12.6 [7.8-17.5] |
| Multi-agent cisplatin | 62.2 [52.3-73.9] | 53.7 [43.8-65.9] | 18.8 [10.2-27.3] | 8.8 [2.6-15.1] |
| Cisplatin-based chemotherapy (including single-agent and multi-agent) | 69.4 [64.0-75.3] | 58.7 [53.1-64.9] | 16.7 [12.3-21.2] | 11.4 [7.6-15.3] |
| Single-agent carboplatin | 68.0 [55.0-84.1] | 40.3 [28.3-57.5] | 30.8 [17.7-43.9] | 13.0 [3.0-23.1] |
| Carboplatin-based chemotherapy | 70.8 [60.5-82.8] | 45.1 [34.7-58.8] | 25.8 [15.4-36.1] | 11.5 [3.8-19.1] |
| Mitomycin-based chemotherapy | 59.5 [49.7-71.2] | 54.0 [44.2-65.9] | 12.1 [5.1-19.2] | 7.4 [1.7-13.0] |