

## CLINICAL INVESTIGATION

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



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**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 radiation therapy is considered the standard regimen for patients with locoregionally advanced HNSCC, there is substantial real-world heterogeneity regarding concomitant chemotherapy in older patients with HNSCC.

**Methods and Materials:** The SENIOR study is an international multicenter cohort study including older patients ( $\geq 65$  years) with HNSCC treated with definitive radiation therapy at 13 academic centers in the United States and Europe. Patients with concomitant chemoradiation were analyzed regarding overall survival (OS) and progression-free survival (PFS) via Kaplan-Meier analyses. Fine-Gray competing risk regressions were performed regarding the incidence of locoregional failures and distant metastases.

**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 (hazard ratio [HR], 1.39 [1.03-1.89];  $P < .05$ ) and a higher incidence of locoregional failures (subdistribution HR, 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 multiagent cisplatin regimens (all  $P > .05$ ). The median cumulative dose of cisplatin was 180 mg/m<sup>2</sup> (IQR, 120-200 mg/m<sup>2</sup>). Cumulative cisplatin doses  $\geq 200$  mg/m<sup>2</sup> were associated with increased OS (HR, 0.71 [0.53-0.95];  $P = .02$ ), increased PFS (HR, 0.66 [0.51-0.87];  $P = .003$ ), and lower incidence of locoregional failures (subdistribution HR, 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 in the standard chemotherapy regimen for older patients with HNSCC who can tolerate cisplatin. Cumulative cisplatin doses are prognostically relevant in older patients with HNSCC. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

## Introduction

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

Concomitant chemotherapy significantly improves survival in patients with HNSCC compared with definitive radiation therapy alone, as reported in the MACH-NC meta-analysis, but the survival benefit appears to decline with increasing age and to be absent in patients aged 70 years and older.<sup>8</sup> Large database analyses based on the Surveillance, Epidemiology, and End Results registry and the National Cancer Database reported conflicting results regarding the value of concomitant chemotherapy in older patients with HNSCC.<sup>9,10</sup> A previous international

multicenter cohort study reported significant improvement in overall survival (OS) and progression-free survival (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.<sup>11</sup>

Although both the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines indicate concomitant high-dose cisplatin (100 mg/m<sup>2</sup> at days 1, 22, and 43) as the treatment standard for definitive chemoradiation, a significant number of treatment centers favor a weekly cisplatin regimen of 40 mg/m<sup>2</sup> for older patients with HNSCC given the reduced toxicity burden for this regimen.<sup>11-14</sup> Oncological equivalence between the 3-weekly high-dose cisplatin regimen and the weekly cisplatin regimen with 40 mg/m<sup>2</sup> has been shown for the postoperative condition.<sup>15</sup> Two large randomized trials, the ConCERT trial (CTRI/2018/03/012422) and the NRG-HN009 trial (NCT05050162), are comparing these 2 cisplatin regimens for definitive chemoradiation. As reported by the ConCERT trial, weekly cisplatin was noninferior to 3-weekly high-dose cisplatin and was better tolerated with less interruptions, hospitalizations, and toxicity.<sup>16</sup>

Besides the controversy regarding cisplatin dosing, further uncertainty exists regarding whether cisplatin may be replaced by alternative agents, such as carboplatin, in older patients with HNSCC. The one noninferiority trial

comparing carboplatin with cisplatin concomitantly to radiation therapy for patients with nasopharyngeal carcinoma showed comparable survival rates and fewer toxicities (renal toxicity, leucopenia, and anemia) for carboplatin.<sup>17</sup> However, there are no data from randomized phase 3 trials comparing cisplatin with carboplatin for non-nasopharyngeal HNSCC. Given the prospective evidence for other regimens, mitomycin C- and taxane-based protocols are also used in the clinical routine.<sup>18-20</sup> However, older patients with HNSCC have been highly underrepresented in clinical trials. The median age was about 55 years in both the ARO 95-06<sup>18</sup> and IAEA mitomycin C trials<sup>19</sup> and 56 years in the University of Maryland trial of carboplatin plus paclitaxel.<sup>20</sup>

Considering the limited evidence regarding the optimal chemotherapy regimen concomitantly to definitive radiation therapy in older adults with HNSCC, we conducted a comprehensive multicenter cohort analysis to examine the effects of different chemotherapy regimens on OS, 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 used chemotherapy regimens across various oncological outcome measures, including locoregional and distant tumor control. Even though there are conflicting definitions regarding when a patient should be considered as “old” or “elderly,”<sup>21</sup> many guidelines indicate 65 years as the threshold.<sup>22,23</sup> Therefore, we decided to use a cutoff of 65 years as an inclusion criterion for our cohort analysis. Recognizing that other guidelines consider 70 years as the threshold for the definition of an older adult<sup>24</sup> and that the MACH-NC meta-analysis reported no benefit of concomitant chemotherapy for patients aged 70 years and older,<sup>8</sup> we also conducted subgroup analyses of patients 70 years and older.

## Methods and Materials

### Study design

The present study comprises a subset of patients who were included in an international registry (SENIOR, NCT05337631) currently consisting of 1100 older adults with LA-HNSCC (Fig. E1). Patient and treatment data were collected retrospectively from 13 academic centers in the United States, Germany, Switzerland, and Cyprus. The present analysis includes 697 patients aged 65 years and older diagnosed with LA-HNSCC 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 radiation therapy alone within the SENIOR 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 carcinoma or radiation

therapy in the head and neck region; presented with distant metastases at treatment initiation; or had cancers of the nasopharynx, salivary glands, or skin or cancers of an unknown primary were excluded.

This study used the seventh 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.<sup>25</sup> The Modification of Diet in Renal Disease 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 Ethics Committee of the University of Freiburg (551/18), Germany, 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 are presented as the median and IQR or absolute number and percentage. Different chemotherapy groups were compared using 1-way analysis of variance for age, CCI, estimated glomerular filtration rate, and radiation therapy dose or  $\chi^2$  tests for categorical variables. OS and PFS were calculated using the Kaplan-Meier method. Death, local or locoregional progression, and development of DMs were considered events for PFS. Endpoints were calculated from the start of radiation therapy until an event or last follow-up date, with patients being censored at the last date of follow-up. Proportional hazards models were used to evaluate the incidence of LRFs and DMs, with death considered a competing risk. Multivariate Cox proportional hazards analyses were conducted regarding OS, and Fine-Gray proportional hazards models with death as a competing risk were used to determine the incidence of LRFs and DMs.

For regression analyses, multiple imputation of missing data was conducted using k-nearest neighbor imputation, in which the 5 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, the inferences drawn from them may not be reproducible. A  $P$  value  $<.05$  was considered 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

**Table 1** Baseline characteristics of 697 patients 65 years and older who underwent definitive chemoradiation for locoregionally advanced head and neck squamous cell carcinoma between 2005 and 2019

Characteristic	Median (IQR) or no. (%)
Age, y	71 (68-76)
Sex	
Female	215 (30.8)
Male	482 (69.2)
ECOG performance status	
0	226 (32.4)
1	364 (52.2)
≥2	96 (13.8)
Missing	11 (1.6)
Charlson Comorbidity Index	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)
Radiation therapy dose, Gy	70.0 (69.3-70.4)

(Continued)

**Table 1** (Continued)

Characteristic	Median (IQR) or no. (%)
Radiation therapy completion	
Radiation therapy completed	633 (90.8)
Radiation therapy 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)

Patients were categorized according to initially prescribed chemotherapy regimen (eg, patients initially treated with cisplatin and then switched to carboplatin were included in the cisplatin group).  
Abbreviations: ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus.

status ≤1 and 502 had a CCI ≤2 (72.0%), indicative of relatively few comorbidities. Tumors were most commonly located in the oropharynx (n = 383, 54.9%), followed by the 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. Approximately one-fifth (n = 151, 22%) presented with human papillomavirus (HPV)-positive oropharyngeal carcinomas. Radiation therapy was administered at a median dose of 70.0 Gy (IQR, 69.3-70.4 Gy), and 633 patients (90.8%) completed the prescribed radiation therapy course. 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%), 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%). Descriptive statistics according to the type of concomitant systemic treatment are shown in [Table E1](#).

Among patients treated with single-agent cisplatin, the median cumulative cisplatin dose was 180 mg/m<sup>2</sup>, and 146 patients (48% of patients with known cumulative cisplatin dose) achieved a cumulative dose of ≥200 mg/m<sup>2</sup>. The median cumulative cisplatin dose of patients receiving any type of cisplatin-containing regimen (n = 451 with known cumulative cisplatin dose) was also 180 mg/m<sup>2</sup>, and 191 patients (42%) were exposed to a cumulative dose of ≥200 mg/m<sup>2</sup> ([Table E2](#)). Patients treated with weekly 30 to 40

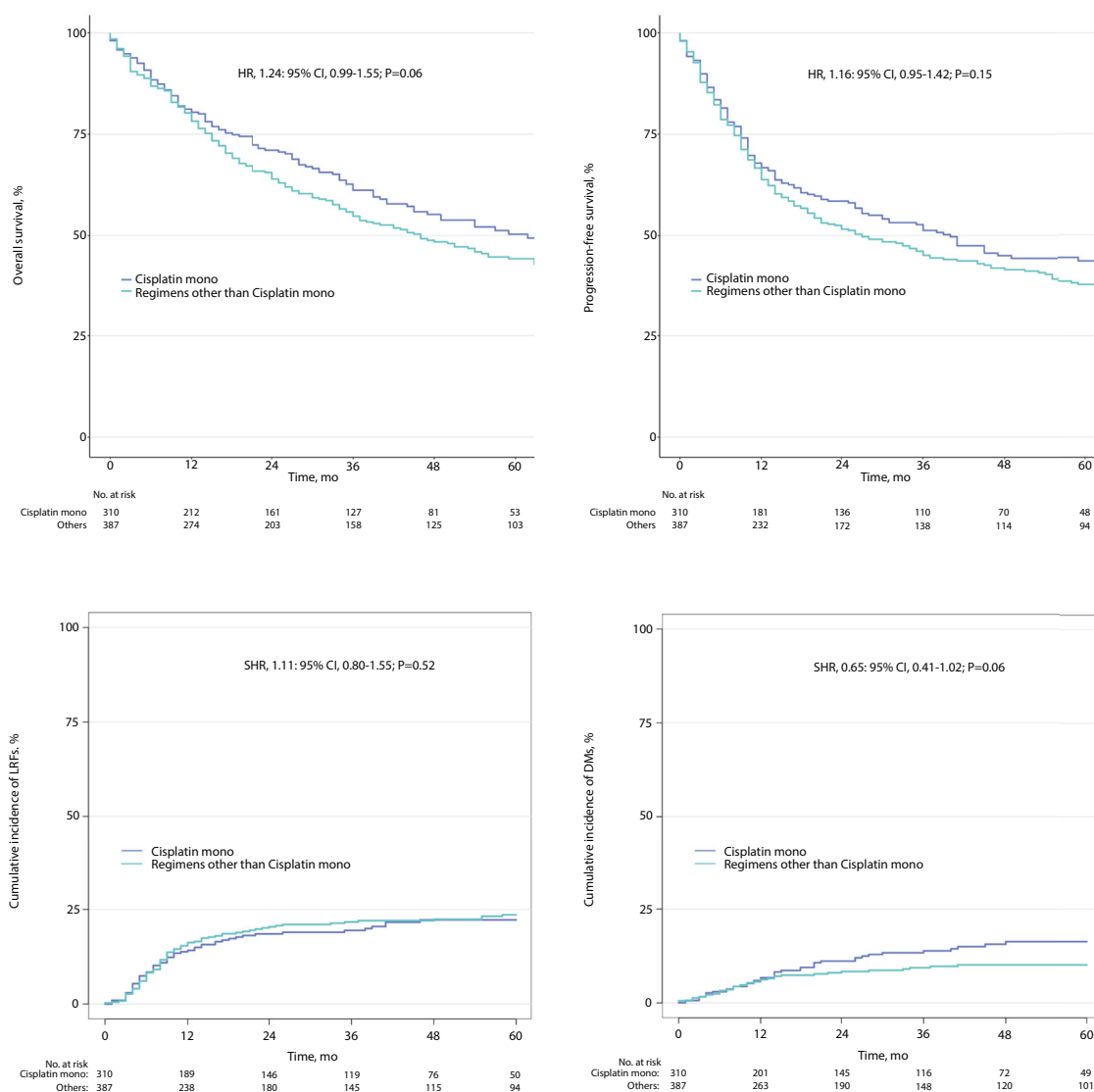
mg/m<sup>2</sup> cisplatin (n = 157) received a median cumulative dose of 180 mg/m<sup>2</sup>, of whom 83 (53%) completed  $\geq 5$  cycles of weekly cisplatin (Table E3). The vast majority of weekly cisplatin regimens consisted of 40 mg/m<sup>2</sup> as a single dose (n = 130, 83%).

## Comparison of cisplatin with 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 regimens other than single-agent cisplatin exhibited a nonsignificant trend toward lower OS (HR, 1.24; 95% CI, 0.99-1.55;  $P = .06$ ), whereas their PFS (HR, 1.16; 95% CI, 0.95-1.42;  $P = .15$ ), incidence of LRFs (subdistribution HR [SHR], 1.11; 95% CI, 0.80-1.55;  $P = .52$ ), and incidence of DMs (SHR, 0.65; 95% CI, 0.41-1.02;  $P = .06$ ) did not significantly differ from those of patients treated with single-agent cisplatin (Fig. 1). In patients aged  $\geq 70$  years, treatment with single-agent cisplatin resulted in improved OS (HR, 1.35; 95% CI,

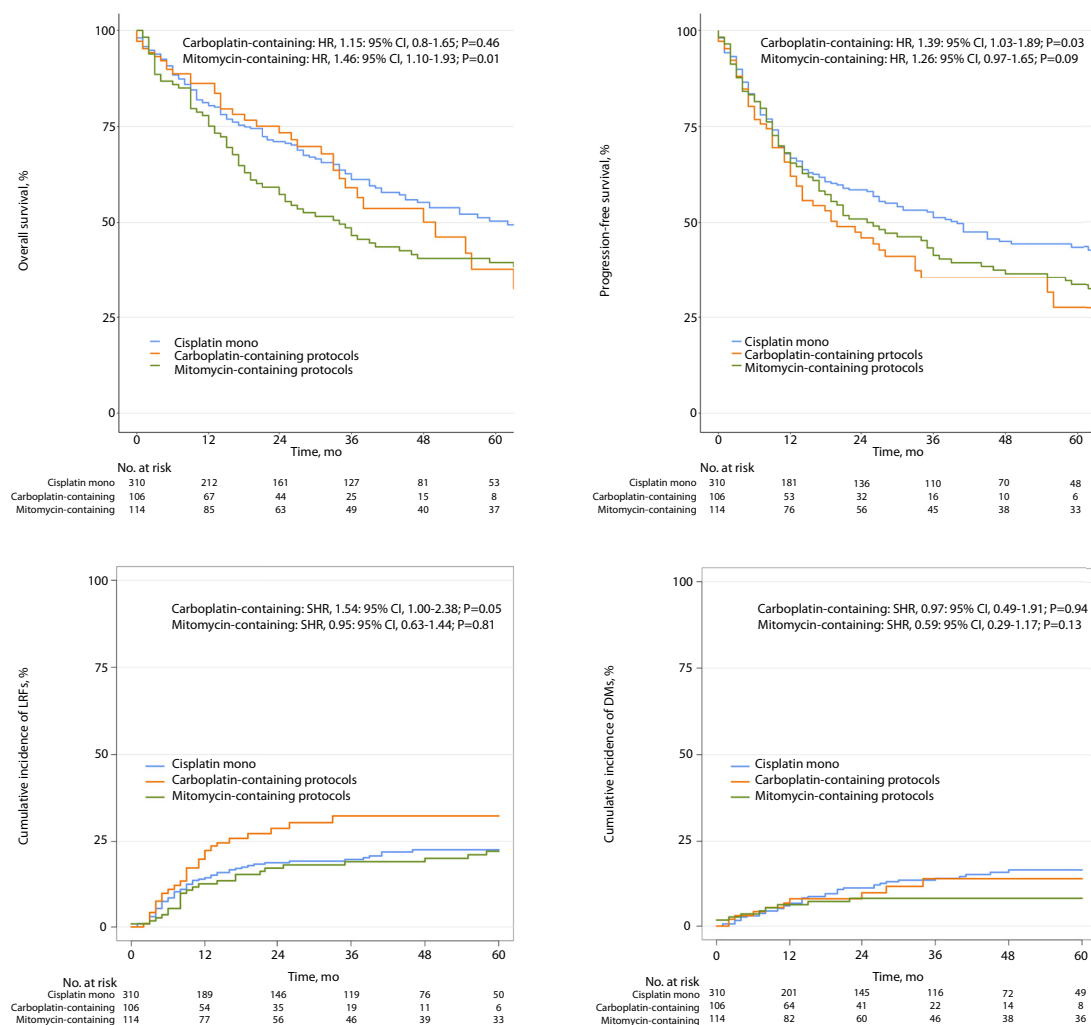


**Fig. 1.** Overall survival, progression-free survival, incidence of locoregional failures, and incidence of distant metastases of patients 65 years and older with head and neck squamous cell carcinoma receiving either single-agent cisplatin or other chemotherapy regimens, including multiagent cisplatin, carboplatin-based, and mitomycin C-based regimens, concomitantly with definitive radiation therapy. *Abbreviations:* HR = hazard ratio; SHR = subdistribution hazard ratio.

1.03-1.77;  $P = .03$ ), whereas their incidence of LRFs did not significantly differ (SHR, 1.24; 95% CI, 0.81-1.90;  $P = .31$ ) from that of patients treated with other regimens (Fig. E2).

Cisplatin-based regimens (including both single-agent cisplatin and multiagent 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, whereas the 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;  $P = .22$ ) for cisplatin-based regimens did not significantly differ from that of other regimens (Fig. E3). However, in the multivariate Cox regression model, use of neither single-agent cisplatin (Table E4) nor cisplatin-based chemotherapy (Table E5) was an independent prognostic parameter for OS.

As concomitant carboplatin is often discussed as an alternative to cisplatin, we compared single-agent cisplatin with carboplatin-containing regimens, including carboplatin mono, carboplatin plus paclitaxel, carboplatin plus docetaxel, and carboplatin plus 5-fluorouracil (Fig. 2). We found that carboplatin-containing regimens were associated with reduced PFS (HR, 1.39; 95% CI, 1.03-1.89;  $P < .05$ ) and a higher incidence of LRFs (SHR, 1.54; 95% CI, 1.00-2.38;  $P = .05$ ) compared with single-agent cisplatin but were associated with comparable OS (HR, 1.15; 95% CI, 0.80-1.65;  $P = .46$ ) and incidence of DMs (SHR, 0.97; 95% CI, 0.49-1.91;  $P = .94$ ). We found the same in the subgroup of patients aged  $\geq 70$  years (Fig. E4). Patients treated with mitomycin C-containing regimens exhibited significantly lower OS (HR, 1.46; 95% CI, 1.10-1.93;  $P = .01$ ); however,



**Fig. 2.** Overall survival, progression-free survival, incidence of locoregional failures, and incidence of distant metastases of patients 65 years and older with head and neck squamous cell carcinoma receiving single-agent cisplatin, carboplatin-based regimens, or mitomycin C-based regimens concomitantly with definitive radiation therapy. *Abbreviations:* HR = hazard ratio; SHR = subdistribution hazard ratio.

**Table 2** Summary of oncological data for the analyzed chemotherapy regimens of older adults who underwent definitive chemoradiation for locoregionally advanced head and neck squamous cell carcinoma between 2005 and 2019

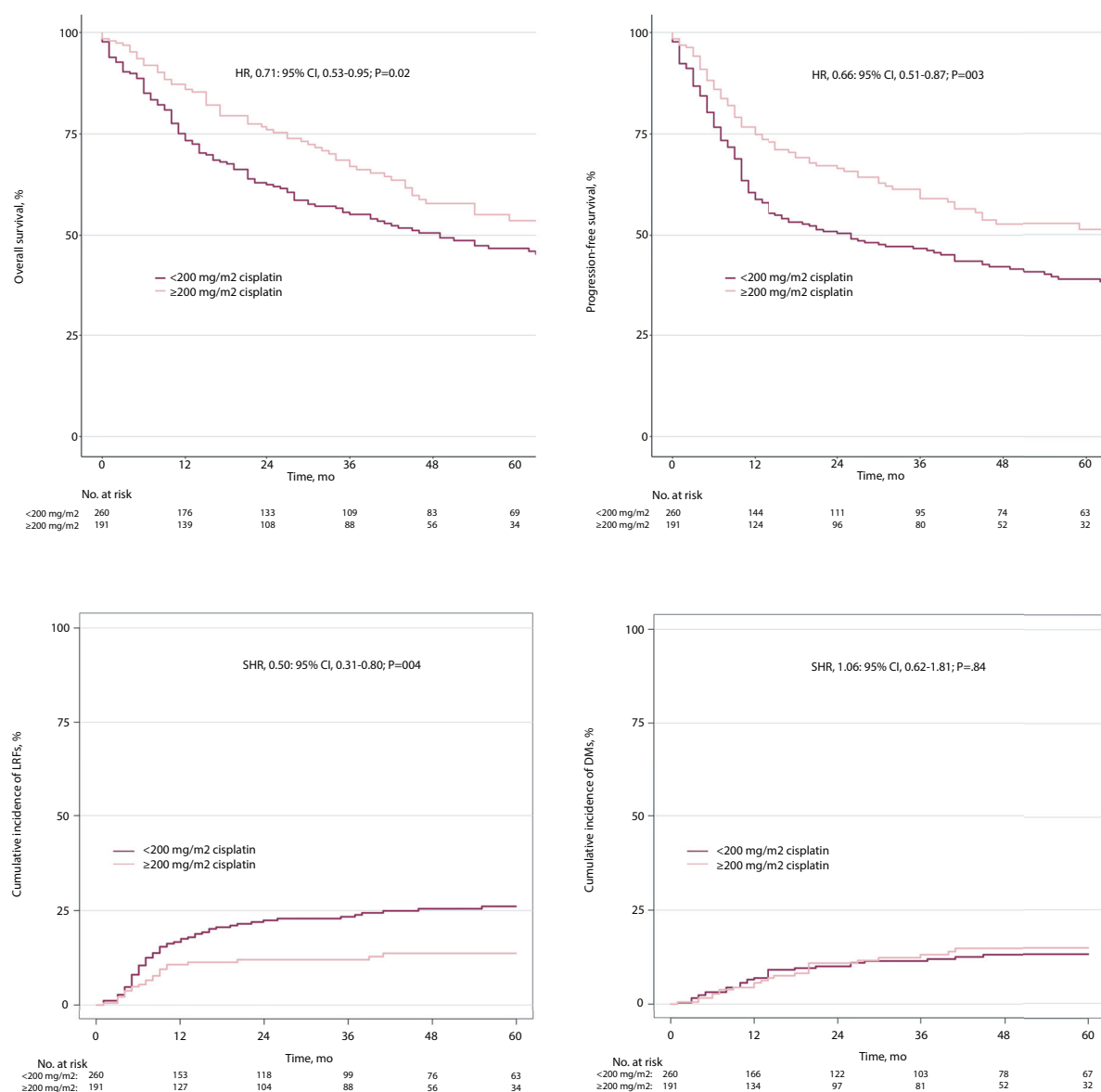
Regimen	2-y OS	2-y PFS	2-y LRF incidence	2-y DM incidence
Entire cohort (patients aged $\geq 65$ y)				
Single-agent cisplatin	71.1 (65.8-76.7)	58.5 (53.0-64.6)	18.5 (13.9-23.1)	11.1 (7.3-14.8)
Multiagent cisplatin	63.2 (55.7-71.6)	54.5 (46.9-63.2)	17.3 (11.1-23.5)	8.4 (3.8-13.0)
Cisplatin-based chemotherapy (including single-agent and multiagent)	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 of patients aged $\geq 70$ y				
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)
Multiagent 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 multiagent)	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)
Data are presented as percentages (95% CI). Abbreviations: DM = distant metastases; LRF = local and/or locoregional failure; OS = overall survival; PFS = progression-free survival.				

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 (Fig. 2). Subgroup analyses for mitomycin C–based regimens in the cohort of patients aged 70 years and older are shown in Figure E4.

Addition of further chemotherapeutic agents (eg, 5-fluorouracil) to single-agent cisplatin did not translate into 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, 0.66; 95% CI, 0.36-1.19;  $P = .17$ ) compared with single-agent cisplatin alone (Figs. E5 and E6). In general, multiagent chemotherapy protocols yielded comparable oncological outcomes compared with single-agent protocols (Fig. E7). Subgroup analyses for patients with HPV-positive and HPV-negative oropharyngeal cancer are shown in Figures E8 to E11. Even though patient numbers were rather small for this subgroup analysis, older adults with HPV-positive oropharyngeal cancer ( $n = 151$ ) treated with single-agent cisplatin exhibited significantly longer OS compared with patients with HPV-positive oropharyngeal cancer receiving other regimens (HR, 2.58; 95% CI, 1.25-5.32;  $P = .01$ ). Comparative analyses including the oncological outcomes of patients treated with radiation therapy alone are shown in Figures E12 and E13. Table 2 summarizes the oncological outcomes at 2 years after chemoradiation according to the type of concomitant systemic treatment.

### Prognostic value of cumulative cisplatin dose

As a median cumulative cisplatin dose of at least 200 mg/m<sup>2</sup> is considered a prognostically relevant threshold in the general HNSCC population receiving definitive chemoradiation, we also analyzed this issue in our cohort of older patients with HNSCC (Fig. 3). Cumulative doses  $\geq 200$  mg/m<sup>2</sup> 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 ( $\leq 100$  mg/m<sup>2</sup>, 101-200 mg/m<sup>2</sup>, and  $> 200$  mg/m<sup>2</sup>) were compared revealed a dose-response relationship. Patients receiving up to 100 mg/m<sup>2</sup> exhibited the worst OS and PFS (Fig. E14). The incidence of LRFs was significantly reduced in patients treated with  $> 200$  mg/m<sup>2</sup> compared with patients receiving  $\leq 100$  mg/m<sup>2</sup> (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 (Figs. E15 and E16). However, in the multivariate regression analyses, a median cumulative cisplatin dose of at least 200 mg/m<sup>2</sup> was not prognostic for OS (HR, 0.71; 95% CI, 0.42-1.07;  $P = .10$ ) or the incidence of LRFs (SHR, 0.69; 95% CI, 0.35-1.35;  $P = .28$ ) (Tables E6 and E7). When the cumulative cisplatin dose was entered as continuous variable into the multivariate analyses, it was an independent favorable



**Fig. 3.** Overall survival, progression-free survival, incidence of locoregional failures, and incidence of distant metastases of patients 65 years and older with head and neck squamous cell carcinoma according to cumulative cisplatin dose administered during chemoradiation. *Abbreviations:* HR = hazard ratio; SHR = subdistribution hazard ratio.

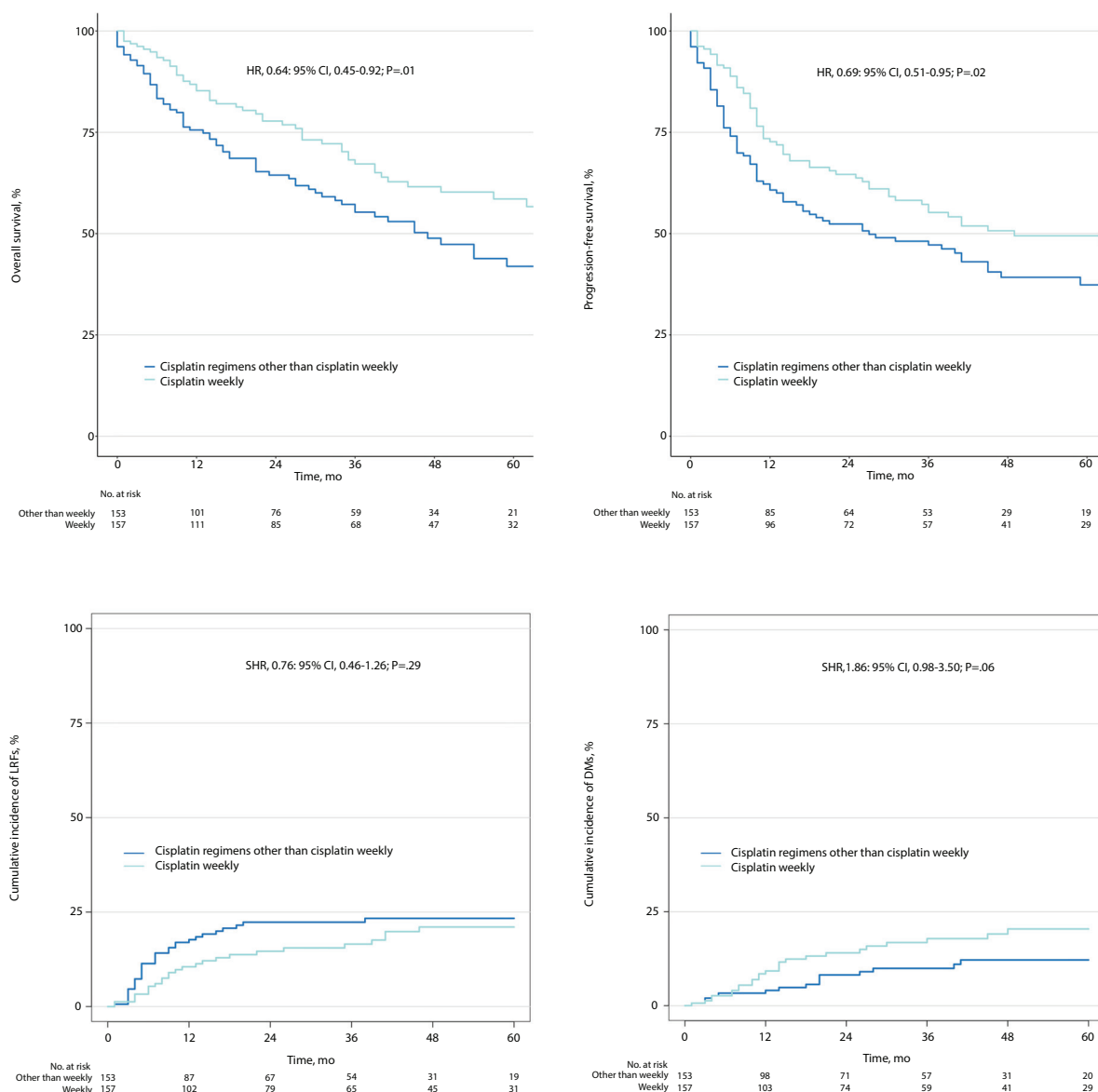
prognostic variable in terms of OS (HR, 0.996; 95% CI, 0.993-0.999;  $P = .009$ ), whereas the association between the cumulative cisplatin dose and the incidence of LRFs was not statistically significant (SHR, 0.995; 95% CI, 0.990-1.000;  $P = .06$ ) (Tables E8 and E9).

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 (eg, cisplatin 20 mg/m<sup>2</sup> at days 1-5 and 29-33; cisplatin 20 mg/m<sup>2</sup> at days 1-5, 22-26, and 43-47), whereas there was no significant difference in 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;  $P = .06$ ) (Fig. 4). There were no significant differences in oncological outcomes between patients treated with weekly cisplatin and patients receiving

high-dose 3-weekly cisplatin (Fig. E17), but only a few patients ( $n = 9$ ) received high-dose 3-weekly cisplatin. Cumulative cisplatin doses did not significantly differ between weekly cisplatin and other single-agent cisplatin regimens (mean, 182 mg/m<sup>2</sup> [weekly] vs 172 mg/m<sup>2</sup> [other regimens];  $P = .193$ ; Table E10).

## 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



**Fig. 4.** Overall survival, progression-free survival, incidence of locoregional failures, and incidence of distant metastases of patients 65 years and older with head and neck squamous cell carcinoma according to type of cisplatin administration. Cisplatin 30 to 40 mg/m<sup>2</sup> weekly was compared with all other applied single-agent cisplatin regimens (eg, 100 mg/m<sup>2</sup> on days 1, 22, and 43; 20 mg/m<sup>2</sup> on days 1-5 and 29-33; 20 mg/m<sup>2</sup> on days 1-5, 22-26, and 43-37; 33 mg/m<sup>2</sup> on days 1-3, 22-24, and 43-45; 6 mg/m<sup>2</sup> daily; see supplementary Table 2). *Abbreviations:* HR = hazard ratio; SHR = subdistribution hazard ratio.

nor cisplatin-based regimens were independent parameters for 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 multiagent chemotherapy is not superior to single-agent chemotherapy,<sup>26</sup> our data do not support multiagent cisplatin regimens such as cisplatin plus 5-fluorouracil. A previous retrospective multicenter analysis reported similar oncological outcomes but significantly fewer

toxicities after single-agent cisplatin compared with cisplatin plus 5-fluorouracil.<sup>27</sup> In addition, the toxicity profile of 5-fluorouracil (eg, cardiotoxicity, diarrhea, and mucositis) makes its use challenging in the older HNSCC population when given in combination with cisplatin.<sup>5,28</sup> A retrospective analysis of patients with LA-HNSCC treated with chemoradiation in 2 Dutch cancer centers found significantly lower chemotherapy completion rates for carboplatin plus 5-fluorouracil than for single-agent 3-weekly cisplatin 100 mg/m<sup>2</sup>.<sup>29</sup> Another retrospective study observed that rates of late toxicity, defined as the presence of percutaneous endoscopic gastrostomy tube or tracheostomy, were higher with

carboplatin plus 5-fluorouracil (25%) compared with single-agent cisplatin (8%).<sup>30</sup> The results of other multiagent cisplatin protocols, such as cisplatin plus paclitaxel,<sup>31,32</sup> have also shown considerable risks for severe toxicities.

The known prognostic value of cumulative cisplatin dose in the general HNSCC population was validated in older patients with HNSCC.<sup>33</sup> To the best of our knowledge, this cohort study is the largest analysis of the prognostic value of cumulative cisplatin dose in older adults with LA-HNSCC. When entered as continuous variable, cumulative cisplatin dose remained an independent prognostic variable for OS, providing strong evidence of the need to improve supportive care measures (eg, intravenous hydration protocols and state-of-the-art antiemetic treatments) to ensure high cumulative cisplatin doses. However, considering the lack of prognostic benefit of a cumulative cisplatin dose of  $\geq 200$  mg/m<sup>2</sup> in the multivariate regression analysis, the optimal cumulative target dose for the older HNSCC population remains a matter of debate. Our real-world data are in accordance with patterns-of-care analyses in which weekly cisplatin is the preferred schedule of cisplatin administration in older patients with LA-HNSCC.<sup>12,34</sup> 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,<sup>15,35</sup> weekly 40 mg/m<sup>2</sup> cisplatin may be especially attractive for older patients with HNSCC who exhibit higher hazards for nephrotoxicity and ototoxicity.<sup>36-38</sup>

The finding that carboplatin-based regimens were associated with significantly reduced PFS, mainly mediated by a higher incidence of LRFs, indicates 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 patients with HNSCC with contraindications to cisplatin. A meta-analysis of 3 randomized clinical trials, 8 retrospective studies, and 1 matched-pair analysis revealed comparable 3-year survival and tumor control rates, although 5-year survival rates were higher for cisplatin.<sup>39</sup>

Both the National Comprehensive Cancer Network (as category 1) and European Society for Medical Oncology (for patients unfit for cisplatin; level of evidence II, grade of recommendation A) guidelines indicate that carboplatin plus 5-fluorouracil may be a possible chemotherapy regimen for patients with HNSCC.<sup>40,41</sup> As carboplatin plus 5-fluorouracil was only administered to 5 patients in our cohort, we cannot make any conclusions regarding the efficacy of this protocol in the older HNSCC population. The mean age was about 56 years in both the GORTEC 99-02 trial<sup>42</sup> and the GORTEC 94-01 trial<sup>43</sup> for the carboplatin plus 5-fluorouracil groups, and no patient was older than 75 years, making extrapolation of the 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,<sup>44,45</sup> 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 could be considered in older adults with very good performance status but specific contraindications to cisplatin (eg, renal or hearing impairments).<sup>46</sup> Considering the comparable OS between single-agent cisplatin and carboplatin-based regimens, which mainly consisted of single-agent carboplatin, as well as the prospective evidence for single-agent carboplatin,<sup>47,48</sup> single-agent carboplatin could be an alternative for patients with contraindications to cisplatin and moderate performance status, although further prospective evidence is warranted.

A recently published randomized phase 3 trial showed improved disease-free survival, locoregional control, and OS after addition of docetaxel to radiation therapy (either definitive [61%] or adjuvant [39%]) in patients with HNSCC unfit for cisplatin without affecting long-term quality of life.<sup>49</sup> The main strength of this trial is that it was the first randomized trial that examined the addition of concomitant systemic treatment for cisplatin-ineligible patients, which was not the inclusion criteria for the Bonner trial or the carboplatin plus 5-fluorouracil trials.<sup>42,43,50</sup> 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 to 1 patient in our cohort, so 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 (eg, breast or prostate cancer) showed acceptable compliance and toxicity rates.<sup>51,52</sup> 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 radiation therapy techniques, as only approximately 20% received intensity-modulated radiation therapy in the DHANUSH trial.

Although our analyses were based on a large international multicenter cohort study and incorporated several oncological endpoints, including incidence of LRFs and DMs, they have some limitations, mainly due to the retrospective nature 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. Therefore, the improved outcomes associated with higher cisplatin doses could be related to the fact that healthier patients were able to receive more cisplatin cycles.<sup>46</sup> However, the fact that higher cumulative cisplatin doses were also prognostic in the multivariate Cox proportional hazards analyses for OS, in which patient age, performance status, and comorbidity burden were included, makes a causative relationship 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, particularly concerning parameters for renal function or performance status, complicating consistent analyses on this issue.<sup>38,53,54</sup>

Third, few patients were treated with high-dose cisplatin (100 mg/m<sup>2</sup> on 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 the 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 exploratory nature of our analyses. The results should therefore be interpreted cautiously, but they nevertheless provide a basis for further prospective studies on the older HNSCC population.

## Conclusion

The results obtained from this cohort study of 697 older patients with LA-HNSCC suggest that single-agent cisplatin can be considered a standard regimen for older adults with LA-HNSCC who exhibit a good performance status and no specific contraindications to cisplatin. As patients who received carboplatin-based chemoradiation exhibited comparable survival rates to patients who received cisplatin-based chemoradiation, carboplatin-based regimens can be considered alternatives for patients with contraindications to cisplatin, but 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 achievement of high cumulative cisplatin doses. Further research is needed to identify the optimal treatment approach for frail patients and patients with contraindications to cisplatin.

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