Survival After Definitive Chemoradiotherapy With Concurrent Cisplatin or Carboplatin for Head and Neck Cancer

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ABSTRACT

Background: For definitive chemoradiotherapy (chemoRT) of head and neck squamous cell carcinoma (HNSCC), cisplatin is the preferred concurrent agent, with superiority over cetuximab for HPV-associated oropharyngeal squamous carcinoma recently shown in 2 randomized trials (RTOG 1016 and De-ESCALaTE). Patients who are not candidates for cisplatin may be treated with carboplatin instead, but its comparative efficacy is unclear. We analyzed nationwide patterns of care and cancer-specific outcomes after cisplatin- versus carboplatin-based chemoRT. **Patients and Methods:** Patients with locoregionally advanced (stages III–IVB according to the 6th and 7th editions of the AJCC Cancer Staging Manual) squamous cell carcinoma of the oropharynx, larynx, or hypopharynx who received definitive radiotherapy (RT) were identified in the linked SEER-Medicare database. The concurrent chemotherapy regimen was determined through corresponding Medicare claims. Death caused by HNSCC (cancer-specific mortality [CSM]) was analyzed with competing risks. Propensity score analysis and multivariable Fine-Gray regression were used to adjust for baseline differences, including age and comorbidity. **Results:** We identified 807 patients who received cisplatin-based chemoRT and 342 who received carboplatin-based chemoRT. Most carboplatin recipients (68%) had combination chemotherapy, predominantly with paclitaxel. Carboplatin- and cisplatin-based chemoRT had similar incidences of death attributable to HNSCC (3-year CSM, 29% vs 26%; *P*=.19), which persisted in propensity score–matched analysis. In addition, no significant difference in overall survival was seen in the matched cohorts. ChemoRT with either cisplatin or carboplatin was superior to RT alone and RT with concurrent cetuximab. In the multivariable model, the adjusted hazard ratio of CSM for carboplatin relative to cisplatin was 1.01 (95% CI, 0.79–1.28; *P*=.94). **Conclusions:** Definitive carboplatin-based chemoRT was equivalent to cisplatin-based therapy and superior to RT alone and RT with concurrent cetuximab. In light of recent results of the RTOG 1016 and De-ESCALaTE trials, our findings suggest that carboplatin-based regimens warrant prospective investigation as an alternative to cisplatin for patients who are not cisplatin candidates.

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Background

In 2019, an estimated 65,000 cases of head and neck (H&N) cancer will be diagnosed in the United States, with approximately 14,000 cancer-related deaths.[1] Many cases of locally or regionally advanced H&N squamous cell carcinoma (HNSCC) are treated with definitive radiotherapy (RT). For these patients, multiple clinical trials and a large meta-analysis have shown superiority of concurrent chemoradiotherapy (chemoRT) compared with RT alone.[2] Platinum chemotherapy has the strongest evidence base and longest clinical track record as the concurrent agent.

Cisplatin and carboplatin are the primary platinum agents used in the treatment of H&N cancer. Despite early interest in carboplatin in the 1990s and its use in several large clinical trials,[3–5] cisplatin has emerged as the preferred and most widely used platinum agent in the United States,[6] and its body of evidence is more extensive. ChemoRT with either cisplatin-based (typically monotherapy) or carboplatin-based (commonly in multiagent combinations) regimens is superior to RT alone, and both confer approximately 10% to 20% absolute overall survival (OS) benefit at 3 years.[3,7] However, cisplatin and carboplatin have significantly different adverse effect profiles. Cisplatin causes more nausea and vomiting, nephrotoxicity, ototoxicity, and neurotoxicity, whereas carboplatin causes more myelosuppression but is generally better tolerated[8]; consequently, carboplatin-based concurrent therapy is frequently administered to patients with comorbidities unable to tolerate cisplatin.

For patients who are not cisplatin candidates, often because of underlying renal dysfunction or hearing loss, concurrent treatment must be performed with a different agent or abandoned altogether. Cetuximab, a

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monoclonal antibody against EGFR, was widely used as an alternative concurrent agent after its combination with RT was shown to be superior to RT alone.[9,10] The RTOG 1016 and De-ESCALaTE trials directly compared cetuximab with cisplatin in patients with p16-positive oropharyngeal cancer. Recent results from both trials showed significantly inferior survival for cetuximab compared with cisplatin,[11,12] and prior studies have also suggested that cetuximab may be inferior to cisplatin for nonoropharyngeal HNSCC.[13,14] Therefore, renewed interest has been shown in identifying a chemoRT regimen more tolerable than cisplatin, without compromising efficacy.

No large or modern clinical trials have compared cisplatin- versus carboplatin-based definitive chemoRT; thus, their relative effectiveness has remained unclear. Similarly, no trials have compared concurrent cetuximab with carboplatin-based therapy. Our study analyzed national patterns of care and cancer outcomes for definitive concurrent chemoRT with cisplatin or carboplatin. Both of these regimens were also compared with RT alone and with concurrent cetuximab. The SEER-Medicare database was used because of its large sample size, national representation of real-life practice patterns and outcomes, cause-of-death information, and availability of systemic therapy, RT, and comorbidity data.

Patients and Methods

Data Source

The SEER registry captures all incident cancers from 17 regional registries covering 30% of the US population. The SEER-Medicare database links SEER cases with Medicare claims, enabling identification of diagnoses and procedures across time using ICD and Healthcare Common Procedure Coding System codes.[13] This study was approved by the Stanford University Institutional Review Board.

Cohort Identification

The SEER-Medicare database was queried for nonmetastatic, locally or regionally advanced (stages III–IVB according to the 6th and 7th editions of the *AJCC Cancer Staging Manual*) SCCs of the oropharynx, larynx, and hypopharynx diagnosed from 2004 through 2013. To ensure adequate capture of claims and to analyze a more uniform population, patients were required to have Medicare Parts A and B and no HMO coverage within 12 months of diagnosis, be enrolled in Medicare for age only, and not have a prior H&N cancer diagnosis.

All patients received definitive RT according to the SEER registry. For the RT-only cohort, patients started treatment within 120 days of diagnosis and received no chemotherapy within 6 months of diagnosis. All other patients in the study received either cisplatin (codes J9060, J9062, C9418) or carboplatin (J9045). Patients with claims for both agents within 6 months of diagnosis were excluded. Codes for RT and other chemotherapy agents and RT start date and duration were defined as described previously.[13] To identify patients treated with concurrent chemoRT and to exclude the use of induction chemotherapy, the initial RT and chemotherapy claims were required to be within 21 days of each other. Figure 1 summarizes the schema used to determine the chemoRT and RT-only cohorts. The cohort of 609 patients treated with definitive RT and concurrent cetuximab was described previously.[13]

Determination of Study Variables and Outcomes

Study variables were obtained directly from the SEER database or were calculated from the Medicare claims as described previously.[13] HPV status was not available; we performed subgroup analyses in oropharyngeal and

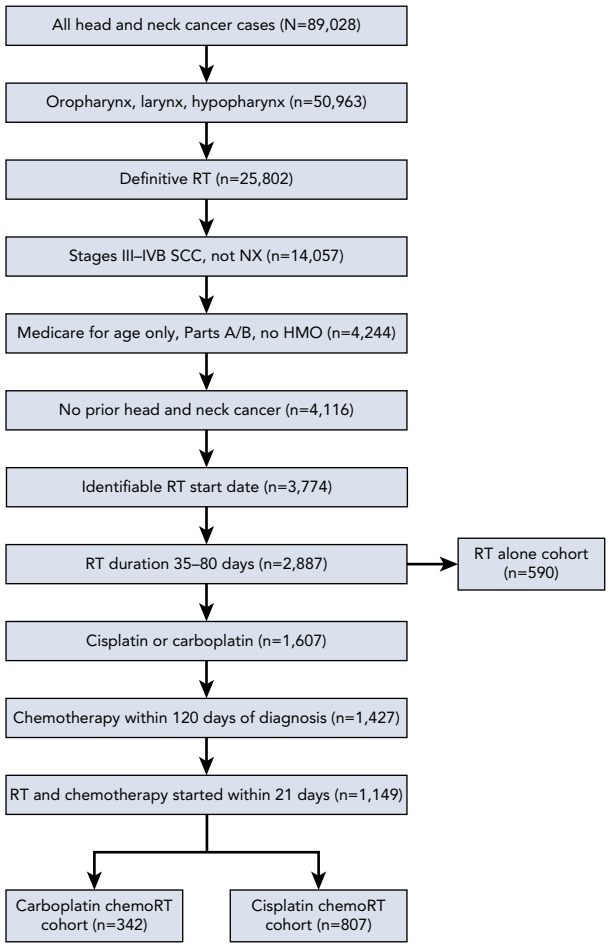

Figure 1. Cohort determination algorithm.
Abbreviations: ChemoRT, chemoradiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma.

nonoropharyngeal carcinoma. The primary study outcome was death attributable to H&N cancer (cancer-specific mortality [CSM]) determined by the SEER cause-specific death classification and cause of death to SEER site recode field. Acute toxicities were analyzed within 3 months of the end of RT, as previously described.[13]

Statistical Analysis

Baseline characteristics were compared using the chi-square or Wilcoxon rank sum test. Multivariable logistic regression was used to identify predictors for receipt of carboplatin versus cisplatin. Cumulative incidence of H&N CSM was estimated in the presence of other-cause mortality as a competing risk. For univariable analysis, CSM was compared using Gray's test.[13,15] For multivariable analysis, the proportional hazards model of Fine and Gray was used to estimate adjusted hazard ratios (HRs) for CSM and acute toxicities. Propensity score analysis was performed using 1:1 matching, as described previously.[13,15] Briefly, propensity scores were generated using logistic regression that incorporated the same covariates as in the multivariable model; matching on the logit of the propensity score between the cisplatin and carboplatin cohorts generated subsets of each that were balanced across all covariates. OS was analyzed using the Kaplan-Meier method and compared using the log-rank test. MATLAB 9.4 (MathWorks) and R version 3.3.3 (R Foundation for Statistical Computing) were used for calculations. All statistical tests were 2-sided and considered significant at $P \leq .05$.

Results

A total of 1,149 patients underwent chemoRT, of whom 807 (70%) received cisplatin and 342 (30%) received carboplatin. Median follow-up was 3.7 years in living patients. In addition, we identified 590 patients treated with definitive RT alone. Table 1 lists baseline characteristics of the cisplatin and carboplatin cohorts. Compared with cisplatin recipients, those treated with carboplatin were older, had higher comorbidity scores, and were less likely to receive intensity-modulated RT (IMRT). In multivariable logistic regression (Table 1), features significantly predictive of receiving carboplatin included increasing age (adjusted odds ratio, 1.07 per additional year; 95% CI, 1.04–1.10; $P < .0001$) and comorbidity score.

Within the carboplatin cohort, 110 patients (32%) received carboplatin monotherapy and 232 (68%) received combination chemotherapy (Figure 2A), which was predominantly with paclitaxel. By contrast, 86% of patients in the cisplatin cohort received cisplatin monotherapy (Figure 2B). H&N CSM was higher for single-agent carboplatin than for multiagent chemotherapy (34% vs 26% at 3 years) (supplemental eFigure 1, available with this article at JNCCN.org), although this difference was not statistically significant in univariable ($P=.43$) or multivariable analysis (adjusted HR, 1.43; 95% CI, 0.93–2.22; $P=.11$). Among patients who received >1 dose of carboplatin, most (84%) had weekly administration, whereas only 5% received it every 3 weeks.

Patients treated with carboplatin-based chemoRT had similar incidence of death attributable to HNSCC compared with those treated with cisplatin-based chemoRT (3-year CSM 29% vs 26%, respectively; $P=.19$). Subgroup analysis of oropharyngeal and nonoropharyngeal sites also showed a similar incidence of CSM between the cisplatin and carboplatin cohorts (supplemental eFigure 2). Both chemoRT cohorts had significantly lower CSM compared with RT alone (3-year CSM, 39%) (Figure 3) and RT with concurrent cetuximab (supplemental eFigure 3).

In the carboplatin cohort, risk of death attributable to other causes (non-CSM) was higher than in the cisplatin cohort (16% vs 11% at 3 years; $P=.05$) (supplemental eFigure 4A), consistent with the older age and higher comorbidity burden of carboplatin recipients. Accordingly, in the unadjusted analysis, OS favored the cisplatin cohort (62% vs 54% at 3 years; $P=.003$) (supplemental eFigure 4B). To adjust for baseline differences between the cisplatin and carboplatin cohorts, propensity score analysis was performed. Patient and tumor characteristics were well-balanced in the matched cohorts (supplemental eTable 1), including age and comorbidity score. Death attributable to HNSCC remained similar in the matched cohorts (3-year CSM, 29% vs 28%; $P=.54$) (Figure 4A), and other-cause mortality and OS were also comparable ($P=.76$ and $P=.35$, respectively) (Figure 4A, B), suggesting a similar level of fitness after propensity score adjustment.

In multivariable Fine-Gray regression, the adjusted HR of CSM for carboplatin relative to cisplatin was 1.01 (95% CI, 0.79–1.28; $P=.94$). Variables significantly predictive of CSM included tumor/nodal stage, age, and nonoropharyngeal disease sites (Table 2). Fine-Gray regression within the matched cohorts yielded similar results (supplemental eTable 2). Analysis of acute toxicities in the matched cohorts revealed no significant differences in rates of dysphagia, dermatitis, mucositis, emergency department visits, or unplanned hospital admissions (supplemental eFigure 5). However, significant differences were seen in inpatient diagnoses between cisplatin and carboplatin recipients with unplanned admissions. For example, cisplatin recipients were more likely to be hospitalized with acute renal failure ($P=.04$), whereas carboplatin recipients had more neutropenia ($P=.03$) and pneumonia ($P=.01$) (supplemental eTable 3).

Table 1. Baseline Patient Characteristics and Predictors of Receiving Carboplatin

	Baseline Characteristics			Logistic Regression	
	Cisplatin	Carboplatin	*P* Value[a]	Adjusted Odds Ratio (95% CI)	*P* Value[a]
Total	807	342			
Sex					
Male	651 (81%)	271 (79%)	.58	Ref	
Female	156 (19%)	71 (21%)		1.08 (0.77–1.52)	.65
Charlson comorbidity score			**<.0001**		
0	511 (63%)	168 (49%)		Ref	
1	111 (14%)	82 (24%)		2.12 (1.48–3.03)	**<.0001**
≥2	185 (23%)	92 (27%)		1.48 (1.07–2.04)	**.02**
Median age (IQR), y	70 (68–74)	72 (68–77)	**<.0001**	1.07 (1.04–1.10) per year	**<.0001**
Median diagnosis year (IQR)	2010 (2007–2012)	2008 (2005–2011)	**<.0001**	0.88 (0.83–0.92) per year	**<.0001**
Race			.23		
White	727 (90%)	300 (88%)		Ref	
Nonwhite	80 (10%)	42 (12%)		1.06 (0.69–1.64)	.79
Region			**<.0001**		
Northeast	142 (18%)	66 (19%)		Ref	
West	106 (13%)	12 (4%)		0.29 (0.14–0.58)	**.0004**
Midwest	101 (13%)	62 (18%)		1.43 (0.90–2.26)	.13
South	458 (57%)	202 (59%)		1.05 (0.72–1.53)	.79
Marital status			.87		
Married	482 (60%)	206 (60%)		Ref	
Other	325 (40%)	136 (40%)		0.98 (0.74–1.29)	.86
Census tract poverty level			.59		
<10%	401 (50%)	170 (50%)		Ref	
10%–20%	236 (29%)	92 (27%)		1.04 (0.75–1.46)	.80
>20%	170 (21%)	80 (23%)		1.22 (0.84–1.78)	.30
Smoking/Tobacco claims			.69		
Absent	200 (25%)	81 (24%)		Ref	
Present	607 (75%)	261 (76%)		1.12 (0.80–1.55)	.51
T stage			.09		
T1/TX	172 (21%)	58 (17%)		Ref	
T2	261 (32%)	124 (36%)		1.42 (0.96–2.08)	.08
T3	225 (28%)	83 (24%)		0.95 (0.60–1.52)	.83
T4	149 (18%)	77 (23%)		1.26 (0.80–1.99)	.32
N stage			.98		
N0	151 (19%)	65 (19%)		Ref	
N1–2a	254 (31%)	109 (32%)		0.93 (0.58–1.48)	.75
N2b–3	402 (50%)	168 (49%)		1.05 (0.67–1.63)	.84
Site			.31		
Oropharynx	475 (59%)	195 (57%)		Ref	
Larynx	236 (29%)	95 (28%)		0.86 (0.60–1.22)	.39
Hypopharynx	96 (12%)	52 (15%)		1.05 (0.69–1.59)	.82

(continued on next page)

Abbreviations: IMRT, intensity-modulated radiotherapy; IQR, interquartile range.
[a]Bold indicates statistically significant *P* value.

Table 1. Baseline Patient Characteristics and Predictors of Receiving Carboplatin (cont.)

	Baseline Characteristics			Logistic Regression	
	Cisplatin	Carboplatin	*P* Value[a]	Adjusted Odds Ratio (95% CI)	*P* Value[a]
IMRT claims			**.003**		
Absent	129 (16%)	80 (23%)		Ref	
Present	678 (84%)	262 (77%)		1.03 (0.70–1.51)	.88

Abbreviations: IMRT, intensity-modulated radiotherapy; IQR, interquartile range.
[a]Bold indicates statistically significant *P* value.

Discussion

The optimal treatment of patients with HNSCC who cannot receive cisplatin is highly controversial. Recently, direct comparisons of cisplatin and cetuximab in RTOG 1016[11] and De-ESCALaTE[12] have shown cetuximab to be significantly inferior to cisplatin in patients with p16-positive oropharyngeal SCC. Prior studies have also suggested that cetuximab is inferior to cisplatin for nonoropharyngeal HNSCC.[13,14] Currently, the question of which concurrent regimen to use in patients with contraindications to cisplatin is of paramount importance. Our study suggests that patients treated with carboplatin-based regimens have cancer-specific outcomes virtually equivalent to those of patients treated with cisplatin-based regimens; hence, patients with a contraindication to cisplatin may be better served with carboplatin-based therapy. Overall rates of acute toxicities did not differ significantly, but among patients who were ill enough to warrant unplanned hospital admission, the inpatient diagnoses reflected the expected adverse event profiles of the concurrent agent that was used.

In our study, patients treated with carboplatin had several key differences in baseline characteristics compared with those treated with cisplatin, as expected from clinical experience. Overall, carboplatin recipients were older and had a higher comorbidity burden than cisplatin recipients; however, no significant difference was seen in risk of death attributable to HNSCC according to the choice of platinum agent, whereas chemoRT with either cisplatin or carboplatin was superior to RT alone and RT with concurrent cetuximab. Furthermore, the propensity score–adjusted analysis showed no difference in OS between the matched cisplatin and carboplatin cohorts. In the multivariable model, the adjusted HR for CSM was 1.01, indicating that outcomes with carboplatin and cisplatin were essentially identical. Moreover, the upper 95% confidence limit of 1.28 was well within the 1.45 noninferiority threshold for the HR of cetuximab relative to cisplatin prespecified in RTOG 1016.

As the largest, most comprehensive comparison of cisplatin- versus carboplatin-based chemoRT to date, our study adds significantly to the existing literature, given that prior studies have largely been single-institution retrospective series and limited in sample size and external validity. In one study, a matched-pair analysis of 65 patients treated with carboplatin and 65 with cisplatin found similar 3-year rates of locoregional control (87% vs 79%; P=.54), freedom from distant metastasis (88% vs 85%; P=.79), and OS (59% vs 68%; P=.24).[16] Similarly, 2 series of patients who received carboplatin/5-FU or cisplatin showed comparable locoregional control, disease-free survival

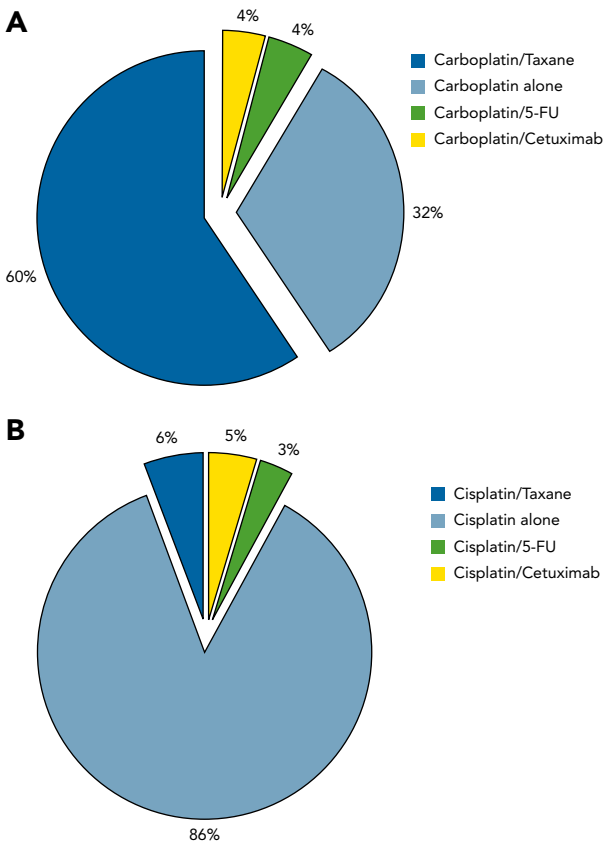

Figure 2. Chemotherapy regimens used in the (A) carboplatin and (B) cisplatin cohorts.

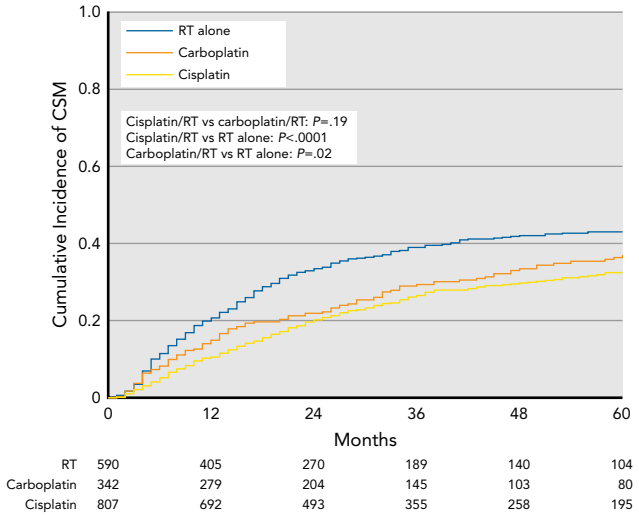

Figure 3. Cumulative incidence of CSM in patients treated with cisplatin-based chemoradiation, carboplatin-based chemoradiation, or RT alone.
Abbreviations: CSM, cancer-specific mortality; RT, radiotherapy.

(DFS), and OS with either regimen.[17,18] A prior SEER-Medicare study restricted to patients with oropharyngeal carcinoma[19] reported no difference between cisplatin- and carboplatin-based chemoRT, but also no difference between carboplatin and cetuximab; this may be because of the limited number of patients treated with carboplatin (n=69). Compared with that study, ours had a substantially larger sample size (finding carboplatin to be superior to cetuximab), included multiple H&N sites, and investigated the patterns of care corresponding to carboplatin monotherapy and combination regimens.

In addition, our results are consistent with findings from 2 small prospective studies that predate modern conformal RT techniques. In both, patients were randomly assigned to RT alone (70 Gy), chemoRT with cisplatin, or chemoRT with single-agent carboplatin.[20,21] Both trials had approximately 40 to 50 patients in each arm and found that the chemoRT arms had superior outcomes compared with RT alone. In the first trial, which used high-dose chemotherapy given every 3 weeks, disease control and survival appeared to favor cisplatin over carboplatin, but the differences were not statistically significant (3-year survival, 52% vs 42%; P=.28).[20] The other trial, which used low-dose daily chemotherapy, reported no differences between cisplatin and carboplatin for 5-year rates of local relapse-free survival (51% vs 48%; P=.75) or survival (32% vs 29%; P=.82).[21] A randomized trial of 206 patients restricted to nasopharyngeal carcinoma also showed similar outcomes for cisplatin and carboplatin,[22] although the relevance of this study to non–nasopharyngeal carcinoma HNSCC is unclear due to differences in disease biology.

Although the aforementioned trials showed superiority of concurrent carboplatin monotherapy compared with definitive RT alone,[20,21] most evidence has focused on carboplatin combination regimens, and a previous randomized trial with 72 patients found no benefit to postoperative carboplatin monotherapy compared with RT alone.[23] The carboplatin regimen most extensively studied prospectively has been carboplatin/5-FU, which was used in the seminal GORTEC 94-01 trial that showed superiority of chemoRT versus RT alone in locoregionally advanced oropharyngeal cancer.[3] More recently, this combination was used in GORTEC 99-02, which compared conventional and accelerated chemoRT

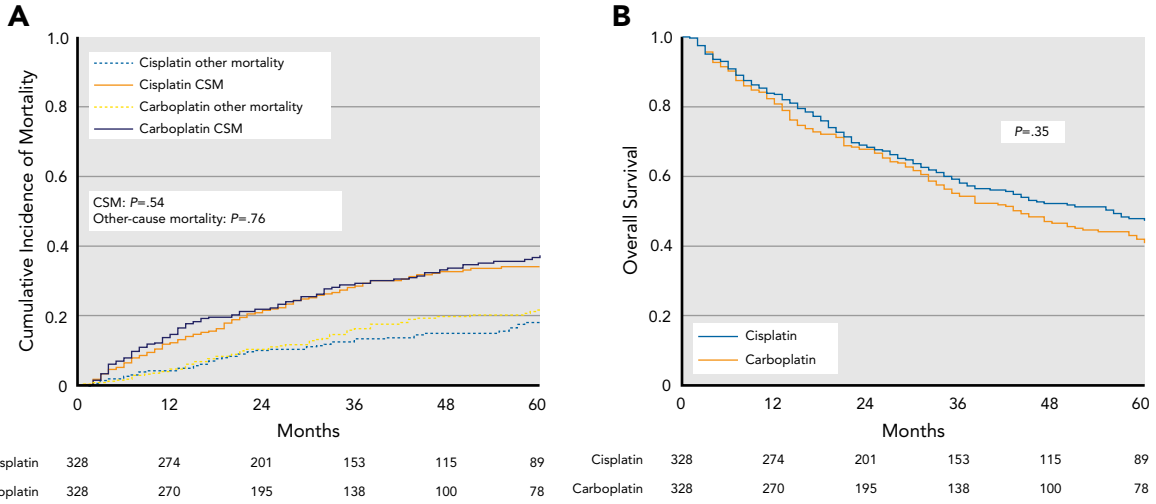

Figure 4. Analysis of (A) CSM and other-cause mortality (non-CSM) and (B) overall survival in the matched cisplatin and carboplatin cohorts.
Abbreviation: CSM, cancer-specific mortality.

Table 2. Multivariable Fine-Gray Regression for Predictors of Cancer-Specific Mortality

	Adjusted Hazard Ratio (95% CI)	*P* Value[a]
Chemotherapy backbone		
Cisplatin	Ref	—
Carboplatin	1.01 (0.79–1.28)	.94
Sex		
Male	Ref	—
Female	0.96 (0.73–1.26)	.76
Charlson comorbidity score		
0	Ref	—
1	1.09 (0.82–1.45)	.55
≥2	0.98 (0.75–1.29)	.88
Age	1.03 (1.01–1.05) per year	**.007**
Diagnosis year	0.96 (0.92–1.00) per year	**.05**
Race		
White	Ref	—
Nonwhite	0.70 (0.48–1.02)	.06
Region		
Northeast	Ref	—
West	0.84 (0.54–1.31)	.44
Midwest	1.02 (0.71–1.48)	.91
South	0.80 (0.59–1.08)	.15
Marital status		
Married	Ref	—
Other	1.21 (0.97–1.50)	.09
Census tract poverty level		
<10%	Ref	—
10%–20%	1.25 (0.96–1.62)	.10
>20%	1.39 (1.03–1.88)	**.03**
Smoking/Tobacco claims		
Absent	Ref	—
Present	1.27 (0.95–1.69)	.10
T stage		
T1/TX	Ref	—
T2	1.10 (0.77–1.55)	.61
T3	1.46 (1.01–2.11)	**.05**
T4	1.82 (1.27–2.61)	**.001**
N stage		
N0	Ref	—
N1–2a	1.17 (0.83–1.65)	.36
N2b–3	1.63 (1.19–2.21)	**.002**
Site		
Oropharynx	Ref	—
Larynx	1.68 (1.28–2.19)	**.0002**
Hypopharynx	1.61 (1.16–2.24)	**.004**
IMRT claims		
Absent	Ref	—
Present	0.87 (0.66–1.15)	.32

Abbreviation: IMRT, intensity-modulated radiotherapy.
[a]Bold indicates statistically significant *P* value.

with accelerated RT alone,[4] and in GORTEC 2007-01, which showed superiority of adding carboplatin/5-FU to RT with concomitant cetuximab.[5] As of early 2019, NCCN listed both high-dose cisplatin and carboplatin/5-FU as category 1 recommendations for concurrent chemoRT, although cisplatin is preferred.[6] In accordance with the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for H&N Cancers, our results support the use of carboplatin-based therapy on par with cisplatin.

Of note, our analysis shows that <5% of the carboplatin cohort received 5-FU or every-3-week administration, indicating a significant departure from national guidelines. Instead, most patients received weekly carboplatin, and the most common combination regimen was carboplatin/paclitaxel, which is an NCCN category 2B recommendation (in the same category as weekly cisplatin, 40 mg/m^2) and is the only concurrent carboplatin regimen besides carboplatin/5-FU listed in the NCCN Guidelines.[6] Outcomes of this regimen have been reported in older single-institution retrospective series, which found approximately 50% DFS and OS at 3 years, and 30% DFS and OS at 5 years.[24,25] Recently, an institutional series using modern RT techniques (IMRT) with concurrent carboplatin/paclitaxel in locoregionally advanced oropharyngeal cancer reported promising 5-year locoregional recurrence-free survival, DFS, and OS rates of 89%, 65%, and 71%, respectively.[26] Although our study was not powered to compare different carboplatin regimens, our finding of overall equivalency between cisplatin and carboplatin (which was mostly combined with paclitaxel) is consistent with the listing of carboplatin/paclitaxel as an alternative option for concurrent therapy in the NCCN Guidelines.[6]

Other, less-studied carboplatin-based regimens described in small series include carboplatin/docetaxel[27,28] and carboplatin/cetuximab.[29] We also observed these

regimens in a small number of patients, although these combinations are not listed in national guidelines. Overall, most patients treated with carboplatin received some form of combination chemotherapy. Only approximately one-third received carboplatin as monotherapy, and single-agent carboplatin tended to be inferior to combination chemotherapy, although this did not reach statistical significance (multivariable P=.11). Firm conclusions regarding the comparative effectiveness of single-agent versus multiagent carboplatin regimens are not possible, given the small size of the single-agent cohort (~100 patients).

The primary limitation of our study is its retrospective nature; therefore, we used competing risks analysis, propensity score analysis, and multivariable regression to adjust for potential confounders. Because there are no large or modern randomized comparisons of cisplatin- versus carboplatin-based chemoRT, our study (although hypothesis-generating) still addresses a crucial gap in knowledge. The SEER-Medicare database also does not contain information regarding RT details (fields, dose, fractionation), recurrence/local control, HPV status for oropharyngeal cancers, and pharmacologic dosing data. Even carboplatin monotherapy can be subject to variations in dosage, depending on clinical practice. However, our study can still be interpreted as an intention-to-treat analysis as in other population-based studies,[30] regardless of the actual amount of chemotherapy received in either cohort. Although HPV status was not available, our results were consistent in subgroup analyses of oropharyngeal carcinoma (which may or may not be HPV-related) and nonoropharyngeal carcinoma (ie, laryngeal and hypopharyngeal cancers), which are not HPV-related. Finally, our study comprised a Medicare-aged population and may not be directly applicable to younger patients (in whom oropharyngeal SCC is more likely to be HPV-positive); however, most patients who are ineligible for cisplatin are older and would be encompassed by our study. Appropriate patient selection for non–cisplatin-based therapy remains challenging and is subject to variations in provider preferences and institutional practices; toxicity may also not be fully captured in a claims-based analysis.

Conclusions

Our study suggests the potential equivalence of cisplatin- and carboplatin-based definitive chemoRT in the treatment of locoregionally advanced HNSCC. Carboplatin-based chemoRT was superior to RT alone and RT with concurrent cetuximab. Interestingly, most carboplatin recipients received combination therapy with paclitaxel and not 5-FU, representing a significant departure from national guidelines. Considering the results of RTOG 1016 and De-ESCALaTE showing cetuximab to be inferior to cisplatin in p16-positive oropharyngeal SCC, our study suggests that carboplatin-based regimens should be investigated further in a prospective fashion as an alternative to cisplatin for patients who are not cisplatin candidates.

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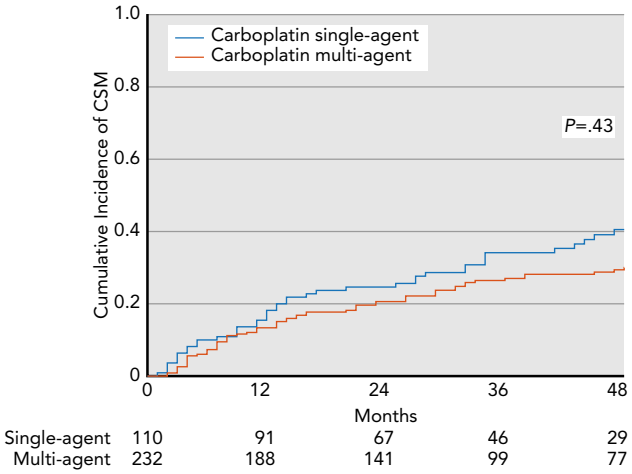
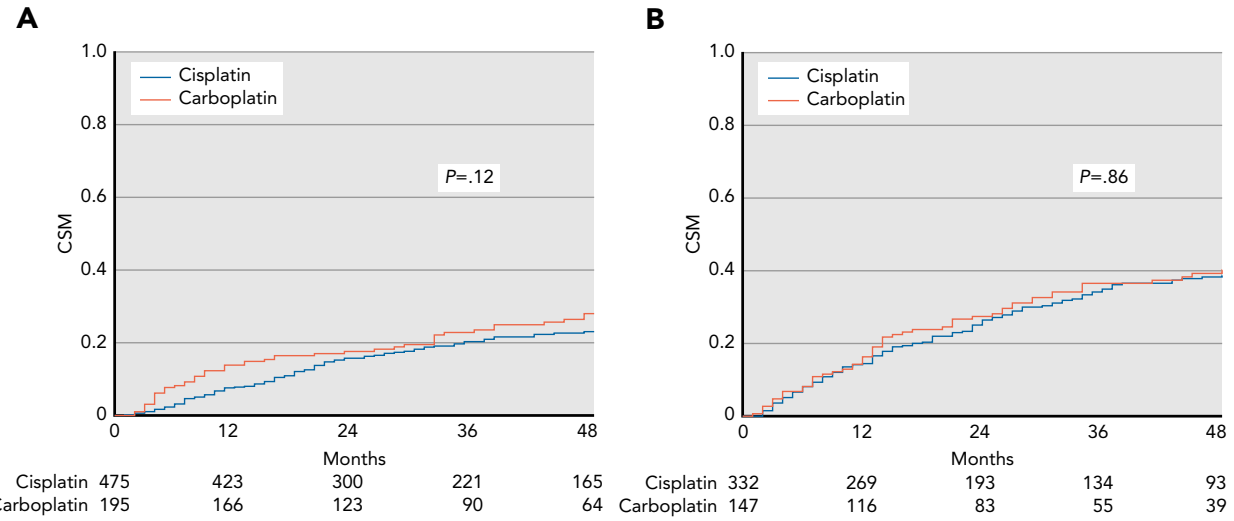
Survival After Definitive Chemoradiotherapy With Concurrent Cisplatin or Carboplatin for Head and Neck Cancer

Michael Xiang, MD, PhD; A. Dimitrios Colevas, MD; F. Christopher Holsinger, MD; Quynh-Thu X. Le, MD; and Beth M. Beadle, MD, PhD

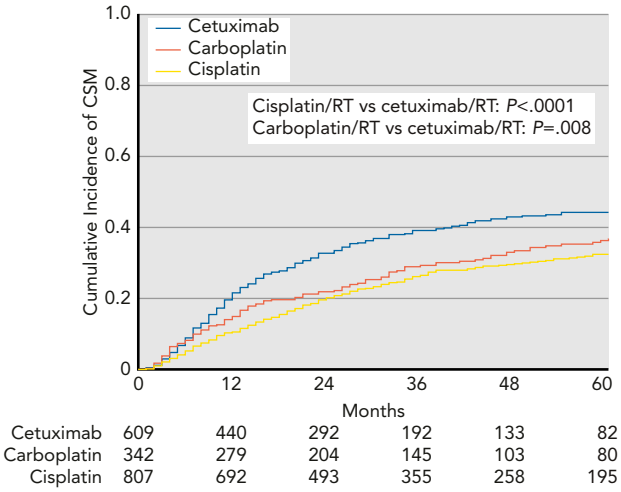
J Natl Compr Canc Netw 2019;17(9):1065–1073



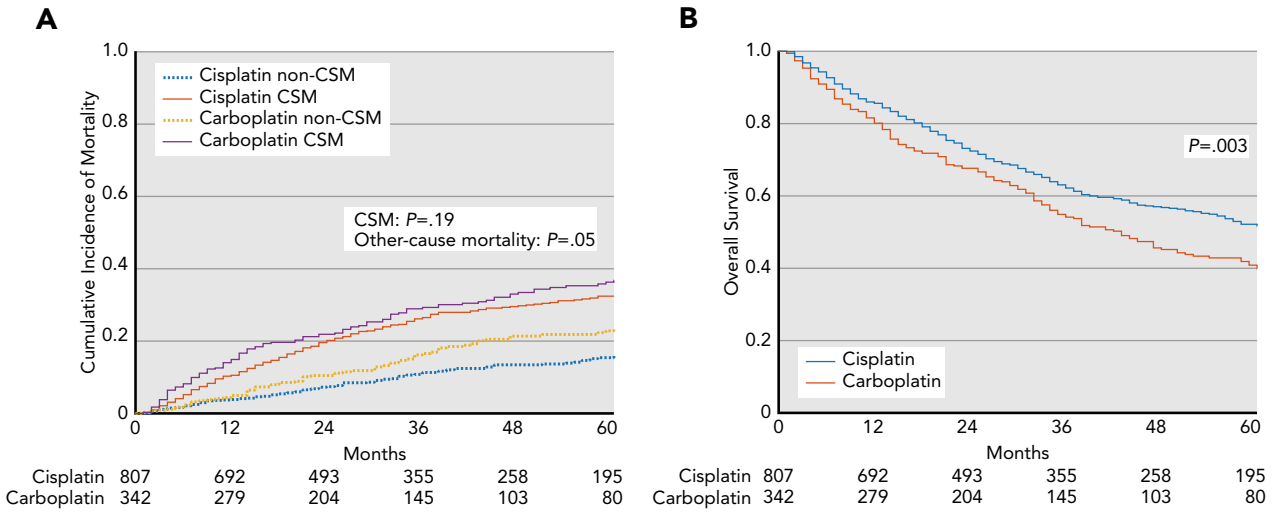
eFigure 1. Cumulative incidence of CSM with single-agent carboplatin versus multiagent carboplatin-based chemotherapy.
Abbreviation: CSM, cancer-specific mortality.



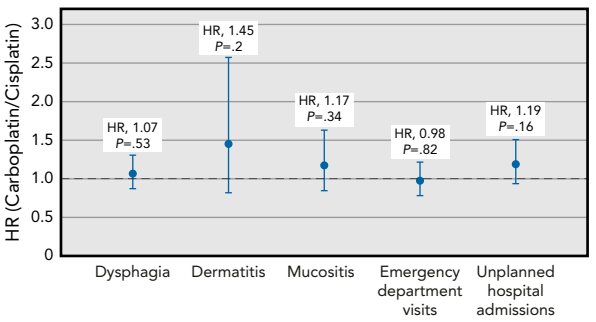
eFigure 2. CSM in subgroup analysis of (A) oropharyngeal and (B) nonoropharyngeal (larynx and hypopharynx) disease sites.
Abbreviation: CSM, cancer-specific mortality.



eFigure 3. CSM for patients who received definitive RT with concurrent cisplatin, carboplatin, or cetuximab.
Abbreviations: CSM, cancer-specific mortality; RT, radiotherapy.



eFigure 4. Analysis of (A) CSM and other-cause mortality (non-CSM) and (B) overall survival in the total cisplatin and carboplatin cohorts.
Abbreviation: CSM, cancer-specific mortality.



eFigure 5. Adjusted HR of acute toxicities (within 3 months of radiation completion) in the matched cisplatin and carboplatin cohorts.
Abbreviation: HR, hazard ratio.

eTable 1. Characteristics of the Propensity Score–Matched Cisplatin and Carboplatin Cohorts

	Cisplatin n (%)	Carboplatin n (%)	*P* Value
Total	328	328	
Sex			.77
Male	258 (79%)	261 (80%)	
Female	70 (21%)	67 (20%)	
Charlson comorbidity score			.98
0	169 (52%)	167 (51%)	
1	71 (22%)	73 (22%)	
≥2	88 (27%)	88 (27%)	
Median age (SD), y	72 (5.3)	72 (5.4)	.94
Median diagnosis year (SD)	2009 (3)	2008 (3.1)	.58
Race			.90
White	289 (88%)	288 (88%)	
Nonwhite	39 (12%)	40 (12%)	
Region			.38
Northeast	63 (19%)	62 (19%)	
West and Midwest	68 (21%)	60 (22%)	
South	197 (60%)	196 (60%)	
Marital status			.94
Married	198 (60%)	199 (61%)	
Other	130 (40%)	129 (39%)	
Census tract poverty level			.82
<10%	156 (48%)	161 (49%)	
10%–20%	88 (27%)	90 (27%)	
>20%	84 (26%)	77 (23%)	
Smoking/Tobacco claims			.65
Absent	80 (24%)	75 (23%)	
Present	248 (76%)	253 (77%)	
T stage			.78
T1/TX	65 (20%)	58 (18%)	
T2	126 (38%)	121 (37%)	
T3	77 (23%)	81 (25%)	
T4	60 (18%)	68 (21%)	
N stage			.86
N0	54 (16%)	59 (18%)	
N1–2a	108 (33%)	104 (32%)	
N2b–3	166 (51%)	165 (50%)	
Site			.77
Oropharynx	199 (61%)	190 (58%)	
Larynx	85 (26%)	92 (28%)	
Hypopharynx	44 (13%)	46 (14%)	
IMRT claims			1.00
Absent	72 (22%)	72 (22%)	
Present	256 (78%)	256 (78%)	

Abbreviation: IMRT, intensity-modulated radiotherapy.

eTable 2. Multivariable Fine-Gray Regression for Predictors of Cancer-Specific Mortality in the Propensity Score–Matched Cohorts

	Adjusted HR (95% CI)	*P* Value[a]
Chemotherapy backbone		
Cisplatin	Ref	
Carboplatin	1.04 (0.80–1.36)	.76
Sex		
Male	Ref	
Female	1.07 (0.77–1.49)	.67
Charlson comorbidity score		
0	Ref	
1	1.29 (0.94–1.78)	.12
≥2	1.09 (0.78–1.52)	.63
Age, y	1.03 (1.00–1.06)	**.03**
Diagnosis year	0.95 (0.89–1.00)	.06
Race		
White	Ref	
Nonwhite	0.70 (0.43–1.15)	.16
Region		
Northeast	Ref	
West	1.31 (0.60–2.87)	.49
Midwest	1.06 (0.68–1.64)	.80
South	0.94 (0.65–1.37)	.74
Marital status		
Married	Ref	
Other	0.98 (0.74–1.30)	.89
Census tract poverty level		
<10%	Ref	
10%–20%	0.95 (0.68–1.33)	.77
>20%	1.06 (0.73–1.55)	.76
Smoking/Tobacco claims		
Absent	Ref	
Present	1.30 (0.90–1.87)	.17
T stage		
T1/TX	Ref	
T2	1.34 (0.86–2.10)	.20
T3	1.57 (0.96–2.56)	.07
T4	1.93 (1.20–3.10)	**.007**
N stage		
N0	Ref	
N1–2a	1.13 (0.74–1.74)	.57
N2b–3	1.41 (0.94–2.12)	.10

(continued)

Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy.
[a]Bold indicates statistically significant *P* value.

eTable 2. Multivariable Fine-Gray Regression for Predictors of Cancer-Specific Mortality in the Propensity Score–Matched Cohorts (cont.)

	Adjusted HR (95% CI)	*P* Value[a]
Site		
Oropharynx	Ref	
Larynx	1.59 (1.11–2.27)	**.01**
Hypopharynx	1.31 (0.86–1.99)	.21
IMRT claims		
Absent	Ref	
Present	1.01 (0.72–1.43)	.95

Abbreviations: HR, hazard ratio; IMRT, intensity-modulated radiotherapy.
[a]Bold indicates statistically significant *P* value.

eTable 3. Frequency of Selected Inpatient Diagnoses in Unplanned Hospitalizations Within 3 Months of End of Radiation Completion in Matched Cohorts

Diagnosis	Frequency		Odds Ratio (95% CI)	*P* Value[a]
	Cisplatin Cohort	Carboplatin Cohort		
Pneumonia	9.6%	18.8%	2.19 (1.19–4.02)	**.01**
Neutropenia	10.1%	18.3%	1.99 (1.10–3.62)	**.03**
Acute renal failure	18.5%	10.8%	0.53 (0.30–0.94)	**.04**
Hypopotassemia	15.7%	8.5%	0.49 (0.26–0.93)	**.03**
Gastrostomy complication	6.2%	13.1%	2.30 (1.11–4.76)	**.03**
Sinoatrial node dysfunction	7.9%	1.9%	0.22 (0.07–0.69)	**.007**
Hyposmolality or hyponatremia	19.1%	13.6%	0.67 (0.39–1.15)	.17
Obstructive chronic bronchitis without exacerbation	1.7%	7.0%	4.42 (1.26–15.52)	**.01**
Volume depletion	37.6%	33.3%	0.83 (0.55–1.26)	.40
Thrombocytopenia	5.1%	1.4%	0.27 (0.07–1.01)	**.04**
Urinary tract infection	7.3%	10.8%	1.54 (0.75–3.13)	.29
Anemia	14.6%	11.3%	0.74 (0.41–1.35)	.36
Nausea with vomiting	8.4%	5.2%	0.59 (0.26–1.32)	.23

[a]Bold indicates statistically significant *P* value.