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Authors

Riaz, Nadeem
Sherman, Eric
Koutcher, Lawrence
et al.

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Concurrent Chemoradiotherapy With Cisplatin Versus Cetuximab for Squamous Cell Carcinoma of the Head and Neck

Nadeem Riaz, MD[*], **Eric Sherman, MD**[†], **Lawrence Koutcher, MD**[*], **Lauren Shapiro, MD**[*], **Nora Katabi, MD**[‡], **Zhigang Zhang, PhD**[§], **Weiji Shi, MS**[§], **Mathew Fury, MD**[†], **Richard Wong, MD**[‖], **Suzanne Wolden, MD**[*], **Shyam Rao, MD, PhD**[*], and **Nancy Lee, MD**[*]

[*]Departments of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

[†]Departments of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

[‡]Departments of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

[§]Departments of Epidemology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

[‖]Departments of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Objectives—We previously reported inferior outcomes for locally advanced head and neck cancer treated with cetuximab (C225) versus cisplatin (CDDP). We now examine if this difference persists when accounting for HPV status and update outcomes on the entire cohort.

Materials and Methods—From 3/106 to 4/1/08, 174 locally advanced head and neck cancer patients received definitive treatment with RT and CDDP (n = 125) or RT and C225 (n = 49). Of these, 62 patients had tissue available for HPV analysis.

Results—The median follow-up was 47 months. The 3-year loco-regional failure, disease-free survival, and overall survival for CDDP versus C225 were 5.7% versus 40.2% ($P < 0.0001$), 85.1% versus 35.4% ($P < 0.0001$), and 90.0% versus 56.6% ($P < 0.0001$), respectively. In the subset with tissue, there was no difference in rates of HPV or p16 positivity between the 2 groups. In this subset, the 3-year loco-regional failure, disease-free survival, and overall survival for CDDP versus C225 were 5.3% versus 32.0% ($P = 0.01$), 86.8% versus 43.2% ($P = 0.002$), and 86.7% versus 76.9% ($P = 0.09$), respectively. Multivariate analysis continued to show a benefit for CDDP.

Conclusions—With longer follow-up and the inclusion of HPV and p16 status for about one third of patients where tissue was available, we continued to find superior outcomes with concurrent CDDP versus C225.

Keywords

head and neck cancer; radiation; cisplatin; cetuximab; HPV

Reprints: Nancy Lee, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. leen2@mskcc.org.

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In the past 2 decades definitive chemoradiotherapy has become the standard of care for the treatment of locally advanced head and neck cancer (LAHNC). The VA Larynx and EORTC studies demonstrated that chemoradiotherapy improves organ preservation without sacrificing overall survival (OS) compared with upfront surgery.[1,2] However, these studies were not designed to determine if chemotherapy was a necessary component of treatment. Subsequently, multiple phase III randomized trials demonstrated an OS advantage in the treatment of LAHNC for concurrent chemoradiotherapy versus radiotherapy alone.[3–5] A meta-analysis of the randomized evidence found a 6.5% absolute improvement in 5-year OS[6] with concurrent chemoradiotherapy compared with radiotherapy alone. This analysis identified cisplatin (CDDP) as the most effective single agent to be delivered concurrently with radiotherapy.

A drawback of concurrent chemoradiotherapy with CDDP is increased short-term morbidity and long-term sequale from treatment. The discovery of the targeted agent cetuximab (C225) seemed to offer a possibly less toxic replacement. C225 is a monoclonal antibody directed at the epidermal growth factor receptor, which is often overexpressed in LAHNC. Bonner et al[7] conducted a randomized trial comparing concurrent C225 and RT versus RT alone in LAHNC and found that C225 improved both loco-regional control (LRC) and OS. Analysis of quality of life scores between the 2 arms demonstrated no difference, suggesting C225 is very well tolerated.[8] An update to the study with 5-year results continues to demonstrate an improvement in OS, although LRC or disease-free survival (DFS) results were unavailable.[9]

The study by Bonner and colleagues[7–9] was conceived and conducted before it was clear that concurrent treatment with chemotherapy was superior to radiotherapy alone. An earlier meta-analysis published 1 year after the initiation of the Bonner and colleague's study, concluded "the routine use of chemotherapy is debatable."[10] However, in the same time period as Bonner and colleague's study was published, other randomized trials clearly demonstrated the superiority of concurrent chemoradiotherapy over radiotherapy alone. Yet, many practitioners have started to replace CDDP with C225 without a direct head-to-head randomized comparison.

We previously published our center's experience with CDDP/RT and C225/RT in the treatment of LAHNC and found CDDP/RT was superior in terms of OS and LRC.[11] A major limitation of that work was the lack of highly prognostic HPV data,[12] and this may have confounded our results. Here we present our updated experience with these 2 agents, and further analyze a subset of patients in whom tissue was available for HPV analysis.

MATERIALS AND METHODS

A total of 221 consecutive patients with newly diagnosed squamous cell carcinoma of the oropharynx, larynx, or hypopharynx treated definitively with concurrent chemoradiotherapy between March 1, 2006 and April 1, 2008 at our center were retrospectively reviewed. Only patients who received concurrent CDDP or C225 were examined. Detailed patients exclusion criteria as well as the final patient characteristics on 174 patients have been previously published[11] and are reviewed in Table 1. Of these 174 patients, 62 patients had

tissue for HPV analysis and their detailed characteristics are displayed in Table 2. Seventy-two percent of these patients had oropharyngeal primaries.

Patients who had <5-pack-year smoking history were considered nonsmokers. The CDDP and C225 groups were balanced except that CDDP patients were younger, had better renal function, and were more likely to be treated at a regional network site. Our institutional review board issued a waiver of informed consent for this study.

Pathology

HPV and p16 status could be determined in 61 and 59 cases, respectively. HPV was determined by in situ hybridization with a Ventana HPV family III probe. p16 status was determined by immunohistochemistry and was deemed positive when >50% of the tumor demonstrated diffuse cytoplasmic and nuclear staining. For the purposes of this study patients were considered HPV positive if either the in situ hybridization or p16 tests were positive.

Treatment

All patients were treated with intensity-modulated radiotherapy to 69.96 Gy at 2.12 Gy per fraction to the planning target volume, which encompassed the gross tumor volume. Details of radiotherapy fractionation and targeting were previously described.[11] CDDP was delivered at 100 mg/m^2 every 3 weeks with intent to deliver 3 cycles (50 mg/m^2 over 2 d was also permitted). C225 was delivered with a loading dose of 400 mg/m^2 m during the week before initiation of intensity-modulated radiotherapy (IMRT), and then for a maximum of 7 additional doses at 250 mg/m^2 during IMRT. Reasons for selecting C225 over CDDP were also previously described.[11]

Statistical Analysis

The Kaplan-Meier method, Cox Proportional hazards, and the competing-risks method were used to analyze outcomes. Loco-regional failure (LRF) was analyzed with death being regarded as a competing risk and defined as the date of loco-regional recurrence or documentation of persistence of disease. DFS was defined as any evidence of disease after treatment or death. For both of these outcomes, if a patient underwent a neck dissection within 6 months of chemoradiotherapy, this was not considered an event, but rather a part of the upfront management strategy. All outcomes began at the first day of radiotherapy. Multivariate models were constructed using variables with a *P*-value <0.1 on univariate analysis (UVA), with a stepwise forward selection procedure. Baseline clinical and pathologic characteristics between groups were compared using either the χ^2 test or Fisher exact test.

RESULTS

Treatment Delivered

The compliance to IMRT was excellent, with only 5 patients not receiving the prescribed dose of radiotherapy. The median number of cycles of C225 delivered was 7 (range, 5 to 8). The median total dose of CDDP delivered was 200 mg/m^2 (range, 100 to 300 mg/m^2). Of

the 62 patients in whom tissue was available, 39 received CDDP and 23 received C225. In the CDDP group 42% were HPV positive compared with 35% in the C225 group ($P = 0.58$). A total of 83% of the CDDP group and 74% of the C225 group were p16 positive ($P = 0.62$).

Outcomes in the Entire Cohort

The median follow-up in surviving patients for the entire cohort was 47 months. With extended follow-up,[11] the 3-year LRF rate was 5.7% versus 40.2% in favor of CDDP/RT ($P < 0.0001$) (Fig. 1A). The 3-year DFS was 85.1% versus 35.4% in favor of CDDP ($P < 0.0001$) (Fig. 1B). Multivariate analysis continued to show improved DFS in the CDDP group (HR [hazard ratio] = 0.18; 95% CI [confidence interval], 0.10–0.32). We previously showed that subsite (oropharynx vs. hypopharynx/larynx) did not alter the results for either DFS or LRC. OS was also better in the CDDP patients, with 3-year rates of 90.0% versus 56.6% ($P < 0.0001$). Multivariate analysis continued to show a benefit in OS for CDDP versus C225 (HR = 0.20; 95% CI, 0.11–0.37). We previously performed a propensity score analysis for OS and DFS that showed similar results.[11]

Outcomes in the Subset With Tissue Available

In the subset of patients with tissue available (n = 62), the median follow-up was 48.3 months. The 3-year rates of LRF were 8.4% versus 32% ($P = 0.01$) in favor of the CDDP/RT group. On UVA of all 62 patients, HPV-positive patients showed nonstatistically significant decreased LRF (HR = 0.46, 95% CI, 0.12–1.75) (Fig. 2A). Multivariate analysis for LRF was not performed in this subset due to a limited number of events.

The 3-year DFS was 86.8% and 43.2% in favor of CDDP ($P = 0.002$). Death occurred in 7 of 39 CDDP patients (2 of whom started on CDDP and switched to C225) and in 8 of 23 C225 patients. UVA in the subset with tissue showed HPV-positive patients had an improved DFS (HR = 0.30, 95% CI, 0.12–0.74) (Fig. 2B). Multivariate analysis continued to show improved DFS (HR = 0.28, 95% CI, 0.12–0.69) with CDDP (Table 3). The 3-year OS between the 2 treatment groups was 86.7% and 76.9% ($P = 0.09$). UVA showed HPV-positive patients had an improved OS (HR = 0.25, 95% CI, 0.08–0.74).

Late Toxicity

For the entire cohort, late grade 3 or 4 toxicity developed in 16.8% of the CDDP/RT group compared with 21.7% in the C225/RT group ($P = 0.46$). Fifteen patients were feeding tube–dependant 9 months after completing RT or died with a feeding tube in place, 8% in the CDDP versus 10.4% in the C225 group ($P = 0.61$). This is in accordance with our previously reported findings of no significant difference in toxicity between the 2 treatment arms.[11]

DISCUSSION

We previously reported data from our institution suggesting that CDDP/RT was superior to C225/RT for LRC, DFS, and OS[11] in locally advanced SCC of the head and neck. One major criticism of that work was the lack of HPV/p16 information, which may have inadvertently influenced outcomes. Here, we report updated follow-up on the entire cohort and focus on a third of patients for which tissue was available for HPV and p16 staining.

Our data continue to suggest that the superior outcomes of patients treated with CDDP/RT, and that these results are unlikely to be solely attributable to known prognostic imbalances between the CDDP/RT and C225/RT groups.

Additional retrospective and prospective data from other institutions has recently emerged that suggests C225 may not be an adequate replacement for CDDP. The TREMPLIN study was a phase II randomized study comparing induction chemotherapy followed by concurrent chemoradiotherapy with either CDDP or C225 in patients with locally advanced SCC of the larynx or hypopharynx.[13] Of the 153 patients enrolled, 116 responders to induction chemotherapy were randomized to concurrent CDDP (n = 60) or concurrent C225 (n = 56). Those investigators found 12 (21%) patients in the C225 arm developed a local recurrence compared with 5 (8%) in the CDDP arm ($P = 0.08$). Ultimate local control after surgical salvage and other outcomes were similar between the 2 groups. However, the increased rate of local failure suggests less effective radiosensitization with C225.

Similar to our study, investigators from Washington University retrospectively examined their experience with concurrent CDDP (n = 33) versus C225 (n = 30) in LAHNSCCs.[14] Patients who either received induction chemotherapy or primary surgery were excluded. Patients in the 2 groups were well balanced for T stage, N stage, and HPV status. At a mean follow-up of 30 months, they found significantly worse DFS (79% vs. 27%, $P < 0.001$) and OS (72% vs. 25%, $P < 0.001$) in patients treated with concurrent C225.

We have also reviewed our experience with another regimen of concurrent chemoradiotherapy (carbo/5-FU, n = 52) compared with C225 or CDDP.[15] Patients in the carbo/5-FU or C225 groups had worse performance status, worse renal function, and higher T-stage. Four-year LRF was similar between carbo/5 FU and CDDP groups (9.7 vs. 6.3%, $P = 0.42$), however, was significantly worse for the C225 group (40.2%, $P = 0.002$). OS was also similar between the carbo/5-FU and CDDP groups, however, was significantly worse for the C225 group (HR = 4.01, $P < 0.001$).

To our knowledge, there is only a single retrospective study from the University of Alabama demonstrating similar outcomes between concurrent CDDP and C225.[16] This study differed from ours in that patients were treated with conventional radiotherapy instead of IMRT. More importantly, the Alabama study included patients treated with other agents in addition to CDDP, and hence was not a true comparison between CDDP and C225. Another study commissioned by Bristol-Meyers-Squib performed an indirect comparison of results from the Bonner study to 4 other studies evaluating CDDP, and concluded that outcomes between the 2 agents were similar.[17] However, indirect comparisons are controversial and require baseline hazard rate between studies to be similar. This assumption was unlikely to be met in this case given very different study populations and time eras for studies included.

Subgroup analysis from the Bonner study seemed to suggest that patients with an HPV-like phenotype may derive the most benefit from concurrent C225 (ie, those with an oropharynx primary, advanced neck disease, and smaller primary tumors). This prompted, RTOG 10–16, which is currently directly comparing of C225 + RT versus CDDP + RT, in HPV-positive patients, and should help definitively answer this question. Although it is accruing well, the

final results will not be available for several years. Another randomized trial (ClinicalTrials.gov Identifier: NCT00820248) is comparing CDDP/RT to panitumumab (another monoclonal EGFR inhibitor) and RT. However, the latter arm is receiving treatment with accelerated fractionation, whereas the former is receiving conventional fractionation, making a direct comparison between EGFR inhibition and CDDP difficult.

As HPV-positive patients have an improved prognosis,[12] they would initially appear to be ideal to consider substituting C225 for CDDP. However, in the metastatic setting, evidence has recently emerged that EGFR inhibition may be less effective in HPV-positive patients than in HPV-negative patients.[18,19] In the SPECTRUM study, panitumumab improved OS when added to chemotherapy in HPV-negative patients (11.8 vs. 8.6 mo), but not in HPV-positive patients (10.9 vs. 12.1 mo).[18] In BIBW 2992, HPV-negative patients had a higher response rate to EGFR inhibition (7/48, 14.5%) compared with HPV-positive patients (1/17, 5.8%).[19] Finally, the meta-analysis indicates that the benefit of concurrent chemotherapy is the largest in oropharyngeal patients (5-y difference in OS of 8.1%).[20] We did not have a large enough number of patients to compare the efficacy of C225 in HPV-positive versus HPV-negative patients.

We did not identify a significant difference in the rates of grade 3 or 4 toxicity between the 2 groups. One small retrospective study identified increased acute toxicity with C225 versus CDDP, although there was higher compliance with treatment with the C225 group.[21] In contrast to the Bonner study which found similar rates of toxicity between radiotherapy with or without C225, and a comparison of QOL between arms was similar.[16]

Of note, on multivariate analysis in the subset with tissue we found primary site, instead of HPV status as significant for DFS. Both these clinical parameters are highly correlated, and we believe primary site happened to just have a slightly stronger association in our cohort by chance. Excluding primary site, from analysis, HPV status would have been significant on multivariate analysis.

In conclusion, with longer follow-up and the inclusion of HPV and p16 status for about one third of patients, our previous findings of improved outcomes with concurrent CDDP compared with concurrent C225 were upheld. We believe our results along with emerging data from other institutions highlight the need for caution at substituting C225 for CDDP in patients who are candidates for platinum. RTOG 10–16 is currently addressing this question, and until results are available we believe CDDP remains the preferred concurrent treatment.

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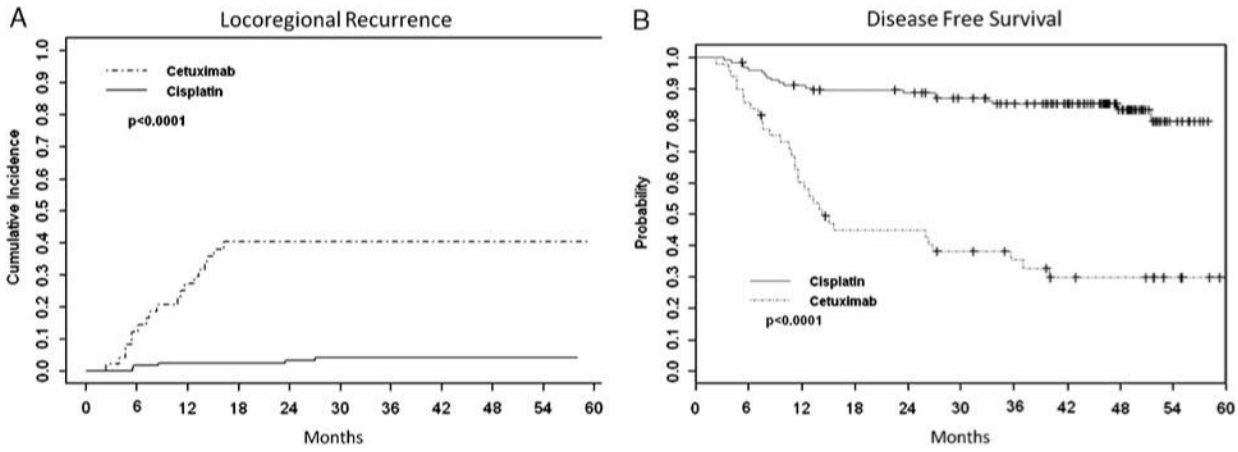

FIGURE 1.

A, Loco-regional control and (B) disease-free survival in entire population (n = 174).

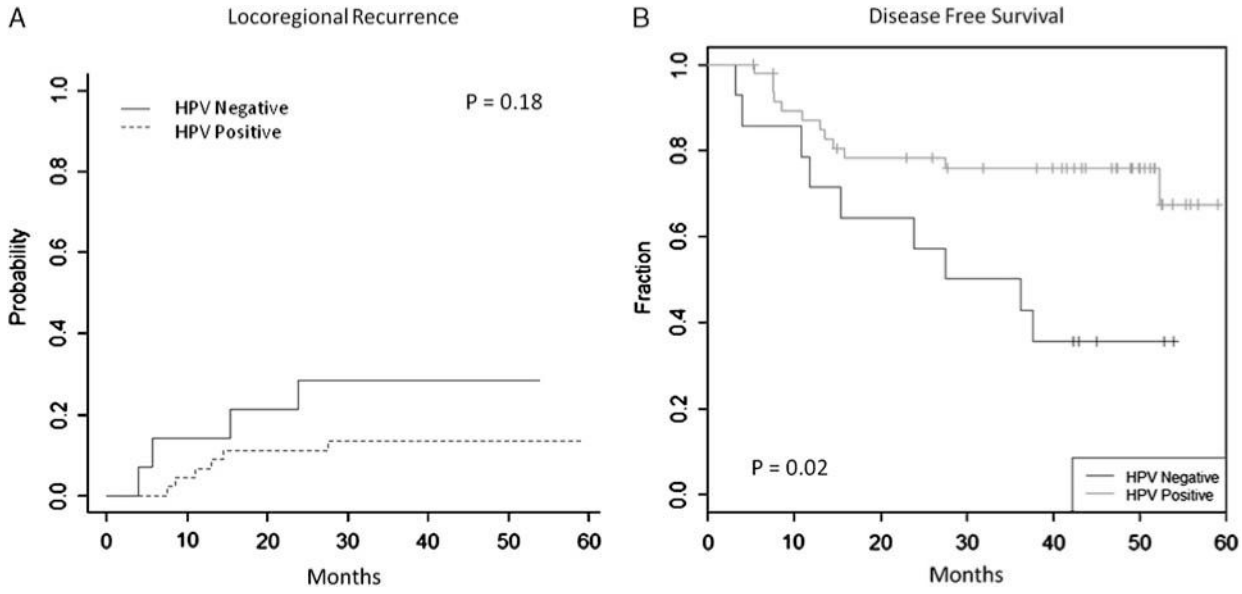

FIGURE 2.

A, Loco-regional control and (B) disease-free survival in patients with HPV status (n = 62).

TABLE 1

Patient Characteristics (Overall Cohort)

Characteristics	CDDP/RT (n [%])	C225/RT (n [%])	*P*
Sex			0.17
Male	108 (86)	38 (78)	
Female	17 (14)	11 (22)	
Age			< 0.001
< 71	118 (94)	29 (52)	
≥71	7 (6)	20 (41)	
KPS			0.21
≥90	87 (70)	29 (52)	
≤80	38 (30)	20 (41)	
Site			0.24
Oropharynx	98 (78)	34 (69)	
Hypopharynx/larynx	27 (22)	15 (31)	
T stage			0.21
T1–T2	81 (65)	26 (53)	
T3–T4	44 (35)	23 (47)	
N Stage			0.97
N0–N1	42 (34)	17 (35)	
N2–N3	83 (66)	32 (65)	
Neck dissection before XRT			0.51
Yes	7 (6)	4 (8)	
No	118 (94)	45 (92)	
Creatnine clearance			< 0.001
≥60	121 (97)	36 (73)	
< 60	4 (3)	13 (27)	
Hemoglobin			0.3
≥12	119 (95)	44 (90)	
< 12	6 (5)	5 (10)	
Albumin			0.05
≥4	116 (93)	40 (82)	
< 4	9 (7)	9 (18)	
Tobacco history			0.81
Never	42 (34)	19 (39)	
Former	60 (48)	22 (45)	
Current	23 (18)	8 (16)	

C225 indicates cetuximab; CDDP, cisplatin; KPS, Karnofsky Performance Status; RT, radiation therapy.

TABLE 2

Patient Characteristics (HPV Subset)

Characteristics	CDDP/RT (n [%])	C225/RT (n [%])	*P*
Sex			1.00
Male	31 (79)	18 (78)	
Female	8 (21)	5 (22)	
Age			0.0004
<71	37 (95)	13 (57)	
≥71	2 (5)	10 (43)	
KPS			0.8
≥90	25 (64)	14 (61)	
≤80	14 (36)	9 (39)	
Site			0.32
Oropharynx	30 (77)	15 (65)	
Hypopharynx/larynx	9 (23)	8 (35)	
HPV			
p16 +	30 (83)	17 (74)	0.51
HPV ISH +	16 (42)	8 (35)	0.57
HPV or p16 +	31 (86)	17 (74)	0.31
T stage			0.2
T1–T2	28 (72)	12 (52)	
T3–T4	11 (28)	11 (48)	
N stage			0.82
N0–N1	15 (38)	9 (39)	
N2–N3	24 (62)	14 (61)	
Neck dissection before XRT			0.14
Yes	1 (3)	3 (13)	
No	38 (97)	20 (87)	
Creatnine clearance			0.09
≥60	37 (95)	18 (78)	
< 60	2 (5)	5 (22)	
Hemoglobin			1
≥12	37 (95)	22 (96)	
< 12	2 (5)	1 (4)	
Albumin			0.41
≥4	36 (92)	19 (83)	
< 4	3 (8)	4 (17)	
Tobacco history			0.96
Never	13 (33)	8 (35)	
Former	18 (46)	11 (48)	
Current	8 (21)	4 (17)	

C225 indicates cetuximab; CDDP, cisplatin; KPS, Karnofsky Performance Status; RT, radiation therapy.

TABLE 3

Statistical Analysis for Disease-free Survival in Subset of Patients With Tissue

	UVA		MVA	
Variables	***P***	**HR**	***P***	**HR**
Age	0.006			
< 71		1.00		
≥71		3.46		
KPS	0.21			
90–100		1.00		
≤80		1.73		
Primary site	0.005		0.008	
Oropharynx		1.00		1.00
Hypopharynx/larynx	3.49		3.27	
T stage	0.12			
T1–T3		1.00		
T4		2.42		
N stage	0.5			
N0–1		1.00		
N2–3		0.74		
Creatnine clearance	0.47			
≥60		1.00		
< 60		1.58		
HPV status	0.009			
Other		1.00		
HPV + or p16 +	0.30			
Hemoglobin	0.1			
≥12		1.00		
< 12		3.45		
Albumin	0.12			
≥4		1.00		
< 4		2.42		
Tobacco history				
Never		1.00		
Former	0.04	4.83		
Current	0.005	9.50		
Drug	0.003		0.006	
C225		1.00		1.00
CDDP		0.27		0.28

C225 indicates cetuximab; CDDP, cisplatin; HR, hazard ratio; KPS, Karnofsky Performance Status; MVA, multivariate analysis; UVA, univariate analysis.