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ORIGINAL RESEARCH

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# Deployment of cisplatin in Veterans with oropharyngeal cancer: toxicity and impact on oncologic outcomes

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## Abstract

**Objective:** Cisplatin forms the backbone of systemic chemotherapy treatment for oropharyngeal squamous cell carcinoma (OPSCC). The ideal cisplatin dosing regimen remains yet to be fully defined for achieving optimal efficacy and toxicity profiles in patients with comorbidity.

**Methods:** We retrospectively reviewed oncologic and toxicity data for patients with OPSCC treated at the Michael E. DeBakey Veterans Affairs Medical Center between 2000 and 2020 who initiated curative intent, definitive chemo-radiation with one of three single agent regimens: high dose (HD) cisplatin, low dose (LD) cisplatin or cetuximab.

**Results:** Patients with HPV-associated tumors and nonsmokers demonstrated improved overall and disease-free survival along with locoregional and distant metastatic control regardless of chemotherapy regimen. Regardless of regimen selection, patients which received a cumulative cisplatin dose ≥200 mg/m$^2$ had a lower rate of distant metastasis. The HD regimen resulted in a greater fraction (75% vs. 50%) of patients receiving a cumulative cisplatin dose ≥200 mg/m$^2$ and a comparable measured toxicity burden compared to the LD regimen.

**Conclusions:** Both HD and LD cisplatin regimens can be safely delivered to a Veteran OPSCC patient population which should allow for straightforward application of conclusions drawn from completed and active clinical trials testing cisplatin regimens.

**Level of Evidence:** 4.

KEYWORDS

cetuximab, cisplatin, creatinine, distant metastasis, locoregional recurrence, oropharyngeal squamous cell carcinoma, Veteran

## 1 | INTRODUCTION

For the last half century, treatment for locally advanced stage head and neck squamous cell carcinoma (LA-HNSCC) has centered on the basic principle of multimodality treatment. Whereas for surgically resectable disease, this has led to an increase in the use of adjuvant external beam radiotherapy (EBRT), for patients slated to definitive EBRT this has meant the incorporation of neoadjuvant or concurrent chemotherapy into treatment algorithms.[1,2] Today, in the United States, platinum agents, more specifically cisplatin, represent the standard of care for patients receiving multimodality non-surgical treatment. Although hardly a benign agent, cisplatin has now been tested head-to-head against multiple other conventional cytotoxic regimens, targeted agents, and more recently immune checkpoint inhibitors (ICIs) and to date, no study has identified a more effective agent in the setting of LA-HNSCC.[3–5] Cetuximab was initially explored as a radiosensitizing agent nearly two decades ago.[6] Although enthusiasm was driven at first by the promises of high efficacy and a favorable toxicity profile, subsequent clinical experience including two recently completed clinical trials[4,5] have confirmed that cetuximab is no less toxic than cisplatin while demonstrating substantially inferior antitumor activity.

Optimal utilization of cisplatin when given concurrently with radiotherapy remains unclear in part because oncologic impact and toxicity remain incompletely elucidated. Over the last three decades, most cooperative group and multi-institutional therapeutic trials have utilized high dose (HD) cisplatin regimens consisting of 100 mg/m$^2$ every 3 weeks given for two to three cycles.[4,5,7] In clinical practice, weekly cisplatin at 40 mg/m$^2$ is now commonly used. Multiple randomized prospective trials have demonstrated improved toxicity profiles with once weekly dosing although some have called into question the efficacy of this newer regimen in terms of oncologic control.[8,9] NRG Oncology HN009 is expected to provide a definitive answer to questions regarding HD versus low dose (LD) antitumor effectiveness and toxicity. However, given entrenched clinical practice patterns across the United States, there is potential that even level I data will fail to generate homogeneous treatment patterns.

The treatment of oropharyngeal squamous cell carcinoma (OPSCC), now the most rapidly increasing disease site among the larger group of LA-HNSCC, in the Veteran population presents a challenging therapeutic dilemma. On one hand, Veterans with OPSCC are older, with a higher comorbidity burden compared to the general population and thus a reduced ability to tolerate toxic chemotherapy regimens. On the other hand, Veterans consistently demonstrate inferior oncologic

**TABLE 1** Patient and tumor characteristics.

| | | All patients (164) | | Cisplatin HD (78) | | Cisplatin LD (63) | | Cetuximab (23) | |
|---|---|---|---|---|---|---|---|---|---|
| | | *N* | % | *N* | % | *N* | % | *N* | % |
| Age (mean) | | 62.5 | | 58.8 | | 65.6 | | 66.2 | |
| Sex | Male | 160 | 97.56 | 77 | 98.7 | 60 | 95.2 | 23 | 100.0 |
| | Female | 4 | 2.44 | 1 | 1.3 | 3 | 4.8 | 0 | 0.0 |
| Race | White | 132 | 80.49 | 67 | 85.9 | 52 | 82.5 | 13 | 56.5 |
| | Black | 28 | 17.07 | 9 | 11.5 | 11 | 17.5 | 8 | 34.8 |
| | Other | 4 | 2.44 | 2 | 2.6 | 0 | 0.0 | 2 | 8.7 |
| P16 | Positive | 103 | 62.80 | 42 | 53.8 | 45 | 71.4 | 16 | 69.6 |
| | Negative | 38 | 23.17 | 20 | 25.6 | 13 | 20.6 | 5 | 21.7 |
| | NA | 23 | 14.02 | 16 | 20.5 | 5 | 7.9 | 2 | 8.7 |
| Tobacco | <10pcky | 31 | 18.90 | 16 | 20.5 | 10 | 15.9 | 5 | 21.7 |
| | ≥10pcky | 93 | 56.71 | 59 | 75.6 | 24 | 38.1 | 10 | 43.5 |
| | NA | 40 | 24.39 | 3 | 3.8 | 29 | 46.0 | 8 | 34.8 |
| *T* | 1 | 33 | 20.12 | 17 | 21.8 | 11 | 17.5 | 5 | 21.7 |
| | 2 | 56 | 34.15 | 26 | 33.3 | 19 | 30.2 | 11 | 47.8 |
| | 3 | 41 | 25.00 | 20 | 25.6 | 18 | 28.6 | 3 | 13.0 |
| | 4 | 34 | 20.73 | 15 | 19.2 | 15 | 23.8 | 4 | 17.4 |
| *N* | 0 | 20 | 12.20 | 4 | 5.1 | 11 | 17.5 | 5 | 21.7 |
| | 1 | 21 | 12.80 | 6 | 7.7 | 10 | 15.9 | 5 | 21.7 |
| | 2a | 15 | 9.15 | 10 | 12.8 | 4 | 6.3 | 1 | 4.3 |
| | 2b | 65 | 39.63 | 36 | 46.2 | 24 | 38.1 | 5 | 21.7 |
| | 2c | 30 | 18.29 | 16 | 20.5 | 10 | 15.9 | 4 | 17.4 |
| | 3 | 13 | 7.93 | 6 | 7.7 | 4 | 6.3 | 3 | 13.0 |

Abbreviations: HD, high dose regimen; LD, low dose regimen; pcky, pack-years.

outcomes to the general population, which we have shown is driven by more aggressive disease biology which extends to the otherwise favorable HPV-associated OPSCC subset of disease.[10–13] Optimal deployment of cisplatin in this population remains far from clear and granular institutional datasets are lacking. In the current manuscript we compared the antitumor activity and toxicity profile of three commonly utilized single agent regimens: HD cisplatin, LD cisplatin, and cetuximab in a Veteran population treated at a single tertiary institution. The data summarized below provide insight into some of the potential difficulties that will be encountered in the Veteran population when translating clinical trial findings into clinical practice.

## 2 | MATERIALS AND METHODS

Following approval from Baylor College of Medicine and the Michael E. DeBakey Veteran's Administration (MEDVAMC) Institutional Review Boards, we reviewed the medical records of Veterans with previously untreated OPSCC between January 1, 2000 and January 1, 2020. Collection and analysis of the current data were performed in a manner consistent with existing standards for clinical research (Declaration of Helsinki, US Federal Policy for the Protection of Human Subjects). Inclusion criteria included: (1) primary OPSCC, (2) tissue diagnosis at the MEDVAMC, and (3) curative intent, NCCN compliant treatment delivery at the MEDVAMC. Exclusion criteria included: (1) treatment at an outside institution, (2) recurrent disease at presentation, and (3) incomplete course of EBRT due to early cessation or treatment break >5 days. Patients which received neoadjuvant/induction chemotherapy were not included in the analysis; patients initially slated to a multi-drug regimen (e.g., carboplatin/paclitaxel) were not included in the analysis. Demographic information was recorded including age, gender, race, smoking history, and alcohol consumption. Smoking history was collected at the time of initial diagnosis as "pack-years." Clinical and pathologic features were analyzed according to the American Joint Commission on Cancer (Staging Manual 7th Edition) staging system. Results of diagnostic procedures including imaging results, biopsies, and fine needle aspirations as well as the treatments rendered and the associated dates were recorded.

HD cisplatin was defined as initiation of treatment with a starting cisplatin dose of 50–100 mg/m$^2$. In the entire cohort, one patient was started at 50 mg/m$^2$, one at 60 mg/m$^2$, four at 75 mg/m$^2$, nine at 80 mg/m$^2$, and the rest at 100 mg/m$^2$. LD cisplatin was defined as initiation of treatment with a starting cisplatin dose of 30–40 mg/m$^2$. In the entire cohort, five patients started at 30 mg/m$^2$ and the rest at 40 mg/m$^2$. Cetuximab was initiated at a loading dose of 400 mg/m$^2$ in 22 out of 23 patients, with one patient starting at 250 mg/m$^2$.

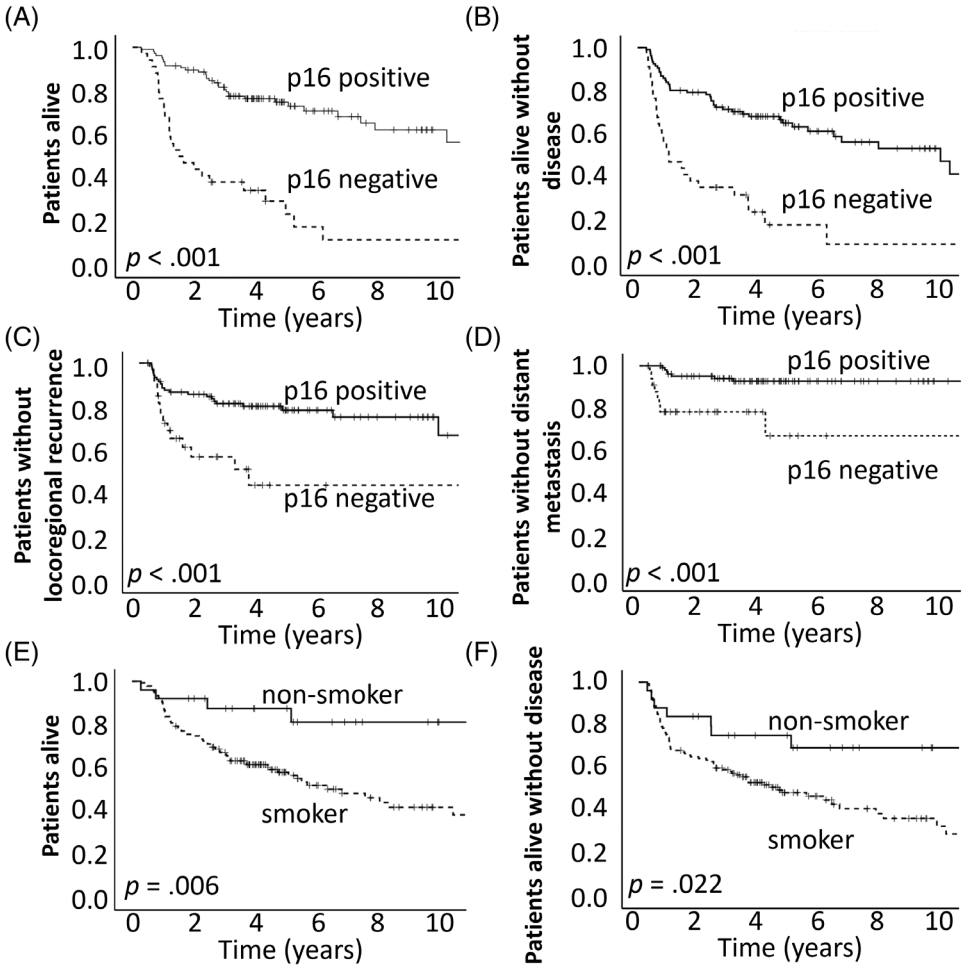


**FIGURE 1** Survival and recurrence patterns. Overall survival was positively impacted by p16 positivity (A) and nonsmoker (E) status. Disease free survival was positively impacted by p16 positivity (B) and nonsmoker status (F). p16 positive patients demonstrated reduced rates of locoregional recurrence (C) and distant metastasis (D).

All patients received curative intent treatment using standard techniques and fractionation. In the HD group, three patients did not complete the prescribed dose of radiation (actual Gy delivered 12, 38, and 62). In the LD group, one patient did not complete the prescribed dose of radiation (actual Gy delivered 40Gy). In the HD group, an additional five patients missed more than four fractions of radiation, but all patients completed the intended dose of radiation; mean radiation time = 54.3 calendar days; median radiation time = 51 calendar days. In the LD group, an additional seven patients missed more than four fractions of radiation but all patients completed the intended dose of radiation; mean radiation time = 50.60 calendar days; median radiation time = 50 calendar days. In the cetuximab group all patients completed radiation and none missed more than four fractions of radiation; mean 52.70 days; median = 50.

## 2.1 | Statistical analysis

Endpoints included time to locoregional or distant recurrence and death. Imaging studies were used as a surrogate in the absence of a pathological report documenting recurrence. Locoregional control (LRC—date of diagnosis to date of locoregional recurrence [LRR]), LRR (date of diagnosis to date of LRR), distant metastatic control (DMC—date of diagnosis to date of distant metastasis), relapse-free or

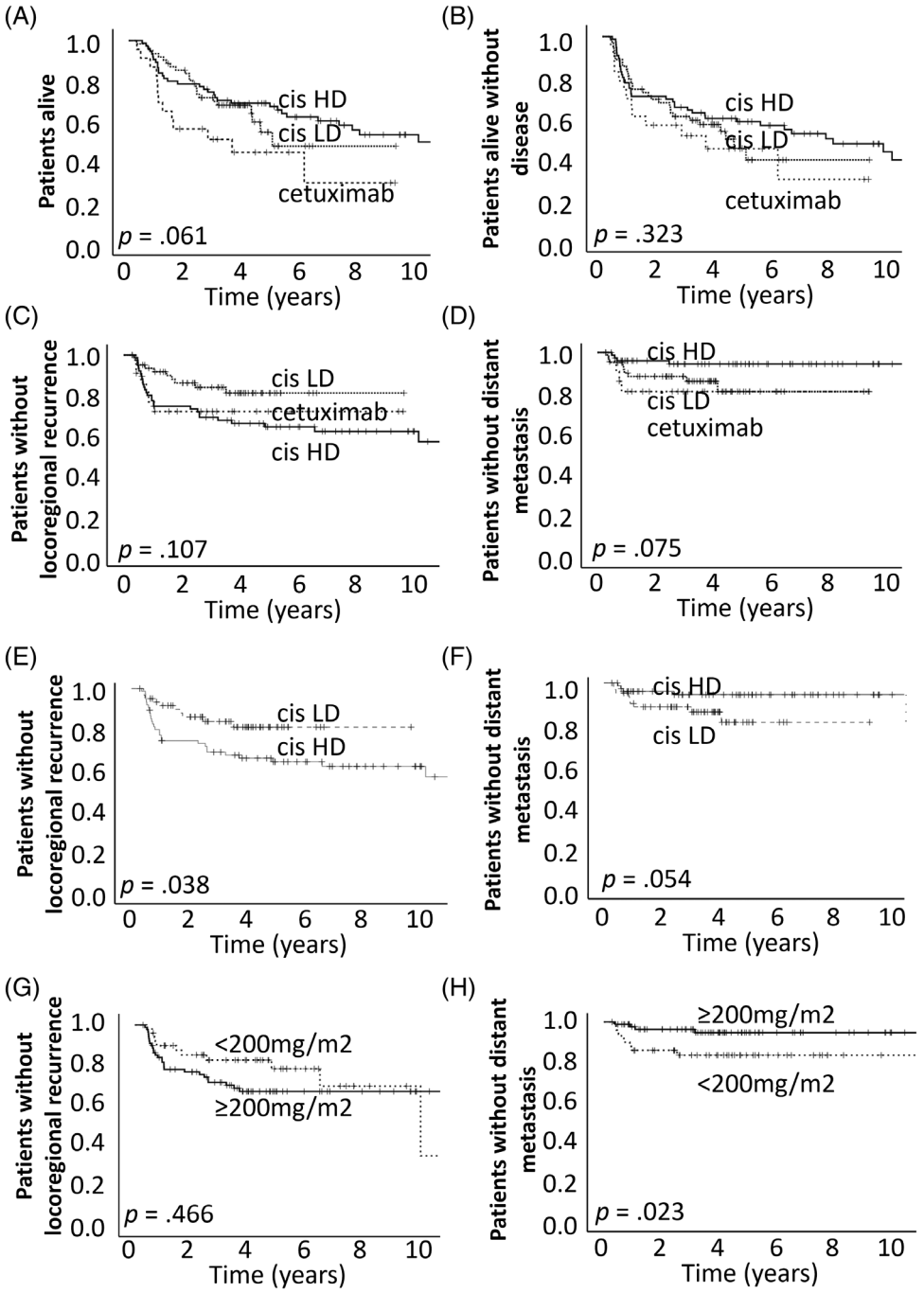


**FIGURE 2** Impact of systemic agent on oncologic outcomes. Overall survival (A), disease free survival (B), locoregional recurrence (C), distant metastatic control (D) were not impacted significantly by agent selection. When cetuximab was removed from the analysis, the LD regimen was associated with improved locoregional control (E) and the HD regimen was associated with improved distant metastatic control (F). Delivery of more than 200 mg/m$^2$ of cisplatin did not significantly impact locoregional recurrence (G) but resulted in a significantly lower rate of distant metastasis (H). HD, high dose; LD, low dose.

disease-free survival (date of primary diagnosis to date of recurrence; RFS/DFS), and overall survival (date of diagnosis to last documented hospital note; OS) were calculated. Associations between clinical, biological, and pathologic variables were determined by two-sided Fisher's exact tests. Actuarial survival rates were generated using the Kaplan–Meier method coupled to log-rank statistics. Multivariate analysis was performed using Cox regression. Statistical calculations were performed with SPSS (IBM SPSS Statistics version 25). For all statistics, *p*-values were considered to be statistically significant if below a threshold of .05 (two-sided). For individual statistical tests and/or correlations, details are provided in the following section.

## 3 | RESULTS

A total of 164 OPSCC patients were included in the analysis (Table 1), a majority of which received either HD or LD cisplatin; only 23 patients were initiated on cetuximab treatment concurrent with EBRT. Most patients were male, with a mean age of 62.5 years. HD cisplatin patients were slightly younger compared to LD cisplatin patients (*p*-value <.01) and cetuximab patients (*p*-value <.01). A majority of patients had HPV-associated disease as demonstrated by clinical standard p16 immunohistochemistry and a majority of patients had >10 pack-year tobacco exposure history, consistent with larger cohorts we have previously published.[10–12,14] Three quarters of patients presented with >N1 disease and nearly half (45%) presented with T3–4 disease. Oncologic outcomes tracked along expected patterns, with HPV-associated disease demonstrating significantly improved OS, DFS, LRC, and DMC (Figure 1A–D). Tobacco exposure impacted both OS and DFS significantly (Figure 1E,F). Taken together, these data indicate that the cohort size permits the measurement of oncologic differences resulting from expected clinical parameters consistent with previous literature and our institutional experience.

Overall, OS, DFS, LRC, and DMC were not significantly impacted by cisplatin regimen or cetuximab utilization, although DMC trended toward significance (Figure 2). Whereas LRC was not impacted by delivery of at least 200 mg/m$^2$, DMC was significantly higher in OPSCC patients which received more than 200 mg/m$^2$ throughout the course of treatment. Because total cisplatin dose impacted DMC, we performed a recursive partitioning analysis using the OS parameter to identify threshold effects. We identified a statistically significant threshold at 240 mg/m$^2$ (logworth 2.4) and a secondary threshold at 195 mg/m$^2$ (logworth 2.38), without further separation based on lower total cisplatin doses achieved.

We utilized relevant clinical parameters (HPV-association, T-classification, N-classification, and tobacco exposure) along with cisplatin regimen (HD vs. LD) to conduct a multivariate analysis for OS, DFS, LRC, and DMC. Cisplatin regimen selection significantly correlated with OS, DFS, and DMC but not LRC (Table 2). When total cisplatin dose delivered was dichotomized by 200 mg/m$^2$, delivery of more than 200 mg/m$^2$ was associated with a significantly improved OS and DMC but had no impact on DFS and LRC (Table 3). Among patients slated to the HD regimen, 73% received at least 200 mg/m$^2$, whereas among patients slated to the LD regimen, only 56% reached this oncologically significant threshold. The total amount of cisplatin delivered to the HD cohort prior to development of first dose limiting toxicity (DLT) was significantly higher compared to that delivered to the LD cohort (Figure 3; patients planned for only two doses of HD cisplatin were excluded from this analysis; patients in which chemotherapy was held for one or more cycles or which were transitioned to a different regiment were included in this analysis). The toxicity profile of the two cisplatin regimens was very similar, with comparable maximal creatinine (Cr) levels, minimal hemoglobin (Hgb), and white blood cell (WBC) counts measured during the treatment period, although minimal platelet (Plt) levels favored the HD regimen ($p < .001$) (Figure 4).

**TABLE 2** Multivariate analysis of oncologic outcomes as a function of cisplatin regimen.

| **Overall survival** | | | | |
|---|---|---|---|---|
| **Variable** | ***p*-Value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| P16 | ***<.001*** | 0.210 | 0.104 | 0.424 |
| *T* | .106 | 1.343 | 0.939 | 1.922 |
| *N* | ***.022*** | 1.256 | 1.034 | 1.526 |
| Tob | ***.037*** | 4.769 | 1.100 | 20.680 |
| CIS regimen | ***.020*** | 0.609 | 0.401 | 0.926 |
| **Disease free survival** | | | | |
| **Variable** | ***p*-Value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| P16 | ***<.001*** | 0.154 | 0.071 | 0.337 |
| *T* | .732 | 0.941 | 0.662 | 1.336 |
| *N* | ***.008*** | 1.297 | 1.07 | 1.574 |
| Tob | ***.029*** | 3.739 | 1.144 | 12.219 |
| CIS regimen | ***.048*** | 0.679 | 0.463 | 0.997 |
| **Locoregional recurrence** | | | | |
| **Variable** | ***p*-Value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| P16 | ***.001*** | 0.227 | 0.091 | 0.567 |
| *T* | .910 | 1.024 | 0.676 | 1.551 |
| *N* | ***.008*** | 1.402 | 1.092 | 1.800 |
| Tob | .108 | 3.284 | 0.770 | 14.002 |
| CIS regimen | .598 | 0.869 | 0.515 | 1.466 |
| **Distant metastatic control** | | | | |
| **Variable** | ***p*-Value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| P16 | ***.021*** | 0.039 | 0.002 | 0.610 |
| *T* | .262 | 0.262 | 0.151 | 1.674 |
| *N* | ***.022*** | 1.798 | 1.09 | 2.966 |
| Tob | .984 | >1000 | 0.000 | >1000 |
| CIS regimen | ***.029*** | 0.679 | 0.115 | 0.888 |

*Note*: Bold values signifies $p < 0.05$.

**TABLE 3** Multivariate analysis of oncologic outcomes as a function of total cisplatin dose.

| Overall survival | | | | |
|---|---|---|---|---|
| **Variable** | ***p*-value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| *T* | ***.016*** | 1.579 | 1.088 | 2.291 |
| *N* | .156 | 1.162 | 0.944 | 1.429 |
| Tob | ***.027*** | 9.857 | 1.298 | 74.865 |
| p16 | ***<.002*** | 0.152 | 0.07 | 0.328 |
| CIS 200 mg/m$^2$ | ***.005*** | 0.36 | 0.178 | 0.731 |
| **Disease free survival** | | | | |
| **Variable** | ***p*-value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| *T* | .901 | 1.023 | 0.716 | 1.461 |
| *N* | .125 | 1.175 | 0.956 | 1.445 |
| Tob | ***.015*** | 5.912 | 1.402 | 24.928 |
| p16 | ***<.001*** | 0.145 | 0.064 | 0.328 |
| CIS 200 mg/m$^2$ | .086 | 0.584 | 0.316 | 1.078 |
| **Locoregional recurrence** | | | | |
| **Variable** | ***p*-Value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| *T* | .713 | 1.085 | 0.702 | 1.679 |
| *N* | .067 | 1.284 | 0.982 | 1.679 |
| Tob | .068 | 6.497 | 0.869 | 48.561 |
| p16 | ***.001*** | 0.203 | 0.077 | 0.530 |
| CIS 200 mg/m$^2$ | .742 | 0.878 | 0.405 | 1.903 |
| **Distant metastatic control** | | | | |
| **Variable** | ***p*-value** | **Exp (B)** | **95% CI lower** | **95% CI upper** |
| *T* | .104 | 0.218 | 0.035 | 1.370 |
| *N* | .127 | 1.611 | 0.874 | 2.971 |
| Tob | .982 | >1000 | 0.000 | NA |
| p16 | ***.011*** | 0.005 | 0.000 | 0.285 |
| CIS 200 mg/m$^2$ | ***.010*** | 0.078 | 0.011 | 0.543 |

*Note*: Bold values signifies $p < 0.05$.

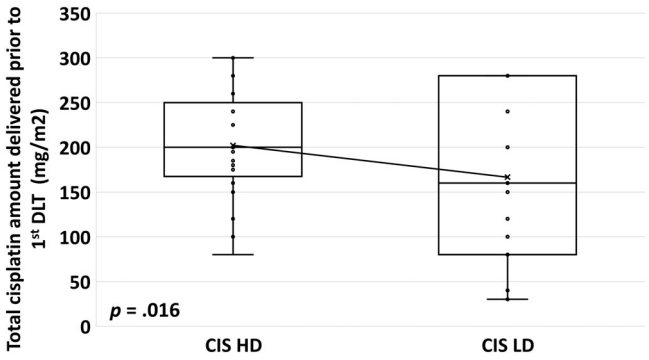


**FIGURE 3** Total dose of cisplatin as a function of dosing regimen. CIS HD, high dose cisplatin regimen; CIS LD, low dose cisplatin regimen. Figure summarizes the total dose of cisplatin delivered prior to first dose limiting toxicity (DLT) event.

## 4 | DISCUSSION

Multiple clinical trials over the past four decades have established single agent cisplatin as the primary chemotherapeutic agent used for concurrent chemoradiotherapy for LA-HNSCC in both the definitive and adjuvant settings.[7,15–17] Most trials to date have utilized HD cisplatin regimens but their widespread use is hindered by an association with high acute toxicity and related complications of administration such as inpatient admission. More and more clinicians have shifted toward using LD, weekly cisplatin regimens despite the lack of large randomized, controlled trials demonstrating equipoise of these treatment regimens. Indeed, a desire for a less toxic concurrent therapeutic agent led to the early adoption of cetuximab as a radio sensitizing agent after its addition to radiation showed improved OS compared to radiation alone in 2006.[18] However, two subsequent trials comparing cetuximab to cisplatin failed to establish non-inferiority of the former, and the antibody has therefore quickly fallen out of favor except for instances where other agents are contraindicated.[5,19] In an attempt to utilize existing prospective data to compare efficacy and toxicity of HD and LD cisplatin, two separate groups compiled three large meta-analyses of LA-HNSCC patients treated with chemoradiotherapy in both the definitive and adjuvant settings. Analyses from both groups suggested that OS outcomes were similar for HD and LD when combined with conventional radiotherapy. However, whereas one group concluded that these data suggested that either regimen could be used, the second group cautioned that, given the multi-source data for their analysis, their findings could not support a recommendation for the use of LD, weekly cisplatin and that a randomized-controlled clinical trial directly comparing HD to LD cisplatin in the definitive setting was necessary to make a final determination.[20,21] Since the publication of these analyses, a non-inferiority trial by the Japanese Clinical Oncology Group (JCOG) comparing HD and LD cisplatin with concurrent radiation in the adjuvant setting has completed and concluded that LD cisplatin is non-inferior and is associated with lower acute toxicity than HD cisplatin.[22] In contrast, a recent update of results from a phase III non-inferiority study of 300 LA-HNSCC patients reported significantly higher LRC and survival rates for patients receiving HD cisplatin.[23] As a result of these conflicting data, NRG Oncology has opened HN-009 to compare the HD and LD cisplatin regimens head-to-head in the definitive treatment of LA-HNSCC (NCT05050162).

Given the overall higher comorbidity burden, more aggressive disease biology and concomitant inferior oncologic outcomes of Veterans with OPSCC, the results and applicability of HN-009 in the decade to come are of utmost importance to this population.[10–13] Retrospective data analysis of over 2000 Veterans showed that when comorbidities and other factors such as smoking/alcohol use as well as site and stage of cancer are taken into account, HD and LD cisplatin treatment resulted in similar OS but with increased toxicity for the HD group.

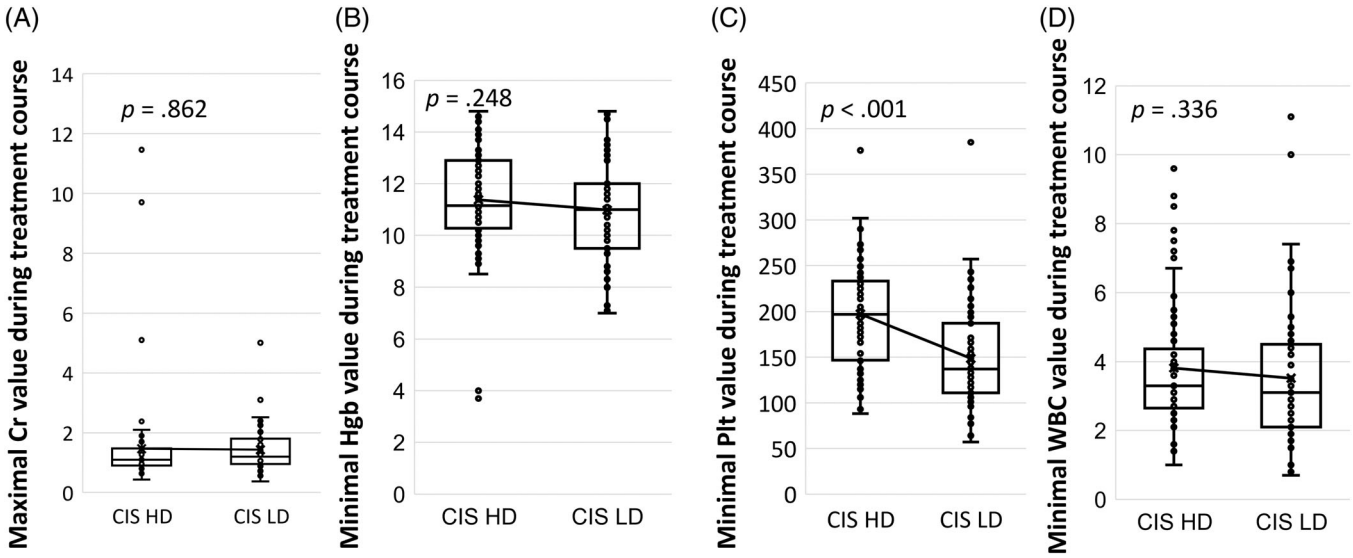


**FIGURE 4** Toxicity patterns. CIS HD, high dose cisplatin regimen; CIS LD, low dose cisplatin regimen; Cr, creatinine; Hgb, hemoglobin; Plt, platelets; WBC, white blood cell.

However, when these factors were not taken into account, HD cisplatin significantly outperformed LD cisplatin in the overall population and more specifically for patients with OPSCC.[24,25] Such retrospective analyses are not ideal however, and thus a prospective head-to-head comparison is still necessary to definitively determine whether treatment with HD versus LD cisplatin can deliver equipoise in OS outcomes. However, even these results may need to be interpreted with caution, especially in a Veteran population with a higher comorbidity burden than the general population. Therefore, we believe it to be of utmost importance that Veterans are included in HN-009, and the current study is partly an attempt to assess feasibility in regard to tolerance and outcomes of HD cisplatin treatment at a granular, institutional level.

Most of the results of this study fall in line with previous, well-established observations made in both the general and Veteran population with OPSCC. Patients with HPV-associated OPSCC exhibited significantly better OS and DFS as well as significantly lower rates of LRR and DM than those with HPV-independent OPSCC. Tobacco exposure also predictably was associated with worse outcomes in OS and DFS though not LRR and DMs in multivariate analysis. Also, cetuximab underperformed both HD and LD cisplatin regimens as has been shown in prospective trials.[5,19] Finally, exposure to a cumulative cisplatin dose of 200 mg/m$^2$ or higher was associated with a significant improvement of OS and translated to a decrease in DMs though LRR and DFS were not impacted.

Comparing patients, their outcomes, and treatment related toxicities in regard to treatment with HD versus LD cisplatin resulted in several interesting observations. While patients in the HD group were on average younger than those in the LD group, they also had a lower percentage of p16 positive tumors and almost double the amount of ≥10 pack year smokers than patients in the LD group. Though initial survival analysis suggested no statistically significant difference in OS and DFS between HD and LD cisplatin, multivariate analysis considering factors such as p16 status, T- and N- stage, and tobacco exposure revealed that HD cisplatin resulted in significantly improved OS, DFS, and DMC compared to LD cisplatin. Limited toxicity data suggest comparable rates of renal toxicity, anemia, and leukopenia in the HD and LD cisplatin treated patients with a significantly lower absolute platelet count in the LD cisplatin group. Additionally, compliance with radiation treatment was comparable between HD and LD cisplatin treated patients with 96% and 98% of patients completing the total prescribed dose of radiation, respectively, and 6.4% and 11.1% of patients missing more than four fractions but completing the total dose of radiation, respectively. This analysis, while not entirely at odds with that presented by Bauml et al. in Veterans, does suggest that Veterans with OPSCC may benefit from HD cisplatin over a LD regimen and that cisplatin-specific toxicity need not lead to significantly higher DLTs in the HD group. Indeed, patients in our study treated with HD cisplatin received significantly higher cumulative doses of cisplatin prior to their first DLT. Accordingly, 30% more patients in the HD group reached the oncologically relevant cumulative cisplatin dose of 200 mg/m$^2$ which reviews and meta-analyses of prospective trials have shown to be a significant cisplatin dose threshold associated with therapeutic efficacy.[26,27] Consistent with these prior reports, patients in our study receiving 200 mg/m$^2$ or higher of cisplatin exhibited increased OS compared to those receiving less.

Our current study has several limitations including a small sample size, retrospective nature, and limited toxicity data. Also, unlike the similar but less granular, multi-institutional study in Veterans conducted by Bauml et. al, we did not correct for patient comorbidities, however, our multivariate analysis did attempt to control for other tumor and patient related factors such as p16 status, stage, and smoking status. Overall, the results and analysis presented in this single institutional retrospective review once again illustrate the importance of a large, randomized trial comparing HD and LD cisplatin for concurrent chemoradiation for definitive treatment of OPSCC. Moreover,

the study highlights the importance and confirms the feasibility of including Veterans in this landmark clinical trial.

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## CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to disclose.

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## REFERENCES

1. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC group. *Radiother Oncol*. 2021;156:281-293.
2. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013;31:845-852.
3. Rosenthal DI, Liu L, Lee JH, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck*. 2002;24:115-126.
4. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393:40-50.
5. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019;393:51-60.
6. Bonner J, Giralt J, Harari P, et al. Cetuximab and radiotherapy in laryngeal preservation for cancers of the larynx and hypopharynx: a secondary analysis of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2016;142:842-849.
7. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091-2098.
8. Mashhour K, Hashem W. Cisplatin weekly versus every 3 weeks concurrently with radiotherapy in the treatment of locally advanced head and neck squamous cell carcinomas: what is the best dosing and schedule? *Asian Pac J Cancer Prev*. 2020;21:799-807.
9. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-Every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol*. 2018;36:1064-1072.
10. Sandulache VC, Hamblin J, Lai S, et al. Oropharyngeal squamous cell carcinoma in the veteran population: association with traditional carcinogen exposure and poor clinical outcomes. *Head Neck*. 2015;37:1246-1253.
11. Wilde DC, Castro PD, Bera K, et al. Oropharyngeal cancer outcomes correlate with p16 status, multinucleation and immune infiltration. *Mod Pathol*. 2022;35:1045-1054.
12. Zevallos JP, Kramer JR, Sandulache VC, et al. National trends in oropharyngeal cancer incidence and survival within the veterans affairs health care system. *Head Neck*. 2021;43:108-115.
13. Zevallos JP, Sandulache VC, Hamblin J, et al. Impact of race on oropharyngeal squamous cell carcinoma presentation and outcomes among veterans. *Head Neck*. 2016;38:44-50.
14. Lai S, Wenaas AE, Sandulache VC, et al. Prognostic significance of p16 cellular localization in oropharyngeal squamous cell carcinoma. *Ann Clin Lab Sci*. 2016;46:132-139.
15. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937-1944.
16. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945-1952.
17. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21:92-98.
18. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567-578.
19. Maddalo M, Borghetti P, Tomasini D, et al. Cetuximab and radiation therapy versus cisplatin and radiation therapy for locally advanced head and neck cancer: long-term survival and toxicity outcomes of a randomized phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2020;107:469-477.
20. Mohamed A, Twardy B, Zordok MA, et al. Concurrent chemoradiotherapy with weekly versus triweekly cisplatin in locally advanced squamous cell carcinoma of the head and neck: comparative analysis. *Head Neck*. 2019;41:1490-1498.
21. Szturz P, Wouters K, Kiyota N, et al. Low-dose vs. high-dose cisplatin: lessons learned from 59 chemoradiotherapy trials in head and neck cancer. *Front Oncol*. 2019;9:86.
22. Kiyota N, Tahara M, Mizusawa J, et al. Weekly cisplatin plus radiation for postoperative head and neck cancer (JCOG1008): a multicenter, noninferiority, phase II/III randomized controlled trial. *J Clin Oncol*. 2022;40:1980-1990.
23. Noronha V, Patil VM, Menon NS, et al. Six-year follow-up from the weekly-three-weekly study comparing cisplatin once-a-week to once-every-three-weeks as concurrent chemoradiation for locally advanced head and neck squamous cell carcinoma. *J Clin Oncol*. 2022;40:6071.
24. Bauml JM, Vinnakota R, Anna Park YH, et al. Cisplatin versus cetuximab with definitive concurrent radiotherapy for head and neck squamous cell carcinoma: an analysis of veterans health affairs data. *Cancer*. 2019;125:406-415.
25. Bauml JM, Vinnakota R, Anna Park YH, et al. Cisplatin every 3 weeks versus weekly with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck. *J Natl Cancer Inst*. 2019;111:490-497.
26. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014;32:2940-2950.
27. Otty Z, Skinner MB, Dass J, et al. Efficacy and tolerability of weekly low-dose cisplatin concurrent with radiotherapy in head and neck cancer patients. *Asia Pac J Clin Oncol*. 2011;7:287-292.

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