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# Triweekly carboplatin as a potential de-intensification agent in concurrent chemoradiation for early-stage HPV-associated oropharyngeal cancer

Shawn Iganej[a,*], Bryce W. Beard[a], Jergin Chen[a], Gary L. Buchschacher Jr.[b], Iman A. Abdalla[b], Lester D.R. Thompson[c], Onita Bhattasali[a]

[a] Southern California Permanente Medical Group, Department of Radiation Oncology, 4950 Sunset Boulevard, Los Angeles, CA 90027, United States
[b] Southern California Permanente Medical Group, Department of Hematology/Oncology, 1515 North Vermont Avenue, Los Angeles, CA 90027, United States
[c] Southern California Permanente Medical Group, Department of Pathology, 5601 De Soto Avenue, Woodland Hills, CA 91365, United States

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ABSTRACT

*Objective:* We compared high-dose cisplatin (HDC) vs. triweekly carboplatin (TC)-based chemoradiation in patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

*Materials and Methods:* A retrospective review was conducted from 2006 to 2015 of 421 patients with locally advanced p16-positive OPSCC receiving definitive radiotherapy concurrent with 3 cycles of HDC (100 mg/m$^2$, n = 230) or TC (AUC = 5, n = 191). Three-year locoregional recurrence (LRR), distant metastasis (DM), overall recurrence rate (ORR), overall survival (OS), and cause-specific survival (CSS) are reported. HDC and TC were compared accounting for age, sex, comorbidity index score, smoking history, T stage, and N stage.

*Results:* For all-comers, no difference was observed between HDC and TC for any outcome except for ORR which was lower in patients receiving HDC (12% vs. 17%, p = 0.03). On stage-based analysis, no difference was observed between agents for any outcome for stage I or II disease. However, patients with stage III disease receiving HDC had lower rates of LRR (9% vs. 21%, p = 0.03), DM (7% vs. 28%, p = 0.006), and ORR (14% vs. 40%, p = 0.002), and superior OS (89% vs. 78%, p = 0.04) and CSS (95% vs. 80%, p = 0.02). Patients receiving HDC experienced higher rates of grade 3 leukopenia (25% vs. 11%, p < 0.001), weight loss ≥20% from baseline (21% vs. 8%, p < 0.001), and gastrostomy-tube placements (66% vs. 27%, p < 0.001).

*Conclusion:* TC demonstrated comparable outcomes to HDC for stage I or II HPV-associated OPSCC but was inferior to HDC for stage III disease. TC was associated with less toxicity and may be a potential de-intensification agent for early-stage disease.

## Introduction

Concurrent chemoradiation using high-dose triweekly cisplatin (HDC) is considered the standard of care for locally advanced head and neck squamous cell carcinoma (LAHNSCC) and the preferred regimen by NCCN guidelines [1]. The basis for these guidelines stems from the results of multiple randomized studies and meta-analyses showing the superiority of cisplatin-based chemoradiation over radiation alone for LAHNSCC [2–4]. However, the majority of patients enrolled in trials showing the benefit of intense chemoradiation regimens using HDC had p16-negative LAHNSCC. It is now known that HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) has a considerably more favorable prognosis when compared to HPV-negative OPSCC [5,6]. In fact, due to these findings, the 8th edition of American Joint Committee on Cancer (AJCC) now distinguishes HPV-associated OPSCC as a separate entity, and many patients who were considered to carry the prognosis of stage III-IV disease are now being recategorized to have stage I or II disease [7,8]. Subsequently, numerous de-intensification efforts have been undertaken in these more favorable patients [9–12].

Concurrent HDC significantly increases acute toxicity and may increase late non-cancer mortality [4]. Therefore, one way to de-escalate definitive chemoradiation in these patients would be to replace this regimen with other chemotherapy agents that are better tolerated. In 2004, a randomized study by the Hellenic Cooperative Oncology group comparing concurrent HDC (100 mg/m$^2$) to triweekly carboplatin (TC) (AUC = 7) showed no statistically significant difference in outcomes and both regimens were superior to radiotherapy alone in the definitive treatment of LAHNSCC [13]. Since that time, some medical oncologists at our institution began employing TC at a moderate dose (AUC = 5) instead of HDC in hopes of better tolerance and compliance with

* Corresponding author.
*E-mail address:* shawn.x.iganej@kp.org (S. Iganej).

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treatment. Herein we report the outcomes of concurrent chemoradiation with HDC versus TC in our population of patients with p16-positive OPSCC.

## Methods and Materials

### *Study population and design*

A retrospective review was conducted at a single institution from February 2006 to September 2015 after obtaining approval from the institutional review board. Patients eligible for inclusion had stage III-IVB (AJCC 7th edition staging) histologically-confirmed p16-positive OPSCC. Central pathology review was performed with p16 immunohistochemical staining employed as a surrogate for HPV-positivity and obtained for all patients with standardized reporting. Positive cases were interpreted to be ≥70% nuclear and cytoplasmic immunoreactivity [14]. Patients with prior head and neck radiotherapy or other malignancy (except for non-melanomatous skin cancers) within the previous five years were excluded from this analysis. Other exclusion criteria included induction chemotherapy or oncologic surgery of any kind prior to definitive chemoradiation. Once all eligible patients were identified, stage conversion to the AJCC 8th edition for HPV-related disease was applied for this analysis.

### *Statistical analysis*

Baseline patient and disease characteristics and toxicity outcomes were compared with *t*-test for continuous variables and Chi-square test for categorical variables. Treatment failure and survival outcomes were defined as the length of time from the day of treatment completion. Outcomes analyzed included locoregional recurrence, distant metastasis, overall recurrence rate, progression-free survival, overall survival, and cause-specific survival. Disease control and survival outcomes were determined by the Kaplan-Meier method with three-year outcomes reported. A multivariate Cox proportional hazards model was used for analysis of all disease control and survival outcomes accounting for age, sex, Charlson Comorbidity Index (CCI) score, smoking history (< 10 pack-years vs. ≥10 pack-years), T stage, and N stage (AJCC 8th edition). Stage-based analyses were also performed adjusted for age, sex, CCI, and smoking history. The statistical significance level was set at 0.05.

### *Treatment and surveillance*

Patients received upfront definitive intensity modulated radiotherapy (IMRT) to a dose of 66–70 Gy (median 70 Gy) with simultaneous-integrated boost technique concurrent with a planned 3 cycles of either HDC (100 mg/m2) or TC (AUC = 5) on days 1, 22, and 43. Planned neck dissections were not performed for any patients. All patients underwent weekly on-treatment examinations. Toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. A treatment break was defined as one lasting two days or longer. The first post-treatment evaluation with clinical exam and nasopharyngoscopy was performed approximately one month after completion of concurrent chemoradiation. Subsequent follow-up was scheduled initially every two to three months and gradually transitioned to every six months until five years at which point patients had the option of annual surveillance in the head and neck clinic or routine care with their primary care provider. The most common follow-up schedule included a three-month post-treatment PET/CT or CT neck and annual chest x-ray. Additional imaging was obtained when clinically indicated based on patient-reported symptoms or abnormal findings on examination at the discretion of the treating physicians.

**Table 1**
Baseline characteristics of study cohort.

| | Cisplatin (n = 230) | Carboplatin (n = 191) | p-value |
|---|---|---|---|
| Median age (years) | 58 (33–77) | 62 (35–83) | < **0.001** |
| Male | 207 (90.0%) | 168 (88.0%) | 0.50 |
| Subsite | | | 0.53 |
| Tonsil | 126 (54.8%) | 106 (55.5%) | |
| Base of tongue | 97 (42.2%) | 83 (43.5%) | |
| Soft palate | 5 (2.2%) | 1 (0.5%) | |
| Pharyngeal wall | 2 (0.9%) | 1 (0.5%) | |
| T stage* | | | 0.19 |
| 1 | 55 (24.0%) | 26 (13.6%) | |
| 2 | 82 (35.7%) | 83 (43.5%) | |
| 3 | 49 (21.3%) | 45 (23.6%) | |
| 4 | 44 (19.1%) | 37 (19.4%) | |
| N stage* | | | 0.41 |
| 0 | 9 (3.9%) | 8 (4.2%) | |
| 1 | 161 (70.0%) | 142 (74.4%) | |
| 2 | 58 (25.2%) | 38 (19.9%) | |
| 3 | 2 (0.9%) | 3 (1.6%) | |
| TNM stage* | | | 0.64 |
| 1 | 104 (45.2%) | 94 (49.2%) | |
| 2 | 80 (34.8%) | 58 (30.4%) | |
| 3 | 46 (20.0%) | 39 (20.4%) | |
| Smoking status | | | 0.94 |
| Never smoker | 93 (40.4%) | 81 (42.4%) | |
| Former smoker | 97 (42.2%) | 74 (38.7%) | |
| Current smoker | 40 (17.4%) | 36 (18.9%) | |
| ≥10 pack-year smoker | 97 (42.2%) | 73 (38.2%) | 0.41 |
| Mean Charlson Comorbidity Index | 3.7 | 4.3 | < **0.001** |

* AJCC 8th edition.

## Results

From February 2006 through September 2015, 421 patients with p16-positive OPSCC received definitive IMRT concurrent with either HDC (n = 230) or TC (n = 191). Median follow-up for surviving patients was 47 months (range 16–135). Patient characteristics are listed in Table 1. Patients who received HDC were younger than those who received TC (median age 58 vs. 62, p < 0.001) and had lower CCI scores (3.7 vs. 4.3, p < 0.001); the two cohorts were otherwise well-balanced with respect to other baseline patient and disease characteristics including TNM stage and smoking history.

### *Overall recurrence rates and patterns of failure*

For the entire study population, 3-year overall recurrence rates were lower for the HDC cohort, 12% vs. 17% (p = 0.03) for patients who received TC. On stage-based analyses, a statistically significant difference for this parameter was only found in stage III patients, 14% vs. 40% (p = 0.002), with similar overall recurrence rates for stage I and stage II patients when comparing the two chemotherapy groups (Table 2).

For all-comers, no difference in 3-year incidences of locoregional recurrence or distant metastasis was found, with locoregional recurrence rates of 7% and 8% (p = 0.10) and distant metastasis rates of 8% and 12% (p = 0.21) for the HDC and TC groups, respectively. However, for those with stage III disease, there were statistically significant lower rates of locoregional recurrence (9% vs. 21%, p = 0.03) and distant metastasis (7% vs. 28%, p = 0.006) in those who received HDC, with no such differences found in those with lower stage disease (Table 2).

### *Overall survival and cause-specific survival*

Three-year overall survival and cause-specific survival for the entire HDC and TC groups were 92 vs. 90% (p = 0.90), and 95% vs. 93% (p = 0.39), respectively. However, 3-year overall survival was superior for those with stage III disease who were treated with HDC, 89% vs.

**Table 2**
Three-year disease control and survival outcomes and adjusted hazard ratios.

| | | Cisplatin | Carboplatin | Hazard ratio (HR) | p-value |
|---|---|---|---|---|---|
| Locoregional recurrence | | | | | |
| | All-comers | 7% | 8% | 0.53 (0.25–1.13) | 0.10 |
| | Stage I | 6% | 3% | 1.60 (0.39–6.64) | 0.52 |
| | Stage II | 5% | 10% | 0.38 (0.09–1.59) | 0.19 |
| | Stage III | 9% | 21% | 0.22 (0.06–0.84) | **0.03** |
| Distant metastasis | | | | | |
| | All-comers | 8% | 11% | 0.66 (0.34–1.28) | 0.21 |
| | Stage I | 6% | 7% | 0.87 (0.27–2.82) | 0.82 |
| | Stage II | 10% | 6% | 1.63 (0.47–5.71) | 0.45 |
| | Stage III | 7% | 28% | 0.15 (0.04–0.58) | **0.006** |
| Overall recurrence rate | | | | | |
| | All-comers | 12% | 17% | 0.55 (0.32–0.94) | **0.03** |
| | Stage I | 9% | 10% | 0.78 (0.30–2.02) | 0.61 |
| | Stage II | 13% | 13% | 0.88 (0.35–2.23) | 0.78 |
| | Stage III | 14% | 40% | 0.20 (0.07–0.55) | **0.002** |
| Overall survival | | | | | |
| | All-comers | 92% | 90% | 0.96 (0.54–1.71) | 0.90 |
| | Stage I | 94% | 92% | 1.03 (0.38–2.78) | 0.96 |
| | Stage II | 93% | 95% | 2.19 (0.74–6.51) | 0.16 |
| | Stage III | 89% | 78% | 0.34 (0.12–0.97) | **0.04** |
| Cause-specific survival | | | | | |
| | All-comers | 95% | 93% | 0.73 (0.36–1.49) | 0.39 |
| | Stage I | 95% | 96% | 1.24 (0.36–4.26) | 0.73 |
| | Stage II | 94% | 98% | 1.26 (0.33–4.82) | 0.73 |
| | Stage III | 95% | 80% | 0.18 (0.04–0.76) | **0.02** |

78% ($p = 0.04$). Three-year cause-specific survival was also in favor of the HDC cohort (95% vs. 80%, $p = 0.02$). No differences in either overall survival or cause-specific survival were noted in those with stage I or II disease (Table 2).

### *Toxicity and compliance*

Median total radiation dose and treatment duration were similar between the two chemotherapy groups. There was no difference in the percent of patients who required some chemotherapy dose modification between HDC and TC (48% vs. 49%, $p = 0.70$); however, HDC recipients were less likely to complete all three cycles of chemotherapy (77% vs. 84%, $p = 0.03$). Among patients in the HDC group, 16% received 2 cycles, and 7% received 1 cycle of chemotherapy. In the TC group, 14% of patients received 2 cycles, and 2% received 1 cycle of chemotherapy. Grade 3 leukopenia was more common with HDC (25% vs. 11%, $p < 0.001$), while rates of grade 3 anemia, grade 3 thrombocytopenia, and grade 3 nephrotoxicity were similar between the two groups. Patients receiving HDC were more likely to have a gastrostomy tube placed prophylactically than patients receiving TC (45% vs. 2%, $p < 0.001$). Among the cohort of patients who did not undergo prophylactic gastrostomy tube placement, those who received HDC had a higher rate of reactive gastrostomy tube placements (38% vs. 25%, $p = 0.02$). More patients in the HDC group were noted to have weight loss greater than 20% within 3 months of treatment completion (21% vs. 8%, $p < 0.001$). Although HDC recipients were more likely to have gastrostomy tubes greater than 100 days after treatment completion (34% vs. 16%, $p < 0.001$), there was no difference in gastrostomy tube rates at one year. The rate of emergency room visits during or within 30 days of treatment completion was higher in patients receiving HDC (50% vs. 32%, $p < 0.001$), however this did not result in a higher rate of hospital admissions. Forty-two (18%) HDC recipients and 25 (13%) TC recipients required a treatment break lasting 2 days or longer, but this difference was not statistically significant ($p = 0.20$). Toxicity outcomes are listed in detail in Table 3.

**Table 3**
Comparison of Toxicity Outcomes.

| | Cisplatin [n (%)] | Carboplatin [n (%)] | p-value |
|---|---|---|---|
| Grade 3 toxicities | | | |
| Leukopenia | 57 (24.8%) | 21 (11.0%) | < **0.001** |
| Anemia | 9 (3.9%) | 3 (1.6%) | 0.25 |
| Thrombocytopenia | 6 (2.6%) | 2 (1.0%) | 0.42 |
| Renal injury | 5 (2.2%) | 1 (0.5%) | 0.31 |
| Weight loss ≥ 20% | 49 (21.3%) | 16 (8.4%) | < **0.001** |
| Gastrostomy tube placement | | | |
| Any placement | 152 (66.1%) | 51 (26.7%) | < **0.001** |
| Prophylactic placement | 104 (45.2%) | 4 (2.1%) | < **0.001** |
| Reactive placement (among those remaining) | 48 (38.0%) | 47 (25.0%) | **0.017** |
| Gastrostomy tube post-treatment | | | |
| 100 days | 79 (34.4%) | 30 (15.7%) | < **0.001** |
| 1 year | 9 (4.9%) | 9 (17.7%) | 0.36 |
| Emergency room visit within 30 days of treatment | 115 (50.0%) | 61 (31.9%) | < **0.001** |
| Hospitalization within 30 days of treatment | 78 (33.9%) | 56 (29.3%) | 0.37 |

## Discussion

According to the NCCN guidelines, HDC is the preferred concurrent chemotherapy for the definitive treatment of LAHNSCC including HPV-associated OPSCC [1]. This recommendation is based on the proven superiority of this regimen when compared to radiotherapy alone or radiotherapy with cetuximab in multiple randomized trials [3,4,15,16]. The acute and potential late toxicities associated with concurrent chemoradiation using HDC are well documented [3,4]. While carboplatin monotherapy is not mentioned as an NCCN alternative to HDC, combination therapy with carboplatin and 5-fluorouracil (5-FU) is listed as a category 1 option based on the results of randomized studies from France [17,18]. These studies compared radiation alone (given either in conventional or accelerated fashion) with and without 2 or 3 cycles of carboplatin (70 mg/m$^2$ per day for 4 days) and 5-FU (600 mg/m$^2$ per day by continuous infusion over 4 days) and showed improvement in

local control and survival with concurrent chemoradiation. The employment of this GORTEC regimen is not prevalent in the United States due to the inconvenience of a 4-day infusion as well as anticipated increased rates of mucositis and hematological toxicities with the addition of 5-FU.

Due to the concerns for the morbidities associated with HDC and the GORTEC regimen, oncologists at our institution began using TC following the publication of a randomized study that showed no statistically significant difference in outcomes of patients with LAHNSCC when treated with either HDC or TC. In this three-arm randomized trial conducted by the Hellenic Oncology Group, both chemotherapy regimens were superior to radiotherapy alone in terms of disease control and survival. Although this study used a triweekly bolus dose of AUC = 7, we chose a more modest bolus dose of AUC = 5 based on a report from Queen Elizabeth Hospital which determined the maximum tolerated dose of TC to be close to AUC = 4.5 when used concurrently with radiotherapy in the treatment of head and neck cancers [19]. Herein, we report our experience treating patients with p16-positive OPSCC with either HDC or TC. We found that for the entire study population, HDC was modestly superior to TC in terms of recurrence rates with no difference in survival between the two groups. However, subgroup analysis based on AJCC 8th edition staging revealed that the small difference noted for the entire cohort appeared to stem from a rather large difference in outcomes for stage III patients whereas stage I and II patients performed similarly regardless of concurrent agent.

Recently, the results of two randomized studies, RTOG 1016 and De-ESCALaTE, comparing cetuximab and HDC-based chemoradiation in HPV-associated OPSCC were reported. Although the design of the trials varied somewhat in terms of the study population, radiation fractionation, and the number of HDC cycles delivered, both studies showed significantly inferior disease control and overall survival in the cetuximab arms. These reports highlight the need for a cautious approach to de-escalation efforts, particularly those that involve eliminating chemotherapy or replacing HDC with other regimens that may be better tolerated without careful patient selection. Although the superiority of HDC over cetuximab was noted in all stages of disease in both trials, the largest difference in efficacy outcomes and overall survival were noted in those with stage III disease. Most notably, the De-ESCALaTE trial showed a 2-year overall survival detriment with cetuximab of nearly 26% (67% vs. 93%) in stage III disease compared to only a 5% difference (98% vs. 93%) in those with stage I and II disease.

Perhaps one of the most striking findings from our report is the superiority of HDC to TC in lowering the rates of distant metastasis for stage III patients. At first glance, one might consider this observation rather unexpected, as historically, it has been reported that the benefit of concurrent chemoradiation is limited to improving local control over radiation alone [3,4,17]. However, it is also well documented that the pattern of recurrence for p16-positive OPSCC differs from those with p16-negative disease. Distant metastasis accounts for a higher percentage of total failures in p16-positive disease whereas locoregional recurrence is the predominant mode of failure in those with p16-negative disease [5,6]. Furthermore, p16-positive disease is more sensitive to chemotherapy and, therefore, it is not surprising that an active agent such as cisplatin delivered at a high dose might have a better chance at eradicating microscopic distant metastasis in this setting [9]. This observation has also been noted in the treatment of nasopharyngeal carcinoma, another chemosensitive malignancy, where cisplatin not only improves local control but also lowers the incidence of distant failures when added to radiotherapy alone [20,21]. Consistent with our findings, both De-ESCALaTE and RTOG 1016 also revealed that HDC reduces the incidence of distant metastases, although the reduction was not statistically significant in the RTOG trial and only showed a trend towards a difference ($p = 0.09$). This borderline result in the RTOG trial may have been due to the fact that only two cycles of HDC were given in that study as opposed to three cycles in the De-ESCALaTE trial. The majority of patients on our study also received three cycles of chemotherapy, and despite the fact that a modestly lower percentage of patients were able to receive all three doses of HDC compared to TC, a benefit in distant control was noted. Our study, in concordance with De-ESCALaTE, suggests that HDC plays an important role in preventing the development of distant relapse in this disease and should not be eliminated or replaced by agents that are not as active, such as carboplatin or cetuximab, particularly in higher stages of disease where the risk of distant failure is considerable.

In the last decade, it has been widely reported that p16-positive OPSCC has a much better prognosis than its p16-negative counterpart, with 3-year survival exceeding 80% in the majority of these reports. This led to the proposal of a new staging system by the ICON-S study which was later implemented in the AJCC 8th edition [7,8]. Consequently, many institutions have undertaken efforts to de-intensify treatment for HPV-associated OPSCC. The majority of these efforts have centered around radiation dose reduction and/or employing regimens deviating from the use of HDC [9,10,15,16,22]. Perhaps an equally important finding from our study is the fact that in stage I and II p16-positive disease, we found no significant difference in any oncologic outcome between HDC and TC with both groups performing well. Whether any chemotherapy is needed for stage I and II patients with HPV-associated OPSCC is unclear. However, the fact that HDC showed superiority over cetuximab in RTOG 1016 and De-ESCALaTE, even in stage I and II disease, does not particularly bode well for de-intensification efforts that include complete elimination of chemotherapy such as HN002 [22]. In this recently closed trial, patients with stage I and II low-risk HPV-associated OPSCC are randomized to either 60 Gy of accelerated radiotherapy alone or the same dose of radiotherapy delivered with conventional fractionation concurrent with weekly cisplatin 40 $mg/m^2$. Since we now know that 70 Gy with either accelerated or conventional radiotherapy with cetuximab is inferior to the same dose of radiotherapy with HDC in low-risk p16-positive OPSCC, one could extrapolate that 60 Gy of accelerated radiotherapy alone is bound to be inadequate, as concurrent cetuximab with radiotherapy, i.e., the inferior arm of the RTOG 1016 and De-ESCALaTE, has already been shown to be superior to radiotherapy alone. This assertion is based on the registration trial of cetuximab reported by Bonner and the subsequent subgroup analysis that showed adding cetuximab to radiotherapy improves local control and overall survival in LAHNSCC regardless of p16 status [23,24]. Nevertheless, the inferiority of cetuximab to HDC does not necessarily mean that other concurrent regimens cannot replace HDC, particularly in earlier stages of the disease.

Our study suggests that TC (AUC = 5) may be a suitable replacement for HDC in stage I and II p16-positive OPSCC since it resulted in similar disease control with meaningful treatment de-intensification. We saw lower morbidity for TC across several objective parameters such as the need for feeding tubes and hematological toxicities. Although patients who received HDC were more likely to receive a prophylactic gastrostomy tube, among the group of patients who did not undergo prophylactic placement, there was still a higher rate of reactive placements in the HDC group. While we did not report on comparison of other morbidities such as ototoxicity and peripheral neuropathy due to inconsistent documentation in our database, other studies have previously shown a lower incidence of these side effects with carboplatin as well [25].

As with any retrospective study, our report has certain limitations. First, we used p16 as a surrogate for HPV-positivity, which is the accepted standard, but did not perform studies that document transcriptionally active HR-HPV E6 and E7 messenger RNA by in situ hybridization. It is well characterized that increased p16 expression is a downstream consequence of HPV infection due to oncoprotein E7-induced inactivation of tumor suppressor Rb [26]. It is possible that alternative pathways may lead to p16 overexpression in HPV-negative disease, although a report from IMCL-9815 found p16 status to be sufficiently concordant with HPV status, and recent guidelines from the

College of American Pathologists consider p16 status to be an acceptable surrogate for determination of HPV status with p16-positive tumors considered to be very likely HPV-positive [14,24]. Another consideration is that the triweekly dose of AUC = 5 of carboplatin given to our patients was chosen by our oncologists based on a small dose escalation study from the Queen Elizabeth Hospital, and no randomized trial has compared concurrent chemoradiation using TC at this dose to radiotherapy alone in LAHNSCC [19]. The randomized Greek study cited earlier in the discussion which showed superiority of concurrent chemoradiation over radiation alone used a higher dose of TC (AUC = 7). It is possible that this higher dose of TC could perform better in terms of efficacy although it might also compromise its tolerance. Furthermore, although we did not find a statistically significant difference in disease outcomes when comparing TC and HDC in stage I and II disease, a small difference cannot be ruled out. It is possible that a large randomized study could detect such a difference, as was the case in RTOG 1016 and De-ESCALaTE. Conversely, there is a built-in patient selection bias in retrospective comparisons such as ours, as evident by the fact that patients receiving TC were older and had higher CCI scores; these imbalances may have exaggerated the difference in outcomes in stage III disease.

In summary, this study suggests that TC-based chemoradiation has comparable efficacy to HDC-based chemoradiation in early-stage p16-positive OPSCC but performs inferiorly in stage III disease. TC may be implemented as a substitute for patients who are considered ineligible for cisplatin, particularly those with less advanced disease. TC should not be employed in cisplatin-eligible patients with stage III disease. TC demonstrated a more favorable toxicity profile when compared to HDC and, in conjunction with its comparable efficacy, may be a potential de-intensification agent for early-stage p16-positive OPSCC. A prospective comparison of TC to HDC in early-stage HPV-associated OPSCC is warranted.

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## Declaration of Competing Interest

None declared.

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