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Comparison of high-dose Cisplatin-based chemoradiotherapy and Cetuximab-based bioradiotherapy for p16-positive oropharyngeal squamous cell carcinoma in the context of revised HPV-based staging

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ABSTRACT

Aim: To perform a comparison of Cisplatin vs. Cetuximab in p16-positive oropharyngeal squamous cell carcinoma (OPSCC) in the context of the revised HPV-based staging.

Background: Previous reports comparing these agents in head and neck cancer have included heterogenous disease and p16-status.

Materials and methods: A retrospective review was conducted from 2006 to 2016 of patients with p16-positive OPSCC who underwent definitive radiotherapy concurrent with either triweekly Cisplatin ($n = 251$) or Cetuximab ($n = 40$). AJCC 8th Edition staging was adapted.

Results: Median follow-up for surviving patients was 40 months. On multivariate analysis for all-comers, comparing Cisplatin and Cetuximab, 3-year locoregional recurrence (LRR): 6% vs. 16% ($p = 0.07$), 3-year distant metastasis (DM): 8% vs. 21% ($p = 0.04$), 3-year overall recurrence rate (ORR): 11% vs. 29% ($p = 0.01$), and 3-year cause-specific survival (CSS): 94% vs. 79% ($p = 0.06$), respectively. On stage-based subgroup analysis, for stage I—II disease, 3-year LRR: 5% vs. 10% ($p = 0.51$), 3-year DM: 7% vs. 16% ($p = 0.32$), 3-year ORR: 10% vs. 23% ($p = 0.15$), and 3-year CSS: 95% vs. 82% ($p = 0.38$). For stage III disease, 3-year LRR: 10% vs. 40% ($p = 0.07$), 3-year DM: 9% vs. 43% ($p = 0.07$), 3-year ORR: 15% vs. 55% ($p = 0.04$), and 3-year CSS: 94% vs. 57% ($p = 0.048$).

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Conclusions: When given concurrently with radiotherapy, Cetuximab and triweekly Cisplatin demonstrated comparable efficacy for AJCC 8th Edition stage I–II p16-positive OPSCC. However, Cetuximab appeared to be associated with higher rates of treatment failure and cancer-related deaths in stage III disease. Upon availability of the RTOG 1016 trial results, analysis based on the revised HPV-based staging should be performed to confirm these findings.

1. Background

Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is now established as a distinct clinical entity with favorable patient outcomes compared to other squamous cell carcinoma (SCC) of the head and neck that are commonly associated with heavy tobacco and alcohol use.[1] Because of this, there are ongoing attempts to de-intensify treatment to minimize treatment-related toxicities without compromising disease control. High-dose Cisplatin concurrent with radiation therapy is considered the standard of care for locally advanced SCC of the head and neck (LASCCHN) but is a regimen associated with considerable toxicity. Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, emerged as a potential alternative to Cisplatin-based radiotherapy after demonstrating a locoregional control and survival benefit when added to radiation for LASCCHN in a randomized trial.[2] This benefit was maintained specifically in p16-positive OPSCC.[3]

While the addition of Cetuximab to radiation is known to improve patient outcomes over radiation alone, there is no randomized evidence thus far comparing the efficacy of Cetuximab to high-dose Cisplatin. RTOG 1016 is a phase III randomized clinical trial designed to answer this question specifically for patients with HPV-associated OPSCC; it is now closed to accrual, but the results are not yet mature. Several institutions have retrospectively performed comparisons of Cisplatin and Cetuximab in LASCCHN with conflicting findings.[4–8] The majority of these reports comprise a heterogenous population of all LASCCHN without exclusively evaluating outcomes in patients with p16-positive OPSCC. To complicate matters further, the new AJCC 8th Edition Cancer Staging Manual now distinguishes p16-positive OPSCC as an entity separate from its p16-negative counterpart to more accurately prognosticate outcomes for this population.[9] Here, we report our institutional experience treating p16-positive OPSCC with definitive radiotherapy concurrent with either high-dose Cisplatin or Cetuximab in the context of revised HPV-based staging.

2. Materials and methods

2.1. Study design

A retrospective review was conducted at a single-institution from November 2006 through September 2016 after obtaining approval from the institutional review board. Consecutive patients eligible for inclusion underwent definitive management for TNM stage I–III (cT1-2N1-3 or cT3-4N0-3) (American Joint Committee on Cancer (AJCC) 8th Edition staging) histologically-confirmed p16-positive OPSCC with radiation therapy concurrent with either triweekly high-dose Cisplatin ($n = 251$) or Cetuximab ($n = 40$). Patients who received induction chemotherapy or oncologic surgery of any kind prior to definitive management were excluded from analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanoma skin cancer) within the previous five years. Central pathology review was performed, with p16 immunohistochemical staining obtained for all patients, with positive cases interpreted to be strong and diffuse, >75% nuclear and cytoplasmic immunoreactivity.[10] A minimum of one year of follow-up was required for all surviving patients.

2.2. Treatment

Patients received intensity-modulated radiation therapy (IMRT) to a planned dose of 66–70 Gy with simultaneous-integrated boost technique concurrent with either high-dose Cisplatin (100 mg/m^2 triweekly) or Cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly). Reasons for receiving Cetuximab rather than Cisplatin were predominantly due to patient and physician preference with the exception of patients who were thought to be suboptimal candidates for high-dose Cisplatin due to baseline renal dysfunction or hearing impairment ($n = 9$). All patients underwent weekly on-treatment examinations. A treatment break was defined as one lasting two days or longer. At our institution, we did not prophylactically place gastrostomy tubes for nutritional support prior to treatment initiation. Rather, they were placed at the discretion of the treating physician if swallowing became significantly impaired during treatment or if patients experienced weight loss exceeding 10% of their baseline weight.

Evaluation with clinical exam and nasopharyngoscopy was performed one month following completion of treatment. 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 head and neck clinic or routine care with their primary care provider. Post-treatment imaging studies were obtained periodically at the discretion of the treating including a baseline positron emission tomography (PET) scan in over 95% of the patients. No planned neck dissections were performed.

2.3. Statistical analysis

Patient 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 (LRR), distant metastasis (DM), overall recurrence rate (ORR), and cause-specific survival (CSS). Disease control and survival outcomes were estimated by the Kaplan–Meier method. Multivariate analysis was conducted for all disease control and survival outcomes for all-comers as well as for TNM stage-based subgroups using a Cox proportional hazards model accounting for age (<65 vs. >65), T stage, N stage, and smoking history (>10 pack-years). The statistical significance level was set at 0.05.

3. Results

3.1. Patient and tumor characteristics

Detailed patient clinical characteristics are listed in Table 1. Median follow-up for surviving patients was 40 (range: 14–115) months. Patients who received Cisplatin were younger than those who received Cetuximab (median age 57 vs. 70 years, $p < 0.001$) and were more commonly male (90% vs. 78%, $p = 0.03$). There was a trend for a higher proportion of patients with a smoking history ≥10 pack-years in the Cetuximab group (41% vs. 57%, $p = 0.06$). Otherwise, patients were well-balanced with respect to T stage, N stage, and overall TNM stage.

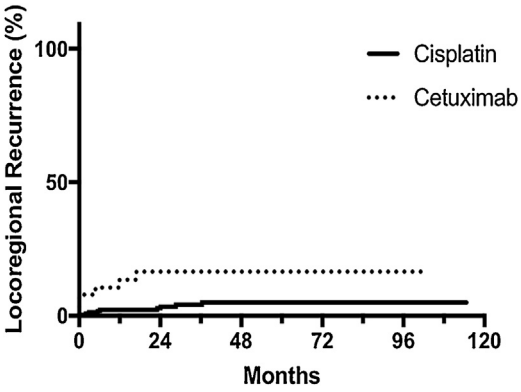

Fig. 1 – Locoregional recurrence.

3.2. Disease control and survival outcomes

On univariate analysis among all-comers, there was a significant difference in 3-year LRR rates between Cisplatin and Cetuximab: 6% vs. 16% (hazard ratio (HR) = 0.35 [0.14–0.91], $p = 0.03$). respectively (Fig. 1). On multivariate analysis, this difference was not significant (HR) = 0.36 [0.12–1.07], $p = 0.07$). Subgroup analysis based on TNM stage showed no difference in 3-year LRR rates between Cisplatin and Cetuximab for stage I—II disease: 5% vs. 10% (HR = 0.61 [0.14–2.64], $p = 0.51$); how-

Table 1 – Patient and tumor characteristics.

	Cisplatin ($n = 251$) No. of patients (%)	Cetuximab ($n = 40$) No. of patients (%)	p-value
Median age (years)	57 (33–78)	70 (40–86)	**<0.001**
Sex			**0.03**
Male	227 (90.4%)	31 (77.5%)	
Female	24 (9.6%)	9 (22.5%)	
Subsite			0.45
Tonsil	143 (57.0%)	19 (47.5%)	
Base of tongue	102 (41.0%)	21 (52.5%)	
Soft palate	4 (1.6%)	0 (0.0%)	
Pharyngeal wall	2 (0.8%)	0 (0.0%)	
T classification			0.56
T1	61 (24.3%)	6 (15.0%)	
T2	86 (34.3%)	16 (40.0%)	
T3	56 (22.3%)	11 (27.5%)	
T4	48 (19.1%)	7 (17.5%)	
N classification			0.11
N0	10 (4.0%)	4 (10.0%)	
N1	175 (69.7%)	31 (77.5%)	
N2	61 (24.3%)	4 (10.0%)	
N3	5 (2.0%)	1 (2.5%)	
AJCC 8th Edition TNM Stage			0.83
Stage I	113 (45.0%)	20 (50.0%)	
Stage II	86 (34.3%)	12 (30.0%)	
Stage III	52 (20.7%)	8 (20.0%)	
>10 Pack-year Smoking History	102 (40.6%)	23 (57.5%)	0.06

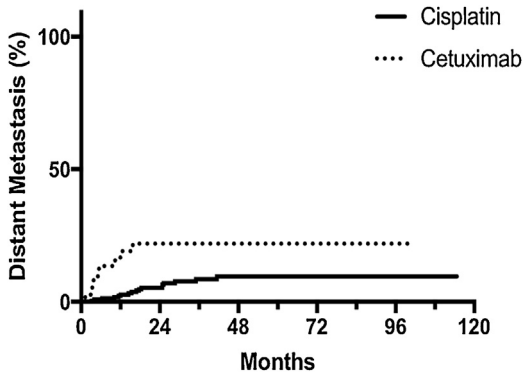

Fig. 2 – Distant metastasis.

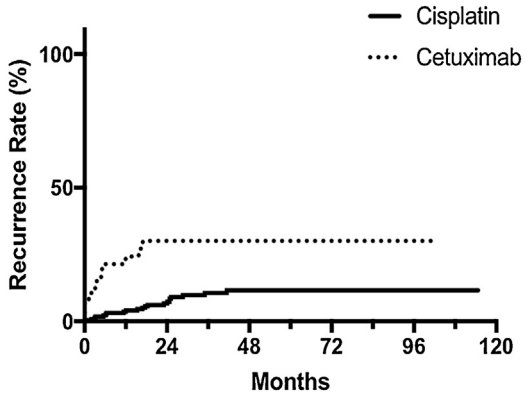

Fig. 3 – Overall recurrence rates.

ever, there was a trend toward a lower 3-year LRR rate in the Cisplatin group for stage III disease: 10% vs. 40% (HR = 0.19 [0.03–1.16], $p = 0.07$).

On univariate analysis, the 3-year DM rate was lower in the Cisplatin group: 8% vs. 21% (HR = 0.31 [0.13–0.71], $p = 0.006$) (Fig. 2). This difference remained significant on multivariate analysis (HR = 0.38 [0.15–0.97], $p = 0.04$). On subgroup analysis, there was no difference in 3-year DM rates between Cisplatin and Cetuximab for stage I—II disease: 7% vs. 16% (HR = 0.55 [0.17–1.77], $p = 0.32$), but there was a trend toward a lower 3-year DM rate in the Cisplatin group for stage III disease: 9% vs. 43% (HR = 0.21 [0.04–1.11], $p = 0.07$).

Among the entire cohort, on univariate analysis, the 3-year ORR was lower among patients who received Cisplatin: 11% vs. 29% (HR = 0.32 [0.16–0.65], $p = 0.002$) (Fig. 3). On multivariate analysis, Cisplatin remained associated with significantly lower ORR compared to Cetuximab (HR = 0.37 [0.16–0.82], $p = 0.01$). On subgroup analysis, there was no difference in 3-year ORR between Cisplatin and Cetuximab for stage I—II disease: 10% vs. 23% (HR = 0.49 [0.19–1.31], $p = 0.15$); however, among patients with stage III disease, Cisplatin was associated with lower 3-year ORR: 15% vs. 55% (HR = 0.20 [0.04–0.96], $p = 0.04$).

For all-comers, univariate analysis demonstrated a significant difference in 3-year CSS in favor of the Cisplatin group: 94% vs. 77% (HR = 0.32 [0.14–0.73]. $p = 0.007$) (Fig. 4). On multivariate analysis, this difference lost significance (HR = 0.40

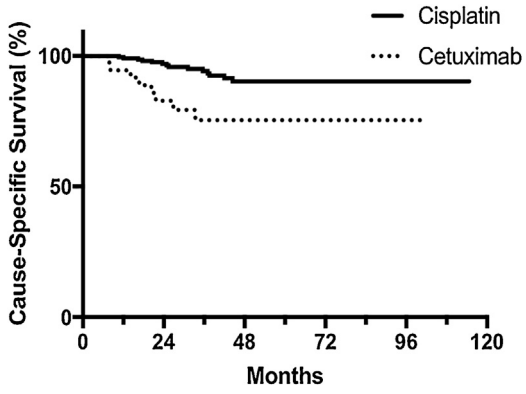

Fig. 4 – Cause-specific survival.

[0.15–1.03], $p = 0.06$). On subgroup analysis, there was no difference in 3-year CSS between Cisplatin and Cetuximab for stage I—II disease: 95% vs. 82% (HR = 0.58 [0.18–1.93], $p = 0.38$); among patients with stage III disease, 3-year CSS was superior in patients who received Cisplatin: 94% vs. 57% (HR = 0.19 [0.04–0.98], $p = 0.048$). Disease control and survival outcomes are outlined in Tables 2 and 3.

3.3. *Treatment compliance and toxicity*

In the Cisplatin group, 46% of patients required some systemic agent dose modification compared to only 18% in the Cetuximab group ($p < 0.001$); however, there was no significant difference in the percentage of patients who required cycle reduction, 24% vs. 15% ($p = 0.19$), respectively. Among patients in the Cisplatin group, 53% of patients received all three cycles at the planned dose of 100 mg/m^2, and 89% of patients received at least 200 mg/m^2 over the course of treatment. Patients who required transition to a different regimen due to poor tolerance of Cisplatin received either tri-weekly Carboplatin ($n = 17$), weekly Cisplatin ($n = 8$), or weekly Carboplatin ($n = 1$). There was no difference in the incidence of radiation treatment breaks required between Cisplatin and Cetuximab: 16% vs. 15% ($p = 0.83$). Patients who received Cisplatin were more likely to have gastrostomy tube placement than patients who received Cetuximab: 67% vs. 38 ($p = 0.001$); however, there was no difference in median time to gastrostomy tube removal following completion of treatment: 3.6 months vs. 4.3 months ($p = 0.61$), respectively. There was also no difference in gastrostomy-tube dependence rates at one year or upon death between Cisplatin and Cetuximab: 9% vs. 13% ($p = 0.51$), respectively. There was one treatment-related death in the Cetuximab group due to septic shock and two treatment-related deaths in the Cisplatin group due to cardiopulmonary arrest and septic shock.

4. Discussion

In this retrospective study of patients treated definitively for p16-positive OPSCC, when given concurrently with radiotherapy, high-dose Cisplatin and Cetuximab appeared to demonstrate comparable efficacy for AJCC 8th Edition stage I—II disease; however, Cetuximab was associated with higher

Table 2 – Disease control and survival outcomes for all-comers at 3 years on univariate analysis.

	Cisplatin	Cetuximab	Hazard ratio (HR)	*p*-value
Locoregional recurrence	6%	16%	0.35 [0.14–0.91]	**0.03**
Distant metastasis	8%	21%	0.31 [0.13–0.71]	**0.006**
Overall recurrence	11%	29%	0.32 [0.16–0.65]	**0.002**
Cause-specific survival	94%	77%	0.32 [0.14–0.73]	**0.007**

Table 3 – Disease control and survival outcomes on multivariate and stage-based subgroup analysis.

	Cisplatin	Cetuximab	Hazard ratio (HR)	*p*-value
Locoregional recurrence				
All-comers	6%	16%	0.36 [0.12–1.07]	0.07
Stage I–II	5%	10%	0.61 [0.14–2.64]	0.51
Stage III	10%	40%	0.19 [0.03–1.16]	0.07
Distant metastasis				
All-comers	8%	21%	0.38 [0.15–0.97]	**0.04**
Stage I–II	7%	16%	0.55 [0.17–1.77]	0.32
Stage III	9%	43%	0.21 [0.04–1.11]	0.07
Overall recurrence				
All-comers	11%	29%	0.37 [0.16–0.82]	**0.01**
Stage I–II	10%	23%	0.49 [0.19–1.31]	0.15
Stage III	15%	55%	0.20 [0.04–0.96]	**0.04**
Cause-specific survival				
All-comers	94%	77%	0.40 [0.15–1.03]	0.06
Stage I–II	95%	82%	0.58 [0.18–1.93]	0.38
Stage III	94%	57%	0.19 [0.04–0.98]	**0.048**

rates of treatment failure and cancer-related deaths for patients with stage III disease. When reviewing outcomes among all-comers, Cetuximab was associated with inferior distant control and ORR in comparison to high-dose Cisplatin. After subgroup analysis, in the context of revised HPV-based staging, there were no differences between Cisplatin and Cetuximab with respect to tumor control or CSS for stage I—II disease. For stage III disease, there was a trend toward inferior LRR and DM outcomes in patients who received Cetuximab leading to inferior ORR and CSS.

To our knowledge, this is the largest study performing a comparison of these agents exclusively for p16-positive OPSCC. We observed a 3-year LRR rate of 16% in the Cetuximab group, similar to the 3-year LRR rate of 13% reported by Rosenthal et al. in their p16-positive cohort treated with Cetuximab-based radiotherapy.[3] Our 3-year LRR rate of 6% in the Cisplatin group was relatively low, particularly in comparison to the 14% 3-year LRR rate for patients with p16-positive disease reported from RTOG 0129; however, it should be noted that RTOG 0129 excluded patients with T1N+ or T2N1 (AJCC 7th Edition staging) disease, whereas our study was inclusive of all node-positive disease, and so lower failure rates might be expected.[1] On multivariate analysis, patients who received Cetuximab experienced inferior distant control compared to patients in the Cisplatin group with 3-year DM rates of 21% vs. 8%. Similarly, Weller et al. noted higher distant failure among HPV-associated OPSCC patients who received Cetuximab in comparison to Cisplatin-based radiotherapy: 23% vs. 5% at 2 years.[11]

Although overall recurrence rates were higher in the Cetuximab group as a whole, analysis by TNM stage revealed that the difference between systemic agents was only significant in stage III disease. This is consistent with other reports in the literature which show favorable outcomes for earlier stage patients, even with radiotherapy alone.[12,13] Patients with HPV-associated stage I—II disease may not require high-dose Cisplatin to achieve acceptable disease control, and therefore, a de-intensified regimen with concurrent Cetuximab may be sufficient for early-stage disease. Whether concurrent systemic therapy is necessary at all for early-stage disease is an important question that is the subject of investigation in NRG HN002. In this de-intensification study, patients with stage I and II p16-positive OPSCC (excluding those with bilateral, matted, and low-neck lymphadenopathy) with limited smoking history are randomized to accelerated radiotherapy alone to 60 Gy or conventional radiotherapy to 60 Gy with concurrent weekly Cisplatin.

Other institutions have performed retrospective comparisons of Cisplatin and Cetuximab with mixed results although largely suggesting inferiority of Cetuximab. These studies predominantly evaluate differences in outcomes between these agents in all LASCCHN and not specifically p16-positive OPSCC. In a report from Memorial Sloan Kettering Cancer Center (MSKCC), Koutcher et al. found that Cetuximab was significantly inferior to Cisplatin for locoregional control (LRC), failure-free survival (FFS), and overall survival (OS) in patients with LASCCHN with large absolute differences between the two groups, and a follow-up publication from the same institution by Riaz et al. found there was no difference in the rate of p16-positivity between the two cohorts; however, outcome differences between the two agents for p16-positive patients were not reported.[4,5] Similarly, Levy et al. found improved LRC and distant control (DC) among patients who were treated with Cisplatin as well as a non-significant trend toward improved OS.[8] Ou et al. found superior LRC for patients treated with Cisplatin compared to Cetuximab regardless of

p16 status.[7] This study noted superior progression-free survival (PFS) in the Cisplatin group, but only a trend toward superior PFS when patients were divided by p16 subgroup, although small numbers may have accounted for their inability to demonstrate significance. On the other hand, Strom et al. found no difference between Cisplatin and Cetuximab in LRC, DM, or OS for LASCCHN without assessment of the p16 status; of note, this study observed a patient imbalance with more advanced nodal disease in the group that received Cisplatin which may have affected the outcomes.[6]

As with any retrospective study, there are inherent biases which we attempted to account for through our analyses. Patients who received Cetuximab were older than those who received Cisplatin. We chose CSS as the appropriate endpoint for this study in order to exclude the impact of intercurrent disease death that could potentially confound results for other survival endpoints such as progression-free or overall survival. The reluctance to use systemic therapy in older patients is supported by multiple studies in the literature including the meta-analysis by Pignon et al. which found that patients older than 70 did not benefit from the addition of chemotherapy to locoregional treatment.[14] Similarly, an unplanned subgroup analysis of the Bonner study showed that patients aged 65 or older did not benefit from the addition of Cetuximab to radiation.[15] Because of this, we performed multivariate analysis to evaluate the independent prognostic impact of Cetuximab which remained significantly inferior to Cisplatin for CSS in stage III disease even after accounting for age.

Although results from RTOG 1016 are not yet available, there is randomized data comparing high-dose Cisplatin to Panitumumab, an EGFR-inhibitor similar to Cetuximab, for LASCCHN. CONCERT-2, a phase II randomized study designed to compare high-dose Cisplatin to Panitumumab concurrent with accelerated-fractionation radiotherapy, found superior 2-year PFS for patients in the Cisplatin group.[16] When subgroup analysis was performed based on p16 status, there was no difference in LRR between Cisplatin and Panitumumab for p16-positive patients ($n = 24$), but there was a trend toward higher LRR rates in p16-negative patients ($n = 75$) who received Panitumumab. The Canadian HN.6 trial, which compared Cisplatin-based standard-fractionation radiotherapy to Panitumumab-based accelerated-fractionation radiotherapy in LASCCHN, was unable to demonstrate non-inferiority of Panitumumab to Cisplatin, finding no change in efficacy based on p16 status, and concluded that concurrent chemoradiation with Cisplatin should remain the standard of care.[17]

It should be noted that this study reports on patients who have p16-positive OPSCC and not exclusively those with HPV-positive disease. All patients in the study underwent p16 immunohistochemical testing, and the commonly accepted threshold of 75% was interpreted as p16-positive. Increased p16 expression is a downstream effect of HPV infection due to inactivation of the tumor suppressor Rb by the oncoprotein E7.[18] However, not all disease that overexpresses p16 is HPV-positive, and there are alternate pathways that may overexpress p16 in HPV-negative disease such that p16 expression is not a completely accurate surrogate for HPV status. In a future investigation, it would be helpful to collect both p16 and HPV status on tissue samples to further prognosticate patient outcomes. Nevertheless, a report from the IMCL-9815 study suggests that p16-positive status is sufficiently concordant with HPV-positive status among patients with OPSCC, and p16 testing is widely employed as an HPV surrogate in the clinical setting.[19]

Finally, in concordance with other reports in the literature, our study found that Cetuximab was better tolerated than Cisplatin.[4,8] There was a higher rate of dose modifications in the Cisplatin group although nearly 90% of patients received at least 200 mg/m^2. Acutely, there was a higher rate of gastrostomy tube placement in the Cisplatin group, but there was no difference in long-term gastrostomy tube dependence rates.

5. Conclusions

In conclusion, Cetuximab-based bioradiotherapy demonstrated comparable efficacy when compared to high-dose Cisplatin-based chemoradiotherapy in patients with stage I—II HPV-associated oropharyngeal cancer; however, there were higher rates of treatment failure and cancer-related deaths associated with Cetuximab for patients with stage III disease. Although patients who received Cetuximab were older than those in the Cisplatin group, multivariate analysis accounting for this imbalance showed that the use of Cetuximab was an independent predictor of inferior outcomes for patients with advanced disease. Upon availability of the RTOG 1016 trial results, analysis based on the revised HPV-based staging should be performed to confirm these findings.

Conflict of interest

None declared.

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