Oral Oncology 95 (2019) 74–78

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Impact of chemotherapy regimen on treatment outcomes in patients with HPV-associated oropharyngeal cancer with T4 disease treated with definitive concurrent chemoradiation

Onita Bhattasali[a], Joan J. Ryoo[a], Lester D.R. Thompson[b], Iman A. Abdalla[c], Jergin Chen[a], Shawn Iganej[a,*]

[a] Southern California Permanente Medical Group, Department of Radiation Oncology, Los Angeles, California, United States
[b] Southern California Permanente Medical Group, Department of Pathology, Woodland Hills, California, United States
[c] Southern California Permanente Medical Group, Department of Hematology/Oncology, Los Angeles, California, United States

ARTICLE INFO

Keywords:
Oropharyngeal cancer
Squamous cell carcinoma
Human papilloma virus
P16-positive
T4 disease
Chemoradiation
Radiotherapy
Cisplatin
Cetuximab
Carboplatin

ABSTRACT

Objectives: Although human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is typically associated with a good prognosis, patients with T4 disease experience relatively high rates of treatment failure. Our aim was to identify predictors of relapse among patients with clinical T4 disease.

Material & Methods: A retrospective review was conducted of 93 consecutive patients who underwent definitive concurrent chemoradiation for HPV-associated OPSCC with clinical T4 disease from July 2006 to December 2015. Three-year outcomes, including locoregional recurrence (LRR), distant metastasis (DM), overall survival (OS), and cancer-specific survival (CSS), were examined and reported from the date of treatment completion. Multivariable analysis using a Cox proportional hazards model was performed to test associations between outcome and patient and disease characteristics as well as chemotherapy regimen (high-dose cisplatin (HDC) vs. other).

Results: Median follow-up for surviving patients was 50 months (range 18–133). For all-comers, 3-year rates of LRR, DM, OS, and CSS were 15%, 19%, 79%, and 86%, respectively. On multivariable analysis, the only factor prognostic for patient outcomes was the chemotherapy regimen. For patients who received HDC vs. an alternative regimen, 3-year LRR, DM, OS, and CSS, were 9% vs. 20% ($p = 0.09$), 10% vs. 28% ($p = 0.04$), 89% vs. 67% ($p = 0.04$), and 96% vs. 77% ($p = 0.02$), respectively.

Conclusion: In patients with HPV-associated OPSCC bearing clinical T4 disease, receipt of a concurrent systemic agent other than HDC resulted in increased treatment failure and inferior survival. This analysis suggests that HDC should remain the preferred concurrent regimen for these patients.

Introduction

Definitive concurrent chemoradiation (CCRT) generally results in excellent outcomes for patients with human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC); yet, there exist subgroups which may be at higher risk of treatment failure and, consequently, inferior survival [1,2]. Specifically, patients with T4 disease have been shown to be at higher risk of distant failure compared to patients with less advanced T stages. O'Sullivan et al. reported a 3-year distant control rate of 90% among all-comers with HPV-associated disease but found that those with T4 disease had a 3-year distant control rate of only 78% [3]. The objective of this analysis was to identify predictors of failure among patients with HPV-associated OPSCC bearing T4 disease treated with definitive CCRT.

Material & Methods

We conducted a retrospective review of 93 consecutive patients who underwent definitive CCRT in an integrated healthcare system for histologically-confirmed HPV-associated OPSCC with clinical T4 disease from July 2006 to December 2015. Institutional review board approval was obtained (IRB #5968 and #11178). Patients who underwent oncologic surgery or received induction chemotherapy prior to definitive management were excluded from analysis, as were patients with prior

* Corresponding author at: Southern California Permanente Medical Group, Department of Radiation Oncology, 4950 Sunset Boulevard, Los Angeles 90027, California, United States.
E-mail address: shawn.x.iganej@kp.org (S. Iganej).

https://doi.org/10.1016/j.oraloncology.2019.06.007
Received 16 January 2019; Received in revised form 27 April 2019; Accepted 7 June 2019
Available online 11 June 2019
1368-8375/

head and neck radiotherapy or other known malignancies (excluding non-melanomatous skin cancers) within the previous five years. Immunohistochemical staining for p16 was performed on all biopsy specimens confirming diagnosis, and pathology was centrally reviewed with standardized p16 reporting. Positive cases were interpreted to be > 70% nuclear and cytoplasmic immunoreactivity [4]. Nodal staging was updated to the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual for the purpose of this analysis as it has been shown to be more prognostic compared to older staging systems [2,5].

Patients received intensity modulated radiation therapy to a planned dose of 70 Gy with simultaneous-integrated boost technique. All patients received systemic therapy concurrent with radiation. Concurrent agents employed included high-dose cisplatin (HDC) (100 mg/m^2) (n = 46), triweekly carboplatin (AUC = 5) (n = 37), cetuximab (n = 7), weekly cisplatin (40 mg/m^2) (n = 2), and weekly carboplatin (AUC = 2) (n = 1). Reasons for receipt of an agent other than HDC included physician preference (n = 27), elderly age/performance status (n = 9), renal dysfunction (n = 6), and hearing impairment (n = 4). Evaluation with clinical examination 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 physician. Post-treatment imaging studies were obtained periodically at the discretion of the treating physician. There were no planned neck dissections in this cohort.

All patients underwent a minimum follow-up of 18 months. Three-year disease control and survival outcomes are reported from the date of treatment completion. Outcomes examined were locoregional recurrence (LRR), distant metastasis (DM), overall survival (OS), and cancer-specific survival (CSS). Disease control and survival outcomes were estimated by the Kaplan-Meier method. Multivariable analysis was conducted for all disease control and survival outcomes using a Cox proportional hazards model including patient and disease characteristics of age, smoking history (≥10 pack-years vs. < 10 pack-years/never), nodal stage, presence of matted lymphadenopathy (ML), overt radiographic extracapsular extension (ORECE), low-neck lymphadenopathy (LNL), retropharyngeal lymphadenopathy (RP), and chemotherapy regimen (HDC vs. other). LNL was defined as involvement of levels IV and/or Vb. ML was defined as multiple lymph nodes abutting one another with loss of the intervening fat planes. ORECE was defined as clear loss of the integrity of the nodal capsule with infiltration of disease into adjacent structures excluding adjacent lymph nodes as would be defined by ML. Two-sided statistical analysis was performed with the significance level set at 0.05.

Results

Detailed patient and disease characteristics are listed in Table 1. Median follow-up for surviving patients was 50 months (range 18–133). Median age was 61 years (range 36–86). Forty-three percent of patients reported a smoking history of at least 10 pack-years. Fifty-one percent of patients received a systemic agent other than HDC. Patients who received HDC were younger than those who received a non-HDC agent: median age 60 vs. 65, respectively (p = 0.001); the two groups were otherwise similar with respect to baseline characteristics.

Results of multivariable analysis of the prognostic impact of patient and disease characteristics are listed in Table 2**.** For all-comers, the 3-year LRR was 15%. No factors demonstrated significant prognostic impact for LRR, although there was a trend toward lower LRR rates in patients who received HDC vs. those who did not: 9% vs. 20% (HR = 3.10 (0.82–11.67), p = 0.09) (Fig. 1**).** The 3-year DM rate for all-comers was 19%. Employment of HDC was associated with lower rates of DM compared to that observed when alternative concurrent regimens were used: 10% vs. 28% (HR = 3.49 (1.03–11.82), p = 0.04), for HDC and non-HDC, respectively **(**Fig. 2**).** No other factor analyzed demonstrated prognostic significance. The 3-year OS rate for all-comers was 79%. Receipt of a concurrent agent other than HDC was the only factor associated with inferior OS: 89% vs. 67% (HR = 2.56 (1.04–6.32), p = 0.04) for HDC vs. non-HDC, respectively (Fig. 3**).** The 3-year CSS rate for all-comers was 86%. Receipt of a non-HDC regimen was associated with inferior CSS: 77% vs. 96% (HR = 5.07 (1.33–19.36), p = 0.02) **(**Figure 4**).** The remaining factors analyzed did not demonstrate prognostic impact in this cohort.

Subgroup analysis was performed by comparing only the two most common regimens employed, HDC and triweekly carboplatin. No difference was observed in LRR between HDC and triweekly carboplatin (HR = 2.25 (0.68–7.41). p = 0.18). Patients who received triweekly carboplatin had inferior distant control compared to HDC (HR = 3.36 (1.48–7.59), p = 0.02). There was a trend toward inferior OS in patients who received triweekly carboplatin (HR = 2.18 (0.89–5.31), p = 0.08). CSS was inferior in patients who received triweekly carboplatin (HR = 4.16 (1.32–13.11), p = 0.02).

Discussion

When accounting for potential confounding factors, we found that patients with HPV-associated OPSCC with T4 disease who received HDC achieved superior distant disease control compared to patients who received an alternative systemic agent. Receipt of an agent other than HDC also resulted in a difference in LRR rates which did not reach statistical significance on multivariable analysis, perhaps due to the small sample size. However, OS and CSS were superior among patients who received HDC, which may have resulted from the combined improvement in locoregional and distant control in this cohort.

OPSCC mediated by HPV is now known to be associated with a more

Table 1
Baseline Characteristics of Study Cohort.

	All-comers N = 93	HDC recipients N = 46	Alternative agent recipients N = 47	p-value[a]
Medan age, years (range)	61 (36–86)	60 (36–76)	65 (46–86)	0.001
N stage				0.69
N0	10 (11%)	6	4	
N1	42 (45%)	20	22	
N2	40 (43%)	20	20	
N3	1 (1%)	0	1	
Smoking history ≥ 10 pack-years	40 (43%)	22	18	0.41
Matted lymphadenopathy	24 (26%)	9	15	0.24
Overt radiographic ECE	17 (18%)	10	7	0.43
Retropharyngeal lymphadenopathy	24 (26%)	10	14	0.48
Low-neck lymphadenopathy	10 (11%)	5	5	0.99

[a] p-value corresponds to comparison of HDC and alternative agent.

Table 2
Multivariate Analysis for Disease Control and Survival Outcomes at Three Years.

Multivariate Analysis	Locoregional Recurrence		Distant Metastasis		Overall Survival		Cancer-specific Survival	
Factor Analyzed	Hazard Ratio	p-value	Hazard Ratio	p-value	Hazard Ratio	p-value	Hazard Ratio	p-value
Age	0.95 [0.89–1.01]	0.08	1.03 [0.97–1.09]	0.33	1.02 [0.97–1.06]	0.52	1.01 [0.95–1.07]	0.79
N stage	1.03 [0.42–2.55]	0.95	1.42 [0.67–3.05]	0.36	1.44 [0.76–2.71]	0.26	1.52 [0.66–3.51]	0.32
Smoking history ≥ 10 pack-years	0.47 [0.13–1.72]	0.26	1.68 [0.58–4.85]	0.34	1.22 [0.53–2.80]	0.65	0.90 [0.30–2.73]	0.85
Matted lymphadenopathy	3.06 [0.73–12.89]	0.13	1.02 [0.27–3.92]	0.98	1.23 [0.42–3.59]	0.70	0.69 [0.15–3.19]	0.64
Overt radiographic ECE	0.20 [0.02–2.13]	0.18	2.11 [0.37–11.88]	0.40	1.23 [0.32–4.70]	0.76	1.61 [0.23–11.13]	0.63
Retropharyngeal lymphadenopathy	0.87 [0.23–3.26]	0.84	1.22 [0.39–3.87]	0.73	0.69 [0.24–1.99]	0.49	0.69 [0.18–2.70]	0.60
Low-neck lymphadenopathy	0.33 [0.06–1.92]	0.22	1.05 [0.22–5.10]	0.95	1.31 [0.38–4.57]	0.67	0.75 [0.11–4.86]	0.76
Receipt of agent other than HDC	3.10 [0.82–11.67]	0.09	3.49 [1.03–11.82]	0.04	2.56 [1.04–6.32]	0.04	5.07 [1.33–19.36]	**0.02**

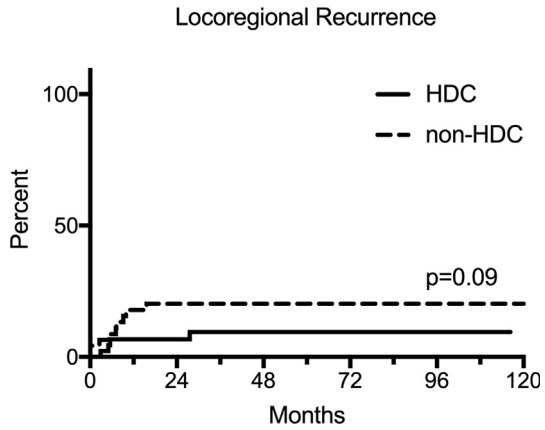

Fig. 1. Locoregional Recurrence for Patients who Received High-dose Cisplatin vs. an Alternative Concurrent Agent.

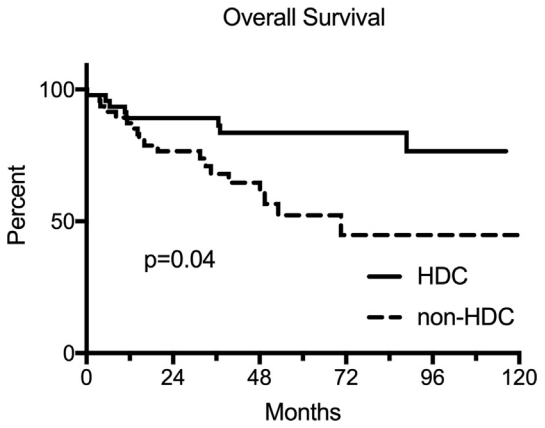

Fig. 3. Overall Survival for Patients who Received High-dose Cisplatin vs. an Alternative Concurrent Agent.

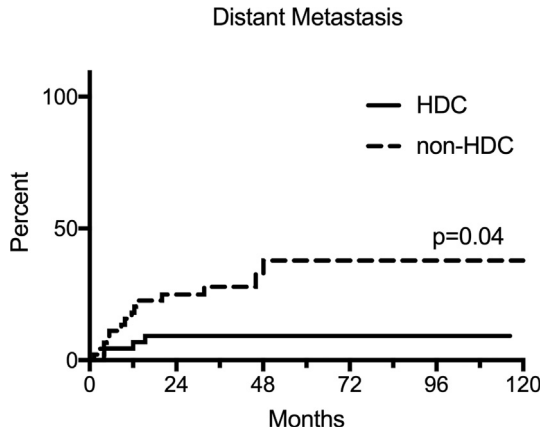

Fig. 2. Distant Metastasis for Patients who Received High-dose Cisplatin vs. an Alternative Concurrent Agent.

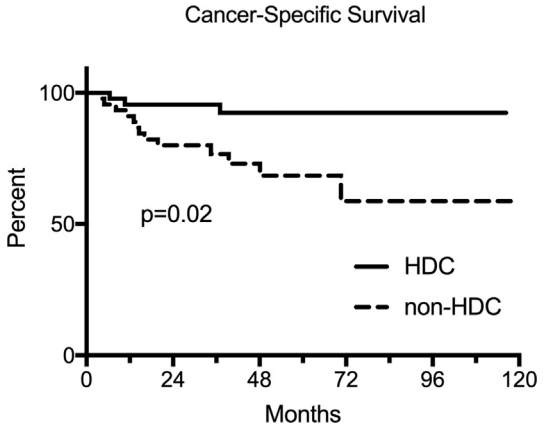

Fig. 4. Cancer-specific Survival for Patients who Received High-dose Cisplatin vs. an Alternative Concurrent Agent.

favorable prognosis than HPV-negative OPSCC, in large part due to the landmark study published by Ang et al. which demonstrated a 3-year overall survival difference of 25% [1]. Patients with HPV-associated OPSCC are often cured after definitive therapy and may live for several decades thereafter with the chronic toxicities of CCRT to the head and neck, which can greatly impact quality of life. Given this dramatic increase in treatment efficacy and survival, the focus of many investigations thus has shifted from improving cure rates to minimizing toxicity through “de-escalated” therapy. One possible method of deintensification is modifying the concurrent systemic agent chosen for definitive CCRT. Per the National Comprehensive Cancer Network (NCCN) guidelines, the preferred regimen for concurrent therapy is high-dose triweekly cisplatin [6]. Unfortunately, this is a systemic agent associated with substantial acute and late toxicities, and patients often have medical comorbidities which preclude its administration.

Clinical investigation is ongoing to determine if alternative systemic therapies with less morbidity can be employed in HPV-associated OPSCC without compromising disease control. Cetuximab, an epidermal growth factor receptor inhibitor, is one such agent which has garnered interest as an alternative concurrent therapy after demonstrating a locoregional control and survival benefit over radiotherapy alone among patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) [7,8]. Subgroup analysis demonstrated the benefit was sustained specifically for HPV-associated OPSCC [9]. Although cetuximab with radiotherapy is superior to radiotherapy alone, recent data published from RTOG 1016 and the De-ESCALaTE HPV Trial Group demonstrate inferior disease control and survival with cetuximab when compared to HDC [10,11]. On subgroup analysis, the

inferiority of cetuximab was most pronounced for advanced T stage disease. The De-ESCALaTE study, while intended for "good-risk" HPV-associated disease, did not exclude advanced T stages, perhaps due to the fact that T stage was not incorporated into the risk stratification in the original Ang study [1]. The negative prognostic impact of T4 disease has since been established in the literature. A study by O'Sullivan and colleagues found a 3-year distant control rate of 93% in patients with T1-3 disease in contrast to a 78% control rate in patients with T4 disease [3]. Despite this fact, patients with T4 disease were enrolled in multiple de-intensification trials. Future de-intensification protocols should exclude patients with such a high-risk of distant failure as their disease control is vulnerable to further compromise with de-escalated therapies.

Another method of treatment deintensification is to employ cisplatin in a low-dose weekly regimen. A systematic review of prospective studies including over 4000 LASCCHN patients comparing HDC to weekly cisplatin (dose $\leq 50\ mg/m^2$) in both the post-operative and definitive settings was unable to identify a difference in treatment efficacy between the two regimens and observed increased compliance with decreased toxicity using weekly cisplatin as part of definitive treatment [12]. Weekly cisplatin is used with the intent of providing a radio-sensitizing effect; however, there is a theoretical concern that the dose may be too low to provide a distant control benefit, which is of particular importance in HPV-associated OPSCC. Nevertheless, weekly cisplatin at a modest dose of $30\ mg/m^2$ has demonstrated a distant control benefit in nasopharyngeal carcinoma, a highly chemo-sensitive tumor similar to HPV-associated OPSCC [13]. Several studies have suggested that a cumulative cisplatin dose of $200\ mg/m^2$ is optimal for improved outcomes in head and neck cancer [14–16]. In particular, a systematic review conducted by Strojan and colleagues suggested that this cumulative dose of cisplatin is thought to be beneficial regardless of weekly or triweekly delivery. However, while a cumulative dose of $200\ mg/m^2$ is achievable on a weekly schedule, it is not known if this regimen is inferior to a similar cumulative dose delivered on a triweekly schedule.

Noronha and colleagues conducted a phase III randomized study comparing HDC to weekly cisplatin in patients with LASCCHN treated with CCRT with definitive intent [17]. The study failed to demonstrate its primary endpoint of non-inferior locoregional control in the weekly cisplatin arm, but it should be noted that the dose of weekly cisplatin used in the trial was only $30\ mg/m^2$, which is lower than what is more commonly used in the United States and employed at our institution. A randomized comparison of HDC and weekly cisplatin at $40\ mg/m^2$ may have a different result. Furthermore, the population in the Noronha study included all head and neck subsites, although predominantly comprised of oral cavity cancers treated in the adjuvant setting. Consequently, these results may not be applicable to the management of HPV-associated OPSCC which has a different tumor biology and may be more chemotherapy sensitive than HPV-unrelated disease.

The Hellenic Cooperative Oncology Group previously conducted a phase III randomized trial of radiotherapy concurrent with HDC or triweekly carboplatin (AUC = 7) vs. radiotherapy alone among patients with LASCCHN and found that outcomes were superior with combined modality treatment: 3-year survival rates were 52%, 42%, and 18%, respectively. Unfortunately, the study was not powered to assess the difference between cisplatin and carboplatin [18]. At our institution, some physicians have employed a more moderate triweekly carboplatin dose (AUC = 5) in hopes of improving tolerance and compliance with therapy, particularly for HDC-ineligible patients. This regimen was chosen based on a dose-escalation study conducted by the Queen Elizabeth Hospital which found acceptable mucositis rates using an AUC of 4.5 [19]. We recently reported the results of our retrospective study comparing this regimen to HDC; patients with stage I-II HPV-associated OPSCC performed well regardless of concurrent agent, but patients with stage III disease who received triweekly carboplatin experienced inferior outcomes [20].

One limitation of this study is its retrospective nature, which may have allowed for underlying biases and imbalances between the comparison groups. For instance, although the majority of patients who received an alternative agent did so due to physician preference, patients who received HDC were younger than those who did not. This difference may have impacted survival outcomes. Multivariable analysis was performed to account for potential confounding factors such as age, though with a relatively small sample size, there may have been other hidden imbalances. To mitigate additional potential biases, we specifically analyzed cancer-specific deaths and found that the superiority of HDC was maintained for CSS. A second limitation of this study is that the non-HDC comparison group included multiple different regimens rather than a single regimen. It is possible that one or more of these alternative agents could perform comparably to HDC; however, small sample sizes precluded individual comparisons. Of note, while cetuximab is now known to be inferior to cisplatin, only a small portion of our cohort received this agent. Therefore, the differences noted in our study are unlikely to be driven by cetuximab alone.

In summary, this retrospective study of patients with HPV-associated OPSCC bearing clinical T4 disease demonstrated that receipt of a non-HDC concurrent systemic agent resulted in significantly higher rates of DM and inferior OS and CSS, with a trend toward higher rates of LRR. In the era of HPV-related disease, high cure rates are achievable, and patients are living long enough to experience the lasting morbidity of CCRT. However, systemic agent deintensification should be approached with caution in HPV-associated OPSCC and avoided if possible in patients with clinical T4 disease who are already known to be at high risk of treatment failure.

Declaration of Competing Interest

None declared.

Acknowledgements

The authors thank Hannah Herrera for her assistance with data collection.

Role of Funding Source

This research is supported in part by a grant from the Regional Research Committee of Kaiser Permanente Southern California (KP-RRC-20161103). The committee was not involved in the preparation of this manuscript.

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