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Treatment outcomes in oropharynx cancer patients who did not complete planned curative radiotherapy

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ABSTRACT

Purpose: To evaluate outcomes in oropharyngeal cancer (OPC) patients who did not complete their planned curative radiation therapy (RT).

Methods: OPC Patients who received less than planned curative RT dose between 2002 and 2016 were identified for analysis. HPV status was assessed. Radiation dose was normalized for fractionation variations using biological effective doses assuming tumor $\alpha/\beta = 10$ Gy [BED10]. Outcomes were compared using BED10. Multivariable and univariable analysis identified OS predictors.

Results: From a total of 80 patients who did not complete therapy, 64 patients were eligible for analysis. RT incompletion was due to: RT side effects (n = 23), patients' decision (n = 21), disease progression or metastases (n = 3), and other causes (n = 7). Median BED10 (Gy) was 56.2 for the HPV-positive and 58 for the HPV-negative. Three-year OS was 74% vs 13% ($p < 0.001$) for the HPV-positive (n = 29) and HPV-negative (n = 24), respectively. HPV-positive patients who received BED10 ≥ 55 had higher OS than those received BED10 < 55 (94% vs 47%, $p = 0.002$) while no difference in OS by BED10 ≥ 55 vs < 55 for the HPV-negative (12 vs 13%, p = NS). HPV-positive status was associated with a higher OS (HR 12.5, 95% CI, 4.54 to 33.3, $p < 0.001$). A total of 37 patients were available to estimate TD_{50} for local control assessment. TD_{50} (BED10) was estimated at 60.5 Gy for HPV-negative patients compared to 27.2 Gy for HPV-positive patients.

Conclusion: Overall, in patients with incomplete treatment, HPV-positive OPC patients demonstrated a better OS compared to HPV-negative patients. HPV-positive patients who received BED10 ≥ 55 have higher rates of OS.

Introduction

As established by both NRG Oncology and GORTEC cooperative groups, the standard of care for stage III or IV OPC is a combination of 70 Gy of radiation therapy (RT) with concurrent platinum-based chemotherapy [1,2]. With the current standard treatment, HPV-positive OPC patients have substantially higher disease-free survival (DFS) and overall survival (OS) rates compared to the HPV-negative population [1].

However, a portion of patients do not complete treatment. These patients have been considered to have poor outcomes as both radiation dose and duration of treatment are correlated with tumor control and survival [3]. However, the relative impact of locoregional therapy on outcomes in patients with less than curative doses has not been reported. These outcomes are being investigated in the context of dose de-escalation studies such as NRG-HN002 (NCT02254278). Of note, OPC patients have been reported to have prolonged survival even after metastatic disease development [4].

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In the absence of clinical trials addressing the minimum required radiotherapy dose for HPV-positive OPC patients while maintaining the current excellent survival, there is an opportunity to explore information from patients unable to complete the planned radiation therapy dose. Such data may inform the minimum safe alternative dose for frail patients with limited management options or may assist in design of future clinical trials of dose de-escalation. In this study, we report survival outcomes and TD_{50} for locoregional control of OPC patients who did not complete their planned radiotherapy.

Methods

Study population

After institutional research ethics board approval, all patients with previously diagnosed, pathologically confirmed primary OPC SCC, treated with curative intent in our institution between 2000 and 2016 with radiation therapy with or without chemotherapy were identified. Patients who received less than full planned RT dose were identified for further analysis from our prospective outcomes database. Patients who died prior to RT completion were excluded from this analysis. Clinical information including outcomes was retrieved from the Head and Neck Anthology of Outcome system (HN-Anth), in which clinical and outcome data were prospectively collected at point-of-care since 2003, using the Formatted Anthology Synoptic Tick (FAST) sheet process [5]. Charts were retrospectively retrieved to confirm specific fields if required. Clinical information for patients treated before 2003 was compiled in the HN-Anth from the patient records retrospectively, whereas for those treated after 2003 the clinico-pathological and treatment parameters are prospectively recorded using the FAST process.

HPV status

HPV status was assessed by p16INK4A (p16) immunohistochemistry staining as a surrogate marker on all available tissue blocks. Strongly or diffusely positive p16 staining was classified as HPV-positive, while focal or absence of p16 staining was classified as HPV-negative [6]. A portion of patients only had fine needle aspiration (FNA) biopsies which were not satisfactory for HPV status assessment and classified as HPV-unknown.

Diagnostic approach

Staging evaluation consisted of history and physical examination, head and neck CT and/or MRI, and chest x-ray and/or CT chest. All tumors were histologically confirmed and were staged by the American Joint Committee on Cancer/International Union against Cancer sixth edition TNM criteria [7,8].

Treatment approach

Treatment decisions were based upon consensus institutional head and neck practice guidelines and customized where needed according to the extension of the tumor, patient co-morbidity, and performance status. All patients underwent (CT)-treatment planning for either conventional 3D-conformal sequential shrinking-field RT (3D-CRT) (before 2005) or single-phase-simultaneous- integrated-boost IMRT (from 2005 onwards). All RT plans were peer-reviewed for quality assurance according to departmental standards [9].

In our institution, stage III-IV patients receive either CRT or RT-alone using altered fractionation regimens. CRT generally comprised 70 Gy in 35 fractions, over 7 weeks (5 fractions/week), concurrently with cisplatin (100 mg/m^2, weeks 1, 4, 7 of radiotherapy). Patients not suitable for high dose cisplatin received instead weekly concurrent cisplatin 40 mg/m^2. Use of cetuximab drug, epidermal growth factor receptor inhibitory (EGFRI), was limited to four patients were not eligible for cisplatin. RT-alone is reserved for those ineligible for chemotherapy due to medical contraindications, elderly (> 70 year-old) patients, or due to patient's refusal of chemotherapy. RT-alone regimens generally consisted of accelerated fractionation schedules (Table 1).

Table 1
Details of treatment among the HPV-known status patients.

Treatment Characteristics	Patients with HPV-Known status			
	HPV-Positive (n = 29)		HPV-Negative (n = 24)	
	No.	%	No.	%
Planned RT-alone regimens				
70 Gy/35 fractions/7 weeks	20	69	10	42
70 Gy/35 fractions/6 weeks	7	24	8	33
64 Gy/40 fractions/4 weeks	0	0	2	8
60 Gy/25 fractions/5 weeks	1	3.5	4	17
51 Gy/20 fractions/4 weeks	1	3.5	0	0
RT Technique				
IMRT	26	90	20	84
VMAT	1	3	1	4
3DCRT	2	7	3	12
Radiation Dose				
Median Dose	62		55.6	
Range	16–68		4–68	
Median BED10	56.2		58.1	
Range	19.2–66.4		4.8–69.3	
BED10 ≥55	16	55	14	58
BED10 < 55	13	45	10	42
Concurrent CRT	17	59	9	38
Cisplatin	15	88	7	78
Dose				
Median	380		282	
Range	80–550		130–405	
Cetuximab	2	12	2	22
Cause of Stopping treatment				
Side Effects of RT	9	31	10	42
Patient's Decision/Non-compliance	17	59	8	33
Disease Progression/metastases	0	0	2	8
Other emergencies	3	10	4	17
Deaths	8	27	20	83
Cause of Death				
Index Cancer	5	62	12	60
Other Cause	3	38	8	40

Abbreviations: HPV = human papillomavirus; HPV-positive = human papillomavirus related; HPV-negative: human papillomavirus unrelated; RT = radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric arc therapy; 3DCRT = three dimensional conformal radiotherapy; BED = biologically effective dose; CRT = chemoradiotherapy.

This variability in radiation fractionation makes any meaningful comparison of treatment results difficult. Radiation therapy dose was normalized for fractionation variations using biological effective dose and corrected for overall treatment time.

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{Ln2(T - Tk)}{\alpha Tp}$$

where: n is the number of dose fractions of d Gy; α/β = 10 Gy is the ratio of intrinsic radiosensitivity to repair capacity of the basal mucosal cells; T is the overall treatment time; Tk = 7 days is the time to compensatory repopulation of oral and pharyngeal mucosal cells after start of radiotherapy; Tp = 2.5 days is the time to double the cell population during radiotherapy; and $\alpha = 0.35\ Gy^{-1}$ [10].

Evaluation and follow-up

Patients were assessed in the clinic 4–6 weeks after the end of RT or more frequently when clinically required. Imaging studies included CT or MRI of the head and neck were undertaken around 8–12 weeks following RT to assess treatment response. Post-treatment evaluation and clinical assessment was performed at 3 months intervals in the first 2 years, every 4 months in the 3rd year, every 6 months up to 5 years, and annually thereafter. Patients who did not complete initial therapy had the same follow-up schedule. Local and regional recurrence were diagnosed based on clinical, radiological and/or histological confirmation. Patients' follow-up was supplemented from provincial death records.

Statistical methods

Overall survival was calculated with the Kaplan-Meier method. OS was defined from date of RT end to date of death or last follow-up if still alive. In the event that cause of death was unknown, death was classified as death from index cancer. Deaths from other causes were treated as a competing risk. Multivariable and univariable analyses were performed to identify outcome predictors for OS using Cox proportional hazards model.

Three year OS outcome was compared between HPV-positive vs. HPV-negative vs. HPV-Unknown. Furthermore, 3-y OS for patients who received BED10 ≥ 55 was compared to those who received < 55 in each groups of HPV-positive and HPV-negative separately. The variables included in the models were: HPV status (positive, negative and unknown), age (continuous variable), gender, smoking pack-years classified (> 10 vs. < 10), drinking alcohol (yes or no), T-category (T1-2 vs. T3-4), N-category (N1-2b vs. N2c-3) as per O'Sullivan et al. [11], ECOG performance status (ECOG 0-1 vs. ECOG 2-3), BED10 (< 55 vs. ≥ 55) and treatment modality (RT-alone vs. CRT). A p-value of 0.05 or less was considered statistically significant.

Estimation of TD_{50} for local-regional control

Patients with HPV-unknown status or less than three months follow-up from the end of treatment were excluded from this analysis. Fitting to a probit function was performed separately for each set of data of HPV-positive and HPV-negative using Matlab R2013b (Mathworks Inc, Natick, MA, USA).

Results

Patient characteristics

From the total of 1873 patients treated with curative intent for OPC, 80 patients did not complete curative therapy. Excluding 16 patients who passed away prior to RT completion, a total of 64 patients were eligible for analysis. HPV status was identified for 53 (82%) of 64 patients: 29 (45%) HPV-positive and 24 (37%) HPV-negative. HPV status remained unknown for 11 patients (17%); 10 patients had FNA biopsies and one tissue block could not be located to determine the HPV status retrospectively for the study purposes. The details of patients and tumor characteristics were compared between the HPV-positive vs. HPV-negative vs. HPV-unknown cohorts (Table 2). HPV-positive patients were younger and had less tobacco and alcohol exposure. HPV-positive tumors were almost exclusively of tonsil or tongue base origin, and had lower T- and higher N-category, compared to the HPV-negative.

RT was not completed for multiple reasons including: RT side effects (n = 23, 35%), patients' decision due to non-compliance or refusing more treatment (n = 21, 33%), disease progression and/or distant metastases (n = 3, 5%), and intercurrent illness requiring urgent medical intervention such as myocardial infarction, stroke, or other emergencies (n = 7, 11%).

Table 2
Demographic and Clinical Characteristics of HPV-positive, HPV-negative and HPV-unknown patients.

Demographic or clinical characteristics	All Patients						
	HPV-Positive (n = 29)		HPV-Negative (n = 24)		HPV-Unknown (n = 11)		
	No.	%	No.	%	No.	%	*p*
Male	24	83	17	71	10	91	0.39
Age, years							0.016
Median	61		67		65		
Range	44–81		42–87		51–70		
Smoking							0.0018
Current	11	38	19	79	3	27	
Former	7	24	4	17	6	55	
Never	11	38	1	4	2	18	
Pack-years							0.0041
< 10	6	33	0	0	1	11	
> 10	12	67	23	100	8	89	
Missing	11		1		2		
Alcohol (yes)	14	50	15	68	4	36	0.19
ECOG status							0.51
ECOG 0-1	28	97	19	90	10	91	
ECOG 2-3	1	3	2	10	1	9	
Missing	0		3		0		
T Category							0.0019
T1	8	28	0	0	0	0	
T2	6	21	2	8	1	9	
T3	5	17	14	58	5	45	
T4a	4	14	5	21	5	45	
T4b	6	21	3	12	0	0	
T							0.0017
T1-2	14	48	2	8	1	9	
T3-4	15	52	22	92	10	91	
N Category							0.4
N0	1	3	4	17	1	9	
N1	3	10	4	17	0	0	
N2a	2	7	0	0	2	18	
N2b	8	28	7	29	2	18	
N2c	11	38	8	33	4	36	
N3	4	14	1	4	2	18	
N							0.56
N0-N2b	14	48	15	62	5	45	
N2c-N3	15	52	9	38	6	55	
UICC/AJCC stage 6th edition grouping							
III	3	10	6	25			
IV	26	90	18	75			
Disease Subsite							
Base of Tongue	10	34	7	29	5	45	
Lateral Wall	0	0	2	8	0	0	
Posterior Wall	0	0	3	12	0	0	
Soft Palate	0	0	3	12	0	0	
Superior Wall	0	0	0	0	1	9	
Tonsil	11	38	1	4	4	36	
Tonsillar Pillar	0	0	1	4	0	0	
Tonsillar Fossa	8	28	7	29	1	9	0.0052

Abbreviations: HPV = human papillomavirus; HPV-positive = human papillomavirus related; HPV-negative: human papillomavirus unrelated; HPV-Unknown: human papillomavirus unknown status; UICC = international union against cancer; AJCC = American joint committee on cancer.

Treatment characteristics

Concurrent CRT was initiated in 34 of 64 (53%) patients, while 30 (47%) patients received radiation alone. Details of systemic therapy and radiation therapy dose and modality are summarized in Table 1. Median BED10 was 52.6 (range: 19–66) for the HPV-positive cohort and 58 (5-69) and 53.3 (6-68.4) for the HPV-negative and HPV-

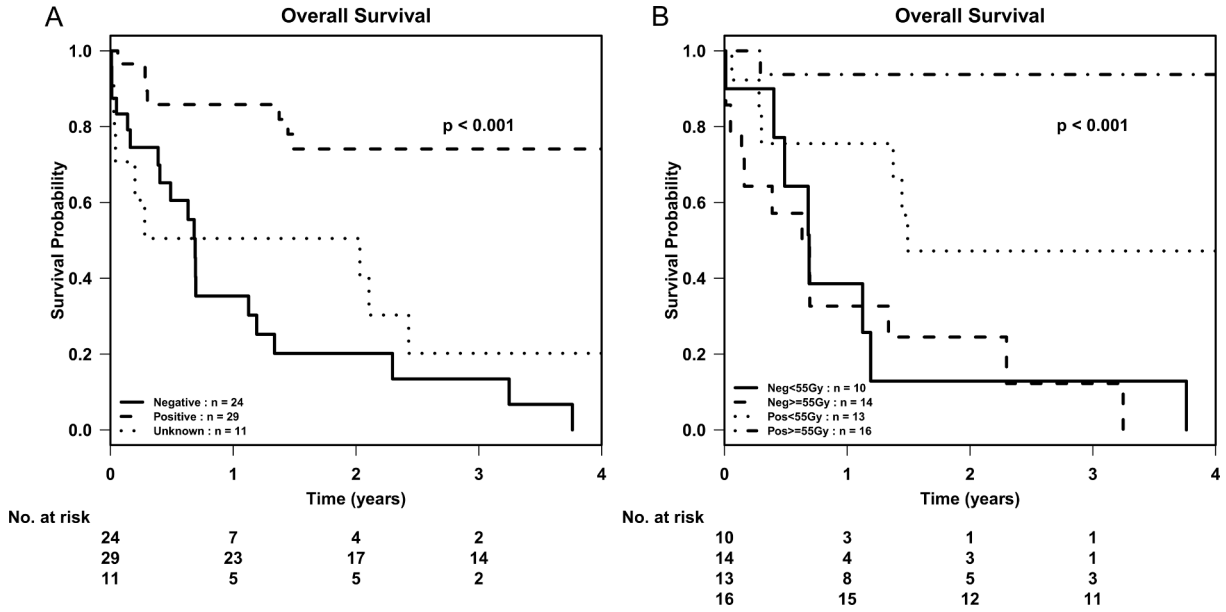

Fig. 1. Overall survival of 64 patients who didn't completed the full planned radiotherapy dose. (A) HPV-positive (n = 29) vs. HPV-negative (n = 24) vs. HPV-unknown (n = 11). (B) HPV-positive received BED10 (≥55 vs < 55) (n = 16 and 13 respectively) vs. HPV-negative received BED10 (≥55 vs < 55) (n = 14 and 10 respectively).

unknown cohorts, respectively. Using a median value of BED10 ≥55, patients exceeding this value differed by HPV status: 14 (58%) of HPV-positive patients, 16 (55%) of HPV-negative, and 4 (36%) of HPV-unknown.

Clinical outcomes

Median follow-up was 1.3 years. Median follow-up for surviving patients was 3 years. The 3y-OS was 74% vs 13% vs 20% (p < 0.001) for the HPV-positive, HPV-negative, and HPV-unknown cohorts, respectively (Fig. 1.A). HPV-positive patients who received BED10 ≥55 (n = 16) had higher 3-year OS compared to those received BED10 < 55 (n = 13) (94% vs 47%, p = 0.002) while no difference in OS by BED10 ≥55 vs < 55 for the HPV-negative (12 vs 13%, p = NS) (Fig. 1.B). While the HPV-positive OS rate remained stable beyond 3 years following treatment even for cohort received BED10 < 55, the HPV-negative OS curve continued to decline (Fig. 1.B). Plot for received radiotherapy dose and follow-up time by HPV and vital status (Fig. 2).

The estimated 3 year local control (LC), regional control (RC) and distant control (DC) was 78%, 86% and 84% respectively in the HPV-known population. LC was 96% (n = 1) and 56% (n = 10) in HPV-positive and HPV-negative respectively. RC was 92% (n = 3) and 76% (n = 5) in HPV-positive and HPV-negative respectively. DC was 89% (n = 3) and 77% (n = 6) in HPV-positive and HPV-negative respectively. The median time to local-regional failure was 14 months (range, 12–32) and 10.5 months (range, 0–23 months) in HPV-negative and HPV-positive patients respectively. Treatment of recurrence via salvage neck dissection was performed for one HPV-negative patient and 2 HPV-positive patients.

Univariable and multivariable analysis for OS

Univariable analysis for the overall study group revealed that the adverse predictors for OS were HPV-negative status [hazard ratio (HR): 6.66 (95% CI: 2.9–16.66), p < 0.001], smoking history of > 10 pack-years [1.01 (1–1.02), p = 0.01], older age [1.05 (1.01–1.09), p = 0.025], T3-4 [3.58 (1.38–9.25), p = 0.008], and RT-alone [1.98 (1.01–3.85), p = 0.046]. HPV status remained significant within known HPV group [0.13 (95% CI: 0.05–0.32, p < 0.001]. Multivariable analysis for the known HPV cohort showed that HPV-positive status remained significant and was associated with a higher OS [12.5, (4.54–33.3), p < 0.001] while the nodal status (N2c-N3) was associated with a lower OS [HR 3.48 (1.55–7.8), p = 0.002].

TD_{50} for local-regional control

There were 12 HPV-negative and 25 HPV-positive patients available for fitting to dose-response curves to estimate TD_{50} for local-regional control. For HPV-positive patients, the TD_{50} (in BED10) was estimated at 27.2 Gy compared to 60.5 Gy for HPV-negative patients (Fig. 3). The TD_{50} corresponds to a EQD2 dose of 23.5 Gy for HPV-positive and 62.3 Gy for HPV-negative.

Discussion

This study, a natural trial of dose variation with prospective follow-up, provides new information on the natural history of patients with incomplete radiotherapy stratified by HPV status. In this cohort, HPV-positive OPC had a better 3y OS compared to HPV-negative patients, 74% and 13% respectively. HPV-positive OPC represents a distinct entity with different treatment response [12]. Similar to other retrospective [1,11,13–14] and prospective [15] studies, superior survival is confirmed in HPV-positive compared to HPV-negative patients following either RT-alone or CRT approaches. Furthermore, in this analysis, HPV-positive patients who received a higher dose of radiation (BED10 ≥55) have higher rates of OS than those who received less treatment (BED10 < 55). However, about half of those who received low doses (BED10 < 55) survived for more than 3 years. Additionally, no impact of dose was identified in HPV-negative population in relation to BED10s, suggesting relative radioresistance.

To our knowledge, there are limited studies of the incidence of incomplete radiotherapy in a large population-based sample in Europe or North America. Clinical outcomes after premature discontinuation of curative and adjuvant head and neck irradiation have been recently reported from (Lazarev, et al., 2018) with two- year and four-year overall survival was 61% and 52% respectively [16]. However, only 38% (n = 22) had OPC and the effect of the HPV status was not reported. In that study, a total dose of 50 Gy in 25 fractions was thought

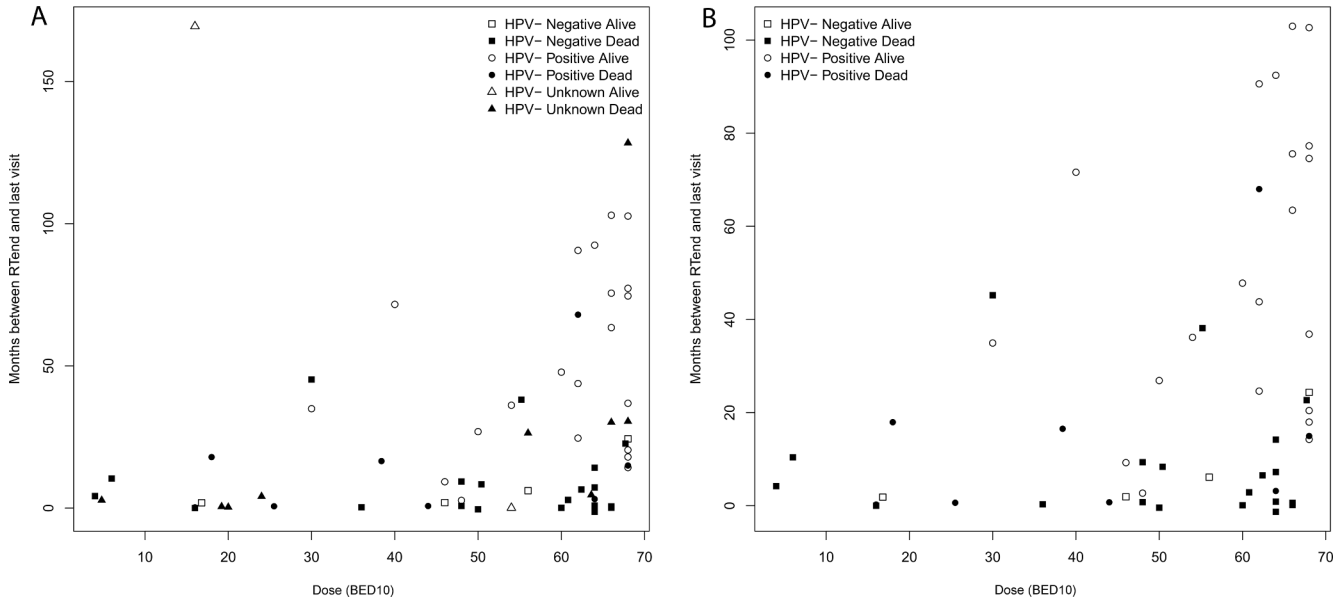

Fig. 2. Plot for received radiotherapy dose and follow-up time by HPV and vital status. (A) HPV-positive (n = 29) vs. HPV-negative (n = 24) vs. HPV-unknown (n = 11). (B) HPV-positive (n = 29) vs. HPV-negative (n = 24).

to have been associated with a relative therapeutic benefit, it was not clear how consistent the fractionation was in this group. By comparison, in our analysis, we attempted to account for both differing total dose and time effects using BED10 dose.

The exploration of dose response in OPC has become a critical area for clinical trials development. A number of published and ongoing clinical trials are exploring de-intensification in HPV-positive patient groups, both in radical and adjuvant settings. BED10 (Gy) for the suggested reduced RT dose used in those studies is calculated and compared to our findings and to the standard RT dose established by GORTEC in Table 3.

NRG-HN002 (NCT02254278) trial has randomized T1-T2, N1-N2b or T3, N0-N2b, HPV-positive OPC patients to 60 Gy in 30 fractions (2 Gy per fraction) with weekly cisplatin, 40 mg/m^2 for 6 weeks vs. 60 Gy in 30 fractions (2 Gy per fraction) in 5 weeks using 6 fractions per week. ECOG 3311 (NCT01898494) trial randomized intermediate risk cT1-2N1-2b stage III-IV OPC patients, HPV-positive, close margin, after *trans*-oral resection with neck dissection to radiotherapy of 50 Gy in 25 fractions (2 Gy per fraction) in 5 weeks vs. 60 Gy in 30 fractions (2 Gy per fraction) in 6 weeks. Both trials closed to accrual and waiting for the results with the primary objective is to evaluate the 2-year progression free survival (PFS) in HPV-positive OPC patients treated with low-dose RT.

The fact that our analysis detected that half of HPV-positive patients still have 3y OS even with BED10 < 55, further supports the idea of dose de-escalation in this population. Patients with T1–T3, N0–N2b, smoking less than 10 packs per year, are suitable for treatment de-intensification as found by O'Sullivan et al. [11]. As per Chera et al. [15], the pathologic complete response rate is 86% even with less intense radiotherapy with 60 Gy of IMRT and weekly low-dose cisplatin in those with favorable-risk HPV-positive OPC, with evidence of decreased morbidity compared with standard therapies. Similarly, ECOG 1308 (NCT01084083) has published the results of phase II trial of induction chemotherapy (paclitaxel, carboplatin, cetuximab) followed by reduced-dose radiation and weekly cetuximab in favorable-risk patients with HPV-positive OPC population [17]. For patients with primary-site complete clinical response treated with 54 Gy in 28 fractions, 2-year PFS and 2- year OS rates were 85% and 94% respectively [17]. Radiation dose reduction resulted in significantly improved swallowing and nutritional status.

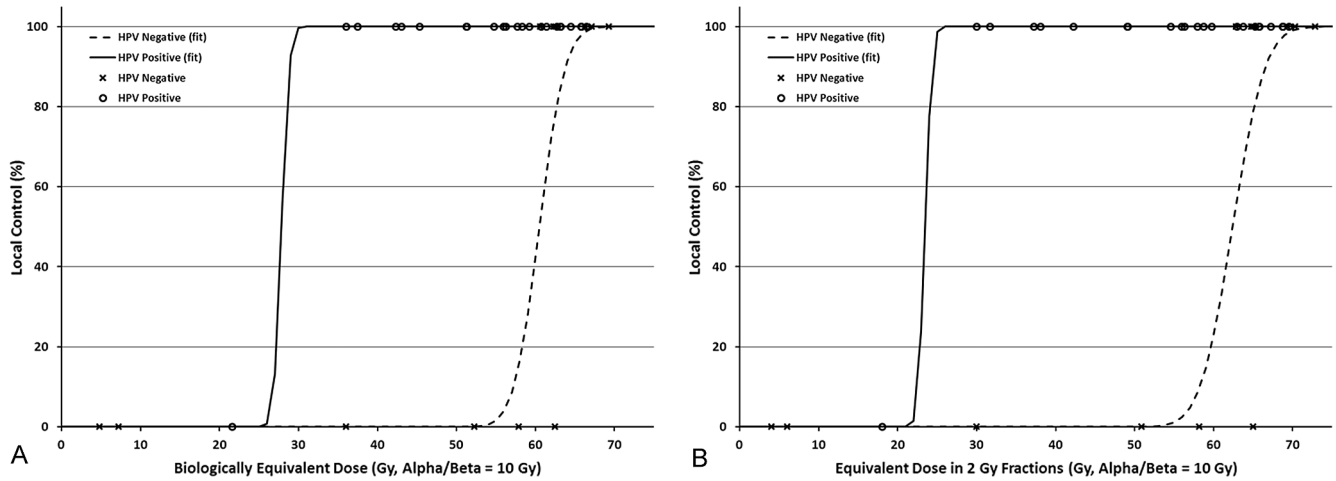

Fig. 3. Fit dose response curve for local-regional control for HPV-positive (n = 25) vs. HPV-negative (n = 12). (A) TD_{50} (BED10) is 27.2 Gy for HPV-positive and 60.5 Gy for HPV-negative. (B) TD_{50} (EQD2) is 23.5 Gy for HPV-positive and 62.3 Gy for HPV-negative for EQD2.

Table 3
Comparison of BED10s used in de-intensification clinical studies, treating patients with favorable HPV-positive OPC, to the established RT dose by GORTEC group.

Clinical study	Type of study	Role of radiotherapy (RT)	Prescribed RT dose/fractions	Prescribed BED10 (Gy)	Chemo-therapy (CT)	Outcomes
GORTEC 99-02 Arm A [2]	Phase 3 randomized trial	Radical conventional CRT	70 Gy/35 fractions/7 weeks	65.52 Gy	Concurrent carboplatin-fluorouracil	PFS
ECOG 1308 Arm 1 [18]	Phase 2 prospective trial	Radical post induction CT	54 Gy/28 fractions/5.5 weeks	54.24 Gy	Induction CT: paclitaxel, carboplatin, cetuximab followed by Weekly cetuximab	2-yr PFS
ECOG 1308 Arm2 [18]			69.3 Gy/33 fractions/6.5 weeks	68.01 Gy	Induction CT: paclitaxel, carboplatin, cetuximab followed by Weekly cetuximab	
ECOG 3311 Arm B (NCT01898494)	Phase 2 randomized trial	Adjuvant post-surgery	60 Gy/30 fractions/6 weeks	58.14 Gy	No CT	2-yr PFS
ECOG 3311 Arm C (NCT01898494)			50 Gy/25 fractions/5 weeks	50.76 Gy	No CT	
NRG-HN002 Arm 1 (NCT02254278)	Phase 2 randomized trial	Radical	60 Gy/30 fractions/6 weeks	58.14 Gy	Weekly cisplatin	2-yr PFS
NRG-HN002 Arm 2 (NCT02254278)			60 Gy/30 fractions/5 weeks	62.76 Gy	No CT	
Chera et al. [15]	Phase 2 prospective study	Radical	60 Gy/30 fractions/6 weeks	58.14 Gy	Weekly cisplatin	pCR
Our study	Retrospective study	Radical	Multiple schedules as Table 2	55 Gy (delivered)	± Cisplatin or Cetuximab	3-yr OS LRC

Abbreviations: BED = biologically effective dose; OPC = oropharyngeal cancer; RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy; PFS = progression free survival; OS = overall survival; pCR = pathologic complete response; LRC = loco-regional control.
GORTC = Groupe Oncologie Radiotherapie Tete et Cou; ECOG = Eastern Cooperative Oncology Group; NRG is a newly constituted National Clinical Trials Network (NCTN) group created through the coordinated efforts of the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group(GOG).

There are patients with OPC whom OS is negatively affected by either biological or clinical features or both. Some of these features are known to us and others remain unclear. As HPV status is a proven important biological factor that affects the OS in this population, N2c-N3 remains an adverse clinical predictor for OS as shown in our study and previously reported in others [18]. However, nodal status has been de-emphasized in the HPV-positive OPC population [19] and in the 8th edition AJCC staging system.

Peter's et al. [20] reported a decrement in 2-year OS and freedom from loco-regional failure (FFLRF) in a major radiotherapy protocol deviation in treatment of advanced head and neck cancer. Plan non-compliance was categorized as incorrect target definition, defective planning where dose distribution was inadequate to cover the correctly defined gross disease to protocol specifications, excessively prolonged treatment and incorrect dose prescription. From the 861 patients entered into the trial, 26 patients whose treatment was aborted before they had received at least 60 Gy were excluded. Although there were 199 patients with HPV- known status from 465 patients with OPC, all gross disease was still required to receive a minimum of 66.5 Gy to be considered as a complaint plan. As there is a subset of the OPC patients who might need the standard dose of RT, there may be another category of patients who OS will not be compromised with less RT dose, and others who only require a palliative dose to achieve the locoregional control. Our findings that half of the HPV- positive patients who received BED10 < 55 survived for 3 years, may encourage other researchers to explore the relationship of dose and outcome effect. This may allow development of a tool to assist us in selecting the optimal RT dose for each patient.

Our study suggested that radiotherapy alone was identified to be a negative predictor for OS and this is not surprising as patients who receive RT-alone are usually ineligible for combined modality mostly due to medical contraindication or being elderly and frail. However, it is important to realize that the prognostic significance of HPV was found in both patients incompletely treated with CRT or with radiotherapy alone [21]. Overall, HPV-positive RT-alone stage IV demonstrated lower survival but comparable disease control vs. CRT [11].

Consistent with expectations, TD_{50} analysis suggests that HPV-positive patients have a lower dose requirement than that of the HPV-negative patients. In this cohort, the TD_{50} was 27.2 Gy for BED10 or 23.5 Gy for EQD2 for the endpoint of locoregional control. In our centre, we often treat patients with locally advanced head and neck cancer who have good performance status with palliative intent of two courses of 25 Gy in 10 fractions separated by one week to allow for toxicity recovery and disease reassessment. Our data suggests that even half of that regimen (one course of 25 Gy in 10 fractions, BED10 = 31.3 Gy) may be sufficient for locoregional control for low risk HPV-positive patients who may only be able to receive palliative radiation. Despite the good appearance of the fit curves, due to the small numbers of events, this analysis should be considered hypothesis-generating only pending further validation datasets.

Our study is limited by its exploratory nature as discontinuation of radiotherapy was not planned or intended. Delivered dose and fractionation was not uniform in either time or total dose so BED10 was utilized to attempt to normalize variations in dose. However, both the TD_{50} estimates should be used cautiously as the model and fit were based on a small number of patients. In addition, patients without documented local control assessment were excluded from follow-up and this may bias the outcomes toward improved local control if patients lost to follow-up were also those with local failure. Unfortunately, the modest sample size combined with the low event rate for this favorable disease prevented us from performing a multivariable analysis on LC, RC and DC (total number of events was limited to 11 local, 9 regional, and 12 distant failures).

We were able to confirm the viability status from the provincial death records to verify the overall survival. However, as most of this cohort were noncompliance to treatment, they were noncompliance for

follow-up and some patients did not attend post-treatment appointments for local control assessment. A follow-up in patients who discontinue treatment early can be challenging; hence it is possible that rates of loco-regional recurrence or distant metastases were underestimated. In addition, clinical follow-up is essential to identify patients with local failure for timely intervention to avoid progression of disease and a reduced chance for cure. Toxicity and complications of RT should be monitored closely to ensure an early and appropriate interventions if required. For this cohort, clinical evaluation should be performed perpetually and more frequently in the first two years comparing to those who are more compliant and completed their treatment. In this population clinical follow-up started with clinical assessment 2–4 weeks after the end of RT, or earlier when clinically required. Accordingly, clinical visit interval will gradually increase and may meet the standard follow up eventually if appropriate. However, the low compliance rate occurred despite the mechanisms we have in place to help non-compliant patients return for follow-up care.

Conclusions

In patients who did not complete curative dose of radiotherapy, HPV-positive OPC patients showed a higher OS compared to HPV-negative patients. HPV-positive patients who received BED10 ≥ 55 Gy have higher rates of OS, but nearly half of those who received BED10 < 55 Gy still survived for more than 3 years. Estimates of TD_{50} suggest even low dose of radiation may be associated with local control and prolonged survival in some patients with HPV-positive OPC. All of these results should be confirmed in studies with larger sample size to optimize the statistical power.

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Declaration of Competing Interest

All authors indicated no potential conflicts of interest.

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