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Five-year outcomes of sparing level IB in node-positive, human papillomavirus–associated oropharyngeal carcinoma: A safety and efficacy analysis

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ABSTRACT

Introduction: The conformality of modern intensity modulated radiation therapy (IMRT) allows avoidance of the submandibular glands (SMG) in select patients, potentially improving late xerostomia. This study explores the safety and efficacy of this approach in select oropharyngeal carcinoma (OPC) patients.

Methods: Patients with T1-2N+ human papillomavirus (HPV)-associated OPC treated with definitive IMRT at one institution from 2009 to 2014 were identified. Patients were divided into 3 groups: bilateral level IB targeted (A, n = 16), a single level IB targeted (B, n = 61), and bilateral IB spared (C, n = 9). Outcomes were reviewed to identify the rate of level IB regional recurrence. Odds ratios were calculated for xerostomia between groups.

Results: Level Ib was targeted in 93 instances (54.1%) and avoided in 79 instances (45.9%). Mean SMG doses were significantly lower when level IB was spared compared to when targeted (37.5 Gy vs 67.5 Gy; $P < 0.0001$). Median doses to oral cavity decreased with increasing level Ib sparing (40.7 Gy [A] vs 35.4 Gy [B] vs 30.7 [C]; $P = 0.002$). The rate of late grade ≥2 xerostomia was significantly lower in patients with bilateral 1b sparing (53% in A vs 0% in C; $P = 0.007$). Sparing 1b unilaterally resulted in a non-significant decrease in late grade ≥2 xerostomia ($P = 0.181$). No regional failures were identified in levels IB (median follow up = 59.3 months).

Conclusion: Sparing level IB is safe in T1-2N+ HPV+ OPC. Avoiding level Ib translates into significantly lower SMG and oral cavity doses. Larger studies are needed to validate these findings and the impact of this technique.

Introduction

In the intensity modulated radiation therapy (IMRT) era, the incidence of long-term xerostomia has improved due to reduced integral dose to normal structures [1]; however, xerostomia remains a very common acute and long term side effect of head and neck radiotherapy. Significant dose to the salivary glands affects both the composition and quantity of saliva production, often resulting in long-term xerostomia and a significant decrease in quality of life [2–4]. Furthermore, radiation induced xerostomia can predispose patients to dental decay and significant oral comorbidity [5,6]. While there are treatments to reduce the risk of xerostomia related complications, as well as saliva substitutes and sialogogic agents for symptomatic relief, primary prevention remains the focus for improvement of patient outcomes [5]. Therefore, techniques to minimize post-radiation xerostomia while maintaining oncologic outcomes are of considerable interest.

In addition to minimizing dose to parotid glands and oral cavity [1], avoidance of the submandibular glands (SMGs) is one technique of active investigation to further improve outcomes of long-term xerostomia. The preservation of function of the SMG is of importance

Abbreviations: SMG, submandibular gland; IMRT, intensity modulated radiation therapy; HPV, Human papillomavirus; OPC, oropharyngeal carcinoma; LRC, locoregional control; OS, overall survival; KPS, Karnofsky Performance Status; DM, distant metastasis; CTCAE, Common Terminology Criteria for Adverse Events

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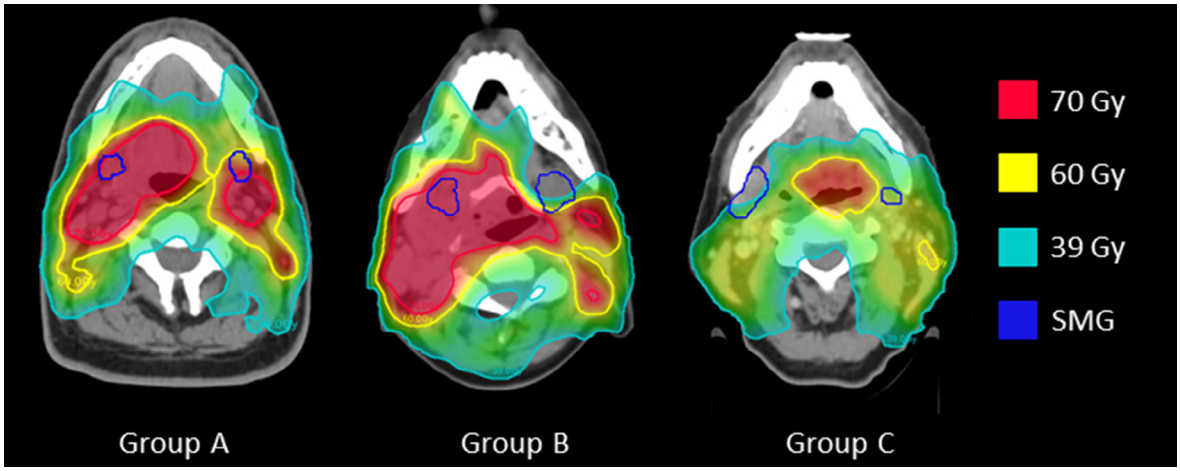

Fig. 1. Dosimetric heat map examples for each group. Group A includes both 1b levels in the target volume; Group B includes one 1b level; Group C spares both level 1b levels. Submandibular glands are outlined in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

because their production of salivary mucins are involved in both lubrication and protection of the oral mucosa [7]. Additionally, the SMGs are responsible for the basal rate of unstimulated salivary production. The loss of this baseline rate of saliva production results in the subjective sensation of oral dryness that persists regardless of whether the patient is eating [8,9].

Prior to modern techniques that allow precise volumetric tumor volumes, SMG transfer to the submental space during primary surgical tumor excision was employed to increase distance from the radiation target volume, yielding improved xerostomia outcomes [10,11]. For patients treated non-operatively, this requires an additional procedure and may no longer be advantageous with the conformality of modern IMRT. Significant functional preservation of the SMG is seen at doses less than 39 Gy [6,8,9,12,13], which may be achievable with the omission of the level Ib neck station in treatment planning. The complete omission of level Ib station is based on the observation that involvement of 1b neck nodes is rare in node-positive oropharynx carcinoma (OPC) when the extent of neck disease burden is limited to one nodal level [9,14,15]. This study explores the safety and efficacy of this approach in select node-positive human papillomavirus (HPV)-associated OPC patients, comparing the avoidance of the level IB neck level either unilaterally or bilaterally with traditional bilateral level IB coverage.

Methods

Patient selection

From a retrospective institutional review board–approved registry, patients with non-metastatic T1-2, node-positive, HPV-associated oropharyngeal carcinoma treated with definitive or post-operative IMRT with or without chemotherapy at a single institution were selected. Patients treated from 2009 were included and the data cutoff was done in January 2014 to assure long term follow up on each patient. Only HPV-associated tumors were included in this study after confirmation with p16 immunohistochemical staining and/or in-situ hybridization for HPV DNA. Patients with positive lymph node metastasis were identified by characteristic CT or PET/CT imaging findings. Disease characteristics were described with T and N stage according to AJCC 8th Edition guidelines. Patient demographics, including age, gender, and race, were extracted from this database and used to compare groups and to examine predictors of early and late xerostomia. Other descriptive demographics included Karnofsky Performance Status (KPS) and Charlson comorbidity index. Extent of smoking was quantified as smoking pack-years and heavy ethanol abuse defined as more than eight drinks per week for women and fifteen drinks per week for men was also taken into consideration.

Treatment

Patients included in the study were treated curatively with either definitive radiation or primary surgery and post-operative radiation with or without systemic chemotherapy. Any patient with evidence of distant metastatic disease at the time of initial staging was excluded. Systemic therapy included platinum based agents (cisplatin or carboplatin) with or without 5-fluorocuracil or alternatively, cetuximab. All patients were treated with radiotherapy via modern IMRT treatment planning. The retropharyngeal nodes were covered in the treatment volume in all patients. While in the earlier portion of this study, avoidance of level Ib was uncommon; in more recent years, we routinely avoid clinically uninvolved level Ib, even in the presence of level 2a nodes. Level Ib was treated on the involved neck in patients who had multiple nodal levels (e.g. levels 2 and 3) with nodal metastases. The SMG was spared in patients with single nodal level involvement. The decision to target the level Ib nodes was made separately for each side of the neck based on these criteria. Patients with bilateral Ib neck nodes targeted were defined as group A, those with a unilateral Ib neck nodes targeted were defined as group B, and those with bilateral Ib neck nodes avoided were defined as group C (Fig. 1).

Oncologic outcomes and toxicity

The end points for this study included local and regional control rates as well as xerostomia. Local recurrence and regional recurrence in the neck, especially at the IB level were quantified in order to measure locoregional control rate (LRC). LRC was defined as the time from the date of diagnostic biopsy until recurrence, local or regional, or last oncologic follow up. Overall survival (OS) was also of interest, and defined as the time from date of diagnostic biopsy until patient death or last known alive. Distant metastasis (DM) was defined as the time from date of diagnostic biopsy until recurrence below the neck or last oncologic follow up. Toxicities were physician-assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Xerostomia was measured at oncologic follow up and stratified by the time that had passed since radiotherapy. Acute xerostomia was considered grade 2 xerostomia up until 3 months after the end of radiotherapy. Late xerostomia was considered grade 2 xerostomia after two years. Intermediate xerostomia was also measured in between acute

and late xerostomia and defined as grade 2 xerostomia between 3 months and 24 months. To be conservative in quantifying improved xerostomia, patients with no comment on xerostomia at subsequent oncologic visits were assumed to be at the same grade as commented in a previous visit. Xerostomia was not assumed to be improved from a previous visit unless specifically commented on. In order to conservatively quantify xerostomia, follow up visits in which xerostomia was not specifically commented on were assumed to have the same grading of xerostomia as previous visits.

Statistical analyses

T-tests or chi-square analyses were used to compare continuous and categorical patient descriptive variables. The differences amongst xerostomia in the groups were assessed using a Chi-square test and pairwise comparison. Odds ratios for xerostomia were calculated for groups B and C in comparison to the control group A. The Kaplan-Meier technique was used to analyze locoregional control, distant control and overall survival. The differences amongst groups for oncologic outcomes were compared using the log-rank test. Median follow-up and median dosage to the oral cavity and SMG were compared using non-parametric Wilcoxon analyses. JMP Pro version 13 was used to compute all analyses and produce graphics.

Results

Patient selection

Altogether, 86 T1-2N+ HPV-associated oropharyngeal carcinoma patients with 172 level IB stations were identified and included in this study and then divided into groups A, B, and C. Median follow up for all patients was 59.3 months (range 3.0–102.1 months). The descriptive statistics for this cohort are outlined in Table 1. The majority of patients had unilateral level IB (Group B) station included in the treatment plan. Of the 172 level IB stations, 93 (54.1%) were targeted and 79 (45.9%) were avoided. When IB was targeted, the SMG was included in the treatment plan target except for four patients who had the SMG carved out of the treatment target. One patient in group C had a synchronous bilateral tonsil cancer and was included in the study.

Table 1
Patient demographical information and descriptive statistics.

	A (n = 16)	B (n = 61)	C (n = 9)	p-value
Caucasian	16 (100%)	56 (91.8%)	9 (100%)	p = 0.70
African American	0	3 (4.9%)	0	
Hispanic	0	2 (3.3%)	0	
Median age	57.6	59.2	63.8	p = 0.71
Male	15 (93.8%)	54 (88.5%)	8 (88.9%)	p = 0.83
Never smoker	6 (37.5%)	22 (36.1%)	5 (55.6%)	p = 0.24
Former smoker	10 (62.5%)	30 (49.1%)	2 (22.2%)	
Active smoker	0	9 (14.8%)	2 (22.2%)	
Median smoking pack-years	10	8	0	p = 0.72
Heavy ethanol abuse	2 (12.5%)	5 (8.2%)	1 (11.1%)	p = 0.85
KPS 90-100	14 (87.5%)	54 (88.5%)	6 (66.7%)	p = 0.21
KPS 90 or below	2 (12.5%)	7 (11.5%)	3 (33.3%)	
Charlson 0	10 (62.5%)	41 (67.2%)	6 (66.7%)	p = 0.97
Charlson 1	2 (12.5%)	10 (16.4%)	1 (11.1%)	
Charlson 2	1 (6.3%)	4 (6.5%)	1 (11.1%)	
Charlson > 2	3 (18.8%)	6 (9.8%)	1 (11.1%)	
Median follow up	63.0	59.8	51.5	p = 0.053
Tonsil	5 (31.3%)	29 (47.5%)	6 (66.7%)	p = 0.01
BOT	11 (68.8%)	32 (52.5%)	2 (22.2%)	
Posterior wall	0	0	1 (11.1%)	
T1	5 (31.3%)	32 (52.5%)	5 (55.6%)	p = 0.29
T2	11 (68.8%)	29 (47.5%)	4 (44.4%)	
N1	3 (18.8%)	57 (93.4%)	7 (77.8%)	p ≤ 0.01
N2	10 (62.5%)	1 (1.6%)	2 (22.2%)	
N3	3 (18.8%)	3 (4.9%)	0	

Treatment and related dosimetric outcomes

The entire cohort was treated with definitive (n = 78, 90.7%) or postoperative (n = 8, 9.3%) radiotherapy. Systemic therapy was used in the majority of patients and with no difference between groups (A, 93.8%; B, 91.8%; C, 77.8%; $P = 0.36$). Most patients received platinum based therapy, while the remaining received cetuximab (A, 20%; B, 26.8%; C, 14.3%; $P = 0.089$).

All patients were treated curatively with radiotherapy using an IMRT treatment plan with a median dose to planning target volume in group A of 72 Gy, and in group B and C of 70 Gy. The full details of the dosimetric outcomes for the parotid glands, oral cavity, and SMGs based on neck and level 1b sparing are shown in Table 2. The target volume dose tended to be higher in patients whose IB stations were targeted: mean dose 71.4 Gy in group A, mean dose 70.5 Gy in group B, and mean dose 66.9 in group C. The majority of patients were treated with the neck targeted bilaterally (n = 74, 86.1%) while a minority were treated unilaterally (n = 12, 13.9%). Twenty-six patients (32.2%) underwent adaptive re-planning during the treatment course. The median of the mean SMG dose was 44.5% lower in the patients whose corresponding level Ib neck level was omitted (37.5 Gy vs 67.5 Gy; $P = 0.0001$). The median of the mean dose to the oral cavity was also decreased with increased level Ib sparing (A, 40.7 Gy; B, 35.4 Gy; C, 30.7 Gy; $P = 0.002$).

Oncologic outcomes and patterns of failure

After a median follow up of 59.3 months (A, 63.0 months; B, 59.8 months; C, 51.5 months; $P = 0.053$), there were no local or regional recurrences regardless of whether level IB was included in the treatment plan (Fig. 2). Three patients recurred distantly (one in group A, two in group B), including one to bone and two to the lung or mediastinum. Five year OS was also excellent with no significant difference between groups (A: 85.9%, B: 91.5%, C: 100%; $P = 0.528$). Seven patients underwent neck dissection soon after radiotherapy due to concern on imaging for potentially persistent disease. One of these patients had a positive neck node on resection and had no evidence of failure at the latest follow up. Seven patients (8.1%) had died at the time of analysis; three due to distant failure, one due to other comorbidity, and three due to other unrelated cancers (one leukemia, one cholangiocarcinoma, and one due to new oral cavity primary).

Xerostomia and toxicity

Overall xerostomia improved over time and correlated with increased level 1b sparing (Fig. 3). Acute ≥grade 2 xerostomia was prevalent in all groups, but occurred most often in those with at least the unilateral level IB targeted (A vs B vs C: 81.3% 85.3% vs 44.4%; $P = 0.0162$). In between 3 months and up until 2 years after treatment, the rate of ≥grade 2 xerostomia in group A was stable, while group B had improved ≥grade 2 xerostomia rates and group C had resolution of all previous ≥grade 2 xerostomia (A vs B vs C: 80.0% vs 62.3% vs. 0%; $P \leq 0.001$). Late ≥grade 2 xerostomia significantly decreased with decreasing IB coverage (A vs B vs C: 53.3% vs 34.5% vs 0%; $P = 0.0284$). Rates of xerostomia broken down by grade with a pairwise comparison with Group A as the reference are shown in Table 3.

Discussion

Even with the improved conformity in contemporary treatment planning, xerostomia continues to be a significant side effect of head and neck radiotherapy. Level IB lymph nodes have been historically included in elective nodal volumes for head and neck radiotherapy plans. The rationale for excluding level IB lymph nodes is based on two Sanguineti, et al. studies which examined patterns of nodal involvement for oropharynx patients based on surgical pathology findings. These

Table 2
Dosimetric Outcomes. Dosimetric outcomes stratified by grouping, neck targeting, and 1b targeting. Doses shown are the median of the group of mean organ doses. P-values are represented by Pearson Chi-squared test for categorical variables and non-parametric Wilcoxon test for continuous variables.

	Group A (n = 16)	Group B (n = 61)	Group C (n = 9)	*P*=
Mean parotid dose	30.8 Gy	28.7 Gy	23.7 Gy	< 0.001
Mean oral cavity dose	40.7 Gy	35.4 Gy	30.7 Gy	0.002
Mean SMG dose	66.2 Gy	55.0 Gy	39.4 Gy	< 0.001
Unilateral neck targeted	0 (0%)	7 (11.4%)	5 (55.6%)	< 0.001
Bilateral neck targeted	16 (100%)	54 (88.6%)	4 (44.4%)	
	Bilateral neck (n = 74)	Unilateral neck (n = 12)		
Mean parotid dose	29.2 Gy	20.2 Gy		< 0.001
Mean oral cavity dose	37.0 Gy	29.1 Gy		< 0.001
Mean SMG dose	63.1 Gy	28.2 Gy		< 0.001
	1b targeted (n = 93)	1b omitted (n = 79)		
Mean parotid dose	31.3 Gy	26.0 Gy		< 0.001
Mean oral cavity dose	37.3 Gy	33.8 Gy		0.007
Mean SMG dose	67.5 Gy	37.5 Gy		< 0.001

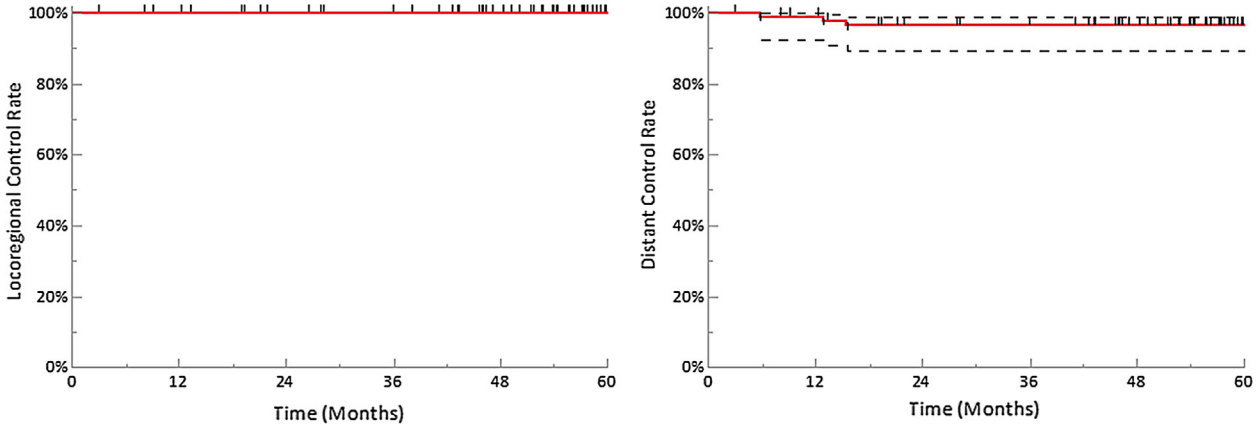

Fig. 2. Left: Locoregional control for all groups. Right: Distant control rate for all groupswith 95% confidence intervals.

studied demonstrated that the risk of subclinical IB metastasis is rare (less than 5 percent) in node positive oropharynx squamous cell carcinoma when less than two ipsilateral nodal levels are involved [14–16]. Based on these surgical patterns of involvement, our institutional practice has been to exclude IB from elective coverage unless there is multi-station involvement. Here, we demonstrate reduced doses to the SMG when level Ib was spared which subsequently correlated to reduce rates of ≥grade 2 xerostomia. While the most dramatic differences were observed when bilateral level Ib were spared, sparing even one side of level Ib had significantly reduced SMG doses and improved rates of xerostomia. However, there are a multitude of other factors, including variance in dose to the parotid glands and oral cavity, which affect xerostomia outcomes. While increased level Ib sparing was associated with lower xerostomia rates, we cannot conclude that this is the sole reason for improved outcomes. This study with long-term follow-up on all patients shows a negligible nodal recurrence rate, validating the safety of this approach.

The decreased SMG dose in group C in comparison to group A is consistent with several other retrospective reviews that omit the SMG itself instead of the entire IB neck level in a variety of head and neck disease sites [17–20]. Due to heterogeneity of reporting, it is difficult to compare outcomes across retrospective reviews. A study similar in design completed at Memorial Sloan-Kettering in 2015 compared patients with bilateral IB spared (n = 40) against patients with bilateral IB targeted (n = 85) and showed similar results: decreased submandibular, oral cavity, and contralateral parotid dose with improved patient reported xerostomia while maintaining locoregional control (median follow up of 23.2 months) [21]. A byproduct of sparing the 1b neck level is a lower dose to the oral cavity, which also likely contributes to decreased rates of xerostomia [22]. Our study is important as it demonstrates that even at five years, there are no observed local failures with our approach, thus validating the findings of Sanguineti et al.

HPV-associated disease is a separate entity from HPV-negative disease, as described in the recent AJCC 8th Edition staging, and the relationship between HPV status and risk of IB recurrence remains to be defined. Previous studies included both HPV-positive and negative patients, yet consist of a majority of HPV-positive patients [14–16]. We limited our study to exclusively HPV-associated disease to help correspond with future treatment regimens that are based on tumor HPV status and AJCC 8th Edition staging criteria. Furthermore, HPV-associated oropharyngeal cancer occurs more often in younger and healthier patients than HPV-negative disease, highlighting the importance of minimizing xerostomia and improved quality of life in the long term [23].

This study has several limitations. Xerostomia is a complex problem affected by many variables, some of which may not have been measured in this study. Grading xerostomia subjectively can lead to considerable variation in outcome reporting and future studies could benefit from objective measures such as salivary gland scintigraphy or measurement of salivary flow rate [5]. Patient reported outcomes are an important measure of functional preservation and future studies must incorporate them in demonstrating the value of this approach. Regardless, the objective SMG and oral cavity dose limitations as well as the reduction in significant xerostomia is powerful evidence that supports the widespread adoption of level Ib sparing in appropriately selected patients to optimize SMG and oral cavity sparing.

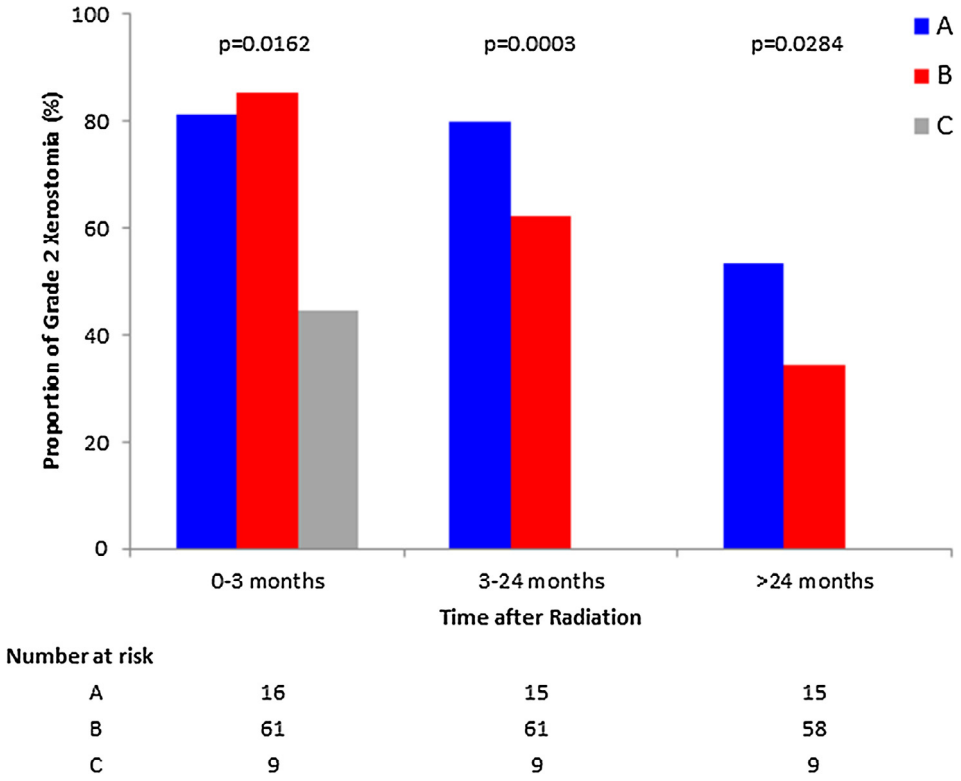

Fig. 3. Grade 2 Xerostomia Outcomes. Bar graph of grade 2 xerostomia outcomes stratified by time: acute xerostomia (0–3 months), intermediate xerostomia (3–24 months), and late xerostomia (> 24 months). P-values are for chi-square test for the entire group.

Table 3
Grading of Xerostomia with Odds Ratios. Xerostomia stratified by grade at acute, intermediate and late time points.

	Grade 0	Grade 1	Grade 2+	P = [a]	P = [b]	Odds Ratio[c]
0–3 months						
Group A (n = 16)	0	19% (3)	81% (13)	Ref	Ref	Ref
Group B (n = 61)	2% (1)	13% (8)	85% (52)	0.753	0.695	1.33 (0.316–5.634)
Group C (n = 9)	0	56% (5)	44% (4)	0.058	0.058	0.18 (0.030–1.137)
3–24 months						
Group A (n = 15)	0	20% (3)	80% (12)	Ref	Ref	Ref
Group B (n = 61)	5% (3)	33% (20)	62% (38)	0.375	0.195	0.41 (0.105–1.621)
Group C (n = 9)	22% (2)	78% (7)	0	0.001	< 0.001	< 0.01
24 months or more						
Group A (n = 15)	7% (1)	40% (6)	53% (8)	Ref	Ref	Ref
Group B (n = 58)	24% (14)	41% (24)	34% (20)	0.237	0.181	0.46 (0.146–1.454)
Group C (n = 9)	44% (4)	56% (5)	0	0.011	0.007	< 0.01

[a] P-value for difference in groups based on grades.
[b] P-value for difference between groups based on ≥grade 2 xerostomia or not.
[c] Odds ratio for grade 2 or worse xerostomia with Group A as the reference group with 95% confidence interval.

Conclusion

Sparing level IB, either contralaterally or bilaterally, is safe in select T1-2, node-positive HPV-associated oropharyngeal cancer. Patients without multi-station ipsilateral nodal involvement may not need elective coverage of level IB, as shown with no IB nodal failures at nearly 5-year median follow-up. Level Ib sparing translates into significantly lower SMG and oral cavity dose, which correlate with improved patient toxicity outcomes. Larger studies are needed to validate these early findings and the impact of this technique on late xerostomia and other functional outcomes.

Conflicts of Interest statement

R.B. Ross: none.
A. Juloori: none.
V. Varra: none.
M.C. Ward: none.
S. Campbell: none.
N.P. Joshi: none.
N.M. Woody: none.
E. Murray: none.
P. Xia: none.
J.F. Greskovich Jr.: none.
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