International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Re-evaluation of Ipsilateral Radiation for T1-T2N0-N2b Tonsil Carcinoma at the Princess Margaret Hospital in the Human Papillomavirus Era, 25 Years Later

Shao Hui Huang, MD, MSc, MRT(T),* John Waldron, MD,*,† Scott V. Bratman, MD, PhD,* Jie Su, MSc,‡ John Kim, MD,* Andrew Bayley, MD,* John Cho, MD, PhD,* Meredith Giuliani, MD,* Andrew Hope, MD,* Jolie Ringash, MD,* Aaron Hansen, MD,§ John R. de Almeida, MD, MSc,† David Goldstein, MD, MSc,† Bayardo Perez-Ordonez, MD,‖ Ilan Weinreb, MD,‖ Li Tong, MD, BSc,* Wei Xu, PhD,‡ and Brian O'Sullivan, MD*,†

Departments of *Radiation Oncology, †Otolaryngology—Head & Neck Surgery, and ‡Biostatistics, §Division of Medical Oncology, and ‖Department of Pathology, The Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada

Received Nov 8, 2016, and in revised form Dec 16, 2016. Accepted for publication Jan 2, 2017.

Summary

This study describes the results of ipsilateral radiation therapy for T1-T2N0-N2b tonsillar cancer in the human papillomavirus (HPV) era, 25 years after the final accrual of our historical 1970 to 1991 cohort. It shows equally high locoregional control and survival for HPV-positive and

Purpose: To report the outcome of ipsilateral radiation therapy (RT) in human papillomavirus (HPV)-positive (HPV+) patients and HPV-negative (HPV−) patients with T1-T2N0-N2b tonsillar cancer treated 25 years after our initial historical cohort.

Methods and Materials: Patients with T1-T2N0-N2b tonsillar cancer who received ipsilateral RT or bilateral RT between 1999 and 2014 were reviewed. Overall survival (OS), local control (LC), regional control (RC), and grade 3 to 4 late toxicity (LT) were compared between ipsilateral RT and bilateral RT within HPV+ and HPV− patients, separately.

Results: HPV status was ascertained in 379/427 (88%) consecutive patients (ipsilateral RT: 62 HPV+, 34 HPV−; bilateral RT: 240 HPV+ 240, 41 HPV−). The proportion of ipsilateral RT by N category for HPV+ and HPV− patients were as follows: N0: 24/37 (65%) versus 28/48 (74%); N1: 21/49 (43%) versus 4/9 (44%); N2a:

Reprint requests to: Shao Hui Huang, MD, MSc, MRT(T), Department of Radiation Oncology, The Princess Margaret Cancer Centre, University of Toronto, 610 University Ave, Toronto, Ontario, M5G 2M9, Canada. Tel: (416) 581-7781; E-mail: shaohui.huang@rmp.uhn.on.ca

Supported by the Bartley-Smith/Wharton, the Gordon Tozer, the Wharton Head and Neck Translational, Dr Mariano Elia, and Petersen-Turofsky Funds, and The Joe & Cara Finley Center for Head & Neck Cancer Research at the Princess Margaret Cancer Foundation.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 98, No. 1, pp. 159−169, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.01.018

HPV-negative patients receiving ipsilateral versus bilateral radiation therapy. The original principles of patient selection for ipsilateral radiation therapy are discussed and remain universally applicable in the current HPV era.

10/39 (26%) versus 1/4 (25%); and N2b: 7/177 (4%) versus 1/24 (4%), respectively. Of the patients receiving ipsilateral RT, 94/96 (98%) were treated with RT alone. The median follow-up time was 5.03 years. The respective 5-year rates of OS, LC, RC, and LT were similar between ipsilateral RT and bilateral RT for the HPV+ patients (OS: 89% vs 87%, $P=.55$; LC: 97% vs 98%, $P=.65$; RC: 98% vs 97%, $P=.27$; LT: 17% vs 12%, $P=.83$) and HPV− patients (OS: 63% vs 48%, $P=.27$; LC: 90% vs 80%, $P=.19$; RC: 94% vs 83%, $P=.14$; LT: 15% vs 22%, $P=.36$). Of the 96 patients receiving ipsilateral RT, contralateral neck failure (CNF) occurred in 1/52 HPV+ patients and 1/34 HPV− patients. The 5-year CNF rates were 2% (95% CI: 1-9) (HPV+: 2% [0-14]; HPV−: 3% [0-21], $P=.66$). Five local failures (2 HPV+; 3 HPV−) and no distant failures were seen. The 5-year rates of LC, RC, and LT were 97% versus 90% ($P=.24$), 98% versus 94% ($P=.25$), and 18% versus 15% ($P=.75$) for the HPV+ and HPV− cohorts, respectively. Osteoradionecrosis occurred in 9 patients: 6/47 (13%) treated with conventional RT and 3/49 (6%) with intensity modulated RT ($P=.32$).

Conclusion: Ipsilateral radiation to selected patients with T1-T2N0-N2b tonsillar cancer results in equally excellent outcomes regardless of tumor HPV status.

Introduction

We previously described a cohort of tonsillar cancer patients from 1970 to 1991 in whom we addressed the safety, advantages, and pitfalls of ipsilateral radiation therapy (RT) (1). We demonstrated that contralateral neck failure (CNF) was rare and that ipsilateral RT for selected well-lateralized tonsillar cancer is safe and beneficial, allowing preservation of salivary gland function. However, "geographic miss" could occur with posterior or medial extension at that time because of a lack of cross-sectional imaging for staging and RT planning, minimal written treatment guidelines, insufficient peer-review quality assurance, and compromised dose distributions with the use of wedge-pair techniques (2). The local control (LC) rate for the cohort was only 77%.

Twenty-five years have passed since the last patient in the original report was treated. Since then, treatment guidelines have been implemented, with real-time peer-review quality assurance guidelines in our institution analogous to those in the TROG02.02 trial (3). RT techniques have also been revolutionized: improved sensitivity of medical imaging for staging and RT planning have enhanced target delineation, intensity modulated RT (IMRT) planning and treatment delivery techniques have enabled improvements in tumor coverage and normal tissue sparing, and daily computed tomography (CT)-based volumetric image guidance (IG-IMRT) has assured precision of treatment delivery. Another important change is the increasing incidence of human papillomavirus (HPV)-mediated oropharyngeal cancer (HPV+ OPC) (4). Compared with traditional smoking-mediated HPV-negative (HPV−) OPC, HPV+ OPC is more radiosensitive and chemosensitive, with consequent superior outcomes (5). However, owing to a propensity for earlier lymph node (LN) involvement of HPV+ OPC, some authors reported increased bilateral LN presentations for HPV+ T1-T2 tonsillar cancer (6, 7), raising concerns about the safety of ipsilateral neck management (7, 8). However, interpretation may be hindered by variable cohort size, low HPV ascertainment rates, minimal attention to the descriptions of the laterality of candidate primary lesions, and lack of outcome data. Others have reported that tumor HPV status does not change the pattern of LN presentation (9, 10), supporting the notion that ipsilateral RT remains safe in the HPV era (11). Several recent publications continue to show low CNF rates in patients treated with ipsilateral RT (12, 13) whereas one report described a marginally higher CNF after ipsilateral RT in HPV+ OPC patients (14).

In view of the unsettled debate regarding the safety of ipsilateral RT for HPV+ tonsillar cancer, we conducted this retrospective review of a prospectively assembled cohort of T1-T2 tonsillar cancers treated with ipsilateral and bilateral RT in our institution during the HPV era. The primary objective was to assess whether ipsilateral RT remains safe and CNF remains low for HPV+ patients; the secondary objective was to report LC for both HPV+ and HPV− patients using contemporary RT techniques and approaches.

Methods

Study population

After research ethics board approval, all T1-T2N0-N2b tonsillar cancers treated with definitive RT from 1999 to 2014 were reviewed. Patients were identified from a bioclinical anthology of outcomes database (15) containing prospectively recorded clinical information and outcomes. Tumor HPV status was tested with p16 staining retrospectively for cases before 2009 and prospectively from 2009 onward. Strong/diffuse p16 immunostaining was

classified as HPV+, and negative p16 staining was HPV− (16, 17). Equivocal cases received polymerase chain reaction (PCR) to confirm high-risk HPV. Staging was by 7th edition TNM classification (18-20) undertaken in a multidisciplinary setting involving clinical and endoscopic examination and contrast-enhanced computed tomography (CT). Magnetic resonance imaging (MRI) was performed if base of tongue (BOT) involvement was suspected. Positron emission tomography (PET) was not routinely available and was used only occasionally during enrollment in a clinical trial (NCT00147472) or under health jurisdiction approval for occult primary cervical nodal disease presentations after 2013.

Radiation therapy planning, treatment, and follow-up

The decision to treat with ipsilateral or bilateral RT followed written institutional management policies and was discussed in a weekly peer-reviewed quality assurance round. The criteria to use ipsilateral RT took into account both primary and neck factors determined from the original analysis (1). Ipsilateral RT was considered for N0-N2a disease in very lateralized tonsillar primaries limited to the lateral one-third of the "hemi-structure" of the BOT or soft palate, defined as $\leq$1 cm of superficial mucosa of "hemi-structure" extension, without muscle involvement or any suspicion of deeper penetration (Fig. 1). N2b disease was generally treated with bilateral RT until recently, where ipsilateral RT was considered for small-volume N2b disease when imaging showed no suspicion of contralateral neck involvement. Any patient with suspected contralateral neck disease but not meeting the criteria for frank nodal involvement on that side received bilateral RT, although the lower N category would be assigned according to TNM rules (20). RT alone was given for N0-N1 disease and was preferred for N2a and small-volume N2b disease. HPV status was not considered at the time of decision.

All patients underwent CT $\pm$ MR simulation. Three-dimensional (3D) conformal RT (3D-RT) was used for patients before 2005; IMRT became the standard of care from 2005 onward. Three-dimensional conformal RT used a homolateral oblique wedge-pair technique with $\geq$1 cm clearance from the lateral aspect of the target to the beam edge (1). IMRT used an arrangement of 5 to 6 beams. Daily image guidance was performed for the IMRT cohort to ensure precision of RT delivery.

Follow-up was undertaken in a multidisciplinary setting according to institutional protocol (21). CT/MRI was performed 8 to 12 weeks after RT to assess treatment response. Postradiation neck dissection (ND) was performed only if clinical evaluation, radiologic evaluation, or both indicated possible persistent neck disease based on our response-driven protocol described previously (22, 23). PET-CT was used only in a clinical trial setting (NCT00147472). Routine surveillance was undertaken at 3-month intervals for the first 2 years; 4-month intervals in years 2 to 3, 6-month intervals for years 3 through 5, and annually thereafter. Local or regional failures were recorded based on histologic confirmation, and distant failure relied on radiologic evidence, histologic evidence, or both.

Statistical analysis

Clinical characteristics and outcomes were compared between patients receiving ipsilateral versus contralateral RT

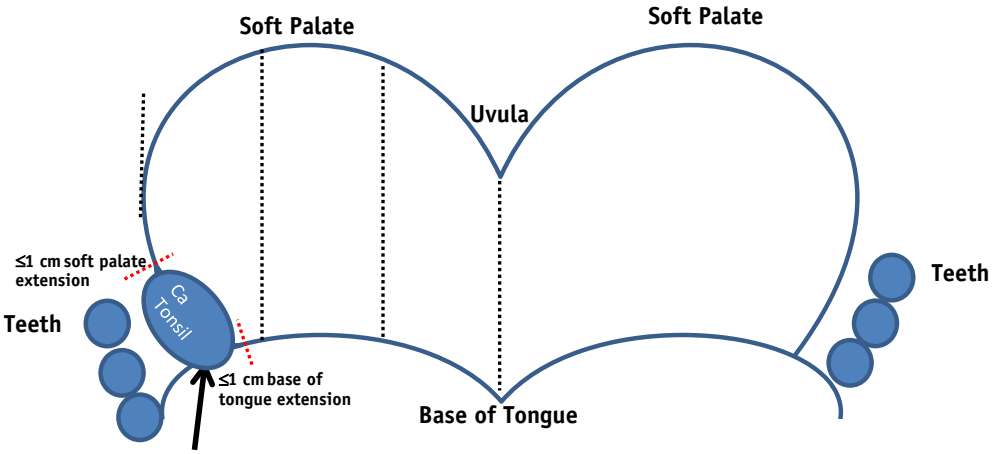

Fig. 1. Schematic diagram depicting "very-lateralized" primary suitable for consideration of ipsilateral radiation therapy.

Table 1 Clinical characteristics of HPV+ and HPV− patients treated with ipsilateral RT

Covariate	Full sample (n=96)	HPV negative (n=34)	HPV positive (n=62)	*P* value
Case no.	96	34	62	
Median FU, y (range)	5.7 (1.0-17.6)	6.9 (1.0-17.6)	4.3 (2.0-10.4)	
Median age, y (range)	58 (42-93)	69 (54-93)	57 (42-85)	**<.001**
Sex				.054
Female	25 (26)	13 (38)	12 (19)	
Male	71 (74)	21 (62)	50 (81)	
Zubrod PS				**.008**
0	65 (68)	19 (56)	46 (74)	
1-2	21 (22)	13 (38)	8 (13)	
Unknown	10 (10)	2 (6)	8 (13)	
Smoking pack-years				**<.001**
Median (range)	22 (0-135)	40 (0-90)	18 (0-135)	
Smoking history				**<.001**
Current	32 (33)	19 (56)	13 (21)	
Former	50 (52)	14 (41)	36 (58)	
None	14 (15)	1 (3)	13 (21)	
Excessive drinking history				**<.001**
Yes	36 (38)	20 (59)	16 (26)	
No	55 (57)	11 (32)	44 (71)	
Unknown	5 (5)	3 (9)	2 (3)	
T category				**.002**
T1	40 (42)	7 (21)	33 (53)	
T2	56 (58)	27 (79)	29 (47)	
N category				**<.001**
N0	52 (54)	28 (82)	24 (39)	
N1	25 (26)	4 (12)	21 (34)	
N2a	11 (11)	1 (3)	10 (16)	
N2b	8 (8)	1 (3)	7 (11)	
Treatment modality				.54
RT alone	94 (98)	34 (100)	60 (97)	
Chemo-RT	2 (2)	0	2 (3)	
RT technique				.53
3D conformal	47 (49)	15 (44)	32 (52)	
IMRT	49 (51)	19 (56)	30 (48)	
RT regimen				
51 Gy/20 fx/4 wk, QD	18 (19)	7 (20)	11 (18)	
60 Gy/25 fx/5 wk, QD	53 (55)	23 (68)	30 (48)	
64 Gy/40 fx/4 wk, BID	2 (2)	1 (3)	1 (2)	
66-70 Gy/33-35 fx/6.5-7 wk, QD	23 (24)	3 (9)	20 (32)	
Status				**.001**
Alive	71 (74)	18 (53)	53 (85)	
Deceased	25 (56)	16 (47)	9 (15)	
5-year outcomes				
Overall survival	79% (71-89)	63% (47-84)	88% (80-98)	**<.001**
Local control	94% (87-98)	90% (70-97)	97% (87-99)	.240
Regional control	97% (90-99)	94% (77-98)	98% (86-100)	.250
Contralateral neck failure	2% (1-9)	3% (0-14)	2% (0-21)	.660
Distant control	100%	15% (6-39)	100%	>.999
Grade 3-4 LT	17% (10-28)		17% (9-32)	.750
Type of grade 3-4 LT				
Bone*	9	6	3	
Larynx	1	1	0	
Dysphagia	3	2	1	
Soft tissue fibrosis	2	2	0	

Abbreviations: 3D = 3-dimensional; BID = twice daily; Chemo = chemotherapy; FU = follow-up; fx = fractions; IMRT = intensity modulated radiation therapy; HPV− = human papillomavirus negative; HPV+ = human papillomavirus positive; LT = late toxicity; QD = once daily; RT = radiation therapy; wk = weeks; Zubrod PS = Zubrod performance scale.

Bold *P* value: statistical significance.

* Bone toxicity included any grade of osteoradionecrosis. The radiation therapy regimens used for the 9 patients were as follows: 51 Gy/20 fx/4 wk: n=3; 60 Gy/25 fx/5 wk: n=4 (3D conformal: 3; IMRT: 1); 66-70 Gy/33-35 fx: n=2 (all IMRT).

within the HPV+ and HPV− cohorts separately, and between HPV+ versus HPV− for patients receiving ipsilateral RT, using nonparametric Kruskal Wallis tests for continuous variables and the Fisher exact tests for categoric variables. Overall survival (OS) was calculated by the Kaplan-Meier method, and LC, regional control (RC), distant control (DC), and grade 3 to 4 late toxicities (LT, excluding percutaneous endoscopic gastrostomy tube [PEG] dependency) were estimated by competing-risk methods (death without failure of interest was considered a competing risk). All time to events were calculated from the date of diagnosis except LT, which was calculated from RT completion. All tests were 2-tailed, with P values $<.05$ considered significant.

Results

Among 427 consecutive T1-T2N0-N2b tonsillar cancer patients (HPV+ 302; HPV−: 75; unknown HPV: 50), ipsilateral and bilateral RT was administered to 102 (24%) and 325 patients, respectively. The proportion of patients receiving ipsilateral RT diminished with higher N category (Supplement E1; available online at www.redjournal.org). Supplement E2 (available online at www.redjournal.org) depicts the typical dose distribution of ipsilateral RT with either 3D-RT or IMRT technique.

Clinical characteristics and outcomes in the ipsilateral radiation therapy cohort

Among the ipsilateral RT cohort (n = 102), HPV status was available in 96 (94%) patients, including 62 HPV+ and 34 HPV−. The N categories were as follows: N0: 52, N1: 25, N2a: 11; N2b: 8. The number of involved LNs and nodal levels for the 8 N2b were as follows: 2 LNs at 1 level (n = 1); 2 LNs at 2 levels (n = 2); 3 LNs at 2 levels (n = 4); 7 LNs at 2 levels (n = 1). No patients underwent postradiation ND. HPV+ patients were younger (median: 57 vs 69 years), had better Zubrod performance scale and fewer smoking pack-years (median 18 vs 40) (both $P<.01$) with less current smokers (21% vs 56%) (all $P<.01$) (Table 1). In addition, the HPV+ cohort comprised more T1 (53% vs 21%, $P=.002$) and clinical N+ disease (61% vs 18%, $P<.001$). All patients underwent RT alone except for 2 HPV+ patients (1 N2a and 1 N2b) who received CRT.

The median follow-up time was 6.0 years (HPV+: 6.9; HPV−: 4.3 years). Although OS was higher among HPV+ patients than in HPV− patients (88% vs 63%, $P<.01$), the 5-year LC (97% vs 90%, $P=.24$) and RC (98% vs 94%, $P=.25$) were similar (Fig. 2). Compared with 3D-RT (n = 47), IMRT patients (n = 49) had nonsignificantly higher LC (96% [73-99] vs 91% [78-97], $P=.19$) and RC (100% vs 94% [80-98], $P=.09$).

Local failure occurred in 2 HPV+ and 3 HPV− patients. No distant failures occurred. Regional failure manifested in 3 patients: 1 patient with in-field regional failure (T2N0 HPV−) also had local failure, and 2 patients had CNF (1 HPV+ and 1 HPV−). The 5-year CNF rates were 2% (95% CI: 1-9) (HPV+: 2% [0-14]; HPV−: 3% [0-21], $P=.66$) (Table 1). Both had T2N1 disease treated with 60 Gy in 25 fractions over 5 weeks of RT alone with the use of homolateral wedge-pairs. The HPV+ (T2N1) patient in whom contralateral neck RT had been unsuccessful had a single contralateral level 3 LN 2.5 years after RT. He underwent salvage ND and was disease free 12 years later. The HPV− (T2N1) patient experienced recurrence in contralateral levels 2, 3, and 5 nodes 6 months after RT. Salvage ND with reirradiation achieved 8 subsequent disease-free years.

Acute toxicity was not recorded prospectively. Prophylactic PEG was inserted in 4 (6%) HPV+ and 3 (9%) HPV− patients. All had PEG removal within 5 months after RT. Grade 3 to 4 LT occurred in 11 (18%) HPV+ (3D-RT: 9; IMRT: 2) and 4 (12%) HPV− (3D-RT: 1; IMRT: 3) patients. Osteoradionecrosis (ORN) (any grade) occurred in 9 patients: 6/47 (13%) treated with conventional RT and 3/49 (6%) with IMRT ($P=.32$). The RT regimens used for the 9 patients with ORN were as follows: 51 Gy in 20 fractions over 4 weeks (51 Gy/20 fractions/4 weeks) (2.55 Gy/fraction): 3/18 (17%); 60 Gy/25 fractions/5 weeks (2.4 Gy/fraction): 4/53 (7.5%); 66 to 70 Gy/33 to 35 fractions/6 to 7 weeks (2 Gy/fraction): 2/23 (9%). No cases of severe xerostomia were recorded. The actuarial rate of grade 3 to 4 LT was similar between the HPV+ and HPV− cohorts (18% vs 15%, $P=.75$) (Table 1) and between IMRT and 3D-RT (11% [5-27] vs 18% [10-34], $P=.68$).

Clinical characteristics and outcomes of ipsilateral versus bilateral radiation therapy

The clinical characteristics and outcomes in HPV+ and HPV− patients treated with ipsilateral RT versus bilateral RT are shown in Table 2. Notably, patients receiving ipsilateral RT were highly selected with less extensive neck disease and lower N category. As expected, more chemotherapy was administered in the bilateral RT cohorts.

The median follow-up time was 5.0 years. LC and RC were similar between ipsilateral and bilateral RT for both HPV+ and HPV− disease. DC was lower in bilaterally treated patients in both HPV+ patients (92% vs 100%, $P=.02$) and HPV− patients (78% vs 100%, $P=.004$) (Table 2).

Neck failure without local failure occurred in 6 patients (4 HPV+ and 2 HPV−) from the bilateral RT cohort and 2 patients (1 HPV+ and 1 HPV−) from the ipsilateral RT cohort. There were 4 HPV+ patients with neck failure in the bilateral RT cohort; 3 (1 T1N2a, 2 T2N2b) underwent salvage ND. The remaining HPV+ (T1N2b) patient had a positive fine needle aspiration (FNA) from a persistent node 5.5 months after RT but refused ND. His persistent LN became fibrotic 1.5 years after RT without any intervention. The 2 HPV− (T2N2a and T2N2b) patients in the bilateral

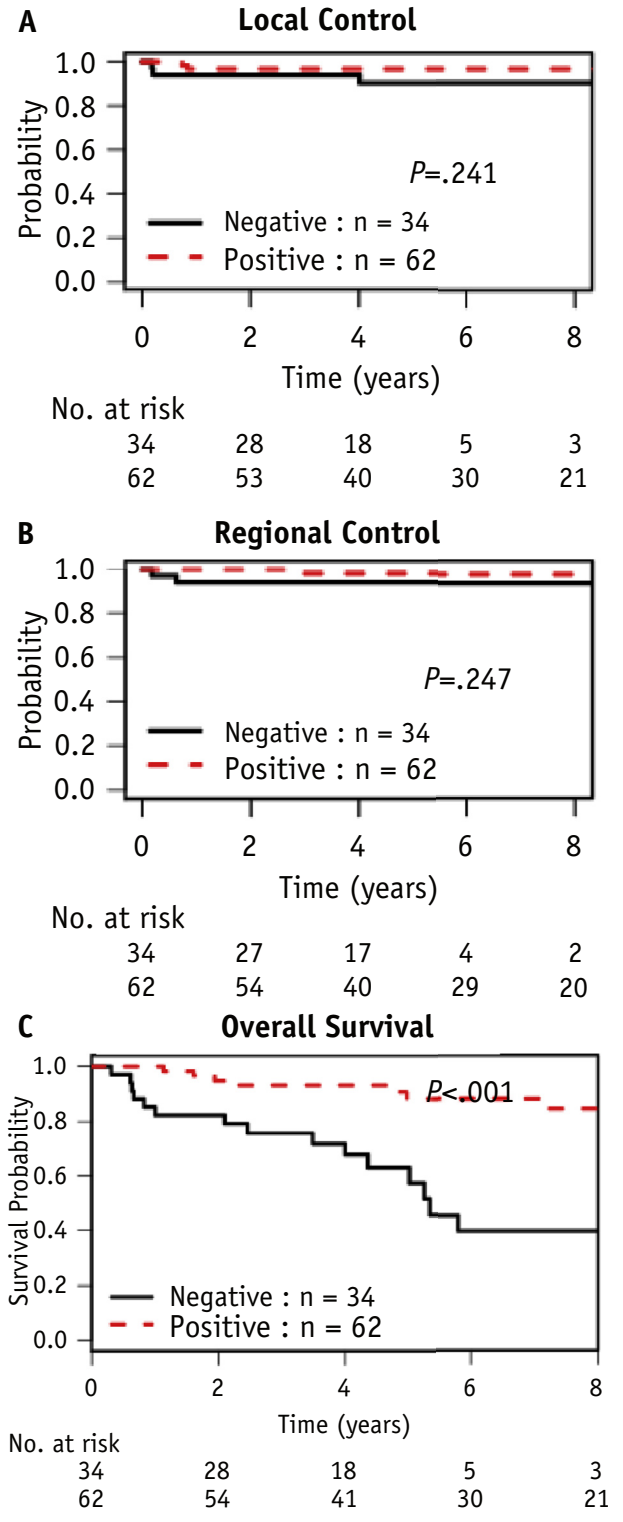

Fig. 2. (A) Local control, (B) regional control, and (C) overall survival in HPV+ and HPV− patients treated with ipsilateral radiation therapy.

RT cohort in whom RT to the neck was unsuccessful had persistent neck disease after RT, but both died shortly after.

Other than PEG dependency, grade 3 to 4 LT was similar in the bilateral RT and ipsilateral RT cohorts for both HPV+ and HPV− patients (Fig. 3). The actuarial rate of PEG dependency at 12 months was higher in the bilateral RT cohort (4.3% [2.3-7.2] vs 0%) (Table 2). For RT alone, PEG insertions were used in 15 of 144 (10%) bilateral patients versus 5/94 (5%) ipsilateral patients during RT, and they remained in situ 6 months later in 10 of 15 bilateral versus 0 of 5 ipsilateral patients.

Discussion

This single-institution study shows exemplary disease control and survival with ipsilateral RT for selected T1-T2N0-N2b tonsillar cancer patients treated in the HPV era. It is one of the largest series demonstrating excellent outcomes after ipsilateral RT in both HPV+ and HPV− OPC patients.

Overt LN(s) occur more often in HPV+ than in HPV− OPC patients. A small series (7, 8) reported that HPV+ OPC had more frequent bilateral/contralateral presenting nodal disease and questioned the safety of ipsilateral RT for HPV+ patients. A recent publication reported a marginally higher CNF in p16+/HPV+ patients treated with ipsilateral RT; although "significant extension" onto the soft palate or BOT was considered a contraindication to ipsilateral RT, a precise definition was not provided (14). By contrast, the current study observed equally high RC rates for HPV+ ipsilateral versus bilateral (98% vs 97%) RT. This supports the American College of Radiology (ACR) expert panel's suggestion that HPV status is not a deterrent to ipsilateral RT (24).

We emphasize that the exemplary outcomes observed in the current cohort were achieved by careful case selection according to the principles established from our initial publication 15 years ago (1). In the current study, ipsilateral RT was applied to only 24% of the study population, mostly N0-N2a and rarely N2b disease. This contrasts with 36% (228/642) of all tonsillar cases (all T and N categories) described previously (1). Although the reasons for these reduced rates are clearly multifactorial, they were usually not recorded prospectively, and therefore we are left to speculate. More stringent selection criteria derived from the historical cohort excluded T1-T2 tonsillar primaries with >1 cm soft palate or BOT extension, and more advanced T categories, from ipsilateral RT in the current cohort. Equivocal contralateral LN(s) also compelled physicians to use bilateral RT because of concerns about potential occult contralateral disease. The majority of patients in the current study had CT/MRI only for routine staging. It is conceivable that additional PET-CT or ultrasound-guided FNA could help further identify eligible patients for ipsilateral RT. IMRT may have also resulted in a more liberal use of bilateral treatment because of the perception that IMRT "spares" the contralateral parotid, thereby providing minimal potential gain from excluding the opposite neck. Finally, in the HPV era, clinicians may be more inclined to prescribe bilateral treatment because of putative concerns

Table 2 Clinical characteristics of ipsilateral versus bilateral RT in HPV+ and HPV− OPC

Covariate	HPV+ bilateral	HPV+ ipsilateral	*P* value	HPV− bilateral	HPV− ipsilateral	*P* value
Case no.	240	62		41	34	
Median FU, year (range)	4.9 (0.5-16.7)	6.9 (1.0-17.6)		4.5 (0.8-8.4)	4.3 (2.0-10.4)	
Age						
Median (range)	57 (31-82)	57 (42-85)	.990	66 (44-84)	69 (54-93)	.250
Sex			>.999			.470
Female	49 (20)	12 (19)		12 (29)	13 (38)	
Male	191 (80)	50 (81)		29 (71)	21 (62)	
Zubrod PS			**<.001**			.780
0	206 (86)	46 (74)		23 (56)	19 (56)	
1-2	32 (13)	8 (13)		17 (41)	13 (38)	
Unknown	2 (1)	8 (13)		1 (2)	2 (6)	
Smoking pack-years			.300			.210
Median (range)	10 (0-90)	18 (0-135)		30 (0-80)	40 (0-90)	
Smoking history			.057			.510
Current	52 (22)	13 (21)		20 (49)	19 (56)	
Former	103 (43)	36 (58)		17 (41)	14 (41)	
None	85 (35)	13 (21)		4 (10)	1 (3)	
Excessive alcohol history			.310			
Yes	85 (35)	16 (26)		29 (71)	20 (59)	
No	149 (62)	44 (71)		10 (24)	11 (31)	
Unknown	6 (2)	2 (3)		2 (5)	3 (9)	
T category			**.030**			.550
T1	90 (38)	33 (53)		6 (15)	7 (21)	
T2	150 (62)	29 (47)		35 (85)	27 (79)	
N category			**<.001**			**<.001**
N0	13 (5)	24 (39)		10 (24)	28 (82)	
N1	28 (12)	21 (34)		5 (12)	4 (12)	
N2a	29 (12)	10 (16)		3 (7)	1 (3)	
N2b	170 (71)	7 (11)		23 (56)	1 (3)	
Treatment modality			**<.001**			**<.001**
RT alone	114 (48)	60 (97)		30 (73)	34 (100)	
Chemo-RT	126 (52)	2 (3)		11 (27)	0	
RT technique			**<.001**			**.026**
3D conformal	35 (15)	32 (52)		8 (20)	15 (44)	
IMRT	205 (85)	30 (48)		33 (80)	19 (56)	
Feeding tube insertion	156 (65)	4 (6)	**<.001**	18 (44)	3 (9)	**<.001**
Feeding tube at 6 mo	7.5% (5-11)	0	**<.001**	24% (12-38)	0	**<.001**
Vital status						
Alive	208 (87)	53 (85)		20 (49)	18 (53)	
Deceased	32 (13)	9 (15)		21 (51)	16 (47)	
Local failure	5 (2)	2 (3)		8 (20)	3 (9)	
Regional failure	10 (4)	1 (2)*		7 (17)	2 (6)†	
Distant failure	18 (8)	0		9 (22)	0	
5-year outcomes						
Overall survival	87% (83-92)	89% (80-98)	.550	48% (34-96)	63% (47-84)	.270
Local control	98% (96-99)	97% (87-99)	.650	80% (63-89)	90% (70-97)	.190
Regional control	97% (93-98)	98% (86-100)	.270	83% (66-91)	94% (77-98)	.140
Distant control	92% (87-95)	100%	**.022**	78% (60-88)	100%	**.004**
Grade 3-4 LT	12% (9-18)	17% (9-32)	.830	22% (11-47)	15% (6-39)	.360
PEG dependency (1 y)	2.8% (1.2-5.5)	0%		13% (5-26)	0	
Type of grade 3-4 LT	**34**	**11**		**7**	**4**	
Bone	15	6		3	3	
Larynx	0	1		0	0	
Dysphagia	3	2		2	1	
Soft tissue fibrosis	5	2		1	0	
Other	11	0		1	0	

Abbreviations: FU = follow-up; HPV− = human papillomavirus negative; HPV+ = human papillomavirus positive; LT = late toxicity; OPC = oropharyngeal cancer; PEG = percutaneous endoscopic gastrostomy tube; RT = radiation therapy; Zubrod PS = Zubrod performance scale.
Bold *P* value: statistical significance.

* One T2N1 HPV+ right tonsillar cancer patient had a single left level 3 node 2.5 years after radiation therapy, which was salvaged with neck dissection. This patient remained disease free 12 years after neck failure.

† One T2N1 HPV− left tonsillar cancer patient had 3 right neck lymph nodes (levels 2, 3, and 5), which was salvaged with neck dissection followed by reirradiation. This patient remained disease free 8 years after neck failure.

that HPV+ tonsillar cancer has a higher risk of occult contralateral disease.

Ongoing debate exists regarding the selection criteria for ipsilateral RT. An ACR expert panel did not recommend ipsilateral RT for tonsil primaries with >1 cm invasion into soft palate or BOT, nor for N2b or greater neck disease (24). Although we maintain that ≤1 cm superficial involvement of soft palate or BOT is safe, suspicion of

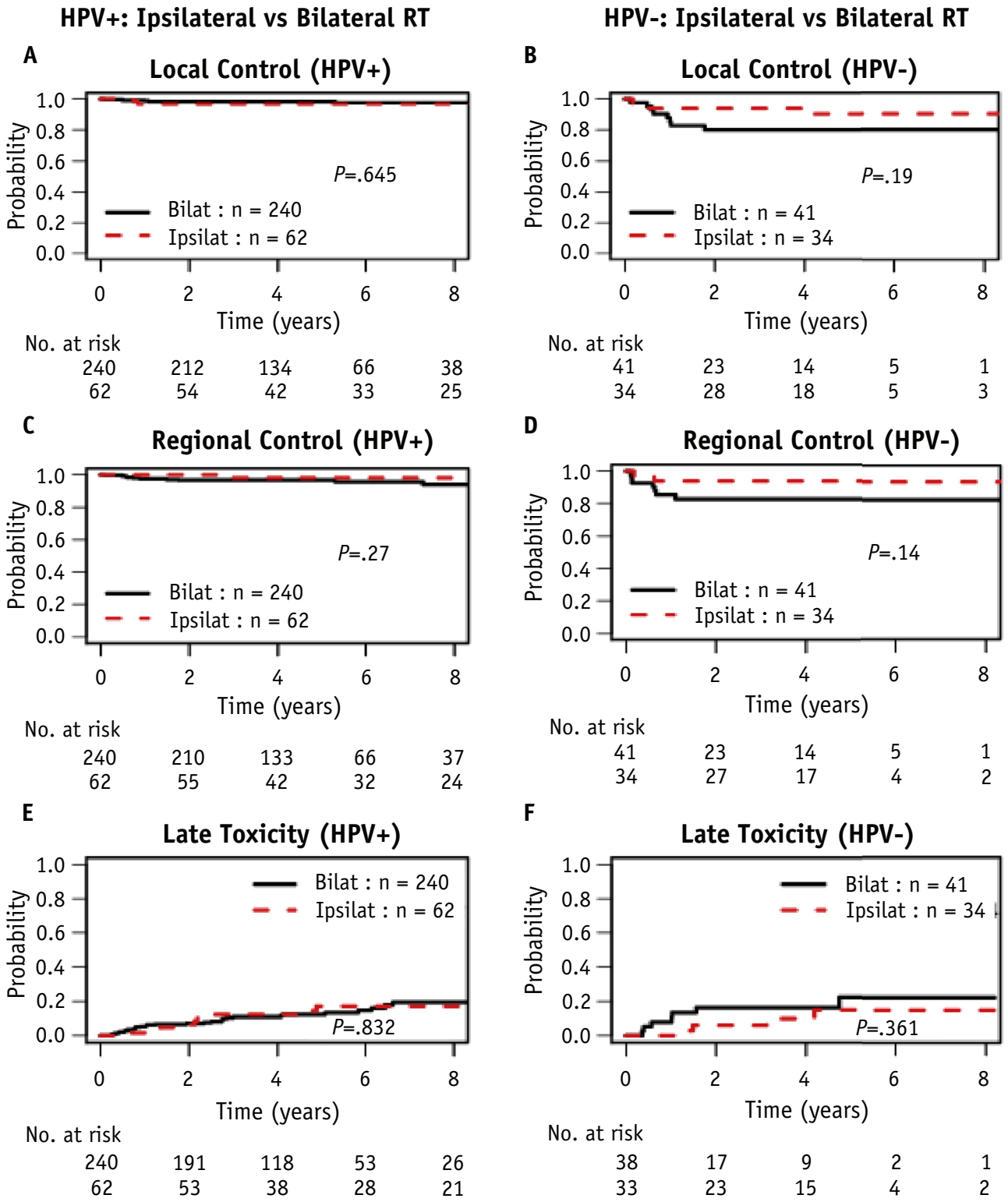

Fig. 3. (A, B) Local control, (C, D) regional control, and (E, F) grade 3 to 4 late toxicity in HPV+ and HPV− patients treated with ipsilateral versus bilateral radiation therapy.

Table 3 Selected recent series on outcomes of ipsilateral RT for tonsillar cancer

Study, y	Ipsilateral RT cohort	Contralateral neck failure
Current study, 2016	1999-2014: n=96 T1: 40 T2: 56 HPV+: 62; HPV−: 34 Median FU: 6 years	N=2/96 (2.1%) N0: 0/52 N1: 2/25 N2a: 0/11 N2b: 0/8
Kennedy et al, 2016 (25)	1984-2012: n=76 T1: 41 T2: 35 HPV status: NA Median FU: 7.1 years	N=1/76 (1.3%) N0: 0/27 N1: 0/15 N2a: 0/8 N2b: 1/26 (salvaged)
Ye et al, 2015 (14)	2001-2007: n=53 (HPV+; 17 HPV−) T1: 22 T2: 28 T3: 3 Median FU: 5.7 years	N=4/53 HPV+ (7.5%) (no detail on HPV−) N0: 0/15 N1: 3/18 N2a: 1/7 N2b: 0/11 N3: 0/2
Dan et al, 2015 (11)	2003-2014: n=61 T1: 29 T2: 30 T3: 2 Median FU: 3.1 years	N=1/61 (1.6%) N0: 0/0 N1: 0/15 N2a: 0/14 N2b: 1/31 (salvaged) N3: 0/1
Liu et al, 2014 (13)	1990-2002: n=58 (HPV+ 9; HPV− 6) T1: 9 T2: 30 T3: 17 T4:1 Tx: 1 Median FU: 8.5 years	N=0/58 N0: 0/25 N1: 0/14 N2a: 0/10 N2b: 0/4 N3: 0/5
Lynch et al, 2014 (28)	1995-2011: n=136 T1: 57 T2: 74 T3: 5 Median FU: 4.2 years	N=8/136 (5.9%) N0: 1/28 N1: 1/20 N2a: 0/31 N2b: 6/55 (all salvaged) N3: 0/2
Koo et al, 2013 (27)	2003-2011 N=20 T1: 7 T2: 12 T3: 1 Median FU: 5.3 years	N=0/20 N0: 0/2 N1: 0/8 N2a: 0/2 N2b: 0/8
Al-Mamgani et al, 2013 (26)	2000-2011: n=185 T1: 50 T2: 122 T3: 13 Median FU: 4.1 years	N=2/185 (1.1%) N0: 1/92 N1: 0/43 N2a: 0/18 N2b: 1/32 (salvaged)
Chronowski et al, 2011 (12)	1970-2007: n=102 Tx: 17 T1: 52 T2: 33 Median FU: 3.2 years	N=2/102 (1.9%) N0: 2/33 N1: 0/23 N2a: 0/21 N2b: 0/22 Nx: 0/3
Rusthoven et al, 2009 (29)	2003-2007: n=20 T1: 11 T2: 7 T3: 2 Median FU: 1.6 years	N=0/20 N0: 0 N1: 0/4 N2a: 0/3 N2b: 0/13

(*continued on next page*)

Table 3 (*continued*)

Study, y	Ipsilateral RT cohort	Contralateral neck failure
Total	T1: 318 T2: 427 T3: 43	N = 20/807 (2.5%) N0: 2/274 (0.7%) N1: 6/185 (3.2%) N2a: 1/125 (1.0%) N2b: 9/210 (4.8%) N3: 0/10 (0%) Nx: 0/3

Abbreviations: FU = follow-up; HPV = human papillomavirus; NA = not available.

deeper invasion should be approached cautiously (1). A rational contention is possible for ipsilateral RT for N2b if patients can be closely followed up and contralateral neck failure, if any, is identified early and is amenable to surgical salvage. The aggregated frequency of CNF by N category reported in selected recent published series (11-14, 25-29) showed that only 9 (4.3%) of 210 patients with N2b disease treated with ipsilateral RT experienced contralateral failure and is similar to N1 disease (6/185: 3.2%) ($P = .59$) (Table 3). All patients with N2b disease who experienced contralateral neck failure received salvage therapy. Interestingly, none of 11 patients with N3 disease experienced failure on the contralateral neck after ipsilateral RT.

Whether ipsilateral RT is suitable for N2b disease is especially relevant in the HPV era because more than one-third of HPV+ patients and about a quarter of HPV− patients present with N2b disease (30). We acknowledge that the N2b ipsilateral RT cases reported in the literature are highly selected. The N2b categories can span a range from 2 low-volume nodes confined to 1 level up to multiple bulky nodes involving the entire ipsilateral neck. It is clear that the N2b category itself may be too broad to solely define eligibility for ipsilateral RT. Future investigations could potentially focus on more refined subgroups of N2b disease. The NRG-HN002 HPV+ deintensification trial (NCT02254278) will provide some data on this important issue because ipsilateral RT is an option for N2b tonsil primaries without extra-capsular extension confined to ipsilateral level II. If the trial indicates that ipsilateral RT is safe for such HPV+ N2b disease, it might also infer suitability to HPV− patients, given that many studies have shown a similar topographic nodal distribution (10).

The advantage of ipsilateral RT lies in its potential for reduced toxicity. Saliva preservation has been shown to be more likely with ipsilateral RT (31). Sparing contralateral normal tissue could also be beneficial to reduce dose to the larynx, pharyngeal constrictors, mandible, oral cavity, and other structures and consequently improve swallowing function. In this study, only 7 of 96 patients (2 CRT; 5 RT alone) received prophylactic PEG insertions, and all were removed within 5 months after RT. By contrast, 10 of 15 patients receiving bilateral RT alone had PEGs in situ 6 months after RT. Avoiding radiation exposure to contralateral normal tissue would also be important to reserve radiation as a treatment option in the event that a second primary emerges on the contralateral side, inasmuch as many of these patients are smokers and remain at risk of a smoking-related second primary. We acknowledge that severe LTs still exist in the ipsilateral RT cohort. The main toxicity was ORN of mandible, occurring in 9 patients (13% in conventional and 6% in IMRT). The incidence of ORN was reported to be dose dependent (32). The relatively higher ORN rates in the current study may be related to a high proportion of hypofractionation RT regimens (74%) used in our institution. In the current study, 7 of 9 ORN patients were treated with 2.4 to 2.55 Gy/fraction, but we were unable to obtain mandibular doses for individual patients. Careful planning to minimize the volume of mandible receiving high doses combined with image guidance to maximize mandibular sparing could further reduce the ORN risk.

One of the pitfalls of ipsilateral RT described in our previous publication was unsatisfactory LC, possibly because of compromised tumor coverage related to limited imaging quality, absence of treatment guidelines for target coverage, lack of peer-reviewed quality assurance, and technical restrictions with conventional RT. The LC rates were significantly improved with adequate target coverage after the implementation of written policies in the latter period of the original study. The LC rates in the current study are now even higher. Besides improved dose distributions, the higher LC rate is also attributable to better target delineation, to staging migration associated with improved imaging quality in the present cohort, and to refinement of peer-reviewed quality assurance for target delineation and dose distribution.

It is concluded that this study shows high disease control rates with ipsilateral radiation in selected T1-T2N0-N2b tonsillar cancer patients regardless of HPV status. Our data support the continued use of ipsilateral radiation in the current HPV era for selected T1-T2N0-N2a, and possibly T1-T2N2b, tonsillar cancer when one also considers other evidence in the literature. The principles of case selection and adherence to guidelines for the use of this approach remain relevant. Conservatively, ≤ 1 cm superficial involvement of the soft palate or BOT is safe, but suspicion of deeper invasion should be approached cautiously. More sensitive measures to ascertain the equivocal contralateral LN(s) could improve selection. Prospective clinical trials addressing the suitability of ipsilateral radiation for

lateralized tonsillar cancer with T1-T2N0-N2b disease would further confirm the safety and efficacy of this approach.

References

1. O'Sullivan B, et al. The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. *Int J Radiat Oncol Biol Phys* 2001;51:332-343.
2. Gelinas M, Fletcher GH. Incidence and causes of local failure of irradiation in squamous cell carcinoma of the faucial arch, tonsillar fossa and base of the tongue. *Radiology* 1973;108:383-387.
3. Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: Results from TROG 02.02. *J Clin Oncol* 2010;28:2996-3001.
4. Habbous S, Chu KP, Qiu X, et al. The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000 to 2010 at a comprehensive cancer centre. *Cancer Epidemiol* 2013;37:820-829.
5. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol* 2013;31:543-550.
6. Olzowy B, Tsalemchuk Y, Schotten KJ, et al. Frequency of bilateral cervical metastases in oropharyngeal squamous cell carcinoma: A retrospective analysis of 352 cases after bilateral neck dissection. *Head Neck* 2011;33:239-243.
7. Shoushtari AN, Meeneghan M, Trehame GC, et al. Clinical nodal staging of T1-2 tonsillar squamous cell carcinoma stratified by p16 status and implications for ipsilateral neck irradiation. *Cancer J* 2010;16:284-287.
8. Chepeha D, Eisbruch A. Commentary: Clinical nodal staging of human papillomavirus-related oropharyngeal cancer. *Cancer J* 2010;16:283.
9. Galloway TJ, Lango MN, Burtness B, et al. Unilateral neck therapy in the human papillomavirus ERA: Accepted regional spread patterns. *Head Neck* 2013;35:160-164.
10. Amsbaugh MJ, Yusuf M, Cash E, et al. Distribution of cervical lymph node metastases from squamous cell carcinoma of the oropharynx in the era of risk stratification using human papillomavirus and smoking status. *Int J Radiat Oncol Biol Phys* 2016;96:349-353.
11. Dan TD, Raben D, Schneider CJ, et al. Freedom from local and regional failure of contralateral neck with ipsilateral neck radiotherapy for node-positive tonsil cancer: Updated results of an institutional clinical management approach. *Oral Oncol* 2015;51:616-621.
12. Chronowski GM, Garden AS, Morrison WH, et al. Unilateral radiotherapy for the treatment of tonsil cancer. *Int J Radiat Oncol Biol Phys* 2012;83:204-209.
13. Liu C, Dutu G, Peters LJ, et al. Tonsillar cancer: The Peter MacCallum experience with unilateral and bilateral irradiation. *Head Neck* 2014;36:317-322.
14. Ye A, Bradley KL, Kader H, et al. Patterns of relapse in squamous cell carcinoma of the tonsil: Unilateral vs. bilateral radiation in the HPV-era. *Cureus* 2015;7:e322.
15. Wong K, Huang SH, O'Sullivan B, et al. Point-of-care outcome assessment in the cancer clinic: Audit of data quality. *Radiother Oncol* 2010;95:339-343.
16. Shi W, Kato H, Perez-Ordonez B, et al. Comparative prognostic value of HPV16 E6 mRNA compared with in situ hybridization for human oropharyngeal squamous carcinoma. *J Clin Oncol* 2009;27:6213-6221.
17. El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: A guide for interpretative relevance and consistency. *Head Neck* 2012;34:459-461.
18. Edge S, Byrd DR, Compton CC, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer New York Dordrecht Heidelberg London; 2011.
19. Sobin L, Gospodarowicz M, Wittekind C. International Union Against Cancer: TNM Classification of Malignant Tumours. 7th ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2010.
20. Sobin L, Brierley JD, Gospodarowicz, et al. Principles of cancer staging. In: O'Sullivan B, Brierley JD, editors. UICC Manual of Clinical Oncology. 9th ed. Chichester, West Sussex, UK: John Wiley & Sons; 2015. p. 34-39.
21. Huang SH, Perez-Ordonez B, Weinreb I, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral Oncol* 2013;49:79-85.
22. Huang SH, et al. Patterns of failure and histopathologic outcome predictors following definitive radiotherapy and planned neck dissection with residual disease. *Head Neck* 2012;34:913-922.
23. Huang SH, et al. Temporal nodal regression and regional control after primary radiation therapy for N2-N3 head-and-neck cancer stratified by HPV status. *Int J Radiat Oncol Biol Phys* 2013;87:1078-1085.
24. Expert Panel on Radiation Oncology—Head & Neck Cancer, Yeung AR, Garg MK, Lawson J, et al. ACR appropriateness criteria® ipsilateral radiation for squamous cell carcinoma of the tonsil. *Head Neck* 2012;34:613-616.
25. Kennedy WR, Herman MP, Deraniyagala RL, et al. Ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *Eur Arch Otorhinolaryngol* 2016;273:2151-2156.
26. Al-Mamgani A, van Rooij P, Fransen D, et al. Unilateral neck irradiation for well-lateralized oropharyngeal cancer. *Radiother Oncol* 2013;106:69-73.
27. Koo TR, Wu HG. Long-term results of ipsilateral radiotherapy for tonsil cancer. *Radiat Oncol J* 2013;31:66-71.
28. Lynch J, Lal P, Schick U, et al. Multiple cervical lymph node involvement and extra-capsular extension predict for contralateral nodal recurrence after ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *Oral Oncol* 2014;50:901-906.
29. Rusthoven KE, Raben D, Schneider C, et al. Freedom from local and regional failure of contralateral neck with ipsilateral neck radiotherapy for node-positive tonsil cancer: Results of a prospective management approach. *Int J Radiat Oncol Biol Phys* 2009;74:1365-1370.
30. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): A multicentre cohort study. *Lancet Oncol* 2016;17:440-451.
31. Jensen K, Overgaard M, Grau C. Morbidity after ipsilateral radiotherapy for oropharyngeal cancer. *Radiother Oncol* 2007;85:90-97.
32. Tsai CJ, Hofstede TM, Sturgis EM, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2013;85:415-420.