Original Article

Comparison of Unilateral Versus Bilateral Intensity-Modulated Radiotherapy for Surgically Treated Squamous Cell Carcinoma of the Palatine Tonsil

Re-I Chin, BA [1]*; Yuan James Rao, MD [1]*; Michael Y. Hwang, MD[2]; Christopher R. Spencer, MD[1]; Michael Pierro, MD[3]; Todd DeWees, PhD[1]; Pranav Patel, MD[4]; Parul Sinha, MBBS[5]; Hiram A. Gay, MD[1]; Mackenzie Daly, MD[1]; Bruce H. Haughey, MBChB[6]; Brian Nussenbaum, MD[5]; Douglas R. Adkins, MD[7]; James S. Lewis Jr, MD[8]; and Wade L. Thorstad, MD[1]

BACKGROUND: The authors hypothesized that unilateral intensity-modulated radiotherapy (IMRT) would decrease toxicity compared with bilateral IMRT for patients with lateralized palatine tonsillar cancer and a neck classification of N0 to N2b, with similar oncological outcomes. **METHODS:** A total of 154 patients were treated with postoperative IMRT from 1997 through 2013. Data were collected prospectively from 2005 to 2013 and retrospectively collected before 2005. Of those patients with lateralized primary and N0 to N2b disease, 48 received unilateral IMRT (group 1) and 59 received bilateral IMRT (group 2); a total of 47 patients had nonlateralized primary or N2c to N3 disease and received bilateral IMRT (group 3). **RESULTS:** The median follow-up was 5.5 years. The 5-year locoregional control rates were similar in group 1, group 2, and group 3 (100%, 96%, and 94%, respectively; pooled comparison: $P = .39$ and group 1 vs group 2 comparison: $P = .19$). The 5-year overall survival rates were similar in group 1, group 2, and group 3 (85%, 79%, and 76%, respectively; pooled comparison: $P = .60$ and group 1 vs group 2 comparison: $P = .25$). There were no contralateral neck recurrences noted among unilaterally treated patients. Unilateral IMRT reduced acute toxicity and improved patient-reported quality of life compared with bilateral IMRT. **CONCLUSIONS:** Unilateral IMRT appears to reduce acute toxicity and achieves oncological outcomes similar to those of bilateral IMRT in selected patients with lateralized palatine tonsillar cancer with a neck classification of N0 to N2b. ***Cancer* 2017;123:4594-607.** © *2017 American Cancer Society.*

KEYWORDS: head and neck, intensity-modulated radiotherapy (IMRT), oropharynx, quality of life, squamous cell carcinoma, tonsillar cancer, unilateral radiation.

INTRODUCTION

The development of radiotherapy (RT) volumes for patients with head and neck cancer is a balance between maximizing cure and minimizing treatment-related side effects. In the 2-dimensional era, cancer of the tonsil usually was treated with RT to both sides of the neck and the oropharynx.[1] With advances in 3-dimensional conformal and intensity-modulated RT (IMRT), it became possible to selectively reduce the treatment fields.[2] Unilateral neck RT has been shown to decrease toxicity, including xerostomia, dysphagia, fibrosis, and edema, compared with bilateral RT.[3]

To the best of our knowledge, groups from British Columbia[4] and Princess Margaret Hospital in Toronto[5] were among the first to report the outcomes of unilateral neck RT in patients with lateralized palatine tonsillar cancer using 2-dimensional or 3-dimensional conformal techniques. The majority of patients in these series had T1-2/N0-1 disease. Locoregional control (LRC) rates of 75% to 77% were reported. A decade later, reports from The University of Texas MD Anderson Cancer Center (MDACC)[6] and Rotterdam[7] presented the outcomes of unilateral neck RT with IMRT, again with excellent results. It is interesting to note that the study from MDACC reported local control rates in the primary site and ipsilateral neck of 100%, and no contralateral recurrences were noted among patients with multiple

Corresponding author: Wade L. Thorstad, MD, Department of Radiation Oncology, Washington University School of Medicine, 4921 Parkview Pl, Campus Box 8224, St. Louis, MO 63110; thorstad@wustl.edu

[1]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri; [2]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [3]Department of Internal Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; [4]Department of Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [5]Division of Head and Neck Surgery, Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri; [6]Head and Neck Surgery, Florida Hospital Celebration Health, Celebration, Florida; [7]Division of Hematology and Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri; [8]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee

*The first 2 authors contributed equally to this article.

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ipsilateral lymph nodes (N2b classification). In contrast, another group from the Netherlands[8] reported a contralateral disease recurrence rate of 6% after unilateral RT in patients with N0 to N2b disease.

Significant controversy remains regarding the use of unilateral RT in some subgroups of patients with palatine tonsillar cancer, particularly in those with N2b neck disease. The 2011 American College of Radiology (ACR) Appropriateness Criteria[9] recommended bilateral RT for this subgroup of patients, but some authors challenged this recommendation.[10,11] In light of this controversy, we hypothesized that the location of the primary tumor was more important than the lymph node stage of the ipsilateral neck and the presence of extracapsular extension (ECE). The study institution initiated an IMRT program for patients with tonsillar cancer in 1997, has been staging patients using [^{18}F]fludeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) since 2000, and has prospectively collected data for the majority of patients. Since 2007, we have routinely treated patients with lateralized tonsillar cancer (>1 cm from midline) with unilateral RT. In this report, we present the clinical outcomes of patients with lateralized palatine tonsillar cancer who underwent surgical resection (transoral laser microsurgery/transoral robotic surgery) and subsequent adjuvant therapy with unilateral or bilateral IMRT with an emphasis on patients with N2b disease, treatment toxicity, and quality of life (QOL).

METHODS AND MATERIALS

Patient and Tumor Characteristics

From January 1997 through January 2013, a total of 154 patients with squamous cell carcinoma of the palatine tonsil received postoperative IMRT as part of curative-intent treatment at Washington University School of Medicine. Data were collected retrospectively for patients treated from 1997 through 2004 and was prospectively collected from 2005 through 2013. The study was approved by the Institutional Review Board.

Patients were staged according to the seventh edition of the American Joint Committee on Cancer staging manual.[12] Patients were evaluated by a multidisciplinary tumor board involving otolaryngology, radiation oncology, medical oncology, pathology, and radiology. Radiologic staging included neck CT in all patients and FDG-PET/CT was used routinely after 2000. p16INK4A (p16) staining was used as a surrogate marker for human papillomavirus (HPV) status.[13-17] Positive p16 staining by immunohistochemistry was defined as nuclear and cytoplasmic p16 staining of > 75% of the tumor cells.[18,19]

In September 2007, we began to routinely assign patients with lateralized primary tumors and lymph node classification N0 to N2b to receive unilateral neck IMRT. Tumors were classified as lateralized if they measured >1 cm from the midline.[10] This practice eventually became our standard institutional policy for these patients. Before September 2007, approximately 85% of patients (51 of 60 patients) who were eligible for unilateral IMRT according to the current policy received bilateral treatment. This was according to the standard of care at that time, which recommended bilateral treatment for patients with early-stage tonsillar cancer. After September 2007, approximately 89% of patients (42 of 47 patients) who were eligible for unilateral IMRT according to the policy received unilateral treatment. Over the duration of the study, patients with nonlateralized primary tumors or N2c to N3 disease received bilateral neck IMRT.

Patients were classified into 3 groups according to the treatment strategy. Group 1 (48 patients) included patients who had lateralized primary tumors and N0 to N2b disease and received unilateral neck IMRT. Group 2 (59 patients) included patients who had lateralized primary tumors and N0 to N2b disease and received bilateral neck IMRT. Patients in group 2 typically were treated before 2007, as discussed above. Group 3 patients (47 patients) had nonlateralized tumors or N2c to N3 lymph node disease and were treated with bilateral neck IMRT.

Surgery

All patients underwent tonsillectomy. The surgical technique was open tonsillectomy in 3.7% of patients and transoral in 96.3% of patients. Specifically, resection was transoral laser microsurgery in 51.4% of patients, transoral bovie resection in 23.3% of patients, transoral robotic surgery in 1.9% of patients, and unknown transoral surgical technique in 19.6% of patients. The patients treated with an unknown transoral surgical technique underwent tonsillectomy at outside institutions, but the original surgical notes were no longer available for review. Ipsilateral neck dissection was performed in 78% of patients (120 of 154 patients), and bilateral neck dissection was performed in 20% of patients (30 of 154 patients). Neck dissection typically was performed in lymph node levels II to IV. Bilateral neck dissection was indicated for an FDG-avid contralateral lymph node on PET or CT evidence of contralateral lymph node metastasis (>1 cm on short axis or central necrosis) if PET was not performed.

Radiotherapy

Adjuvant RT by IMRT was delivered to all patients at a median of 7 weeks after surgery. Macroscopic (gross) tumor volumes (GTVs) were contoured based on physical examination, nasopharyngoscopic examination, and FDG-PET/CT, as well as surgical and pathology reports. CT simulation scans were fused with preoperative CT and/or FDG-PET/CT scans. Any disease extending into the pharyngeal lumen that was surgically removed was manually removed from the primary tumor volume. The high-risk clinical target volume was defined as the primary tumor (pGTV + 1.5-2.0 cm) and positive lymph nodes (nGTV + 0.5-1.0 cm). The elective clinical target volume was defined as the uninvolved elective neck. These volumes were expanded by 0.5 cm to obtain a planning target volume. The dose to the tumor bed without residual mass was 66 grays (Gy) or 60 Gy in 33 or 30 fractions of 2 Gy each over the course of 7 or 6 weeks. Dose painting was used in the elective neck to 54 Gy or 52 Gy in fractions of 1.63 Gy or 1.73 Gy per day.

The contralateral neck routinely was spared in patients treated after 2007 as discussed above (group 1) for patients with lateralized tonsillar tumors and N0 to N2b disease. Before 2007, these patients were routinely treated with bilateral RT (group 2). Unilateral RT was permitted for patients with limited base-of-tongue or soft palate extension as long as the tonsil primary extension was >1 cm from the midline. Lymph node ECE status was not a factor in the decision to use unilateral or bilateral RT. Patients with tonsillar tumors extending within ≤1 cm from the midline or those with lymph node N2c to N3 disease received bilateral neck treatment (group 3). IMRT dose constraints and optimization parameters are shown in Supporting Information Table 1.

Chemotherapy

Concurrent chemotherapy was delivered to patients with tumors with high-risk features defined as ECE and/or positive surgical margins. A close (<0.5 cm) margin in itself was not an indication for chemotherapy. Chemotherapy was not routinely delivered until the European Organization for Research and Treatment of Cancer (EORTC) 22931 and Radiation Therapy Oncology Group (RTOG) 9501 trials validated the role of adjuvant chemoradiation in 2004.[20,21] Concurrent chemotherapy was delivered in 49% of patients (76 of 154 patients), and included cisplatin (67 of 76 patients); carboplatin and paclitaxel (7 of 76 patients); docetaxel, cisplatin, and 5-fluorouracil (1 of 76 patients); and cetuximab (1 of 76 patients).

Toxicity

Toxicity during treatment was assessed retrospectively at the completion of RT using the standard Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).[22] Factors assessed included mucositis, dermatitis, xerostomia, dysphagia, weight loss, rash, nausea, and vomiting. Reactive gastrostomy tubes (G-tubes) were placed for weight loss of >10% during or after RT. G-tubes were removed after RT if the patient was fed only by mouth and did not experience weight loss. Patients were recorded as having a long-term G-tube if it was present at last follow-up.

Quality of Life

Patient-reported Outcomes QOL (PROQOL) was assessed prospectively using the M.D. Anderson Dysphagia Inventory (MDADI)[23] and the University of Michigan Xerostomia Questionnaire (XQ) starting in June 2007.[24] These questionnaires were mailed to patients who were treated prior to the time of prospective data collection. Data were collected before RT, during RT, and at every follow-up.

Follow-Up

Patients underwent a physical examination and neck CT at 6 to 8 weeks after RT. Starting in 2000, patients also received FDG-PET/CT at 10 to 16 weeks after RT. Subsequently, patients were evaluated every 3 months to 4 months with additional imaging if indicated. After 4 years, examinations occurred annually. Chest CT or x-ray was performed annually.

Statistical Analysis

The primary endpoint of the current study was LRC and the secondary endpoints were overall survival (OS) and acute treatment toxicity and patient-reported QOL. Patient and tumor characteristics, patterns of disease recurrence, and toxicity profiles were compared using the Fisher exact test, chi-square test, and logistic regression. All events were measured from the date of diagnosis. LRC included freedom from disease recurrence in the tonsil or neck lymph nodes with censoring at the time of death or last follow-up. OS was calculated until death and censored at the time of last follow-up. Kaplan-Meier analysis was performed to compute the estimates for LRC and OS and the log-rank test was used for comparison. A multivariate Cox proportional hazards model was created using a forward stepwise method ($P = .05$ for entry and $P = .05$ for removal). Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported. Repeated

measures analysis was used to compare longitudinal PROQOL. Statistical analyses were reported for the overall group of patients (groups 1, 2, and 3) as well as the subset of patients who were eligible for unilateral treatment (groups 1 and 2). Toxicity assessments included all patients with available toxicity or PROQOL endpoints. Multivariate logistic regression was performed to estimate the odds ratios (ORs) of factors associated with reactive and long-term G-tube use using a forward stepwise method ($P = .05$ for entry and $P = .05$ for removal). A P value $< .05$ was considered statistically significant and all P values were 2-sided.

RESULTS

Patient and Tumor Characteristics

There were 48 patients in group 1, 59 patients in group 2, and 47 patients in group 3. The overall median follow-up was 5.5 years (range, 0.5-17.3 years). The median follow-up was 4.2 years (range, 0.7-15.7 years) in group 1, 7.8 years (range, 0.3-17.3 years) in group 2, and 5.4 years (range, 0.7-13.7 years) in group 3. The median follow-up was 4.3 years (range, 0.3-7.3 years) for the 28 patients with N2b disease who received ipsilateral RT. Approximately 34% of patients (53 of 154 patients) were classified with pT1 disease, 39% (60 of 154 patients) were classified with pT2 disease, 17% (26 of 154 patients) were classified with pT3 disease, 7% (11 of 154 patients) were classified with pT4a disease, 1% (1 of 154 patients) were classified with pT4b disease, and 2% (3 of 154 patients) were classified with pTX disease. Approximately 5% of patients (8 of 154 patients) were classified with pN0 disease, 10% (15 of 154 patients) were classified with pN1 disease, 17% (26 of 154 patients) were classified with pN2a disease, 55% (84 of 154 patients) were classified with pN2b disease, 8% (12 of 154 patients) were classified with pN2c disease, and 6% (9 of 154 patients) were classified with pN3 disease. Approximately 76% of patients (117 of 154 patients) had lateralized tumors. Approximately 71% of patients (110 of 154 patients) were p16 positive, 8% (13 of 154 patients) were p16 negative, and 20% (31 of 154 patients) had unknown p16 status. This breakdown was similar in the 28 patients with N2b disease who received ipsilateral RT, among whom 79% (22 of 28 patients) were p16 positive, 4% (1 of 28 patients) were p16 negative, and 18% (5 of 28 patients) had unknown p16 status. Invasion of the base of the tongue or soft palate was present in 29% and 15%, respectively, of patients in group 1. Lymph node ECE was present in 37 of 48 patients (77%) who received unilateral RT. Additional patient and tumor characteristics are shown in Table 1 and Supporting Information Table 2.

Staging Imaging

All patients received neck CT and 71% (109 of 154 patients) received staging FDG-PET/CT. FDG-PET/CT was used in 69% of patients in group 1 (33 of 48 patients), 68% of patients in group 2 (40 of 59 patients), and 77% of patients in group 3 (36 of 47 patients).

Locoregional Control

Approximately 3% of patients (5 of 154 patients) developed locoregional recurrence. The median time to locoregional recurrence was 0.6 years (range, 0.2-2.1 years). The 1-year and 5-year LRC rates among all patients were 97% and 97%, respectively. The 1-year and 5-year LRC rates were 100% and 100%, respectively, for group 1; 98% and 96%, respectively, for group 2; and 94% and 94%, respectively, for group 3. The LRC was not found to be significantly different between unilateral and bilateral RT in the overall group of patients ($P = .39$) and the patients who qualified for unilateral RT under the current policy of the study institution (groups 1 and 2) ($P = .19$), as seen in Figure 1A. On multivariate analysis, older age at the time of cancer diagnosis (HR, 1.19; 95% CI, 1.01-1.42 [$P = .048$]) was the only factor found to be associated with LRC (Table 2). Older age at diagnosis (HR, 1.15; 95% CI, 1.02-1.29 [$P = .02$]) also was the only factor found to be associated with LRC in the subset of patients eligible for unilateral IMRT (groups 1 and 2), as seen in Supporting Information Table 3.

Distant Metastasis

Approximately 8% of patients (12 of 154 patients) developed distant metastasis. The median time to the identification of distant metastasis was 1 year (range, 0.2-2.7 years). The 1-year and 5-year actuarial rates of freedom from distant metastasis were 93% and 91%, respectively, for group 1; 96% and 91%, respectively, for group 2; and 98% and 89%, respectively, for group 3. The freedom from distant metastasis rate was not found to be significantly different between unilateral and bilateral RT in the overall group of patients ($P = .88$) and the patients who qualified for unilateral RT under the current policy of the study institution ($P = .53$), as seen in Figure 1B. No patient-related or treatment-related factors were found to be statistically associated with distant metastasis.

Patterns of Tumor Recurrence

There were no contralateral neck recurrences reported in patients treated with unilateral or bilateral IMRT. One

TABLE 1. Patient and Tumor Characteristics

Characteristic	Group 1: Lateralized Primary and N0-N2b, Unilateral IMRT		Group 2: Lateralized Primary and N0-N2b, Bilateral IMRT		Group 3: Nonlateralized Primary or N2c-N3, Bilateral IMRT		P[a]
	No.	%	No.	%	No.	%	
All patients (n=154)	48		59		47		
Retrospective cohort	5	10%	39	66%	20	43%	
Prospective cohort	43	90%	20	34%	27	57%	**<.01**
Median follow-up (range), y	4.2	0.7-15.7	7.8	0.3-17.3	5.4	0.7-13.7	**<.01**
Mean age (range), y	53	27-84	54	37-76	54	36-77	NS
Age, y							
≤50	27	56%	31	53%	28	60%	
>50	21	44%	28	47%	19	40%	NS
Sex							
Male	35	73%	54	92%	43	91%	
Female	13	27%	5	8%	4	9%	**<.01**
Race							
White	45	94%	55	93%	43	91%	
Black	3	6%	4	7%	2	4%	
Other	0	0%	0	0%	2	4%	NS
Smoking status							
Unknown	1	2%	2	3%	3	6%	
No	18	38%	15	25%	18	38%	
Yes	29	60%	42	71%	26	55%	NS
Tumor lateralized							
No	0	0%	0	0%	37	79%	
Yes	48	100%	59	100%	10	21%	**<.01**
Base of tongue invasion							
Unknown	3	6%	4	7%	1	2%	
No	31	65%	40	68%	32	68%	
Yes	14	29%	15	25%	14	30%	NS
Soft palate invasion							
Unknown	3	6%	4	7%	1	2%	
No	38	79%	47	80%	26	55%	
Yes	7	15%	8	14%	20	43%	**<.01**
Tumor grade							
Unknown	32	67%	8	14%	15	32%	
1	9	19%	33	56%	25	53%	
2	5	10%	16	27%	7	15%	
3	2	4%	2	3%	0	0%	**.03**
p16 status							
Unknown	10	21%	17	29%	4	9%	
Negative	2	4%	5	8%	6	13%	
Positive	36	75%	37	63%	37	79%	NS
FDG-PET/CT staging							
No	15	31%	19	32%	11	23%	
Yes	33	69%	40	68%	36	77%	NS
T classification							
pT1	23	48%	23	39%	7	15%	
pT2	18	38%	27	46%	15	32%	
pT3	6	13%	5	8%	15	32%	
pT4a	0	0%	2	3%	9	19%	
pT4b	0	0%	0	0%	1	2%	
pTX	1	2%	2	3%	0	0%	**<.01**
N classification							
pN0	5	10%	1	2%	2	4%	
pN1	5	10%	7	12%	3	6%	
pN2a	10	21%	12	20%	4	9%	
pN2b	28	58%	39	66%	17	36%	
pN2c	0	0%	0	0%	12	26%	
pN3	0	0%	0	0%	9	19%	**<.01**
Group AJCC stage							
II	3	6%	1	2%	1	2%	
III	6	13%	7	12%	3	6%	
IVA	39	81%	51	86%	32	68%	
IVB	0	0%	0	0%	11	23%	**<.01**

TABLE 1. *Continued*

Characteristic	Group 1: Lateralized Primary and N0-N2b, Unilateral IMRT		Group 2: Lateralized Primary and N0-N2b, Bilateral IMRT		Group 3: Nonlateralized Primary or N2c-N3, Bilateral IMRT		P[a]
	No.	%	No.	%	No.	%	
Surgical margin status							
Unknown	5	10%	7	12%	4	9%	
Negative	22	46%	17	29%	16	34%	
Positive	4	8%	8	14%	7	15%	
Close < 0.5 cm	17	35%	27	46%	20	43%	NS
Neck dissection							
Unknown	1	2%	3	5%	0	0%	
Ipsilateral	38	79%	50	85%	32	68%	
Bilateral	9	19%	6	10%	15	32%	NS
No. of involved LNs							
Unknown	1	2%	2	3%	0	0%	
0	4	8%	5	8%	4	9%	
1	15	31%	14	24%	13	28%	
2-5	23	48%	31	53%	18	38%	
≥6	5	10%	7	12%	12	26%	NS
LN size (largest), cm							
Unknown or no LN	8	17%	20	34%	7	15%	
≤3	18	38%	20	34%	16	34%	
>3	22	46%	19	32%	24	51%	NS
Extracapsular extension							
Unknown or no LN	6	13%	12	20%	4	9%	
Negative	5	10%	7	12%	5	11%	
Positive	37	77%	40	68%	38	81%	NS
Radiation dose, Gy							
≤65	33	69%	13	22%	11	23%	
>65	15	31%	46	78%	36	77%	**<.01**
Concurrent chemotherapy							
No	22	46%	37	63%	19	40%	
Yes	26	54%	22	37%	28	60%	NS

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; FDG-PET, [^{18}F]fludeoxyglucose-positron emission tomography; Gy, grays; IMRT, intensity-modulated radiotherapy; LN, lymph node; NS, not statistically significant.
[a] *P* values in bold denote statistical significance.

tonsil recurrence occurred in a patient with a pT4a, p16-negative tonsil tumor who was treated with bilateral RT for pN2c disease. Ipsilateral neck recurrences occurred in 0% of patients in group 1 (0 of 48 patients), 3% of patients in group 2 (2 of 59 patients), and 4% of patients in group 3 (2 of 47 patients). All neck recurrences occurred within the irradiated volume. No tumor-related or treatment-related factors were found to be statistically associated with the pattern of disease recurrence.

Overall Survival

Approximately 27% of patients (42 of 154 patients) died during the follow-up period. The causes of death were tonsillar cancer in 12% of patients (5 of 42 patients), second primary cancer in 31% (13 of 42 patients), noncancer causes in 17% (7 of 42 patients), and unknown causes in 40% (17 of 42 patients). The 1-year and 5-year OS rates among all patients were 95% and 80%, respectively. The 1-year and 5-year actuarial rates of OS were 98% and 85%, respectively, for group 1; 90% and 79%, respectively, for group 2; and 98% and 76%, respectively, for group 3. The OS rate was not significantly different between unilateral and bilateral RT in the overall group of patients ($P = .60$) and the patients who qualified for unilateral RT under the current policy of the study institution ($P = .25$), as seen in Figure 1C. ECE and the number of lymph nodes also were not found to be significantly associated with OS and LRC on univariate analysis. On multivariate analysis, older age at the time of cancer diagnosis (HR, 1.04; 95% CI, 1.01-1.08 [$P = .03$]), p16 status (HR, 0.35; 95% CI, 0.15-0.83 [$P = .02$]), and increasing T classification (pT4a vs pT1: HR, 6.34 [95% CI, 1.48-27.29; $P = .01$] and pT3 vs pT1: HR, 4.61 [95% CI, 1.36-15.62; $P = .01$]) were found to be associated with survival. Age (HR, 1.06; 95% CI, 1.01-1.12 [$P = .03$]) and p16 status (HR, 0.29; 95% CI, 0.11-0.83 [$P = .02$])

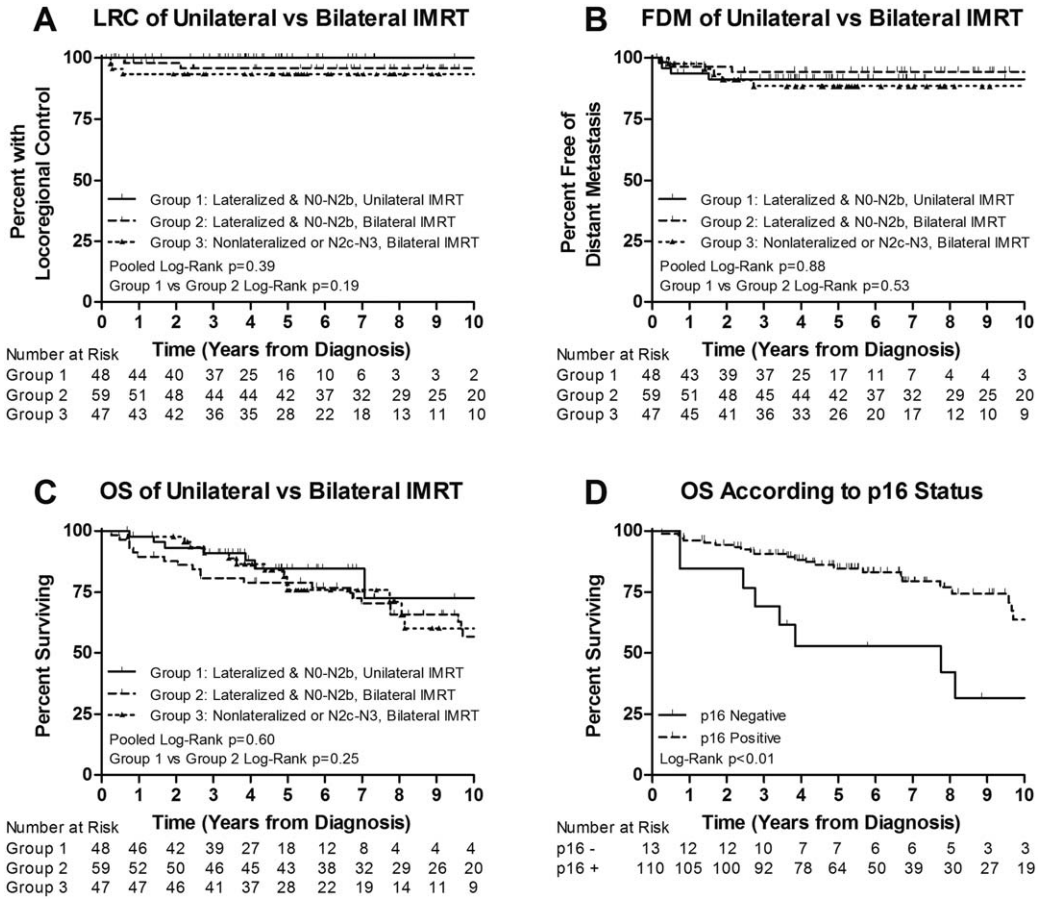

Figure 1. Kaplan-Meier plots of (A) locoregional control (LRC), (B) freedom from distant metastasis (FDM), and (C) overall survival (OS) according to unilateral versus bilateral intensity-modulated radiotherapy (IMRT) and (D) OS according to p16 status of the tumor.

were the only factors found to be associated with survival in the multivariate analysis that included only those patients eligible for unilateral IMRT (groups 1 and 2), as seen in Supporting Information Table 3. Locoregional recurrence (HR, 6.56; 95% CI, 2.25-19.14 [$P<.01$]) and the development of distant metastasis (HR, 7.21; 95% CI, 3.58-14.50 [$P<.01$]) were associated with a higher likelihood of death.

Toxicity

CTCAE toxicity could be assessed from available records in 90% of patients who were treated with unilateral IMRT and 89% of patients who were treated with bilateral IMRT. Unilateral RT was associated with significantly lower acute toxicity scores, as seen in Table 3. In particular, grade 3 mucositis was lower (35% vs 16%), grade 1 to 3 xerostomia was lower (59% vs 16%), and grade 3 weight loss was lower (44% vs 21%). Scores for dermatitis, dysphagia, rash, nausea, and vomiting were not found to be significantly different. A G-tube already was in place before the initiation of RT in 17% of patients treated bilaterally (18 of 106 patients) and 6% of patients treated unilaterally (3 of 48 patients), and this difference was not statistically significant ($P = .08$). Among patients who did not have a G-tube before the start of IMRT, 49% (43 of 88 patients) who were treated bilaterally and 18% (8 of 45 patients) who were treated unilaterally required a reactive G-tube ($P<.01$). Approximately 25% of patients treated bilaterally (26 of 106 patients) and 2% of patients treated unilaterally (1 of 48 patients) had a long-term G-tube present at the time of last follow-up ($P<.01$). Bilateral neck RT (OR, 4.90; 95% CI, 2.28-10.53 [$P<.01$]) and concurrent chemotherapy (OR, 2.41; 95% CI, 1.21-4.78 [$P = .01$]) were found to be associated with increased odds of reactive G-tube on multivariate logistic regression. Bilateral neck RT (OR, 8.18; 95% CI, 1.86-36.02 [$P<.01$]) but not chemotherapy ($P = .76$) was associated with increased odds of long-term G-tube being present at

TABLE 2. Univariate and Multivariate Analysis of Locoregional Control and Overall Survival

	Locoregional Control	Overall Survival
Univariate analysis		
Radiation laterality	NS	NS
Age (per y)	HR, 1.10 (95% CI, 1.01-1.19); ***P*=.03**[a]	HR, 1.05 (95% CI, 1.01-1.08); ***P*<.01**[a]
Sex	NS	NS
Race	NS	NS
p16 status (positive vs negative)	HR, 0.10 (95% CI, 0.01-0.71); ***P* = .02**	HR, 0.31 (95% CI, 0.14-0.70); ***P*<.01**
T classification		
T1 (reference)		
T2	NS	HR, 3.14 (95% CI, 1.26-7.88); ***P* = .02**
T3	NS	HR, 3.82 (95% CI, 1.35-10.77); ***P* = .01**
T4a	NS	HR, 6.26 (95% CI, 2.01-19.50); ***P*<.01**
T4b	NS	NS
N classification	NS	NS
No. of positive LNs	NS	NS
Extracapsular extension	NS	NS
Surgical margin status	NS	NS
Concurrent chemotherapy	NS	NS
Multivariate analysis		
Radiation laterality	NS	NS
Age (per y)	HR, 1.19 (95% CI, 1.01-1.42); ***P* = .048**	HR, 1.04 (95% CI, 1.01-1.08); ***P* = .03**
Sex	NS	NS
Race	NS	NS
p16 status (positive vs negative)	NS	HR, 0.35 (95% CI, 0.15-0.83); ***P* = .02**
T classification		
T1 (reference)		
T2	NS	NS
T3	NS	HR, 4.61 (95% CI, 1.36-15.62); ***P* = .01**
T4a	NS	HR, 6.34 (95% CI, 1.48-27.29); ***P* = .01**
T4b	NS	NS
N classification	NS	NS
No. of positive LNs	NS	NS
Extracapsular extension	NS	NS
Surgical margin status	NS	NS
Concurrent chemotherapy	NS	NS

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LN, lymph node; NS, not significant.
[a] *P* values in bold denote statistical significance.

the time of last follow-up. Detailed results of the multivariate logistic regression are shown in Supporting Information Table 4.

Patient-Reported Outcomes QOL

PROQOL data were available for 53% of patients overall and 87% of patients who were treated unilaterally. Baseline QOL scores between patients receiving unilateral and bilateral RT were not significantly different. Repeated measures analysis demonstrated that PROQOL as measured by MDADI, in which a larger number denotes a better PROQOL, was superior in patients in the unilateral RT group compared with the bilateral RT group across all posttreatment time points for the global (70 vs 58; $P = .03$) (Fig. 2A), physical (63 vs 50; $P<.01$), and functional (78 vs 65; $P<.01$) domains. No significant difference was found in the emotional domain (70 vs 64; $P = .12$). Repeated measures modeling of the Xerostomia Questionnaire, in which a smaller number denotes a better PROQOL, also demonstrated that posttreatment PROQOL was superior in the unilateral group (39 vs 58; $P<.01$) (Fig. 2B). The presented PROQOL comparisons were between patients treated unilaterally (group 1) and those treated bilaterally (pooled group 2 and group 3). A comparison of PROQOL between group 1 and group 2 is presented in Supporting Information Figure 1, although few patients in group 2 had available PROQOL data (6 patients).

DISCUSSION

In the current study, we present the outcomes of a retrospective series of patients with palatine tonsillar cancer who were treated with postoperative unilateral or bilateral IMRT. For patients without bilateral neck disease, the primary selection criteria for unilateral RT was a well-lateralized primary tumor (>1 cm from the midline) regardless of ipsilateral lymph node classification or lymph node ECE. We observed an excellent 5-year LRC

TABLE 3. Acute Toxicity as Measured by Common Terminology Criteria for Adverse Events of Groups 1, 2, and 3 at the Completion of Radiotherapy

	0		1		2		3		
Toxicity Score	No.	% (Row)	No.	% (Row)	No.	% (Row)	No.	% (Row)	*P*[a]
Mucositis									
Group 1	13	33%	10	25%	10	25%	7	18%	**<.01**
Group 2	4	8%	5	10%	25	50%	16	32%	
Group 3	8	19%	3	7%	16	37%	16	37%	
Dermatitis									
Group 1	9	23%	12	30%	16	40%	3	8%	NS
Group 2	11	22%	10	20%	28	56%	1	2%	
Group 3	11	26%	11	26%	15	35%	6	14%	
Xerostomia									
Group 1	34	85%	0	0%	5	13%	1	2%	**<.01**
Group 2	24	48%	11	22%	15	30%	0	0%	
Group 3	15	35%	11	26%	15	35%	2	5%	
Pharyngitis									
Group 1	40	100%	0	0%	0	0%	0	0%	**<.01**
Group 2	39	78%	2	4%	6	12%	3	6%	
Group 3	29	67%	6	14%	5	12%	3	7%	
Esophagitis									
Group 1	39	98%	0	0%	0	0%	1	2%	NS
Group 2	41	82%	0	0%	4	8%	5	10%	
Group 3	35	81%	2	5%	2	5%	4	9%	
Laryngitis									
Group 1	40	100%	0	0%	0	0%	0	0%	NS
Group 2	47	94%	3	6%	0	0%	0	0%	
Group 3	40	93%	2	5%	1	2%	0	0%	
Dysphagia									
Group 1	38	95%	1	2%	1	2%	0	0%	NS
Group 2	48	96%	0	0%	2	4%	0	0%	
Group 3	37	86%	2	5%	1	2%	0	0%	
Weight loss									
Group 1	26	65%	5	13%	0	0%	9	22%	**<.01**
Group 2	19	38%	8	16%	4	8%	19	38%	
Group 3	15	35%	4	9%	3	7%	21	49%	
Rash									
Group 1	39	98%	1	2%	0	0%	0	0%	NS
Group 2	47	94%	3	6%	0	0%	0	0%	
Group 3	43	100%	0	0%	0	0%	0	0%	
Nausea									
Group 1	34	85%	2	5%	4	10%	0	0%	NS
Group 2	45	90%	1	2%	4	8%	0	0%	
Group 3	34	79%	3	7%	4	9%	2	5%	
Vomiting									
Group 1	37	93%	1	2%	2	5%	0	0%	NS
Group 2	48	96%	0	0%	2	4%	0	0%	
Group 3	39	90%	0	0%	2	5%	2	5%	
Cough									
Group 1	40	100%	0	0%	0	0%	0	0%	NS
Group 2	50	100%	0	0%	0	0%	0	0%	
Group 3	42	98%	0	0%	1	2%	0	0%	
Hoarseness									
Group 1	39	98%	1	2%	0	0%	0	0%	NS
Group 2	49	98%	1	2%	0	0%	0	0%	
Group 3	41	95%	2	5%	0	0%	0	0%	
External otitis									
Group 1	40	100%	0	0%	0	0%	0	0%	NS
Group 2	49	98%	1	2%	0	0%	0	0%	
Group 3	43	100%	0	0%	0	0%	0	0%	
Dehydration									
Group 1	39	98%	1	2%	0	0%	0	0%	NS
Group 2	48	96%	0	0%	0	0%	2	4%	
Group 3	40	93%	1	2%	0	0%	2	5%	

TABLE 3. *Continued*

Presence of G-tube	No	% (Row)	Yes	% (Row)	P^a
Gastrostomy tube prior to IMRT					
Group 1	45	94%	3	6%	
Group 2	56	95%	3	5%	
Group 3	32	68%	15	32%	.12
Reactive gastrostomy tube[b]					
Group 1	37	82%	8	18%	
Group 2	34	61%	22	39%	
Group 3	11	34%	21	66%	**<.01**
Long-term gastrostomy tube					
Group 1	47	98%	1	2%	
Group 2	47	80%	12	20%	
Group 3	33	70%	14	30%	**<.01**

Abbreviations: IMRT, intensity-modulated radiotherapy; NS, not statistically significant.
No grade 4 or 5 toxicities were observed in any treatment group.
[a] *P* values in bold denote statistical significance.
[b] Only those patients who did not have a gastrostomy tube placed prior to IMRT were included in the analysis regarding reactive gastrostomy tubes.

rate of 97%, which was not significantly different between patients with tumors that were treated with unilateral or bilateral RT. One of the goals of the current study was to clarify whether it is appropriate to treat patients with tumors with an N2b classification with unilateral neck RT. In the current study, 28 patients treated with unilateral RT had N2b disease (58%), and no contralateral recurrences were observed. It is interesting to note that all patients in the current series underwent surgical resection of the tonsil primary tumor, and the majority of patients underwent unilateral neck dissection and staging FDG-PET. These 3 factors allowed for pathological staging of the primary tumor and ipsilateral neck disease, as well as potentially reducing the risk of occult contralateral disease.[25]

To the best of our knowledge, the only prospective study regarding unilateral neck RT in patients with tonsillar cancer published to date was by Rusthoven et al, who delivered unilateral RT to 14 of 20 patients with tonsillar cancer with N1 to N2b disease and observed no in-field or contralateral recurrences.[26] The majority of patients had T1 to T2 (18 of 20 patients) and N2b (13 of 20 patients) disease and unilateral treatment was only given for tumors without involvement of the base of the tongue or soft palate. Several large retrospective series also reported similar results. In the MDACC series of unilateral RT, approximately 22% of patients (22 of 102 patients) had N2b disease and no patients with N2b disease developed a contralateral disease recurrence.[6] It is interesting to note that the patients with N2b disease had shorter follow-up than the median of 39 months reported because they were treated later in the study period. The MDACC study did not define its use of tumor lateralization in selecting patients, although all patients had tumors classified as T1 to T2 and none of the patients had base-of-tongue involvement. Another confounding factor was that 5 patients with N2b disease received systemic chemotherapy. In the Rotterdam series, approximately 17% of patients had well-lateralized tonsillar cancer with N2b disease and 1 contralateral recurrence was reported in a patient with T1N2b disease.[7] Ye et al also reported no recurrences among 11 patients with well-lateralized tonsillar cancer with N2b disease who were treated with unilateral RT.[27] Dan et al reported the results of patients treated with unilateral RT in a community setting including 31 patients with N2b disease, and observed 1 contralateral recurrence in this group.[28] Several other studies also reported no contralateral recurrences.[10,29]

In contrast, other studies have reported modest recurrence rates after unilateral RT for the treatment of patients with palatine tonsil squamous cell carcinoma. Vergeer et al reported a series of 123 patients who were treated with surgery followed by ipsilateral RT for tonsil tumors >1 cm from the midline.[8] A total of 7 contralateral recurrences occurred, with 4 reported in patients with N2b disease. N2b disease was found to be a significant predictor of contralateral recurrence in this study. The Royal Marsden Hospital reported a retrospective series of patients treated with unilateral RT for tumors limited to the lateral one-third distance from the midline.[30] This study included 55 patients with N2b disease and reported contralateral recurrences in 7 of these patients. Publications from the University of Florida and Norwich University also reported contralateral recurrences.[31,32] It is interesting to note that the 2011 ACR Appropriateness Criteria[9] recommends bilateral RT for patients with N2b

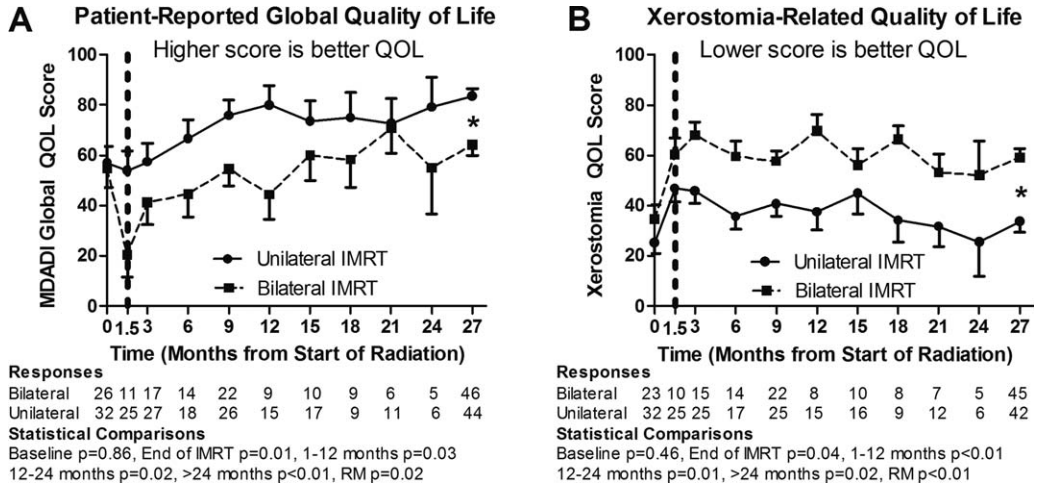

Figure 2. Longitudinal patient-reported quality of life (QOL). (A) Patient-reported global QOL as measured by the 20-question University of Texas MD Anderson Cancer Center Dysphagia Inventory (MDADI). A higher score denoted better patient-reported QOL. (B) Patient-reported xerostomia as measured by the 6-question University of Michigan Xerostomia Questionnaire (XQ). A higher score denoted worse patient-reported xerostomia. 0 month indicates evaluation before intensity-modulated radiotherapy (IMRT); 1.5 month, evaluation at the end of IMRT; subsequent months, evaluation at post-IMRT follow-up. The dotted vertical line at 1.5 months represents the end of IMRT. Error bars represent the standard error of the mean. RM indicates repeated measures analysis, adjusting for time period and the interaction between time period and laterality of treatment. *Evaluations from time points at 27 months or later (>2 years after IMRT) were pooled into the 27-month time point to demonstrate the long-term outcome.

disease or higher. The 2016 ACR Appropriateness Criteria[33] has not readdressed this question. The American Society for Radiation Oncology consensus guideline published in 2017 recommended unilateral RT for patients with well-lateralized (confined to the tonsillar fossa) T1 to T2 tonsillar cancer and N0 to N1 classified disease.[34] It also recommended unilateral RT for patients with lateralized (<1 cm of soft palate extension but without involvement of the base of the tongue) T1 to T2, N0 to N2a tonsillar cancer without clinical or radiographic evidence of ECE.

Advanced ipsilateral neck disease may not independently increase the risk of contralateral disease recurrence. For example, to the best of our knowledge, anatomic and lymphatic mapping studies[35-37] have not identified connections between opposite lymph node regions I to IV of the neck.[38,39] Therefore, it may be that contralateral lymph node disease occurs because the primary tumor approaches the midline, resulting in contralateral metastasis,[38] or because the tumor invades a region with extensive submucosal lymphatics such as the tongue or floor of the mouth.[40] One possible explanation for the contralateral disease recurrences noted in some studies is that advanced ipsilateral neck disease could thus be a surrogate marker for the propensity of the primary tumor to metastasize. Lim et al analyzed 43 patients with tonsillar cancer who underwent elective lymph node dissection of the contralateral, clinically lymph node-negative neck.[41] They reported a 14% rate of contralateral involvement, and 6 of 7 patients with T3 to T4 tumors, which often are within 1 cm of the midline, had occult contralateral disease. In the current series, only 13% of patients with pT3 to pT4 disease (6 of 48 patients) received unilateral RT. However, the majority of patients in the current study who received unilateral RT had N2a to N2b disease (38 of 48 patients; 78%). The findings of the current study are in keeping with the recent report by Rackley et al, who reported the outcomes of a series of 81 patients with lateralized tonsillar cancer and N0 to N2b lymph node disease.[42] With a median follow-up of 5.7 years, they reported no contralateral disease recurrences and a 5-year OS rate of 91% and a 5-year LRC rate of 95%. These outcomes are similar to that of the patients in group 1 in the current study, with a 5-year OS rate of 85% and a 5-year LRC rate of 100%. These findings suggest that unilateral RT is appropriate for patients with lateralized primary tumors and N0 to N2b neck disease.

One potential benefit of unilateral IMRT is a reduction in treatment-related toxicity.[43,44] We observed a decrease in mucositis, xerostomia, and weight loss with unilateral neck RT. Importantly, the need for a reactive and long-term G-tube also was found to be reduced. The findings of the current study are similar to those of a prospective PROQOL study by Al-Mamgani et al, who

reported that unilateral RT was associated with improved QOL in patients with oropharyngeal cancer.[43] In the current study, global and xerostomia-related QOL from the end of treatment to 2 years after RT was found to be superior in patients treated with unilateral RT. These findings demonstrate the durable benefit of unilateral RT.

There are several limitations to the current study. Although no patients in the current study cohort developed contralateral neck recurrence, the modest sample size may not be large enough to capture the potential 5% to 7% risk of contralateral neck disease recurrence. Because there were no contralateral lymph node recurrences noted, patterns of failure could not be correlated with ECE, a possible risk factor for contralateral lymph node recurrence.[30] In the current study, ECE was not found to be significantly associated with OS or LRC, a finding that is consistent with recent literature that questions the importance of ECE as a risk factor.[45,46] For the rare patient who does develop a recurrence in the contralateral neck, the sparing of RT on the side of recurrence may reduce the toxicity of an attempted salvage with RT and/or surgical technique. In a recent analysis, Guo et al found surgical salvage was associated with improved OS for patients with recurrent locoregional disease in both HPV-positive and HPV-negative oropharyngeal cancer.[47]

In addition, the RT volume was not randomized but rather was based on a shift in institutional policy around 2007, when patients with lateralized tumors were assigned to unilateral RT. The shift in institutional policy was not instantaneous, but was associated with a transition period during which patients were highly selected. The RT volume and dose to the pharynx were not controlled for, and these variables can affect QOL outcomes.[48,49] Furthermore, stage migration, evolving technology and technique, and groups with different follow-up times are inevitable in a retrospective study spanning 17 years. However, PET imaging was introduced after the first 3 years of the study, all patients were treated with IMRT, and the median follow-up for the most recently treated group was adequate at 4.2 years, which somewhat mitigates these concerns.

Another limitation of the unilateral versus bilateral RT PROQOL comparison is that reporting bias may be present because a higher percentage of patients treated with unilateral RT completed PROQOL questionnaires compared with patients treated with bilateral RT. Furthermore, few patients in group 2 had available PROQOL data (6 patients) because they were treated before we routinely distributed the PROQOL questionnaires. Therefore, the PROQOL comparison is in reality mostly between patients in groups 1 and 3. The PROQOL comparison also could be confounded by more extensive surgery and tumor, or larger RT fields at the primary tumor site for group 3 compared with group 1. Despite these limitations, we believe that this still is a useful comparison, and that the majority of the differences in PROQOL might be attributed to the omission of RT to the contralateral neck. Indeed, the acute CTCAE treatment toxicities between group 2 and group 3 were similar, which leads us to speculate that these individuals also may have similar QOL outcomes. The rates of reactive G-tube placement during and after RT and the presence of a G-tube at the time of last follow-up, both surrogate measures of QOL, also support that unilateral RT was associated with a superior QOL. These endpoints are valuable because they are less prone to the recall bias inherent with the reporting of toxicity due to the retrospective nature of this analysis.

Conclusions

In the current study, unilateral neck IMRT in patients with lateralized tonsillar cancer and N0 to N2b disease did not appear to compromise LRC, and was associated with a lower rate of acute toxicity and use of G-tubes, and better patient-reported QOL compared with bilateral IMRT. The results of the current study support the efficacy and benefit of unilateral IMRT in properly selected patients with lateralized palatine tonsillar cancer.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Re-I Chin, Yuan James Rao, and **Christopher R. Spencer** contributed to the conceptualization and methodology of the project. **Re-I Chin, Yuan James Rao, Michael Y. Hwang, Christopher R. Spencer, Michael Pierro, Pranav Patel**, and **Parul Sinha** contributed to the data collection. **Yuan James Rao** and **Todd DeWees** contributed to the formal analysis. **Re-I Chin, Yuan James Rao**, and **Michael Y. Hwang** contributed to the writing. All the authors contributed to the article edits and revision. **Wade L. Thorstad** is responsible for the overall content as guarantor.

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