HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2022 August 01; 113(5): 1054–1062. doi:10.1016/j.ijrobp.2022.04.035.

Unilateral Radiation Therapy for Tonsillar Cancer: Treatment Outcomes in the Era of Human Papillomavirus, Positron-Emission Tomography, and Intensity Modulated Radiation Therapy

Nicolette Taku, MD, MPhil, MPH[*], **Gregory Chronowski, MD**[*], **G. Brandon Gunn, MD**[*], **William H. Morrison, MD**[*], **Neil D. Gross, MD**[†], **Amy C. Moreno, MD**[*], **Renata Ferrarotto, MD**[‡], **Steven J. Frank, MD**[*], **C. David Fuller, MD, PhD**[*], **Ryan P. Goepfert, MD**[†], **Jack Phan, MD, PhD**[*], **Stephen Y. Lai, MD, PhD**[†], **Jay P. Reddy, MD**[*], **David I. Rosenthal, MD**[*], **Adam S. Garden, MD**[*]

[*]Departments of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas;

[†]Departments of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas;

[‡]Departments of Head and Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas

Abstract

Purpose: The goal of this study was to evaluate disease, survival, and toxic effects after unilateral radiation therapy treatment for tonsillar cancer.

Methods and Materials: A retrospective study was performed of patients treated at our institution within the period from 2000 to 2018. Summary statistics were used to assess the cohort by patient characteristics and treatments delivered. The Kaplan-Meier method was used to determine survival outcomes.

Results: The cohort comprised 403 patients, including 343 (85%) with clinical and/or radiographic evidence of ipsilateral cervical nodal disease and 181 (45%) with multiple involved nodes. Human papillomavirus was detected in 294 (73%) tumors. Median follow-up time was 5.8 years. Disease relapse was infrequent with local recurrence in 9 (2%) patients, neck recurrence in 13 (3%) patients, and recurrence in the unirradiated contralateral neck in 9 (2%) patients. Five- and 10-year overall survival rates were 94% and 89%, respectively. Gastrostomy tubes were needed in 32 (9%) patients, and no patient had a feeding tube 6 months after therapy.

Conclusions: For patients with well-lateralized tonsillar tumors and no clinically evident adenopathy of the contralateral neck, unilateral radiation therapy offers favorable rates of disease outcomes and a relatively low toxicity profile.

Corresponding author: Adam Garden, MD; agarden@mdanderson.org.

Introduction

More than half a century ago, it was recognized that oropharyngeal cancer (OPC), including tonsillar carcinoma, frequently metastasized to cervical lymph nodes.[1] It was further observed that patients who received radiation therapy to the primary tumor and gross adenopathy (ie, “partial neck irradiation [PNI]”) subsequently developed disease recurrence in unirradiated lymphatic regions of the neck. These observations led Fletcher et al[1] to deliver “elective neck irradiation (ENI)” to the clinically uninvolved neck in patients treated for OPC. In 1971, they published the results of a retrospective study comparing ENI to PNI and reported crude nodal recurrence rates of <2% for patients treated with ENI versus >10% for PNI.[2]

As a result of the aforementioned study, radiation therapy to the bilateral neck has been the mainstay of treatment for nearly all patients treated with radiation therapy for OPC.[3] Whole neck radiation was historically delivered using a 3-field technique, with parallel-opposed beams treating the primary tumor and upper cervical lymph nodes and an anterior beam treating the midjugular and supraclavicular lymph nodes. Although modern radiation therapy treatment techniques, including intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), achieve more conformal radiation therapy dose distributions to targeted regions and greater sparing of normal head and neck structures, radiation therapy treatment to the bilateral neck continues to be associated with several short- and long-term side effects, including xerostomia, dysphagia, gastrostomy-tube dependence, and soft tissue fibrosis.[4,5]

Subsequent to the adoption of ENI, many clinicians inquired as to whether radiation therapy target volumes could be reduced, including omission of treatment to the contralateral neck, for carefully selected patients with OPC, thereby decreasing radiation therapy−related morbidity. This question was primarily posed for patients with malignancies of the tonsil, as it is lateralized compared with the other structures of the oropharynx. Two early studies evaluating unilateral radiation therapy described low rates of contralateral neck recurrence after radiation therapy treatment of the ipsilateral neck for tonsillar cancer in patients with small primary tumors (cT1–2) and no or minimal lymph node involvement (cN0–1).[6,7] Furthermore, current consensus guidelines from the American College of Radiology and the American Radium Society recommend definitive or adjuvant unilateral radiation therapy to the ipsilateral neck (with or without chemotherapy) for well lateralized, tonsil-confined tumors with minimal lymph node involvement, independent of human papillomavirus (HPV) status.[8,9]

A previous study reported the outcomes of 102 patients with tonsillar cancer who received unilateral radiation therapy.[10] Although the results were favorable, the majority of these patients were treated before recognition of the effect of the HPV on OPC and few had N2b disease. The goal of this study was to evaluate disease and survival outcomes after unilateral radiation therapy for OPC in an era of high rates of HPV positivity where the majority of patients with HPV-associated disease have small primary tumors with associated lymphadenopathy. Additionally, we report toxicity outcomes within the context of modern

radiation therapy treatment techniques, principally IMRT (including VMAT) and proton therapy.

Methods and Materials

After obtaining institutional review board approval, a clinical database maintained in the Department of Radiation Oncology at our institution was queried for patients treated with unilateral radiation therapy for tonsillar cancer. Inclusion criteria were newly diagnosed, nonmetastatic, squamous cell carcinoma of the tonsil and at least 18 years the time of diagnosis. Exclusion criteria was a prior malignancy of the head and neck. Patients treated between 2000 and 2018 are the subject of this study.

To approximate the percentage of patients treated with unilateral radiation therapy a separate search was performed to determine the case number of patients with “early-stage” tonsillar cancer irradiated during the years of interest. The query was for patients classified as T1-2, N0-N2b.

Tumor staging

A comprehensive review of the medical records of the patients identified as being treated with unilateral radiation was performed for identifying and verifying patient, tumor, and treatment characteristics. All patients underwent multi-disciplinary consultation with a dedicated team of head and neck surgical, radiation, medical, and dental oncologists. Pretreatment assessment included physical examination, flexible fiberoptic examination of the pharyngeal mucosa, and radiographic imaging (computed tomography [CT] scan, positron emission tomography (PET)/CT and/or x-ray) of the head, neck, and chest. Patients were eligible for unilateral radiation therapy if staging studies demonstrated a well lateralized primary tumor confined to the tonsillar fossa, no more than 1 cm extension of the primary tumor to the soft palate, no evidence of base of tongue involvement, tumor size of 4 cm or less after diagnostic tonsillectomy, and clinical N0-N2b disease. Treatment of patients with level IV neck involvement was discouraged but not an absolute contraindication, especially in the latter years of the study period.[11] For the purposes of this study, clinical stages are presented in accordance with seventh edition of the American Joint Committee on Cancer TNM (tumor, node, metastasis) system.[12]

Treatment

All patients underwent radiation therapy simulation with CT scan and customized thermoplastic mask. Patients treated in the early 2000s received 3-dimensional conformal radiation therapy. However, the vast majority of patients in the study received IMRT, as this modality was introduced into our clinic during the study period and eventually became the standard of care. Our initial approach reserved IMRT for the primary site and upper neck, with appositional beams employed for the treatment of the lower neck. Electrons were infrequently used to boost nodal disease. Our treatment techniques evolved such that all target volumes were treated with VMAT rather than a multifield static-gantry approach. Proton therapy was available in the latter years of the study period, and patients received either 3-dimensional passive protons or intensity modulated proton therapy (IMPT).

The clinical target volumes (CTV) and organs at risk were segmented using a treatment planning software, with delineation of 2 CTVs. The CTV1 included gross disease with a 5- to 8-mm margin. A virtual gross target volume was created for patients who underwent surgical procedures before radiation therapy during which gross disease was removed. The CTV1 for these cases was delineated in a manner similar to that of intact gross disease. The CTV2 included regions of suspected subclinical disease. For coverage of the tonsillar primary site, the CTV2 extended to mid-line on the soft palate and included the following: (1) the lateral oropharyngeal wall/tonsillar bed from the maxillary tuberosity to the hyoid (if not in CTV1), (2) the parapharyngeal space and varying amounts of pterygoid musculature, and (3) 5 to 10 mm of base of tongue. For coverage of the regional lymph nodes basins, the CTV2 included ipsilateral neck levels II to IV, and VII (ie, retropharyngeal nodes) in clinically node negative patients and ipsilateral neck levels IB to V, and VII in clinically node positive patients. A 3- to 5-mm expansion of the CTV2 was used to create the planning target volume for photon treatment plans.

Patients with gross disease received doses of 60 to 70 Gy to the CTV1, typically delivered in 30 to 33 fractions at 2 to 2.2 Gy per fraction. In the postoperative setting, doses to the CTV1 varied from 57 to 66 Gy, depending on the type of surgery and pathology findings. The CTV2 was prescribed doses ranging from 54 to 60 Gy. Because surgery was often performed on either the primary tumor or nodal disease, thereby leaving gross disease in the unoperated site, many patients received radiation therapy treatment with simultaneous definitive and adjuvant intent.

On occasion, the CTVs were subdivided to permit differential doses to the primary site of disease and regional lymph node basin. For example, a patient with cT1N1 disease but with a small primary tumor and bulky nodal disease may have received 66 Gy to the primary tumor and 70 Gy to the involved, regional lymph nodes. The CTV2 was also subdivided into intermediate-risk and low-risk target volumes, which were determined by proximity to the CTV1 and/or prior surgical intervention. Decisions regarding chemotherapy were individualized based on the clinical stage and, when applicable, surgical pathology findings.

Statistical analysis

Summary statistics were used to assess the patient cohort by age, sex, smoking history, HPV status, and treatments delivered. Medical records were reviewed for the development of primary failure, neck failure, and/or distant metastasis during the follow-up period. The Kaplan-Meier method was used to determine survival rates. Progression-free survival events included any disease recurrence or death. The date of diagnosis was used as time zero for calculation of survival outcomes. All statistical analyses were performed with R software, version 3.6.3 (R Foundation for Statistical Computing), including the Survfit package for survival analyses.

Results

Patient and tumor characteristics

The query of our databases for the overall number of patients irradiated during the study years having T1–2, N0–2b tonsillar carcinoma identified 978 patients. Four hundred and three patients were treated with unilateral radiation and met inclusion criteria for this study. Patient and tumor characteristics are presented in Table 1. The median age at diagnosis was 56 years (interquartile range, 50–63 years) and there was a male sex predominance. Of the 301 (75%) tumors for which HPV/p16 testing was performed, nearly all (n = 294; 98%) were associated with HPV.

All patients had CT of the head and neck. PET was obtained in 239 patients (59%) including 198 of the patients (67%) with HPV-mediated disease. Sonogram of the neck was obtained in 110 (27%) and 84 (28%) of the overall cohort and HPV-positive subgroup, respectively.

Tumor classifications were T1 in 243 (60%) patients, T2 in 114 (28%), T3–4 in 4 (1%), and Tx in 42 (10%). Cervical lymph node classifications were N0 in 60 (15%) patients, N1 in 93 (23%), N2a in 56 (14%), N2b in 181 (45%), and Nx in 13 (3%). Eight patients had radiographic evidence of an ipsilateral retropharyngeal node. Seventy-five patients (19%) had nodes inferior to level 2, including 14 (3%) with level 4 adenopathy. The size of the largest node in the 343 patients who had cervical adenopathy ranged from 0.7 to 6 cm with the median 2.9 cm.

Treatment

Treatment characteristics are presented in Table 2. Two-hundred and ten (52%) patients underwent tonsillectomy or transoral robotic surgery confirming pathologic evidence of a primary tonsillar tumor and presented to radiation therapy without clinical or radiographic evidence of gross disease. Additionally, 150 (37%) patients had no gross evidence of regional lymph node involvement before radiation therapy due to cN0 disease (60 patients), excisional lymph node biopsy (46 patients), or selective neck dissection (46 patients). Two patients were both cN0 and pN0 after elective neck dissections. Three patients had neck dissections and presented to radiation with gross recurrent or residual disease. Pathologic findings of the 90 patients who had nodal disease removed and were without gross cervical adenopathy at the time of radiation are detailed in Table 3. No patient had a contralateral neck dissection.

The median radiation therapy dose to the CTV1 was 66 Gy (interquartile range, 66–69 Gy). Three hundred and forty-one (85%) patients were treated with IMRT/VMAT, 43 (11%) received proton therapy, and 19 (5%) received 3-dimensional conformal radiation therapy. With respect to systemic therapy, 27 (7%) patients were treated with induction chemotherapy, 131 (33%) were managed with concurrent chemotherapy, and 6 (1%) received both induction and concurrent chemotherapy. Concurrent chemotherapy agents were primarily cetuximab in 71 (52%) patients and cisplatin in 58 (42%) patients.

Survival outcomes

The median follow-up time for evaluation of survival outcomes was 5.8 years (range, 0.3–17.6 years), during which there were 9 (2%) treatment failures of the primary site, 13 (3%) treatment failures of the neck (4 ipsilateral, 9 contralateral), 14 (3%) distant metastases, and 36 (9%) deaths. Nine (6%) patients with cN2b disease developed nodal recurrence. Six (67%) patients with primary site disease recurrence also developed disease recurrence of the neck. Locoregional disease control was achieved in all 14 patients with distant metastases at last follow-up. The 2- and 5-year rates were 98% and 97% for local control and 98% and 96% for regional control. The 2-, 5-, and 10- year rates were 98%, 94%, and 89% for overall survival (Fig. 1) and 94%, 90% and 84% for progression-free survival (Fig. 2).

The T- and N-classifications of the 9 patients who developed recurrences in the contralateral neck were the following: T1, 4 patients; T2, 5 patients; N0, 1 patient; N1, 2 patients; and N2b, 6 patients. Of the 8 patients who were node positive, 2 had disease in level 3 (including 1 patient with retropharyngeal nodal disease), and 1 in level 4. Seven of the patients had HPV-associated tumors, with the 2 other patients' tumor status unknown. Six were never smokers. Five patients had PET staging and 1 had ultrasound. Eight patients were treated with IMRT and 1 with IMPT. Four patients were treated with radiation alone, 4 received concurrent cetuximab and 1 patient (who had level 4 adenopathy) received both induction chemotherapy and concurrent cisplatin. Recurrence in the contralateral neck was detected at 3 to 13 months after radiation in 6 patients, and at 4 to 5 years after radiation in 3 patients. Six patients had successful salvage therapy and were alive without disease. One patient was lost to follow-up at the time of diagnosis of recurrence, and 2 have died with disease. The 2 patients who died with disease also had primary site recurrence, 1 preceding the contralateral recurrence, and 1 subsequent to the contralateral recurrence. One patient had concurrent primary and contralateral neck recurrence and had successful salvage with immunotherapy and surgery. Among the 6 patients who had successful salvage, all had neck dissection, and 3 had adjuvant radiation to the previously unirradiated neck. Table 4 summarizes details of these 9 patients with contralateral neck recurrent disease.

Toxic effects

Gastrotomy tubes were placed in 32 (9%) of 377 patients with known gastrostomy tube status, including 14 (10%) of 137 patients who received concurrent chemoradiotherapy and 1 (2%) of 43 patients who received proton radiation therapy. Posttreatment complications at 6 months or more after radiation therapy completion included osteoradionecrosis (n = 13, 3%) and cranial neuropathy (n = 7, 2%). No feeding tubes were present at 6-month follow-up among patients without disease recurrence.

Outcomes for HPV-associated tonsillar cancer

The demographic and treatment characteristics of 294 patients with HPV-associated cancers are also detailed in Tables 1 and 2. The median follow-up time for evaluation of survival outcomes was 5.0 years (range, 0.3–14 years), during which there were 7 (2%) treatment failures of the primary site, 10 (3%) treatment failures of the neck (3 ipsilateral, 7 contralateral), 7 (2%) distant metastases, and 14 (5%) deaths. The 2-year and 5-year rates

of overall survival were 99% and 96%, respectively. Twenty-two (7%) patients required gastrostomy tube placement during treatment.

Discussion

We report disease and toxicity outcomes for a cohort of over 400 patients treated with unilateral radiation therapy for tonsillar cancer. With a treatment period of 18 years and a median follow-up time of 5.8 years, our study demonstrates favorable disease outcomes with unilateral radiation therapy. Our 5-year rates of local and regional control of greater than 95% are consistent with prior studies of disease outcomes after unilateral radiation therapy for tonsillar cancer with 5 or more years of median follow-up time.[13–17] In a retrospective review of 427 patients with cT1-T2, cN0-N2b tonsillar cancer, Huang et al[13] compared outcomes for 102 patients treated with unilateral radiation therapy to 325 patients treated with bilateral radiation therapy. They described very high rates of disease control and survival and notably, there was no difference in local control, regional control, or overall survival between patients treated with unilateral and those treated with bilateral radiation therapy.

The majority of patients in our study for whom HPV/p16 testing was performed were found to have HPV-associated disease. Subanalysis of this population demonstrated infrequent disease recurrence, occurring in less than 5% of patients at a median of 5.0 years of follow-up time. Additionally, overall survival was high with a rate of 99% at 2-years' follow-up decreasing modestly to 96% at 5 years' time. Despite accounting for nearly 75% of the study population, patients with HPV-associated tonsillar cancer constituted only 38% of patient deaths.

Nearly all patients (85%) had regional lymph node involvement at diagnosis, including >60% of patients with cN2a-b disease at diagnosis. Limited evidence exists to suggest that cN2a-b disease, particularly cN2b may be associated with increased risk for contralateral neck recurrence. Two retrospective studies that included patients with N2b disease observed that all the contralateral neck recurrences occurred in their patients with multiple nodes, and the 10% to 14% recurrence rates are the highest rates reported in the literature.[18,19] This is in contradistinction to our findings as we report a crude recurrence rate in the contralateral (unirradiated) neck of 3% in patients presenting with cN2b disease. Our finding is consistent with the <3% rate reported by Al-Mamgani et al[3] in their literature review of 343 patients with N2b disease.[4]

The rate of contralateral nodal recurrence is often the primary end point in studies of ipsilateral therapy, but the more important question might be how survival is affected. However, with event rates so low, this is a difficult question to address. Al-Mamgani et al[3] in their review of >1100 patients found that only 19 of 27 patients had contralateral recurrence in the absence of other disease recurrence. Furthermore, salvage neck dissection was only reported for 15 patients, though the success rate was 73%. We described 5 patients with isolated contralateral recurrences all successfully salvaged, similar to the description of Lynch et al[19] who despite reporting high rates of contralateral recurrence in N2b patients also describe 100% successful salvage. These low rates of recurrence combined with high

rates of salvage both in the ipsilateral radiation setting as well as for patients with HPV-associated disease in general[20,21] provide further evidence to support the elimination of ENI of the contralateral neck (in carefully selected patients with OPC, such as those included in this analysis) without decrement in disease outcomes.

Inadequate oral nutrition secondary to mucositis, odynophagia, and dysphagia is a well-recognized side effect of radiation therapy for OPC, including patients treated for early-stage disease.[22] In a multi-institutional retrospective review of gastrostomy tube use among 2315 patients treated definitively with standard doses of IMRT for OPC, Setton et al[23] reported gastrostomy tube placement in 28% of patients with clinical stage I to II disease and 55% of patients with clinical stage III to IV disease (cT1–2, cN0–2). NRG Oncology HN002 investigated dose de-escalated IMRT of 60 Gy to gross disease and 48 Gy to elective nodal regions for patients treated for HPV-associated OPC and reported gastrostomy tube placement rates of 21.7% and 15.8% for patients treated with and without chemotherapy, respectively.[24] In both studies, the majority of patients received radiation therapy to the bilateral neck. Comparatively, we found rates of treatment-related side effects to be low as reflected by the low rates of gastrostomy tube placement in this study: less than 10% of all patients and only 2% of those treated with proton therapy. In an era during which treatment de-intensification is of clinical interest, our study highlights the benefits of radiation therapy volume reduction through unilateral radiation therapy with respect to both disease control and side effect minimization. Furthermore, dose and volume de-intensification are not mutually exclusive.

Our study supports the use of unilateral therapy for tonsillar disease confined to the fossa, even when clinical staging demonstrates multiple metastatic lymph nodes. However, it is difficult to change practices long ingrained in our training. For example, 33% of patients enrolled in NRG Oncology HN002 were stratified to unilateral radiation therapy but only 12% received this treatment. In their reevaluation of practices, Huang et al observed that only 24% of their patients received unilateral therapy, compared with their historical control of 36%.[13] Our results suggest that ENI of the contralateral neck can be eliminated in more patients with OPC. Future studies of unilateral radiation therapy regarding appropriate patient selection, its use in the definitive versus postoperative setting,[25] patient selection based on lymphoscintigraphy and/or sentinel lymph node biopsy, and whether indicated for patients with lateralized base of tongue primary tumors are warranted.

There are several limitations to this retrospective report. The results of HPV/p16 testing were missing for approximately one-fourth of patients, thereby limiting our ability to assess outcomes for HPV-associated versus HPV-negative disease. However, the larger limitation is despite the relatively narrowly defined cohort (tonsil cancer with early staged primaries and either none or ipsilateral cervical adenopathy), the management is quite heterogenous. Only 59% had PET staging as this was not a routine evaluation 20 years ago; still this study has more PET staged patients than other papers on this subject. More so, treatment varied over the 2 decades. Radiation evolved from 3D to IMRT (which also evolved from multifield to VMAT) to IMPT. Evaluation of IMPT is beyond the scope of this study, but this article does present a relatively modest sized subgroup of patients treated with protons. Surgical approaches varied, partly due to diagnostic challenges of both the primary and nodal disease,

as well as the integration of transoral robotic surgery only in the last few years of this study. Decisions regarding chemotherapy were made on an individualized basis, and further reflect the changing role of chemotherapy over these 2 decades. As most patients in our study had small primary disease, induction therapy use in this cohort was uncommon (<10% of patients). Similarly, concurrent chemotherapy has only gained popularity in more recent years, although the evidence for treating patients with T1 disease with chemotherapy due to our defining disease as locally advanced due to nodal disease is quite weak. We cannot assess the effect of chemotherapy use on disease outcomes, though with <15% getting concurrent cisplatin, and few contralateral recurrences and a 10-year OS of 89% it is hard to imagine dramatically improved outcomes.

Quantifying radiographic matted nodes or extranodal extension was not performed, as we did not use radiographic nodal morphology explicitly in either overall treatment management or radiation volume decision making. These morphologic qualities of nodes have only been of recent interest as an additional factor that is associated with prognosis in general and have affected management principally in selecting patients for surgical management (with an expectation that radiographic extranodal extension would predict pathologic nodal extension). We are not aware of data to suggest that these features can affect the probability of subclinical contralateral nodal disease. Additionally, there were no contralateral neck recurrences in the 54 patients with pathologic extranodal disease. This is contrary to the findings of Lynch et al, who found nodal extracapsular spread was associated with contralateral neck recurrence.[19] Still, in a retrospective trial, radiologic morphology of nodes may have implicitly influenced treatment decisions and therefore reflect selection bias.

Ultimately, our study reports long-term outcomes of more than 400 patients with tonsillar cancer who were treated with unilateral radiation therapy at a single institution within the context of consistent patient selection criteria and treatment practice. Less than 1% of the cohort developed recurrence in the contralateral neck and died with disease.

Conclusions

We report very favorable long-term survival and toxicity outcomes for patients with well-lateralized tonsillar cancer treated with unilateral radiation therapy. The majority of patients had HPV-associated disease and were treated with IMRT or proton therapy. Rates of local control, regional control, and overall survival were high. In particular, the disease recurrence rate in the contralateral neck was low. Acute and late toxic effects (including gastrostomy tube placement) were infrequent.

Disclosures

R.F. reports consulting fees from Ayala Pharmaceuticals, Klus Pharma, Bicara Therapeutics, Medscape, and Carevive Systems; payment for expert testimony from Intellisphere; and participation on a data safety monitoring board or advisory board for Regeneron-Sanofi, Ayala Pharmaceuticals, Prelude Therapeutics, and Klus Pharma. C.F. reports grants or contracts from the following: National Science Foundation (NSF)/National Cancer Institute (NCI); Smart and Connected Health Program (R01CA257814); NSF Division of Civil, Mechanical, and Manufacturing Innovation (NSF 1933369); Patient-Centered Outcomes Research Institute (PCS-1609-36195) subaward from Princess Margaret Hospital; The Human BioMolecular Atlas Program Integration; Visualization & Engagement Initiative (OT2OD026675) subaward; Small Business Innovation Research Grant Program; a subaward

from Oncospace, Inc. (R43CA254559); Radiation Oncology and Cancer Imaging Program (P30CA016672); National Institutes of Health (NIH)/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the University of Texas MD Anderson CCSG; NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (1R01CA218148); NIH National Institute of Dental and Craniofacial Research (NIDCR) Exploratory/Developmental Research Grant Program (R21DE031082); NCI Parent Research Project Grant (R01CA258827); NIDCR Establishing Outcome Measures for Clinical Studies of Oral and Craniofacial Diseases and Conditions (R01DE025248); NIH NIDCR Academic Industrial Partnership Grant (R01DE028290); NIH National Institute of Biomedical Imaging and Bioengineering Research Education Programs for Residents and Clinical Fellows Grant (R25EB025787); NSF/NIH Joint Initiative on Quantitative Approaches to Biomedical Big Data Program (R01CA225190); NIH NCI Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Program (R01CA214825); NIH/NCI CCSG Radiation Oncology and Cancer Imaging Program (P30CA016672); Charles and Daneen Stiefel Center for Head and Neck Cancer Oropharyngeal Cancer Research Program; and the Program in Image-Guided Cancer Therapy. C.F. also reports payment for expert testimony from Elekta AB, the American Association for Physicists in Medicine, the University of Alabama-Birmingham, the American Society for Clinical Oncology, the Royal Australian and New Zealand College of Radiologists, the American Society for Radiation Oncology, the Radiological Society of North America, and the European Society for Radiation Oncology, and support for attending meetings or travel from Elekta AB, the American Association for Physicists in Medicine, the University of Alabama-Birmingham, the American Society for Clinical Oncology, the Royal Australian and New Zealand College of Radiologists, the American Society for Radiation Oncology, the Radiological Society of North America, and the European Society for Radiation Oncology. N.G. reports consulting fees from Intuitive Surgical, Genzyme, Dragonfly Therapeutics, and Regeneron, and participates in the scientific advisory board for PDS Biotechnology. N.T. reports a grant from Varian Medical Systems and an R25 Award. All other authors have no disclosures to declare.

Data sharing statement:

Data are available on request owing to privacy/ethical restrictions.

References

1. Fletcher GH, Lindberg RD. Squamous cell carcinomas of the tonsillar area and palatine arch. AJR Am J Roentgenol 1966;96:574–587.
2. Berger DS, Fletcher GH, Lindberg RD, Jesse RH Jr. Elective irradiation of the neck lymphatics for squamous cell carcinomas of the nasopharynx and oropharynx. Am J Roentgenol Radium Ther Nucl Med 1971;111:66–72.
3. Al-Mamgani A, van Werkhoven E, Navran A, et al. Contralateral regional recurrence after elective unilateral neck irradiation in oropharyngeal carcinoma: A literature-based critical review. Cancer Treat Rev 2017;59:102–108. [PubMed: 28779635]
4. Deschuymer S, Mehanna H, Nuyts S. Toxicity reduction in the treatment of HPV positive oropharyngeal cancer: Emerging combined modality approaches. Front Oncol 2018;8:439. [PubMed: 30356651]
5. Taku N, Wang L, Garden AS, et al. Proton therapy for HPV-associated oropharyngeal cancers of the head and neck: A de-intensification strategy. Curr Treat Options Oncol 2021;22:54. [PubMed: 34086150]
6. Jackson SM, Hay JH, Flores AD, et al. Cancer of the tonsil: The results of ipsilateral radiation treatment. Radiother Oncol 1999;51:123–128. [PubMed: 10435802]
7. O'Sullivan B, Warde P, Grice 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. [PubMed: 11567806]
8. 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. [PubMed: 22250010]
9. Tsai CJ, Galloway TJ, Margalit DN, et al. Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary. Head Neck 2021;43:392–406. [PubMed: 33068064]
10. 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. [PubMed: 22019242]

11. Sher DJ, Adelstein DJ, Bajaj GK, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence-Based Clinical Practice Guideline. Pract Radiat Oncol 2017;7:246–253. [PubMed: 28428019]
12. Edge SB, Compton CC. The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–1474. [PubMed: 20180029]
13. Huang SH, Waldron J, Bratman SV, et al. Re-evaluation of ipsilateral radiation for T1-T2N0-N2b tonsil carcinoma at the Princess Margaret Hospital in the human papillomavirus era, 25 years later. Int J Radiat Oncol Biol Phys 2017;98:159–169. [PubMed: 28258895]
14. Liu C, Dutu G, Peters LJ, Rischin D, Corry J. Tonsillar cancer: The Peter MacCallum experience with unilateral and bilateral irradiation. Head Neck 2014;36:317–322. [PubMed: 23729387]
15. Kennedy WR, Herman MP, Deraniyagala RL, et al. Ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. Eur Arch Otorhinolaryngol 2016;273:2151–2156. [PubMed: 26223350]
16. Koo TR, Wu HG. Long-term results of ipsilateral radiotherapy for tonsil cancer. Radiat Oncol J 2013;31:66–71. [PubMed: 23865002]
17. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. Cancer 2017;123:4594–4607. [PubMed: 28881377]
18. Maskell D, Buckley H, Sission K, Roques T, Geropantas K. Ipsilateral neck radiotherapy in N2b well-lateralized tonsil cancer: Approach with caution. Head Neck 2019;41:2937–2946. [PubMed: 31059180]
19. 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. [PubMed: 25052236]
20. Christopherson KM, Moreno AC, Elgohari B, et al. Outcomes after salvage for HPV-positive recurrent oropharyngeal cancer treated with primary radiation. Oral Oncol 2021;113 105125. [PubMed: 33360375]
21. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol 2014;32:3365–3373. [PubMed: 24958820]
22. Bhayani MK, Hutcheson KA, Barringer DA, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: Factors affecting placement and dependence. Head Neck 2013;35:1634–1640. [PubMed: 23322563]
23. Setton J, Lee NY, Riaz N, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. Cancer 2015;121:294–301. [PubMed: 25286832]
24. Yom SS, Torres-Saavedra P, Caudell JJ, et al. Reduced-dose radiation therapy for HPV-associated oropharyngeal carcinoma (NRG Oncology HN002). J Clin Oncol 2021;39:956–965. [PubMed: 33507809]
25. Contreras JA, Spencer C, DeWees T, et al. Eliminating postoperative radiation to the pathologically node-negative neck: Long-term results of a prospective phase II study. J Clin Oncol 2019;37:2548–2555. [PubMed: 31246526]

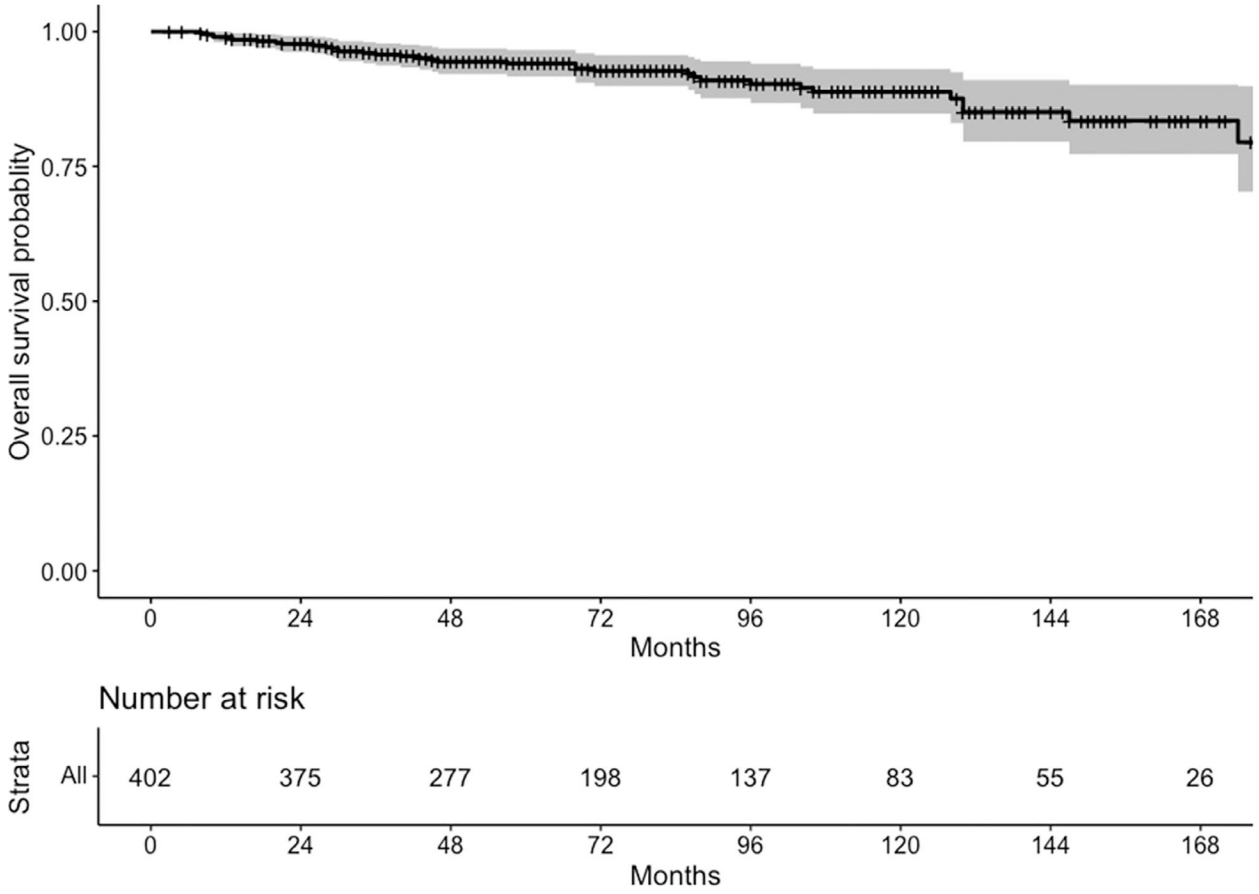

Fig. 1.
Overall survival in 403 patients treated with unilateral radiation for cancer of the tonsil.

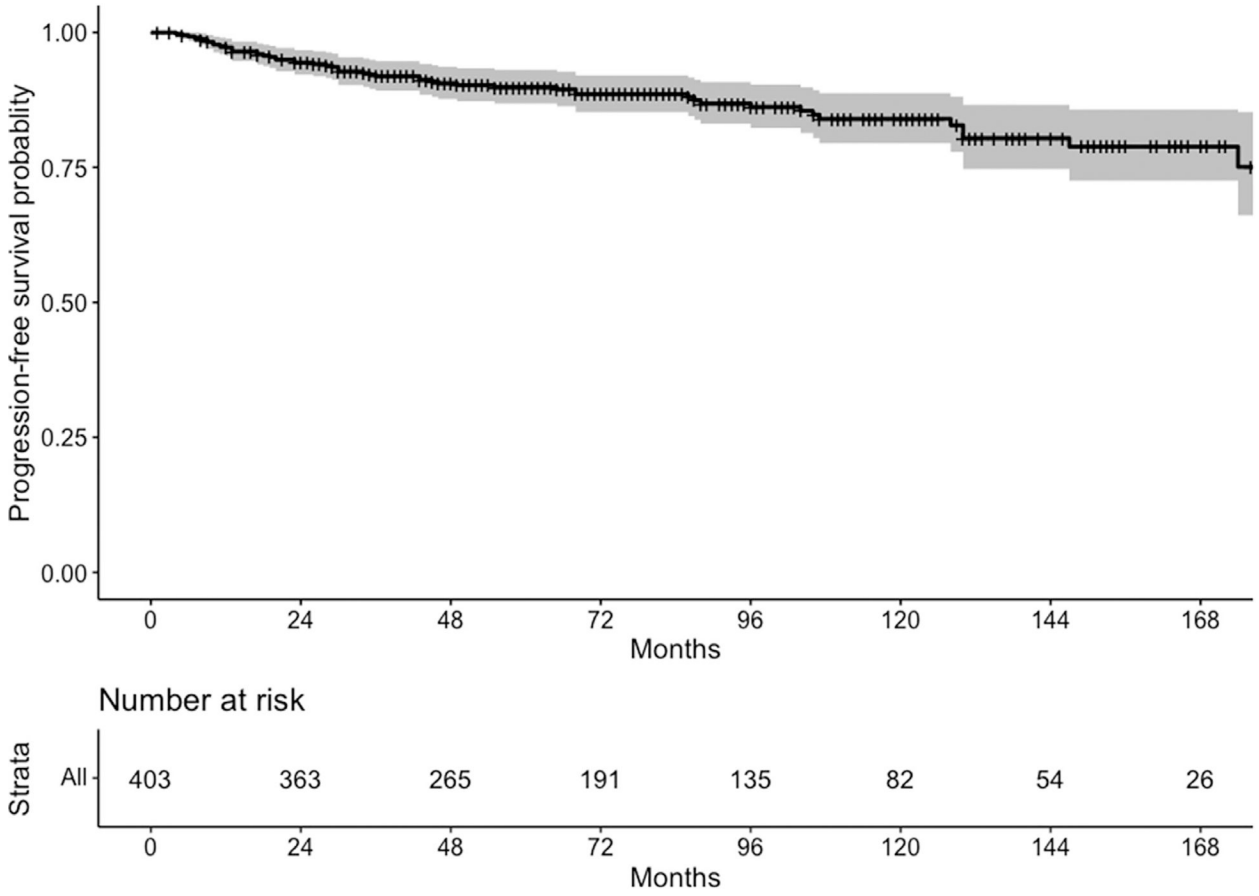

Fig. 2.

Progression-free survival in 403 patients treated with unilateral radiation for cancer of the tonsil.

Table 1

Patient and tumor characteristics for all patients (N = 403) and patients with HPV-associated OPC (n = 294)

Characteristic	All patients	Patients with HPV-OPC
Median age (IQR), y	56 (50–63)	57 (51–64)
Sex		
Male	312 (77.4)	233 (79.3)
Female	91 (22.5)	61 (26.2)
Smoking status		
Never	208 (51.5)	162 (55.1)
Former	106 (26.2)	77 (26.2)
Current	65 (16.1)	53 (18.0)
Missing	24 (5.9)	2 (0.7)
Tumor classification		
T1	243 (60.1)	190 (64.6)
T2	114 (28.2)	86 (29.3)
T3	3 (0.8)	2 (0.7)
T4	1 (0.2)	1 (0.3)
Tx	42 (10.4)	15 (5.1)
Lymph node classification		
N0	60 (14.9)	34 (11.6)
N1	93 (23.1)	64 (21.8)
N2a	56 (13.9)	41 (13.9)
N2b	181 (44.9)	152 (51.7)
Nx	13 (3.2)	3 (1.0)

Abbreviations: HPV = human papillomavirus; IQR = interquartile range; OPC = oropharyngeal cancer.

Data are presented as n (%) unless otherwise indicated.

Table 2

Treatment characteristics for all patients (N = 403) and patients with HPV-associated OPC (n = 294)

Characteristic	All patients	Patients with HPV-OPC
Radiation therapy treatment technique		
3DCRT	19 (4.7)	0 (0.0)
IMRT	341 (84.4)	252 (85.7)
Protons	43 (10.6)	42 (14.3)
Radiation therapy dose (IQR), Gy	66 (66–69)	66 (66–69)
Induction chemotherapy		
Yes	27 (6.7)	20 (6.8)
No	376 (93.1)	274 (93.2)
Concurrent chemotherapy		
Yes	131 (32.5)	117 (39.8)
No	272 (65.1)	177 (60.2)
Induction and concurrent chemotherapy		
Yes	6 (1.5)	5 (1.7)
No	397 (98.3)	289 (98.2)

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; HPV = human papillomavirus; IMRT = intensity modulated radiation therapy; OPC = oropharyngeal cancer.

Data are presented as n (%) unless otherwise indicated.

Table 3

Details of nodal pathology in 90 patients who had surgical removal of their lymphadenopathy

Characteristic	Neck dissection	Excision
Total	44	46
Number of positive nodes		
1	16	37
2	12	2
3–4	9	1
5–6	6	0
Missing	1	6
Extranodal extension	22	32
Largest node, median (range), cm	3.5 (0.5–5.8)	3 (1.5–6)
HPV-associated	36	30

Abbreviation: HPV = human papillomavirus.

Table 4

Details of 9 patients treated with ipsilateral radiation who developed recurrent nodal disease in the contralateral neck

Patient	Smoker	HPV-associated cancer	Staging included PET	T-category	N-category	Size of largest node (cm)	Concurrent drug with radiation	Time to recurrence (from end of radiation) in contralateral neck	Other site(s) of recurrence	Status from time of recurrence
1	Never	Unknown	No	1	0		None	6 mo	None	Alive, 106 mo
2	Former	Yes	No	2	2b	3.0	None	5 mo	Primary and ipsilateral neck	Dead, 65 mo
3	Never	Yes	Yes	1	1	2.0	None	3 mo	None	Alive, 90 mo
4	Never	Yes	Yes	2	2b	1.7	Cetuximab	6 mo	None	Alive, 96 mo
5	Current	Yes	Yes	1	2b	3.6	Cetuximab	55 mo	Primary	Alive, 46 mo
6	Never	Yes	No	2	1	1.7	None	47 mo	None	Alive, 45 mo
7	Never	Unknown	No	1	2b	3.0	Cisplatin	46 mo	None	Alive, 0 mo
8	Former	Yes	Yes	2	2b	2.8	Cetuximab	3 mo	Primary	Dead, 34 mo
9	Never	Yes	Yes	2	2b	2.1	Cetuximab	13 mo	None	Alive, 30 mo

Abbreviations: HPV = human papillomavirus; PET = positron emission tomography.