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Risk and Clinical Risk Factors Associated With Late Lower Cranial Neuropathy in Long-term Oropharyngeal Squamous Cell Carcinoma Survivors

Puja Aggarwal, PhD, BDS, MPH, [1,2] Ryan P. Goepfert, MD, [1] Adam S. Garden, MD, [3] Naveen Garg, MD, [4] Jhankruti S. Zaveri, MPH, [1] Xianglin L. Du, MB, MS, PhD, [2] Michael D. Swartz, PhD, [2] Stephen Y. Lai, MD, PhD, [1] C. David Fuller, MD, PhD, [3] Renata Ferrarotto, MD, [5] Erich M. Sturgis, MD, MPH, [6] Linda B. Piller, MD, MPH, [2] and Katherine A. Hutcheson, PhD [1,3]

[1]Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston
[2]University of Texas School of Public Health, Houston
[3]Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston
[4]Department of Abdominal Imaging, University of Texas MD Anderson Cancer Center, Houston
[5]Department of Thoracic Head and Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston
[6]Department of Otolaryngology–Head and Neck Surgery, Baylor College of Medicine, Houston, Texas
Corresponding author.

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Corresponding Author: Katherine A. Hutcheson, PhD, Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, PO Box 301402, Unit 1445, Houston, TX 77030 (karnold@mdanderson.org).

Author Contributions: Drs Aggarwal and Hutcheson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Aggarwal, Goepfert, Garden, Du, Lai, Fuller, Sturgis, Hutcheson.

Acquisition, analysis, or interpretation of data: Aggarwal, Goepfert, Garden, Garg, Zaveri, Du, Swartz, Fuller, Ferrarotto, Sturgis, Piller, Hutcheson.

Drafting of the manuscript: Aggarwal, Garden, Zaveri, Du, Fuller, Sturgis, Hutcheson.

Critical revision of the manuscript for important intellectual content: Aggarwal, Goepfert, Garden, Garg, Du, Swartz, Lai, Fuller, Ferrarotto, Sturgis, Piller, Hutcheson.

Statistical analysis: Aggarwal, Garden, Du, Swartz, Fuller, Sturgis, Hutcheson.

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Key Points

Question

What are the cumulative incidence of and clinical factors associated with late lower cranial neuropathy (LCNP) among patients with long-term survival of oropharyngeal squamous cell carcinoma?

Findings

In this cohort study of 2021 long-term survivors of oropharyngeal squamous cell carcinoma, 88 (4.4%) were diagnosed with late LCNP; cumulative incidence was 0.024 at 5 years, 0.061 at 10 years, and 0.098 at 15 years of follow-up. T classification and accelerated radiotherapy fractionation were associated with LCNP, and among patients with nonsurgical treatment, induction chemotherapy was also associated with LCNP.

Meaning

Although rare in the overall population, cumulative risk of late LCNP progressed to 10% among the patients in this study cohort, and clinical risk factors reflected greater tumor burden and treatment intensity; further efforts are necessary to investigate risk reduction, surveillance, and management of late LCNP.

This cohort study assesses the cumulative incidence of and clinical factors associated with late lower cranial neuropathy among patients with long-term survival of oropharyngeal squamous cell carcinoma.

Abstract

Importance

Lower cranial neuropathy (LCNP) is a rare, but permanent, late effect of radiotherapy and other cancer therapies. Lower cranial neuropathy is associated with excess cancer-related symptoms and worse swallowing-related quality of life. Few studies have investigated risk and clinical factors associated with late LCNP among patients with long-term survival of oropharyngeal squamous cell carcinoma (OPSCC survivors).

Objective

To estimate the cumulative incidence of and identify clinical factors associated with late LCNP among long-term OPSCC survivors.

Design, Setting, and Participants

This single-institution cohort study included disease-free adult OPSCC survivors who completed curative treatment from January 1, 2000, to December 31, 2013. Exclusion criteria consisted of baseline LCNP, recurrent head and neck cancer, treatment at other institutions, death, and a second primary, persistent, or recurrent malignant neoplasm of the head and neck less than 3 months after treatment. Median survival of OPSCC among the 2021 eligible patients was 6.8 (range, 0.3-18.4) years. Data were analyzed from October 12, 2019, to November 13, 2020.

Main Outcomes and Measures

Late LCNP events were defined by neuropathy of the glossopharyngeal, vagus, and/or hypoglossal cranial nerves at least 3 months after cancer therapy. Cumulative incidence of LCNP was estimated using the Kaplan-Meier method, and multivariable Cox proportional hazards models were fit.

Results

Among the 2021 OPSCC survivors included in the analysis of this cohort study (1740 [86.1%] male; median age, 56 [range, 28-86] years), 88 (4.4%) were diagnosed with late LCNP, with median time to LCNP of 5.4 (range, 0.3-14.1) years after treatment. Cumulative incidence of LCNP was 0.024 (95% CI, 0.017-0.032) at 5 years, 0.061 (95% CI, 0.048-0.078) at 10 years, and 0.098 (95% CI, 0.075-0.128) at 15 years of follow-up. Multivariable Cox proportional hazards regression identified T4 vs T1 classification (hazard ratio [HR], 3.82; 95% CI, 1.85-7.86) and accelerated vs standard radiotherapy fractionation (HR, 2.15; 95% CI, 1.34-3.45) as independently associated with late LCNP status, after adjustment. Among the subgroup of 1986 patients with nonsurgical treatment, induction chemotherapy regimens including combined docetaxel, cisplatin, and fluorouracil (TPF) (HR, 2.51; 95% CI, 1.35-4.67) and TPF with cetuximab (HR, 5.80; 95% CI, 1.74-19.35) along with T classification and accelerated radiotherapy fractionation were associated with late LCNP status after adjustment.

Conclusions and Relevance

This single-institution cohort study found that, although rare in the population overall, cumulative risk of late LCNP progressed to 10% during the survivors' lifetime. As expected, clinical factors associated with LCNP primarily reflected greater tumor burden and treatment intensity. Further efforts are necessary to investigate risk-reduction strategies as well as surveillance and management strategies for this disabling late effect of cancer treatment.

Introduction

Human papillomavirus (HPV)–associated oropharyngeal cancer (OPC) is an increasingly prevalent, highly curable disease, especially among younger patients.[1,2,3,4] These patients will live longer with late adverse effects that may be disparate between different treatment modalities, warranting investigation to support patients with long-term survival of OPC (hereinafter referred to as survivors).[2,3,4] This scenario is highlighted by the substantial rates of late moderate to severe toxic effects (prevalence, 16.5%-20.4%) reported by the Radiation Therapy Oncology Group 1016 among patients with OPC who were positive for HPV.[5]

Lower cranial neuropathy (LCNP) is a rare but permanent, potentially devastating late effect induced by normal tissue injury due to radiotherapy or surgery and other head and neck cancer (HNC) therapies. Treatment-associated fibrosis of nerve tracts or adjacent soft tissues in HNC may lead to delayed progressive neurovascular damage, and eventually LCNP, which is associated with profound functional impairments.[1,2,3,4] Lower cranial neuropathy can occur unilaterally or bilaterally and can affect the glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII) cra-

nial nerves. These nerves are crucial for the oropharyngeal phase of swallowing, speech production, and shoulder function.[6,7,8,9,10,11,12] It is postulated that LCNP potentially leads to accelerated functional decline among patients with HNC and late radiotherapy-associated dysphagia (late RAD), a severe form of dysphagia many years after radiotherapy.[11] Late RAD is associated with extreme swallowing impairment. Approximately 85% of OPC survivors with late RAD develop pneumonia and more than 60% require long-term feeding-tube placement.[11] Oropharyngeal cancer survivors with late LCNP reported substantially worse cancer treatment–related symptoms with the largest effect size and detrimental effects on swallowing, speech, mucus problems, choking, voice, fatigue, and poor swallowing-related quality of life.[8,9]

Hutcheson et al[7] previously reported rates of late LCNP of 2.1% at 5 years and 6.1% at 7 years among 59 OPC survivors. Dong et al[13] more recently reported a crude incidence of cranial neuropathy of 14% among 112 HNC survivors with more than 10 years of follow-up. These studies suggest a progressive increase of LCNP risk over time.[7,13] Further, LCNP has delayed occurrence. Among patients with nasopharyngeal cancer (NPC), LCNP occurrence has been reported as early as 12 to 240 months after radiotherapy. These reports highlight the need for long-term surveillance of LCNP among patients with HNC.[7,10,11]

Cranial nerves are considered radioresistant, but radiotherapy can contribute to acute and late cranial nerve injury.[7] It is postulated that late LCNP may be caused by peripheral nerve and brainstem injury, and radiotherapy-associated peripheral nerve injury may occur by axonal degeneration, suppression of Schwann cell proliferation, and connective tissue fibrosis entrapping nerve fibers.[7] Total radiation dose is most commonly suggested as the chief predisposing factor for LCNP, but the contributing threshold dose is not known.[7] Literature suggests that the dose to regions of interest in the radiotherapy field, including the superior pharyngeal constrictor region, may play a pivotal role in nerve injury.[14] However, previous studies investigating LCNP have predominantly been case series among NPC survivors, and few studies have addressed LCNP among OPC survivors.[15] Therefore, the objective of this study was to estimate the cumulative incidence of late LCNP and identify clinical factors associated with LCNP among long-term survivors of oropharyngeal squamous cell carcinoma (OPSCC). The hypothesis for this study was that 5-year incidence of LCNP would approximate 5%, and the risk of LCNP would correlate with age, tumor subsite and stage, smoking status, systemic therapy, and radiotherapy dose and fractionation.

Methods

Study Population

This retrospective cohort study included patients with OPSCC who completed treatment with curative intent at the University of Texas MD Anderson Cancer Center from January 1, 2000, to December 31, 2013, and were 18 years or older at diagnosis. Waiver of informed consent and study approval was obtained from the institutional review board of MD Anderson Cancer Center. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients who died less than 3 months after treatment and those with secondary primary malignant neoplasms or persistent or recurrent HNC less than 3 months after treatment were excluded. Patients with LCNP due to any cause at the time of cancer diagnosis or with clinical signs of LCNP before or during cancer treatment were also excluded, regardless of their baseline or acute functional status. Patients who developed recurrences, primary malignant neoplasms, or distant metastasis after more than 3 months were censored at the time of the event. Details of study eligibility are presented in Figure 1.

Primary Outcome

The primary outcome was late LCNP status. Late LCNP was abstracted from the medical records as the results of clinical examination of cranial nerve function by the head and neck surgeon, radiation oncologist, and speech pathologist. Radiographic evidence of chronic denervation was considered confirmatory, when available; electromyographic and nerve conduction studies were not routine. Late LCNP status was defined as swallowing-associated neuropathy of cranial nerves IX, X, and XII with minimum onset of at least 3 months after the end of cancer treatment.[15,16,17] The 3-month cutoff for nerve dysfunction was chosen according to the National Cancer Institute Common Toxicity Manual's definition of late radiation effects as occurring 90 days or more after initiation of radiotherapy.[17] Patients with immediate postsurgical LCNP were not included as LCNP cases based on our definition of late onset as at least 3 months. Because cranial nerve XI palsy was inconsistently recorded, it was excluded from analysis, with intent to focus on swallowing-associated LCNP. Medical records were reviewed to identify LCNP cases that were verified by a fellowship-trained head and neck surgeon (R.P.G.). Time to event of LCNP diagnosis and information about competing events were collected. Details are presented elsewhere.[8]

Clinicodemographic Variables

The following variables were abstracted from medical records: age and smoking status at diagnosis, sex, and clinical variables, including T and N categories (American Joint Committee on Cancer's *AJCC Cancer Staging Manual*, 7th edition[18]), HPV status, subsite, OPSCC treatment modality, radiotherapy dose and type, radiotherapy fractionation, chemotherapy, surgery, and ability to eat a solid food diet before treatment (as a clinical surrogate of baseline dysphagia in absence of routine objective swallowing evaluation during the period of review). Survival time was calculated as the difference between the date of the first visit to the head and neck clinic and the date of LCNP diagnosis, competing event diagnosis, or last follow-up.

Statistical Analysis

Data were analyzed from October 12, 2019, to November 13, 2020. Descriptive statistics were computed and cumulative incidence of LCNP was calculated using the Kaplan-Meier method. Log-rank test was used to investigate between-group differences by LCNP status. Multivariable Cox proportional hazards models were fit, univariate analysis was conducted, and candidate clinical factors with $P < .05$ on the Wald test along with literature-based a priori–defined clinically important covariates, including age, tumor subsite, T classification, smoking status, and treatment modal-

ity, were entered into multivariable models.[19] The fit of the final model was tested using the overall goodness-of-fit χ^2 test, and subgroup analyses were conducted. Hazard ratios (HRs) and corresponding 95% CIs were estimated. All reported *P* values were 2-sided and considered statistically significant at $P < .05$. Analysis was conducted using STATA, version 14.0 (StataCorp LLC).

Results

Sample Characteristics

A total of 2021 eligible OPSCC survivors (1740 [86.1%] male and 281 female [13.9%]; median age, 56 [range, 28-86; interquartile range, 50-63] years) with a median survival duration of 6.8 (range, 0.3-18.4) years were included in analysis. Of these, 1369 patients were followed up for 5 years, and 524 had a minimum of 10 years of follow-up. Among the 2021 patients with OPC, 2000 (99.0%) received radiotherapy, 35 (1.7%) underwent transoral robotic surgery, 1365 (67.5%) received chemotherapy, and 511 (25.3%) had neck dissection. Table 1 summarizes the sample data.

Late LCNP

Overall, 88 OPSCC survivors (4.4%) were diagnosed with late LCNP, with median time to neuropathy onset of 5.4 (range, 0.3-14.1) years after treatment. Among LCNP cases, cranial nerve XII neuropathy was most common (69 [78.4%]). Because isolated cranial nerve IX neuropathy was hard to detect, palsies of cranial nerves X and IX were combined and included 39 patients (44.3%). Polyneuropathy of cranial nerves IX, X, and XII was diagnosed in 20 patients with LCNP (22.7%). Among LCNP cases, 56 (63.6%) had ipsilateral, 8 (9.1%) had contralateral, and 23 (26.1%) had bilateral nerve damage to the index OPSCC. For 1 patient with LCNP, laterality was undetermined.

Cumulative Incidence of LCNP

Cumulative incidence of late LCNP among all OPSCC survivors was 0.024 (95% CI, 0.017-0.032) at 5 years, 0.061 (95% CI, 0.048-0.078) at 10 years, and 0.098 (95% CI, 0.075-0.128) at 15 years of follow-up. Figure 2 and Table 1 summarize the cumulative incidence results. Cumulative incidence of LCNP increased proportionally with higher T classification, with the highest incidence of 0.259 (95% CI, 0.154-0.417) among survivors treated for T4 tumors.

Risk Factors for LCNP

Table 2 summarizes univariate and multivariable analysis results. Univariate analysis identified T classification (HR for T4, 6.10; 95% CI, 3.29-11.33), smoking status (HR for current smoking, 1.74; 95% CI, 0.97-3.11), treatment multimodality (HR, 2.09; 95% CI, 1.27-3.44), chemotherapy (HR, 2.13; 95% CI, 1.30-3.50), radiotherapy dose (HR, 1.24; 95% CI, 1.14-1.36), and fractionation schedule (HR, 2.53; 95% CI, 1.63-3.92) as significantly associated with late LCNP. Multivariable Cox proportional hazards regression identified T4 classification (HR, 3.82; 95% CI, 1.85-7.86) and accelerated radiotherapy fractionation (HR, 2.15; 95% CI, 1.34-3.45) as independently associated with

late LCNP status, adjusting for age, subsite, smoking, therapeutic modality, and solid food diet before treatment (Figure 3). Goodness-of-fit χ^2 test for the final model was not statistically significant and the model fit the data well. Univariate and multivariable Cox proportional hazards models for late LCNP in an exploratory subset analysis among patients who were positive for HPV (n = 817) are summarized in eTable 1 in the Supplement.

Subgroup Analysis: LCNP Among Those Treated With Nonsurgical Therapy

Among 1986 patients undergoing nonsurgical treatment, 631 (31.8%) received induction chemotherapy, of whom 243 (38.5%) received a combination of docetaxel (Taxotere), cisplatin (Platinol), and fluorouracil (TPF); 33 (5.2%) received combination cetuximab and TPF (C-TPF); 124 (19.7%) received combination paclitaxel, carboplatin, and cetuximab (PCC); and the remaining 221 (35.0%) received varied induction chemotherapy regimens. At 15 years of follow-up, the cumulative incidence of late LCNP among survivors who received induction TPF was 0.121 (95% CI, 0.063-0.228); C-TPF, 0.099 (95% CI, 0.033-0.279); and PCC, 0.098 (95% CI, 0.038-0.244). Among patients undergoing nonsurgical treatment, induction TPF (HR, 2.51; 95% CI, 1.35-4.67) and induction C-TPF (HR, 5.80; 95% CI, 1.74-19.35) were identified in addition to T classification and accelerated radiotherapy fractionation as significantly associated with late LCNP, adjusting for any concurrent chemotherapy treatment in addition to the covariates in the final model. Multivariable results are summarized in eTables 2 and 3 in the Supplement.

Discussion

This single-center retrospective cohort study in 2021 OPSCC survivors estimated with high precision that late LCNP risk progressed to 10% cumulative risk during the 15-year surveillance period. T classification and accelerated radiotherapy fractionation were independent risk factors of LCNP. Furthermore, among patients with nonsurgical treatment, induction TPF and C-TPF chemotherapy were additional independent risk factors of LCNP.

The steady rise in the cumulative incidence estimates of LCNP within 15 years of diagnosis is of great concern. Most study participants were middle-aged at the time of diagnosis, as evidenced by the interquartile range of 50 to 63 years for age at diagnosis, which is similar to the age distribution of most HPV-positive patients with OPC today.[20] This escalating LCNP risk over time is similar to that of another study among 59 patients who survived OPC, which reported a cumulative risk of 2.1% at 6 years, 6.1% at 7 years, and 11.0% at 8 years of follow-up.[7] Last, the expected performance of risk estimates in subgroup stratifications (as per T classification, treatment modality, and radiotherapy fractionation) support both the accuracy and validity of the cumulative incidence estimates.

Among survivors of HNC, the progressive trajectory of LCNP has long-term clinical implications. A previous study[7] reported severe decline in function over time as measured by multiple functional metrics after LCNP development. Over time, HNC survivors with LCNP may be compelled to modify their diet, need extended meal times, feel self-conscious about eating in social settings, be socially isolated, and experience poor quality of life.[21] Studies have reported worse treatment-related symptoms, poor swallowing-related quality of life, and worse functional metrics, including long-

term feeding tube dependence, lack of normalcy of diet, dietary restrictions in public, weight loss, aspiration pneumonia, and tracheostomy among OPC survivors with late LCNP.[8,9] Likewise, this devastating impact of LCNP was reflected by qualitative remarks observed by patients with LCNP in the present study, which indicated profound distress and suffering with progressive loss of function over time, contributing to patients regretting pursuit of any OPSCC treatment at all. In addition, a recent study[22] reported that OPC incidence is increasing among the older population, who are likely to have comorbidities leading to additional treatment–related morbidity. These findings altogether suggest that as OPC survival probabilities continue to improve, the number of survivors at risk of LCNP-associated functional impairment grows also. These survivors eventually transition from oncologic management to care by primary care physicians with the need for increased surveillance to assess and treat late LCNP.

The results from this study suggest that patients with OPSCC and T4 tumors were a mean of 3.82 times more likely to develop LCNP than those with T1 tumors after adjusting for age, subsite, smoking, therapeutic modality, radiotherapy schedule, and solid food diet before treatment. Identification of T classification as a factor associated with outcome is plausible given that locally advanced OPSCC tumors are bulky with extensive radiotherapy planning target volume, including larger gross tumor volume and clinical target volume.[23] These larger irradiation fields are more likely to include neurovascular structures and cranial nerves, the injury of which may precipitate LCNP. In addition, patients with T4 tumors may have a greater risk of subclinical baseline nerve injury by compression of nerve tracts by larger tumors, despite our attempt to control for baseline LCNP.[24,25,26] Advanced-stage HNC tumors are also treated more aggressively with multimodality regimens, including either chemoradiotherapy or surgery followed by chemoradiotherapy or chemotherapy.[27] Chemoradiotherapy is regarded as standard of care for locally advanced OPSCC, but multimodality therapy can result in acute and persistent tissue changes and may lead to severe acute and late treatment-related morbidity.[27,28]

In this study, patients with OPSCC treated with accelerated radiotherapy fractionation were 2.15 times more likely to develop LCNP than those who received standard radiotherapy fractionation after adjusting for age, subsite, smoking status, T category, therapeutic modality, and solid food diet before treatment. Accelerated radiotherapy fractionation regimens incorporate several radiotherapy fractions per day with goals to shorten total treatment time and overcome tumor cell regeneration, but its use remains controversial.[29,30] Accelerated radiotherapy fractionation may accomplish an increase in mean radiotherapy dose above the standard 10 Gy/wk, which may contribute to an increased possibility of nerve injury.[23] Furthermore, regeneration in some healthy tissues may be slower, and as a consequence of longer half-time for repair, these tissues may be more susceptible to radiotherapy-induced injury.[23] Last, an increase in radiotherapy dose per week may contribute to an increase in early tissue injury, such as mucositis or other severe and protracted acute effects, which may heighten chronic tissue injury and consequential late effects.[23] In the present study, more than 20% of LCNP cases received concomitant boost accelerated radiotherapy, which includes a total radiotherapy dose of 72 Gy, given in 42 fractions during 6 weeks with a twice-daily second boost radiotherapy dose given during last 2 weeks of radiotherapy, and was a prevailing strategy for radiotherapy fractionation at University of Texas MD Anderson Cancer Center during the study period.[30,31,32] Furthermore, Teo et al[32] conducted a trial among patients with NPC and reported that accelerated radiotherapy hyperfractionation was associated

with higher LCNP incidence than conventional fractionation (13.0% vs 8.7%), possibly owing to increased risk of central nervous system injury, including damage to cranial nerves, temporal lobe, and brainstem. Finally, the effect estimates for accelerated radiotherapy in the present study are robust and similar to those of a previous study among NPC, which reported RT fractionation schedule (risk ratio, 2.91) as a substantial factor associated with upper cranial nerve neuropathy but not of LCNP.[33]

Among patients receiving nonsurgical treatment, this study identified induction TPF and C-TPF as risk factors associated with LCNP. Chemotherapy drugs are cytotoxic and modify radiation sensitivity of cells either by altering their cell-cycle phase or by interfering with repair of radiation-initiated double-strand DNA breaks.[34,35] Thus, while enhancing tumor control, they can also contribute to nerve injury. This hypothesis is supported by a previous study[33] of patients with NPC that reported that chemotherapy was significantly associated with cranial neuropathy (relative risk, 1.42); this finding has been reported by other studies as well.[36,37] Thus, although various authors have associated concurrent chemotherapy with LCNP after NPC radiotherapy, the results of this study for the first time, to our knowledge, find an association between induction chemotherapy and elevated risk of LCNP in OPSCC. Our results are also supported by a prospective study among patients with OPC,[38] which reported that induction chemotherapy combined with chemoradiotherapy was significantly associated with moderate to severe RAD 3 to 6 months after radiotherapy. Finally, the role of induction chemotherapy has yet to be established in OPSCC treatment, especially in the context of trials advocating for induction chemotherapy as a potential radiotherapy dose deintensification strategy, with several trials failing to demonstrate overall, recurrence-free, and disease-free survival benefit; therefore, the results of this study merit consideration when considering induction chemotherapy treatment in modern day practice.[39,40,41]

Limitations

This large cohort study estimated LCNP risk, and in accordance with our hypothesis, we identified T classification and accelerated radiotherapy fractionation as important risk factors for LCNP. The study has some limitations. Study participants had varying survival times, and the findings may be susceptible to survival bias. Nonetheless, consistently precise and robust effect estimates of LCNP were identified. The retrospective medical record review may have contributed to some misclassification of variables, but the robust risk and effect estimates suggest minimal impact. Although some LCNP events may have been misclassified owing to a 3-month cutoff as the start of the late period, only 3 of 88 LCNP events were first detected within 3 to 6 months of follow-up after cancer therapy. Testing for HPV was also not conducted in approximately half of the cohort; therefore, accurate estimates of risk based on HPV status could not be assessed. Important questions remain regarding de-escalation strategies for HPV-associated disease as it relates to late effects such as LCNP. De-escalation strategies were not applied for HPV-associated disease at our institution during the study period, thus necessitating future studies to elucidate this situation further. Subset analyses in patients with HPV-associated disease in this data set must be considered exploratory and particularly susceptible to unmeasured selection bias and time-dependent differences that influenced adoption of new treatments.

Contrary to our hypothesis, this study did not identify a significant association between LCNP and smoking. Data on continued smoking status were not available, and a limited number of current smokers were enrolled in the study (294 [14.5%] of the study population), which did not allow robust assessment of the implications of smoking for LCNP. The present study also had small numbers of patients undergoing surgery, thereby limiting the generalizability of the study results to the growing population with OPSCC receiving primary surgery. Importantly, LCNP risk may have been underestimated in this study because neuropathy diagnosis was primarily made via clinical signs of loss of motor function and did not consider loss of sensory function, which is unreliably reported in medical records at our institution. Furthermore, palsy of cranial nerve XI was excluded, and isolated palsy of cranial nerve IX was not detected. Therefore, actual risk of LCNP among OPSCC survivors is likely to be higher than reported in this study.

Conclusions

It is of utmost importance going forward to investigate evidence-based risk identification and early risk reduction strategies for detection, prevention, and management of late LCNP. Furthermore, effective screening interventions may consider the use of patient-reported outcomes tools for surveillance and detection of LCNP. Future studies should further explore treatment details such as radiotherapy dose to organs at risk, induction chemotherapy, and transoral robotic surgery in development of LCNP.[42] Last, it is crucial that HNC treatment selection account for long-term treatment-related morbidity and prioritize treatment based on individual patient preferences to reduce disease burden owing to late adverse effects. Better radiotherapy techniques need to be developed to optimize dose delivery, less toxic chemotherapy agents need to be investigated, and treatment deintensification strategies that maintain cure and prevent late adverse effects warrant exploration.

In this large retrospective cohort study, the lifetime risk estimates of late LCNP during a 15-year follow-up into OPSCC survivorship demonstrate that 1 of 10 OPSCC survivors is likely to develop LCNP. The potential effect of LCNP on quality of life among these OPSCC survivors, typically middle-aged at the time of diagnosis, may be devastating because LCNP and accompanying late RAD are refractory to treatment and permanent. In this study, treatment intensity and primary tumor burden were independently associated with LCNP. Regardless of cancer stage, accelerated fractionation was independently associated with 2-fold elevated risk of LCNP. Last, the long-term treatment-related burden of OPSCC is becoming more apparent, and there is a need to optimize management of OPSCC by maintaining high rates of disease control while minimizing late adverse effects, including LCNP.

Notes

Supplement.

eTable 1. Univariate and Multivariable Cox Proportional Hazards Models for Late LCNP Among Human Papillomavirus (HPV) Positive Patients (n = 817)

eTable 2. Univariate and Multivariable Analysis of Induction TPF and Late LCNP Among Those Treated With Nonsurgical Therapy (n = 1986)

eTable 3. Univariate and Multivariable Analysis of Induction C-TPF and LCNP Among Those Treated With Nonsurgical Therapy (n = 1986)

References

1. Chaturvedi AK, Engels EA, Pfeiffer RM, et al.. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301. doi: 10.1200/JCO.2011.36.4596 [PMCID: PMC3221528] [PubMed: 21969503] [CrossRef: 10.1200/JCO.2011.36.4596]

2. Ang KK, Harris J, Wheeler R, et al.. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. doi: 10.1056/NEJMoa0912217 [PMCID: PMC2943767] [PubMed: 20530316] [CrossRef: 10.1056/NEJMoa0912217]

3. Ritchie JM, Smith EM, Summersgill KF, et al.. Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. *Int J Cancer*. 2003;104(3):336-344. doi: 10.1002/ijc.10960 [PubMed: 12569557] [CrossRef: 10.1002/ijc.10960]

4. Hafkamp HC, Manni JJ, Haesevoets A, et al.. Marked differences in survival rate between smokers and nonsmokers with HPV 16–associated tonsillar carcinomas. *Int J Cancer*. 2008;122(12):2656-2664. doi: 10.1002/ijc.23458 [PubMed: 18360824] [CrossRef: 10.1002/ijc.23458]

5. Gillison ML, Trotti AM, Harris J, et al.. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393(10166):40-50. doi: 10.1016/S0140-6736(18)32779-X [PMCID: PMC6541928] [PubMed: 30449625] [CrossRef: 10.1016/S0140-6736(18)32779-X]

6. Huang AT, Song S, Dominguez LM, Nguyen J, Goldman RA, Reiter ER. Delayed lower cranial neuropathies following primary radiotherapy for oropharyngeal squamous cell carcinoma. *Laryngoscope*. 2013;123(5):1207-1209. doi: 10.1002/lary.23938 [PubMed: 23619622] [CrossRef: 10.1002/lary.23938]

7. Hutcheson KA, Yuk M, Hubbard R, et al.. Delayed lower cranial neuropathy after oropharyngeal intensity-modulated radiotherapy: a cohort analysis and literature review. *Head Neck*. 2017;39(8):1516-1523. doi: 10.1002/hed.24789 [PMCID: PMC5511776] [PubMed: 28452175] [CrossRef: 10.1002/hed.24789]

8. Aggarwal P, Zaveri JS, Goepfert RP, et al.. Symptom burden associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors. *JAMA Otolaryngol Head Neck Surg*. 2018;144(11):1066-1076. doi: 10.1001/jamaoto.2018.1791 [PMCID: PMC6248190] [PubMed: 30193299] [CrossRef: 10.1001/jamaoto.2018.1791]

9. Aggarwal P, Zaveri JS, Goepfert RP, et al.. Swallowing-related outcomes associated with late lower cranial neuropathy in long-term oropharyngeal cancer survivors: cross-sectional survey analysis. *Head Neck*. 2019;41(11):3880-3894. doi: 10.1002/hed.25923 [PMCID: PMC7240804] [PubMed: 31441572] [CrossRef: 10.1002/hed.25923]

10. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: video case reports. *Head Neck*. 2015;37(4):E56-E62. doi: 10.1002/hed.23840 [PubMed: 25043608] [CrossRef: 10.1002/hed.23840]

11. Katherine AH. Late radiation-associated dysphagia (RAD) in head and neck cancer survivors. *Perspect Swal Swal Dis (Dysph)*. 2013;22(2):61-72. doi: 10.1044/sasd22.2.61 [CrossRef: 10.1044/sasd22.2.61]

12. Luk YS, Shum JS, Sze HC, Chan LL, Ng WT, Lee AW. Predictive factors and radiological features of radiation-induced cranial nerve palsy in patients with nasopharyngeal carcinoma following radical radiotherapy. *Oral Oncol*. 2013;49(1):49-54. doi: 10.1016/j.oraloncology.2012.07.011 [PubMed: 22892236] [CrossRef: 10.1016/j.oraloncology.2012.07.011]

13. Dong Y, Ridge JA, Ebersole B, et al.. Incidence and outcomes of radiation-induced late cranial neuropathy in 10-year survivors of head and neck cancer. *Oral Oncol*. 2019;95:59-64. doi: 10.1016/j.oraloncology.2019.05.014 [PMCID: PMC7747216] [PubMed: 31345395] [CrossRef: 10.1016/j.oraloncology.2019.05.014]

14. Awan MJ, Mohamed AS, Lewin JS, et al.. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. *Oral Oncol*. 2014;50(8):746-752. doi: 10.1016/j.oraloncology.2014.05.003 [PMCID: PMC4158823] [PubMed: 24906528] [CrossRef: 10.1016/j.oraloncology.2014.05.003]

15. King AD, Leung SF, Teo P, Lam WW, Chan YL, Metreweli C. Hypoglossal nerve palsy in nasopharyngeal carcinoma. *Head Neck*. 1999;21(7):614-619. doi: 10.1002/(SICI)1097-0347(199910)21:7<614::AID-HED5>3.0.CO;2-I [PubMed: 10487948] [CrossRef: 10.1002/(SICI)1097-0347(199910)21:7<614::AID-HED5>3.0.CO;2-I]

16. Humbert IA. *The Swallowing Pocket Guide*. Northern Speech Services; 2011.

17. National Cancer Institute, Cancer Therapy Evaluation Program. Common toxicity criteria manual: common toxicity criteria, version 2.0. Published June 1, 1999. Accessed May 31, 2018. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf#search=%22late%20radiation%20effects%22

18. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. Springer; 2009:569-571.

19. Hosmer DW Jr, Lemeshow S. *Applied Logistic Regression.* John Wiley & Sons; 2004.

20. Elrefaey S, Massaro MA, Chiocca S, Chiesa F, Ansarin M. HPV in oropharyngeal cancer: the basics to know in clinical practice. *Acta Otorhinolaryngol Ital*. 2014;34(5):299-309. [PMCID: PMC4299160] [PubMed: 25709145]

21. Pedersen A, Wilson J, McColl E, Carding P, Patterson J. Swallowing outcome measures in head and neck cancer—how do they compare? *Oral Oncol*. 2016;52:104-108. doi: 10.1016/j.oraloncology.2015.10.015 [PubMed: 26564310] [CrossRef: 10.1016/j.oraloncology.2015.10.015]

22. Rettig EM, Zaidi M, Faraji F, et al.. Oropharyngeal cancer is no longer a disease of younger patients and the prognostic advantage of human papillomavirus is attenuated among older patients: analysis of the National Cancer Database. *Oral Oncol*. 2018;83:147-153. doi: 10.1016/j.oraloncology.2018.06.013 [PMCID: PMC6500732] [PubMed: 30098771] [CrossRef: 10.1016/j.oraloncology.2018.06.013]

23. Joiner M, van Der Kogel A. *Basic Clinical Radiobiology*. 4th ed. CRC Press; 2009. doi: 10.1201/b15450 [CrossRef: 10.1201/b15450]

24. Garden AS, Kies MS, Morrison WH, et al.. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the early 21st century. *Radiat Oncol*. 2013;8:21. doi: 10.1186/1748-717X-8-21 [PMCID: PMC3576243] [PubMed: 23360540] [CrossRef: 10.1186/1748-717X-8-21]

25. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms? *J Natl Compr Canc Netw*. 2011;9(6):665-673. doi: 10.6004/jnccn.2011.0055 [PubMed: 21636538] [CrossRef: 10.6004/jnccn.2011.0055]

26. Hutcheson KA, Abualsamh AR, Sosa A, et al.. Impact of selective neck dissection on chronic dysphagia after chemo-intensity-modulated radiotherapy for oropharyngeal carcinoma. *Head Neck*. 2016;38(6):886-893. doi: 10.1002/hed.24195 [PubMed: 26339764] [CrossRef: 10.1002/hed.24195]

27. Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2016;91(3):386-396. doi: 10.1016/j.mayocp.2015.12.017 [PubMed: 26944243] [CrossRef: 10.1016/j.mayocp.2015.12.017]

28. Wang SJ. Surveillance radiologic imaging after treatment of oropharyngeal cancer: a review. *World J Surg Oncol*. 2015;13(1):94. doi: 10.1186/s12957-015-0481-1 [PMCID: PMC4358873] [PubMed: 25889162] [CrossRef: 10.1186/s12957-015-0481-1]

29. Thames HD Jr, Peters LJ, Withers HR, Fletcher GH. Accelerated fractionation vs hyperfractionation: rationales for several treatments per day. *Int J Radiat Oncol Biol Phys*. 1983;9(2):127-138. doi: 10.1016/0360-3016(83)90089-5 [PubMed: 6833014] [CrossRef: 10.1016/0360-3016(83)90089-5]

30. Saunders MI. Head and neck cancer: altered fractionation schedules. *Oncologist*. 1999;4(1):11-16. doi: 10.1634/theoncologist.4-1-11 [PubMed: 10337367] [CrossRef: 10.1634/theoncologist.4-1-11]

31. Garden AS, Harris J, Trotti A, et al.. Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: a phase II trial of the radiation therapy oncology group (RTOG 99-14). *Int J Radiat Oncol Biol Phys*. 2008;71(5):1351-1355. doi: 10.1016/j.ijrobp.2008.04.006 [PMCID: PMC2582390] [PubMed: 18640496] [CrossRef: 10.1016/j.ijrobp.2008.04.006]

32. Teo PM, Leung SF, Chan AT, et al.. Final report of a randomized trial on altered-fractionated radiotherapy in nasopharyngeal carcinoma prematurely terminated by significant increase in neurologic complications. *Int J Radiat Oncol Biol Phys*. 2000;48(5):1311-1322. doi: 10.1016/S0360-3016(00)00786-0 [PubMed: 11121628] [CrossRef: 10.1016/S0360-3016(00)00786-0]

33. Kong L, Lu JJ, Liss AL, et al.. Radiation-induced cranial nerve palsy: a cross-sectional study of nasopharyngeal cancer patients after definitive radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1421-1427. doi: 10.1016/j.ijrobp.2010.01.002 [PubMed: 20605344] [CrossRef: 10.1016/j.ijrobp.2010.01.002]

34. Shrieve DC, Loeffler JS. *Human Radiation Injury.* Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

35. Tubbs RS, Spinner RJ, Shoja MM, Rizk E, Barbaro N, Loukas M. *Nerves and Nerve Injuries*. Elsevier Science; 2015.

36. Chen Y, Sun Y, Liang S-B, et al.. Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVB nasopharyngeal carcinoma from endemic regions of China. *Cancer*. 2013;119(12):2230-2238. doi: 10.1002/cncr.28049 [PubMed: 23576020] [CrossRef: 10.1002/cncr.28049]

37. Schiff D, Wen P. *Cancer Neurology in Clinical Practice.* Springer Science & Business Media; 2002.

38. Kamal M, Mohamed ASR, Volpe S, et al.; MD Anderson Head, Neck Cancer Symptom Working Group . Radiotherapy dose-volume parameters predict videofluoroscopy-detected dysphagia per DIGEST after IMRT for oropharyngeal cancer: results of a prospective registry. *Radiother Oncol*. 2018;128(3):442-451. doi: 10.1016/j.radonc.2018.06.013 [PMCID: PMC6595477] [PubMed: 29961581] [CrossRef: 10.1016/j.radonc.2018.06.013]

39. Cohen EE, Karrison TG, Kocherginsky M, et al.. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol*. 2014;32(25):2735-2743. doi: 10.1200/JCO.2013.54.6309 [PMCID: PMC4876357] [PubMed: 25049329] [CrossRef: 10.1200/JCO.2013.54.6309]

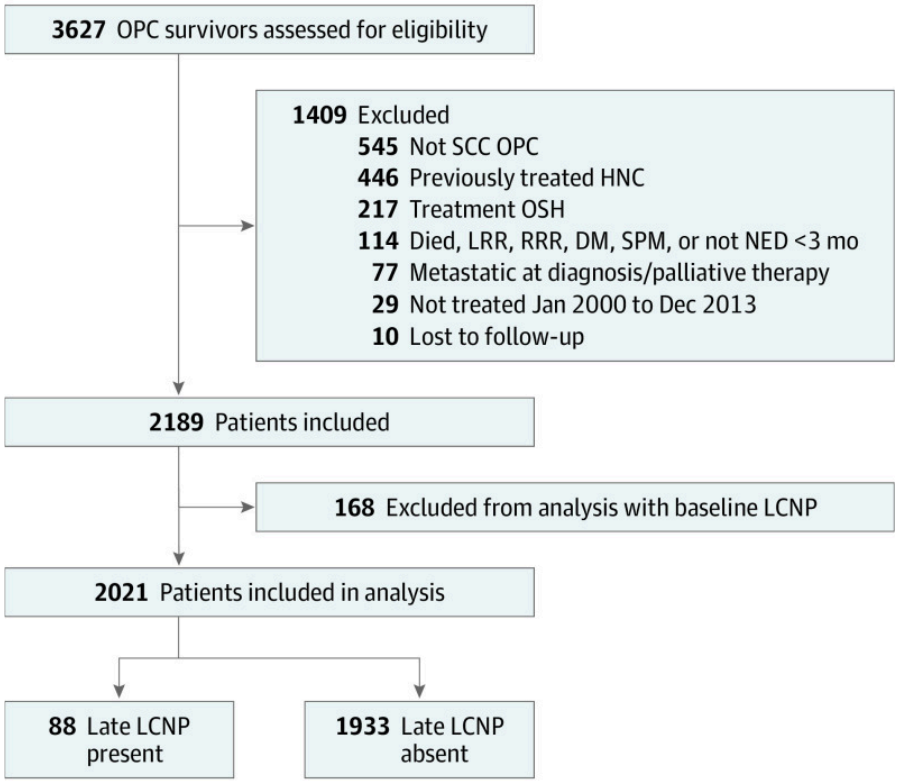
40. Haddad R, O'Neill A, Rabinowits G, et al.. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(3):257-264. doi: 10.1016/S1470-2045(13)70011-1 [PubMed: 23414589] [CrossRef: 10.1016/S1470-2045(13)70011-1]

41. Marur S, Li S, Cmelak AJ, et al.. E1308: Phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx: ECOG-ACRIN Cancer Research Group. *J Clin Oncol*. 2017;35(5):490-497. doi: 10.1200/JCO.2016.68.3300 [PMCID: PMC5455313] [PubMed: 28029303] [CrossRef: 10.1200/JCO.2016.68.3300]

42. Christianen ME, Verdonck-de Leeuw IM, Doornaert P, et al.. Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation. *Radiother Oncol*. 2015;117(1):139-144. doi: 10.1016/j.radonc.2015.07.042 [PubMed: 26320608] [CrossRef: 10.1016/j.radonc.2015.07.042]

Figures and Tables

Figure 1.



CONSORT Flowchart Showing Study Participant Screening and Eligibility Criteria

DM indicates distant metastasis; HNC, head and neck cancer; LCNP, lower cranial neuropathy; LRR, locoregional recurrence; NED, no evidence of disease; OPC, oropharyngeal cancer; OSH, outside hospital; RRR, regional recurrence; SCC, squamous cell carcinoma; and SPM, second primary malignant neoplasm.

Table 1.

Patient Characteristics and Cumulative Incidence of Late LCNP During a 15-Year Follow-up

Variable	Patient group[a]			Cumulative incidence (95% CI)
	All (N = 2021)	LCNP (n = 88)	No LCNP (n = 1933)	
Age at diagnosis, median (range) [IQR], y	56 (28-86) [50-63]	57 (33-80) [51-63]	55 (28-86) [50-63]	NA
Survival time, median (range) [IQR], y[b]	6.8 (0.3-18.4) [4.3-10.2]	5.4 (0.3-14.1) [1.6-8.5]	6.8 (0.3-18.4) [4.4-10.3]	NA
Radiotherapy dose, median (range) [IQR], Gy[b]	70 (40-75) [66-70]	70 (66-73.5) [66-72]	70 (40-75) [66-70]	NA
Radiotherapy fraction, median (range) [IQR][b]	33 (15-44) [28-43]	33 (30-43) [32-40.5]	33 (15-44) [30-33]	NA
Sex				
Female	281 (13.9)	15 (5.3)	266 (94.7)	0.096 (0.055-0.165)
Male	1740 (86.1)	73 (4.2)	1667 (95.8)	0.098 (0.073-0.132)
Primary site				
Tonsil	944 (46.7)	40 (4.2)	904 (95.8)	0.101 (0.0678-0.152)
Base of tongue	945 (46.8)	45 (4.8)	900 (95.2)	0.100 (0.070- 0.142)
Other	132 (6.5)	3 (2.3)	129 (97.7)	0.039 (0.012-0.128)
T classification[c,d]				
1	686 (33.9)	18 (2.6)	668 (97.4)	0.046 (0.027-0.077)
2	770 (38.1)	27 (3.5)	743 (96.5)	0.087 (0.049-0.151)
3	358 (17.7)	20 (5.6)	338 (94.4)	0.178 (0.109-0.283)
4	207 (10.2)	23 (11.1)	184 (88.9)	0.259 (0.154-0.417)
N classification[d,e]				
N0	196 (9.7)	6 (3.1)	190 (96.9)	0.082 (0.031-0.207)
N1 and N2a	510 (25.2)	16 (3.1)	494 (96.9)	0.052 (0.030-0.088)
N2b and N3	968 (47.9)	46 (4.8)	922 (95.2)	0.127 (0.084-0.188)
N2c	347 (17.2)	20 (5.8)	327 (94.2)	0.127 (0.075- 0.211)
HPV status[c]				
Negative	110 (5.4)	6 (5.5)	104 (94.5)	0.142 (0.054-0.345)
Positive	817 (40.4)	22 (2.7)	795 (97.3)	0.080 (0.033-0.175)

Abbreviations: HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; LCNP, lower cranial neuropathy; NA, not applicable; SF, split field; VMAT, volumetric-modulated arc therapy; WF, whole field.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. For LCNP and no LCNP groups, percentages are calculated for the row. Percentages have been rounded and may not total 100.

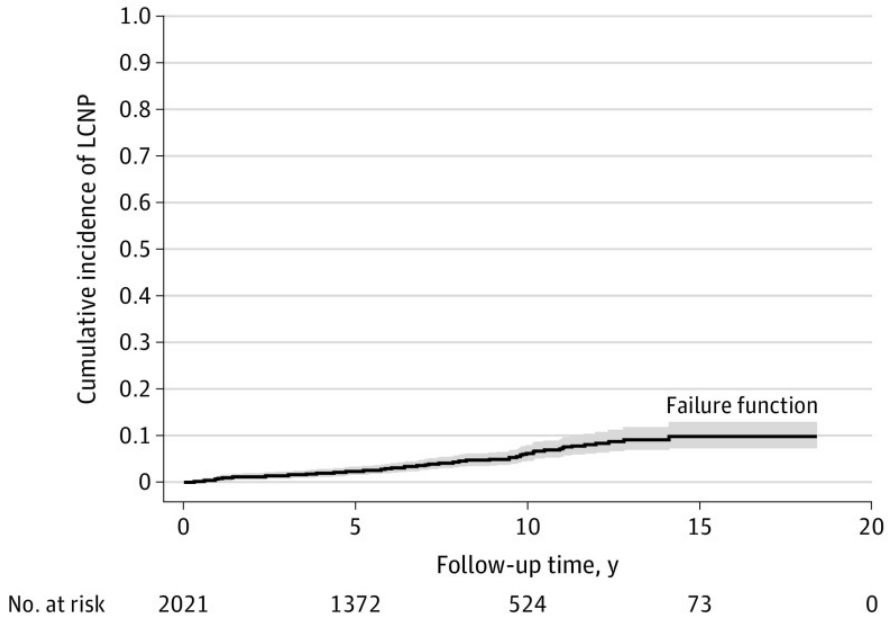
[b] $P < .05$, Kruskal-Wallis test.

[c] $P < .05$, Fisher exact test.

[d] $P < .05$, log-rank test.

[e] From the American Joint Committee on Cancer's *AJCC Cancer Staging Manual*, 7th edition.[18]

Figure 2.



Overall Cumulative Incidence of Late Lower Cranial Neuropathy (LCNP) in Oropharyngeal Squamous Cell Carcinoma Survivors During a 15-Year Surveillance Period

A total of 2021 patients were included. The shaded area indicates the 95% CI.

Table 2.

Univariate and Multivariable Cox Proportional Hazards Models for Late LCNP[a]

Variable	Analysis, HR (95% CI)	
	Univariate	Multivariable
Age at diagnosis	1.02 (1.00-1.04)	1.02 (0.99-1.04)
Radiotherapy dose[b]	1.24 (1.14-1.36)	NA
Radiotherapy fraction[b]	1.11 (1.07-1.16)	NA
Sex		
Female	1 [Reference]	1 [Reference]
Male	0.79 (0.45-1.37)	NA
Primary site		
Other	1 [Reference]	1 [Reference]
Tonsil	1.42 (0.44-4.58)	1.89 (0.58-6.17)
Base of tongue	1.62 (0.50-5.21)	1.85 (0.57-6.05)
T classification[b,c]		
1	1 [Reference]	1 [Reference]
2	1.53 (0.84-2.78)	1.12 (0.60-2.10)
3	2.72 (1.44-5.14)	1.59 (0.76-3.31)
4	6.10 (3.29-11.33)	3.82 (1.85-7.86)[d]
N classification[c]		
N0	1 [Reference]	1 [Reference]
N1 plus N2a	0.85 (0.33-2.17)	NA
N2b plus N3	1.56 (0.67-3.66)	NA
N2c	2.01 (0.81-5.00)	NA
HPV status		
Negative	1 [Reference]	1 [Reference]
Positive	0.67 (0.27-1.66)	NA
Unknown	0.72 (0.31-1.67)	NA
Smoking[b]		
Never	1 [Reference]	1 [Reference]
Former	0.85 (0.53-1.35)	0.76 (0.47-1.22)
Current	1.74 (0.97-3.11)	1.57 (0.86-2.86)

Abbreviations: HPV, human papillomavirus; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; LCNP, lower cranial neuropathy; NA, not applicable; SF, split field; VMAT, volumetric-modulated arc therapy; WF, whole field.

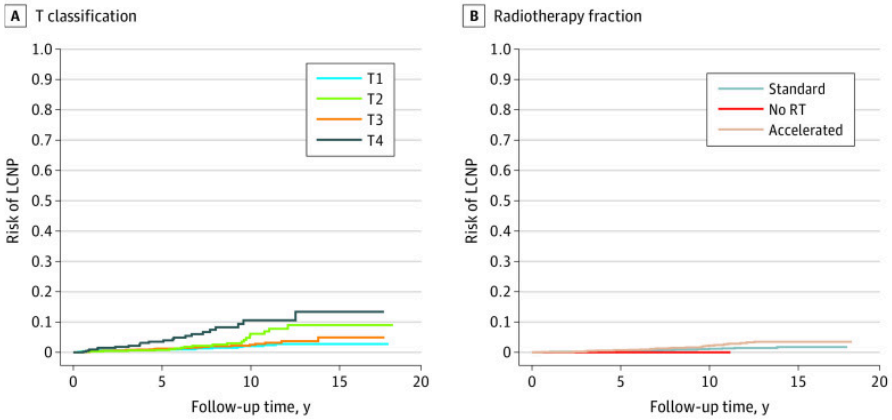
[a] Includes 2021 patients.

[b] $P < .05$ after univariate analysis.

[c] From the American Joint Committee on Cancer's *AJCC Cancer Staging Manual*, 7th edition.[18]

[d] $P < .05$ after multivariable analysis.

Figure 3.



Adjusted Risk of Late Lower Cranial Neuropathy (LCNP) Stratified by T Classification and Radiotherapy (RT) Fraction

Radiotherapy was stratified by no RT, standard, and accelerated fractions. Regression model was adjusted for age, subsite, T classification, smoking, and therapeutic modality.