Title

Early Improved Functional Outcomes in Head and Neck Cancer Patients with Primary Tumor Detection

Journal

The Laryngoscope, 134(2)

ISSN

0023-852X

Authors

Kalavacherla, Sandhya

Bernard, Benjamin

Kim, Sangwoo S

et al.

Publication Date

2024-02-01

DOI

10.1002/lary.30903

Peer reviewed

HHS Public Access

Author manuscript

Laryngoscope. Author manuscript; available in PMC 2024 February 17.

Published in final edited form as:

Laryngoscope. 2024 February ; 134(2): 701–707. doi:10.1002/lary.30903.

Early Improved Functional Outcomes in Head and Neck Cancer Patients with Primary Tumor Detection

Sandhya Kalavacherla, BS,
School of Medicine, University of California San Diego, La Jolla, California, U.S.A.

Benjamin Bernard, MD,
Department of Otolaryngology—Head & Neck Surgery, University of California San Diego, San Diego, California, U.S.A.

Sangwoo S. Kim, MD,
Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, California, U.S.A.

Anna Dornisch, MD, MAS,
Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, California, U.S.A.

Liza Blumenfeld, MA, CCC-SLP,
Department of Otolaryngology—Head & Neck Surgery, University of California San Diego, San Diego, California, U.S.A.; Gleiberman Head and Neck Cancer Center, Moores Cancer Center, University of California, San Diego, California, U.S.A.

Kristen Linnemeyer-Risser, MA, CCC-SLP, BCS-S,
Department of Otolaryngology—Head & Neck Surgery, University of California San Diego, San Diego, California, U.S.A.; Gleiberman Head and Neck Cancer Center, Moores Cancer Center, University of California, San Diego, California, U.S.A.

Parag Sanghvi, MD,
Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, California, U.S.A.; Gleiberman Head and Neck Cancer Center, Moores Cancer Center University of California, San Diego, California, U.S.A.

Theresa Guo, MD
Department of Otolaryngology—Head & Neck Surgery, University of California San Diego, San Diego, California, U.S.A.; Gleiberman Head and Neck Cancer Center, Moores Cancer Center, University of California, San Diego, California, U.S.A.

Abstract

Send correspondence to Theresa Guo, Department of Otolaryngology—Head & Neck Surgery, University of California San Diego, 3855 Health Sciences, DrLa Jolla, CA 92037. twguo@health.ucsd.edu.

Level of Evidence: 4

Additional supporting information may be found in the online version of this article.

2023 Triological Society Combined Sections Meeting, Coronado, CA; January 26–28, 2023.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Objectives: We characterize functional outcomes in head and neck cancer of unknown primary (CUP) based on primary site identification.

Methods: In this retrospective study, CUP cases were categorized as known primaries (KP) if a tumor was localized after diagnostic workup or persisting unknown primaries (UP). Age, sex, HPV status, diagnostic methods, and treatments regimens were collected. Pretreatment and short-term posttreatment (3–6 months after completion of treatment) weights, PHQ-9, Eating Assessment Tool (EAT-10), and Voice Handicap Index (VHI-10) scores were compared between UP and KP.

Results: Among 67 CUP patients, 35 (52.2%) had identified primaries (91.4% oropharyngeal and 8.6% nasopharyngeal). KP patients were younger (58 vs. 64, $p = 0.04$) and more likely to be HPV-positive (88.6% vs. 50%, $p = 0.002$). Overall detection rates were 16.7% for PET/CT, 34.7% for direct laryngoscopy, and 46.6% for transoral robotic oropharyngectomy. Diagnostic workup was not significantly different between groups. Patients with KP received smaller intermediate radiation dose volumes (436.5 vs. 278.9 cc, $p = 0.03$) and lower doses to the cricopharyngeal muscle (41.6 vs. 24.6 Gy, $p = 0.03$).Pretreatment weights, PHQ-9, EAT-10, and VHI-10 scores did not differ between groups. However, posttreatment, UP had greater relative weight loss (−14.1% vs. −7.6%, $p = 0.032$), higher EAT-10 scores (12.5 vs. 3, $p = 0.004$), and higher PHQ-9 scores (6 vs. 1.4, $p = 0.017$). Specifically, UP reported more stressful swallowing, difficulty swallowing solids and pills, and swallowing affecting public eating.

Conclusion: KP patients experienced less weight loss, depression, and reduced swallowing dysfunction, highlighting an early functional benefit of primary tumor identification likely driven by reduced radiation treatment volumes.

Keywords

head and neck cancer management; human papillomavirus—HPV; oropharyngeal squamous cell carcinoma (OPSCC); unknown primary head and neck squamous cell carcinoma

INTRODUCTION

Cancer of unknown primary (CUP) in the head and neck represents cervical squamous cell carcinoma metastasis without identified primary tumor. Although CUP currently comprises approximately 2–5% of all head and neck squamous cell carcinomas (HNSCCs), the incidence of CUP is rising, primarily due to increased oropharyngeal HPV infection rates.[1] In fact, HPV-related HNSCC rates have dramatically increased in the last 20 years, coupled with the decreasing incidence of HPV-negative, tobacco-related HNSCC.[2] HPV-associated oropharyngeal SCCs can easily evade surface detection and present as CUP, often occurring in the crypt epithelium of the palatine or lingual tonsils.[3]

As treatment decision-making for HNSCC centers on primary tumor origin, CUP presents a significant therapeutic challenge. Consequently, an extensive diagnostic workup is often pursued to identify a primary site. Initial diagnostic workup can include biopsy and imaging, with neck CT scan followed by a PET/CT scan.[1] Although PET/CT has success as a first-line primary detection tool, it is limited in detecting small primary, oropharyngeal tumors.[1] Patients may also undergo examination of mucosa under anesthesia with direct laryngoscopy

(DL) with biopsy and/or palatine tonsillectomy.[1] A more extensive surgical search for the unknown primary involves transoral robotic surgery (TORS), an increasingly utilized tool that can provide superior oropharyngeal visualization, with reported detection rates as high as 80%.[1,4] Management for CUP is often comprised of either a neck dissection followed by pathology-guided adjuvant radiotherapy with or without chemotherapy or nonoperative management with definitive chemoradiation.[4]

Within clinical practice, primary detection rates are reportedly as low as 50%.[5,6] Appropriate treatment seeks to maximize the odds of treating the occult primary site while minimizing unnecessary side effects. Although dysphagia is a well-established adverse effect after chemoradiation among HNSCC patients, limited data address whether swallowing dysfunction is compounded in CUP patients given the extensive mucosal irradiation patients undergo.[7,8] In randomized clinical trials oropharyngeal squamous cell carcinoma (OPSCC) patients treated with primary radiation or primary surgery with TORS, there were not clinically significant differences in self-reported swallowing function after treatment.[9] However, greater adverse events were more experiences by patients treated with primary radiation, including hearing loss, tinnitus, alopecia, vomiting, and mucositis.[9] Given the significant adverse effects experienced by OPSCC patients treated with targeted mucosal radiation, we hypothesized that posttreatment functional outcomes would be significantly worse among CUP patients, as they are more likely to undergo larger volume radiation therapy encompassing the pharyngeal axis at risk in persistently unknown primaries. In this retrospective series, we characterize and compare functional outcomes before and after treatment among CUP patients based on whether a primary site was identified.

METHODS

We conducted an Institutional Review Board-approved (Protocol #801098) retrospective review of patient records from 1/1/2016 to 12/31/2021 at the University of California, San Diego. Patients diagnosed with following International Classification of Diseases, 10th Revision codes were queried: C79.89, R22.1, C77.0, R13.10, C76.0, C80.1, K14.8, C09.9, and CO2.9. Patients presenting to our institution with CUP, defined as biopsy-confirmed metastatic squamous cell carcinoma of the neck with an undetectable primary site upon physical exam, were included and those with suspected cutaneous primaries were excluded.

CUP cases were categorized as known primaries (KP) if the primary tumor was localized post-diagnostic workup or persisting unknown primaries (UP) if no primary was identified post-diagnostic workup. Age, sex, smoking status, tumor HPV-p16 status, diagnostic workup procedures, and TNM tumor stage using American Joint Committee on Cancer (AJCC) 7th and 8th editions were collected. Treatment characteristics, including receipt of chemotherapy, radiation, and/or a neck dissection; and treatment dates were also collected. Radiotherapy was further characterized with radiation doses and volumes; specifically, the intermediate-dose planning treatment volume, representing the volume in cubic centimeters (cc) treated with a dose of 60–63 Gy, and mean radiation doses (Gy) administered to the cricopharyngeal muscle, larynx, and oral cavity, was collected.

Functional outcomes of weight, depression, swallowing function, and voice function were collected for each patient at pre- and posttreatment time points. Pretreatment was defined as the period before the initiation of any therapy. The short-term posttreatment period was defined as 3 to 6 months after the completion of the last cancer treatment. For each metric, the most recent documentation before treatment was considered the baseline value. All documentation of each metric in the posttreatment period was collected; if there was more than one data point within the posttreatment period, the median was computed and considered the posttreatment value.

Weight was measured as relative percent weight change between each patient's baseline weight and median posttreatment weight. Depression was measured by patient-reported scores on the Patient Health Questionnaire (PHQ-9) assessment. Patient-reported measures of swallowing function, assessed by the Eating Assessment Tool (EAT-10) questionnaire, and voice function, assessed by the Voice Handicap Index (VHI-10) questionnaire, were collected from speech-language pathology documentation. The EAT-10 and VHI-10 asked patients to rate 10 metrics of swallowing and voice dysfunction, respectively, from 0 to 4. The maximum EAT-10 or VHI-10 score of 40 represent patients' perception of severe dysfunction. All patient data collected from medical records were stored in a password encrypted file.

Statistical Analysis

All analyses were performed using R statistical software (version 4.1.3). Differences in characteristics were assessed with the Student's t-test, Wilcoxon rank sum test, and Chi-squared test. Median pretreatment relative percent weight changes, PHQ-9 scores, EAT-10 scores, and VHI-10 scores were compared between UP and KP using the Wilcoxon rank sum test. Additionally, median intermediate-dose planning treatment volumes and doses administered to the cricopharyngeus, larynx, and oral cavity were compared between UP and KP using Wilcoxon rank sum tests. This analysis was repeated for posttreatment values. Predictive factors of primary detection were assessed with multivariable logistic regression models and presented as an odds ratios (OR) [95% confidence interval].

RESULTS

Patient Characteristics

A total of 67 patients met inclusion criteria (Fig. 1). The primary site was detected in 35 (52.2%) patients. KP patients were younger (58 vs. 64, $p = 0.043$) and more likely to be HPV-positive (88.6% vs. 50%, $p = 0.002$) (Table I). Smoking history was not significantly different between KP and UP. Clinical N and M stages did not differ between UP and KP in both AJCC editions. In a multivariable regression model assessing predictors of primary tumor detection, HPV-positive tumor status was associated with increased detection (OR = 7.3 [2.00–15.42], $p = 0.005$).

Proportions of patients receiving each treatment modality and combination were not significantly different between groups ($p > 0.9$) (Table I). Additionally, total radiation doses were similar between KP and UP (70 Gy vs. 70 Gy, $p = 0.69$) (Table IIA).

However, the median volume receiving the intermediate-dose planning treatment (60–63 Gy) was significantly higher in UP than KP (436.5 cc vs. 278.9 cc, $p = 0.03$) (Table IIA). Furthermore, UP had a significantly higher median dose to the cricopharyngeal muscle (41.6 Gy vs. 24.6 Gy, $p = 0.025$) compared with KP. Mean doses to the larynx and oral cavity were not significantly higher in the UP population. Radiation doses and volumes did not significantly differ by HPV-status (Table IIB).

Primary Tumor Detection

Among KP patients, 32 (94.3%) primary tumors were located in the oropharynx and 3 (8.6%) in the nasopharynx. Within the oropharynx, most primaries were found in the tonsil (37.1%) and base of tongue (42.9%). Other subsites of the oropharynx with detected primaries included the soft palate (2.9%), vallecula (2.9%), and glossotonsillar sulcus (5.7%).

A total of 11 (31.4%) KP were found by PET/CT, 17 (48.6%) by DL with biopsy, and 7 (20%) by TORS (Table III). Overall primary detection success rates were 16.7% for PET/CT, 34.7% for DL with biopsy, and 46.6% for transoral robotic oropharyngectomy. Differences in diagnostic methods used between KP and UP were insignificant ($p = 0.86$).

The primary tumor was detected in 66% of HPV-positive patients and in 20% of HPV-negative patients ($p = 0.004$). Among HPV-positive patients, overall primary detection rates were 19.1% for PET/CT, 41.7% for DL with biopsy, and 58.8% for TORS. Among HPV-negative patients, primary detection rates were 14.2% for PET/CT, 10% for DL with biopsy, and 0% for TORS.

Weight

Pre- and posttreatment weights understood impact of swallowing dysfunction during treatment. Both groups had similar pretreatment weights ($p = 0.57$) (Table IV). However, UP patients experienced a greater relative weight loss between baseline and posttreatment weights (−14.1% vs. −7.6%, $p = 0.032$) compared with KP. In HPV-positive patients, median relative weight loss was greater in UP patients (−15.1% vs −7.6%, $p = 0.004$). No significant difference in median relative weight loss was seen between the two groups in the HPV-negative cohort.

Depression PHQ-9 Scores

Depression was measured in both patient cohorts using PHQ-9 scores. Before treatment, UP reported a higher, albeit non-significant, baseline PHQ-9 score than KP ($p = 0.10$) (Table V). Notably, UP patients had an increase in PHQ-9 scores after treatment, whereas PHQ-9 scores did not increase for KP patients post-treatment. UP had a significantly greater median PHQ-9 score posttreatment compared with KP patients (6 vs. 1.4, $p = 0.017$). Similarly in HPV-positive patients, median PHQ-9 score posttreatment was higher in the UP group. In the HPV-negative cohort, there was no difference between the groups.

Swallowing Outcomes

Functional swallowing changes were assessed with EAT-10 scores. All median pretreatment EAT-10 scores were similar between groups (Table VI). Overall, UP reported worse swallowing functionality posttreatment compared with KP patients (EAT-10 12.5 vs. 3, $p = 0.004$). In the HPV-positive cohort, the median posttreatment EAT-10 score was significantly higher in the UP group (9 vs. 3.5, $p = 0.038$). In the HPV-negative cohort, no comparative data were available. After analyzing patients' answers to symptom-specific items on the posttreatment EAT-10, UP patients reported significantly higher median scores on stressful swallowing (2 vs. 0, $p = 0.01$), difficulty swallowing solids (2 vs. 0, $p = 0.014$), difficulty swallowing pills (1.5 vs. 0, $p = 0.041$), and swallowing interfering with public eating (1.5 vs. 0, $p = 0.019$) than KP.

Voice Outcomes

VHI-10 scores were used to evaluate changes in voice function. Median overall VHI-10 scores were not significantly different between KP and UP patients either pre- or posttreatment (Table Sl). Analyzing patients' symptom-specific scoring, the measure for increased strain in producing voice was significantly higher after treatment in the UP group compared with that in the KP group (3.5 vs. 0, $p = 0.036$). In addition, a significantly higher median posttreatment score among UP for unpredictable voice clarity ($p = 0.05$) was seen. In the HPV-positive cohort, the measure for increased strain in producing voice was significantly higher after treatment in the UP group compared with that in the KP group (3.5 vs. 0, $p = 0.02$). Data were insufficient in the HPV-negative cohort for pre- and posttreatment comparison.

DISCUSSION

Focusing treatment for CUP cases is challenging, often making aggressive treatment regimens the default to treat all potential primary sites. Primary tumor identification can de-intensify treatment by providing precise targets and subsequently minimizing the irradiated volume. However, the functional impact of primary tumor localization is not well characterized. In this analysis, 52.2% of CUP patients had a primary eventually localized, largely in the oropharynx, which parallels previously reported primary detection rates.[5,6] Based on the metrics of weight change, depression, and swallowing function, UP patients experienced poorer functional outcomes posttreatment compared with KP patients, suggesting a significant functional benefit of primary tumor identification.

To our knowledge, we are the first to report functional benefits of primary tumor identification in CUP. Pretreatment values for weight, depression, EAT-10, and VHI-10 metrics were similar between the two groups, making posttreatment comparisons meaningful. Although not statistically significant, UP patients had higher pretreatment PHQ-9, EAT-10, and VHI-10 scores. The underlying etiology for this pattern is unclear but could be attributed to the greater proportion of older and HPV-negative patients in the UP compared with KP. Notably, UP had a higher relative weight loss after treatment compared with KP. Many of these findings were validated in HPV-positive patients, but analysis in

HPV-negative patients was limited due to a small sample size of identified HPV-negative primaries in our cohort.

Weight serves as an objective reflection of a patient's swallowing and overall function; one study demonstrated that in head and neck cancer patients, critical weight loss was a strong negative predictor of disease-specific survival.[10,11] Similarly, depression scores measured by the PHQ-9 were significantly higher after treatment in UP. Importantly, depression has been reported as a predictor of overall 2-year mortality and poor treatment outcomes.[12]

Our analysis further revealed worse self-reported swallowing function based on EAT-10 scores after treatment in UP patients. There is evidence that increasing EAT-10 scores correlate linearly with risk of aspiration, and patients with EAT-10 scores >15 have twice as high of a risk of aspiration as those with EAT-10 scores <15.[13] Posttreatment EAT-10 scores in UP patients was 12.5, approaching this threshold. UP patients specifically reported higher posttreatment scores of stressful swallowing, difficulty swallowing solids, difficulty swallowing pills, and swallowing dysfunction affecting public eating. Preservation of swallowing function has been established as a priority in HNSCC treatment given the devastating effects of dysphagia.[14]

With regard to voice, VHI scores did not differ between groups. Differences in specific metrics of voice strain and unpredictability in voice clarity differed, but the clinical relevance of this is unclear. These outcomes may be impacted by the inclusion of the larynx in radiation field, although radiation doses to the larynx were not significant different.

HPV or p16 positivity in nodal sites is a well-known predictor of oropharyngeal origin.[15] Among all patients with initial CUP presentation, 70.1% were p16-positive. Further, close to 90% of KP patients in our cohort were p16-positive. HPV status was a significant predictor of primary detection (OR = 7.3 [2.00–15.42], $p = 0.005$). Ryan et al. also report a higher cumulative primary tumor identification rate among HPV-positive patients (65%) compared with HPV-negative (26%) patients after TORS lingual tonsillectomy.[6] Additionally, 90% of localized primary tumors in our study were identified in the oropharynx. These patterns are expected—as HPV positivity in CUP is strongly predictive of oropharyngeal origin, specifically the tonsil and base of tongue.[16]

Traditionally, CUP cases have been treated with aggressive radiotherapy to the entire pharyngeal axis to increase the odds of radiating the occult tumor. In the context of these differential functional outcomes between UP and KP, we found that KP patients had smaller intermediate dose radiation planning treating volumes, which directly relates to the degree of irradiation of the pharyngeal axis (Fig. 2). In our cohort, the vast majority of KP were eventually localized to the oropharynx. This cumulatively led to a signficiant decrease in the dose to the cricopharyngeal muscle, which is a known predictor for dysphagia.[17] Currently, a variety of specific dose constraints exist for mean dose to the cricopharyngeal muscle and upper esophageal sphincter complex, ranging from <50 to 60 Gy to reduce the risk of dysphagia[18]; in our practice, we aim to limit the mean dose to <45 Gy. Given that patients with KP had a mean cricopharyngeal dose of 24.6 Gy versus 46.7 Gy in UP, it is likely that this is a strong driver of the differential swallowing outcomes.

Other studies report that primary identification among CUP patients informed treatment de-intensification which could lead to improved functional outcomes.[4,19,20] For instance, Patel et al. report that primary identification rates were improved by TORS, and patients with TORS-identified tumors had de-escalated treatment regimens, including primary management with surgery.[19] Similarly, Durmus et al. report that primary site detection informed the overall de-intensification of treatment through reduction in the radiation dose to the entire upper aerodigestive tract and reduction in chemotherapy administration.[20] The morbidity associated with large volume and high dose radiation is well established; several studies report high rates of xerostomia, feeding tube dependence, new opioid requirements, and dysphagia following aggressive radiation therapy to the head and neck.[21]

This study underscores the need to improve functional outcomes among patients with persisting unknown primaries through advances in diagnostic workup and treatment. Although TORS had the highest primary detection yield in our study, it was only used to work up 25% of UP patients in our cohort. A future challenge is to increase the access to TORS in the diagnostic workup of all UP patients with negative imaging or DL. Regarding treatment, studies show that pharyngeal-sparing radiotherapy among CUP patients who underwent TORS oropharyngeal resection was associated with significantly lower mean weight loss, feeding tube placement, and unplanned hospitalizations during radiation treatment.[22] Similarly, a recent clinical trial demonstrated that treatment sparing of the superior, middle, and inferior pharyngeal constrictor muscles from high-dose radiation had better self-reported swallow function.[23] However, these strategies are not yet standard of care. Lastly, an HPV-positive status among patients with persisting unknown primaries can inform treatment de-intensification. Trials for treatment de-escalation based on HPV status are currently underway, especially given data from recent ECOG 3311, but no consensus exists on factoring in HPV status into de-escalation.[24,25]

The main limitations of this study include its retrospective nature, limiting our ability to infer causation between primary identification and functional outcomes. Additionally, our short-term posttreatment period was defined as 3–6 months after the completion of treatment, which is still within the time period where treatment effects are severe.[26] Further, the retrospective review introduces potential selection bias in which patients underwent functional assessments. Small sample size also limited ability to perform multivariate analyses, which could control for confounding from observed differences between KP and UP groups. Furthermore, due to lack of data we were not able to include more comprehensive functional outcome measures such as the MD Anderson Dysphagia Inventory (MDADI) and video swallow data. Although this study serves as strong, preliminary evidence for functional benefits associated with primary tumor identification, future prospective studies with larger cohorts are needed to assess long-term functional outcomes and complement our findings of decreased weight loss, improved swallowing function, and lower depression rates in patients with identified primary tumors.

CONCLUSIONS

In this retrospective analysis of CUP cases, 52.2% of the patients had a primary localized after diagnostic workup. Patients without an identified primary tumor were more likely to

be older and HPV-negative. Post-treatment, UP patients experienced greater weight loss, depression, and swallowing dysfunction. These data highlight a functional benefit associated with primary tumor identification in CUP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

BIBLIOGRAPHY

1. Ye W, Arnaud EH, Langerman A, Mannion K, Topf MC. Diagnostic approaches to carcinoma of unknown primary of the head and neck. Eur J Cancer Care (Engl). 2021;30(6):e13459. 10.1111/ecc.13459. [PubMed: 33932056]
2. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. Surg Oncol Clin N Am. 2015;24(3):379–396. 10.1016/j.soc.2015.03.001. [PubMed: 25979389]
3. Channir HI, Grønhøj Larsen C, Ahlborn LB, et al. Validation study of HPV DNA detection from stained FNA smears by polymerase chain reaction: improving the diagnostic workup of patients with a tumor on the neck. Cancer Cytopathol. 2016;124(11):820–827. 10.1002/cncy.21753. [PubMed: 27404322]
4. Hatten kM, O'Malley BW Jr, Bur AM, et al. Transoral robotic surgery-assisted endoscopy with primary site detection and treatment in occult mucosal primaries. JAMA Otolaryngol Head Neck Surg. 2017;143(3):267–273. 10.1001/jamaoto.2016.3419. [PubMed: 27930761]
5. Lee MY, Fowler N, Adelstein D, et al. Detection and oncologic outcomes of head and neck squamous cell carcinoma of unknown primary origin. Anticancer Res. 2020;40(8):4207–4214. 10.21873/anticanres.14421. [PubMed: 32727746]
6. Ryan JF, Motz KM, Rooper LM, et al. The impact of a stepwise approach to primary tumor detection in squamous cell carcinoma of the neck with unknown primary. Laryngoscope. 2019;129(7):1610–1616. 10.1002/lary.27625. [PubMed: 30565698]
7. Starmer HM, Tippett D, Webster K, et al. Swallowing outcomes in patients with oropharyngeal cancer undergoing organ-preservation treatment. Head Neck. 2014;36(10):1392–1397. 10.1002/hed.23465. [PubMed: 24038454]
8. Denaro N, Merlano MC, Russi EG. Dysphagia in head and neck cancer patients: pretreatment evaluation, predictive factors, and assessment during radio-chemotherapy. Recommendations Clin Exp Otorhinolaryngol. 2013;6(3):117–126. 10.3342/ceo.2013.6.3.117. [PubMed: 24069513]
9. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol. 2019;20(10):1349–1359. 10.1016/S1470-2045(19)30410-3. [PubMed: 31416685]
10. Campbell BH, Spinelli K, Marbella AM, Myers KB, Kuhn JC, Layde PM. Aspiration, weight loss, and quality of life in head and neck cancer survivors. Arch Otolaryngol Head Neck Surg. 2004;130(9):1100–1103. 10.1001/archotol.130.9.1100. [PubMed: 15381598]
11. Langius JA, Bakker S, Rietveld DH, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. Br J Cancer. 2013;109(5):1093–1099. 10.1038/bjc.2013.458. [PubMed: 23928661]
12. Zimmaro LA, Sephton SE, Siwik CJ, et al. Depressive symptoms predict head and neck cancer survival: examining plausible behavioral and biological pathways. Cancer. 2018;124(5):1053–1060. 10.1002/cncr.31109. [PubMed: 29355901]
13. Cheney DM, Siddiqui MT, Litts JK, Kuhn MA, Belafsky PC. The ability of the 10-item eating assessment tool (EAT-10) to predict aspiration risk in persons with dysphagia. Ann Otol Rhinol Laryngol. 2015;124(5):351–354. 10.1177/0003489414558107 Epub 2014 Oct 30. [PubMed: 25358607]
14. Motz K, Qualliotine JR, Rettig E, Richmon JD, Eisele DW, Fakhry C. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era

of human papillomavirus. JAMA Otolaryngol Head Neck Surg. 2016;142(3):223–228. 10.1001/jamaoto.2015.3228. [PubMed: 26769661]

15. Holmes BJ, Maleki Z, Westra WH. The Fidelity of p16 staining as a surrogate marker of human papillomavirus status in fine-needle aspirates and Core biopsies ofneck node metastases: implications for HPV testing protocols. Acta Cytol. 2015;59(1):97–103. 10.1159/000375148. [PubMed: 25765380]
16. Boscolo-Rizzo P, Del Mistro A, Bussu F, et al. New insights into human papillomavirus-associated head and neck squamous cell carcinoma. Acta Otorhinolaryngol Ital. 2013;33(2):77–87. [PubMed: 23853396]
17. Alterio D, Gerardi MA, Cella L, et al. Radiation-induced acute dysphagia: prospective observational study on 42 head and neck cancer patients. Strahleninduzierte akute Dysphagie: Prospektive Beobachtungsstudie an 42 Kopf-Hals-Malignompatienten. Strahlenther Onkol. 2017;193(11):971–981. 10.1007/s00066-017-1206-x. [PubMed: 28884310]
18. Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S64–S69. 10.1016/j.ijrobp.2009.03.079. [PubMed: 20171520]
19. Patel SA, Parvathaneni A, Parvathaneni U, et al. Post-operative therapy following transoral robotic surgery for unknown primary cancers of the head and neck. Oral Oncol. 2017;72:150–156. 10.1016/j.oraloncology.2017.07.019. [PubMed: 28797451]
20. Durmus K, Rangarajan SV, Old MO, Agrawal A, Teknos TN, Ozer E. Transoral robotic approach to carcinoma of unknown primary. Head Neck. 2014;36(6):848–852. 10.1002/hed.23385. [PubMed: 23720223]
21. Brook I. Early side effects of radiation treatment for head and neck cancer. Cancer Radiother. 2021;25(5):507–513. 10.1016/j.canrad.2021.02.001. [PubMed: 33685809]
22. Grewal AS, Rajasekaran K, Cannady SB, et al. Pharyngeal-sparing radiation for head and neck carcinoma of unknown primary following TORS assisted workup. Laryngoscope. 2020;130(3):691–697. 10.1002/lary.28200. [PubMed: 31411747]
23. Nutting C, Rooney K, Foran B, et al. Results of a randomized phase III study of dysphagia-optimized intensity modulated radiotherapy (do-IMRT) versus standard IMRT (S-IMRT) in head and neck cancer. J Clin Oncol. 2020;38(15):6508. 10.1200/JCO.2020.38.15_suppl.6508.
24. Ferris RL, Flamand Y, Weinstein GS, et al. Phase II randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in Resectable p16+ locally advanced oropharynx cancer: an ECOG-ACRIN cancer research group trial (E3311). J Clin Oncol. 2022;40(2):138–149. 10.1200/JCO.21.01752. [PubMed: 34699271]
25. Golusinski P, Corry J, Poorten VV, et al. De-escalation studies in HPV-positive oropharyngeal cancer: how should we proceed? Oral Oncol. 2021;123:105620. 10.1016/j.oraloncology.2021.105620. [PubMed: 34798575]
26. Sinclair CF, McColloch NL, Carroll WR, Rosenthal EL, Desmond RA, Magnuson JS. Patient-perceived and objective functional outcomes following transoral robotic surgery for early oropharyngeal carcinoma. Arch Otolaryngol Head Neck Surg. 2011;137(11):1112–1116. 10.1001/archoto.2011.172. [PubMed: 22106235]

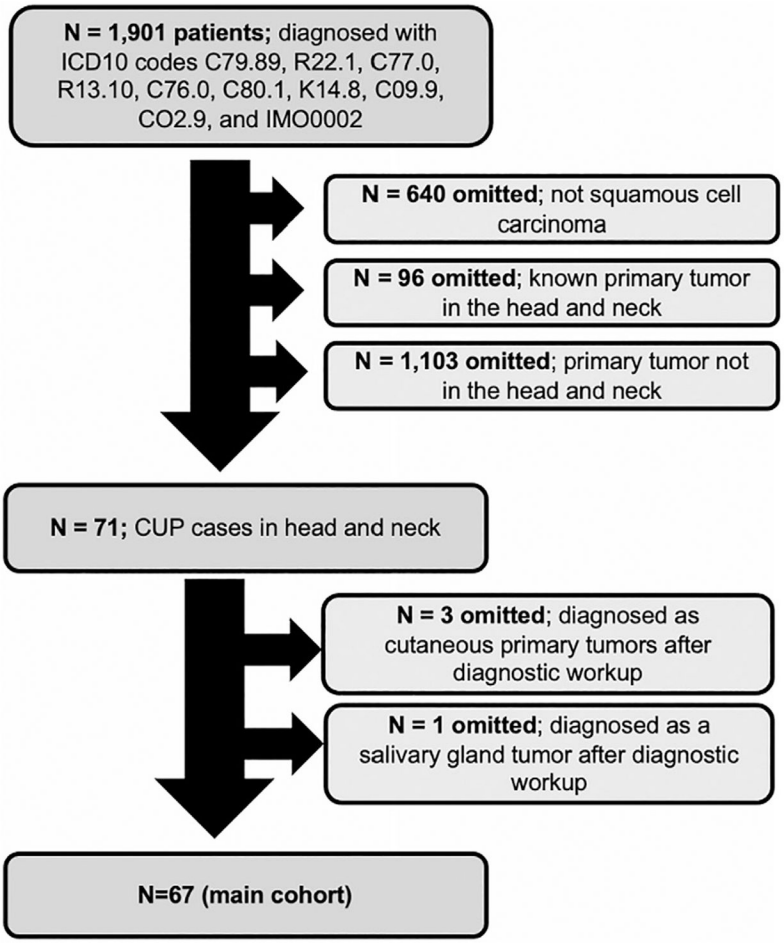

Fig. 1.
Final cohort selection process.

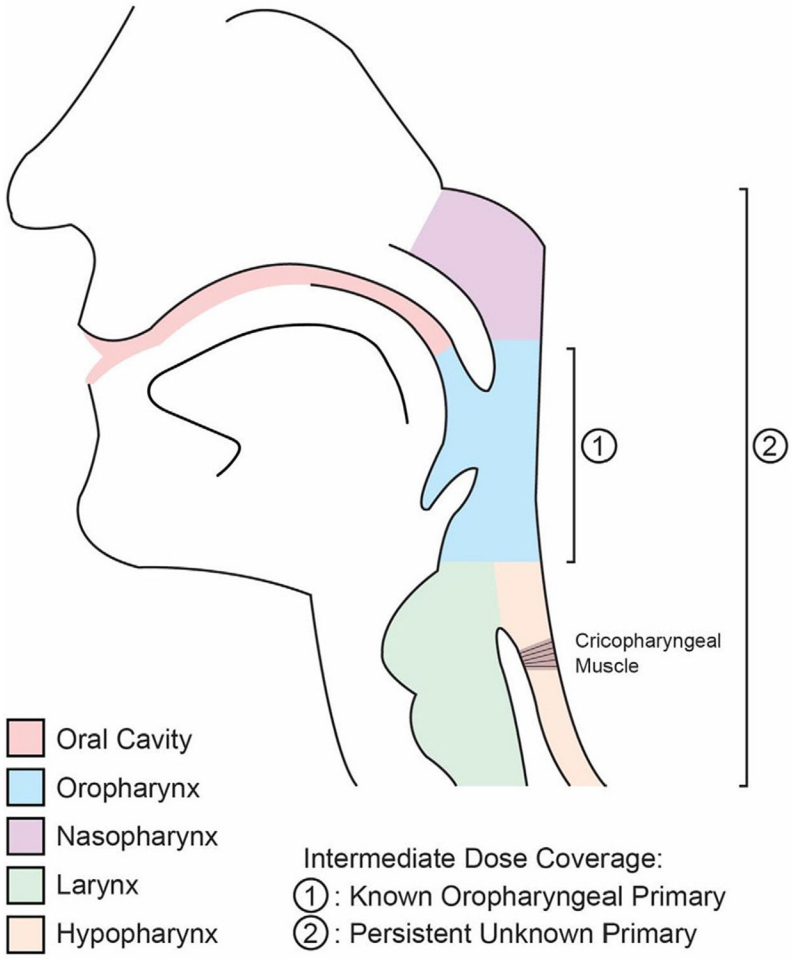

Fig. 2.
Differences in pharyngeal axis irradiation based on primary detection status.

TABLE I.

Demographic and Clinical Characteristics Compared By Primary Detection Status.

N	Known Primary (KP) 35	Unknown Primary (UP) 32	*p* Value
Age (*years*)[a]	58 [42–83]	64 [42–91]	0.04
Gender[b]			0.82
Female	9 (25.8%)	9 (28.1%)	
Male	26 (74.2%)	23 (72%)	
HPV p16 positive[b]	31 (88.6%)	16 (50%)	0.002
Smoking status[b]			0.18
Current	8 (22.8%)	6 (18.8%)	
Former	7 (20%)	13 (40.6%)	
Never	20 (57.1%)	13 (40.6%)	
*Clinical TNM AJCC 8*th *edition stage* T category[b]			<0.001
T0	29 (91%)	32 (100%)	
T1	2 (6.3%)	0 (0%)	
T2	1 (3.1%)	0 (0%)	
T3	0 (0%)	0 (0%)	
N category[b]			0.6
N0	0 (0%)	0 (0%)	
N1	16 (46%)	21 (60%)	
N2	11 (34%)	10 (29%)	
N3	5 (16%)	4 (11%)	
M category[b]			>0.9
M0	31 (97%)	33 (94%)	
M1+	1 (3.1%)	2 (5.7%)	
Treatment [b]			0.66
Chemotherapy monotherapy	2 (5.7%)	0 (0%)	
Radiation monotherapy	4 (11.4%)	2 (6.3%)	
Neck dissection monotherapy	1 (2.9%)	2 (6.3%)	
Chemotherapy + radiation	19 (54.3%)	19 (59.4%)	
Chemotherapy + neck dissection	1 (2.9%)	0 (0%)	
Radiation + neck dissection	4 (11.4%)	3 (9.4%)	
Chemotherapy + radiation + neck dissection	4 (11.4%)	6 (18.8%)	

[a]Median [interquartile range].

[b]*N* (%).

TABLE II.

Radiation Dose and Volume Characteristics Compared Between Patients with Known and Unknown Primary Tumors (A) and HPV-Positive and -Negative Diseases (B).

	A			B		
Radiotherapy Characteristic[a]	**Unknown Primary (UP)**	**Known Primary (KP)**	***p* Value**	**HPV-Positive**	**HPV-Negative**	***p* Value**
Overall radiation dose (Gy)	70 [50–70]	70 [54–70]	0.69	63 [42, 70]	70 [50, 70]	0.73
Intermediate radiation dose (60–63 Gy) volume (cc)	436.5 [351.2, 502.1]	278.9 [157.8, 411.2]	0.03	330 [198.7, 436.5]	469.3 [335.4, 584.9]	0.15
Cricopharyngeal muscle dose (Gy)	46.7 [31.3, 56]	24.6 [22.4, 32.6]	0.02	28 [21.9, 36.4]	38.4 [18, 59.3]	0.57
Larynx dose (Gy)	38.2 [29.9, 50.9]	35.7 [27.2, 42.4]	0.30	36.3 [28.4, 43.4]	35.6 [20, 54.6]	0.75
Oral cavity dose (Gy)	43.5 [29.5, 50.9]	36.5 [30.7, 41.6]	0.57	47 [30.5, 48.8]	44.8 [20.7, 55.8]	0.55

[a]Median [interquartile range].

TABLE III.

Primary Tumor Detection Rate Based on Diagnostic Method and HPV Status.

	PET/CT	DL with biopsy	TORS
Patients who underwent procedure (*N*)	66	49	15
Primary found due to this method[a]	11 (31.4%)	17 (48.6%)	7 (20%)
Overall primary detection rate	16.7%	34.7%	46.6%
HPV+ patients who underwent procedure (*N*)	47	36	12
Primary found due to this method[a]	9 (29%)	15 (22.6%)	7 (48.4%)
Overall primary detection rate among HPV+ patients	19.1%	41.7%	58.8%
Number of HPV-patients who underwent procedure (*N*)	14	10	2
Primary found due to this method[a]	2 (66.7%)	1 (33.3%)	0%
Overall primary detection rate among HPV-patients	14.2%	10%	0%

[a] *N*(%).

TABLE IV.

Pretreatment and Posttreatment Weight Data for Known Primary (KP) and Unknown Primary (UP) Patients.

	Known Primary (KP)	Unknown Primary (UP)	*p* Value
Median pretreatment weight (kg)	84.1 (*N* = 31)	84.1 (*N* = 30)	0.87
Median posttreatment weight (kg)	77.7 (*N* = 31)	74.8 (*N* = 30)	0.57
Median % weight change	−7.6% (*N* = 31)	−14.1% (*N* = 30)	0.03

TABLE V.

Pre-treatment and Post-Treatment PHQ-9 Scores for Known Primary (KP) and Unknown Primary (UP) Patients.

	Known Primary (KP)	Unknown Primary (UP)	*p* Value
Median pretreatment overall PHQ-9 score	2 (*N* = 23)	4 (*N* = 17)	0.10
Median posttreatment overall PHQ-9 score	1.4 (*N* = 15)	6 (*N* = 15)	0.02

TABLE VI.

Pretreatment and Posttreatment EAT-10 Scores for Known Primary (KP) and Unknown Primary (UP) Patients.

EAT-10 Question	Known Primary (KP)	Unknown Primary (UP)	*p* Value
Overall EAT-10 score			
Median pretreatment score	0 (*N* = 18)	9 (*N* = 6)	0.14
Median posttreatment score	3 (*N* = 16)	12.5 (*N* = 6)	0.004
Q1: My swallowing problem has caused weight loss			
Median pretreatment score	0.5 (*N* = 12)	0 (*N* = 4)	0.01
Median posttreatment score	0 (*N* = 15)	2 (*N* = 5)	0.06
Q2: My swallowing problem interferes with my ability to go out for meals			
Median pretreatment score	0.5 (*N* = 8)	1 (*N* = 6)	0.73
Median posttreatment score	0 (*N* = 15)	1.5 (*N* = 6)	0.02
Q3: Swallowing liquids takes extra effort			
Median pretreatment score	0 (*N* = 8)	0 (*N* = 4)	0.36
Median posttreatment score	0 (*N* = 15)	0 (*N* = 4)	>0.9
Q4: Swallowing solids takes extra effort			
Median pretreatment score	0.5 (*N* = 8)	0.5 (*N* = 6)	0.89
Median posttreatment score	0 (*N* = 15)	2 (*N* = 6)	0.01
Q5: Swallowing pills takes extra effort			
Median pretreatment score	0.5 (*N* = 8)	0.5 (*N* = 6)	0.89
Median posttreatment score	0 (*N* = 15)	1.5 (*N* = 6)	0.04
Q6: Swallowing is painful			
Median pretreatment score	0 (*N* = 8)	1.5 (*N* = 4)	0.07
Median posttreatment score	0 (*N* = 15)	0.5 (*N* = 4)	0.27
Q7: Swallowing is stressful			
Median pretreatment score	0 (*N* = 8)	0.5 (*N* = 6)	0.72
Median posttreatment score	0 (*N* = 15)	2 (*N* = 6)	0.01
Q8: The pleasure of eating is affected by my swallowing			
Median pretreatment score	0.5 (*N* = 8)	1.5 (*N* = 4)	0.79
Median posttreatment score	0 (*N* = 15)	1 (*N* = 5)	0.21
Q9: When I swallow, food gets stuck in my throat			

EAT-10 Question	Known Primary (KP)	Unknown Primary (UP)	*p* Value
Median pretreatment score	0 (*N* = 8)	1 (*N* = 4)	0.51
Median posttreatment score	0 (*N* = 15)	0 (*N* = 4)	0.18
Q10: I cough when I eat			
Median pretreatment score	0 (*N* = 8)	0.5 (*N* = 4)	0.36
Median posttreatment score	1 (*N* = 15)	1 (*N* = 5)	0.16