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Metachronous HPV-Associated Squamous Cell Carcinoma of the Oral Tongue Treated with Neoadjuvant Chemoimmunotherapy: A Case Report

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Abstract:

Human papillomavirus (HPV) is a well-established etiologic factor in oropharyngeal squamous cell carcinoma, but its role in oral tongue squamous cell carcinoma (OTSCC) and patterns of recurrence is less clearly defined. A 54-year-old former smoker with multiple comorbidities had HPV-positive pT2N0M0 squamous cell carcinoma of the left lateral tongue and floor of mouth resected in 2022 with partial glossectomy, floor-of-mouth resection, and elective neck dissection, without adjuvant therapy. He remained disease-free following revision tongue debulking for dysplasia in 2024. In February 2026, he presented with a one-month history of a painful right ventral tongue mass impairing oral intake. Examination revealed a 2.5-cm friable exophytic lesion on the right ventral tongue without palpable cervical lymphadenopathy. Punch biopsy demonstrated invasive moderately differentiated squamous cell carcinoma. PET/CT showed an intensely hypermetabolic right tongue lesion with suspicious ipsilateral cervical lymph nodes but no distant metastases; an incidental focus of sigmoid colon uptake was noted. A multidisciplinary tumor board considered the new lesion a metachronous contralateral OTSCC in the setting of prior extensive left tongue surgery and recommended induction chemoimmunotherapy with pembrolizumab, docetaxel, and cisplatin, followed by restaging and reassessment for further surgery or radiotherapy. The patient completed the first cycle with manageable toxicity and preserved oral intake; response assessment after two cycles is pending. This case illustrates metachronous contralateral OTSCC in an HPV-associated setting despite guideline-concordant initial management and highlights the emerging role of induction chemoimmunotherapy as a function-preserving strategy in locally advanced recurrent oral cavity cancer after prior major tongue resection.

Keywords:

oral tongue squamous cell carcinoma; human papillomavirus; metachronous tumor; field cancerization; pembrolizumab

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Introduction

Background

Oral tongue squamous cell carcinoma accounts for a significant proportion of oral cavity malignancies and is traditionally associated with tobacco and alcohol exposure [1, 2]. The prognostic impact of HPV in OTSCC remains controversial, with reported HPV prevalence and outcome differences varying among series, in contrast to the favorable prognosis typically seen in HPV-mediated oropharyngeal squamous cell carcinoma [1–3]. Recurrence of oral cavity cancer may present as local disease, nodal disease, or second primary tumors, and the concept of field cancerization has been proposed to explain multifocal malignancies of the upper aerodigestive tract [4, 5]. Contemporary management of recurrent or metachronous oral tongue cancer must balance oncologic outcomes with functional preservation. Pembrolizumab-based chemoimmunotherapy has demonstrated efficacy in locally advanced head and neck squamous cell carcinoma [6, 7]. We present a patient with prior HPV-positive left lateral tongue squamous cell carcinoma who developed a metachronous contralateral ventral tongue carcinoma four years later, managed with induction chemoimmunotherapy to optimize both disease control and functional preservation.

Case Presentation

A 54-year-old man with a history of type 2 diabetes mellitus, hypertension, gout, obesity, and seizure disorder presented in February 2026 with a complaint of a new mass on the right ventral tongue. He was a former heavy smoker with a long smoking history, having quit in 2022, and denied current alcohol or illicit drug use. There was no known family history of head and neck malignancy.

Prior Cancer History (2022–2024) In 2022, the patient developed a painful ulcerative lesion on the left lateral tongue that progressively interfered with speech and chewing. Cross-sectional imaging of the neck demonstrated a left lateral tongue mass without radiographic lymphadenopathy, corresponding to clinical Stage II (cT2N0M0) oral tongue squamous cell carcinoma by AJCC 8th edition [8]. He underwent left partial glossectomy with floor-of-mouth resection, elective neck dissection of levels I–IV, tracheostomy, radial forearm free flap reconstruction, and split-thickness skin grafting in September 2022. Final pathology revealed moderately differentiated squamous cell carcinoma of the left lateral tongue and floor of mouth, pT2N0M0, Grade 2, with no lymphovascular or perineural invasion and 0 of 53 lymph nodes involved. Margins were negative, with the closest margin measuring 4 mm. Immunohistochemistry for p16 was strongly positive, consistent with HPV-associated disease [9].

Given the T2N0 status, negative margins, and absence of adverse features, no adjuvant radiation or chemotherapy was recommended per multidisciplinary tumor board discussion [10]. The patient recovered well postoperatively, with progressive improvement in swallowing, speech, and articulation following reconstructive surgery and decannulation. Surveillance examinations in the clinic showed no evidence of recurrence.

In November 2024, he underwent revision tongue debulking for non-keratinizing dysplasia and carcinoma in situ at the edge of the reconstructed area. Margins were again negative. Following this procedure, he remained asymptomatic and was noted to have no evidence of disease at his most recent documented follow-up in November 2025.

Current Presentation (2026) Approximately one month prior to the current emergency department visit, the patient noted a new lesion on the inferior aspect of the right side of his tongue. The lesion gradually enlarged and caused dull, constant pain exacerbated by eating. He reported difficulty with certain foods but maintained overall weight and oral intake. He delayed seeking care due to fear that the lesion represented recurrent cancer. He denied dysphagia to liquids, dyspnea, otalgia, fevers, chills, or other systemic symptoms.

On arrival, he was afebrile with stable vital signs and appeared in no acute distress. The general examination was unremarkable. Cranial nerves II–

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XII were grossly intact, and facial skin examination revealed no suspicious lesions.
Intraoral examination showed a well-healed left tongue reconstruction and radial forearm free flap. On the right ventral tongue, there was an approximately 2.5-cm round, fungating, friable, exophytic mass with surrounding erythema and contact bleeding **(Figure 1)**. The floor of the mouth on the right was clear. The oropharynx showed no mucosal lesions, and the tonsils and base of tongue were symmetric without exudate. Neck examination revealed a supple, non-tender neck with midline trachea and no palpable cervical lymphadenopathy or masses. The range of motion was full, and the previous tracheostomy scar was well healed.

Diagnostic Assessment Given the patient's history and concerning examination, an incisional 3-mm punch biopsy of the right ventral tongue mass was performed on February 3, 2026. Histopathologic analysis revealed invasive moderately differentiated squamous cell carcinoma. Additional immunohistochemical testing, including p16, was requested to assess HPV association in the new lesion.

To complete staging, a PET/CT scan was obtained on February 24, 2026. The study demonstrated markedly increased fluorodeoxyglucose (FDG) uptake along the right side of the tongue extending from the midline to the right posterior oral cavity, with a reported maximum standardized uptake value (SUVmax) of 44.0. Mild asymmetric uptake involved the right floor of the mouth (SUVmax 16.0). Multiple bilateral cervical lymph nodes exhibited increased uptake; several right level II nodes (SUVmax 12.8 and 11.0) were considered suspicious for metastatic involvement, whereas subcentimeter left level II nodes (SUVmax up to 7.5) were considered potentially reactive, but metastatic disease could not be excluded. No FDG-avid axillary, mediastinal, or abdominal lymphadenopathy was identified.

In the abdomen and pelvis, a focal area of increased FDG uptake was localized to the sigmoid colon, with a maximum standardized uptake value of 35.7. Radiology interpretation favored an underlying premalignant polyp or early neoplastic process, and colonoscopy was recommended for further evaluation. No additional visceral lesions or osseous metastases were seen.

Therapeutic Intervention The patient's case was presented at a multidisciplinary head and neck tumor board on February 26, 2026. With a new right ventral tongue squamous cell carcinoma arising approximately four years after initial left tongue OTSCC, the lesion was considered a metachronous contralateral oral cavity tumor rather than direct local recurrence. The combination of PET-avid bilateral cervical nodes and the patient's surgical history suggested at least Stage III/IVA disease. Because the patient had already undergone significant resection and reconstruction of the left tongue and floor of the mouth, further extensive surgery on the right tongue was expected to carry substantial risk of functional deficits in speech and swallowing. After discussion of options, including primary surgery with adjuvant therapy versus systemic therapy followed by reassessment, the tumor board recommended induction chemoimmunotherapy. The chosen regimen consisted of pembrolizumab combined with docetaxel and cisplatin, to be administered every three weeks for two cycles, followed by restaging imaging. Depending on the response, subsequent management would include consideration of definitive surgery, radiotherapy, or continued systemic therapy.

The rationale for neoadjuvant chemoimmunotherapy included: (1) potential tumor downstaging to facilitate less morbid surgery; (2) assessment of systemic therapy responsiveness as prognostic information; (3) preservation of surgical option if response is favorable; (4) functional organ preservation if excellent response achieved; and (5) early treatment of potential micrometastatic disease.

On March 10, 2026, the patient received cycle 1, day 1 of induction therapy. Premedications were given according to institutional protocol, followed by pembrolizumab, docetaxel, and cisplatin infusions with post-treatment hydration. Prophylactic pegfilgrastim was applied subcutaneously with instructions for removal the subsequent evening. The patient was discharged with oral ondansetron for nausea and a multimodal analgesic regimen including acetaminophen, non-steroidal anti-inflammatory drugs, and gabapentin. He was advised to maintain adequate hydration, void frequently, and seek emergent care for fevers

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over 100.5°F, dyspnea, chest pain, intractable vomiting, diarrhea, or new numbness or tingling.

Follow-Up and Outcomes At early outpatient follow-up after the first cycle, the patient reported mild fatigue and nausea controlled with ondansetron. Tongue pain persisted but was improved compared with presentation, and he continued to tolerate oral intake without significant weight loss. There were no signs of severe mucositis, neutropenic fever, or other acute complications. A repeat CT scan of the neck was scheduled 1.5–2 weeks after completion of the second cycle of induction therapy to evaluate radiologic response. Colonoscopy was arranged to investigate the incidental sigmoid colon uptake. At the time of this report, the patient remained on induction chemoimmunotherapy with no radiologic evidence of distant metastases; longer-term oncologic and functional outcomes are pending continued follow-up.

Discussion

This case underscores several clinically relevant issues in the management of OTSCC. First, although HPV status is a well-recognized prognostic factor in oropharyngeal squamous cell carcinoma, its significance in OTSCC remains uncertain [1, 2, 4]. Reports suggest that HPV-positive OTSCC may constitute a biologically distinct subset, yet survival advantages compared with HPV-negative disease have not been consistently demonstrated. The development of a metachronous contralateral tongue carcinoma in our patient, despite an HPV-positive index tumor with negative nodes and margins, illustrates that HPV association does not preclude subsequent oral cavity malignancy.

Second, the appearance of a new right ventral tongue lesion after prior left lateral tongue cancer raises the question of second primary tumor versus delayed local-regional recurrence. The concept of field cancerization posits that chronic exposure to carcinogens and, potentially, viral oncogenes creates widespread premalignant changes throughout the mucosa of the upper aerodigestive tract, leading to multiple independent tumors over time [5]. Our patient's history of heavy tobacco use, coupled with HPV-associated disease, likely contributed to this predisposition. In HPV-associated oropharyngeal cancer, second primary tumors in contralateral tonsils have been documented, with molecular analysis demonstrating that the same HPV-16 variant causes both the index tumor and the second primary [6]. Whether a similar mechanism explains our patient's contralateral tongue tumor remains speculative without molecular analysis comparing HPV variants between the two tumors.

Regardless of classification, the case emphasizes the importance of meticulous bilateral oral cavity examinations at every surveillance visit, even in patients with early-stage disease and seemingly favorable pathology. Some authors have documented late recurrences (greater than 5 years) in HPV-positive oropharyngeal cancer, with one case report describing distant metastases 11 years after initial diagnosis [11]. This highlights that HPV-positive status does not preclude recurrence and necessitates long-term surveillance extending beyond typical 2-3 year follow-up intervals.

Third, treatment decisions for recurrent or metachronous OTSCC in previously operated fields must weigh oncologic control against functional outcomes. Repeat partial glossectomy or more extensive resections in a patient with prior free flap reconstruction can result in marked impairment of speech, swallowing, and quality of life. Emerging data support the use of neoadjuvant PD-1 inhibitor-based regimens combined with platinum chemotherapy in resectable head and neck squamous cell carcinoma, demonstrating promising response rates and acceptable toxicity profiles [6, 7].

Recent phase II data showed that neoadjuvant pembrolizumab plus docetaxel and cisplatin achieved an objective response rate of 87.8% with manageable toxicity in locally advanced HNSCC [7]. The KEYNOTE-689 trial and related studies have demonstrated that perioperative pembrolizumab combined with surgery and adjuvant therapy improved outcomes in resectable Stage III-IVA HNSCC [12]. In this case, induction pembrolizumab with docetaxel and cisplatin was selected to achieve tumor cytoreduction, potentially facilitating less morbid surgery or enabling non-surgical definitive therapy, while preserving tongue function as much as possible. The addition of pembrolizumab (anti-PD-1 checkpoint inhibitor) to platinum-based chemotherapy is particularly

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relevant in HPV-associated tumors. HPV-positive head and neck cancers typically demonstrate higher PD-L1 expression and increased tumor-infiltrating lymphocytes compared to HPV-negative tumors, suggesting enhanced immunogenicity [3]. Pembrolizumab has established efficacy in recurrent/metastatic HNSCC, with improved overall survival compared to chemotherapy alone in PD-L1-positive tumors. Combining pembrolizumab with chemotherapy in the neoadjuvant setting may capitalize on synergistic mechanisms: chemotherapy-induced immunogenic cell death may enhance response to checkpoint blockade [6, 7].

Finally, this report demonstrates the value of structured case reporting. Explicit description of patient history, diagnostic reasoning, therapeutic decisions, and follow-up provides transparency and facilitates application of the lessons learned to similar cases. Documentation of multidisciplinary decision-making and the patient's tolerance of novel treatment strategies helps inform future care in this evolving therapeutic landscape.

Conclusion

This case demonstrates that metachronous contralateral oral tongue squamous cell carcinoma can arise in patients with HPV-associated disease despite appropriate initial surgical management and favorable pathologic features. Long-term, meticulous bilateral oral cavity surveillance is therefore essential and should extend beyond conventional 2–3 year follow-up intervals. In anatomically complex recurrences after prior major tongue surgery, induction pembrolizumab-based chemoimmunotherapy within a multidisciplinary framework may offer a pragmatic balance between oncologic control and preservation of speech and swallowing, with response to neoadjuvant therapy guiding the choice and extent of definitive local treatment.

Take Home Messages

Metachronous contralateral HPV-associated oral tongue squamous cell carcinoma can occur years after definitive surgery for early-stage disease.

Vigilant, long-term surveillance of the entire oral cavity is essential, with careful bilateral examination at every visit, extending beyond typical 2-3 year intervals.

In anatomically challenging recurrences after prior major tongue surgery, induction pembrolizumab-based chemoimmunotherapy may offer a pragmatic balance between oncologic control and preservation of speech and swallowing.

Multidisciplinary tumor board evaluation is critical when planning treatment for recurrent or metachronous oral cavity squamous cell carcinoma.

Response to neoadjuvant systemic therapy will guide definitive management, with surgery reserved for patients demonstrating a favorable response and acceptable functional morbidity.

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Figures and Tables

Figure 1. Clinical photograph of the right ventral tongue showing a 2.5-cm fungating, friable, exophytic mass with surrounding erythema.

Table 1. Timeline of diagnosis and treatment events

Date	Event
August 2022	Initial diagnosis: left lateral tongue SCC, HPV-positive
September 2022	Definitive surgery: partial glossectomy, floor of mouth resection, neck dissection I-IV, radial forearm free flap reconstruction
September 2022	Final pathology: pT2N0M0, Grade 2, negative margins
November 2024	Revision tongue debulking for carcinoma in situ

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Journal of Dermatological Case Reports

Date	Event
November 2025	Last documented NED surveillance visit
January 2026	Patient notices new right tongue lesion (approximate)
February 3, 2026	ED presentation with 1-month history of painful mass
February 3, 2026	3-mm punch biopsy performed
February 24, 2026	PET/CT restaging scan
February 26, 2026	Multidisciplinary tumor board discussion
March 10, 2026	Cycle 1 Day 1: pembrolizumab, docetaxel, cisplatin initiated
May 2026 (planned)	Restaging CT scan after cycle 2