**Case 5: Low Risk, High Risk: Adjuvant Therapy in Resected p16+ Oropharyngeal Cancer with ≥5 Positive Ipsilateral Lymph Nodes**

A 50-year-old, previously healthy man presented with a 2-month history of an enlarging left neck mass and odynophagia. He is a never smoker. Physical examination revealed a mobile 2.5 cm left level 2 cervical lymph node. Fine needle aspiration of the node was positive for p16+ squamous cell carcinoma. Positron emission tomographic computed tomography demonstrated at least 2 avid left level 2 cervical lymph nodes with no obvious primary lesion and no distant metastatic disease (Fig 1). Quadroscopy revealed an abnormal lesion in the left palatine tonsil and biopsy was positive for p16+ squamous cell carcinoma. There was no extension of the tonsillar mass to the base of tongue or soft palate. The clinical stage was T1N1M0. The patient proceeded with transoral robotic surgery tonsillectomy and selective lymph node dissection of the left neck (levels 2-4). Two level 2 cervical lymph nodes and 5 level 3 cervical lymph nodes were positive for metastatic carcinoma out of a total of 36 lymph nodes with no evidence of extranodal extension. Pathology from the left tonsil specimen confirmed a 1.5 cm p16+ squamous cell carcinoma with negative surgical margins and no lymphovascular or perineural invasion. The pathologic stage was T1N2.

Fig. 1: Staging positron emission tomographic computed tomography.

**Expert 1: Multistation Radiation**

Over a decade has passed since the prognostic significance of human papillomavirus–status for squamous cell cancers of the oropharynx was demonstrated. Numerous cooperative group efforts have investigated both dose and volume treatment de-escalation in these patients. For this case, in the setting of upfront surgical management with a transoral robotic surgery (TORS)/selective neck approach, given pathologic confirmation of multistation ipsilateral neck disease, we unequivocally recommend adjuvant therapy. In absence of positive margins or extranodal extension, we do not advocate for chemoradiation but instead radiation alone. We favor irradiation of both the primary site and ipsilateral neck. Modern protocols, such as NRG HN-005, allow for unilateral neck treatment in the definitive setting for select patients with well-lateralized primary tumors with minimal nodal disease burden. Although this patient has both level II and III involvement, in the setting of an adequate neck dissection, we are comfortable omitting the contralateral neck. Although there is emerging evidence for uncoupling the primary site from the neck for post-TORS radiation therapy treatment, this paradigm remains in its infancy and lacks randomized validation. Further, omission of the primary site when delivering ipsilateral neck radiation after TORS appears to offer no significant clinical or dosimetric advantage. Based on the evidence from the ECOG-ACRIN 3311 clinical trial, this patient fails to meet criteria for the intermediate-risk group (T1-2 negative/close margins, N1-2 with <1 mm ENE and ≤4 lymph nodes +) and thus is questionable for de-escalated radiation doses. Thus, we recommend treating this patient's operative bed and involved level II and III neck nodal levels to a dose of 60 Gy with elective coverage of the ipsilateral level IV neck to 54 Gy in 30 fractions with intensity-modulated radiotherapy.

**Expert 2: Less Is Not Always More**

First, pretreatment patient selection for surgical resection of oropharynx cancer is of paramount importance, as patients receiving triple modality therapy consistently report higher levels of toxicity, worse quality of life, higher decision regret, and value cure as first priority both pre- and posttreatment. The accuracy of imaging to predict pathologic nodal stage has been variable in the literature. Postoperatively, the patient in question would be considered “intermediate risk” by several clinical trial stratifications, but likely carries a clinically significant risk of both locoregional failure and distant metastases.

In consideration of adjuvant radiation therapy (RT) for this patient, we would not typically give less than 60 Gy postoperatively at our institution. Although pN2 patients have been included in de-escalation trial strategies as “intermediate risk” with only pathologic extranodal extension considered at highest risk, the literature suggests that patients with high nodal count have adverse outcomes. Specifically, OS, PFS, LRC, and DM have been shown to be worse even in the absence of extranodal extension, with the potential for out-of-field locoregional failures in the setting of RT volume de-escalation. The present patient could also be considered for concurrent chemotherapy for these reasons. A proper noninferiority trial to define optimal adjuvant RT dose for intermediate-risk patients seems unlikely, and our field continues to struggle with which patients may be treated with less RT, but this patient likely represents an extreme within the intermediate-risk category.

Although the primary site was resected with negative margins, our institution has not considered the promising phase II data of the AVOID trial yet standard of care, and thus would typically treat both the primary tumor site and the neck. We would expect a primary tumor confined to the anatomic tonsil to drain to the ipsilateral neck only, but, in this particular patient, we would also carefully evaluate and consider treating the contralateral neck. Although we do not use multiple nodes or N2b status (AJCC 7th ed) by itself as an automatic indication for contralateral neck irradiation, this patient had a total of 7 lymph nodes involved in the ipsilateral neck with 5 radiographically occult lymph nodes, likely representing aggressive biology. One must consider the balance of tumor control and toxicity when making the decision to treat the contralateral neck. In our practice, even with bilateral neck RT, we have been able to spare the pharyngeal constrictors and salivary glands to below meaningful dose constraints to minimize toxicity.

**Expert 3: Chemotherapy Only for High-risk Features**

A 50-year-old never smoker presented with p16+ squamous cell carcinoma, confined to the tonsil with 2 avid lymph nodes in the ipsilateral neck, both less than 3 cm. With these pretreatment findings, an initial approach with surgery was almost assured of requiring adjuvant radiation therapy. Two recently published phase 2 randomized trials of surgery or radiation therapy in such patients suggest definitive radiation therapy and concurrent systemic therapy may have lower overall morbidity, and this would have been our recommended initial approach.

Although on Eastern Cooperative Oncology Group (ECOG) 3311 the patient would have been assigned to the adjuvant radiation therapy and concurrent cisplatin arm postoperatively, a recent secondary analysis of NRG/Radiation Therapy Oncology Group (RTOG) 9501/0234 and European Organization for Research and Treatment of Cancer (EORTC) 22391 did not find a cutoff on positive lymph nodes where concurrent systemic therapy demonstrated a significantly improved outcome.

Therefore, we would recommend adjuvant radiation therapy without concurrent chemotherapy given the lack of high-risk features of extranodal extension or a positive margin. With a small T1 tonsillar primary tumor that did not involve the tongue base or soft palate, it may be reasonable to avoid contralateral neck radiation. However, for patients not evaluated by a radiation oncologist pretreatment, caution should be exercised with this approach. Although it may be reasonable to spare the postoperative tonsillar bed in the absence of intermediate-risk features, only low-level evidence supports this approach. We would prescribe 60 Gy at 2 Gy per fraction to the tonsillar bed and involved ipsilateral lymph node levels II and III and 54 Gy at 1.8 Gy per fraction to the elective neck levels IV, V, and VIIb using a simultaneous integrated boost technique.

**Expert 4: Balancing Aggressive Treatment with Minimizing Toxicity**

The patient has a p16-positive, squamous cell carcinoma of the left palatine tonsil, staged as T1N2M0. The patient has already undergone transoral robotic surgery (TORS) with tonsillectomy and selective lymph node dissection of the left neck (levels 2-4). The pathology report shows negative surgical margins and no lymphovascular or perineural invasion, which is favorable.

Our most favored therapeutic approach for this patient would be adjuvant radiotherapy with concurrent chemotherapy, considering the high-risk factors like multiple lymph node involvement (N2 disease). We recommend treating both the primary site and the ipsilateral neck, including levels II, III, and elective coverage of level IV. In the absence of extranodal extension or positive margins, ipsilateral neck radiation is advised. Prescribe a dose of 60 Gy to the primary site and involved nodal levels, and a lower dose of 54 Gy to elective lymph node levels in 30 fractions using intensity-modulated radiotherapy (IMRT).

Concurrent chemotherapy (most commonly cisplatin) is recommended because it has been shown to improve disease-free survival and overall survival in patients with locally advanced head and neck squamous cell carcinoma, particularly when there are high-risk features like multiple lymph node involvement. The p16-positive status of this patient's tumor is a favorable prognostic factor, as p16-positive oropharyngeal cancers tend to have a better response to treatment and improved outcomes. However, given the N2 nodal status, the addition of chemotherapy is still advisable.

In summary, our recommendation for this patient would be adjuvant radiotherapy with concurrent chemotherapy. This approach aims to minimize the risk of locoregional recurrence and improve overall survival, considering the high-risk features in this case. The patient should be closely followed up during and after the treatment to monitor for potential toxicities and assess the response to therapy.

**Expert 5: Whose Neck Is on the Line?**

The landscape of adjuvant treatment in p16+ oropharynx cancers is evolving. This patient has a lateralized p16+ left tonsil squamous cell carcinoma, pT1 pN2 stage II with 5 out of 36 involved lymph nodes, no lymphovascular invasion or perineural invasion, and negative margins. Going from pT1 pN1 to pT1 pN2 changes the 5-year overall survival prognosis from 89% to 70% based on the landmark study by Haughey et al.

Regarding radiation target volumes, the updated Princess Margaret data show excellent outcomes with ipsilateral radiation for well lateralized tonsillar cancers with an aggregate contralateral failure of 4.3% across published series in the setting of multiple neck nodes. A recent series of predominantly Human papillomavirus (HPV)+ tonsil cancers, with 45% having multiple neck nodes, similarly shows 2% contralateral neck failure rate. Although there are intriguing data about omitting coverage of the primary site, this needs further study at the multi-institutional level before becoming standard practice.

In terms of radiation dose, this patient would not have been eligible for the de-escalation arm of Eastern Cooperative Oncology Group 3311 and so we would proceed with standard postoperative dose of 60 Gy. Previous data from our group demonstrate that although pN2 patients are at an elevated risk of both distant and locoregional failure, distant failure predominates.5 This points to a need to address treatment intensification in these patients in the next generation of clinical trials.

For now, given the elevated risk of failure in this group, for patients young and fit enough to tolerate it, we recommend concurrent chemoradiation with cisplatin for this population.

**Expert 6: Too Many Items on the Menu**

Published studies on the topic of de-escalation of adjuvant therapy after Transoral Robotic Surgery for p16+ oropharyngeal cancers have a variety of inclusion criteria and proposed de-escalation schemes.

However, not all p16+ cancers are favorable. Though our standard criteria for addition of chemotherapy to postoperative radiation therapy are the presence of extracapsular extension (ECE) and/or positive surgical margins, with 7 lymph nodes (LN) positive (pN2), we would consider the addition of chemotherapy in this patient who met criteria for the chemoradiation arm of ECOG-ACRIN E3311. Despite trimodality therapy, patients on this arm had a 2-year progression free survival of only 90.7%, with the caveat that the majority also had ECE. Other single institution postoperative trials reporting favorable results also employed concurrent chemotherapy for patients with multiple positive LNs, with or without ECE.

Although the primary was well-confined, given the number of pathologically positive LNs, which was not manifest on pre-operative dual modality imaging, we would default to bilateral LN treatment employing conservative normal tissue constraints with a low threshold for decreasing the elective dose to achieve them.

Little is gained by omission of the primary site and covering the intervening lymphatic tracks giving rise to the involved LNs may be critical.

With regard to dose, we would treat the primary site and involved nodal levels to 60 Gy with any elective LN levels to 50 to 54 Gy using a simultaneous integrated boost technique.

With so many choices for de-escalation on the menu, it is increasingly critical to recognize the patient for whom intensified therapy is most appropriate.