Impact of Induction Chemotherapy on Circulating Tumor DNA in HPV-Associated Oropharyngeal Cancer

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Abstract:

Background: Circulating HPV tumor DNA assays (ctDNA) are increasingly establishing a role in the diagnosis, treatment and after-care of patients with HPV-associated oropharyngeal cancer (HPV-OPC). Using a de-escalation paradigm of neoadjuvant chemotherapy followed by surgery, we have previously observed high and durable cure rates, particularly in non-smokers, with few patients subject to adjuvant radiation and its attendant morbidity. In this study, our aims were to correlate ctDNA, before and after both induction chemotherapy and subsequent definitive treatment.

Methods: A prospective enrollment of 42 patients with HPV-OPC documented by histology, p16 positivity and ISH-confirmed HPV status was undertaken between February 2021 and October 2024. The patients were consented to IRB-approved protocol, assaying ctDNA both before and after induction chemotherapy (Cisplatin and Docetaxyl) and thirdly, following definitive curative treatment (surgery or chemo-radiation). HPV ctDNA assays were conducted by Naveris Laboratory, Boston, USA.

Results: 42 patients were enrolled, 39 male and 3 female, presenting with Stage I to Stage IV disease. Of primary lesions, 22 originated in the tonsil, 17 in the tongue base and three remain unknown. All patients had HPV ctDNA assays before and after three cycles of neoadjuvant chemotherapy, in addition to serial assays commencing two weeks beyond completion of definitive therapy. Definitive therapy consisted of chemoradiation in two patients only, while the remaining 40 underwent surgery. Surgery consisted of transoral resection of the primary lesion in 37 (excluding three with unknown primary) and modified radical neck dissection in 40. Only three of 40 patients managed with definitive surgery subsequently required post-operative radiation (8%): two tonsillar resections with a positive deep margin and one patient with residual extra-nodal disease in the neck dissection specimen. 39 of 42 patients had a detectable HPV ctDNA at diagnosis (Sensitivity 93%). Of two patients managed with chemoradiation, one survived with ctDNA rendered negative following induction chemotherapy, and the other died of disease. One patient with Stage IV disease has been rendered NED with neoadjuvant chemotherapy alone. Of the remaining 36 patients managed with definitive surgery, 28 patients had HPV ctDNA rendered negative by pre-operative chemotherapy, however 13 of these patients were found to have minimal residual disease in their pathology specimens (Specificity 46%). Finally, of 8 patients who were still HPV ctDNA positive despite neoadjuvant chemotherapy, all were confirmed to have minimal residual disease in their surgical specimens (Sensitivity drops to 38% following neoadjuvant chemotherapy). Overall survival is 95%, at follow-up ranging from 7 to 46 months (median 20 months). 38/40 survivors remain NED with negative ctDNA, including six that have required salvage Radiation Therapy for either second primaries or locoregional failure. In all, three quarters of our patients have been spared radiation.

Conclusions: A complete response to induction chemotherapy cannot be reliably predicted by a negative HPV ctDNA assay, but a persistently positive ctDNA is highly predictive of persistent or recurrent HPV-OPC. Neoadjuvant chemotherapy prior to surgery reduces the requirement for radiation in HPV-OPC.