

Improving post-CRT neck assessment in patients with HPV-associated OPSCC (Review)

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Received December 14, 2019; Accepted April 10, 2020

DOI: 10.3892/mco.2020.2094

Abstract. The positive predictive value (PPV) of 12-week post-therapy FDG-PET/CT is low in patients with Human Papillomavirus (HPV)-associated Oropharyngeal Squamous Cell Carcinoma (OPSCC) after treatment with definitive chemoradiation (CRT). Moreover, the diagnostic performance of post-CRT fine needle aspiration (FNA) in detecting persistent disease is unknown in this population. Given these important shortcomings in post-CRT treatment assessment, head and neck oncologists are limited in appropriately selecting patients for consolidative neck dissection, which results in over-treatment of a favorable risk population. Using the PubMed database, we performed a literature review of published series in HPV-associated OPSCC to investigate potential strategies for improvement of post-CRT neck assessment. Several different approaches were found, including continued surveillance with PET/CT, delayed timing of restaging PET/CT, initial response evaluation with multimodality or alternative imaging, and detection of circulating HPV DNA. At present, the optimal approach to post-CRT treatment assessment is unclear; further investigation and incorporation of new technologies and surveillance protocols will be highly beneficial for patients with HPV-associated OPSCC.

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Key words: head and neck neoplasms, papillomaviridae, oropharyngeal neoplasms, chemoradiotherapy, positron-emission tomography, neck dissection

1. Introduction

Current treatment assessment algorithms. Definitive chemoradiation (CRT) is a standard treatment for locally-advanced human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). The response to treatment is assessed with both clinical and radiographic information. In patients without evidence of primary or nodal disease on clinical examination, surveillance imaging is often performed with a 12-week FDG-PET/CT. Both lymph node size and intensity of FDG uptake are used to assess the likelihood of residual disease in the neck and guide the decision to either observe patients or proceed with neck dissection. Both NCCN and UpToDate have published algorithms to assist clinicians with this process (1,2). NCCN recommends observation for negative scans, observation or repeat PET/CT at 3-6 months for equivocal scans, and CT or MRI followed by neck dissection for positive scans (Fig. 1). Negative scans are defined by no or low-grade uptake and positive scans are defined as suspicious for disease. According to UpToDate (Fig. 2), there are five different options depending on imaging and clinical factors. It is recommended that patients undergo salvage surgery for PET positive/CT positive scans and clinical observation for PET negative/CT negative scans. If a patient has a PET negative and CT positive result, 2-3 monthly clinical and radiographic observation is recommended for high-risk patients, while clinical observation is suggested for low-risk individuals, including those with HPV-associated OPSCC. Finally, a repeat PET/CT at 4-6 weeks is recommended for those with equivocal findings.

Low positive predictive value of 12-week PET/CT. Although these surveillance strategies have been shown to promote excellent oncologic control, replacing the policy of planned neck dissections, they may not be broadly applicable to all head and neck cancers (3-7). In HPV-associated OPSCC, the reported positive predictive value (PPV) of 12-week post-therapy PET/CT is low (8-11), likely secondary to the lower pre-test probability of residual nodal disease (12). In a retrospective chart review of 233 patients with HPV-associated OPSCC, Corpman *et al* found that post-treatment PET/CT had a PPV of 13.4% and led to 60 additional imaging studies, 23 additional biopsies, and meaningful salvage therapy in only 3 patients (1.6%) (13). One of the primary limitations of using PET/CT is the lack of a

standardized response criteria for HPV-associated disease. It has become increasingly clear that this disease entity has unique radiographic features, including a longer time to complete lymph node involution (14). This finding has been incorporated into the UpToDate algorithm, which recommends that CT positive/PET negative scans be managed with clinical observation in HPV-associated OPSCC. However, there is currently no effective strategy to manage lymph nodes with residual FDG avidity. Current algorithms guide decision-making by dividing responses into positive and equivocal groups. However, this approach may not be appropriate in HPV-associated disease. In a study of 79 patients with HPV-associated OPSCC on a de-intensification trial, Wang *et al* demonstrated a low PPV for PET/CT when responses were categorized as equivocal/incomplete or incomplete (9 and 13%, respectively) (9). The authors used the Mehanna *et al* trial definitions for nodal response (3), which defined an incomplete response as ‘intense FDG uptake at 12 weeks after chemoradiotherapy, with or without enlarged lymph nodes,’ and equivocal response as ‘mild or no FDG uptake in enlarged nodes or mild FDG uptake in normal-sized nodes.’

Limitations of Post-CRT fine-needle aspiration. While FNA has central importance in the initial workup of head and neck cancers, the utility of post-CRT FNA in detecting persistent neck disease is limited. The accuracy of post-CRT FNA in head and neck cancer has been questioned given the difficulty in interpreting the viability of irradiated cancer cells. In a series of 540 patients with cancers of the oral cavity, oropharynx, hypopharynx, and larynx, van der Van der Putten *et al* found that post-CRT FNA had a specificity of 42% in patients with advanced disease; only 50% of patients with positive cytology had viable disease on neck dissection pathology (15). On the other hand, in a pilot study of 14 patients undergoing FNA before planned neck dissection for persistent lymphadenopathy on imaging, Fleischman *et al* found that the diagnostic accuracy of FNA was 88% at detecting residual head and neck cancer (16). The authors suggested that FNA may be a feasible ancillary diagnostic modality. In truth, the diagnostic performance of post-CRT FNA has not been studied in HPV-associated OPSCC, indicating that future research is needed before clinicians can rely on this modality to reconcile concerning PET/CT findings.

Aims of this article. Given these important shortcomings in post-CRT treatment assessment in patients with HPV-associated OPSCC, physicians are limited in appropriately selecting patients for consolidative neck dissection, which results in over-treatment. This consideration is especially important for patients with HPV-associated disease, a population with a favorable prognosis. Post-CRT neck dissection has important implications on long-term quality of life as it is associated with a higher rate of post-operative complications (17). Therefore, a literature review was performed with the PubMed Database to investigate potential strategies for improvement of post-CRT treatment assessment of the neck in patients with HPV-associated OPSCC.

2. Strategies to improve post-CRT neck assessment

The existing literature highlights several potential strategies to improve post-CRT neck assessment in patients with

HPV-associated OPSCC (Table I), including continued surveillance with PET/CT, delayed timing of restaging PET/CT, initial assessment with multimodality or alternative imaging, and detection of circulating HPV DNA.

Continued surveillance with PET/CT. Numerous publications have promoted the notion of exercising caution when interpreting 12-week PET/CT results, adopting a high threshold for immediate neck dissection, and observing patients with serial imaging (3,9,13). One study was found that systematically evaluated a surveillance strategy in patients with HPV-associated OPSCC (18). In a retrospective analysis of a prospectively collected database, Liu *et al* assessed the utility of a repeat PET/CT, instead of immediate neck dissection, in patients with HPV-associated OPSCC who underwent RT or CRT, and had an incomplete response on 12-week PET/CT (18). The authors enrolled 235 patients with non-metastatic disease; 41 patients underwent 16-week imaging for an incomplete response at 12-weeks, which included both positive and equivocal responses. A positive response was defined as focal FDG uptake greater than the liver and corresponding to a structural abnormality, while an equivocal response was defined as focal FDG uptake less than the liver, greater than adjacent tissue, and corresponding to a structural abnormality. Patients were excluded from undergoing 16-week imaging if they had residual FDG avidity at the primary or distant site on 12-week PET/CT or if they had evidence of clinical nodal progression (n=95). Re-evaluation at a multidisciplinary tumor board was performed for patients with a persistent incomplete response on 16-week imaging. In their analysis, the authors found that 16-week PET/CT reduced the rate of neck dissection from 17 to 2.6% without impacting subsequent regional control; no regional failures occurred in patients who underwent neck dissection following a 16-week PET/CT. Moreover, 29 (71%) patients converted to a complete response on 16-week imaging, only one of which had nodal failure at 49 months post-therapy. Compared to a PPV of 12% for 12-week PET/CT, the PPV of 16-week imaging was 33%. Based on these findings, the authors suggested that a 16-week repeat PET/CT could spare many patients from unnecessary surgeries.

There are several important considerations pertaining to this study. Regarding the inclusion criteria, the authors grouped both positive and equivocal responses as incomplete, which is appropriate given that both an equivocal and positive response pose a clinical dilemma. PET/CT scans with significant FDG avidity may still be false positives in HPV-associated disease. In regard to the exclusion criteria, patients did not undergo repeat PET/CT if they had evidence of clinical nodal progression or had residual FDG avidity at the primary or a distant site on 12-week PET/CT. These exclusion criteria are also reasonable given the increased likelihood of disease in these clinical scenarios. In a retrospective analysis of 146 patients with OPSCC and treated with CRT, Bird *et al* found that all patients with residual FDG-uptake at both the primary site and neck had pathologically confirmed persistent disease (19), indicating that these patients may not be appropriate for observation. Finally, it is important to consider how the authors managed patients with persistent FDG avidity on 16-week imaging. Eight patients had stable FDG avidity on 16-week

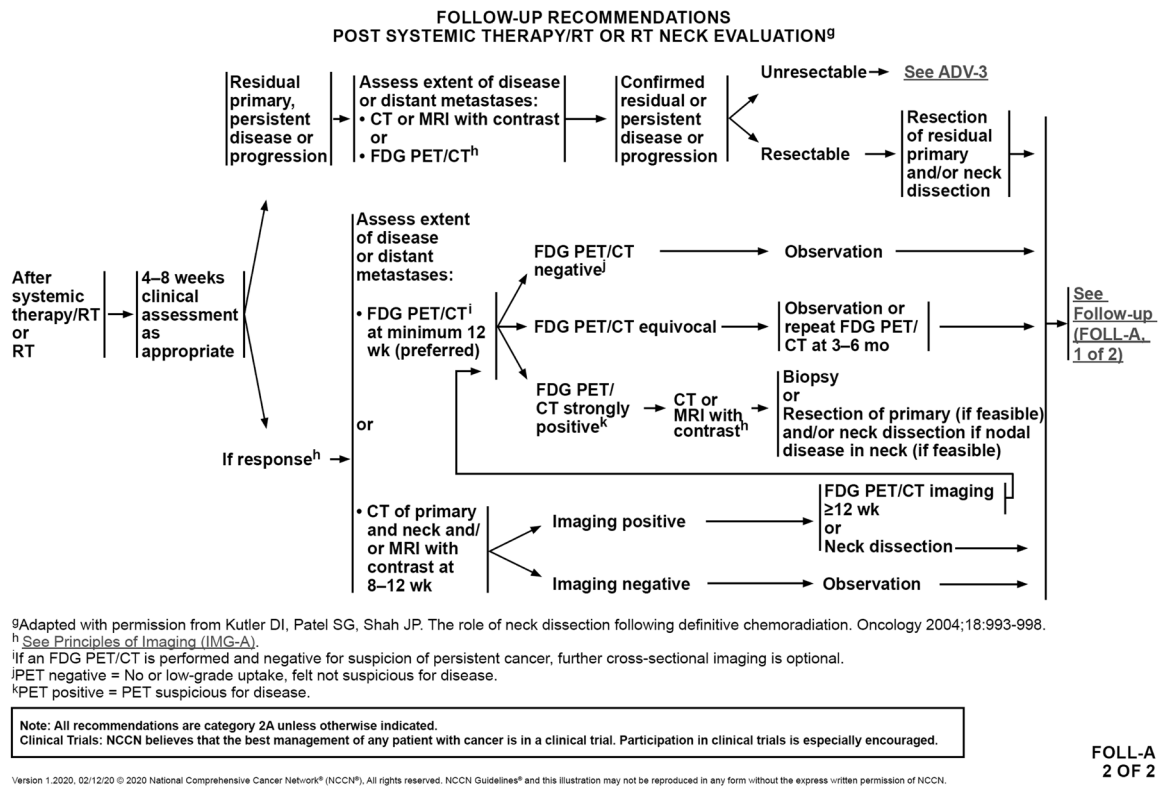


Figure 1. NCCN Follow-up Recommendations for Post Systemic Therapy/RT or RT Neck Evaluation. Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers V.2.2020. © 2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

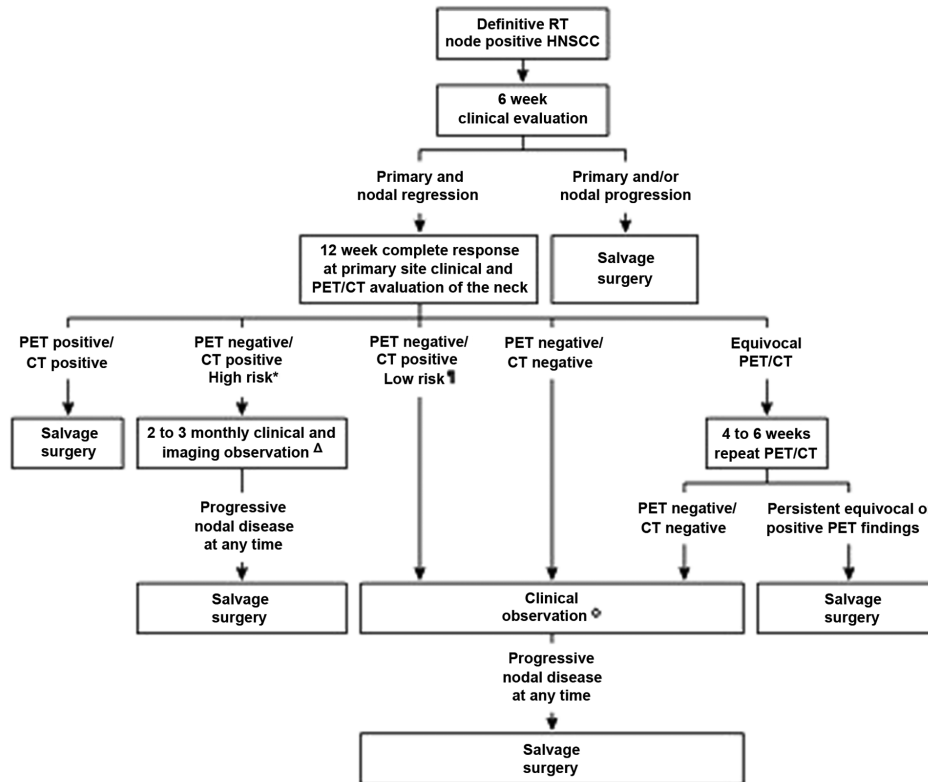
imaging; 4 individuals underwent neck dissection, all of whom had residual disease, and 4 individuals were observed and remained free of disease. Four patients had reduced FDG avidity on 16-week imaging, none of whom had residual disease. Based on these results, the authors recommended that patients with persistent and unchanged FDG avidity on 16-week PET/CT should undergo neck dissection. Given this small number of patients, it is difficult to comment on the appropriate management of patients with residual metabolic activity on repeat PET/CT.

Delayed timing of restaging PET/CT. Delaying the time of restaging PET/CT scan was proposed in a 2014 publication by Vainshtein *et al*, who evaluated the performance of 12-week PET/CT in predicting local and regional failure after CRT (8). The authors retrospectively reviewed and re-classified post-therapy scans in 101 patients with AJCC 7th edition stage III and IV HPV-associated OPSCC, grouping responses into complete, near complete, and less than complete. The PPV of 12-week PET/CT was found to be 33% for detection of nodal disease. Given this low PPV, the authors also assessed the diagnostic performance of surveillance PET/CT scans in 67 patients who did not have any clinical or radiographic suspicion of recurrent disease. The median time

from completion of CRT to first surveillance PET/CT was 7.3 months. All patients (12) with an incomplete response on restaging PET/CT (near and less than complete) achieved a complete response on surveillance PET/CT. The authors reported that surveillance PET/CT had a NPV of 98% and PPV of 83% for detection of regional recurrence. Based on the superior operating characteristics of surveillance PET/CT, the authors suggested that restaging PET/CT could be delayed to 6 months after completion of CRT.

When considering a delay in restaging PET/CT, it is necessary to consider the optimal timing since prolonging assessment could impact patient anxiety, neck dissection complication rates, type of neck dissection (selective versus modified versus radical), regional control, and early detection of distant metastases. In a 2010 retrospective analysis of 105 patients with HNSCC who underwent neck dissection after CRT, Goguen *et al* compared the complication rates and survival outcomes between patients undergoing neck dissection less than 12 weeks versus greater than 12 weeks after CRT (20). The authors found that the two groups did not differ in the rate of surgical complications or survival. This type of analysis has not been performed for patients with HPV-associated OPSCC. In regards to detection of distant metastases, some studies indicate that they occur at later time

Approach to the risk-adapted management of node positive HNSCC post RT



HNSCC: head and neck squamous cell carcinoma; RT: radiation therapy; PET: positron emission tomography; CT: computed tomography; OPSCC: oropharyngeal squamous cell carcinoma; HPV: human papilloma virus.

*High risk: where the perceived risk of residual nodal disease is high, such as suboptimally treated patients due to premature cessation of treatment, unplanned treatment interruptions, or the presence of high-risk primary disease, such as non-OPSCC.

†Low risk: where the perceived risk of residual nodal disease is low, such as HPV associated OPSCC treated optimally.

ΔOngoing clinical and imaging observation until residuum is <1 to 1.5 cm or stable for >6 months.

◊ The frequency of follow-up is based on institutional policy.

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Figure 2. UpToDate's Approach to the Risk-adapted Management of Node Positive Head and Neck Squamous Cell Carcinoma Post-Radiation. From 'Management of the neck following definitive radiotherapy with or without chemoradiotherapy in head and neck squamous cell carcinoma.'

points in HPV-associated OPSCC (21). Therefore, the role of early PET/CT for this purpose may not be significant.

Initial assessment with multimodality or alternative imaging modalities. Several publications have highlighted the use of ancillary imaging modalities to assist with treatment assessment, either alone or in combination with PET/CT. In a retrospective study from 2014, Pellini *et al* investigated the diagnostic performance of a 12-week post-CRT neck ultrasound, MRI, and PET/CT for detection of residual nodal disease (22). The authors prospectively enrolled 36 patients with OPSCC bulky nodal disease (>3 cm) who were treated with definitive CRT. All patients in the study underwent planned neck dissection 3 months after treatment; the pathology reports were used to determine the operating characteristics of the three imaging modalities. Individuals with less than a complete response at the primary site were excluded. For response evaluation, lymph nodes were considered metastatic on ultrasound if they had a 'short axis diameter >7 mm and/or round shape (reduction in the

ratio of maximal longitudinal to maximal axial diameter), unclear boundary or irregular hilar and internal echoes.' When comparing each modality alone and in combination, the authors found that neck ultrasound and PET/CT had the highest NPV (93.3%), while a combination of neck ultrasound, MRI, and FDG-PET/CT had the highest PPV (100%). The authors suggested that neck ultrasound with FDG-PET/CT could be used to identify patients with a complete response, while a combination of ultrasound, MRI, and FDG-PET/CT could be useful in selecting patients who require neck dissection. Of note, the authors did not include information on HPV or p16 status, limiting the applicability of these findings. Moreover, the cost of obtaining three imaging modalities concurrently is an important consideration; the authors argued that these health care expenditures would be offset by a decreased number of unnecessary surgical procedures. It is critical that further research is performed to investigate the cost-effectiveness of this strategy.

Yu *et al* compared the diagnostic performance of diffusion-weighted magnetic resonance imaging (DWI-MRI) and

Table I. Summary of the literature.

Author, year	Level of evidence	Year	Country	Number of subjects	Recommendation for post-CRT treatment assessment	Rationale	(Refs.)
Liu <i>et al.</i> , 2019	4	2019	Australia	235	Repeat PET/CT at 16 weeks for an incomplete response on 12 week imaging, excluding those with clinical nodal progression or residual FDG avidity at the primary or distant disease on initial post-therapy PET/CT.	16-week PET/CT reduced the rate of neck dissection from 17 to 2.6% without impacting subsequent regional control.	(18)
Vainshtein <i>et al.</i> , 2014	4	2014	USA	101	Delay initial post-therapy PET/CT to 6 months after completion of CRT or reserve PET/CT for patients with residual disease on CT at 3 months	6-month PET/CT demonstrated a false positive rate of only 2% and a false negative rate of only 17%.	(8)
Pellini <i>et al.</i> , 2014	4	2014	Italy	36	12-week neck ultrasound with FDG-PET/CT could be an effective strategy to identify patients with a complete response. A combination of ultrasound, MRI, and FDG-PET/CT could be useful in selecting patients who require neck dissection.	A combination of 12-week neck ultrasound and FDG-PET/CT had the highest negative predictive value (93.3%). A combination of US, MRI and FDG-PET/CT had the highest specificity (100%), accuracy (93.8%) and positive predictive value (100%).	(22)
Yu <i>et al.</i> , 2017	4	2017	USA	41	A single DWI-MRI could be used to identify residual neck disease after definitive CRT in patients with oropharyngeal cancer.	Compared to 14-week PET/CT, 8-week DWI-MRI produced similar sensitivity and better specificity. Moreover, the PPV was 50% with DWI-MRI and 25% with PET/CT.	(23)
Lee <i>et al.</i> , 2017	4	2017	UK	55	Plasma HPV DNA can potentially be used to predict response to CRT at both the primary site and lymph nodes in patients with HPV-associated head and neck cancers.	Post-treatment HPV DNA levels in plasma correlated with clinical responses.	(29)

CRT, chemoradiation; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; DWI-MRI, diffusion weight imaging-magnetic resonance imaging; US, ultrasound; PPV, positive predictive value; HPV, human papillomavirus.

PET/CT for detection of persistent neck disease (23). DWI-MRI is a functional imaging modality that allows for calculation of an apparent diffusion coefficient (ADC), which reflects microscopic proton motion; a lower value is associated with the presence of cancer. The rationale for this modality is that it can detect persistent disease earlier as diffusion signals are evident before changes in tumor size. The authors retrospectively reviewed the records of 41 patients with HPV-associated OPSCC who were treated with definitive CRT. DWI-MRI and PET/CT were performed at a median time of 8.6 and 14 weeks, respectively. The mean ADC and lymph node volume were determined for each DWI-MRI; the maximum standardized uptake value (SUV) was measured for each PET/CT. Using a receiver operating characteristic (ROC) analysis, the authors calculated a threshold of 1,500 for ADC and 2.5 for SUVmax. Using these thresholds and the pathology results of either biopsy or neck dissection, the authors found that DWI-MRI had a NPV and PPV of 100 and 50%, while PET/CT had a NPV and PPV of 100 and 25%. Given the earlier and more specific detection of residual nodal disease with DWI-MRI, the authors proposed that this imaging modality could be used to identify residual neck disease after definitive CRT.

This study was not the first to demonstrate the utility of DWI-MRI in head and neck cancer, but was the only publication that limited their analysis to HPV-associated OPSCC. While the higher PPV, equivalent NPV, and earlier time of acquisition support the use of DWI-MRI, it is important to consider the fact that surveillance with PET/CT had shown to be noninferior to planned neck dissection in regards to survival, which may dissuade clinicians from abandoning PET/CT. Further, although the PPV of DWI-MRI was shown to be higher than PET/CT, a value of 50% may still be suboptimal. Another issue is the ability of DWI-MRI to detect residual disease at the primary site. In a 2017 publication with 46 patients with advanced OPSCC, Greuter *et al* reported a PPV of 60.0% for DWI-MRI (24). However, less than half of the cohort had HPV-associated disease. Finally, Yu *et al* highlighted several important limitations of their study, including a small sample size and retrospective design, as well as limitations of DWI-MRI, such as a complex technique and difficulty in evaluation of cystic nodes (23). Therefore, although DWI-MRI may offer earlier and more specific detection of residual neck disease, which could help limit unnecessary neck dissections, this modality also has limitations.

Detection of circulating HPV DNA. The detection of plasma HPV DNA is an exciting new development that may prove useful in detection of residual disease (25-28). Lee *et al* assessed the role of circulating HPV DNA in detection of residual disease after CRT (29). The authors prospectively enrolled 88 patients with locally-advanced head and neck cancers and divided them into test (55) and validation (33) cohorts. All participants had HPV-associated disease, determined by p16 immunohistochemistry (IHC) and E6 RT-PCR, and underwent 12-week PET/CT. Individuals with residual FDG-avid nodes had a neck dissection and those with residual uptake at the primary or distant site underwent biopsy. The authors developed an amplicon-based next generation sequencing (NGS) assay to detect circulating HPV DNA in serum. They collected plasma samples at baseline as well as

6 and 12 weeks post-CRT. To validate the detection assay, the authors compared pre-CRT HPV DNA levels to both p16 IHC and E6 RT-PCR; they reported a sensitivity and specificity of 90% and above. Moreover, the authors correlated post-treatment HPV DNA levels to PET/CT and pathology reports. In the test cohort, HPV DNA levels were below the threshold of detection in all patients (23) with a complete radiological response on 12-week PET/CT. The assay was positive in the only patient with biopsy-proven persistent disease. Further, HPV DNA was undetectable in 3 patients who underwent biopsy at the primary and 1 patient who underwent neck dissection for increased FDG uptake on 12-week PET/CT; the pathology was negative in all 4 cases. In the validation cohort, HPV DNA levels were below the threshold of detection in all 7 patients with a complete radiographic response. Moreover, the assay was negative in 3 patients who underwent neck dissection for increased FDG on 12-week PET/CT; no residual disease was found in any of these patients. Based on these findings, the authors suggested that plasma HPV DNA could be used to help guide treatment decisions and avoid unnecessary surgeries, but commented that their findings require validation in a larger cohort of patients with longer follow-up. Indeed, the study had a small number of patients with residual disease and/or recurrence. Moreover, it would be helpful to compare the utility of this sequencing-based plasma assay to other methods of HPV detection, such as those that involve salivary collection or PCR technology.

3. Conclusions and prospects

This literature review highlights several strategies that have been proposed to improve post-CRT neck assessment in patients with HPV-associated OPSCC. A repeat PET/CT at 16-weeks for patients with an incomplete response on 12-week imaging may help reduce the number of neck dissections without comprising regional control. Delaying the timing of the initial post-therapy PET/CT may improve its PPV by allowing for radiation-induced inflammation to resolve, but the appropriate timing is unknown and has important clinical implications. DWI-MRI may offer an alternative to PET/CT, but has its own limitations. Finally, detection of plasma HPV DNA is an exciting development that may be able to effectively detect residual disease, but it requires further validation in larger cohorts. Given the current limitations of post-CRT assessment of the neck in patients with HPV-associated OPSCC, further investigation of these strategies will be highly beneficial for this population.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MW performed the literature review, wrote the manuscript and edited the final version. MG, LM, TT, NS, DKa, DF and DKr reviewed and edited the manuscript. ST reviewed the published literature, wrote parts of the manuscript, and edited and approved the final version. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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