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Evaluating the potential role of PET-CT in the post-treatment surveillance of head and neck cancer

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The central rationale for active surveillance following the curative treatment of head and neck squamous cell carcinoma (HNSCC) is the belief that earlier detection of recurrent or new primary cancers facilitates earlier initiation of therapy and can favorably impact clinical outcomes. The potential benefits of earlier detection of disease have considerable appeal to many physicians and patients, outweighing the potential risks. Active surveillance in some form is widely applied in oncology practice. A challenge facing the National Comprehensive Cancer Network (NCCN) Head and Neck Cancer Guidelines panel is the relative lack of higher quality evidence to inform specific surveillance recommendations. The panel currently recommends surveillance with 1) history and physical examinations including mirror and fiberoptic exams as clinically indicated; 2) post-treatment imaging of the primary site (and neck, if treated) within six months of treatment completion; 3) chest imaging as clinically indicated for patients with a smoking history per the NCCN Lung Cancer Screening Guidelines; and 4) a consideration of Epstein-Barr Virus/DNA testing in patients after treatment for nasopharynx cancer. Positron emission tomography with computed tomography (PET-CT) after treatment is only specifically mentioned in the context of a decision algorithm for assessing whether to do a neck dissection or observe the neck after chemoradiation or radiation treatment.[1] Otherwise, there is no prescribed role in the NCCN Head and Neck Cancer Guidelines for surveillance imaging including PET-CT in the absence of suspicious signs or symptoms. At the 2014 meeting, the panel reviewed available data on the potential role of PET-CT in the post-treatment setting.

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PET-CT scans are increasingly used for a variety of reasons in the diagnosis and management of advanced HNSCC. For example, in a review of eight studies, PET or PET-CT was able to detect the unknown primary in 51 of 180 patients with an otherwise inconclusive work-up.[2] Further, in patients receiving intensity-modulated radiation therapy (IMRT), fused PET-CT images are used to refine gross target volumes and better tailor radiation treatment fields to reduce toxicity.[3] The potential utility of PET-CT in post-treatment management would seem a logical extension of its demonstrated value in these other settings.

As noted previously, the NCCN Head and Neck Cancer Guidelines recommend considering a PET-CT scan during post-radiation or chemoradiation assessment as part of a risk-stratified approach to assess the need for elective neck dissection. In a meta-analysis of 51 studies involving 2,335 patients, the weighted mean (95% confidence interval) pooled sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET-CT for the post-radiation neck were 72.7% (66.6–78.2%), 87.6% (85.7–89.3%), 52.1% (46.6–57.6%) and 94.5% (93.1–95.7%), respectively.[4] Therefore, rather than all patients proceeding to adjuvant neck dissection, given the high NPV, observation can be considered for patients with non-FDG avid neck lymph nodes measuring <1cm. Sher et al. have analyzed the value of incorporating PET-CT into this decision-making. The most cost-effective strategy for managing the post-chemoradiation neck is reserving neck dissection only for patients with residual disease on PET-CT.[5]

The timing of post-treatment PET-CT imaging can impact on its diagnostic accuracy. PET-CT scans are recommended no sooner than 12 weeks after treatment completion to avoid high rates of equivocal and false positive studies.[6–8] The rate of equivocal studies declines with time since treatment.[9] In patients with initial post-treatment scans that are equivocal for residual disease, a repeat PET-CT scan may help identify patients who can be safely observed without neck dissection.[7]

Evidence supporting the utility of PET-CT in routine surveillance is less clear relative to that available to inform management. While the initial post-treatment PET-CT serves to identify residual disease, studies have shown that a second PET-CT, usually after an interval greater than 6 months, could be useful in detecting late local recurrences.[10,11] For example, in a prospective study, Lowe et al reported a 100% sensitivity of scheduled PET scans completed at 2 and 10 months post-treatment in detecting all locoregional and metastatic disease.[11] Ten of 16 recurrences were found on the first PET and 90% of these were locoregional. Six of 16 recurrences were found on the second PET and 50% were locoregional.[11] In a single institution study utilizing frequent routine PET-CT, Kostakoglu et al. reported earlier detection of recurrent disease by nearly six months compared to physical exam or high resolution CT scans.[12] Ho and colleagues confirmed that surveillance with PET-CT (completed annually for two years in patients with a negative post-treatment scan at 3 months) leads to earlier detection of recurrent disease. However, this study reported no survival benefit at three years in an unselected cohort of HNSCC patients diagnosed with PET-CT detected versus clinically- detected recurrent disease (including both local and distant failure).[9] Future studies are needed to better address whether additional PET-CTs will lead to improved outcomes through the earlier detection of salvageable late local

recurrences. In addition, further evidence is needed to incorporate prior PET-CT results to predict the value of subsequent scans and to determine the optimal interval between assessments.

There is ongoing debate as to the role of routine PET-CT scans beyond the initial post-treatment assessment for the earlier detection of distant metastatic lesions. This debate is further intensified in the setting of human papillomavirus (HPV)-related oropharynx cancer where there are reports of atypical presentation of recurrent metastatic disease[13,14], potentially longer survival following the development of recurrent disease,[15] and possibly, a greater role for resection or local ablative therapy of distant disease. In a study of patients treated with chemoradiation for oropharynx cancer in prospective clinical trials, 86% of recurrences were detected by three years in patients with p16+ tumors.[15] Whether additional imaging could facilitate earlier initiation of therapy and improve clinical outcomes in this cohort, with expected longer survival following recurrence, deserves further study. As experience and knowledge about the natural history of HPV-related oropharynx cancer expands, we will hopefully better understand which patients could benefit from early treatment of metastatic disease or if additional imaging creates a lead time bias associated with the detection of more indolent disease.

The diagnostic performance of PET-CT scans may provide valuable prognostic information and a means to possibly risk-stratify surveillance. Specifically, PET-CT has a very high NPV value in HNSCC for recurrent locoregional and metastatic disease. In a pooled analysis of over 2300 patients, Gupta et al. reported a weighted mean (95% CI) NPV of a single post-treatment PET-CT for the primary site at 95.1% (93.5–96.5%).[4] Other studies have reported NPV of a negative PET-CT closer to 100% when more than one scan is completed over time or completed later in follow-up.[10,12,16,17] There may be a role in future guidelines for combining PET-CT results with clinical characteristics such as HPV-status to inform a more risk-stratified approach to post-treatment follow-up.

To date, once a patient is free of disease, there is no clear evidence to support the routine use of PET-CT in surveillance of asymptomatic survivors of HNSCC. The high sensitivity of PET-CT may lead to false positive results that prompt and warrant subsequent follow-up including biopsies, procedures and imaging. Yet, when used at distinct decision points, PET-CT has proven effective at providing valuable diagnostic and prognostic information that affects management. In light of the changing epidemiology, emerging therapeutic options, and incorporation of value considerations into clinical practice, a further look at the potential role of PET-CT as part of a strategy to better risk stratify and individualize survivorship care will undoubtedly be part of future deliberations of the NCCN Head and Neck Cancer Guidelines panel.

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