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Qualitative ¹⁸F-FDG PET/CT Response Evaluation After Chemotherapy or Radiotherapy for Head and Neck Squamous Cell Carcinoma: Is There an Equivocal Group?

TO THE EDITOR: We read with great interest the recent article by Marcus et al. (1). The objective of this retrospective study on 214 patients with head and neck squamous cell carcinoma was to validate qualitative interpretation criteria for ¹⁸F-FDG PET/CT assessment of response after chemoradiotherapy or radiotherapy in terms of accuracy, reader reliability, and predictive value for survival outcomes. This is an area of particular interest because the use of ¹⁸F-FDG PET/CT for response assessment of head and neck squamous cell carcinoma is becoming increasingly widespread (2). Their Hopkins criteria were used to assign a score of 1–5, with scores of 1–3 considered negative for residual disease. A score of 1 was for focal ¹⁸F-FDG uptake less than activity in the internal jugular vein, a score of 2 was for focal ¹⁸F-FDG uptake more than activity in the internal jugular vein but less than liver uptake, a score of 3 was for likely inflammatory changes, and scores of 4 and 5 were for focal uptake greater than liver uptake. The study demonstrated high interreader agreement and an overall negative predictive value of 91.1%.

The authors stated that “no established qualitative interpretation criteria...have been published” (1). However, Porceddu et al. reported final results in 2011 (3) of a high-quality prospective study on 112 patients evaluating an ¹⁸F-FDG–directed policy for the management of patients with neck node–positive head and neck squamous cell carcinoma after chemoradiotherapy or radiotherapy using qualitative PET response criteria. With some similarity to the Hopkins criteria, these response criteria were prospectively implemented; focal uptake greater than liver background was considered positive, focal uptake less than liver but more than surrounding normal tissues was considered equivocal, and no uptake above background or diffuse uptake without underlying structural abnormality was considered negative. In this prospective study, PET-based nodal assessment had a negative predictive value of 98.1% (3). The most significant difference in this method of classification is the assignment of an equivocal response to focal uptake less than liver background, which would be assigned a score of 1 or 2 and considered negative according to the Hopkins criteria.

The management of this group of equivocal responders in neck lymph nodes in an era in which neck dissections are not routinely performed (4) is a particularly difficult clinical issue. In the study by Porceddu et al. (3), 11 of 112 patients had an equivocal response and 10 of these 11 patients became negative on a repeated PET scan performed within the study protocol after a 4- to 6-wk interval and were spared a neck dissection; None of these 10 patients had subsequent neck failure. We have previously reported our initial experience with ¹⁸F-FDG PET for response assessment (5). In a recent update of our series (6), 10 of 105 patients had an equivocal response according to the reporting criteria published by Porceddu et al. (3); 2 of these 10 patients subsequently had clinicopathologic evidence of lymph node disease.

We believe that the clinical significance and optimal management of focal ¹⁸F-FDG PET uptake below the level of liver background remains uncertain. In light of these differing qualitative response criteria and the higher negative predictive value reported by Porceddu et al. (3) for a negative PET scan, it is possible that the negative predictive value provided by the Hopkins criteria may be improved by separately considering patients with an equivocal response as defined by Porceddu et al. (3). We would be interested to learn whether there is any difference in the negative predictive value reported by Marcus et al. (1) comparing patients who scored a 1, 2, or 3 according to the Hopkins criteria and classified as having a negative scan.

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REPLY: We agree that having an equivocal group is a challenging clinical issue in assessing patients with head and neck squamous cell carcinoma after chemoradiation therapy. The Hopkins criteria (1) are a simple, standardized, qualitative method of assessing therapy,

or a “perceptual quantitation,” based on ^{18}F -FDG uptake in the local blood pool (internal jugular vein) and liver and the intuition of the interpreter. Although we dichotomized the standardized interpretation as negative (scores of 1–3) and positive (scores of 4 and 5) for the purpose of clinical utility, statistical analysis for truth, and outcome prediction, the patients who were categorized as having a score of 3 were the equivocal group in which ^{18}F -FDG uptake was diffuse in an irradiated area and the degree of uptake was greater than that of the liver. This we interpreted as more likely representing radiation-induced inflammation than residual tumor. There were 44 patients categorized into this group (score of 3), and 6 of these patients (13.6%) had disease recurrence by biopsy or within 6 mo of follow-up. There were 68 patients with a score of 1 and 52 patients with a score of 2. Among these patients, 4 (6%) and 5 (9.6%), respectively, had false-negative results, with recurrence within 6 mo as the reference standard. We believe the false-negative numbers in these groups are at the upper limit and conservative, as the reference standard we used was identification of recurrence within 6 mo rather than true residual disease at the time of the PET/CT studies. Hence, the true-negative predictive value for therapy assessment is likely higher than what we reported.

We acknowledge that distinguishing postradiation inflammation from residual tumor is challenging and that perceptual quantitation or standardized qualitative methods (such as recognition of pattern of uptake (2) and degree of uptake, using blood pool and liver ^{18}F -FDG uptake as the reference standard) may be more valuable than numeric quantitation (such as maximum standardized uptake value and other parameters). This approach of perceptual quantitation incorporates the interpreter’s intuition and human intelligence in this difficult challenge with a standardized approach. We continue to evaluate patients categorized as being in an equivocal group (score of 3) to develop a systematic way of resolving postirradiation inflammation versus residual tumor.

We acknowledge that many investigators have used qualitative methods for clinical ^{18}F -FDG PET/CT assessment of head and neck cancer therapy (3,4). However, the Hopkins criteria explicitly standardize the categorization reference as ^{18}F -FDG uptake in the liver and in the background blood pool in the internal jugular vein. In addition, the Hopkins criteria have established that the method is reliable among multiple interpreters and is linked to outcomes in both human papillomavirus–positive and –negative head and neck cancer patients.

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