ORIGINAL ARTICLE

FDG-PET Prediction of Head and Neck Squamous Cell Cancer Outcomes

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Objective: To confirm that high pretreatment uptake of 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) detected by positron emission tomography (PET) measured at the primary head and neck squamous cell carcinoma (HNSCC) and at metastatic nodal disease predicts poor outcomes for HNSCC.

Design and Patients: We enrolled 63 consecutive patients with a histological diagnosis of HNSCC (including tumors of the oral cavity, oropharynx, larynx, and hypopharynx) from September 2000 through June 2003, into a prospective institutional imaging trial. Fifty-four patients (86%) underwent a baseline FDG-PET scan before curative treatment and were eligible for analysis.

Results: A primary tumor standardized uptake value (SUV) of greater than 9.0 predicted inferior local recurrence-free survival (P=.02) and disease-free survival (P=.03). Nodal SUV dichotomized according to the cohort median of 6.1 did not predict for either disease outcome (P=.71 and P=.98, respectively). On proportional hazards analysis, local recurrence and disease event hazard ratios for a primary tumor SUV of 9.0 or greater remained significant or at borderline significance when adjusted for nodal SUV or other clinical covariates.

Conclusions: Our findings support an association between baseline primary tumor FDG SUV and HNSCC outcomes. In contrast, nodal FDG SUV was not predictive. Primary tumor FDG SUV is a promising prognostic factor and may establish the need for intensified locoregional therapy in individual patients. Multiinstitutional imaging trials and further characterization of the biology responsible for elevated FDG uptake in HNSCC will be necessary to confirm the prognostic utility of FDG-labeled PET.

Arch Otolaryngol Head Neck Surg. 2004;130:1361-1367

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Financial Disclosure: None.

TRADITIONAL STAGING OF head and neck squamous cell carcinoma (HNSCC) depends on the site of disease origin, size and extent of the primary tumor, cervical lymph node involvement, and presence or absence of distant metastasis. This system provides a useful framework for prognostication and has been improved by advances in structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). However, this approach continues to be limited by outcome heterogeneity within stage categories, hampering accurate prognostication for individual patients.[1,2] Much effort has gone toward complementing the information provided by the current staging nomenclature with the addition of biological markers such as p53,[3] cyclin D,[4] and epidermal growth factor receptor.[5,6] Although this approach holds promise, it has not yet identified a proven prognostic marker.[7]

An important advance in cancer imaging has been the development of positron emission tomography (PET). Unlike CT or MRI, PET is a physiological imaging technique. It relies on differential uptake of a radiolabeled metabolite or molecule that becomes concentrated in malignant tissues. The most commonly used tracer to date for cancer has been 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG).

FDG-PET can localize a wide variety of tumor types,[8,9] including head and neck disease,[10,11] and can complement the anatomic information provided by CT or MRI. Precise identification of disease sites with FDG-PET can potentially

permit focused delivery of intensified radiation doses and shielding of healthy bystander tissues.[12] However, because FDG-PET also provides in situ characterization of HNSCC metabolic activity, it may represent an important opportunity to predict individual tumor behavior. Uptake of FDG reflects tumor viability and proliferation and has been shown in early clinical series to be a predictor of biological aggressiveness and treatment response in a variety of cancer sites.[13-16] If these findings are confirmed, FDG-PET could be an important multifaceted adjunct to traditional staging and could improve appropriate selection of high-risk candidates for aggressive multimodality therapy.

A number of institutional series suggest that primary tumor FDG uptake is associated with histopathological grade, treatment response, and survival outcomes in HNSCC.[17-22] However, these series were limited in size and placed little emphasis on studying the role of nodal FDG uptake. In this report, we describe our prospective experience with FDG-PET characterization of HNSCC. Our findings support the ability of primary tumor FDG uptake (as measured by standardized uptake value [SUV], a clinically feasible PET measure of tracer uptake) to predict local disease control and disease-free survival. We also show that nodal FDG SUV does not share this predictive capability, a probable reflection of the inability of FDG SUV to characterize the complex biology of metastatic disease. Our findings argue for the pursuit of larger-scale clinical studies to confirm the value of incorporating FDG-PET primary tumor SUV into routine pretreatment characterization of HNSCC. They also suggest that additional biological characterization of HNSCC, improved FDG-PET image analysis, or alternative PET radiotracers will be necessary to better illuminate the phenotype of individual HNSCC tumors with PET.

METHODS

We enrolled 63 consecutive patients from the Veterans Affairs Puget Sound Health Care System, Seattle, Wash, into a prospective FDG-PET imaging study of newly diagnosed HNSCC (including tumors of the oral cavity, oropharynx, larynx, and hypopharynx) from September 2000 through June 2003. The institutional review boards of the University of Washington, Seattle, and Veterans Affairs Puget Sound Health Care System approved the study, and all enrolled patients provided written informed consent. Seven of these patients were excluded from analysis because they presented with incurable recurrent or metastatic disease treated with palliative intent. Two additional patients did not undergo PET, one because of refractory diabetes mellitus and the other owing to acute airway obstruction precipitating immediate surgical intervention. Thus, a total of 54 patients were eligible for subsequent analysis.

All patients who underwent evaluation also underwent systematic staging after direct laryngoscopy and tissue biopsy diagnosis with plain chest radiographs, serum chemistry and liver function panels, and a contrast-enhanced CT scan of the head and neck. We used the American Joint Committee on Cancer version 6 TNM criteria for stage delineation. Baseline staging incorporated all physical findings, diagnostic imaging (including FDG-PET findings), and available pathology results. Treatment decisions did not take into account FDG SUV results. All treatment was performed with curative intent and consisted of definitive radiotherapy with or without chemotherapy or definitive resection with or without adjuvant radiotherapy, as recommended by a multidisciplinary tumor board. Twenty-eight patients were scheduled to receive definitive radiotherapy. Of these, 22 received 69.9 to 70.0 Gy with concurrent systemic therapy; 5 with early-stage disease received only single-fraction radiotherapy at doses of 60.0 to 70.0 Gy; and 1 patient progressed from induction chemotherapy to receive supportive care alone. Of the patients receiving chemoradiotherapy, 12 were treated according to an institutional protocol using weekly induction chemotherapy consisting of docetaxel and carboplatin followed by 69.9 Gy of concomitant boost radiotherapy and concurrent weekly docetaxel-carboplatin therapy. The other 10 patients received single-fraction radiotherapy at doses of 66 to 70 Gy with concurrent weekly chemotherapy consisting of taxane and carboplatin. Twenty-five patients underwent definitive resection and corresponding neck dissection surgery; 17 received adjuvant single-fraction radiotherapy at doses of 60 to 68 Gy. After completion of treatment, patients underwent routine surveillance every 1 to 3 months. Median follow-up for surviving patients was 17.5 months (range, 6-37 months).

FDG-PET imaging was performed with an ADVANCE scanner (General Electric, Milwaukee, Wis) at the University of Washington Medical Center operating in 2-dimensional high-sensitivity mode. Patients underwent overnight fasting, and plasma glucose level was measured before each study. All patients underwent premedication with lorazepam to reduce FDG uptake in skeletal muscle. Approximately 7 to 10 mCi (259-370 MBq) of FDG was administered intravenously to each patient. A postinjection delay of 45 minutes was strictly observed before imaging. This delay was rigorously controlled to eliminate this factor as a source of FDG SUV variability and error, as described previously.[23] Four 15-cm axial fields of view extending inferiorly from the midcranium were imaged. This permitted imaging of the entire liver and upper abdomen. The pelvis, urinary bladder, and lower extremities were excluded from the images. A 3-minute transmission (using a Ge-68 rotating source) image for each field of view was performed and segmented for attenuation correction. Seven-minute emission images were t hen obtained for each field of view. After correction for scattered and random coincidences and photon attenuation, image data were reconstructed by 2-dimensional filtered back-projection onto a $128 \times 128 \times 35$-plane matrix using a Hanning filter that resulted in a reconstructed image resolution of approximately 10 mm. An experienced nuclear medicine specialist (J.R.) prospectively evaluated all FDG-PET images, using corresponding CT images to optimize anatomic orientation. Abnormalities defined by PET were initially identified as any site displaying increased tracer uptake compared with normal surrounding soft tissue. A region of interest was manually defined over the whole extent of increased primary disease tracer uptake to identify maximal primary tumor FDG uptake. For nodal disease, a region of interest was defined over the entire extent of each identified focus of FDG-avid neck disease, and the SUV was calculated separately for each nodal mass. The highest nodal uptake value was used for subsequent correlation of nodal SUV with clinical outcomes. The SUV is a semiquantitative, static measure of radiotracer uptake (in becquerels per milliliter) corrected for amount of injected radioactivity (in becquerels) and patient weight (in grams). It is calculated with the following formula:

$$\text{SUV} = \text{Radioactivity Concentration in Tissue} / (\text{Injected Activity} / \text{Patient Weight}).$$

Table 1. Study Cohort Characteristics*

Characteristic	No. (%)
Male	54 (100)
ECOG performance status	
0	20 (37)
1	25 (46)
2	7 (13)
3	2 (4)
Subsite	
Oral cavity	13 (24)
Oropharynx	21 (39)
Larynx	17 (31)
Hypopharynx	3 (6)
T stage	
T0	2 (4)
T1	4 (7)
T2	13 (24)
T3	21 (39)
T4	14 (26)
N stage	
N0	18 (33)
N1	11 (20)
N2	20 (37)
N3	5 (9)
AJCC stage	
I	2 (4)
II	5 (9)
III	11 (20)
IV	36 (67)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

*Median age of the study sample was 59.5 years (range, 42-78 years). Percentages have been rounded and may not total 100.

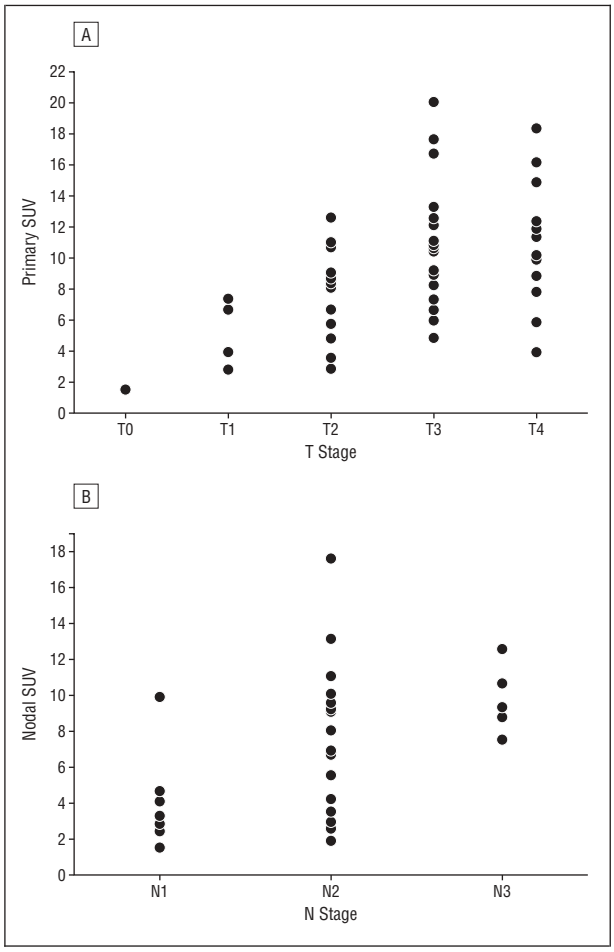

Figure 1. Primary tumor standardized uptake value (SUV) and nodal SUV according to T (A) and N stages (B), respectively.

We used SPSS software, version 11.5 (SPSS Inc, Chicago, Ill) and StatView software, version 5.0 (SAS Software, Berkeley, Calif), for statistical analysis. Local recurrence-free, disease-free, and overall survival times were estimated by the Kaplan-Meier method. Survival times were calculated from the date of definitive radiotherapy completion or the date of definitive surgery. Persistent or recurrent disease at a presenting primary disease site was scored as a local disease failure. Disease-free survival took into account all disease events, including local, regional, and distant failures. We compared primary tumor and nodal disease SUV, as continuous values, with the T stage, N stage, and patient disease status (no evidence of disease vs disease event) by means of nonparametric Kruskal-Wallis and Mann-Whitney testing to account for nonnormal SUV distribution. For subsequent univariate and regression analysis, we dichotomized primary tumor and nodal disease SUV values according to the median values of the study cohort (9.0 for primary disease and 6.1 for nodal disease). We also dichotomized the following clinical covariates: T stage (T0-T2 vs T3-T4), N stage (N0-N1 vs N2-N3), American Joint Committee on Cancer overall stage (stages I-III vs stage IV), Eastern Cooperative Oncology Group performance status (0 vs 1-3), and age (<60 years vs ≥60 years). We performed univariate analysis using the Kaplan-Meier method and log-rank testing to examine the predictive value of dichotomized SUV values and other clinical risk factors for local disease control and disease-free survival at 2 years. Because of the limited number of disease events, we specifically chose to create a bivariate Cox proportional hazards analysis of local disease failure and disease event hazard ratios. This was performed for a primary tumor SUV of 9.0 or greater alone (unadjusted) or adjusted for each of the other dichotomized, tested risk factors. We repeated this proportional hazards analysis in an identical fashion using primary tumor SUV as a continuous value.

RESULTS

The FDG-PET findings correctly localized all clinically identified primary disease, but did not visualize primary tumors in 2 patients with clinical T0 stage disease of the oral cavity or oropharynx. Primary tumor FDG SUV was cataloged as 1.5 for these patients to reflect typical baseline FDG uptake of normal head and neck soft tissues. The FDG-PET findings correctly identified all nodal disease identified by CT imaging. FDG-PET correctly identified small-volume stage N1 or N2 disease in 2 patients with radiologically negative CT scans, but missed small-volume N1 disease in 2 patients with negative CT scans who underwent definitive neck dissection (to include these node-positive patients in our analysis, nodal FDG SUV was cataloged as 1.5 for these patients to reflect typical baseline FDG uptake of normal head and neck soft tissues). The median primary SUV was 9.0 (range, 1.5-20.1), whereas the median nodal SUV was 6.1 (range, 1.5-17.6). Clinical characteristics of the study cohort are summarized in **Table 1**.

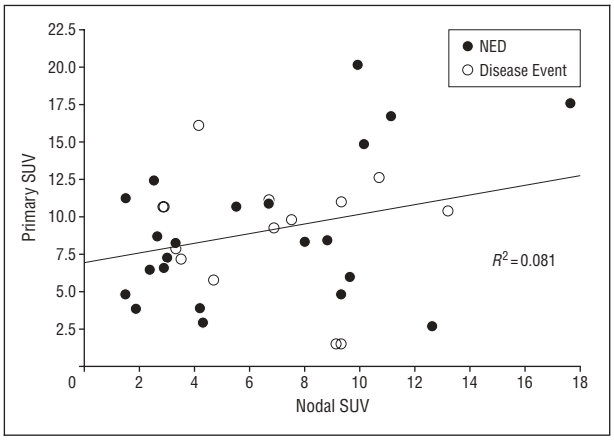

Figure 2. Linear regression plot of primary tumor standardized uptake value (SUV) and nodal SUV. NED indicates no evidence of disease.

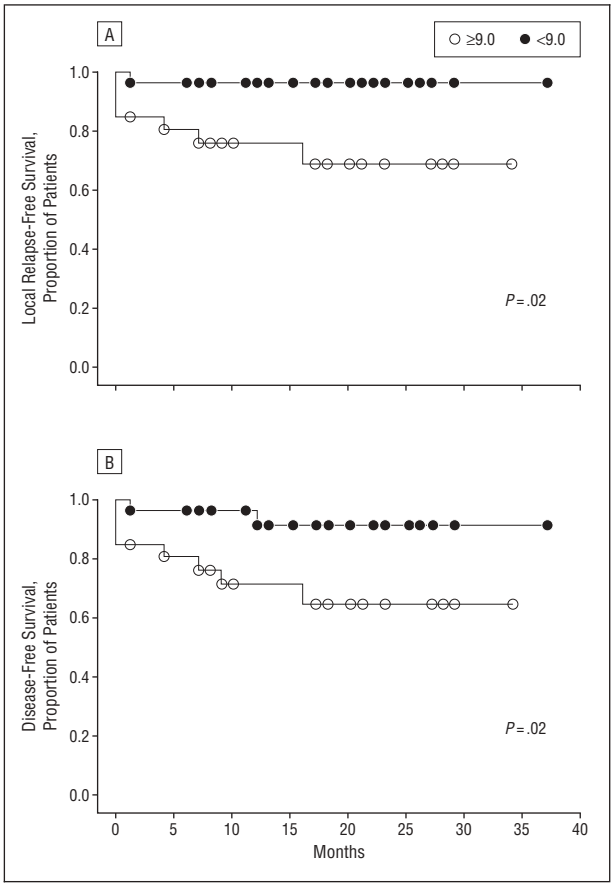

Figure 3. Kaplan-Meier local relapse-free survival (A) and disease-free survival estimates (B) by primary tumor standardized uptake values of 9.0 or greater and less than 9.0. Circles represent censored events.

The T and N stages were good correlates for primary and nodal SUVs (P=.003 and P=.002, respectively, by Kruskal-Wallis testing) (**Figure 1**). Primary and nodal SUVs were not predictive of the presence or absence of a subsequent disease event (P=.30 and P=.91, respectively, by Mann-Whitney testing). Primary and nodal SUVs did not correlate with each other (R^2=0.081 by linear regression) (**Figure 2**).

Table 2. Univariate Log-Rank Testing of Potential Clinical Risk Factors for LRFS and DFS at 2 Years

		LRFS		DFS	
Subgroup	No. of Patients	% of Patients	*P* Value	% of Patients	*P* Value
Primary SUV					
<9.0	28	96	.02	93	.02
≥9.0	26	73		69	
Nodal SUV					
<6.1	18	78	.71	78	.98
≥6.1	18	83		78	
T stage					
T0-T2	19	95	.14	89	.21
T3-T4	35	80		77	
N stage					
N0-N1	29	83	.65	79	.72
N2-N3	25	88		84	
AJCC stage					
I-III	18	83	.86	78	.70
IV	36	86		83	
ECOG performance status					
0	20	90	.41	85	.49
1-3	34	82		79	
Age, y					
<60	27	85	.96	81	.92
≥60	27	85		81	

Abbreviations: AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; LRFS, local relapse-free survival; SUV, standardized uptake value.

On univariate analysis, primary tumor SUV dichotomized according to the cohort median value of 9.0 was predictive of local recurrence-free survival (P=.02 by log-rank test) and disease-free survival (P=.03) (**Figure 3**). Nodal SUV dichotomized according to the cohort median value of 6.1 did not predict for either disease outcome (P=.71 and P=.98, respectively, by log-rank test). Primary and nodal SUVs did not predict overall survival (P=.44 and P=.16, respectively, by log-rank test). Univariate log-rank testing of SUVs and other clinical risk factors for local relapse-free and disease-free survival at 2 years is summarized in **Table 2**. The lack of predictive associations for the non-SUV clinical risk factors may be explained by the small and/or imbalanced sample sizes for these covariates, as well as by the potential confounding influence of an aggressive chemoradiotherapy regimen used at our center for locally advanced disease that provided excellent disease control in patients with poor prognoses. Bivariate Cox proportional hazards analysis showed that the local recurrence and disease event hazard ratios for primary SUV remained significant or at borderline significance when adjusted for dichotomized nodal SUV, T stage, N stage, American Joint Committee on Cancer overall stage, Eastern Cooperative Oncology Group performance status, or age covariates (**Table 3**).

We repeated this proportional hazards analysis using primary tumor SUV as a continuous variable. Continuous primary tumor SUV was not predictive of outcomes, alone or when adjusted for the other clinical fac-

Table 3. Estimated Local Disease Failure and Disease Event HRs for Elevated Primary FDG SUV*

	Local Disease Failure		Disease Event	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	8.2 (1.01-66.84)	.049	4.9 (1.04-23.09)	.045
Adjusted				
Nodal SUV (<6.1 vs ≥6.1)	8.6 (1.01-72.56)	.049	9.5 (1.15-79.17)	.04
T stage (T0-T2 vs T3-T4)	6.4 (0.70-59.29)	.10	4.4 (0.80-23.86)	.08
N stage (N0-N1 vs N2-N3)	8.1 (0.99-66.28)	.051	4.9 (1.02-23.11)	.047
AJCC stage (I-III vs IV)	8.9 (1.07-73.18)	.04	5.4 (1.13-26.19)	.04
ECOG status (0 vs 1-3)	7.8 (0.93-65.27)	.06	4.8 (0.98-23.74)	.053
Age, y (<60 vs ≥60)	8.3 (1.02-68.09)	.047	5.0 (1.05-23.48)	.04

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FDG, fludeoxyglucose F 18; HR, hazard ratio; SUV, standardized uptake value.

*Defined as an FDG SUV of 9.0 or greater. All values were calculated using bivariate Cox proportional hazards analysis, adjusted for each of the listed dichotomized clinical covariates.

tors ($P>.16$ for all). Primary tumor SUVs were compactly distributed, except for a modest tail at the high end. Removal of 3 high SUV data points (>17.0) was required to restore predictive significance for local recurrence ($P=.04$), but did not have a significant impact on disease-free survival ($P=.07$).

COMMENT

Increased glucose metabolism by malignant cells has been recognized for more than 70 years.[24] FDG-PET capitalizes on this phenomenon by localizing the uptake and retention of an ^{18}F-labeled glucose analog (FDG) within metabolically active tumor. Significant evidence has demonstrated that FDG-PET imaging alone[10,11] or directly registered with CT images[12] can accurately localize head and neck disease. Recent series also support a close association between markedly elevated primary tumor FDG uptake and high-risk phenotype for a variety of solid tumors.[13-16] Simultaneous localization and characterization of aggressive disease with the use of FDG-PET could serve as a reliable means to guide intensified locoregional head and neck radiotherapy or surgical treatment, as well as individualized selection of high-risk patients with HNSCC for systemic therapy.

Previous clinical series suggest that highly elevated baseline HNSCC primary tumor FDG SUV predicts a worse prognosis. In 37 patients with HNSCC, Minn et al[18] showed that a primary FDG SUV greater than 9.0 predicted advanced clinical stage, low-moderate histological grade, and poor overall disease survival. Brun et al[20] obtained FDG-PET images in 47 patients with HNSCC treated with definitive radiotherapy. They found that a baseline primary tumor FDG SUV of 9.0 or greater predicted inferior response to radiotherapy, local disease control, and overall survival. Halfpenny et al[19] studied 58 patients with HNSCC treated surgically or with definitive radiotherapy and showed that a primary tumor SUV greater than 10.0 predicted significantly inferior overall survival. Finally, Allal et al[17] obtained primary tumor FDG SUVs in a series of 63 patients with HNSCC receiving radiotherapy-based treatment. A primary tumor FDG SUV greater than 5.5 predicted both inferior local disease control and shorter disease-free survival.

Our findings bolster these results, demonstrating significantly inferior local disease control and disease-free survival in subjects with a primary tumor FDG SUV of 9.0 or greater. Treatment heterogeneity cannot explain this result, since both FDG SUV subgroups were well balanced in this regard (5 vs 4 cases of resection alone, 13 vs 14 cases of radiotherapy-based treatment, and 10 vs 8 cases of resection with adjuvant radiotherapy for the low and high primary tumor FDG SUV subgroups, respectively). Our results also add important caveats. First, we demonstrate that FDG-PET predictive ability is limited to primary FDG SUV. Nodal SUV did not correlate with primary tumor SUV, and nodal FDG SUV of 6.1 or greater did not predict any tested disease outcome. The prognostic utility of nodal FDG SUV has not been well investigated. Only Brun et al[20] studied this issue in a fashion similar to that of our study, and they too did not observe different treatment response or disease control outcomes in subjects with a nodal FDG SUV of 6.0 or greater. Second, we show that primary tumor SUV represented as a continuous variable does not appear to predict HNSCC survival outcomes. Removal of several arbitrary high-end outliers was required to see a relationship with local recurrence. Similar analysis was not described in the previous reports. We did not expect this finding, because greater statistical power should be seen for a linear rather than for a step-function relationship in the proportional hazards analysis. This suggests that increasing primary tumor FDG uptake is not necessarily associated with an aggressive phenotype unless it passes a threshold of severe elevation. However, we caution that these findings are not conclusive; a larger sample size with a greater number of events would be required to confirm or disprove a linear relationship between primary tumor SUV and outcomes.

Our data demonstrate that primary tumor SUV is associated with T stage (Figure 1 and Table 3). Others have also shown that high primary FDG SUV correlates

with advanced disease stage.[18,19] A potential explanation for this would be that large-volume disease simply retains more radiotracer and is more readily detected by PET image reconstruction algorithms. However, these previous series have also shown that HNSCC primary tumor diameter or volume does not correlate with primary FDG SUV.[18,19] Rather than just mirroring raw size, it is likely that highly elevated FDG uptake instead reflects activation of biological pathways associated with tumor viability, aggressiveness, and treatment resistance. In vitro and clinical studies indicate a strong association between glucose or FDG uptake with tumor proliferation, hypoxia, and metabolic activation,[25-27] processes that are associated with poor HNSCC clinical outcomes.[22,28] Confirmation of FDG SUV as a biological predictive marker will require continued validation.

The complex biology of nodal metastasis probably precludes straightforward characterization of nodal disease via a single FDG-PET parameter. The genetic aberrations and microenvironment of metastatic disease can differ significantly from the original primary tumor.[29] Positron emission tomography would also not be expected to optimally image small-volume lymph nodes that could harbor aggressive disease. As a result, the lack of association between nodal FDG SUV and disease outcomes undoubtedly reflects a host of potential biases impacting nodal FDG SUV not associated with disease phenotype.

Alternative PET imaging analysis could potentially characterize nodal disease more accurately. Strategies worthy of future investigation include dynamic FDG uptake measures (ie, FDG metabolic rate [MR FDG]), volumetric pixel-by-pixel FDG uptake analysis that accounts for tracer uptake heterogeneity and tumor asymmetry, or the use of additional PET radiotracers that provide complementary biological information. A study from our group has previously demonstrated that detection of hypoxia in HNSCC with ^{18}F-fluoromisonidazole–PET can offer biological disease characterization beyond that provided by FDG-PET.[30] We are currently confirming early evidence suggesting that baseline ^{18}F-fluoromisonidazole–PET imaging of HNSCC primary and nodal disease complements FDG-PET prognostication of treatment response and disease outcomes (J.R., unpublished data, 2004).

CONCLUSIONS

Our findings support the use of baseline primary tumor FDG SUV as a predictor of HNSCC treatment outcomes. Nodal SUV did not share this ability, prompting a need to better characterize the biological pathways responsible for elevated FDG uptake in HNSCC and to identify other FDG-PET analytical techniques or alternative PET radiotracers that can better capture the complex biology of nodal metastases. Our use of a primary tumor FDG SUV cutoff value of 9.0, although based on the arbitrary median FDG SUV of our study cohort, is remarkably consistent with the cutoff FDG SUVs of 9.0 to 10.0 found by others.[18-20] This signifies the potential utility of this threshold value across different institutions and study populations, and could thus serve as a starting point for prospective formulation of a reliable benchmark in the multi-institutional trial setting.

Submitted for Publication: May 25, 2004; final revision received August 9, 2004; accepted August 19, 2004.
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Funding/Support: This study was supported by grant CA42045 from the National Institutes of Health, Bethesda, Md. Dr Schwartz was supported by awards from the Department of Veterans Affairs (Washington, DC), Veterans Health Administration, Medical Research Service, and Rehabilitation Research & Development Service, and Dr Yueh was supported by career development award CD-98318 from the Health Services Research & Development Service, Veterans Health Administration, Department of Veterans Affairs.
Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.
Acknowledgment: We thank David Mankoff, MD, PhD, for his thoughtful critique of this manuscript, and Barbara Lewellen, our PET clinical imaging staff, and our radiochemistry group for the expert technical support provided at the University of Washington Medical Center, Seattle.

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