PET and PET/CT of the Neck Lymph Nodes Improves Risk Prediction in Patients with Squamous Cell Carcinoma of the Oral Cavity

Chun-Ta Liao*[1,2], Hung-Ming Wang[2,3], Shiang-Fu Huang[1,2], I-How Chen[1,2], Chung-Jan Kang[1,2], Chien-Yu Lin[2,4], Kang-Hsing Fan[2,4], Shu-Hang Ng[2,5], Chuen Hsueh[2,6], Li-Yu Lee*[2,6], Chih-Hung Lin[2,7], and Tzu-Chen Yen[2,8]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [2]Department of Head and Neck Oncology Group, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [3]Department of Medical Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [4]Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [5]Department of Diagnostic Radiology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [6]Department of Pathology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [7]Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; and [8]Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan

We prospectively evaluated the sensitivity and specificity of ^{18}F-FDG PET in the detection of neck lymph node metastases in patients with oral cavity squamous cell carcinoma (OSCC). We also sought to evaluate whether pretreatment PET visual scores in the neck lymph nodes may improve risk stratification. **Methods:** We enrolled 473 OSCC patients (445 men and 28 women; mean age ± SD, 50.9 ± 11.7 y) without distant metastases. All participants underwent ^{18}F-FDG PET within 2 wk before surgery and neck dissection. Histopathology was taken as the reference standard for neck lymph node status. The duration of follow-up was at least 24 mo in all surviving patients. **Results:** ^{18}F-FDG PET correctly diagnosed 164 of 211 patients with neck metastases and 152 of 262 subjects without pathologic neck metastases, resulting in a patient-based sensitivity and specificity of 77.7% and 58.0%, respectively. In Cox models adjusting for age, sex, traditional risk factors, and treatment modality, PET results at the neck lymph nodes were significantly and independently associated with rates of neck control, distant metastasis, disease-free survival, disease-specific survival, and overall survival. Notably, the results of the c-statistics demonstrated that PET score improved the accuracy of risk prediction in terms of overall and disease-free survival rates. **Conclusion:** PET findings at the neck lymph nodes have limited sensitivity and specificity for primary staging of OSCC but improve risk stratification beyond that of traditional risk factors.

Key Words: ^{18}F-FDG PET; oral cavity squamous cell carcinoma; neck; prognosis

Head and neck carcinomas are the sixth most common malignancy reported worldwide, and oral cavity squamous cell carcinoma (OSCC) is the most frequent neoplasm in this region (1). The routine staging method for the preoperative detection of cervical lymph node metastases in OSCC patients consists of physical examination and CT/MRI. The presence and extent of neck lymph node metastases (pN+) significantly affect outcomes and potential treatment strategies in OSCC patients (2–10). Despite the prognostic value of neck lymph node metastases, this factor does not fully explain the extent of variability in the clinical course (2–10).

PET using the radiolabeled glucose analog ^{18}F-FDG has great importance in lymph node imaging (11,12). However, controversy still exists on its routine clinical use in cN0 OSCC patients because of the limited additional value of ^{18}F-FDG PET (13). Unlike other anatomic imaging modalities, PET supplies a semiquantitative metabolic characterization of tissues that may help to predict tumor behavior. In 2 recent studies in nonselected patients with head and neck cancers, the sensitivity and specificity of ^{18}F-FDG PET for identification of lymph node metastases on a neck level-by-level basis were higher than those of CT/MRI (14,15). However, the accuracy of ^{18}F-FDG PET neck staging in OSCC should be evaluated by comparing it against the gold standard of pathologic staging. Unfortunately, this issue has not been fully addressed in previous studies (14–18). Although ^{18}F-FDG PET may be more accurate for lymph node staging than anatomic imaging studies, this, by itself, may not affect patient management and the policy of neck dissection (ND). Therefore, the clinical implications of ^{18}F-FDG PET for primary and nodal staging of patients with OSCC deserve further scrutiny.

^{18}F-FDG PET has prognostic value in OSCC patients (13,19,20). Notably, ^{18}F-FDG uptake in the primary tumor

predicts overall survival in different cancers (*21–26*), including OSCC (*27*). However, little has been reported about the prognostic significance of PET findings in the neck lymph nodes in patients with OSCC. The ability to identify patients who display a poor prognosis would be beneficial in at least 2 ways. First, identifying high-risk patients may reveal a survival benefit from postsurgical adjuvant therapies. Second, a better prognostic stratification may allow the identification of low-risk patients who can achieve adequate survival with less radical approaches. Numerous clinical features and pathologic characteristics have been studied in an attempt to improve risk stratification. These negative prognostic factors include extracapsular spread (ECS), close or positive margins, perineural invasion, level IV or V lymph node metastases, poor differentiation, tumor depth, and the number of metastatic neck lymph nodes (*2–10*). However, the incorporation of functional information derived from PET has the potential to improve prognostic stratification and treatment planning for patients with OSCC. A large cohort of OSCC patients has been and continues to be enrolled in our hospital, allowing us to take advantage of the large sample sizes to demonstrate the potential impact of ^{18}F-FDG PET/CT on various clinical endpoints.

The objective of this study was 2-fold. The first was to prospectively assess the sensitivity and specificity of ^{18}F-FDG PET/CT for detecting neck lymph node metastases in patients with OSCC, with pathologic results as the reference standard. The second was to investigate whether pretreatment visual scores in the neck lymph nodes may improve risk stratification (*28*).

MATERIALS AND METHODS

Study Patients

Between August 2001 and May 2008, patients with a histologic diagnosis of OSCC, a previously untreated tumor scheduled for radical surgery with or without ND, and no other suspected distant metastatic lesions detected by imaging (including MRI/CT and ^{18}F-FDG PET/CT) were eligible for the study. All patients expressed willingness to receive a CT- or ultrasound-guided biopsy or surgical exploration, if necessary. Patients with a previous diagnosis of other malignancies and refusal or inability to receive definitive treatment for the disease were excluded. Patients were also excluded if they had hyperglycemia (defined as a serum glucose level of more than 200 mg/dL) before the PET study, because such levels seem to affect the quality of the PET images adversely.

All participants underwent an extensive presurgical evaluation including ^{18}F-FDG PET/CT within 2 wk before primary surgery (median, 2.0 d; mean ± SD, 3.0 ± 2.8 d; range, 1–14 d). This evaluation included a medical history and complete physical examination, flexible fiberoptic laryngopharyngoscopy, complete blood count and routine blood biochemistry, CT or MRI scans of the head and neck, chest radiographs, bone scan, and liver ultrasound. Primary staging was performed according to the 2002 criteria of the American Joint Committee on Cancer (AJCC) (*29*). The study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (96-0672B). All patients provided their written informed consent.

^{18}F-FDG PET/CT

Patients were instructed to fast for 6 h before the PET study. ^{18}F-FDG (370–444 MBq) was administered intravenously. Before April 2006, all patients (*n* = 280) underwent PET (ECAT EXACT HR+ PET camera; CTI). As of May 2006, all participants (*n* = 193) underwent PET/CT (Discovery ST; GE Healthcare), combining a PET component with a 16-slice spiral CT scanner. For PET/CT scans, oral contrast was administered to patients during the uptake time; no intravenous contrast material was administered for CT scans. Head to midthigh scans were obtained for all patients. Lower limb scanning was performed when indicated. PET and CT images were acquired consecutively, 50 min after the injection of ^{18}F-FDG. CT data were used for low-noise attenuation correction of PET emission data and for fusion with attenuation-corrected PET images. PET images were reconstructed iteratively using an ordered-subset expectation maximization algorithm. PET, CT, and fused PET/CT images were available for review and were displayed in axial, coronal, and sagittal planes. PET data were displayed as noncorrected and attenuation-corrected images as well as in a rotating maximum-intensity projection.

All imaging results were reviewed prospectively by a combined team who had knowledge of the patients' clinical history. Foci of increased ^{18}F-FDG uptake were carefully recorded. Studies showing at least 1 area of increased ^{18}F-FDG uptake with intensity higher than that of surrounding tissues, localized by hybrid images to an area that did not correspond to the physiologic biodistribution of the radiotracer, were defined as positive. Studies showing ^{18}F-FDG activity only in areas of the physiologic tracer biodistribution or no sites of increased uptake were considered negative. Regions of interest were placed and measured over lesions visible on PET images, on simultaneously displayed axial, coronal, and sagittal tomograms. The regions of interest of lesions that were invisible on PET images were located using the corresponding CT images. The highest activity within a region of interest was measured, and the standardized uptake value (SUV) was determined as the highest activity concentration per injected dose per body weight (kg) after correction for radioactive decay. Two experienced nuclear medicine physicians and 1 radiologist interpreted ^{18}F-FDG PET (PET/CT) images. Interpretation was based on visual evaluation, and decisions were reached by consensus. ^{18}F-FDG uptake was graded visually on the following 5-point scale: 0, definitely benign; 1, probably benign; 2, equivocal; 3, probably malignant; and 4, definitely malignant (*14,16*). This score was based on the intensity of focal ^{18}F-FDG uptake, presence of corresponding lymph node on CT, and pattern of tracer distribution. In an effort to improve sensitivity, findings graded as 2, 3, or 4 were considered positive (*30*).

Surgery and Adjuvant Therapy

The primary tumors were excised with safety margins of 1 cm or greater (both peripheral and deep margins). Classic radical or modified NDs (levels I–V) were performed in patients with clinically positive lymph node disease. Supraomohyoid NDs (levels I–III) were performed in clinically node-negative patients. Postoperative radiotherapy (60–66 Gy) was performed on patients with pT4 tumors, positive lymph nodes, or close margins (≤4 mm). Concomitant chemoradiation with cisplatin (50 mg/m^2) biweekly plus daily oral tegafur (800 mg) and leucovorin (60 mg) or cisplatin

TABLE 1
Clinicopathologic Characteristics of Study Participants

Characteristics	Entire cohort (n = 473)			pN+ (n = 211)		
	PET-negative (n = 199)	PET-positive (n = 274)	P	PET-negative (n = 47)	PET-positive (n = 164)	P
Sex			0.381			0.815
Male	185 (93.0)	260 (94.9)		44 (93.6)	155 (94.5)	
Female	14 (7.0)	14 (5.1)		3 (6.4)	9 (5.5)	
Age (y)			0.974			0.970
≤40	38 (19.1)	52 (19.0)		9 (19.1)	31 (18.9)	
>40	161 (80.9)	222 (81.0)		38 (80.9)	133 (81.1)	
Clinical N status			<0.001			<0.001
cN0	176 (88.4)	92 (33.6)		33 (70.2)	26 (15.9)	
cN+	23 (11.6)	182 (66.4)		14 (29.8)	138 (84.1)	
ND			<0.001			<0.001
I–III	194 (97.5)	213 (77.7)		44 (93.6)	111 (67.7)	
I–V	5 (2.5)	61 (22.3)		3 (6.4)	53 (32.3)	
Treatment			<0.001			0.001
Surgery alone	134 (67.3)	80 (29.2)		9 (19.1)	9 (5.5)	
Surgery plus radiotherapy	39 (19.6)	72 (26.3)		15 (31.9)	34 (20.7)	
Surgery plus concomitant chemoradiation	26 (13.1)	122 (44.5)		23 (48.9)	121 (73.8)	
Differentiation			0.228			0.396
Well	53 (26.6)	77 (28.1)		4 (8.5)	25 (15.2)	
Moderate	129 (64.8)	161 (58.8)		36 (76.6)	110 (67.1)	
Poor	17 (8.5)	36 (13.1)		7 (14.9)	29 (17.7)	
Tumor depth (mm)*†			<0.001			0.036
<10	132 (66.3)	112 (41.0)		23 (48.9)	53 (32.3)	
≥10	67 (33.7)	161 (59.0)		24 (51.1)	111 (67.7)	
Close margins (mm)			0.587			0.286
≤4	12 (6.0)	20 (7.3)		5 (10.6)	10 (6.1)	
>4	187 (94.0)	254 (92.7)		42 (89.4)	154 (93.9)	
Pathologic T status			<0.001			0.056
pT1–2	143 (71.9)	132 (48.2)		26 (55.3)	65 (39.6)	
pT3–4	56 (28.1)	142 (51.8)		21 (44.7)	99 (60.4)	
Pathologic N status			<0.001			
pN0	152 (76.4)	110 (40.1)				
pN+	47 (23.6)	164 (59.9)				
Level IV or V metastases			0.022			0.388
No	197 (99.0)	261 (95.3)		45 (95.7)	151 (92.1)	
Yes	2 (1.0)	13 (4.7)		2 (4.3)	13 (7.9)	
pN2c status			0.002			0.090
No	198 (99.5)	258 (94.2)		46 (97.9)	148 (90.2)	
Yes	1 (0.5)	16 (5.8)		1 (2.1)	16 (9.8)	
ECS			<0.001			<0.001
No	187 (94.0)	155 (56.6)		35 (74.5)	45 (27.4)	
Yes	12 (6.0)	119 (43.4)		12 (25.5)	119 (72.6)	
pN+ number			<0.001			0.001
<5 nodes	198 (99.5)	235 (85.8)		46 (97.9)	125 (76.2)	
≥5 nodes	1 (0.5)	39 (14.2)		1 (2.1)	39 (23.8)	
Bone marrow invasion			0.019			0.190
No	177 (88.9)	222 (81.0)		41 (87.2)	129 (78.7)	
Yes	22 (11.1)	52 (19.0)		6 (12.8)	35 (21.3)	
Skin invasion			0.063			0.425
No	187 (94.0)	244 (89.1)		42 (89.4)	139 (84.8)	
Yes	12 (6.0)	30 (10.9)		5 (10.6)	25 (15.2)	
Perineural invasion			<0.001			0.672
No	145 (72.9)	159 (58.0)		24 (51.1)	78 (47.6)	
Yes	54 (27.1)	115 (42.0)		23 (48.9)	86 (52.4)	
Vascular invasion			0.592			0.684
No	196 (98.5)	268 (97.8)		45 (95.7)	159 (97.0)	
Yes	3 (1.5)	6 (2.2)		2 (4.3)	5 (3.0)	
Lymph invasion			<0.001			0.042
No	198 (99.5)	253 (92.3)		46 (97.9)	144 (87.8)	
Yes	1 (0.5)	21 (7.7)		1 (2.1)	20 (12.2)	

*Optimal cutoff value for tumor depth. Tumor depth was defined as measured thickness from surface of normal mucosa to deepest portion of tumor.
†Missing data: tumor depth (n = 1).
Data in parentheses are percentages.

TABLE 2
Tumor Subsites of Study Participants

Tumor subsite	Entire cohort ($n = 473$)			pN+ ($n = 211$)		
	PET-negative ($n = 199$)	PET-positive ($n = 274$)	P	PET-negative ($n = 47$)	PET-positive ($n = 164$)	P
Overall			0.229			0.029
Tongue	75 (37.7)	88 (32.1)		18 (38.3)	51 (31.1)	
Mouth floor	7 (3.5)	7 (2.6)		1 (2.1)	5 (3.0)	
Lip	5 (2.5)	2 (0.7)		1 (2.1)	0	
Buccal	63 (31.7)	116 (42.3)		13 (27.7)	76 (46.3)	
Alveolar ridge	31 (15.6)	42 (15.3)		7 (14.9)	25 (15.2)	
Hard palate	3 (1.5)	4 (1.5)		1 (2.1)	2 (1.2)	
Retromolar	15 (7.5)	15 (5.5)		6 (12.8)	5 (3.0)	

Data in parentheses are percentages.

(30 mg/m^2) weekly was administered to patients with ECS or multiple lymph node metastases (*31,32*).

Data Analysis

All patients were followed for at least 24 mo after surgery or until death. Study participants were followed through May 2010 for 6 outcomes: local control, neck control, distant metastasis, disease-free survival, disease-specific survival, and overall survival. Cumulative survival plots according to the PET score in the neck lymph nodes were univariately evaluated by the Kaplan–Meier analysis (log-rank test). Because the Kaplan–Meier method cannot adjust for the effects of other factors, we used a series of multivariable proportional-hazards models to examine the association between the PET score in the neck lymph nodes and the study outcomes. We first confirmed that the proportional-hazards assumption was met. The hazard ratios for the PET score at the neck lymph node were estimated in a model adjusting for age, sex, and known prognostic factors (ECS, close or positive margins, perineural invasion, level IV or V lymph node metastasis, poor differentiation, tumor depth, at least 5 metastatic neck lymph nodes, and treatment modality) in OSCC patients. To evaluate the ability of the PET score to predict prognosis, we compared the c-statistics for the combination of 8 known clinical and pathologic prognostic factors (ECS, close or positive margins, perineural invasion, level IV or V lymph node metastasis, poor differentiation, tumor depth, presence of at least 5 metastatic neck lymph nodes, and treatment modality) with or without the PET score. In this analysis, we used disease-free and overall survival rates at 5 y as the outcome measures. Statistical calculations were performed with SPSS software (version 17.0; SPSS). The tests for the proportional-hazards assumption were performed with the survival package for R; the areas under the receiver operating characteristic (ROC) curves given by c-statistics were determined with the ROCR package for R (www.r-project.org). Two-sided P values less than 0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the study participants are shown in Tables 1 and 2.

Detection of Neck Metastases with PET

Of the 473 patients examined, 211 were diagnosed with pathologically positive lymph nodes whereas the remaining 262 were without neck metastases. In the entire study cohort, 179 patients had a preoperative PET-negative neck with no ^{18}F-FDG uptake (visual score of 0), 20 had a faint tracer uptake, 49 a mild uptake, 79 a moderate uptake, and 146 an intense uptake (visual score of 4). ^{18}F-FDG PET correctly diagnosed 164 of 211 patients with neck metastases and 152 of 262 patients without pathologic neck metastases, resulting in a sensitivity and specificity of 77.7% and 58.0%, respectively, on a patient-based analysis, using a cutoff of 2 for the ^{18}F-FDG uptake score. Compared with subjects with a PET-negative neck, those with a PET-positive neck showed significant differences in clinical nodal status, ND, treatment modality, tumor depth, pathologic T and N status, pN2c status, ECS, bone marrow invasion, perineural invasion, and lymph invasion (Tables 1 and 2).

The median SUVs were 2.3 (range, 1.4–4.0) for lesions with a score of 1, 2.6 (range, 1.4–4.4) for lesions with a score of 2, 3.5 (range, 2.1–7.9) for lesions with a score of 3, and 6.6 (range, 2.6–24.5) for lesions with a score of 4. When an SUV of 3.1 was used as the cutoff for positive PET results, the ROC analysis showed a patient-based sensitivity and specificity of 79.9% and 59.4%, respectively. The areas under the ROC curves, which represent overall diagnostic performance, did not differ significantly among the 2 analytic methods (visual, 0.81; SUV, 0.83). Therefore, only visual scores were considered for further analysis.

TABLE 3
Results of ^{18}F-FDG PET and Pathologic Tumor Size in pN+ OSCC Patients

PET result	Pathologic tumor size (mm)		
	<6	6–10	>10
Total ($n = 211$)	50 (23.7)	35 (16.6)	126 (59.7)
PET-negative ($n = 47$)	27 (57.4)	14 (29.8)	6 (12.8)
PET-positive ($n = 164$)	23 (14.0)	21 (12.8)	120 (73.2)

Data in parentheses are percentages.
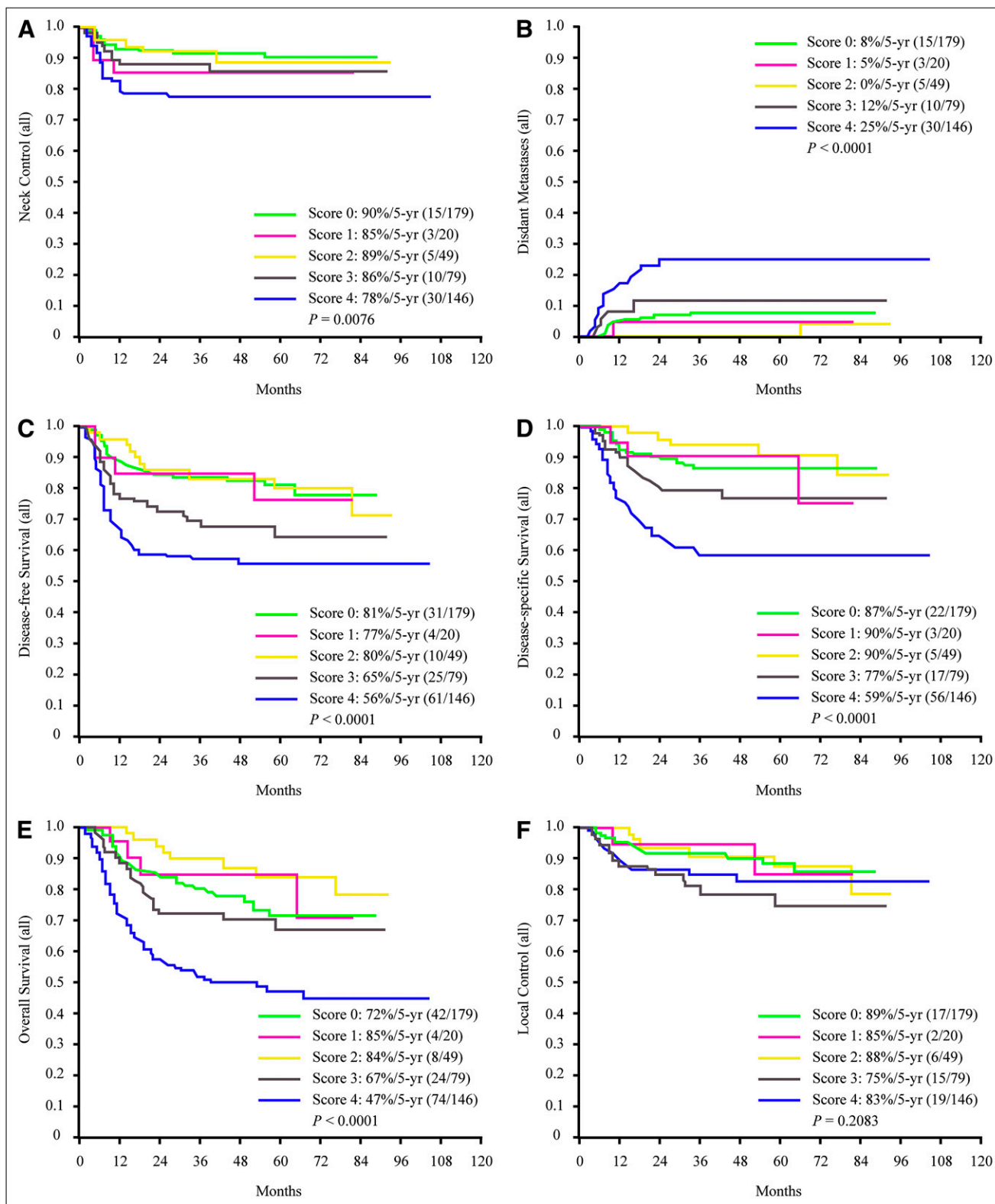
FIGURE 1. Kaplan–Meier curves for study outcomes, by PET scores in neck lymph nodes. Results are presented in terms of neck control (A), distant metastasis (B), disease-free survival (C), disease-specific survival (D), and overall survival rates (E). We observed no association of PET scores with local control (F).

PET Findings and Pathologic Size of Neck Lymph Node Metastasis

The correlation of lymph node size and PET results in the 211 patients diagnosed with positive lymph nodes on histopathology is shown in Table 3. The size distribution of lymph node metastases showed significant differences according to PET results ($\chi^2 = 57.73$, $P < 0.001$).

PET Findings and Clinical Course

Categorization of the entire patient population according to PET scores revealed a statistically significant trend toward higher event rates through increasing PET scores in terms of neck control (Fig. 1A), distant metastasis (Fig. 1B), disease-free survival (Fig. 1C), disease-specific survival (Fig. 1D), and overall survival rates (Fig. 1E). We observed no association of PET scores with local control (Fig. 1F).

Multivariable Analysis of Outcomes

In Cox models adjusting for age, sex, known prognostic factors, and treatment modalities, a PET score of 2 or more in the neck lymph nodes was independently associated with rates of neck control (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.03–2.01; $P < 0.05$), distant metastasis (HR, 1.44; 95% CI, 1.13–2.42; $P < 0.01$), disease-free survival (HR, 1.58; 95% CI, 1.32–2.32; $P < 0.01$), disease-specific survival (HR, 1.39; 95% CI, 1.08–2.07; $P < 0.05$), and overall survival (HR, 1.65; 95% CI, 1.24–2.42; $P < 0.01$). We then determined the c-statistics for the model incorporating established risk factors (ECS, close or positive margins, perineural invasion, level IV or V lymph node metastasis, poor differentiation, tumor depth, presence of at least 5 metastatic neck lymph nodes, and treatment modality) with and without inclusion of the PET score, using disease-free and overall survival rates at 5 y as the outcome measures. The c-statistic for disease-free survival was 0.84 for the risk model without the PET score and 0.90 with the PET score at the neck lymph node ($P < 0.01$, Fig. 2). For overall survival, the c-statistic was 0.83 for the risk model without the PET score and 0.87 with the PET score ($P < 0.05$, Fig. 3).

DISCUSSION

There are 2 principal findings in this study. First, we have shown that PET has suboptimal diagnostic sensitivity and specificity for primary staging of the neck in OSCC patients. However, we found that PET scores at the neck lymph node predicted clinical outcomes in a large group of OSCC patients in an endemic "betel quid chewing" (one of the carcinogens of OSCC) area. Importantly, the PET score improved the accuracy of risk prediction in terms of overall and disease-free survival rates, as assessed by the c-statistics.

Why might PET findings at the neck lymph nodes help predict outcomes even after accounting for established risk factors and in the absence of major diagnostic capacity for primary staging? Our results showed that PET could detect small amounts of macroscopic disease at the neck lymph nodes but did not have acceptable sensitivity in the de-
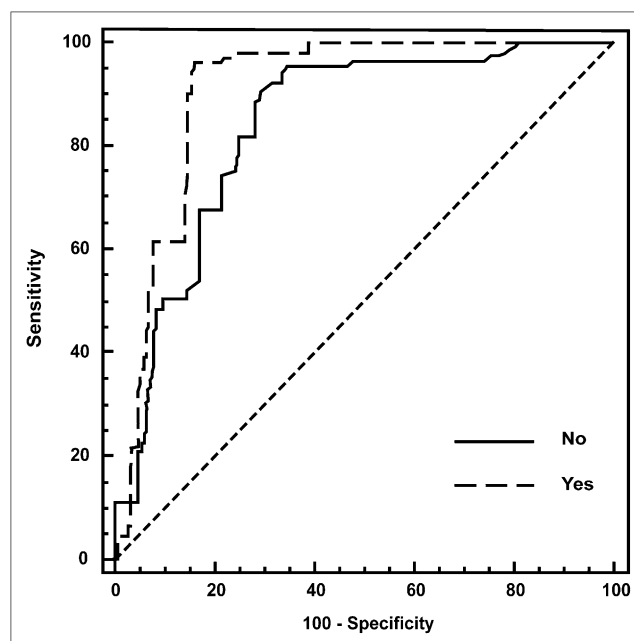
FIGURE 2. ROC curves for disease-free survival rates. Curves are based on risk-prediction models incorporating established risk factors (extracapsular spread, close or positive margins, perineural invasion, level IV or V lymph node metastasis, poor differentiation, tumor depth, presence of at least 5 metastatic neck lymph nodes, and treatment modality) that either included PET score at neck lymph nodes (dotted line) or did not include PET score (solid line). c-statistic was 0.84 for risk model without PET score and 0.90 with PET score at neck lymph nodes ($P < 0.01$).

tection of microscopic disease (Table 3). Because of limited spatial resolution, PET appears insufficiently sensitive to identify microscopic neck lymph node metastases in OSCC patients. An alternative possibility is that neck lymph node metastasis from low-grade primary tumors may display relatively poor uptake of ^{18}F-FDG, leading to a reduced sensitivity. However, an important strength of the use of PET is the ability to measure the intensity of metabolic activity (*17,27*). When added to conventional prognostic factors, we found that the PET score at the neck lymph node did improve the ability to determine which patients will have a poor outcome for disease-free and overall survival and which will remain disease-free at follow-up. These results clearly suggest that PET at the neck lymph node could prove useful in risk stratification or targeting therapies in OSCC patients, even without major diagnostic implications during primary staging. Improvements in prognostic prediction with PET can stem from a variety of sources, including the metabolic discrimination between indolent and aggressive forms of cancers and the possibility of gaining molecular or functional information (*17,27*). The significant improvement of prognostic stratification of PET in the neck lymph node basin highlights the need to use molecular imaging strategies that focus aggressive treatment strategies on OSCC patients most likely to benefit. In the future, one possible approach would be a 2-step strategy that first
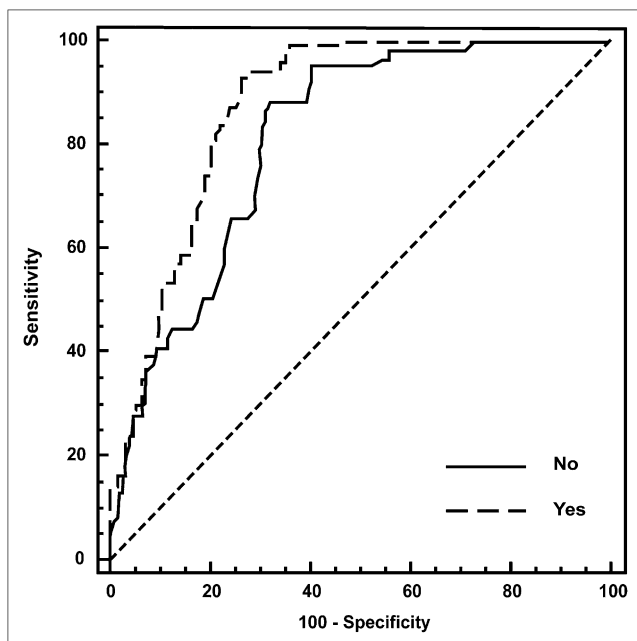
FIGURE 3. ROC curves for overall survival rates. Curves are based on risk-prediction models incorporating established risk factors (extracapsular spread, close or positive margins, perineural invasion, level IV or V lymph node metastasis, poor differentiation, tumor depth, presence of at least 5 metastatic neck lymph nodes, and treatment modality) that either included PET score at neck lymph nodes (dotted line) or did not include PET score (solid line). c-statistic was 0.83 for risk model without PET score and 0.87 with PET score ($P < 0.05$)

tracer. Future studies should address the potential usefulness of other tracers such as 3′-deoxy-3′-^{18}F-fluorothymidine (cell proliferation), O-(2-^{18}F-fluoroethyl)-L-tyrosine (protein translation), ^{18}F-fluoromisonidazole (hypoxia), ^{18}F-arginine-glycine-aspartate (angiogenesis), or ^{18}F-annexin (apoptosis) for nodal staging in OSCC patients.

CONCLUSION

PET findings at the neck lymph nodes showed a limited sensitivity and specificity for primary staging of OSCC patients. However, PET nodal findings have the capacity to improve prognostic stratification for clinical outcomes beyond standard clinical and pathologic risk factors, thus detecting a subgroup of patients with a substantially higher risk. The present study supports the claim that PET at the neck lymph nodes—even without major diagnostic implications for the purpose of primary staging—has clinical validity in the broad sense in OSCC patients without distant metastases. The use of improved prognostic models based on PET findings may also benefit OSCC patients when combined with appropriate risk reduction strategies.

ACKNOWLEDGMENTS

would identify OSCC patients at intermediate risk for the clinical outcomes at follow-up via traditional clinical and pathologic prognostic factors, and then further stratify prognosis based on PET findings at the neck lymph nodes. Additional research is required on the effectiveness of 2-step approaches that use improvement of prognostic stratification after consideration of PET findings at the neck lymph nodes. In addition, careful cost-effectiveness strategies should provide more information concerning the absolute degree of risk and costs to detect high-risk OSCC patients. Identifying OSCC patients at risk for adverse outcomes is a dynamic field, and newer molecular tests and imaging modalities are constantly being evaluated to improve our ability to assess risk more accurately so that the most appropriate follow-up and care can be provided.

Three main limitations of our study deserve mention. Our study sample was entirely of Taiwanese ancestry, and all subjects were living in a betel quid chewing area. This factor may limit the generalizability of our results. Second, in the interest of simplicity, we used a PET score based on the actual data for the purpose of analysis. The areas under the ROC curves, which represent overall diagnostic performance, did not differ significantly among the 2 analytic methods (visual, 0.81; SUV, 0.83). Third, the diagnostic performance of PET was estimated using only ^{18}F-FDG as a

REFERENCES

1. Scully C, Bagan J. Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. *Oral Dis.* 2009;15:388–399.
2. Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. *Oral Oncol.* 2006;42:229–239.
3. Ferlito A, Rinaldo A, Robbins KT, et al. Changing concepts in the surgical management of the cervical node metastasis. *Oral Oncol.* 2003;39:429–435.
4. Iyer SG, Pradhan SA, Pai PS, Patil S. Surgical treatment outcomes of localized squamous carcinoma of buccal mucosa. *Head Neck.* 2004;26:897–902.
5. Kane SV, Gupta M, Kakade AC, D' Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol.* 2006;32:795–803.
6. Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. *Eur J Cancer Prev.* 2007;16:251–256.
7. Liao CT, Chang JT, Wang HM, et al. Survival in squamous cell carcinoma of the oral cavity: differences between pT4N0 and other stage IVA categories. *Cancer.* 2007;110:564–571.
8. Liao CT, Wang HM, Chang JT, et al. Analysis of risk factors for distant metastases in squamous cell carcinoma of the oral cavity. *Cancer.* 2007;110:1501–1508.
9. Liao CT, Chang JT, Wang HM, et al. Salvage therapy in relapsed squamous cell carcinoma of the oral cavity: How and when? *Cancer.* 2008;112:94–103.
10. Liao CT, Chang JT, Wang HM, et al. Analysis of risk factors predictive of local tumor control in oral cavity cancer. *Ann Surg Oncol.* 2008;15:915–922.
11. Al-Ibraheem A, Buck A, Krause BJ, et al. Clinical applications of FDG PET and PET/CT in head and neck cancer. *J Oncol.* August 20, 2009 [Epub ahead of print].
12. Kyzas PA, Evangelou E, Denaxa-Kyza D, et al. ^{18}F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst.* 2008;100:712–720.
13. Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the use of ^{18}F-FDG PET in oncology. *J Nucl Med.* 2008;49:480–508.
14. Ng SH, Yen TC, Chang JT, et al. Oral cavity squamous cell carcinoma with palpably negative neck: a prospective study of 134 patients with ^{18}F-FDG PET and CT/MRI. *J Clin Oncol.* 2006;24:4371–4376.

15. Ng SH, Yen TC, Liao CT, et al. ^{18}F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: a prospective study of 124 patients with histologic correlation. *J Nucl Med.* 2005;46:1136–1143.

16. Yen TC, Chang JT, Ng SH, et al. Staging of untreated squamous cell carcinoma of buccal mucosa with ^{18}F-FDG PET: comparison with head and neck CT/MRI and histopathology. *J Nucl Med.* 2005;46:775–781.

17. Stuckensen T, Kovács AF, Adams S, et al. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. *J Craniomaxillofac Surg.* 2000;28:319–324.

18. Kim SY, Roh JL, Kim JS, et al. Utility of FDG PET in patients with squamous cell carcinomas of the oral cavity. *Eur J Surg Oncol.* 2008;34:208–215.

19. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. *J Natl Compr Canc Netw.* 2009;7: S1–S26.

20. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw.* 2007;5:S1–S22.

21. Ung YC, Maziak DE, Vanderveen JA, et al. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. *J Natl Cancer Inst.* 2007;99:1753–1767.

22. Rebollo Aguirre AC, Ramos-Font C, Villegas Portero R, et al. ^{18}F-fluorodeoxiglucose positron emission tomography for the evaluation of neoadjuvant therapy response in esophageal cancer: systematic review of the literature. *Ann Surg.* 2009;250:247–254.

23. Schöder H, Fury M, Lee N, et al. PET monitoring of therapy response in head and neck squamous cell carcinoma. *J Nucl Med.* 2009;50(suppl):S74–S88.

24. Lai CH, Yen TC, Chang TC. Positron emission tomography imaging for gynecologic malignancy. *Curr Opin Obstet Gynecol.* 2007;19:37–41.

25. Juweid ME. Utility of positron emission tomography (PET) scanning in managing patients with Hodgkin lymphoma. *Hematology (Am Soc Hematol Educ Program).* 2006;1:259–265, 510–511.

26. Shankar LK, Hoffman JM, Bacharach S, et al. National Cancer Institute. Consensus recommendations for the use of ^{18}F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med.* 2006;47:1059–1066.

27. Hofele C, Freier K, Thiele OC, et al. High 2-[^{18}F]fluoro-2-deoxy-d-glucose ([18]FDG) uptake measured by positron emission tomography is associated with reduced overall survival in patients with oral squamous cell carcinoma. *Oral Oncol.* 2009;45:963–967.

28. Ng SH, Chang JT, Chan SC, et al. Nodal metastases of nasopharyngeal carcinoma: patterns of disease on MRI and FDG PET. *Eur J Nucl Med Mol Imaging.* 2004;31:1073–1080.

29. Greene FL, Page DL, Fleming ID, et al. *AJCC Cancer Staging Manual.* 6th ed. New York, NY: Springer-Verlag; 2002.

30. Schöder H, Carlson DL, Kraus DH, et al. ^{18}F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. *J Nucl Med.* 2006;47:755–762.

31. Wang HM, Wang CS, Chen JS, et al. Cisplatin, tegafur, and leucovorin: a moderately effective and minimally toxic outpatient neoadjuvant chemotherapy for locally advanced squamous cell carcinoma of the head and neck. *Cancer.* 2002;94:2989–2995.

32. Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys.* 1996;36:999–1004.