Positive Clinical Impact of an Additional PET/CT Scan Before Adjuvant Radiotherapy or Concurrent Chemoradiotherapy in Patients with Advanced Oral Cavity Squamous Cell Carcinoma

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The aim of this single-center study was to investigate whether obtaining an additional PET/CT scan before adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) could meaningfully improve 2-y disease-free survival (DFS) and disease-specific survival (DSS) rates. **Methods:** Six hundred seventy-four patients with oral cavity squamous cell carcinoma who received adjuvant therapy after radical surgery were included. Of these, 152 patients were initially scheduled to receive an additional preradiotherapy/CCRT PET/CT scan within 1 wk of starting adjuvant therapy. However, 16 patients were excluded because of either medical problems or refusal. Therefore, 136 patients underwent a preradiotherapy/CCRT PET/CT scan (PET group), and 522 did not (NO-PET group). All of the participants were followed up for at least 2 y or censored at the last follow-up. The impact of preradiotherapy/CCRT PET/CT imaging was examined using Kaplan–Meier curves and Cox proportional hazards models. **Results:** Two-year DFS (80% vs. 70%, $P = 0.033$) and DSS (84% vs. 75%, $P = 0.010$) rates were significantly higher in the PET than in the NO-PET group. In the PET group, both DFS and DSS were higher in patients with negative findings than in those without (88% vs. 22% and 91% vs. 36%, respectively; both $P < 0.001$). A prognostic scoring system based on the presence of the 2 independent risk factors in the PET group (extracapsular spread and lymphatic invasion) predicted both DFS ($P = 0.001$ and $P < 0.001$, respectively) and DSS ($P = 0.001$ and $P < 0.001$, respectively). Nineteen patients (14%) had their treatment modified by preradiotherapy/CCRT PET/CT findings. Of these, 15 were treated with curative intent due to the presence of locoregional disease, and 4 received palliative care due to distant metastases. Seven of the 15 patients are currently alive without disease. **Conclusion:** An additional preradiotherapy/CCRT PET/CT scan improves both DFS and DSS in patients with advanced oral cavity squamous cell carcinoma.

Received Jul. 7, 2014; revision accepted Nov. 20, 2014.

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Published online Dec. 18, 2014.

Key Words: oral squamous cell carcinoma; FDG PET/CT; adjuvant therapy

J Nucl Med 2015; 56:22–30
DOI: 10.2967/jnumed.114.145300

Oral cavity squamous cell carcinoma (OSCC) represents a growing burden in Southern Asian countries, including Taiwan (*1*). Despite public health policies aimed at reducing common risky oral habits (e.g., alcohol drinking, betel nut chewing, and cigarette smoking), the incidence of OSCC in the Taiwanese population rose steeply by 30% in the last 5 y. Because of its adverse functional, cosmetic, and prognostic impact, OSCC poses a serious threat to public health and health-care systems and carries heavy personal and societal costs.

Taiwanese OSCC patients are characterized by a high frequency of advanced disease at presentation (52%) (*2*). Notably, more than 80% of all recurrences occur in patients with advanced primary disease, mainly within 2 y of definitive treatment (*3–9*). The key to decreasing recurrence rates is not only to identify (and control) major risk factors, but also to create evidence-based guidelines for the treatment and follow-up of patients with advanced disease (*10–12*). Certain primary tumor biomarkers identified in studies focusing on the role of genetic variants or viruses in OSCC have shown potential utility as predictors or prognostic factors. However, results have been frequently controversial, requiring further verification and validation before being integrated into treatment guidelines (*13–17*). Thus, the major problem in treating OSCC is that prognostic stratification continues to rely on pathologic variables, which are not readily available before radical surgery. In general, patients with advanced disease are treated with adjuvant therapy 6–8 wk after radical surgery (*18,19*). However, such an approach has significant shortcomings, including immunosuppression and pain directly related to food intake. Notably, we have previously shown that 22% of OSCC patients with pathologically positive regional lymph nodes have false-negative PET findings during primary staging (*20*). Ultimately, the evolution of occult metastases to clinically evident disease in the time frame between

radical surgery and adjuvant therapy would result in treatment failures. Moreover, we previously demonstrated that a short time to recurrence (<10 mo) predicts negative outcomes after salvage attempts in patients with disease recurrence diagnosed on clinical grounds (*21*). Furthermore, we were able to show that an additional PET/CT scan before radiotherapy or concurrent chemoradiotherapy (CCRT) may help define adjuvant strategies in advanced OSCC patients through the detection of new unexpected lesions after primary staging (*10*). On the basis of these observations, we hypothesized that an additional preradiotherapy/CCRT PET/CT scan would detect at least half of patients with either rapidly growing regional lymph nodes or distant metastases that were occult at the time of PET imaging performed for primary staging. Of these, at least 12% may change their adjuvant treatment plan and could achieve at least 9% long-term survival by having their clinical management modified by the additional preradiotherapy/CCRT PET findings. Starting from these premises, the aim of the present single-center study was to investigate whether obtaining a PET/CT scan before radiotherapy or CCRT could meaningfully improve (≥9%) disease-free survival (DFS) and disease-specific survival (DSS) rates at 2 y. We also aimed to define the priority of preradiotherapy/CCRT PET/CT imaging among OSCC patients.

MATERIALS AND METHODS

Ethical Statement

The study protocol complied with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (101-0668C and 102-1577C). All patients provided written informed consent to be included in the prospective study. All of the data were securely protected (by delinking identifying information from the main datasets), and access to the information was made available only to investigators, and analyzed anonymously.

Patients

We designed the current study as a single-center investigation. Between January 2000 and May 2012, we identified 674 patients with pathologically proven OSCC who were scheduled to receive adjuvant therapy with radiotherapy or CCRT because of the presence of pathologic risk factors. All of the patients had undergone radical surgery with neck dissection and had no evidence of distant metastases on preoperative imaging studies. Before August 2001, MR imaging or CT was used to screen for metastases, whereas MR imaging/CT and PET/CT were used thereafter. As of October 2008, we obtained an additional PET/CT scan within 1 wk of starting adjuvant therapy with radiotherapy or CCRT. For the purpose of the study, all of the patients enrolled before October 2008 served as controls (NO-PET group, n = 522). The remaining 152 patients who were recruited thereafter were deemed eligible as potential index cases (PET group). Of the 152 patients, 16 did not meet the inclusion criteria (11 subjects were unable to receive adjuvant therapies within 6 wk after radical surgery because of poor general conditions, and 5 patients refused to receive a second PET scan). Finally, 136 patients were included in the PET group (Fig. 1). All of the participants provided their written informed consent before inclusion in the study. All of the patients in the 2 groups were uniformly treated according to the current guidelines or by consensus of our oncology team. All patients expressed willingness to undergo a CT- or ultrasound-guided biopsy or surgical exploration, if necessary. Exclusion criteria were as follows: previous diagnosis of another malignancy, refusal or inability to receive definitive treatment, and presence of hyperglycemia (defined as serum glucose levels > 200 mg/dL). All participants underwent a thorough presurgical evaluation in the 2 wk preceding primary surgery as previously described (*3*). Primary staging was performed in accordance with the criteria from the 2002 American Joint Committee on Cancer (sixth edition) (*22*).

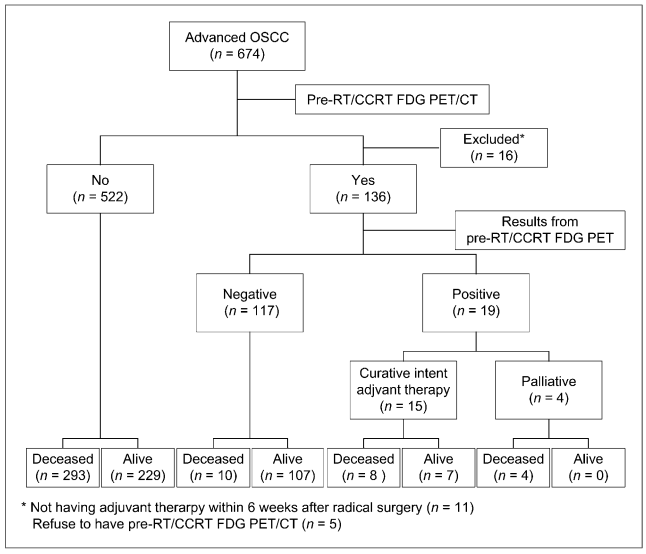

FIGURE 1. Flowchart of study. RT = radiotherapy.

PET/CT Imaging

All of the PET/CT scans were obtained using a Discovery ST 16 PET/CT scanner (GE Healthcare) as previously reported in detail (*10*). We carefully reviewed all PET, CT, and fused PET/CT images as displayed in the axial, coronal, and sagittal planes. We examined both noncorrected and attenuation-corrected PET images, which were also assessed in rotating maximum-intensity projections. Regions of interest were drawn over PET-diagnosed lesions or—in the event of such lesions being absent—using the corresponding CT images. After measuring the highest activity within each region of interest, we calculated the standardized uptake value as the highest activity concentration per injected dose (per body weight in kg) after correction for the radioactive decay. Abnormal foci of increased ^{18}F-FDG uptake on PET/CT images were scored as previously described on a 5-point scale (*10*). In general, positive findings are considered to be present for visual scores of 3 or 4, equivocal results are characterized by a score of 2, and scores of 0 or 1 denote negative findings. However, because the study specifically focused on additional PET/CT imaging at 5–6 wk after radical surgery, only lesions with a score 4 were considered as positive PET/CT findings. All of the PET/CT images were interpreted by consensus of 2 experienced nuclear medicine physicians and 1 radiologist. The results of histopathology were considered as the gold standard.

Treatment Protocol

The surgical principles used for the patients enrolled in this study have been previously reported and were based on the following parameters: primary tumor, surgical margin, classic radical or modified neck dissection (level I–V), supraomohyoid neck dissection (levels I–III), and bilateral neck dissection (*3*). The surgical defects were repaired with primary closure or reconstructed immediately by plastic surgeons using free or local flaps. Postoperative radiotherapy was scheduled within 6–8 wk after radical surgery and administered using a 6 MV x-ray beam produced by a linear accelerator. The total dose, prophylactic radiation dose, boost to the total dose, elective neck irradiation, ipsilateral whole-neck prophylactic irradiation, whole-neck elective irradiation, and radiation fields were determined as previously described (*3*). CCRT consisted of intravenous cisplatin, 30–40

TABLE 1
General Characteristics of Study Participants (n = 658)

Characteristic	n	%	PET group (n = 136)	NO-PET group (n = 522)	P
Age (y)					1.000
≤40	112	17	23 (17)	89 (17)	
>40	546	83	113 (83)	433 (83)	
Treatment modality					1.000
Surgery	17	2	3 (2)	14 (3)	
Surgery + radiotherapy/CCRT	641	98	133 (98)	508 (97)	
Pathologic T status					0.203
pT1–3	394	60	88 (65)	306 (59)	
pT4	264	40	48 (35)	216 (41)	
Pathologic N status					0.110
N0	237	36	57 (42)	180 (35)	
N+	421	64	79 (58)	342(65)	
Pathologic stage					0.123
p stage I–III	214	32	52 (38)	162 (31)	
p stage IV	444	68	84 (62)	360 (69)	
Tumor depth (mm)					0.528
<10	196	30	37 (27)	159 (31)	
≥10	462	70	99 (73)	363 (69)	
Margin status (mm)					0.007
≤4	87	13	28 (21)	59 (11)	
>4	571	87	108 (79)	463 (89)	
Extracapsular spread					0.061
No	397	60	92 (68)	305 (58)	
Yes	261	40	44 (32)	217 (42)	
Cell differentiation					0.194
Well/moderate	574	87	114 (84)	460 (88)	
Poor	84	13	22 (16)	62 (12)	
Perineural invasion					0.001
No	342	52	53 (39)	289 (55)	
Yes	316	48	83 (61)	233 (45)	
Vascular invasion					0.018
No	634	96	126 (93)	508 (97)	
Yes	24	4	10 (7)	14 (3)	
Lymphatic invasion					0.236
No	607	92	128 (94)	479 (92)	
Yes	51	8	8 (6)	43 (8)	
Changes in treatment protocol*					0.456
No	580	88	123 (90)	457 (88)	
Yes	78	12	13 (10)	65 (12)	

*Treatment protocol was not followed as originally planned.
Data in parentheses are percentages.

mg/m^2 weekly or 100 mg/m^2 every 3 wk. Patients in poor general conditions or who refused chemotherapy were treated with postoperative adjuvant radiotherapy alone.

Study Power

Given an α level of 0.05 and a power of 80%, the sample size was calculated, aiming for a 9% improvement in the 2-y DFS from 70% in patients who did not undergo preradiotherapy/CCRT PET/CT imaging. The calculation deemed that at least 126 patients per study arm were required for the study.

Statistical Analysis

Follow-up was continued until May 2014 or until death. All of the time intervals were calculated from the date of the primary treatment

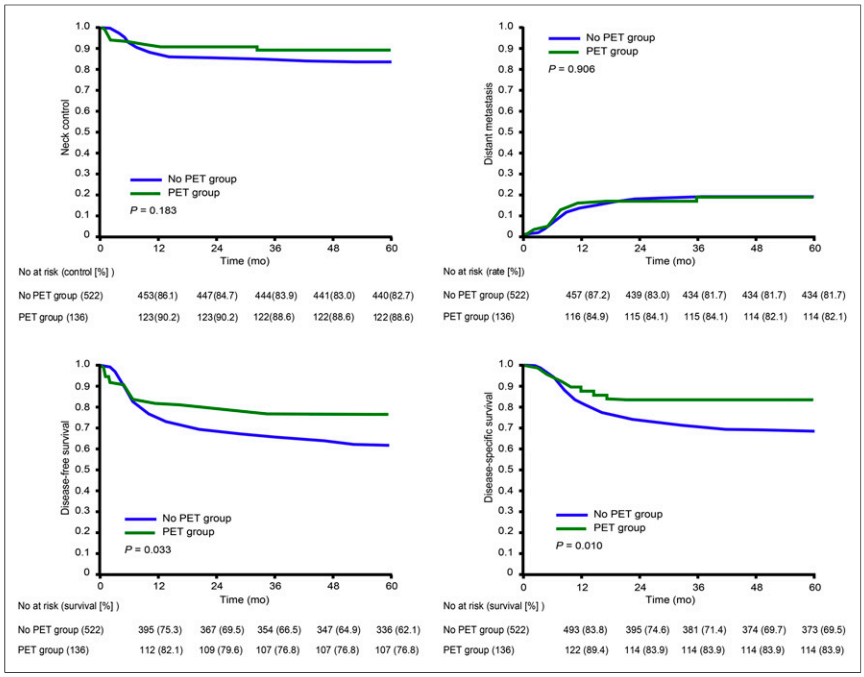

FIGURE 2. Kaplan–Meier curves for different survival endpoints (neck control, distant metastases, DFS, and DSS) in PET and NO-PET groups.

to the event of interest or censored at 2 y for surviving patients. DSS was defined as the survival until death from cancer-related causes. DFS was calculated as the interval until the diagnosis of local recurrence, regional relapse, or distant metastasis. The impact of preradiotherapy/CCRT PET/CT imaging was examined using Kaplan–Meier curves (log-rank test) and multivariate Cox proportional hazards regression models. To address the potential selection bias due to the lack of randomization, we calculated the propensity score for clinical outcomes (DFS and DSS) in both PET and NO-PET groups according to different confounding factors. The proportional hazard assumptions were tested and found to be valid. All analyses were performed using the SPSS software (version 18.0; SPSS Inc.). Statistical significance was defined as a P value of less than 0.05 (2-tailed).

RESULTS

The general characteristics of the PET (n = 136) and NO-PET (n = 522) groups are demonstrated in Table 1. The 2 groups were found to differ significantly in terms of margin status of 4 mm or less, perineural invasion, and vascular invasion. The median follow-up time was 29 mo (mean, 29 mo; range, 2–60 mo) and 58 mo (mean, 62 mo; range, 1–169 mo) in the PET and NO-PET groups, respectively. At the time of analysis, the distribution of events in the PET group was as follows: local recurrence (n = 6; 4%), neck recurrence (n = 14; 10%), and distant metastases (n = 22; 16%). One hundred fourteen patients (84%) were alive. In the NO-PET group, there were 89 patients (17%) with local recurrence, 85 (16%) with neck recurrence, and 88 (17%) with distant metastases. Two hundred twenty-nine patients (44%) were alive.

Outcomes According to Preradiotherapy/CCRT PET/CT Imaging

Figure 2 depicts the clinical outcomes in the PET and NO-PET groups. Compared with patients in the NO-PET group, those in the PET group showed significantly higher 2-y DFS (80% vs. 70%, P = 0.033) and DSS (84% vs. 75%, P = 0.010) rates. To address the potential selection bias due to the lack of randomization, the propensity scores for clinical outcomes in both PET and NO-PET groups were determined according to confounding factors found to have P values less than 0.5 in Table 1. Specifically, the following factors were analyzed: pathologic T status, pathologic N status, pathologic stage, margin status, presence of extracapsular spread, cell differentiation, perineural invasion, vascular invasion, and lymphatic invasion. After applying this procedure, we observed a nonsignificant trend for differences between the PET and NO-PET groups in terms of DFS (adjusted P = 0.081). Notably, a significant difference was found for DSS (adjusted P = 0.033).

Among patients who underwent preadjuvant PET, those with negative findings had significantly higher neck control (96% vs. 50%, $P < 0.001$), DFS (88% vs. 22%, $P < 0.001$), and DSS (91% vs. 36%, $P < 0.001$) rates than those with positive results. Negative PET findings were also as-

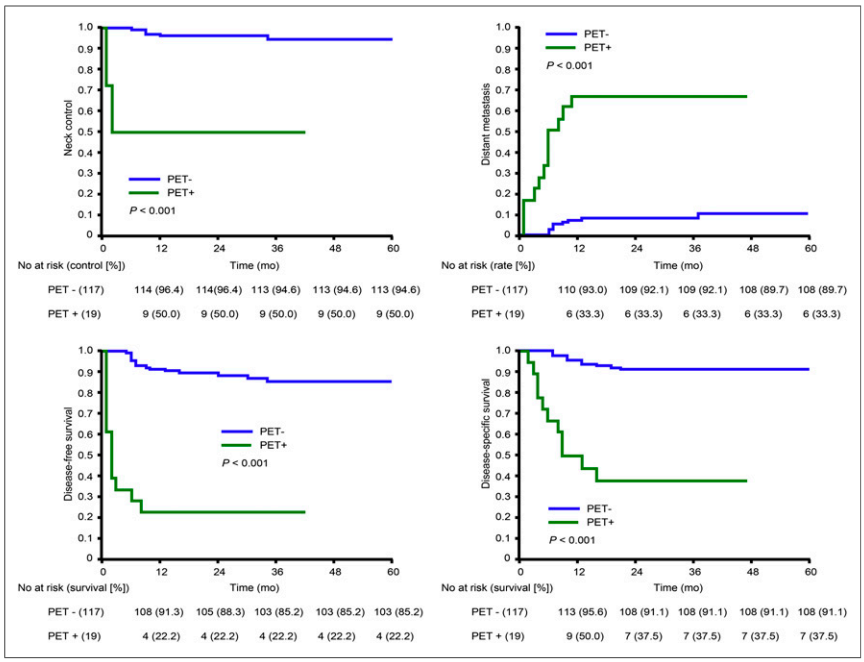

FIGURE 3. Kaplan–Meier curves for different survival endpoints (neck control, distant metastases, DFS, and DSS) according to results (positive vs. negative) of preradiotherapy/CCRT PET/CT scan.

TABLE 2
Multivariable Analysis of 5-Year Control and Survival Rates in PET Group (n = 136)

	Local control		Neck control		Distant metastasis		DFS		DSS		OS	
Risk factor (n)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Extracapsular spread (+) (n = 44)	NS	—	0.003	6.2 (1.8–21.2)	0.001	4.3 (1.8–10.3)	0.001	3.8 (1.7–8.4)	0.001	4.8 (1.9–11.8)	0.003	2.1(1.4–6.5)
Lymphatic invasion (n = 8)	NS	—	0.002	6.7 (2.0–22.8)	<0.001	7.5 (2.6–21.3)	0.001	5.7 (2.1–15.4)	<0.001	7.3 (2.6–20.7)	<0.001	5.6 (2.2–14.3)
Margin status ≤ 4 mm (n = 28)	NS	—	NS	—	NS	—	0.024	2.6 (1.1–6.0)	NS	—	NS	—

DFS = disease free survival; DSS = disease specific survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; NS = not significant.

TABLE 3
Hazard Ratios According to Prognostic Scoring System in PET Group (n = 136)

	Local control		Neck control		Distant metastasis		DFS		DSS		OS	
Scoring system	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Score 0 (n = 88 [65%])	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Score 1 (n = 44 [32%])	NS	—	NS	—	0.007	3.7 (1.4–9.6)	0.022	2.5 (1.1–5.5)	0.004	4.3 (1.6–11.6)	0.003	3.4 (1.5–7.6)
Score 2 (n = 4 [3%])	NS	—	<0.001	47.7 (11.1–204.0)	<0.001	35.7 (9.6–132.3)	<0.001	21.6 (5.7–71.4)	<0.001	36.7 (9.8–137.1)	<0.001	20.3 (6.1–67.2)

DFS = disease free survival; DSS = disease specific survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; NS = not significant.

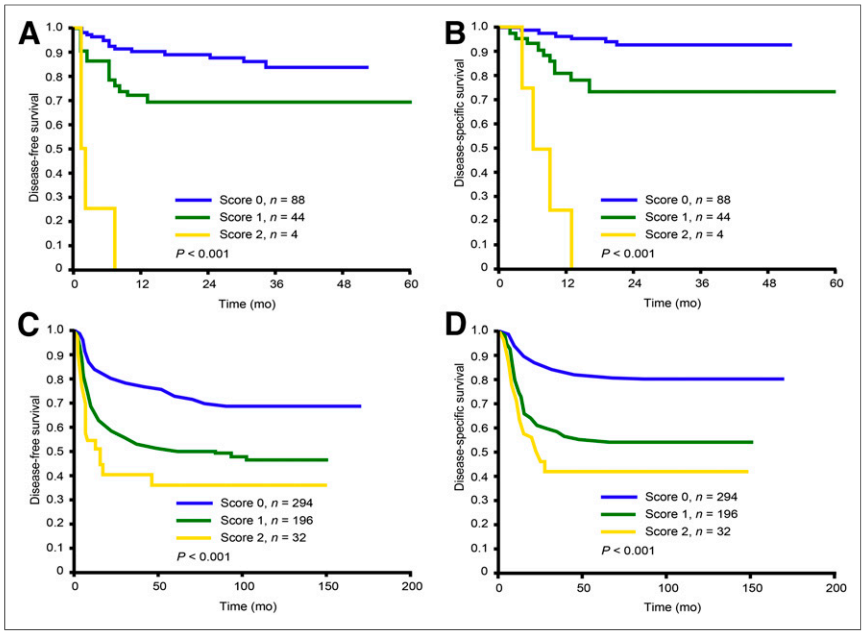

FIGURE 4. Kaplan–Meier curves for different survival endpoints (DFS and DSS) in PET (A and B) and NO-PET (C and D) groups according to prognostic scoring system.

sociated with a lower rate of distant metastasis (8% vs. 67%, $P < 0.001$) (Fig. 3).

Independent Risk Factors and Prognostic Scoring System

We used multivariate analysis to identify the independent predictors of outcomes in the PET group (Table 2). The results indicated that extracapsular spread and lymphatic invasion were independent predictors of neck control rate, distant metastasis rate, DSS, DFS, and overall survival, whereas a margin status of 4 mm or less was independently associated with DFS alone. We then constructed a 3-point prognostic scoring system by summing up the 2 independent prognostic factors (extracapsular spread and lymphatic invasion) by assigning a score of 0 in the absence and 1 in the presence of each variable. As expected, high-risk patients with a score of 2 had a poor prognosis for all survival endpoints, the only exception being local control (Table 3). Intermediate-risk patients with a score of 1 had a worse prognosis than low-risk patients (who scored 0) in terms of DSS, DFS, overall survival, and distant metastasis rates. Although the prognostic score showed a significant association with both DFS and DSS in the PET group (both $P < 0.001$), these results were expected because such a scoring system was constructed on the basis of the findings obtained in the 136 patients of the PET group. To validate the usefulness of this score, we tested its prognostic impact in the PET group in terms of DFS and DSS rates. Notably, the score retained its significant prognostic value in the NO-PET group (Fig. 4, PET group, A–B; NO-PET group, C–D; both $P < 0.001$).

Clinical Impact of Preradiotherapy/CCRT PET/CT Imaging

Preradiotherapy/CCRT PET/CT imaging identified unexpected lesions in 26 patients (Table 4). Nineteen patients showed true-positive PET findings confirmed by either histopathology or imaging follow-up (all of these lesions had a score of 4 on PET/CT scans). In contrast, 7 patients did not have a final confirmation of PET results. In the PET group, patients with a prognostic score of 1−2 were more likely to have positive findings than those with a score of 0 (score 1, odds radio = 4.02, $P = 0.012$; score 2, odds ratio = 41.00, $P = 0.003$). According to our prognostic scoring system, 6 of the 19 patients with PET true-positive results had a score of 0 (low-risk), 10 had a score of 1 (intermediate-risk), and 3 had a score of 2 (high-risk). In the low-risk group, 3 patients had local disease, 1 had regional disease, 1 had locoregional disease, and the remaining 1 had multiple distant metastases to the lung. The latter patient received supportive treatment and died of disease. The remaining 5 patients were treated with curative-intent CCRT. Three are currently alive without disease, 1 is alive with disease, and 1 died. All of the 7 intermediate-risk patients who were found to have locoregional disease had received CCRT with curative intent. Of these, 3 died of disease and 2 are currently alive without disease. Similarly, all of the 3 patients in the high-risk group showed locoregional disease and received CCRT with curative intent. Unfortunately, all of them died within 10 mo of surgery. Among the 7 patients with lack of confirmation, 4 did not have any treatment change (patients 20, 21, 22, and 24). Although patient 23 had lesions with a PET score of 3 at level 2 right neck lymph nodes and at a middle right lung lesion, the results of neck lymph node biopsy were negative. Despite a dose change in the right neck region, additional radiotherapy at the lung was not performed and the patient died of respiratory failure due an extensive pleural effusion. In 2 other cases (patients 25 and 26), radiotherapy dose and field were changed despite negative results on neck lymph node biopsies. On the basis of these findings, we concluded that PET yielded false-positive results in patients 20, 21, 22, and 24. However, it is difficult to classify PET results as true- or false-positive in patients 23, 25, and 26 (Table 4). The clinicopathologic characteristics and clinical outcomes of the 15 OSCC patients experiencing DFS events after radical surgery and who showed negative findings on preradiotherapy/CCRT PET/CT are summarized in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). The corresponding images are reported in the supplemental materials. Among these 15 patients, 11 died and 4 were alive without evidence of disease. No false-negative findings were found on preradiotherapy/CCRT PET/CT imaging.

DISCUSSION

This study is the first, to our knowledge, to describe the impact of preradiotherapy/CCRT PET/CT imaging in a large series of OSCC patients who were scheduled to receive adjuvant therapy after radical surgery. Our present investigation was prompted by previous findings demonstrating that PET/CT is superior to conventional imaging modalities (CT and MR imaging) for primary staging, especially at the neck lymph nodes. Moreover, patients who present with advanced OSCC at diagnosis are generally treated with adjuvant therapy 6–8 wk after radical surgery. Treatment planning in such patients is generally based on the results

TABLE 4
Clinicopathologic Characteristics and Clinical Outcomes of OSCC Patients Who Had Positive Findings on Preradiotherapy/CCRT PET/CT Imaging

Case no.	Primary cancer site	Primary staging	Prognostic scoring system			Pre-RT/CCRT PET findings	Evidence	Adjuvant treatment modification	Outcomes	Follow-up (mo)
			Extracapsular spread	Lymphatic invasion	Score					
1	Left tongue	pT2N0M0	N	N	0	Local, LN (left N3)	Imaging follow-up	Curative CCRT*	NED	49
2	Right tongue	pT4aN1M0	N	N	0	LN (right, level IV)	Tissue proven	Curative CCRT†	NED	24
3	Right bucca	pT4aN0M0	N	N	0	Local	Imaging follow-up	Curative CCRT*	NED	42
4	Left bucca	pT2N0M0	N	N	0	Lung	Imaging follow-up	Palliation	DOD	4
5	Left tongue	pT3N0M0	N	N	0	Local	Imaging follow-up	Curative CCRT*	NED	34
6	Left bucca	pT4aN0M0	N	N	0	Local	Imaging follow-up	Curative CCRT*	DOD	12
7	Right tongue	pT4aN2bM0	P	N	1	LN (left, level V)	Tissue roven	Curative CCRT†	NED	47
8	Right bucca	pT2N2bM0	P	N	1	Local	Imaging follow-up	Curative CCRT*	NED	26
9	Right tongue	pT4aN2cM0	P	N	1	LN (left, level IV)	Imaging Follow-up	Curative CCRT†	DOD	13
10	Right tongue	pT2N2bM0	P	N	1	LN (left, level I, II, III)	Tissue proven	Curative CCRT†	DOD	16
11	Left tongue	pT2N2bM0	P	N	1	LN (right, level III, V)	Imaging follow-up	Curative CCRT†	NED	31
12	Right tongue	pT2N2cM0	P	N	1	LN (right, level III, IV)	Tissue proven	Curative CCRT†	DOD	9
13	Right bucca	pT4aN2bM0	P	N	1	Lung	Imaging follow-up	Palliation	DOD	2
14	Left bucca	pT3N2bM0	P	N	1	Local, LN (left, level III), lung	Tissue proven	Palliation	DOD	5
15	Left mouth floor	pT4aN2bM0	P	N	1	Lung	Imaging follow-up	Palliation	DOD	3
16	Right alveolar ridge	pT4aN1M0	P	N	1	Local	Imaging follow-up	Curative CCRT*	DOD	8
17	Right bucca	pT4aN2bM0	P	P	2	Local, LN (left, level V and parotid)	Tissue proven	Curative CCRT†	DOD	4
18	Right bucca	pT4aN2bM0	P	P	2	LN (left, level IV and parotid)	Imaging follow-up	Curative CCRT‡	DOD	9
19	Right alveolar ridge	pT3N2bM0	P	P	2	LN (right, level V and left, parotid)	Tissue proven	Curative CCRT†	DOD	6
20	Left retromolar trigone	pT4aN0M0	N	N	0	Lung score 3§	Imaging follow-up	Radiotherapy	NED	36
21	Right buccal	pT4aN0M0	N	N	0	Lung score 3§	Imaging follow-up	Radiotherapy	NED	33
22	Right retromolar trigone	pT2N0M0	N	N	0	Local (right mandible, score 3§)	Tissue-proven negative	Radiotherapy	NED	60
23	Left tongue	pT2N2bM0	N	P	1	LN (right, level II, score 3§), lung, score 3§	Tissue-proven (LN) negative	Curative CCRT†	DOD (pleural effusion)	8
24	Left alveolar ridge	pT4aN0M0	N	N	0	Local (left upper gum, score 3§)	Tissue-proven negative	Radiotherapy	NED	33
25	Left tongue	pT2N2bM0	P	N	1	LN (right level III, V, score 3§)	Tissue-proven negative	Curative CCRT†	NED	32
26	Right alveolar ridge	pT4aN1M0	N	N	0	LN (right, level V, left SCF, both scores 3§)	Tissue-proven negative	Curative CCRT†	NED	28

*Change RT dose; †Change RT dose and field; ‡Change field; §PET/CT score.

ES = extracapsular spread; LI = lymphatic invasion; RT = radiotherapy; N = negative; LN = lymph node; P = positive; NED = no evidence of disease, DOD = died of disease; SCF = supraclavicular fossa.

of primary staging before surgery and pathology findings after radical dissection. However, some patients may be understaged during primary staging procedures, mostly because of the potential presence of undetectable micrometastases to lymph nodes or distant organs (*19*). Notably, pain related to radical surgery and reconstructive operations, depressive symptoms, and poor appetite with reduced food intake are excruciating problems in the period between surgery and adjuvant therapy. In this scenario, the growth of occult metastases to clinically evident disease during this time frame would ultimately result in treatment failure. On the basis of our preliminary study (*10*), an additional preradiotherapy/CCRT PET/CT scan may increase the likelihood of diagnosing previously undetected lesions. We believe that such an advantage might result in significant clinical management changes and improved outcomes in advanced OSCC patients.

Herein, we demonstrated that 2-y DFS and DSS rates were significantly higher in the PET than in the NO-PET group (10% and 9%, respectively). In this study, 19 patients (14%) were found to have early recurrent lesions and had their clinical management modified by preradiotherapy/CCRT PET/CT findings (Table 4). Of these, 15 patients were treated with curative intent after modification of treatment field and dosage, whereas adjuvant treatment was changed to palliation in 4 patients. After a follow-up period ranging from 24 to 49 mo, 7 of the 15 patients who received curative-intent treatment were disease-free. Notably, 37% (7/19) of the patients with positive PET results detected within 2 mo of radical surgery would be cured by prompt salvage treatment, suggesting that a short time to recurrence may not be necessarily associated with negative outcomes. Without the additional preradiotherapy/CCRT PET/CT scan, patients with early recurrence would have experienced not only a delayed diagnosis but also a significant undertreatment, ultimately diminishing their likelihood of successful salvage (*21*). Taken together, these findings indicate that a preradiotherapy/CCRT PET/CT scan may improve the clinical management of OSCC patients by avoiding unnecessary curative attempts (associated with futile patient suffering and inefficient health-care expenditures) and improving survival rates through modifications of adjuvant strategies.

Because preradiotherapy/CCRT PET/CT imaging may significantly increase health-care costs, it is important to define its priority based on the presence of a specific risk factor profile. To this aim, we devised a prognostic scoring system based on the 2 independent risk factors (extracapsular spread and lymphatic invasion) identified in multivariate analysis. We suggest that a preradiotherapy/CCRT PET/CT scan may be justified for all of the intermediate- or high-risk patients (with a score of 1 or 2). Accordingly, these patients showed a reasonably high likelihood of positive findings, being 23% (10/44) in patients with a score 1 and 75% (3/4) in those with a score 2. Notably, preradiotherapy/CCRT PET/CT imaging also demonstrated prognostic significance in high-risk patients with a score of 2. All of the 3 high-risk patients with positive PET/CT results died of disease within 10 mo after surgery because of multiple distant metastases. Further research is needed to establish whether adjuvant therapy with curative intent should be avoided in such patients. Although a cost-effectiveness analysis is needed before making final recommendations, it is important to emphasize that negative results on preradiotherapy/CCRT PET/CT imaging were associated with better clinical outcomes.

Some limitations apply to the reported findings. Because the sample studied consisted of Taiwanese patients enrolled in a betel-quid-chewing endemic area, the results might not apply to other populations that did not have the oral habit of betel quid chewing. Second, the study was not randomized, and potentially more patients with an unfavorable risk profile may have been chosen for preradiotherapy/CCRT PET/CT imaging (Table 1). However, this potential selection bias would result in an attenuation of the positive clinical impact of an additional PET scan, which was not eventually observed in our study. Well-conducted randomized multicenter trials are eagerly awaited to confirm and expand our findings. Finally, external validation of our prognostic score across broader patient populations is needed.

CONCLUSION

We observed that OSCC patients who underwent preradiotherapy/CCRT PET/CT exhibited improved DFS (by 10%) and DSS (by 9%) when compared with patients who did not, underscoring the value of this approach for implementing changes in management and improving survival. We are unaware of the integration of PET data into treatment planning in the National Comprehensive Cancer Network clinical practice guideline of head and neck cancer. An additional preradiotherapy/CCRT PET/CT scan may be justified for patients with advanced OSCC who present with extracapsular spread or lymphatic invasion.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. This work was financially supported by the Ministry of Science and Technology, Taiwan (grant NMRPG3B6311-3B6313) and the Chang Gung Memorial Hospital at Linkou (grants CMRPG370061-370063, CMRPG3B0021-3B0023, and CMRPG371501-371503). No other potential conflict of interest relevant to this article was reported.

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