Differential Roles of ^{18}F-FDG PET in Patients with Locoregional Advanced Nasopharyngeal Carcinoma After Primary Curative Therapy: Response Evaluation and Impact on Management

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This prospective study compares the efficacies of whole-body ^{18}F-FDG PET and a conventional work-up (CWU) in evaluating the treatment response for patients with locoregional advanced nasopharyngeal carcinoma (NPC) after primary curative therapy and investigates the impact of PET on patient management. **Methods:** Patients who had locoregional advanced NPC (stages III and IVa-b, staged by ^{18}F-FDG PET and CWU) and who had completed primary curative therapy for 3 mo were enrolled. The curative therapy consisted of concurrent chemoradiotherapy with or without induction chemotherapy. All of the patients also underwent ^{18}F-FDG PET and CWU to evaluate the response. The criteria for final diagnosis were based on pathology or subsequent follow-up for at least 6 mo. Rates of detection by ^{18}F-FDG PET and CWU and the impact on management were determined on site and patient bases, respectively. **Results:** From January 2002 to August 2005, 131 patients with NPC were eligible, including 71 patients with stage III NPC (group A) and 60 patients with stage IVa-b NPC (group B). Twelve patients were proven to have residual tumors. ^{18}F-FDG PET had a higher overall sensitivity than CWU in group A (100% vs. 25%) and group B (91.7% vs. 58.3%). The overall specificity of PET was significantly higher than that of CWU in group B (97.6% vs. 91.7%; $P = 0.019$) but was slightly lower in group A (95.7% vs. 96.7%). The overall accuracy of PET also was significantly higher than that of CWU in group B (97.2% vs. 89.4%; $P = 0.002$) but was similar to that of CWU in group A (95.8% vs. 95.3%). PET resulted in management changes in 11 patients (15.4%; 11/71) in group A, with positive and negative impacts on 3 and 8 patients, respectively. In group B, the management of 26 of 60 patients (43%) was changed as a result of PET and included positive impacts on 23 patients and negative impacts on 3 patients. **Conclusion:** ^{18}F-FDG PET plays differential roles in patients with stage III NPC and stage IVa-b NPC after primary curative therapy. PET has higher sensitivity and specificity in evaluating the response and results in better management of patients with stage IVa-b NPC. PET has a less prominent impact on patient management but higher sensitivity in patients with stage III NPC.

Key Words: ^{18}F-FDG PET; nasopharyngeal carcinoma; residual tumor; clinical impact; response evaluation

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Nasopharyngeal carcinoma (NPC) is different from other head and neck cancers and should be considered a distinct study topic. For patients with locoregional advanced NPC, concurrent chemoradiotherapy (CCRT) is the current standard treatment because of the high risk of treatment failure and systemic spreading (*1*). However, even after CCRT with the modern intensity-modulated radiotherapy technique (IMRT), many patients still experience treatment failure (*2,3*).

Conventional imaging modalities for evaluating the treatment response in NPC patients include the nasopharyngeal scope, CT, MRI, bone scanning, and abdominal sonography. However, false-negative (FN) or false-positive (FP) findings are not unusual. For example, postradiation mucositis crust may hinder a flexible endoscopy examination (*4*). Soft tissue in the irradiated nasopharynx on MRI can pose the diagnostic question of whether or not it harbors a viable tumor (*4–6*). Bone marrow metastases and small metastatic lesions also are easily neglected (*7–10*). Although successful salvage treatment is possible even for patients with limited distant failure (*11–13*), the low accuracy of conventional modalities and the slowly regressive nature of NPC often place the clinician in a decision dilemma (*14*).

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^{18}F-FDG PET has shown its potential in the management of patients with NPC, including initial staging (*7,10,15*), detecting local residual or recurrent disease (*16,17*), specifying the nature of equivocal MRI findings for recurrence (*18*), and evaluating the treatment response after induction chemotherapy (*19*). Although several studies have proved the superiority of PET in detecting residual or recurrent NPC, most have focused on the assessment of the local tumor. Recently, Yen et al. retrospectively investigated the role of whole-body ^{18}F-FDG PET in detecting recurrent or residual NPC and reported high sensitivity and specificity (*9*). However, a comparison of whole-body ^{18}F-FDG PET and a conventional work-up (CWU) in evaluating residual NPC and the impact of PET on the management of patients with NPC after therapy have yet to be addressed. Therefore, we conducted this prospective study to explore the roles of ^{18}F-FDG PET in these 2 aspects.

MATERIALS AND METHODS

Patients

This prospective study was approved by the institutional review board of our hospital and required written informed consent from all patients. Patients who had locoregional advanced NPC (stage III or stage IVa-b, as determined with the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM staging system) and who had completed primary curative therapy for 3 mo were eligible to enter this study. The initial staging modalities for these patients comprised whole-body ^{18}F-FDG PET and CWU, including head and neck MRI, nasopharyngeal fiberscope examination, bone scanning, chest radiography, and abdominal sonography. Primary curative therapy consisted of CCRT with the IMRT technique. Some patients who had stage IVa-b NPC and who were participating in another randomized trial investigating the efficacy of neoadjuvant therapy received induction chemotherapy before CCRT. Three months after the treatment, these patients also underwent whole-body ^{18}F-FDG PET and the same CWU to evaluate the response. All scans were performed in 2 wk. After the imaging survey, a clinical and imaging follow-up for at least 6 mo was mandatory unless the patient died. Patients who were reluctant to comply with the follow-up schedule or whose tumors were not World Health Organization (WHO)–classified types I–III were excluded from this study.

CCRT and Induction Chemotherapy

The chemotherapy regimen of CCRT was the intravenous administration of cisplatin at 50 mg/m^2 on day 1 and the oral administration of tegafur plus uracil at 300 mg/m^2/d and leucovorin at 60 mg/d for 14 d. Radiation was administered by using 6-MV photon beams for 2 Gy per fraction, every fraction per day, 5 d per week. The radiotherapy area included the gross tumor area with at least 1-cm margins and the whole neck for 46 Gy and then cone down boost to the initial gross tumor area with close margins to a total of 72 Gy for T1–T3 tumors and 76 Gy for T4 tumors. IMRT was administered to all patients.

The induction chemotherapy regimen consisted of the intravenous administration of mitomycin at 8 mg/m^2, epirubicin at 60 mg/m^2, and cisplatin at 60 mg/m^2 on day 1. Fluorouracil at 450 mg/m^2 and leucovorin at 30 mg/m^2 were given on day 8. This cycle was repeated every 3 wk.

^{18}F-FDG PET

The ^{18}F-FDG used for the PET studies was produced by the Institute of Nuclear Energy Research of Taiwan. ^{18}F-FDG PET images were obtained by use of an ECAT EXACT HR+ camera (CTI) at a full width at half maximum of 4.5 mm and a transaxial field of view of 15 cm. All patients fasted for at least 6 h before the PET scan. The serum glucose level was measured before the intravenous administration of 370 MBq (10 mCi) of ^{18}F-FDG. Diazepam at 5 mg was given orally to reduce ^{18}F-FDG uptake in the skeletal muscles. After the intravenous injection of ^{18}F-FDG, the patients were kept at rest in a quiet, dimly lit room for at least 40 min. Talking, walking, or other physical activities were avoided to reduce muscle uptake.

The patients were scanned while lying supine along the central axis of the PET table. Seven sequential emission images were obtained from the head to the upper thigh, requiring 56 min in the 2-dimensional mode. Transmission scans were obtained with ^{68}Ge rod sources for attenuation correction (3 min per bed position). The emission and transmission scans were obtained in an alternating sequence per bed position. The reconstruction of both transmission and emission scans was done with accelerated maximum-likelihood reconstruction and ordered-subset expectation maximization (2 iterations, 8 subsets).

Image Interpretation and Analysis

The ^{18}F-FDG PET images were visually interpreted by 3 experienced nuclear medicine physicians without knowledge of the results of CWU. ^{18}F-FDG accumulation was classified with a 5-point scale as follows: 0, normal; 1, probably normal; 2, equivocal; 3, probably abnormal; and 4, definitely abnormal (Fig. 1). Grades 3 and 4 were considered to be positive results, whereas grades 0–2 were classified as negative results. The lesion was interpreted visually, and the standardized uptake value of ^{18}F-FDG uptake was used as an accessory reference only. The results of MRI and other CWU methods also were classified with this grading system.

Outcome Determination and Patient Management

The findings of ^{18}F-FDG PET and CWU were discussed jointly by our NPC research team, consisting of nuclear medicine physicians, head and neck radiologists, otolaryngologists, medical oncologists, and radiation oncologists. When possible, imaging-guided biopsy was performed for lesions that were suspected of being malignant. When a biopsy of a suspicious lesion was not feasible or yielded a negative result in patients with positive imaging findings, close clinical or imaging follow-up for at least 6 mo was pursued. In view of the high local failure rate (*20*) but low accuracy of CWU in detecting residual tumor for patients with stage IVa NPC (*16,17*), our strategy for these patients was modified. If the result of CWU for patients with stage IVa NPC was normal or probably normal (score of 0 or 1), then the patient received regular follow-up; if the result was equivocal (score of 2), then the patient was closely monitored; if the result was probably abnormal (score of 3), then the patient was closely monitored if there were no symptoms or signs of treatment failure or, in cases with symptoms or signs of treatment failure, additional imaging or biopsy was indicated; and if the result was definitely abnormal (score of 4), then biopsy was indicated.

The results of ^{18}F-FDG PET and CWU then were classified as true-positive (TP), true-negative (TN), FP, or FN results according to the results of biopsy and subsequent follow-up. Patients with

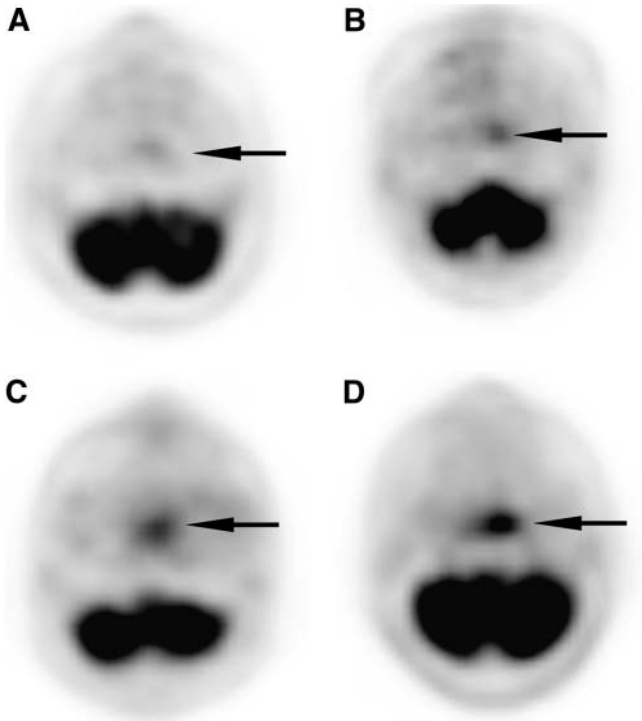

FIGURE 1. Categorization of level of uptake of ^{18}F-FDG at primary site. (A) Mild accumulation of ^{18}F-FDG (score of 1; arrow). (B) Equivocal increase in ^{18}F-FDG accumulation (score of 2; arrow). (C) Probably abnormal increase in ^{18}F-FDG uptake (score of 3; arrow). (D) Definitely abnormal accumulation of ^{18}F-FDG (score of 4; arrow).

residual tumors confined to the previous primary tumor site were classified as having local failure. Patients with residual tumors involving neck lymph nodes were classified as having regional failure. Finally, patients with tumors in areas beyond the primary and regional nodal sites were classified as having systemic or distant failure.

Further management for patients was based on the consensus of the research team. Management plans before and after acknowledgment of PET findings were separately recorded in a computer database.

Follow-up of Patient Status

The follow-up status of a patient was classified as follows: no evidence of disease (NED), alive with disease (AWD), died with disease (DWD), or died as a result of other causes without evidence of disease according to the most recent follow-up. The time of follow-up was counted from the completion of primary therapy.

Clinical Impact

The clinical impact of changes in treatment management attributable to ^{18}F-FDG PET was determined on a patient-by-patient basis. The impact was defined as follows: negative if FP PET findings led to unnecessary, additional invasive procedures or imaging follow-up; no change if PET had the same findings as CWU and did not affect management; or positive if management was modified because of the discovery of unexpected residual or second primary tumors or TN PET findings (histologically unproven residual lesions were found by CWU but were not seen by ^{18}F-FDG PET, and these lesions regressed without treatment).

Statistical Analysis

Independent Student t tests and χ^2 tests were used to compare the patients' ages and other characteristics in different groups. The McNemar test was used to determine whether the sensitivity, specificity, and accuracy of ^{18}F-FDG PET were significantly different from those of CWU. All statistical tests were 2 tailed.

RESULTS

Patients

Between January 2002 and August 2005, 136 eligible patients were enrolled in this study. Four patients were excluded because of a reluctance to receive regular follow-up for at least 6 mo. One patient with nasopharyngeal adenoid cystic carcinoma also was excluded. Therefore, a total of 131 patients were eligible for the final analysis. The characteristics of the enrolled patients are listed in Table 1. Patients with initial stage III disease and stage IVa-b disease were classified as group A and group B, respectively.

Twelve patients were proven to have residual tumors on the basis of histopathologic biopsy results or confirmation of the corresponding imaging findings, whereas the remaining patients were diagnosed to be in complete remission after a clinical or imaging follow-up period of at least 6 mo. Of the 12 patients with treatment failures, 2 had local failures, 4 had regional failures, 2 had systemic failures, 1 had concomitant local and regional nodal failures, 2 had concomitant local and systemic failures, and 1 had concomitant regional and systemic failures.

Response Evaluation

Local Sites. Table 2 shows the statistical analysis of PET and CWU in evaluating the treatment response. Five patients were proven to have local failures. All residual tumors were detected by PET, whereas 2 in each group were missed by CWU (Fig. 2). In group A, 1 and 2 FP results were noted for PET and CWU, respectively. In group B,

TABLE 1
Patient Characteristics (n = 131)

Characteristic*	Stage III (group A)	Stage IVa-b (group B)	P
No. of patients	71	60	
Age (y), mean ± SD	48 ± 12	L51 ± 13	0.33
Sex			0.56
Male	48	44	
Female	23	16	
Cell type			0.78
WHO type II	24	17	
WHO type III	47	43	
Curative treatment			
CCRT	71	60	
Induction chemotherapy		30	

*Data are reported as number of patients, unless otherwise indicated.

TABLE 2
Results of ^{18}F-FDG PET and CWU in Evaluating Treatment Response Based on Site

Site	Group	Evaluation method	FN	TP	TN	FP	% Sensitivity (95% CI)	% Specificity (95% CI)	% Accuracy (95% CI)
Local	A	^{18}F-FDG PET	0	1	69	1	100	98.6 (92.3−100.0)	98.6 (92.4−100.0)
		CWU	1	0	68	2	0	97.1 (90.1−99.7)	95.8 (88.1−99.1)
	B	^{18}F-FDG PET	0	4	55	1	100	98.2 (90.4−100.0)	98.3 (91.1−100.0)
		CWU	1	3	48	8	75.0 (19.4−99.4)	85.7 (73.8−93.6)	85.0 (73.4−92.9)
Regional lymph node	A	^{18}F-FDG PET	0	3	65	3	100	95.6 (87.6−99.1)	95.8 (88.1−99.1)
		CWU	2	1	64	4	33.3 (0.8−90.6)	94.1 (85.6−98.4)	91.5 (82.5−96.8)
	B	^{18}F-FDG PET	0	3	55	2	100	96.5 (87.9−99.6)	96.7 (88.5−99.6)
		CWU	1	2	53	4	66.7 (9.4−99.2)	93.0 (83.0−98.1)	91.7 (81.6−97.2)
Distant	A	^{18}F-FDG PET	0	0	66	5	NA	93.0 (84.3−97.7)	93.0 (84.3−97.7)
		CWU	0	0	70	1	NA	98.6 (92.4−100.0)	98.6 (92.4−100.0)
	B	^{18}F-FDG PET	1	4	54	1	80.0 (28.4−99.5)	98.2 (90.3−100.0)	96.7 (88.5−99.6)
		CWU	3	2	54	1	40.0 (5.3−85.3)	98.2 (90.3−100.0)	93.3 (83.8−98.2)
Overall	A	^{18}F-FDG PET	0	4	200	9	100	95.7 (92.0−98.0)	95.8 (92.1−98.0)
		CWU	3	1	202	7	25.0 (0.6−80.6)	96.7 (93.2−98.6)	95.3 (91.5−97.7)
	B	^{18}F-FDG PET	1	11	164	4	91.7 (61.5−99.8)	97.6 (94.0−99.3)	97.2 (93.6−99.1)
		CWU	5	7	154	14	58.3 (27.7−84.8)	91.7 (86.4−95.4)	89.4 (84.0−93.5)

CI = confidence interval; NA = not available.

there were many more FP results for CWU than for PET. The specificities and accuracies of PET and CWU were similar in group A. In group B, however, PET showed higher sensitivity, specificity, and accuracy than CWU, and the difference in specificities was significant ($P = 0.04$).

Regional Lymph Nodes. Six regional nodal failure sites in 6 patients were finally proven. Four were at level II, 1 was at levels II–IV, and 1 was at the supraclavicular fossa. PET correctly identified all 6 residual tumors, whereas CWU missed 2 in group A and 1 in group B. PET and CWU produced FP findings in 5 and 8 patients, respectively. In both groups, PET showed higher sensitivity than CWU but specificity similar to that of CWU. The accuracies of PET were slightly higher than those of CWU.

Distant Sites. Five patients were proven to have distant failures; all of them were in group B. One had multiple bony metastases, 2 had multiple hepatic metastases, and the remaining 2 had solitary metastases at the sacrum and at the liver. PET correctly detected metastatic lesions in all patients except for 1 patient with multiple hepatic metastases. This case also was missed by CWU. At the initial PET and CWU, this patient was thought to have local failure only. Imaging follow-up was pursued because of lack of clinical symptoms or signs of local failure. Three months later, the patient underwent whole-body PET and CWU again. In addition to progression of the local mass, multiple hepatic metastases also were noted. CWU also missed distant metastatic lesions in another 2 patients; 1 had a solitary sacral bone metastasis, and the other had a solitary hepatic metastasis.

PET produced 6 FP results at distant sites; 5 were in the lungs (Fig. 3), and 1 was in the lumbar spine. These lesions were identified to be inflammatory disease on the basis of the findings of corresponding chest CT or spine MRI scans. All of the inflammatory lesions had regressed in the follow-up images without treatment. In contrast, only 2 FP results were produced by CWU. One was in the cervical spine marrow, and the other was in a mediastinal lymph node. The

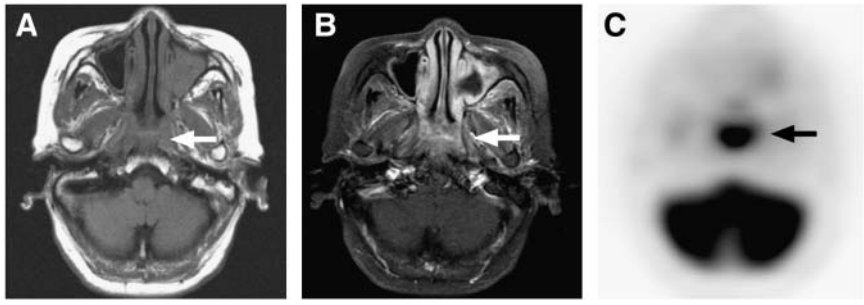

FIGURE 2. Data for 63-y-old patient with stage IVa NPC 3 mo after CCRT. Images from unenhanced (A) and enhanced (B) axial T1-weighted MRI revealed mild symmetric mucosal thickening at nasopharynx, suggestive of postradiation change (arrows). (C) Corresponding ^{18}F-FDG PET image revealed hypermetabolic lesion in nasopharynx, indicative of residual tumor (arrow). Biopsy revealed residual NPC.

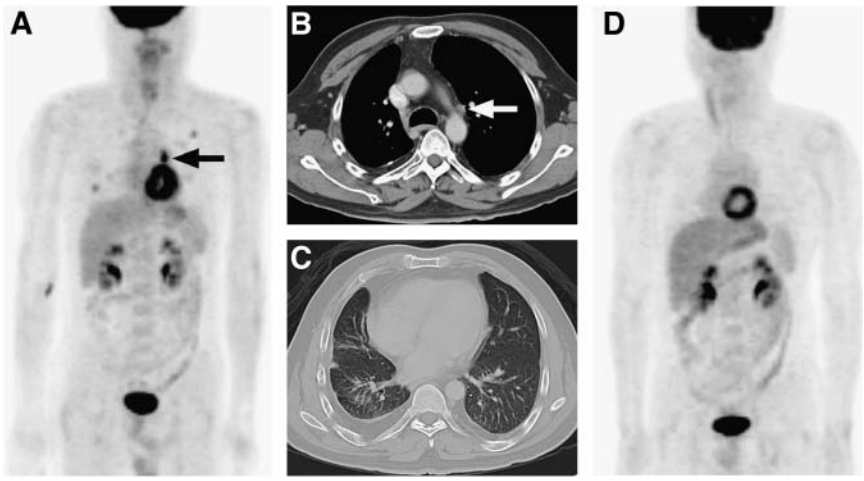

FIGURE 3. Data for 49-y-old patient with stage III NPC 3 mo after CCRT. (A) Whole-body maximum-intensity projection image from ^{18}F-FDG PET revealed scattered hypermetabolic lesions in bilateral lung fields and left pulmonary hilar region (arrow). Lung metastases and left hilar nodal metastasis were suspected. (B) Chest CT was performed for confirmation. Contrast-enhanced transaxial image revealed small left hilar lymph node, suggestive of reactive lymphadenopathy (arrow). (C) Transaxial CT image at lung window revealed peribronchial infiltrations in right middle and lower lobes as well as bilateral pleural effusion. Inflammatory disease was diagnosed. (D) Follow-up PET scan 9 mo later without treatment showed complete disappearance of hypermetabolic lesions.

cervical spine and mediastinal lymph node lesions were presumed to be benign in nature because they were stationary or had regressed in the follow-up images without treatment. At the distant sites, PET also showed higher sensitivity than CWU, but specificity was lower.

Overall. In group A, the overall sensitivity of PET was higher than that of CWU, but the overall specificities and accuracies were similar. In group B, the overall sensitivity of PET was higher than that of CWU, but the difference was not significant ($P = 0.125$). However, the overall specificity and accuracy of PET were significantly higher ($P = 0.019$ and $P = 0.002$, respectively).

Second Primary Tumor

Three second primary tumors were suggested by PET. One thyroid lesion was proven to be papillary thyroid carcinoma. A suspected breast cancer case was diagnosed as a rib fracture on the basis of the coregistered PET/CT image. A tongue lesion also was noted by MRI and diagnosed as a fibroepithelial polyp by histopathologic analysis.

Clinical Impact of ^{18}F-FDG PET on Patient Management After Therapy

Table 3 shows the impact of ^{18}F-FDG PET on patient management after therapy. Management plans for 37 of 131 patients (28%) were changed because of PET: 11 patients in group A and 26 patients in group B. For the 11 group A patients, the impact of PET was positive in 3 but negative in 8. On the other hand, the impact of PET in group B was positive in 23 patients and negative in 3 patients.

TABLE 3
Clinical Impact of ^{18}F-FDG PET on Management of 131 Patients with NPC After Curative Treatment

		No. (%) of patients with the following impact:		
Group	No. of patients	Negative	No change	Positive
A	71	8 (11)	59 (85)	3 (4)
B	60	3 (5)	34 (57)	23 (38)

Table 4 shows the changes in patient management. Of the 3 patients with positive impacts in group A (patients 1–3), 2 received curative CCRT because of unexpected locoregional residual tumors discovered by PET. The third, with a mediastinal lymph nodal metastasis suggested by CWU, avoided unnecessary thoracoscopic biopsy because of the negative PET finding. Of the 8 patients with negative impacts, 2 had FP PET findings at the local or regional sites (patients 4 and 5). Locoregional recurrence occurred in 1 of these patients but was considered to be unrelated because of the late recurrence time. Six patients received extra CT or MRI scans because of FP PET findings at the distant or second primary sites (patients 6–11).

In group B, management plans for 2 patients were changed to salvage CCRT because of unexpected locoregional residual tumors found by PET (patients 12 and 13). For the 2 patients with a solitary metastasis discovered by PET, palliative chemotherapy with or without local radiotherapy was arranged (patients 14 and 15). Of note, the frequency of imaging follow-up in 28% (17/60) of patients who had stage T4 disease and whose CWU after therapy showed equivocal or probably abnormal results (score of 2 or 3) at the local sites was reduced because of negative corresponding PET results (patients 16–32; Fig. 4). One patient whose MRI showed marrow metastasis at the C5 spine avoided unnecessary palliative treatment because of TN PET findings (patient 33).

Negative impacts for 3 patients were noted in group B. These patients received extra follow-up PET or MRI because of FP PET findings at local, regional, or distant sites (patients 35–37). The patient who had been thought to have regional failure experienced rib metastasis 18 mo later without concomitant regional nodal recurrence.

TABLE 4
Changes in Treatment Management Attributable to ^{18}F-FDG PET and Its Associated Clinical Impact

Patient(s)	Group	Scan findings		Final diagnosis	Management plan		Follow-up time (mo)	Final status*	Impact	Remarks*
		CWU	PET		Before PET	After PET				
1	A	CR	LRF	LRF	iFU	CST	16	NED	P	
2	A	CR	RF	RF	iFU	CST	27	NED	P	
3	A	SF	CR	CR	Biopsy	iFU	28	NED	P	
4	A	CR	LF	CR	iFU	More iFU	35	NED	N	
5	A	CR	RF	CR	iFU	Biopsy	32	AWD	N	Locoregional recurrence 30 mo later
6–9	A	CR	SF	CR	iFU	More iFU	16–28	NED	N	Pulmonary inflammation
10	A	CR	SF	CR	iFU	More iFU	15	NED	N	Inflammatory lumbar spine disease
11	A	CR	Second primary	CR	iFU	More iFU	21	NED	N	Rib fracture
12	B	CR	LF	LF	iFU	CST	6	DWD	P	
13	B	CR	RF	RF	iFU	CST	10	DWD	P	
14	B	CR	SF	SF	iFU	PT	20	AWD	P	Solitary hepatic metastasis
15	B	CR	SF	SF	iFU	PT	24	NED	P	Solitary bony metastasis at sacrum
16–32	B	EL or sLF	CR	CR	iFU	Less iFU	12–38	NED	P	
33	B	SF	CR	CR	PT	iFU	15	NED	P	
34	B	CR	Second primary	Second primary	iFU	Thyroidectomy	17	NED	P	Papillary thyroid carcinoma
35	B	CR	LF	CR	iFU	More iFU	27	NED	N	Osteoradionecrosis
36	B	CR	RF	CR	iFU	More iFU	32	AWD	N	Solitary rib metastasis 18 mo later
37	B	CR	SF	CR	iFU	More iFU	27	NED	N	Pulmonary inflammation

*See text for details.

CR = complete remission; CST = curative salvage treatment; EL = equivocal local lesion (score of 2); iFU = imaging follow-up; LF = local failure; LRF = locoregional failure; N = negative; P = positive; PT = palliative treatment; RF = regional failure; SF = systemic failure; sLF = suspected local failure (score of 3).

DISCUSSION

The efficacy of whole-body ^{18}F-FDG PET in patients with NPC after therapy is still unclear. The previous retrospective study of Yen et al. demonstrated a sensitivity of 92%, a specificity of 90%, and an accuracy of 91% for whole-body ^{18}F-FDG PET in detecting residual or recurrent NPC (*9*), but the timing of PET after treatment in that study varied from 4 to 70 mo, and the stages were not addressed. In light of the high cost of PET and the diverse failure rates in NPC patients at different stages, prospective studies on specific patient groups are necessary to optimize the use of ^{18}F-FDG PET.

Considering the high incidence of residual disease and distant metastases in patients with locoregional advanced NPC after therapy, we prospectively compared the efficacies of whole-body ^{18}F-FDG PET and CWU in these patients. In the present study, the overall sensitivity, specificity, and accuracy of PET were high and ranged from 91.7% to 100%. With respect to PET, the overall sensitivity of CWU was much lower. Up to 50% (8/16) of the sites of failure in the present study were missed by CWU. The overall specificity of CWU was significantly lower in group B ($P = 0.019$), a finding that was probably attributable to the significantly higher specificity of PET in evaluating the

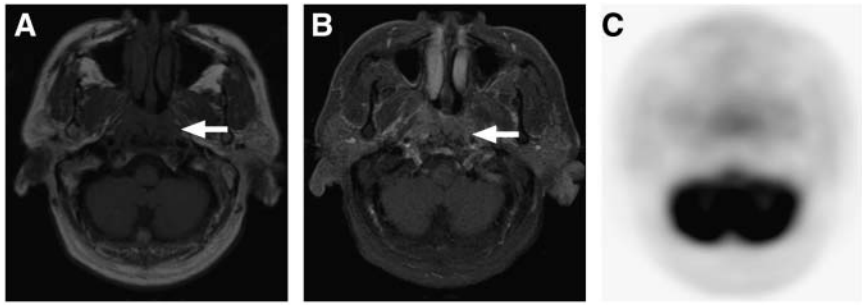

FIGURE 4. Data for 57-y-old patient with stage IVa NPC 3 mo after CCRT. Images from unenhanced (A) and enhanced (B) axial T1-weighted MRI revealed bulky soft-tissue mass (arrows) in nasopharynx with marrow replacement in underlying skull base, suggestive of residual tumor. (C) Corresponding PET image revealed no abnormal uptake of ^{18}F-FDG in this area. Lesion regressed on subsequent MRI scans.

local response in group B ($P = 0.04$). Similar results were reported in our previous study (*16*). By virtue of the higher specificity, the overall accuracy of PET was significantly higher than that of CWU in group B ($P = 0.002$). Conversely, PET provided less of a contribution with respect to response evaluation in group A.

The sensitivities of ^{18}F-FDG PET were higher than those of CWU at local, regional, or distant sites. Conversely, the specificities varied at different lesion sites. The specificity of PET was significantly higher than that of CWU in assessing the local site in group B. At the regional nodal site, the specificities of ^{18}F-FDG PET and CWU were similar. At the distant site, the specificity of PET was lower than that of CWU. The majority of FP PET results occurred in the lungs (5/6; 83.3%). We previously had reported rates of FP PET results of 50%–60% in assessing lung lesions in patients with stage M0 NPC (*7,10*). In the present study, the rates of FP results were even higher. All 5 pulmonary lesions suggested by PET were proven to be inflammation. The reason is not clear. However, it may be related to opportunistic infection caused by compromised immunity after CCRT. This drawback should be seriously regarded because the lungs are one of the most common sites for distant metastases from NPC. Other PET tracers with higher specificities for malignancy, such as ^{18}F-fluoroethyl-L-tyrosine or ^{18}F-fluorocholine, may be helpful in this respect (*21,22*).

^{18}F-FDG PET also played differential roles in patient management in the 2 groups studied here. In group A, only 4% of the patients had positive PET-related impacts. Thus, it seems that routine examination with PET after treatment is not cost-effective in this group. Conversely, PET-related positive impacts were found in 38% of the group B patients. The major positive impacts in this group fell into 2 categories. One was to reduce unnecessary imaging follow-up in patients with initial T4 disease ($n = 17$); the other was to disclose unexpected residual or second primary tumors ($n = 5$). Despite the high local failure rate for patients with stage IVa NPC, the accuracy of CWU in monitoring the local response is not satisfactory, even for MRI (*16–17*). Thus, it is difficult for a clinician to design a proper strategy for monitoring these patients. Close imaging follow-up is necessary for patients with equivocal (score 2) CWU findings because of the possibility of FN results. In contrast, biopsy may not be mandatory for every patient thought to have residual disease (score 3) because of the high rate of FP results. We previously had reported that ^{18}F-FDG PET showed a high accuracy in detecting local residual tumor in patients with stage IVa NPC (*16*). After knowing this advantage of PET, we began to reduce the frequency of imaging follow-up in these patients with negative PET results. In the present study, 17 patients with stage IVa NPC and with equivocal or probably abnormal MRI findings at the local site underwent fewer follow-up imaging scans because of negative PET results. All of them still remained disease free after being monitored for 12–38 mo.

Patients with stage IVa-b NPC run a greater risk of treatment failure than do patients with other stage M0 NPCs. In the present study, 15% (9/60) of the patients with initial stage IVa-b disease still had residual tumors after treatment. Without PET, 44% (4/9) of them would not have been identified. On the basis of these benefits, patients with stage IVa-b NPC at our center are encouraged to receive ^{18}F-FDG PET after therapy at the present time.

A debatable issue is the standard CWU modalities for NPC. At some centers, chest CT and abdominal CT are used instead of chest radiography and abdominal sonography to evaluate metastases in the lungs and liver. CT has been shown to have a higher accuracy in detecting liver and lung metastases for many cancers. However, a very low yield of contrast-enhanced CT of the thorax in staging advanced NPC has been reported (*23*). Chest radiography and abdominal sonography are still commonly used in areas in which NPC is endemic, even in recent prospective studies (*24–26*). Thus, the benefit of CT for detecting lung or liver metastases in NPC patients is not well established yet and deserves further exploration.

The detection rate would change if the rate of treatment failure varied. In the present study, all patients received whole-body ^{18}F-FDG PET for primary staging. We previously had reported that PET could aid in revealing distant metastases in 11% (10/95) of patients with negative CWU findings (*7*) and regional nodal metastases in 12% (12/101) of patients with negative MRI findings (*27*). Consequently, the number of patients with subclinical distant and neck node diseases in the present study would be smaller than that in other series without staging by PET; thus, a better treatment outcome might be achieved. Also, all of our patients received IMRT with concomitant chemotherapy, and half of the patients with stage IVa-b NPC also underwent induction chemotherapy. Such multidisciplinary therapy might improve the outcome of treatment. Therefore, our data should be interpreted with caution because of the diverse staging and treatment modalities among different centers. Further studies with a larger patient population and longer follow-up times are necessary to confirm these preliminary results and determine the prognostic value of PET.

CONCLUSION

The roles of ^{18}F-FDG PET in patients with stage III NPC and stage IVa-b NPC after primary curative therapy are different. Both the sensitivity and the specificity of PET in revaluating the treatment response for patients with stage IVa-b NPC were higher than those of CWU. For patients with stage III NPC, the sensitivity of PET was higher, but the specificities of PET and CWU were similar. PET resulted in positive impacts on management in one third of patients with stage IVa-b NPC. The main positive impacts were reducing unnecessary imaging follow-up in patients with T4 disease and disclosing unexpected residual or

second primary tumors. Conversely, the impact on patients with stage III NPC was less prominent.

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