NASOPHARYNGEAL CARCINOMA SPECIAL FEATURE: FULL PAPER

Clinical significance of the post-radiotherapy 18F-fludeoxyglucose positron emission tomography response in nasopharyngeal carcinoma

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Objective: The aim of the present study was to evaluate the clinical significance of the post-radiotherapy 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) response for detecting residual disease and predicting survival outcome in patients with nasopharyngeal cancer.

Methods: We reviewed 143 patients with nasopharyngeal cancer who underwent 18F-FDG PET within 6 months after completion of radiotherapy between 2001 and 2012. 18F-FDG PET findings at the primary tumor (T–) and regional lymph nodes (N–) were separately assessed and considered negative [PET (–)] or positive [PET (+)] depending on the remaining focal increased uptake of 18F-FDG that was greater than that of the surrounding muscle or blood vessels. The standard of reference was histopathological confirmation or clinical/imaging follow-up. Overall survival (OS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRRFS) rates were estimated from the date of the start of radiotherapy.

Results: The median follow-up period was 73 months (range, 9–182 months). Overall, 83 and 66% of patients achieved T–PET (-) and N–PET (-) responses, and the negative-predictive values (NPVs) for T– and N– were 100 and 99%, respectively. The sensitivity, specificity, and positive-predictive value were 100, 84, and 8% for T–, and 67, 80, and 7% for N–, respectively. The 5-year OS, DMFS, and LRRFS rates were 83, 83, and 87%, respectively, and patients with N–PET (+) with SUV_{max} >2.5 showed significantly inferior 5-year OS and DMFS rates than patients with N–PET (-) or N–PET (+) with SUV_{max} ≤2.5 (44 *vs* 86%, *p* = 0.004; 36 *vs* 85%, *p* < 0.001).

Conclusion: In patients that have received definitive (chemo)radiotherapy for nasopharyngeal cancer, 18F-FDG PET within 6 months of completion of treatment has a high NPV for predicting residual disease and is prognostic for long-term treatment outcomes. Patients with remaining focal increased uptake of 18F-FDG at lymph nodes may benefit from more aggressive treatments, and further studies are needed to validate the clinical significance of post-radiotherapy 18F-FDG PET.

Advances in knowledge: We found that post-radiotherapy 18F-FDG PET findings have a high NPV for detecting residual disease and are a significant prognostic factor for treatment outcomes.

INTRODUCTION

Nasopharyngeal cancer is an uncommon cancer with a distinct geographic distribution.[1] The standard treatment is radiotherapy or concurrent chemoradiotherapy, and CT and/or MRI have been used to evaluate the treatment response. These evaluations are mainly based on morphology and are thus, somewhat limited in their ability to differentiate post-radiotherapy tissue changes such as edema, fibrosis, and necrosis from residual or

recurrent disease. Moreover, tumor regression may continue for several months after radiotherapy. Because viable tumor lesions may have higher glucose metabolism than post-radiotherapy tissue and because post-radiotherapy metabolic changes may precede morphologic tumor regression, several studies have compared the diagnostic accuracy of post-radiotherapy 18F-FDG PET with that of CT and/or MRI.[2–9] However, in most studies, because the diagnostic accuracies of residual disease and recurrent disease were analyzed together as

a group,[2,3,5,8–12] the ability of the post-radiotherapy ^{18}F-FDG PET response to detect residual disease remains unclear. Only a few studies have evaluated the role of the post-radiotherapy ^{18}F-FDG PET response in detecting residual disease, mainly at the primary tumor site, with a ^{18}F-FDG PET timing of 3 months after radiotherapy completion, despite the lack of studies investigating the optimal timing of ^{18}F-FDG PET for response evaluation in nasopharyngeal cancer.[6,7,13,14] More-over, to our knowledge, only one study has investigated the prognostic value of the post-radiotherapy ^{18}F-FDG PET response for predicting survival outcomes.[13]

Therefore, in the present study, we evaluated (1) the clinical significance of the post-radiotherapy ^{18}F-FDG PET response for detecting residual disease at primary tumors as well as at regional lymph nodes (LNs) and for predicting survival outcomes in patients with nasopharyngeal cancer, and (2) the clinical signifi-cance of the post-radiotherapy ^{18}F-FDG PET response depending on the timing of post-radiotherapy ^{18}F-FDG PET.

PATIENTS AND METHODS
Patients
We retrospectively reviewed patients with non-disseminated nasopharyngeal cancer who were treated with definitive radio-therapy and underwent post-radiotherapy ^{18}F-FDG PET eval-uation at Asan Medical Center between December 2001 and December 2012. Among a total of 149 patients who were treated between December 2001 and December 2012, 6 were excluded due to the ^{18}F-FDG PET timing of >6 months after radiotherapy completion ($n = 5$) and a follow-up period of <6 months ($n = 1$). Finally, 143 patients were included. Patients underwent pretreat-ment evaluations including medical history, physical examina-tion, laboratory tests, fiberoptic nasopharyngoscopy with biopsy, CT and/or MRI of the head and neck, chest radiography, and ^{18}F-FDG PET. The stage was determined by the seventh edition of the AJCC staging system. This study was approved by the Insti-tutional Review Board of Asan Medical Center, and the need for written informed consent was waived due to the retrospective nature of the study.

TREATMENT
The treatment details were described in our previous reports.[15,16] Radiotherapy was performed with 6- or 15 MV photon beams from a linear accelerator (Varian, Palo Alto, CA), and most patients (90.9%) were treated with intensity-modulated radi-ation therapy. The total radiation dose was typically 70–78 Gy for the gross tumor volume, 60 Gy for a high-risk clinical target volume, and 46 Gy for a low-risk clinical target volume. During radiotherapy, concurrent chemotherapy with cisplatin was delivered every week (40 mg m^{-2}) or every 3 weeks (80 mg m^{-2} or 100 mg m^{-2}). In some patients, cisplatin based chemo-therapy was performed before radiotherapy. Concurrent and/or induction chemotherapy was performed depending on the stage, organ function, and physician's decision. During the treatment, patients were interviewed weekly with evaluations including complete blood count, body weight, and a physical examination.

^{18}F-FDG PET IMAGING AND INTERPRETATION
The ^{18}F-FDG PET imaging details were described in our previous reports.[15,16] Patients were instructed to fast for at least 6 h, and all patients had serum glucose concentrations of <150 mg dl^{-1}. The emission scans were performed 50–70 min after the intra-venous administration of ^{18}F-FDG (approximately, 7.4 MBq per kilogram of body weight) from the skull base to the prox-imal thigh. Before November 2004, ^{18}F-FDG PET scans were performed using an ECAT HR+ (Siemens Medical Systems). After December 2004, ^{18}F-FDG PET/CT scans were performed either with a Biograph Sensation 16, Biograph TruePoint 40 (Siemens Medical Systems), Discovery 690, or Discovery STE 8 (GE Medical Systems). Post-radiotherapy ^{18}F-FDG PET findings were separately assessed for primary tumors (T–) and regional LNs (N–) and considered negative [T–PET (-) and N–PET (-)] or positive [T–PET (+) and N–PET (+)] depending on the remaining focal or asymmetric increased uptake of ^{18}F-FDG that was greater than that of the surrounding muscle or blood vessels. For patients with positive ^{18}F-FDG PET findings, maximum standardized uptake values (SUV$_{max}$) were calculated. We also defined stricter secondary PET (+) criteria that only included focal increased uptake of ^{18}F-FDG with SUV$_{max}$ >3 for T– [T–PET (+, SUV3) *vs* T–PET (-, SUV3)] and SUV$_{max}$ >2.5 for N– [N–PET (+, SUV2.5) *vs* N–PET (–, SUV2.5)]. Figure 1 shows representative post-radiotherapy ^{18}F-FDG PET findings for primary tumors and regional LNs. The post-radiotherapy ^{18}F-FDG PET findings were retrospectively reviewed by a board-cer-tified radiation oncologist (YJ) and were cross-referenced with the original clinical ^{18}F-FDG PET reports.

FOLLOW-UP
1 month after the completion of radiotherapy, physical examina-tion and fiberoptic nasopharyngoscopy were performed; post-ra-diotherapy ^{18}F-FDG PET evaluations were typically performed 1–3 months after completion of radiotherapy. The standard of reference for residual disease was histopathological confirmation or progression on clinical/imaging follow-up within 6 months after completion of radiotherapy. In patients with T–PET (+) findings or suspicious residual lesions on CT or MRI, and biopsy was performed depending on the findings of fiberoptic nasopha-ryngoscopy. Mucosal irregularity or a protruding lesion on fiber-optic nasopharyngoscopy was considered abnormal findings, and biopsy was performed for that lesion. If the biopsy result was positive, salvage wide excision was considered. Neck ultra-sonography was performed in patients with N–PET (+) findings or persistent cervical lymphadenopathy on physical examina-tion, CT, or MRI, and percutaneous needle aspiration biopsy was performed, except for definitely benign LNs that were oval in shape and had a central echogenic fatty hilum. If the biopsy results were positive, salvage neck dissection was considered. Patients were followed up periodically at 3 month intervals for the first 3 years and every 6 months or 1 year thereafter with physical examinations and fiberoptic nasopharyngoscopy with or without CT, MRI, or ^{18}F-FDG PET.

STATISTICS
The sensitivity, specificity, positive-predictive value (PPV), and negative-predictive value (NPV) for detecting residual disease

Figure 1. Representative post-radiotherapy ^{18}F-FDG PET findings for primary tumors and regional LNs. (a) Negative ^{18}F-FDG PET finding for primary tumor [T–PET (-)] (b) Positive ^{18}F-FDG PET finding for primary tumor [T–PET (+)] with SUVmax >3 [T–PET (+, SUV3)] (c) Positive ^{18}F-FDG PET finding for primary tumor (T–PET (+)), but SUVmax ≤ 3 [T–PET (–, SUV3)] (d) Negative ^{18}F-FDG PET finding for regional LNs (N–PET (–)) (e) Positive ^{18}F-FDG PET finding for regional LNs [N–PET (+)] with SUVmax >2.5 [N–PET (+, SUV2.5)] (f) Positive ^{18}F-FDG PET finding for regional LNs [N–PET (+)], but SUVmax ≤ 2.5 [T–PET (–, SUV2.5)]. ^{18}F-FDG PET, fludeoxyglucosepositron emission tomography; LN, lymph node; SUV, standardized uptake value.
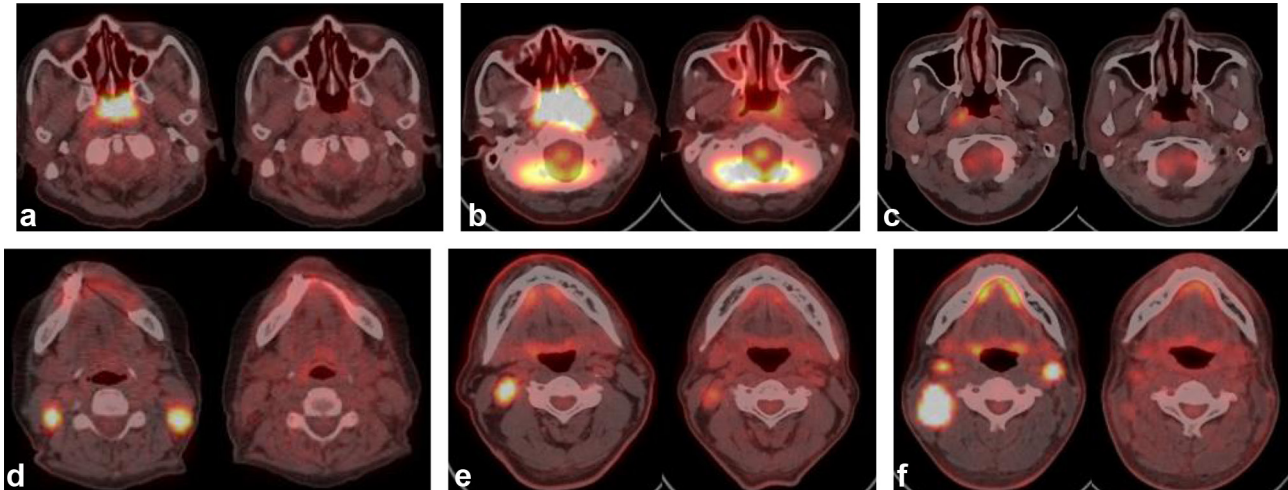
were separately calculated for T– and N–. Overall survival (OS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRRFS) rates were estimated from the date of the start of radiotherapy to the date of death from any cause or last follow-up, to the date of distant metastasis (DM) or last follow-up, to the date of locoregional recurrence (LRR) or last follow-up, respectively, by the Kaplan-Meier method. Univariate and multivariate analyses by Cox proportional hazards models were performed to evaluate the prognostic impact of post-radiotherapy ^{18}F-FDG PET findings and other clinical variables on survival outcomes, and log-rank tests were performed to compare survival outcomes. We also performed subgroup analyses depending on the timing of the post-radiotherapy ^{18}F-FDG PET evaluation (before 1.5 months *vs* after, and before 3 months *vs* after). Multivariate Cox proportional hazards models were built with clinical variables with a *p*value of < 0.1 by univariate analysis. All statistical tests were 2-sided and performed at the 5% level of significance using SPSS version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

The median patient age was 49 years and the male/female ratio was 2.8. The overall stages were I, II, III, and IV in 7, 20, 40, and 33% of patients, respectively, and most patients (92%) received concurrent chemoradiotherapy (Table 1). Residual diseases were proven in three patients, and sites of residual diseases were regional LNs in one patient and both the primary tumor and regional LNs in two patients. The remaining 140 patients (98%) were considered to have no residual disease after clinical and imaging follow-up of at least 6 months.

The median interval from completion of radiotherapy to post-radiotherapy ^{18}F-FDG PET was 1.4 months (range, 0.6–5.2 months). The PET timings were <1.5 *vs* ≥1.5 months after completion of radiotherapy in 73 *vs* 70 patients, respectively, and

Table 1. Patient characteristics

Characteristics	No. (%)
Age (years)	
Median (range)	49 (13–78)
Gender	
Male/fFemale	105 (73)/38 (27)
T stage (AJCC seventh)	
T1/T2/T3/T4	42 (29)/31 (22)/35 (25)/35 (25)
N stage (AJCC seventh)	
N0/N1/N2/N3	21 (15)/46 (32)/57 (40)/19 (13)
Overall stage (AJCC seventh)	
I/II/III/IV	10 (7)/29 (20)/57 (40)/47 (33)
Pathologic classification	
Keratinizing squamous cell carcinoma	5 (4)
Non-keratinizing carcinoma	119 (83)
Basaloid squamous cell carcinoma	1 (1)
Unspecified	18 (13)
Radiotherapy dose (Gy)	
Median (range)	70 (64–78)
Induction chemotherapy	
Yes/No	36 (25)/107 (75)
Concurrent chemoradiotherapy	
Yes/No	132 (92)/11 (8)

AJCC, American Joint Committee on Cancer.

<3 *vs* ≥3 months after completion of radiotherapy in 123 *vs* 20 patients, respectively. The diagnostic values of post-radiotherapy ^{18}F-FDG PET findings for detecting residual disease are shown in Table 2. For primary tumors, 119 patients (83%) achieved T–PET (-) responses and 24 patients (17%) were T–PET (+) with a median SUV_{max} of 3.4 (range, 1.6–4.8). In 119 patients with T–PET (-), no residual disease was confirmed at least 6 months after completion of radiotherapy, giving a NPV of 100%. Among 24 patients with T–PET (+) findings, 22 patients were examined with fiberoptic nasopharyngoscopy, and biopsies were performed for 4 patients with abnormal findings. Two patients were pathologically confirmed to have residual disease, and the SUV_{max} of these patients were 3.9 and 4.7 on ^{18}F-FDG PET obtained 3.7 months and 1.1 months after radiotherapy, respectively. For the remaining 22 patients with T–PET (+) findings, no residual diseases were confirmed at least 6 months after completion of radiotherapy. The sensitivity, specificity, and PPV were 100, 84, and 8%, respectively. When we applied T–PET (+, SUV3) criteria, specificity and PPV increased to 91 and 13%, but the ^{18}F-FDG PET findings were still false positive in 13 patients. The prevalence of residual disease at the primary site was similar between PET timings of <1.5 months and ≥1.5 months (1.4 *vs* 1.4%), but different between PET timings of <3 months and ≥3 months (0.8 *vs* 5.0%). Depending on the PET timing, in patients with PET timing of <1.5 months, the PPV and NPV were 8 and 100% according to T–PET (+) criteria, and 13 and 100% according to T–PET (+, SUV3) criteria. In patients with PET timing of ≥1.5 months, the PPV and NPV were 9 and 100% according to T–PET (+) criteria, and 14 and 100% according to T–PET (+, SUV3) criteria. PPVs increased to 25 and 50% on ^{18}F-FDG PET scans obtained ≥3 months after radiotherapy according to the T–PET (+) and T–PET (+, SUV3) criteria, respectively.

For regional LNs, 113 patients (79%) achieved N–PET (-) responses and 30 patients (21%) were N–PET (+) with a median SUV_{max} of 2.3 (range, 1.4–5.6). Among 113 patients with N–PET (-), residual disease was pathologically confirmed in 1 patient. That patient had no focal increased uptake of ^{18}F-FDG 1.3 months after completion of radiotherapy, but cervical lymphadenopathy was persistent on physical examination and CT 4.3 months after completion of radiotherapy. In the remaining 112 patients, no residual disease was confirmed at least 6 months after completion of radiotherapy, giving a NPV of 99%. Among 30 patients with N–PET (+), residual diseases were confirmed in 2 patients by pathologic confirmation (*n* = 1) or progression on follow-up imaging (*n* = 1), and these 2 patients were the same patients who had residual disease at primary tumor sites. The SUV_{max} were 2.9 and 1.7 on ^{18}F-FDG PET 3.7 months and 1.1 months after radiotherapy, respectively. The sensitivity, specificity, and PPV were 67, 80, and 7%, respectively. When we applied N–PET (+, SUV2.5) criteria, the sensitivity, specificity, PPV, and NPV were 33, 94, 11, and 99%, respectively. In nine patients with N–PET (+, SUV2.5) findings, we prescribed neck ultrasonography, and eight of nine patients underwent neck ultrasonography. Except for two patients with LN appearance of definitely benign, biopsies were performed in six patients, and results were negative in four patients and positive in two patients. Among two patients with positive result, one patient with an initial stage of T2N1M0,

who had positive biopsy result on LN with SUV_{max} of 3.8 on ^{18}F-FDG PET obtained at 1.6 months, experienced negative conversion of biopsy result at 7.7 months after radiotherapy. In that patient, during the delay of salvage neck dissection due to general weakness, the size of the LN was decreased and the biopsy result had converted to negative. Although DM developed 20.4 months after radiotherapy, no regional recurrence occurred during the follow-up period of 92.9 months. The prevalence of residual disease at LNs was 2.7 *vs* 1.4% for PET timings of <1.5 *vs* ≥1.5 months and 1.6 *vs* 5.0% for PET timings of <3 *vs* ≥3 months. Depending on the PET timing, in patients with PET timing of <1.5 months, the PPV and NPV were 5 and 98% according to N–PET (+) criteria, and 0 and 97% according to N–PET (+, SUV2.5) criteria. In patients with PET timing of ≥1.5 months, the PPV and NPV were 9 and 100% according to N–PET (+) criteria, and 25 and 100% according to N–PET (+, SUV2.5) criteria. PPVs increased to 50 and 100% on ^{18}F-FDG PET obtained ≥3 months after radiotherapy according to N–PET (+) and N–PET (+, SUV2.5) criteria, respectively.

The median follow-up period was 73 months (range, 9–182 months), and the patterns of failure were LRR, DM, and both in 12 (8%), 20 (14%), and 5 (4%) patients, respectively. The 5year OS, DMFS, and LRRFS rates were 83, 83, and 87%, respectively (Figure 2A). The results of univariate and multivariate analyses for survival outcomes are presented in Tables 3 and 4. In multivariate analysis, age, overall stage, and N–PET (+, SUV2.5) were significant prognostic factors for OS with hazard ratio (HR) of 1.046, 4.308, and 5.523, respectively. The 5-year OS rates were significantly inferior in patients with N–PET (+, SUV2.5) than in patients with N–PET (-, SUV2.5) (44 *vs* 86%, *p* = 0.004) (Figure 2B). Regarding DMFS, sex, N stage, and N–PET (+, SUV2.5) were significant prognostic factors with HR of 6.381, 8.005, and 8.816, respectively. The 5-year DMFS rates were significantly inferior in patients with N–PET (+, SUV2.5) than in patients with N–PET (-, SUV2.5) (36 *vs* 85%, *p* < 0.001) (Figure 2C). Regarding LRRFS, T stage (HR = 3.093) was a significant prognostic factor. In the subgroup analysis of patients with a PET timing of <1.5 months, N–PET (+) (HR = 5.695, *p* = 0.046) and T stage (HR = 6.013, *p* = 0.039) were significant prognostic factors for LRRFS in multivariate analysis. Patients with N–PET (+) on ^{18}F-FDG PET obtained <1.5 months after radiotherapy had inferior LRRFS than patients with N–PET (-) (5-year LRRFS, 96 *vs* 75%, *p* = 0.011) (Figure 2D). However, neither N–PET (+) nor T stage was a significant prognostic factor for LRRFS in patients with a PET timing of ≥1.5 months, and 5 year LRRFS rates of N–PET (-) and N–PET (+) were not significantly different (84 and 82%, *p* = 0.804) (Figure 2E).

DISCUSSION

In our present study, the post-radiotherapy ^{18}F-FDG PET response showed a high NPV for residual disease at primary tumors (100%) as well as at regional LNs (99%), regardless of its timing (before 1.5 months *vs* after, and before 3 months *vs* after). These excellent NPVs were similar to the findings of previous meta-analyses of the role of post-radiotherapy ^{18}F-FDG PET in head and neck cancer.[17–19] The reported pooled mean NPVs ranged from 95 to 96.3% for T– and from 88.3 to

Table 2. Diagnostic values of post-radiotherapy ^{18}F-fludeoxyglucose PET for detecting residual disease

Site	PET (+) criteria	PET timing, months	Residual disease (%)	True-positive	False-positive	True-negative	False-negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Primary tumor	T–PET (+) : focal uptake (+)	Overall (n = 143)	2 (1.4)	2	22	119	0	100	84	8	100
		<1.5 (n = 73)	1 (1.4)	1	12	60	0	100	83	8	100
		≥1.5 (n = 70)	1 (1.4)	1	10	59	0	100	86	9	100
		<3.0 (n = 123)	1 (0.8)	1	19	103	0	100	84	5	100
		≥3.0 (n = 20)	1 (5.0)	1	3	16	0	100	84	25	100
	T–PET (+, SUV3) : focal uptake (SUV$_{max}$ >3)	Overall (n = 143)	2 (1.4)	2	13	128	0	100	91	13	100
		<1.5 (n = 73)	1 (1.4)	1	7	65	0	100	90	13	100
		≥1.5 (n = 70)	1 (1.4)	1	6	63	0	100	91	14	100
		<3.0 (n = 123)	1 (0.8)	1	12	110	0	100	90	8	100
		≥3.0 (n = 20)	1 (5.0)	1	1	18	0	100	95	50	100
Lymph node	N–PET (+) : focal uptake (+)	Overall (n = 143)	3 (2.1)	2	28	112	1	67	80	7	99
		<1.5 (n = 73)	2 (2.7)	1	18	53	1	50	75	5	98
		≥1.5 (n = 70)	1 (1.4)	1	10	59	0	100	86	9	100
		<3.0 (n = 123)	2 (1.6)	1	27	94	1	50	78	4	99
		≥3.0 (n = 20)	1 (5.0)	1	1	18	0	100	95	50	100
	N–PET (+, SUV2.5) : focal uptake (SUV$_{max}$ >2.5)	Overall (n = 143)	3 (2.1)	1	8	132	2	33	94	11	99
		<1.5 (n = 73)	2 (2.7)	0	5	66	2	0	93	0	97
		≥1.5 (n = 70)	1 (1.4)	1	3	66	0	100	96	25	100
		<3.0 (n = 123)	2 (1.6)	0	8	113	2	0	93	0	98
		≥3.0 (n = 20)	1 (5.0)	1	0	19	0	100	100	100	100

PET, positron emission tomography; SUV$_{max}$, maximum standardized uptake value.

Figure 2. Survival outcomes. (A) OS, DMFS, and LRRFS rates in all patients. (B) OS rates depending on the post-radiotherapy ^{18}F-FDG PET finding at regional LNs. (C) DMFS rates depending on the post-radiotherapy ^{18}F-FDG PET finding at regional LNs. (D) LRRFS rates depending on the post-radiotherapy ^{18}F-FDG PET finding at regional LNs in patients who underwent an ^{18}F-FDG PET evaluation <1.5 months after radiotherapy. (E) LRRFS rates depending on the post-radiotherapy ^{18}F-FDG PET finding at regional LNs in patients who underwent an ^{18}F-FDG PET evaluation ≥1.5 months after radiotherapy. ^{18}F-FDG PET, fludeoxyglucosepositron emission tomography; DMFS, distant metastasis-free survival; LN, lymph node; LRRFS, locoregional recurrence-free survival; OS, overall survival.
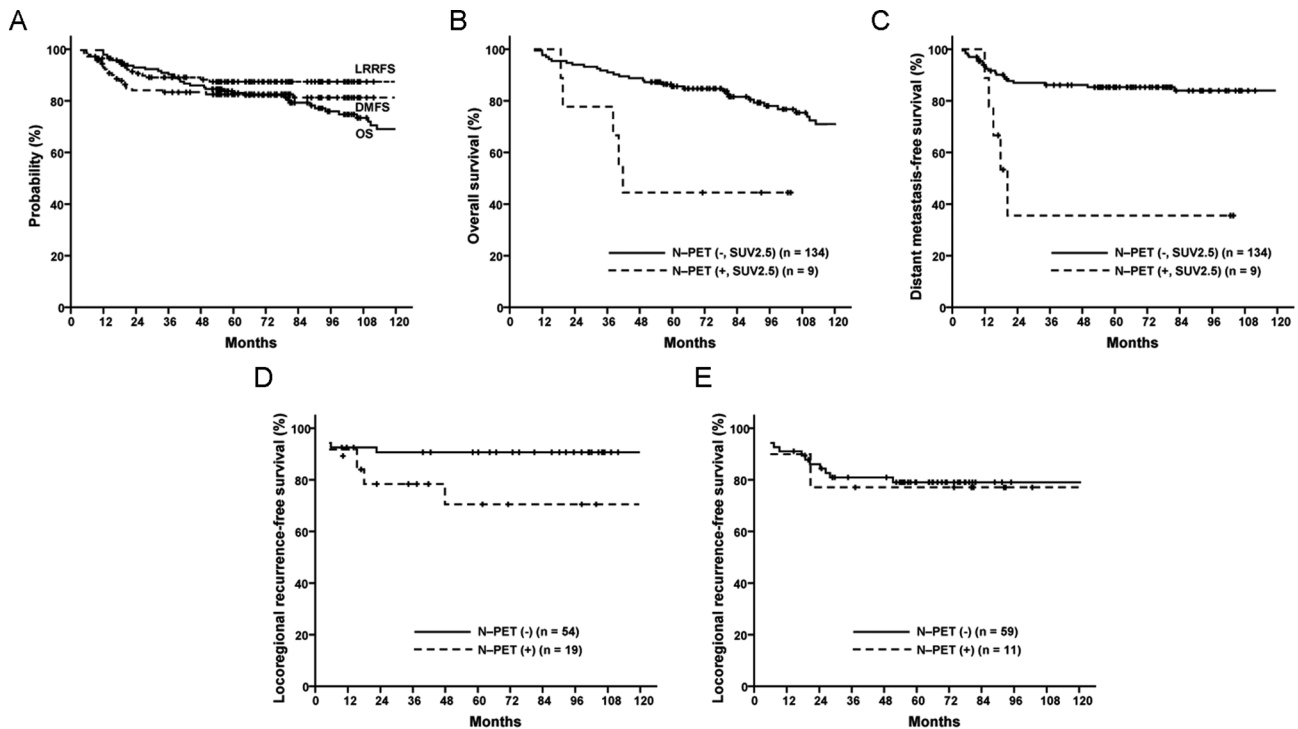
96% for N−, and these meta-analyses concluded that negative post-radiotherapy findings might be highly suggestive of the absence of viable tumors. Recently, Mehanna et al randomized patients with squamous cell carcinoma of oropharynx, hypopharynx, and larynx, who had advanced nodal disease and received chemoradiotherapy, to planned neck dissection *vs* PET-CT-guided surveillance.[20] In PET-CT-guided surveillance group, neck dissection performed only in patients without complete response on PET-CT at 12 weeks after chemoradiotherapy, but survival rate was similar with that in the planned neck dissection group. In contrast to our current findings, several previous studies have reported high false-negative rates ranging from 20 to 86% for an early ^{18}F-FDG PET response <3 months after completion of radiotherapy.[21–26] The difference in the NPV of an early ^{18}F-FDG PET response between these earlier studies and our current analysis may have two possible explanations. First, because the reference standard of those studies, with the exception of the study by Greven et al, were planned neck dissections performed 6 to 12 weeks after completion of radiotherapy, some patients with delayed histologic remission, who showed positive histology at 6 to 12 weeks but might have achieved spontaneous histologic remission afterward, might have been considered false-negative.[21–26] Second, because the biologic characteristics of nasopharyngeal cancer differ from those of other head and neck cancers, the NPV of an early ^{18}F-FDG PET response in the present study might not be the same as that in previous studies that included various types of head and neck cancers. In the earlier studies, nasopharyngeal cancers were only a small portion of the samples or were excluded.[21–26] Although, regarding the role of an early ^{18}F-FDG PET response, no study has only included nasopharyngeal cancers, two prospective studies, in which half of patients had nasopharyngeal cancer, reported excellent NPVs of 98.5 to 100%, similar to those of our present study.[27,28]

The PPV of post-radiotherapy ^{18}F-FDG PET has been considered suboptimal. In meta-analyses for head and neck cancer, the pooled mean PPVs ranged from 52.7 to 75% for T− and from 49 to 72.3% for N−.[17–19] In our present study, the PPVs were 8 and 7% for T− and N−, respectively, which are low compared with previous findings. The poor PPVs in the current study might be related to several factors. First, the prevalence of residual disease was as low as 2% for T− and 3% for N−. Second, we did not use background liver activity for the definition of PET (+) criteria. In some recently reported studies, positive PET findings were differentiated from equivocal PET findings defined as a focal increased uptake of ^{18}F-FDG greater than surrounding normal tissue activity but less than liver background activity. The PPVs ranged from 43 to 63% when equivocal PET findings were classified as positive PET findings and from 71.1 to 77.8% when equivocal PET findings were classified as negative PET findings.[29–32]

Table 3. Univariate Cox proportional hazards model for survival rates

Factors	Overall survival rates		Distant metastasis-free survival rates		Locoregional recurrence-free survival rates	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	1.043 (1.018–1.069)	0.001[*]	0.992 (0.966–1.018)	0.544	1.015 (0.981–1.050)	0.405
Male	1.582 (0.733–3.412)	0.242	4.666 (1.100–19.796)	0.037[*]	1.805 (0.519–6.281)	0.353
T4	1.642 (0.852–3.165)	0.138	1.276 (0.533–3.056)	0.584	3.093 (1.192–8.027)	0.020[*]
N2-3	1.997 (1.064–3.750)	0.031[*]	5.190 (1.781–15.127)	0.003[*]	2.268 (0.799–6.443)	0.124
Overall Stage III-IV	3.457 (1.357–8.806)	0.009[*]	10.326 (1.397–76.351)	0.022[*]	1.890 (0.543–6.579)	0.317
Radiotherapy dose	1.000 (0.998–1.001)	0.451	1.000 (0.998–1.001)	0.661	1.000 (0.998–1.002)	0.819
Induction chemotherapy	0.632 (0.309–1.295)	0.210	0.875 (0.349–2.193)	0.776	1.622 (0.600–4.386)	0.341
Concurrent chemoradiotherapy	1.088 (0.336–3.522)	0.888	1.053 (0.248–4.469)	0.944	0.660 (0.151–2.885)	0.580
T–PET (+)	1.273 (0.624–2.599)	0.507	0.989 (0.339–2.883)	0.983	1.604 (0.523–4.921)	0.408
T–PET (+, SUV3)	1.707 (0.756–3.851)	0.198	1.312 (0.392–4.388)	0.660	2.092 (0.601–7.280)	0.246
N–PET (+)	2.084 (1.100–3.948)	0.024[*]	2.020 (0.871–4.685)	0.101	2.324 (0.859–6.288)	0.097
N–PET (+, SUV2.5)	3.747 (1.437–9.772)	0.007[*]	5.011 (1.851–13.562)	0.002[*]	1.064 (0.141–8.029)	0.952

[*] $p < 0.05$
PET, positron emission tomography; SUV, standardized uptake value; CI, confidence interval.

Table 4. Multivariate Cox proportional hazards model for survival rates

| Factors | Overall survival rates | | Distant metastasis-free survival rates | | Locoregional recurrence-free survival rates | |
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	1.046 (1.021–1.070)	<0.001[*]				
Male			6.381 (1.481–27.490)	0.013[*]		
T4					3.093 (1.192–8.027)	0.020[*]
N2-3	1.196 (0.575–2.489)	0.632	8.005 (2.615–24.501)	<0.001[*]		
Overall stage III-IV	4.308 (1.669–11.119)	0.003[*]	4.538 (0.472–43.679)	0.190		
N–PET (+)					2.183 (0.805–5.920)	0.125
N–PET (+, SUV2.5)	5.523 (2.053–14.862)	0.001[*]	8.816 (3.030–25.653)	<0.001[*]		

[*]$p < 0.05$
CI, confidence interval; PET, positron emission tomography; SUV, standardized uptake value.

Considering previously reported results, the PPVs might be increased if we excluded equivocal PET findings from the definition of positive PET criteria, but the PPVs in that studies seemed also to be suboptimal to determine the necessity of salvage treatment. Further studies appear to be needed to evaluate the appropriate interpretation and management of equivocal PET findings. Third, the timings of PET were typically 1–3 months after completion of radiotherapy, somewhat earlier than the generally recommended timing. When we performed subgroup analysis according to PET timing, the PPV of PET with a timing ≥3 months was similar to that of previous studies and better than that of PET with a timing <3 months (25 *vs* 5% for T–; 50 *vs* 4% for N–). However, direct comparison of the value of post-radiotherapy ^{18}F-FDG PET by timing obtained is inappropriate due to the selection bias from the retrospective nature of present study. In patients with a PET timing ≥3 months, the prevalence of residual disease was also higher than in patients with a PET timing <3 months for both T– (5 *vs* 0.8%) and N– (5 *vs* 1.6%), respectively, and these differences in the prevalence might contribute to the superiority of PPV in PET with a timing of ≥3 months. Although the optimal time for post-radiotherapy ^{18}F-FDG PET evaluations remains to be established, most studies recommended that the first follow-up ^{18}F-FDG PET be performed 3 months after completion of radiotherapy to reduce false-positive findings by post-radiotherapy inflammatory reactions. However, even in studies that evaluated the role of delayed post-radiotherapy ^{18}F-FDG PET performed 4 months after radiotherapy, the PPVs ranged from 19 to 47% for T– and from 29 to 63% for N–,[30,31,33] ant that still seem to be suboptimal to determine the necessity of salvage treatment. Further less invasive evaluations are needed for the positive post-radiotherapy ^{18}F-FDG PET response to rule out false-positive findings.

The ^{18}F-FDG PET is based on metabolic activity and may reflect biologic aggressiveness. Numerous studies have investigated the prognostic values of pretreatment ^{18}F-FDG PET, but to our knowledge, only one earlier study has investigated the prognostic value of the post-radiotherapy ^{18}F-FDG PET response in predicting survival outcomes in nasopharyngeal cancers.[13] In the study by Chan et al,[13]

which included 165 patients with locoregionally advanced nasopharyngeal cancers, complete metabolic remission was a significant prognostic factor for disease-free survival and OS. In our present study, the post-radiotherapy ^{18}F-FDG PET response at regional LNs was a significant prognostic factor for survival outcomes [N–PET (+, SUV2.5) for OS and DMFS in overall patients; N–PET (+) for LRRFS in patients with a PET timing <1.5 months], even though it had a poor PPV for the detection of residual disease. When we consider that N–PET (+, SUV2.5) and N–PET (+) had limited PPVs of 11 and 7%, most N–PET (+, SUV2.5) and N–PET (+) responses seemed to be related to the delayed regression of metabolic activity and/or inflammatory reactions at regional LNs, rather than the presence of viable residual tumors, and this delayed regression might translate into poor survival outcomes. Further studies seem to be needed to determine the prognostic value of delayed regression of metabolic activity and/or inflammatory reactions on regional LNs and to demonstrate whether patients with remaining focal increased uptake of ^{18}F-FDG at LNs benefit from more aggressive treatments.

Our current study had some notable limitations. First, because of the retrospective nature of our analysis, patient and treatment characteristics were heterogeneous. Second, because of the long inclusion period, from 2001 to 2012, various types of ^{18}F-FDG PET scanners were used. There might be interscanner variability as well as biological and technological variabilities. Third, we did not use background liver activity for the definition of PET (+) criteria. Nevertheless, our present report is one of the few studies to date to evaluate the clinical significance of the post-radiotherapy ^{18}F-FDG PET response for detecting residual disease in nasopharyngeal cancers and included a relatively large number of patients with long-term follow-up. Moreover, we also investigated the prognostic value of the post-radiotherapy ^{18}F-FDG PET response for predicting survival outcomes, and ^{18}F-FDG PET responses were separately assessed for primary tumors and regional LNs. In addition, to our knowledge, our current study is one of the few studies to investigate the clinical significance of the post-radiotherapy ^{18}F-FDG PET response according to the timing of post-radiotherapy ^{18}F-FDG PET in nasopharyngeal cancers.

CONCLUSIONS

Post-radiotherapy ^{18}F-FDG PET findings have high NPVs for the detection of residual disease and are a significant prognostic factor for OS and DMFS. Patients with residual focal increased uptake of ^{18}F-FDG at LNs may benefit from more aggressive treatments, and further studies seem to be needed to validate the clinical significance of post-radiotherapy ^{18}F-FDG PET.

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