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Planned FDG PET-CT Scan in Follow-Up Detects Disease Progression in Patients With Locally Advanced NSCLC Receiving Curative Chemoradiotherapy Earlier Than Standard CT

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Abstract: The role of positron emission tomography-computed tomography (PET-CT) in surveillance of patients with nonsmall cell lung cancer (NSCLC) treated with curatively intended chemoradiotherapy remains controversial. However, conventional chest X-ray and computed tomography (CT) are of limited value in discriminating post-radiotherapy changes from tumor relapse. The aim of this study was to evaluate the clinical value of PET-CT scan in the follow-up for patients with locally advanced (LA) NSCLC receiving concomitant chemoradiotherapy (CCRT).

Between 2009 and 2013, eligible patients with stages IIB–IIIB NSCLC were enrolled in the clinical trial NARLAL and treated in Odense University Hospital (OUH). All patients had a PET-CT scan scheduled 9 months (PET-CT9) after the start of the radiation treatment in addition to standard follow-up (group A). Patients who presented with same clinical stage of NSCLC and received similar treatment, but outside protocol in OUH during this period were selected as control group (group B). Patients in group B were followed in a conventional way without PET-CT9. All patients were treated with induction chemotherapy followed by CCRT.

Group A included 37 and group B 55 patients. The median follow-up was 16 months. Sixty-six (72%) patients were diagnosed with progression after treatment. At the time of tumor progression, patients in group A had better performance status (PS) than those in group B ($P = 0.02$). Because of death (2 patients), poor PS (3) or retreatment of relapse (9), only 23 patients had PET-CT9 in group A. Eleven (48%) patients were firstly diagnosed with progression by PET-CT9 without any clinical symptoms of progression. The median progression-free survival (PFS) was 8.8 months in group A and 12.5 months in group B ($P = 0.04$). Hazard function PFS showed that patients in group A had higher risk of relapse than in group B.

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Additional FDG PET-CT scan at 9 months in surveillance increases probability of early detection of disease progression in advanced NSCLC patients treated with curatively intended CCRT.

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Abbreviations: CCRT = concurrent chemoradiotherapy, CCT = concomitant chemotherapy, CT = computed tomography, ESMO = European Society for Medicine Oncology, FDG = 18-fluorodeoxyglucose, FEV1 = forced expiratory volume in 1 second, IMRT = intensity modulated radiotherapy, LA = locally advanced, NCCN = National Comprehensive Cancer Network, NSCLC = nonsmall cell lung cancer, OS = overall survival, PET-CT = positron emission tomography-computed tomography, PFS = progression-free survival, RT = radiotherapy, SBRT = stereotactic body radiation therapy.

INTRODUCTION

Nonsmall cell lung cancer (NSCLC) makes up for around 85% of all lung cancer cases which is the leading cause of cancer death worldwide. Thirty percent of the patients are inoperable at diagnosis due to the loco-regional advanced (LA) stage.¹ Definitive concurrent chemoradiotherapy (CCRT) is the standard of care for these patients in good performance status.^{1–4} Despite a high objective tumor response rate (60%–70%) provided by CCRT,² the prognosis of the patients in inoperable stages IIIA and IIIB remains poor with 5-year overall survival (OS) rates at 12% to 16%^{3,5,6} in clinical trials. The poor survival is not only caused by a high rate of local and distant relapses, but also due to comorbidity caused by, for example, age and smoking. The majority of the relapses are diagnosed within 2 years after commencement of radiotherapy (RT). The median progression-free survival (PFS) is 10 to 12 months^{5–7} and the first and second year PFS rates are 40% and 23%, respectively.³ In theory, early detection of loco-regional relapse may increase survival as radical treatment may be possible.

To assess the impact of routine scanning in locally advanced (LA) NSCLC, Benamore et al⁸ compared patients performing intensive radiologic follow-up with those having less intensive examination. No significant difference in time to relapse and survival was found. However, the routine tests for patients in that study were chest X-ray and computed tomography (CT) which may be insufficient to discriminate between postradiotherapy changes and tumor relapse.⁹ CT scan with or without contrast every 6 months for 2 years is recommended for follow-up by the National Comprehensive Cancer Network (NCCN) guidelines.^{10,11} However, 64% of patients with progressive disease present with clinical symptoms outside of scheduled follow-up visit.⁸ The local guidelines at our centre

recommend follow-up with CT scan every 3 months for the first 2 years and every 6 months for another 3 years after definitive RT. Different guidelines are reflecting the lack of evidence that early detection and treatment of recurrence leads to a better outcome.¹¹ ¹⁸F-Fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) scan is a key imaging examination in the primary diagnosis and staging of NSCLC due to its superiority in the detection of lung lesion and mediastinal lymph node, as well as distant metastasis.¹² In the recent years, an increasing amount of studies have shown that FDG PET-CT was highly accurate for the detection of recurrence. FDG PET-CT, as part of a surveillance program, showed positive findings in 29 (34%) asymptomatic patients with NSCLC who underwent curative resection.¹³ Jimenez-Bonilla et al¹⁴ evaluated the value of FDG PET-CT scan in the detection of relapse in 55 patients which were suspicious of recurrence of NSCLC and the sensitivity and specificity were 100% and 78%, respectively. FDG PET combined with diagnostic chest CT found regional progression in 10 out of 24 patients with early-stage NSCLC after stereotactic body radiation therapy (SBRT) while CT scan alone detected no recurrence.¹⁵

Nevertheless, the routine use of FDG PET-CT in the surveillance of patients treated for NSCLC remains controversial. The major issue is that posttreatment inflammation may persist for quite some time, giving “false-positive” FDG-uptake.¹⁶ Henderson et al¹⁷ reported that a substantial proportion of patients with no evidence of recurrence maintained moderate FDG uptake at 12 months after SBRT. Performing FDG PET-CT in the initial phase after RT may result in overestimation of FDG-uptake. According to NCCN and European Society for Medicine Oncology (ESMO) guidelines, PET is not indicated for routine follow-up.^{10,11}

In our institution, LA-NSCLC patients were offered enrollment in Danish randomized phase II clinical trial (NARLAL) and had as part of the study a scheduled FDG PET-CT at 9 months (PET-CT9) after commencement of CCRT. Patients who did not enter the trial, were followed with CT without a scheduled PET-CT at 9 months, since FDG PET-CT has not been part of routine follow-up in NSCLC patients treated with definitive CCRT in our institution.

To evaluate the clinical value of FDG PET-CT scan on surveillance, we compared patients in the trial with the patients treated off-trial with conventional follow-up.

MATERIALS AND METHODS

Patients

From May 2009 to August 2013, 37 patients (group A) with stages IIB–IIIB were treated with definitive CCRT at our institution as part of the national NARLAL trial. As part of the trial, they had a PET-CT scheduled at 9 months (± 1 month, PET-CT9) after the start of RT in addition to the conventional follow-up schedule. A group of 55 patients (group B) was treated outside the trial with curative intent at the department during this period. These patients were not included in NARLAL because they did not fulfill the eligibility criteria including low compliance for follow-up due to geographic factor (17 patients), comorbidity (8) (active infection, ischemic heart disease, and paralysis), side effects of induction chemotherapy (1), patients' refusal to participate in the clinical trial (5), other active malignancies within 5 years (6), benign pleural effusion (3), prior chemotherapy for lung cancer (1), and forced expiratory volume in 1 second (FEV1) < 1.0 (1), or other unspecified reasons (11). The conventional follow-up for group B consisted

of CT scan every 3 months after RT start and clinical examinations as previously described.¹⁸ FDG PET-CT was performed in case recurrent disease was suspected.

To be included in this study, the patients had to have histologically or cytologically confirmed NSCLC, clinical American Joint Committee of Cancer stages IIB–IIIB,¹⁹ performance status 0–1 on the ECOG scale, weight loss $< 10\%$ in 6 months and adequate hepatic and renal function. Each patient underwent basic laboratory studies, CT scans of chest and upper abdomen with contrast and FDG PET-CT scan before treatment. Baseline demographics (age, gender, smoking status, performance status, pathological type, stage) were registered in all patients as well as the frequency of follow-up visit. Approval was granted by the Institutional Review Board for conducting this study.

Treatment

All patients in groups A and B were treated with 2 cycles of induction chemotherapy before CCRT. Chemotherapeutic agents consisted of i.v. Carboplatin (area under the curve, AUC = 5, day 1) and p.o. Vinorelbine (60–80 mg/m², days 1 and 8). Patients in group A received 60 Gy/30 fractions (F) (20 patients) or 66 Gy/33 F (17 patients) concurrent with p.o. Vinorelbine 50 mg 3 times a week during RT as part of the NARLAL trial.²⁰ Patients in group B underwent 1 cycle of i.v. Carboplatin (AUC = 5) and p.o. Vinorelbine (60–80 mg/m²) as concomitant chemotherapy (CCT) during RT 66 Gy/33 F. All patients were treated 5 fractions a week by intensity modulated radiation therapy (IMRT) with an energy of 6 MV. All treatment plans were optimized to have 95% PTV receiving at least 95% prescribed dose. Critical organ dose tolerances were defined as maximum dose of esophagus ≤ 66 Gy, lung V20 $\leq 40\%$, spinal cord ≤ 45 Gy, heart V50 $\leq 20\%$. No elective nodal irradiation was performed.

Follow-up

Patient surveillance was conducted at the Department of Oncology and all data were documented in the clinical files. After RT, follow-up monitoring was at regular intervals: starting 3 months after commencing RT and thereafter every 3 months. After 2 years the follow-up interval was 6 months for another 3 years. The evaluation at each visit included medical history, physical examination, pulmonary function, and a CT scan. When recurrent disease was suspected from a CT scan, an FDG PET-CT scan was conducted, and, if possible, a tumor biopsy was taken from the lesion. Patients in group A had a PETCT9 even if no recurrence was suspected. Recurrent disease was defined using RECIST 1.1. No patient was lost for follow-up. Data cut off was June 1, 2014.

PET-CT Image

FDG PET-CT data were acquired by a General Electric Discovery FDG PET-CT scanner. Patients had to be fasting for at least 6 hours before the examination. Patients were injected with FDG which was calculated based on the weight (4–6 MBq/kg). After a rest period of 60 minutes (time needed for uptake of FDG), PET and CT images were acquired. A whole-body PET scan and a diagnostic low-dose CT was performed from the vertex of skull to the upper thighs. Tumor is evaluated based on visual analysis on PET reviewed side-by-side with CT.

Statistics Analyses

OS was defined from commencement of RT to the date of death or censored at the time of last follow-up if the patients alive at time of

evaluation. PFS was defined from the start of RT to the first event (disease progression or death from any cause). Patients alive without progression were censored at the date of last follow-up. The date of recurrence was defined as the date of the CT or FDG PET-CT scan first detecting local–regional or distant recurrence.

Patients and treatment characteristics were summarized by descriptive statistics. The comparisons of characteristics between the 2 groups were analyzed by Chi-square test. Survival curve was estimated using Kaplan–Meier method. A 2-sided log-rank test was used to evaluate the difference between survival curves. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS (Statistics Package for Social Science) version 19.0 for windows.

RESULTS

A total of 92 patients were enrolled in this study. The median age of all patients was 66 years (40–81 years). Baseline characteristics of the entire study population are summarized in Table 1. There was no significant difference between the 2 groups with respect to age, performance status, sex, smoking status, histological subtype, T stage, and N stage. The median potential follow-up of all patients was 23 months, 34 months for group A and 23 months for group B. No significant difference of follow-up time was found between the 2 groups ($P = 0.46$).

In group A, 23 (62%) patients underwent FDG PET-CT9 and 14 did not because of death (2 patients), poor PS (3 patients), or retreatment of relapse (9 patients). For these 14 patients, disease progression was identified during the first 8 months of follow-up and their PFS were from 2 to 7.6 months.

Disease Progression

The overall incidence of recurrent disease was 72%. In group A, 3 (10%) patients had PS 2, 1 (3.3%) had PS 3 and no

one had PS 4 when diagnosed with recurrent disease. In group B, 11 (30.6%) patients had PS 2, 2 (5.6%) had PS 3 and 1 (2.8%) had PS 4. Patients in group A had better PS than those in group B at the time of relapse ($P = 0.02$). Because of poor PS, 1 patient in group A and 7 patients in group B could not receive chemotherapy after disease recurrence.

The treatment after relapse consisted of systemic treatment (chemotherapy and targeted therapy) or local treatment (surgery and RT). For local treatment, only 5 patients received surgery with curative intention including 2 pneumonectomies, 1 adrenal gland resection, and 1 laparoscopic liver resection in group B, and 1 bronchoscopic argon plasma coagulation combined with mediastinal radiation in group A. Some patients underwent palliative radiation to relieve symptoms. The lines and duration of systemic treatment, dose and cycles of chemotherapy did not differ between the 2 groups. The characteristics of patients and treatment after disease progression are summarized in Table 2.

For the patients with PET-CT9, 16 (70%) patients had recurrent disease including loco-regional only in 12 (52%), and both loco-regional and distant in 4 (17%). For 11 (48%) patients, disease progressions were detected by PET-CT9 without accompanying symptoms. When diagnosed with relapse, 14 (88%) patients with PET-CT9 received chemotherapy and 2 patients rejected chemotherapy for personal reasons.

Overall Survival and Progression-Free Survival

The 1- and 2-year OS rates of the entire population were 82% (84% in group A and 81% in group B) and 48% (48% vs. 47%), respectively. Median OS was 23.5 months (21.6 in group A vs. 23.5 in group B). No significant difference of OS existed between 2 groups ($P = 0.89$) (Fig. 1A). The median PFS was 9.9 months (8.8 in group A vs. 12.5 in group B). Patients in group B had a significantly longer overall PFS compare to those in group A

TABLE 1. Baseline Characteristics of All Patients (N = 92)

Characteristics	Total No.	Group A, No. (%)	Group B, No. (%)	P-Value
Sex				
Male	49	22 (60)	27 (49)	0.33
Female	43	15 (40)	28 (51)	
Age, y				
≤70	69	29 (78)	40 (73)	0.54
>70	23	8 (22)	15 (27)	
Histology				
SCC	33	11 (28)	22 (41)	0.13
Adenocarcinoma	46	23 (62)	23 (41)	
Others	13	3 (8)	10 (18)	
PS				
0	35	15 (40)	20 (36)	0.69
1	57	22 (60)	35 (64)	
T stage				
T0–2	52	22 (60)	30 (55)	0.64
T3–4	40	15 (40)	25 (45)	
N stage				
N0–1	17	4 (11)	13 (24)	0.12
N2–3	75	33 (89)	42 (76)	
Smoking				
Never	18	5 (14)	13 (24)	0.23
Smoker*	74	32 (86)	42 (76)	

PS = performance status, SCC = squamous cell carcinoma.

*Never smoker included never smoker and former smokers quitting smoking for more than 10 years.

TABLE 2. Characteristics and Treatment of Patients After Disease Progression

Characteristics	Total No.	Group A, No. (%)	Group B, No. (%)	P-Value
PS postprogression				
0–1	48	26 (87)	22 (61)	0.02
≥2	18	4 (13)	14 (39)	
Systemic therapy*				
0	18	5 (17)	13 (36)	0.11
1 line	29	17 (56)	12 (33)	
≥2 lines	19	8 (27)	11 (31)	
Duration of systemic therapy				
≤3 mo	38	15 (50)	23 (64)	0.40
3–6 mo	15	9 (30)	6 (17)	
>6 mo	13	6 (20)	7 (19)	
Re-chemo				
No	20	6 (20)	14 (39)	0.10
Yes	46	24 (80)	22 (61)	
Chemo-cycles				
0	20	6 (20)	14 (39)	0.23
1–6 cycles	32	16 (53)	16 (44)	
≥7 cycles	14	8 (27)	6 (17)	
Chemo-dose				
100%	39	21 (87)	18 (82)	0.90
75%	7	3 (13)	4 (18)	

* Systemic therapy included chemotherapy and targeted therapy.

($P=0.04$) (Figure 1B). Cumulative incidences of death were similar between 2 groups (Figure 1C). However, hazard function PFS showed that patients in group A had higher risk of relapse than in group B (Figure 1D). The slopes of the cumulative hazard were almost the same before and after 9 months which showed that the difference between the curves was within the 9-month time window. For patients with progression, median OS was 33.2 months in group A and 22.2 months in group B, but there was no significant difference ($P=0.81$).

DISCUSSION

FDG PET-CT scan has been widely used as a routine imaging modality in the diagnosis of NSCLC. However, its value in surveillance is still controversial. Recent studies have shown that FDG PET-CT is valuable in detecting local recurrence during follow-up, since it is superior in distinguishing recurrence from benign conditions such as atelectasis, scar, and radiation fibrosis compared to conventional imaging.^{21–23} In this study, we scheduled FDG PET-CT scan for local advanced NSCLC patients with CCRT to assess the role of FDG PET-CT in surveillance. The effect of FDG PET-CT in detecting local recurrence was retrospectively assessed in 154 patients with inoperable NSCLC receiving SBRT by Takeda et al.²² All of 17 local recurrent tumors were diagnosed by FDG PET-CT while CT had a limited ability to distinguish tumor recurrence from scar or fibrotic change.²² When annually FDG PET-CT was added to postoperative surveillance in NSCLC after curative resection, 26 (52%) recurrences were detected by both FDG PET-CT and chest CT and 19 (37%) recurrences were confirmed only by FDG PET-CT.²⁴

Follow-up FDG PET-CT is useful for post treatment evaluation in patients with NSCLC, but its clinical value depends mainly on when it is performed. Van Loon et al²³ followed 100 NSCLC patients 3 months after curatively intended RT ± chemotherapy with FDG PET-CT. FDG

PET-CT detected recurrent disease potentially amenable for radical treatment in 3% of patients. Thus, it seemed that only a very small proportion benefited from surveillance using FDG PET-CT scan. The reason may be low accuracy of FDG PET-CT in the initial phase after RT due to radiation changes such as inflammation, congestion, or edema.²⁵ Furthermore, only a few patients relapsed in the first 3 months after treatment. According to 10- to 12-month median PFS^{5–7} in patients with inoperably advanced NSCLC, patients in our study performed FDG PET-CT at 9 months after the start of RT. In 37 patients in group A, 23 (62%) underwent PET-CT9 and 11 (48%) were firstly diagnosed progression by this FDG PET-CT while no patient had clinical symptoms. It suggested that progressive disease not inducing any abnormality was detected early by the planned FDG PET-CT scan. In the study by Toba et al, an FDG PET-CT was performed in NSCLC patients without clinical and radiological recurrence after curative resection at least once a year. In 18 asymptomatic patients with recurrent disease, 17 (94%) were correctly diagnosed by FDG PET-CT.²⁶

With conventional follow-up without use of FDG PET-CT, suspicion of NSCLC relapse frequently occurs when patients were symptomatic, but there may be limited therapeutic option at diagnosis and little treatment benefit because of poor PS or large tumor burden. Cisplatin-based chemotherapy improves survival and quality of life in patients with PS 0–1, while the patients in poor PS have less benefit of chemotherapy.^{27,28} This may indicate that early detection of a relapse by use of FDG PET-CT in asymptomatic patients may increase survival. In our study, patients in group A with planned PET-CT9 had a better performance status than those in group B with only conventional follow-up schedule after diagnosis of progression ($P=0.02$). More patients in group B did not receive chemotherapy compared with those in group A (39% vs. 20%) although there was no significant difference. This may suggest that early detection of progression lead to better PS and a higher chance of chemotherapy. For

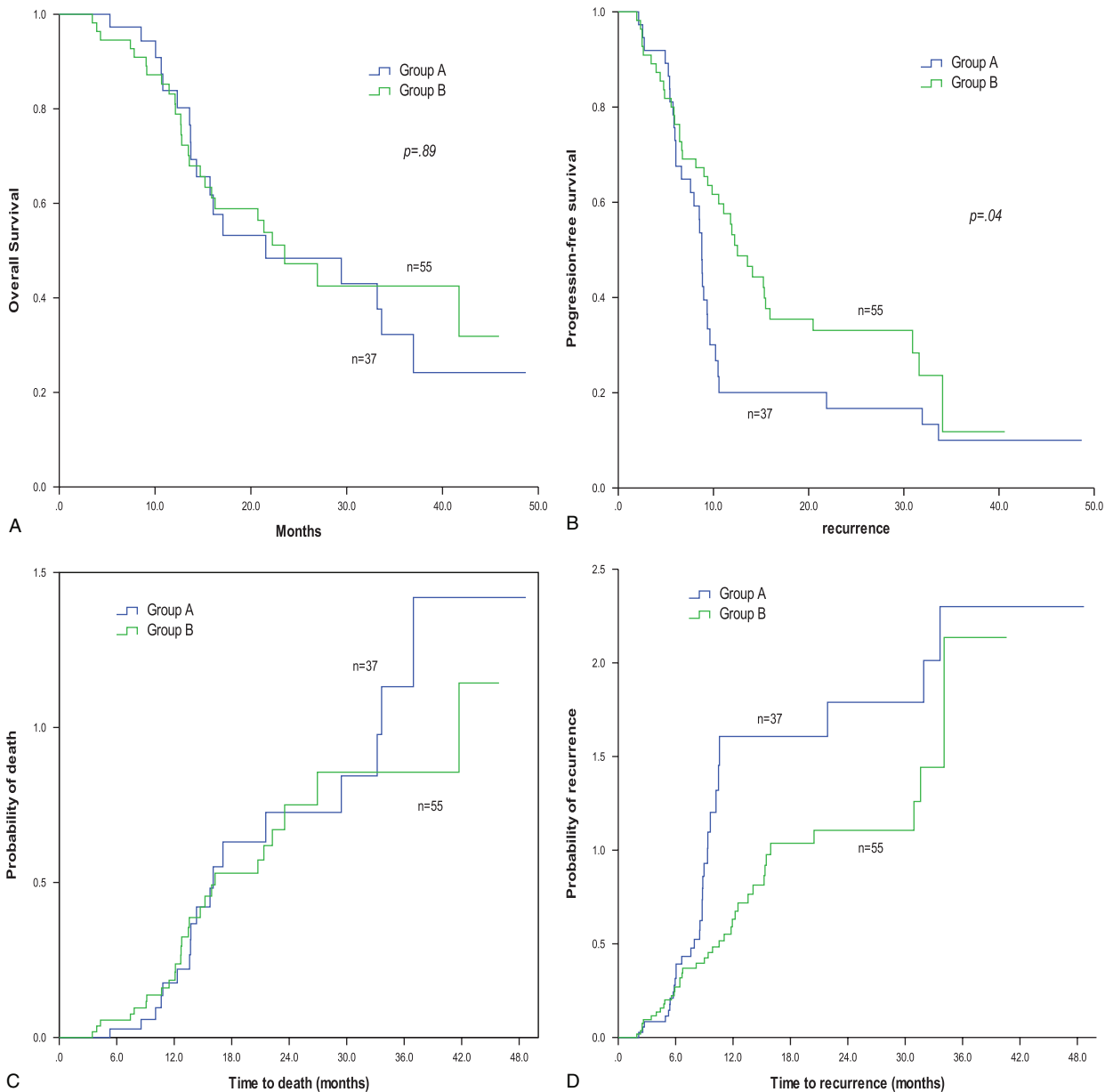


FIGURE 1. Overall survival, progression-free survival and cumulative hazard OS and PFS in 2 groups. OS (A) was not significantly different in 2 groups, while PFS (B) was significantly longer in group B than in group A. Cumulative incidences of death were similar between 2 groups (C). However, hazard function PFS showed that patients in group A had higher risk of relapse than in group B (D). The slopes of the cumulative hazard PFS were almost the same before and after 9 months which showed that the difference between the curves were within the 9-month time window.

patients with NSCLC who had relapsed after complete resection, PS at the diagnosis of recurrence was the independent prognostic factor of postrecurrence survival.²⁸ Patients with better PS at recurrence had a higher rate of application of chemotherapy and selection of best supportive care.²⁸

Until now, researches have failed to demonstrate that early detection of recurrent disease by FDG PET-CT improved survival in NSCLC, but there might be indications that patients with loco-regional relapse survived longer than those with distant metastases when diagnosed relapse by FDG PET-CT.¹⁴ In our study, the median PFS was 3.8 months shorter in group A (8.8 months) than in group B (12.5 months) and the

risk of recurrence was higher in group A reflecting that disease progression was detected earlier in patients performing additional FDG PET-CT at 9 months than those with only conventional follow-up. However, no statistically significant OS benefit was observed between the 2 groups. There may be a bias between groups A and B in our study, but it is expected to be such that group A is doing better than group B since some of the patients in group B had comorbidities that prevented them from being in the NARLAL trial.

PFS is a commonly used endpoint in clinical trials to assess the effect of cancer treatment but it is important to be aware that measured values depend on the method used to measure PFS.

Comparing PFS directly in different studies may lead to a lead time bias when the follow-up schedules are not identical. The intensive follow-up in group A is the reason for the worse PFS observed here in comparison with group B since the OS is remarkable similar.

In summary, our study demonstrates that additional FDG PET-CT scan at 9 months in surveillance increases probability of early detection of disease progression in advanced NSCLC patients treated with curatively intended CCRT. However, this study has several limitations. First, it was not a prospective study. The control group consisted of patients receiving similar but not identical therapeutic regimen. Secondly, the sample size was small and the statistical power of testing difference in treatment and survival between 2 groups was limited. Further studies are needed to analyze the value of FDG PET-CT on follow-up of patients with NSCLC after curatively intended RT.

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