ORIGINAL ARTICLE

Surveillance With Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography of Patients With Stage I-to-III Lung Cancer After Completion of Curative treatment (SUPE_R): A Randomized Controlled Trial

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ABSTRACT

Introduction: Post-treatment surveillance is recommended for NSCLC owing to a high risk of recurrence, but evidence on the optimal surveillance method is lacking. This trial evaluates fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) versus contrast-enhanced CT (ceCT) for surveillance in patients with NSCLC.

Methods: In this multicenter, randomized controlled trial (SUPE_R, ClinicalTrials.gov NCT03740126), patients with stage IA-to-IIIC NSCLC were randomized one-to-one to standard surveillance (ceCT) or surveillance with [18F]FDG PET/CT after completion of curative treatment. The primary outcome was the proportion of recurrences treated with curative intent. Secondary outcomes included time to recurrence (TTR) and overall survival (OS).

Results: Between February 2019 and February 2022, 750 patients were randomized to PET/CT (n = 373) or CT (n = 377). Recurrences occurred in 164 patients (22%). The proportion of recurrences treated with curative intent was identical in the PET group (42/87) and CT group (37/77), both 48% ($p = 0.98$). More recurrences were detected through scheduled follow-up in the PET group (90%) than in the CT group (77%; $p = 0.02$). There were no significant differences in TTR (hazard ratio 1.12, 95% confidence interval 0.82–1.52, $p = 0.48$) or OS (hazard ratio 0.97, 95% confidence interval 0.66–1.43, $p = 0.89$) between groups.

Conclusions: Surveillance with [18F]FDG PET/CT did not improve rates of curatively treated recurrences, TTR, or OS compared with ceCT in patients with NSCLC after curative treatment. These findings do not support the routine use of [18F]FDG PET/CT for post-treatment surveillance in this patient population.

Keywords: PET/CT; NSCLC; Cancer recurrence; Surveillance

Introduction

Lung cancer remains a leading cause of morbidity and mortality despite advances in early diagnosis and treatment.[1–3] Among the different subtypes, NSCLC accounts for 85% of cases.[4] Patients with NSCLC who complete treatment with curative intent face a considerable risk of recurrence, ranging from 20% to 61% depending on the stage and type of treatment received.[5,6] Importantly, effective treatment options exist for recurrent cases, particularly when detected early while lesions are still small and localized.[7,8]

Surveillance is generally recommended to enable early detection of recurrences, with guidelines suggesting using contrast-enhanced computed tomography (ceCT) of the chest and abdomen every 6 months for 2 years and then annually.[9,10] In Denmark, a more frequent surveillance strategy has been implemented, involving ceCT scans every 3 months for 2 years and then every 6 months up to 5 years.[11] The optimal surveillance strategy remains contentious owing to insufficient high-quality evidence supporting specific regimens.[12] Nonetheless, retrospective studies have reported that 22% to 40% of recurrences are missed by current surveillance methods, indicating potential for improvement.[5,13]

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) has become central to lung cancer staging owing to its improved accuracy in detecting nodal and metastatic disease.[14] In the surveillance setting, it has reported promise in distinguishing benign lesions from recurrence when the results of CT are inconclusive.[15] A meta-analysis from 2014 found that [^{18}F]FDG PET/CT reported superior sensitivity and specificity for detecting lung cancer recurrence to CT.[16] In addition, up to 37% of recurrences detected by [^{18}F]FDG PET/CT are not identified by CT during surveillance, predominantly extrathoracic metastases that conventional CT scans sometimes miss.[17] Even so, a recent randomized pilot study comparing the two modalities found comparable performance in PET/CT and ceCT for post-treatment surveillance.[18] Most of these studies on [^{18}F]FDG PET/CT for surveillance have been limited in size or retrospective, highlighting the need for further research to establish its role in a prospective, randomized setting.[19]

The primary aim of this study was to evaluate the potential of [^{18}F]FDG PET/CT in post-treatment follow-up of patients with NSCLC to improve early recurrence detection and increase the number of recurrences amenable to curative treatment. A secondary aim was to collect blood samples for circulating tumor DNA (ctDNA) analysis, which has reported promise for early detection of recurrence.[20] Analysis of these blood samples is ongoing and will be reported separately.

Materials and Methods

Study Design and Participants

This study was a national, multicenter, open-label, randomized clinical trial. Patients were recruited from 17 departments of pulmonology and oncology across 10 hospitals, covering all five administrative health care regions of Denmark. The primary objective was to compare [^{18}F]FDG PET/CT with ceCT in terms of the proportion of detected recurrences amenable to curative therapy.

Eligible patients were those diagnosed with stage IA-to-IIIC NSCLC according to the eighth edition of the American Joint Committee on Cancer TNM staging system and referred for curative intent treatment, including complete resection (with or without adjuvant chemotherapy), stereotactic body radiation therapy, or definitive chemoradiotherapy. Exclusion criteria were Eastern Cooperative Oncology Group performance status greater than 2, concurrent or previous malignant disease, participation in another interventional study, disease progression within the first 3 months after treatment, persons deprived of liberty or under guardianship, and pregnancy or breastfeeding.

Patients were recruited before treatment to obtain a baseline blood sample for ctDNA analysis. After completion of curative treatment, patients were eligible for randomization into the main study if their first scheduled surveillance scan (at 2–3 months after treatment) found no evidence of disease. To ensure adequate enrollment, eligible patients who were not recruited before treatment could also be enrolled directly at their first follow-up visit after completing treatment.

All patients provided written informed consent. The study was approved by the Regional Committee on Health Research Ethics (H-18009536) and the Danish Data Protection Agency, and is registered on ClinicalTrials.gov (NCT03740126). The study protocol has been published elsewhere.[21]

Randomization and Procedures

Eligible patients were randomized one-to-one to either standard surveillance (referred to as the CT group) or [^{18}F]FDG PET/CT surveillance (referred to as the PET group), stratified by health care region and sex. The randomization sequence was pregenerated and centrally managed using Research Electronic Data Capture (REDCap).[22,23]

The CT group underwent ceCT scans of the chest and abdomen every 3 months, following the current standard of care in Denmark. The PET group followed the same 3-month surveillance schedule as the CT group, with every

other CT scan replaced by an [18F]FDG PET/CT scan, starting from the first postrandomization assessment. Both groups underwent the assigned surveillance regimen for 2 years after the end of treatment or until recurrence was detected.

Investigators were permitted to perform any diagnostic procedures necessary to diagnose or rule out suspected recurrence, including ordering an [18F]FDG PET/CT scan for patients assigned to the CT group.

[18F]FDG PET/CT scans were performed following standardized protocols drawn up at each participating site, adhering to European Association of Nuclear Medicine recommendations for [18F]FDG PET/CT acquisition and reconstruction.[24] Patients fasted for a minimum of 4 hours before examination and were injected with a dose of approximately 3 to 4 MBq/kg of [18F]FDG 60 minutes before the PET/CT scan, performed from vertex to midthigh. All PET/CT scans were interpreted by both a certified nuclear medicine physician and a radiologist, following standard clinical practice at each site. ceCT scans were performed according to established clinical protocols at each participating site, typically covering the thorax and upper abdomen, with contrast enhancement unless medically contraindicated.

To ensure consistency and quality across sites, all PET/CT scanners used in the study underwent quality control before study initiation. Each participating department submitted two phantom scans for each system, using the same reconstruction protocol used for routine [18F]FDG PET/CT scans. The scans included a cylindrical phantom for calibration and standardized uptake value bias calculation and a National Electrical Manufacturers Association (NEMA) Body (IQ) Phantom for recovery coefficient calculation. All systems met the minimum specifications defined by the European Association of Nuclear Medicine Research Ltd.[25]

Outcomes and Sample Size

The primary outcome was the proportion of recurrences that could be treated with curative intent. A sample size of 330 patients with recurrence (165 patients per group) was needed to detect a 15% increase in the proportion of recurrences treated with curative intent, from 31% to 46%, with a two-sided significance level of 0.05 and 80% power. Assuming 45% of patients would experience a relapse within 24 months, the inclusion of 734 patients was needed. Accounting for potential dropout, the aim was to include 750 patients (375 per arm).

Secondary outcomes included time to verified recurrence, overall survival, survival for patients with recurrence, performance status at the time of recurrence, and the number and type of invasive procedures and related adverse events.

Suspected recurrence was diagnosed through further imaging, invasive procedures, and multidisciplinary team (MDT) consensus at the attending physicians' discretion but with histologic confirmation obtained whenever possible. No distinction was made between disease recurrence and secondary primary lung cancer. Treatment intent, whether curative or palliative, was determined by the MDT. Time to recurrence (TTR) was defined as the number of days from the first post-treatment surveillance scan to the date of confirmed recurrence, determined either by the date of the MDT assessment or the date of biopsy confirmation if an MDT assessment date was unavailable.

Survival status was recorded yearly after the end of the assigned surveillance schedule until 5 years after treatment. Overall survival (OS) was defined as the number of days from the first post-treatment surveillance scan to the day of death from any cause. This report presents interim survival data because the entire 5-year follow-up has not yet been completed at the time of analysis.

Statistical Analysis

All analyses were conducted in the intent-to-treat population. Categorical values were presented as counts and percentages, and continuous variables as means and SDs. Categorical values were compared using Pearson's chi-square or Fisher's exact test for independent samples.

Median OS was estimated through the Kaplan-Meier method. Cox proportional hazard regression adjusted for stratification factors (health care region and sex) was used to assess OS and TTR hazard ratios, along with 95% confidence intervals (CIs) and model-based *p*-values. The proportional hazards assumption was tested using Schoenfeld residuals. Median follow-up was estimated using the reverse Kaplan-Meier method. Adverse event rates and the rate of additional diagnostic procedures to diagnose recurrence were reported as incidence rate ratios (IRR) and compared using Poisson regression.

Post hoc analyses included analysis of unadjusted hazard ratios (HRs) for OS and TTR by disease stage, treatment, recurrence type, and sex. Moreover, primary and secondary end points were evaluated in the per-protocol population, defined as a CT group with patients who completed at least one postrandomization ceCT scan and no scheduled PET/CT scans and a PET group with patients who completed at least one postrandomization scheduled PET/CT scan.

All *p*-values were two-sided, with values <0.05 deemed statistically significant. All analyses were

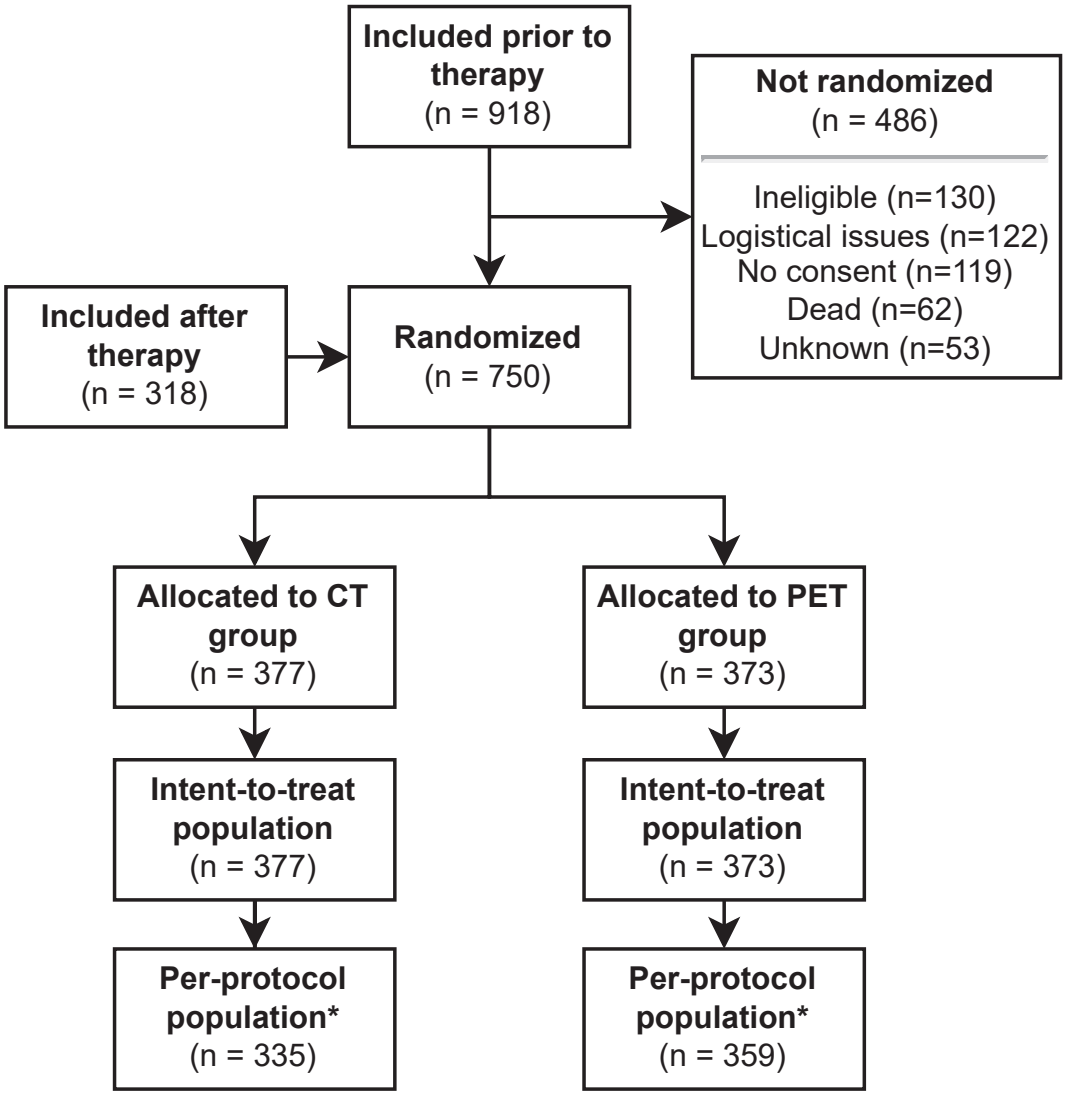

Figure 1. Study flow diagram. *Per-protocol population defined as patients in the CT group who completed at least one postrandomization contrast-enhanced CT scan and no scheduled fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) scans and patients in the PET group who completed at least one postrandomization scheduled [^{18}F]FDG PET/CT scan. CT, computed tomography; PET, positron emission tomography.

conducted using R software (version 4.4.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Between February 2018 and June 2020, 918 patients with NSCLC were recruited before treatment (Fig. 1). Of these, 486 were excluded from randomization owing to various reasons, primarily ineligibility (n = 130), logistical issues (n = 122), and withdrawal of consent (n = 119). The remaining eligible patients recruited before treatment and an additional 318 patients included at their first follow-up visit after treatment were randomized between February 2019 and February 2022 to either the PET group (n = 373) or the CT group (n = 377) and were included for analysis in the intent-to-treat population.

The mean age of patients in the intent-to-treat population was 68.7 years (SD 8.4; Table 1); 442 patients (59%) were female; 516 (69%) were former smokers; 159 (21%) were current smokers, and disease stages were distributed as follows: 533 (71%) in stage I, 112 (15%) in stage II, and 105 (14%) in stage III. Adenocarcinoma was the predominant histologic type, occurring in 549 patients (73%). Moreover, 591 patients (79%) underwent surgery with or without adjuvant chemotherapy, whereas 108 (14%) received stereotactic body radiation therapy, and 51 (7%) underwent combined chemoradiotherapy. The baseline characteristics were similar in the PET and CT groups.

Procedures and Adherence to Protocol

In the PET group, 1171 scheduled [^{18}F]FDG PET/CT scans were performed; 345 of 373 patients (92%)

Table 1. Baseline Characteristics

Characteristic	PET Group (n = 373)	CT Group (n = 377)
Age—mean (SD)	68.7 (8.3)	68.7 (8.5)
Sex		
Female	219 (59)	223 (59)
Male	154 (41)	154 (41)
Smoking status		
Former	259 (69)	257 (68)
Current	76 (20)	83 (22)
Never	38 (10)	37 (10)
Histologic diagnosis		
Adenocarcinoma	276 (74)	273 (72)
Squamous cell carcinoma	88 (24)	84 (22)
Other	9 (2)	20 (5)
Clinical stage		
I	268 (72)	265 (70)
II	57 (15)	55 (15)
III	48 (13)	57 (15)
Treatment		
Surgery	289 (77)	302 (80)
Wedge resection	28 (8)	26 (7)
Lobectomy	253 (68)	254 (67)
Bilobectomy	5 (1)	11 (3)
Pneumonectomy	3 (1)	9 (2)
Surgery type not available	0 (0)	2 (1)
With adjuvant chemotherapy	45 (12)	40 (11)
Stereotactic body radiation therapy	59 (16)	49 (13)
Chemoradiotherapy	25 (7)	26 (7)
With durvalumab consolidation	8 (2)	3 (1)

Data are presented as n (%) unless otherwise specified.
CT, computed tomography; PET, positron emission tomography.

underwent PET/CT scans at 6 months after completion of therapy, 286 of 330 (87%) at 6 to 12 months, 265 of 299 (89%) at 12 to 18 months, and 248 of 267 (93%) at 18 to 24 months. In the CT group, 2326 scheduled CT scans were performed. In addition, 30 scheduled [^{18}F]FDG PET/CT scans were performed in the CT group owing to protocol violations or suspected recurrence.

Fewer additional, unscheduled imaging procedures to confirm or exclude recurrence were performed in the PET group than in the CT group (70 versus 130, IRR 0.54, 95% CI 0.41–0.73, $p < 0.01$; Table 2). Notably, 42 additional [^{18}F]FDG PET/CT scans were conducted in the PET group, whereas 100 such scans were performed in the CT group (IRR 0.42, 95% CI 0.29–0.60, $p < 0.01$). Conversely, more invasive diagnostic procedures to confirm or exclude recurrence were performed in the PET group than in the CT group (147 versus 88, IRR 1.69, 95% CI 1.3–2.21, $p < 0.01$), including more CT-guided biopsies (43 versus 25, IRR 1.74, 95% CI 1.07–2.88, $p = 0.03$) and endoscopic biopsies (63 versus 39, IRR 1.63, 95% CI 1.1–2.45, $p = 0.02$).

Fourteen adverse events due to invasive diagnostic procedures occurred in the PET group and nine in the CT group (IRR 1.57, 95% CI 0.69–3.77, $p = 0.29$). Adverse events included infection, bleeding, and pneumothorax.

Recurrence Detection and Treatment

Median follow-up for recurrence was 21.2 months (interquartile range 20.4–22.0). Recurrences were detected in 87 of 373 patients (23%) in the PET group and 77 of 377 (20%) in the CT group ($p = 0.34$; Table 3). Regarding the primary end point, recurrence was treated with curative intent in 42 of 87 (48%) in the PET group and 37 of 77 (48%) in the CT group, with no significant difference between groups ($p = 0.98$). Among all 79 recurrences treated with curative intent, 32 (41%) underwent surgery; 25 (32%) received stereotactic body radiation therapy, and nine (11%) received combined chemoradiotherapy.

Overall, 78 of 87 recurrences (90%) in the PET group and 59 of 77 (77%) in the CT group were detected through scheduled surveillance ($p = 0.02$). Recurrence was suggested in 225 of 2435 surveillance scans (9%) in the PET group compared with 135 of 2356 (6%) in the CT group ($p < 0.01$). Additional workup to diagnose or rule out suggested recurrence was required in 166 of 373

Table 2. Additional Diagnostic Procedures to Diagnose Recurrence

Procedure	PET Group	CT Group	IRR (95% CI)	*p*-Value
Invasive diagnostic procedure (any)	147	88	1.69 (1.3-2.21)	<0.01
Surgical biopsy	16	9	1.8 (0.81-4.25)	0.16
Ultrasound-guided biopsy	18	9	2.02 (0.93-4.72)	0.08
CT-guided biopsy	43	25	1.74 (1.07-2.88)	0.03
Endoscopic biopsy	63	39	1.63 (1.1-2.45)	0.02
Other invasive procedures	7	6	1.18 (0.39-3.66)	0.77
Imaging procedure (any)	70	130	0.54 (0.41-0.73)	<0.01
CT	11	11	1.01 (0.43-2.36)	0.98
MRI	17	19	0.9 (0.47-1.74)	0.76
[^{18}F]FDG PET/CT	42	100	0.42 (0.29-0.6)	<0.01

Data are presented as counts. *p*-Values were calculated using Poisson regression.
CI, confidence interval; CT, computed tomography; [^{18}F]FDG PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; IRR, incidence rate ratio; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 3. Recurrence Characteristics

Characteristic	CT Group	PET Group	*p*-Value
Recurrence detection			
Surveillance scans with suspected recurrence	135/2356 (6%)	225/2435 (9%)	<0.01
Additional workup because of suspected recurrence	132/377 (35%)	166/373 (45%)	<0.01
Confirmed recurrence	77/377 (20%)	87/373 (23%)	0.34
Detected at scheduled follow-up	59/77 (77%)	78/87 (90%)	0.02
MDT and biopsy verified	43/77 (56%)	52/87 (60%)	0.61
MDT verified only	13/77 (17%)	12/87 (14%)	0.58
Biopsy verified only	9/77 (12%)	11/87 (13%)	0.85
Imaging verified only (no MDT)	12/77 (16%)	12/87 (14%)	0.75
ECOG performance status at recurrence			
0–1	58/77 (75%)	62/87 (71%)	0.56
2–4	11/77 (14%)	15/87 (17%)	0.61
Not available	8/77 (10%)	10/87 (11%)	0.82
Recurrence extent			
Intrathoracic recurrence	50/77 (65%)	48/87 (55%)	0.20
Distant recurrence	14/77 (18%)	19/87 (22%)	0.56
Both	13/77 (17%)	18/87 (21%)	0.53
Not available	0/77 (0%)	2/87 (2%)	0.50[a]
Recurrence treatment intent			
Curative-intent treatment	37/77 (48%)	42/87 (48%)	0.98
Palliative-intent treatment	34/77 (44%)	41/87 (47%)	0.70
No initial treatment	4/77 (5%)	3/87 (3%)	0.71[a]
Not available	2/77 (3%)	1/87 (1%)	0.60[a]

Data are presented as n (%). *p*-Values were obtained using Pearson's chi-square test of independence unless otherwise noted.
CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MDT, multidisciplinary team; PET, positron emission tomography.
[a]Obtained using Fisher's exact test.

patients (45%) in the PET group and 132 of 377 patients (35%) in the CT group ($p < 0.01$). Of the 87 recurrences in the PET group, 48 (55%) were intrathoracic only; 19 (22%) were distant only, and 18 (21%) were both intrathoracic and distant. Disease extent was not available for two patients in the PET group. Similarly, of the 77 recurrences in the CT group, 50 (65%) were intrathoracic only; 14 (18%) were distant only, and 13 (17%) were both intrathoracic and distant.

There was no difference in TTR between groups (HR 1.12, 95% CI 0.82–1.52, $p = 0.48$; Fig. 2*A*). This finding was consistent when the analysis was restricted to patients with confirmed recurrence (HR 0.85, 95% CI 0.62–1.17, $p = 0.31$; Fig. 2*B*).

Overall Survival

The median survival follow-up was 29.7 months (interquartile range 21.5–38.2). Median OS was not reached in either arm. There was no significant difference in OS between the study arms (HR 0.97, 95% CI 0.66–1.43, $p = 0.89$; Fig. 3*A*). This was also the case when comparing OS only for patients with recurrence (HR 1.03, 95% CI 0.62–1.71, $p = 0.90$; Fig. 3*B*).

Post Hoc Analysis

Subgroup analyses found no differences in OS or TTR in any subgroup. Analysis of the per-protocol population also revealed no differences in survival, detection of recurrences, or treatment of recurrences between the groups. All post hoc analyses are provided as supplementary material (Appendix, Supplementary Data 1).

Discussion

Surveillance to detect recurrence is generally recommended for patients who have completed curative treatment for lung cancer. Despite this, some recurrences are missed by current surveillance methods, which may affect patient outcomes. Several studies have found improved survival rates for patients with surveillance-detected recurrences compared with symptom-detected recurrences.[5,13,17] Although [^{18}F]FDG PET/CT has been proposed as a potentially superior method for recurrence detection, its effectiveness in routine surveillance remains unclear. To our knowledge, this study represents the first large-scale, prospective multicenter randomized trial directly comparing [^{18}F]FDG PET/CT with standard ceCT for surveillance in patients with NSCLC.

Previous studies have suggested the potential benefits of [^{18}F]FDG PET/CT in post-treatment surveillance of patients with lung cancer. Choi et al.[17] found that 37% of recurrences were detected only with PET-CT in a prospective study in 358 patients after resection. Similarly,

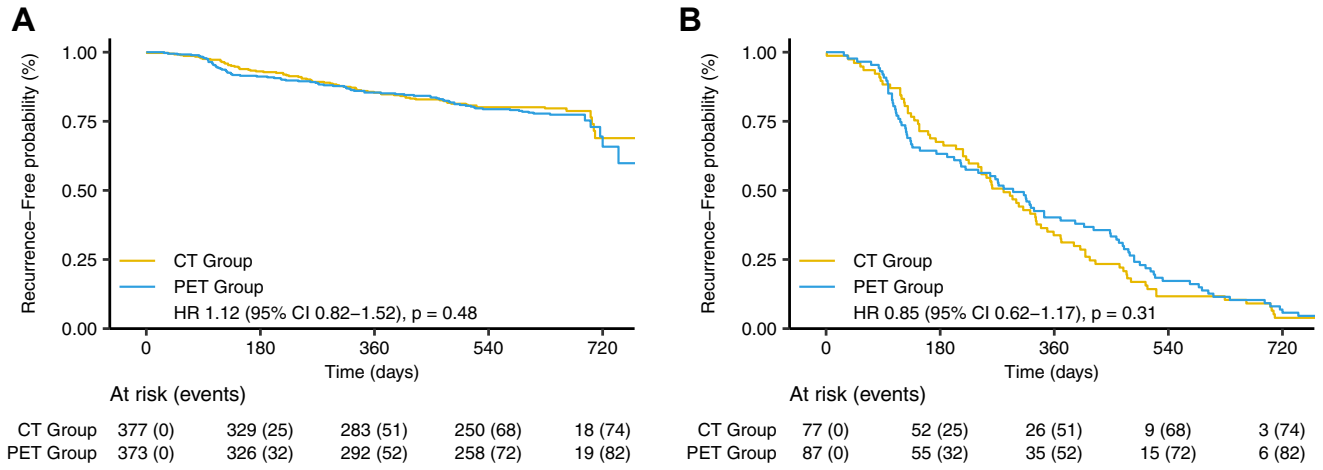

Figure 2. Time to recurrence. Kaplan-Meier curves for time to recurrence for *(A)* the entire intention-to-treat population and *(B)* patients with confirmed recurrence by surveillance group. Curves are truncated at 24 months. CI, confidence interval; CT, computed tomography; HR, hazard ratio; PET, positron emission tomography.

Dane et al.[26] reported that PET/CT detected all recurrences in their cohort, whereas noncontrast CT alone identified only 56%. A meta-analysis from 2014 found superior diagnostic performance of PET/CT (sensitivity 90%, specificity 90%) to that of CT alone (sensitivity 78%, specificity 80%) in indirect comparisons.[16] Recent retrospective studies have further supported these findings, reporting excellent diagnostic performance of [^{18}F]FDG PET/CT, with sensitivities of 98% to 99% and specificities of 97% to 98%.[27,28] Yet, the advantages of [^{18}F]FDG PET/CT are less clear when directly compared with CT in prospective trials. A pilot randomized trial in 96 patients found no differences in diagnostic performance between [^{18}F]FDG PET/CT and CT for post-treatment surveillance.[18] The authors also found no difference in time to event or number of curable recurrences between PET/CT and CT surveillance groups. Similarly, a recent meta-analysis reported no difference in recurrence detection rates between [^{18}F]FDG PET/CT and standard surveillance techniques.[12]

These results align with recent evidence suggesting that more intensive surveillance does not improve patient outcomes. A randomized controlled trial (IFCT-0302) by Westeel et al.,[29] involving 1775 patients with NSCLC after surgery, found no difference in OS between minimal follow-up and CT-based follow-up groups (HR = 0.95, 95% CI 0.83–1.10, $p = 0.49$). A meta-analysis by Galjart et al.,[30] encompassing 13 studies with 26,162 patients with lung cancer, concluded that intensive follow-up did not affect OS or increase curative treatment rates. This lack of benefit was observed across various cancer types when considering high-quality evidence.

Our study's findings and recent evidence challenge the idea that more intensive imaging in lung cancer surveillance ultimately leads to better patient outcomes. Several factors may contribute to our findings. First, we expected a curative treatment rate of 31% in the CT group, which is similar to that reported by Westeel et al.[29] (29%). Surprisingly, the rate of curative treatment in both groups was higher than expected (48%), exceeding the predicted rate for [^{18}F]FDG PET/CT surveillance (46%). One explanation for this discrepancy might be the exclusion of patients with recurrence at the first follow-up scan if these early recurrences were less amenable to curative treatment. Nevertheless, the high rate of curative treatment could also be attributed to the possible benefits of the frequent surveillance schedule used in Denmark, which might mask any potential benefit of [^{18}F]FDG PET/CT. Second, some recurrences and second primary lung cancers may represent occult metastases present but undetectable at initial staging. It has been suggested that patients with NSCLC with distant failure disseminate early, potentially having metastatic disease at the time of initial diagnosis.[31] Meta-analyses have found lymph node micrometastases in 25% of patients classified as node-negative and bone marrow micrometastases in 25% of patients with apparently localized disease.[32,33] Both were associated with an increased risk of recurrence and inferior survival.[34] Such undiagnosed metastatic disease could limit the benefits of intensive surveillance, given these patients may present with extensive disease precluding salvage therapy regardless of when or how it is detected.

The higher number of invasive diagnostic procedures in the PET group (IRR 1.69, 95% CI 1.30–2.21, $p < 0.01$) is probably a direct result of the increased rate of suggestive findings on surveillance scans (9% versus 6%, $p < 0.01$), which necessitated diagnostic workup. These additional procedures did not yield more confirmed

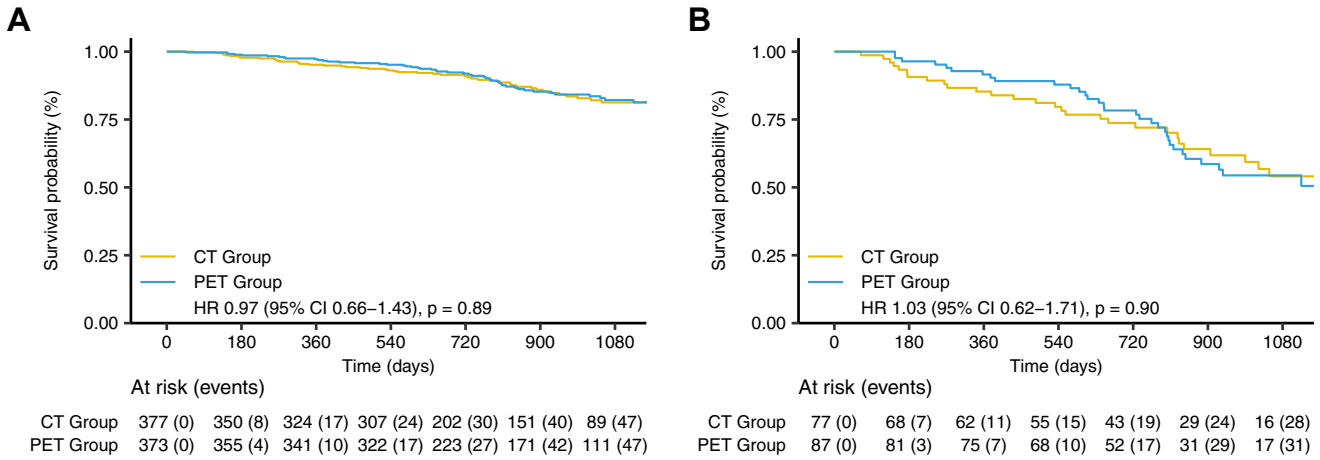

Figure 3. Overall survival. Kaplan-Meier curves for overall survival for *(A)* the entire intention-to-treat population and *(B)* patients with confirmed recurrence by surveillance group. Curves are truncated at 36 months. CI, confidence interval; CT, computed tomography; HR, hazard ratio; PET, positron emission tomography.

recurrences (23% versus 20%, $p = 0.34$), indicating that the increased diagnostic workup in the PET group represented potentially unnecessary procedures. Even so, this does raise the question of whether some PET-detected abnormalities might represent true recurrences that were not confirmed, perhaps owing to the ability of PET to detect smaller, metabolically active lesions that are challenging on which to perform a biopsy. Whether these suspected recurrences would be diagnosed with longer follow-up is unclear.

This study has several strengths. The multicenter, randomized design addresses limitations of previous retrospective studies and smaller trials, providing more robust evidence on [^{18}F]FDG PET/CT's role in post-treatment surveillance.[17,18] Our study included patients across various disease stages and treatment modalities from all regions of Denmark, with minimal exclusion criteria, ensuring a broad representation of real-world patients with NSCLC and strengthening the generalizability of our findings. The distribution of these characteristics was generally consistent with national statistics from the Danish Lung Cancer Group, particularly when considering only patients who receive curative treatment.[35]

Our study also has several limitations. First, the recurrence rate was lower than expected (22% versus 45%), which could be attributed to the high proportion of patients with early-stage disease (86% stage I–II) and of surgical cases (79%). This recurrence rate is consistent with previous studies with similar patient compositions. For instance, Lou et al.[5] reported a 20% recurrence rate for patients with stage I-to-II disease, whereas Gambazzi et al.[18] observed a 29% recurrence rate in a population with 75% of patients with stage I-to-II disease. Although the lower-than-expected recurrence rate reduced statistical power, it is unlikely to have any meaningful impact on our findings. Nevertheless, the low number of patients with stage III disease and those who received chemoradiotherapy limits conclusions about the effectiveness of [^{18}F]FDG PET/CT surveillance in these subgroups. Second, many patients included before treatment were not randomized, potentially biasing results. This was primarily due to ineligibility, lack of consent, or death, although logistical issues also contributed to patient loss. Third, the study's single-country setting with intensive surveillance might limit applicability to regions with less frequent protocols. Fourth, our study did not include any postrecurrence end points. Although improving the rate of curative-intent treatment of recurrence is important for improving patient outcomes, survival after palliative treatment, or disease-free survival after curative-intent treatment could provide a more direct measure of the clinical benefit of PET/CT. Finally, the PET group was limited to PET/CT scans only at alternating surveillance timepoints and only for two years, whereas the usual follow-up time extends up to 5 years. Therefore, we cannot determine whether using PET/CT exclusively or for surveillance beyond this period could have had a greater impact.

On the basis of the findings of this study, we do not recommend routine use of [^{18}F]FDG PET/CT for recurrence detection in patients who are asymptomatic after curative treatment for lung cancer. Our results found no difference in the rate of curative treatments for recurrence between the PET and CT groups, and we found no differences in TTR or OS between the groups. Although [^{18}F]FDG PET/CT increased the number of recurrences detected by scheduled imaging, this did not translate into improved patient outcomes. [^{18}F]FDG PET/CT is also associated with more invasive procedures to

diagnose suspected recurrence, higher costs, and increased radiation exposure, estimated to be an additional 8 to 16 mSv per year for patients in the PET arm of our study.

Our results and recent findings highlight the importance of evidence-based approaches in post-treatment surveillance and suggest that we might need to re-evaluate current follow-up methods. It should be explored whether patients at lower risk might benefit from less intensive surveillance strategies, such as using low-dose CT thorax or less frequent imaging, potentially reducing costs and radiation exposure without compromising the ability to detect recurrences in a timely manner. Moreover, blood samples collected during this study are currently being analyzed to determine whether ctDNA analysis could detect recurrence earlier or identify patients at high risk for further examination, with preliminary results showing promise.[36]

In conclusion, we found no benefit in using [18F]FDG PET/CT over ceCT for post-treatment surveillance in patients with NSCLC. Despite detecting more suspected recurrences, [18F]FDG PET/CT did not improve curative treatment rates, TTR, or OS. These findings suggest that ceCT remains the preferred option for routine surveillance, considering its comparable efficacy, lower costs, and reduced radiation exposure.

CRediT Authorship Contributor Statement

Kasper Foged Guldbrandsen: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Visualization, Project administration, Funding acquisition.

Martin Bloch: Data Curation, Writing - Review & Editing, Project administration.

Kristin Skougaard: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing.

Liza Sopina: Methodology, Writing - Review & Editing.

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Disclosure

Prof. Laursen reports receiving royalties from Munksgaard and speaker fees from AstraZeneca, Chiesi Pharma AB, GlaxoSmithKline, and Boehringer Ingelheim, outside the present work. Dr. Møller reports receiving speaker fees from Pfizer and Olympus Denmark A/S, outside the present work. Prof. Fischer reports receiving institutional grants from Aage and Johanne Louis-Hansen Foundation, Danish ctDNA Centre, and EU Horizon Research Project, and in-kind contribution from Roche Global Diagnostics for analysis of circulating tumor DNA. Dr. Saghir reports receiving speaker fees from Chiesi Pharma AB and holds leadership positions in Danish Lung Cancer Group, Danish Lung Cancer Screening Group, and Nordic Thoracic Oncology Group, outside the present work. Prof. Dahl reports receiving consulting fees from Grifols and Takeda, and speaker fees from Chiesi Pharma AB and Grifols, outside the present work. Prof. Petersen reports receiving institutional research grants from Novo Nordisk Foundation, Medtronic, and X-vivo; speaker fees from Medtronic, AstraZeneca, and Boehringer Ingelheim; travel support from AstraZeneca; and serves on advisory boards for AstraZeneca, BMS, Roche, and MSD, outside the present work. Dr. Frank reports serving as Chair of Danish Society of Clinical Oncology, outside the present work. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.04.003.

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