Comparing Two Imaging Methods for Follow-Up of Lung Cancer Treatment: A Randomized Pilot Study

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Background. **Scientific data on the image modality to be used in postcurative treatment surveillance of non-small cell lung cancer patients are scarce.**

This prospective randomized pilot trial compared the performance of integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) and contrast-enhanced computed tomography (CE-CT).

Methods. **After termination of curative-intent treatment, patients were randomly assigned to the PET-CT or the CE-CT group. Imaging was performed every 6 months for 2 years. If suspicious radiologic findings were detected or patients became symptomatic, a diagnostic workup was initiated. Sensitivity, specificity, and positive predictive value for detecting cancer recurrence were calculated for both imaging procedures.**

Results. **The study enrolled 96 patients. In 14 of 50 patients (28%) in the PET-CT group and in 14 of 46 patients (30%) in the CE-CT group, a suspicious radiologic finding was confirmed as cancer recurrence after diagnostic workup. False-positive findings were detected in 11 patients (22%) of the PET-CT group and in 8 patients (17%) of the CE-CT group. The sensitivity, specificity, and positive predictive value for detecting cancer recurrence (95% confidence interval) were 0.88 (0.62 to 0.98), 0.62 (0.42 to 0.79), and 0.56 (0.35 to 0.76) for PET-CT and 0.93 (0.68 to 1.00), 0.72 (0.53 to 0.87), and 0.64 (0.41to 0.83) for CE-CT, respectively.**

Conclusions. **The results of our study suggest that PET-CT is not superior to CE-CT in detecting cancer recurrence during 2 years after curative-intent treatment of non-small cell lung cancer.**

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Non-small cell lung cancer (NSCLC) occurs frequently, and despite curative-intent treatment, cancer-related deaths are common in the affected population. After curative-intent treatment, the risks of cancer recurrence and second primary lung cancer have been reported to be as high as 6% to 10% per person-year and 3% to 6% per person-year, respectively [1]. National and international guidelines therefore recommend systematic surveillance after curative-intent treatment of NSCLC; however, neither the duration of surveillance nor the appropriate imaging protocols have been defined to date.

Uncontrolled and mostly retrospective data suggest that computed tomography (CT) of the chest plays a role in posttreatment surveillance of NSCLC patients with respect to detection of second primary lung cancer [2], detection of recurrence [3], and survival [4]. The techniques of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG–PET) and integrated ^{18}F-FDG–PET-CT (PET-CT) play an increasing role in tumor staging of NSCLC because their sensitivities and specificities have been shown to be superior to those of a CT scan [5, 6]. Many guidelines discourage the use of ^{18}F-FDG–PET or PET-CT in posttreatment surveillance [7], mainly due to the lack of scientific data, fear of false-positive findings, and the costs of these methods.

The current prospective randomized pilot study compared PET-CT with contrast-enhanced CT (CE-CT) of the chest in posttreatment surveillance of NCSCL patients. The objective of this study was to assess and compare the diagnostic performance of the two imaging procedures based on the hypothesis that PET-CT would correctly identify cancer relapse/second primary lung cancer (subsequently referred to as cancer recurrence) more frequently than CE-CT during 2 years after curative-intent treatment of NSCLC patients.

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Patients and Methods

This was a single-center 1:1 randomized parallel group pilot superiority study. The study protocol of this prospective study was approved by our Ethics Committee (Kantonale Ethikkommission Aargau, Switzerland, Protocol No 2011/045). Written informed consent was obtained from all participants. This clinical trial was registered on the ISRCTN Registry (ISRCTN16281786).

All patients treated for histologically confirmed NSCLC at the Cantonal Hospital Aarau, Switzerland, were screened for the current study between October 11, 2011, and August 29, 2014. Each patient with NSCLC received PET-CT for tumor staging and was evaluated by an interdisciplinary board before treatment commenced. Patients were included in the current study if they were aged 18 years or older, had an ^{18}F-FDG–PET–positive tumor, had a tumor stage of I to III (or IV, if patients presented with solitary, completely resected brain metastases), and had completed a curative-intent treatment for NSCLC. Curative-intent treatment was defined as anatomic surgical lung resection alone, surgical resection plus neoadjuvant chemotherapy, surgical resection plus adjuvant chemotherapy, or radiotherapy/chemotherapy alone. Exclusion criteria were (1) lack of written informed consent, (2) insufficient knowledge of the German language, and (3) impaired kidney function (glomerular filtration rate <30 mL/min).

After completing curative-intent treatment, study participants were randomly assigned to the PET-CT group or CE-CT group. The randomization process was computerized and generated on Excel software (Microsoft, Redmond, WA), without blocking.

During the 2-year follow-up period, a clinical examination and the respective imaging procedure were performed at 6-month intervals. If there was radiologic suspicion of cancer recurrence, the patient completed the study and underwent a diagnostic workup, which consisted of at least one of the following procedures: nonscheduled PET-CT or CE-CT scan, nonscheduled brain CT, bronchoscopy, or therapeutic-intent surgical intervention. Cancer recurrence was to be confirmed histologically unless there was clear evidence of metastatic disease. Patients who had no suspicious radiologic finding but presented with symptoms of recurrence between scheduled imaging scans completed the study as well and underwent a diagnostic workup. The predefined study outcomes are summarized in Table 1.

Scheduled surveillance images and the results of additional investigations performed due to a suspicious radiologic finding or symptoms of recurrence were discussed at our weekly interdisciplinary board. Decisions concerning type of diagnostic workup and therapeutic steps were also discussed at the board.

For the PET with ^{18}F-FDG, a dose regimen of 5 MBq/kg body weight was used. The PET scans were started 60 minutes after tracer injection, scanning from the vertex of the skull to the middle of the thigh. A Biograph MCT 40 PET scanner (Siemens, Erlangen, Germany) was used with high-resolution reconstruction software, also incorporating the time-of-flight information in the reconstruction algorithm. Low-dose CT scans were performed for attenuation correction of the PET images. The PET scanner was fully cross-calibrated, allowing accurate standard uptake value measurements. This was performed according to the manufacturer's recommendations and was based on the regulations of the Swiss health authorities.

Table 1. Definition of Codes (Outcomes)

Code	Definition
A	Study termination at 24 months without a suspicious radiologic finding
B	Scheduled imaging shows a suspicious radiologic finding
B1	Diagnostic workup reveals no cancer
B2	Diagnostic workup reveals cancer recurrence
C	
C1	Symptomatic recurrence before first scheduled imaging
C2	Symptomatic recurrence between scheduled imaging

Multidetector CT examinations of the chest were performed using a 64 or a 320 detector-row CT scanner (Aquilion 64 CT/Aquilion ONE CT; Toshiba Medical Systems, Otawara, Japan). All chest multidetector CT examinations were conducted according to our routine low-dose chest multidetector CT protocol, including craniocaudal direction, supine with both arms raised above the head, single breath hold, and a scan volume that ranged from the level of the diaphragm to a level just above the thoracic inlet. The injected volume of contrast medium (Iopromide 300, Ultravist 300; Bayer Vital Gmbh, Leverkusen, Germany) was tailored to the individual body weight: 60 mL at 2 mL/s for less than 50 kg or 80 mL at 2.5 mL/s at 50 kg or heavier with a fixed contrast delay of 35 seconds.

Radiation dose exposure was systematically reduced by various methods, including automatic exposure control (Toshiba Sure Exposure 3D) and iterative reconstruction algorithms (Toshiba Adaptive Iterative Dose Reduction ADIR 3D).

When the trial was designed, the sensitivity of PET-CT and CE-CT for mediastinal nodal staging of NSCLC was considered to be 85% [8] and 57% [6], respectively. With the assumption that in posttreatment surveillance the difference in sensitivity between the two imaging methods would be the same, according to the formula introduced in the study by Lehr [9], 42 patients in each group would be necessary to detect a difference between PET-CT and CE-CT in identifying cancer recurrence with 80% power and 0.05 level of significance.

Statistica 10.0 software (StatSoft, Inc, Tulsa, OK) was used for statistical analyses. Absolute numbers, percentages, median, and interquartile range (IQR) were used to describe the study population. Time-to-event curves were created for the PET-CT and the CE-CT group by applying the Kaplan-Meier method and were compared by the log-rank test. Sensitivity, specificity, and positive predictive value were calculated with 95% confidence intervals (CI)

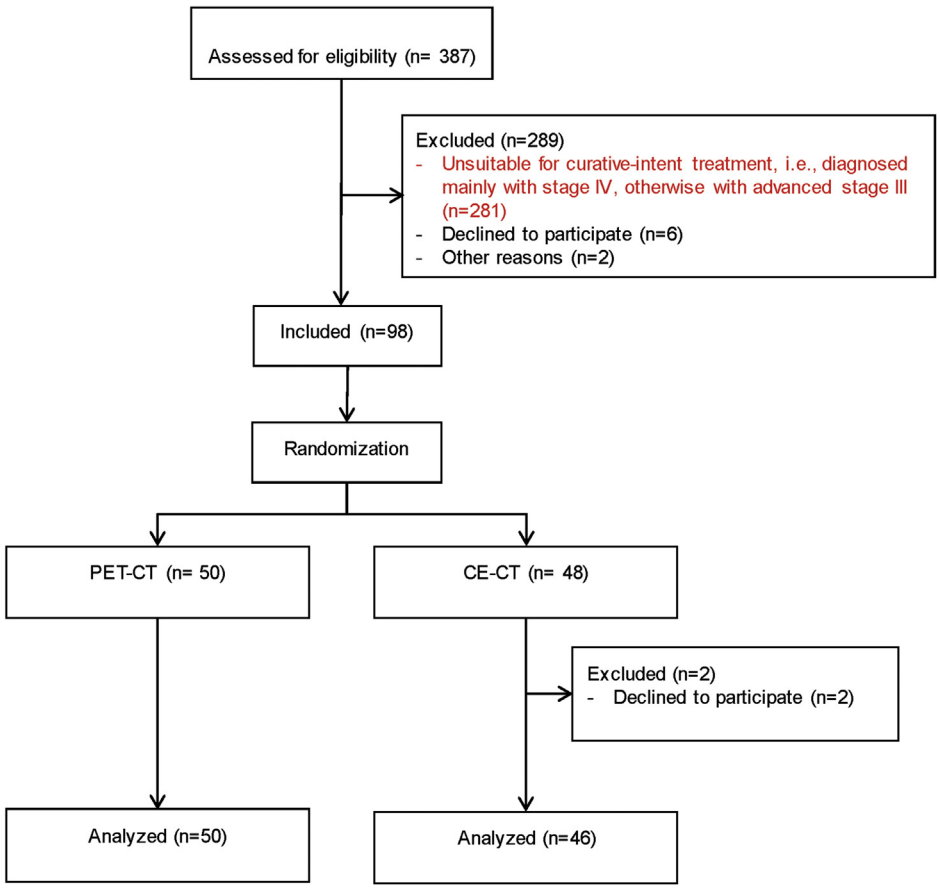

Fig 1. Study flowchart. (CE-CT = contrast-enhanced computed tomography; PET-CT = integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography.)

for both imaging procedures, thereby not taking patients into account who showed symptomatic recurrence before the first scheduled imaging. Given that there are different curative-intent treatment approaches for NSCLC, we conducted a sensitivity analysis restricted to patients treated by surgical intervention to assess the validity of observed test parameters for the most common treatment approach. The χ^2 test and the Fisher exact test were used to compare study results between imaging procedures. A p value of less than 0.05 was considered to be statistically significant.

Results

The trial's flowchart is shown in Figure 1. Of 48 patients in the CE-CT group, 46 were analyzed after 2 patients declined to participate and were excluded. The baseline characteristics of the 96 patients who were included and analyzed are summarized in Table 2. The characteristics were similar between groups. No loss to follow-up or death occurred during the 2 years of follow-up. The applied surgical procedure was dependent on the tumor location and comorbidity of the patients. Lobectomy was most frequently performed.

A total of 130 surveillance PET-CTs and 138 surveillance CE-CTs were performed. The patients' clinical outcomes are reported in Table 3. Over the study course, radiologic suspicion of cancer recurrence was found in 25 patients (50%) in the PET-CT group and 22 (48%) in the CE-CT group. In 14 patients of each group, the suspicious radiologic finding was confirmed as cancer recurrence. The sensitivity, specificity, and positive predictive value for detecting cancer recurrence were 0.88, 0.62, and 0.56, respectively, for the PET-CT group. The analysis of the CE-CT group yielded comparable results, with the sensitivity, specificity, and positive predictive value being 0.93, 0.72, and 0.64, respectively (Table 4). Findings of the sensitivity analysis restricted to patients treated by surgical intervention were overall comparable to those of the main analysis. The sensitivity/specificity were 0.87/0.67 for PET-CT and 0.92/0.81 for CE-CT, and the positive predictive value was 0.59 for PET-CT imaging and 0.71 for CE-CT imaging.

Most patients with a false-positive radiologic finding had an initial cancer stage of I or II independent of study group (PET-CT group: 11 of 11 [100%]; CE-CT group: 6 of 8 [75%]). In these patients with false-positive results, the following diagnostic procedures were performed. Scans were repeated within 6 months after suspicious radiologic finding in 3 patients of the PET-CT group and in 4 patients of the CE-CT group. There were 5 patients of the PET-CT group and 2 patients of the CE-CT group, who

Table 2. Baseline Characteristics of the Two Study Groups

Characteristic[a]	PET-CT (n = 50)	CE-CT (n = 46)	*p* Value[b]
Age, years	67 (61–74)	61 (56–70)	0.023
Female sex	17 (34)	12 (26)	0.443
COPD			0.927
None	26 (52)	23 (50)	
GOLD I and II	20 (40)	20 (43)	
GOLD III and IV	4 (8)	3 (7)	
Histologic type of tumor			0.558
Adenocarcinoma	34 (68)	27 (59)	
Squamous cell carcinoma	15 (30)	17 (37)	
Other	1 (2)	2 (4)	
NSCLC stage[c]			0.418
I	21 (42)	23 (50)	
II	18 (36)	10 (22)	
III	9 (18)[d]	12 (26)[d]	
IV[e]	2 (4)	1 (2)	
Therapy			0.774
Surgery alone	33 (66)	27 (59)	
Surgery +			
Adjuvant chemotherapy	8 (16)	11 (24)	
Neoadjuvant chemotherapy	5 (10)	3 (7)	
Radiotherapy +/– chemotherapy	1 (2)	2 (4)	
Other	3 (6)	3 (7)	

[a] Data presented as median (interquartile range) or number (%). [b] Fisher exact test (except for age comparison). [c] According to International Association for the Study of Lung Cancer, 7th Edition. [d] All stage IIIA. [e] Categorized as stage IV due to solitary brain metastases that were completely resected.

CE-CT = contrast-enhanced computed tomography; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NSCLC = non-small cell lung cancer; PET-CT = integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography.

received complementary scans with the other imaging procedure under study (ie, CE-CT or PET-CT). Endobronchial ultrasound/bronchoscopy was the most common invasive procedure, applied in 3 patients of each study group. Two patients in the PET-CT group underwent an open biopsy.

Seven patients (14%) in the PET-CT group and 9 (20%) in the CE-CT group experienced potentially curable cancer recurrence. Overall, diagnosis of cancer recurrence after diagnostic workup of a suspicious radiologic finding revealed recurrence in the remaining lung, recurrence in intrathoracic lymph nodes, or multiple metastases in 6, 3, and 5 patients of the PET-CT group, respectively, and in 6, 5, and 3 patients of the CE-CT group, respectively.

Table 4. Sensitivity, Specificity, and Positive Predictive Value of Posttreatment Imaging Surveillance of Non-Small Cell Lung Cancer Patients

Variable	PET-CT[a]	CE-CT[a]	*p* Value[b]
Sensitivity (95% CI)	0.88 (0.62–0.98)	0.93 (0.68–1.00)	1.000
Specificity (95% CI)	0.62 (0.42–0.79)	0.72 (0.53–0.87)	0.577
Positive predictive value (95% CI)	0.56 (0.35–0.76)	0.64 (0.41–0.83)	0.767

[a] Patients with cancer recurrence that was confirmed histologically or characterized by the presence of metastases were defined as "true positives." [b] Fisher exact test.

CE-CT = contrast-enhanced computed tomography; CI = confidence interval; PET-CT = integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography.

For both groups, time to suspicious radiologic finding by scheduled surveillance imaging is illustrated in Figure 2. No relevant difference in the time-to-event curves was apparent ($p = 0.528$ by log-rank test). Symptomatic cancer recurrence between scheduled study investigations was documented in 2 patients in the PET-CT group after 240 days and 183 days and in 1 patient in the CE-CT group after 565 days. These patients (code C2, see Table 1) had brain metastases and multiple metastases in the PET-CT group, and pulmonary recurrence in the CE-CT group.

Among the 39 patients without symptomatic cancer recurrence or some suspicious radiologic finding during the 2 years of follow-up (code A), cancer recurrence developed in the year after study completion in 2 patients in the PET-CT group after 6 months and 7 months, respectively, and 1 patient in the CE-CT group after 12 months after study completion. All patients had pulmonary recurrence.

Comment

Imaging surveillance after curative-intent treatment of NSCLC is recommended by many national and

Table 3. Clinical Outcomes in the Two Study Groups

Outcome	PET-CT (n = 50) No. (%)	CE-CT (n = 46) No. (%)	*p* Value[a]
Uneventful after 24 months (code A)	18 (36)	21 (46)	0.336
No cancer after diagnostic work-up of suspicious radiologic finding (code B1)	11 (22)	8 (17)	0.571
Diagnosis of cancer recurrence after diagnostic work-up (code B2)	14 (28)	14 (30)	0.793
Symptomatic recurrence before first scheduled imaging (code C1)	5 (10)	2 (4)	0.287
Symptomatic recurrence between scheduled imaging (code C2)	2 (4)	1 (2)	0.607

[a] By χ^2 test.

CE-CT = contrast-enhanced computed tomography; PET-CT = integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography.

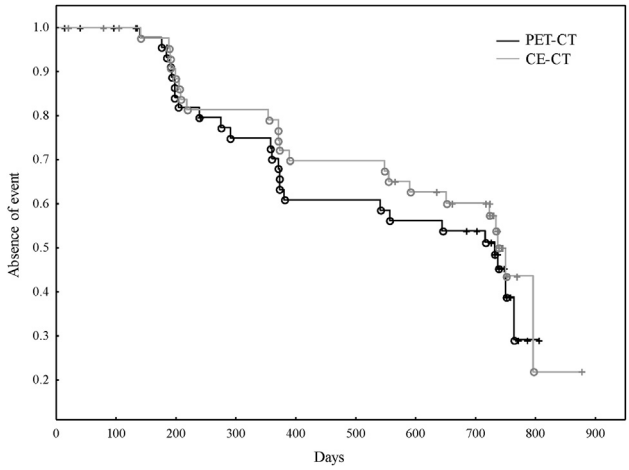

Fig 2. Kaplan-Meier plot for patients with a suspicious radiologic finding in a scheduled integrated ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) or contrast-enhanced computed tomography (CE-CT) investigation.

international societies, despite the paucity of well-designed prospective studies that support these recommendations. The duration and modality of imaging are not well defined and heterogeneous guidelines exist [7]. The current study compared PET-CT and CE-CT of the chest in cancer surveillance after curative-intent treatment of NSCLC in a randomized pilot study. We found that the sensitivity, specificity, and positive predictive value were comparable between the two imaging procedures. PET-CT may thus not be associated with a clear advantage over CE-CT in detecting cancer recurrence during 2 years after curative-intent treatment of NSCLC.

In an earlier, nonrandomized study in NSCLC patients, Takenaka and colleagues [10] found a sensitivity for PET-CT of 0.82, which is almost identical to the PET-CT sensitivity of 0.88 assessed in our study. The authors performed both PET-CT and standard radiologic examinations (eg, chest roentgenogram, CT, ultrasonography, and magnetic resonance imaging) every 6 months for at least 24 months. In our population, the sensitivity of 0.93 for CE-CT was more favorable than the sensitivity of 0.73 for the standard radiologic examinations in the Takenaka study. This might be related to the fact that more patients in our study had advanced initial stages of NSCLC (ie, stage II or higher). The latter may also explain the different overall recurrence rates of only 13% in the Takenaka study compared with approximately 30% in our study. In fact, recurrence rate and time of recurrence observed in our study were in accordance with several previous studies [1, 11, 12].

There is a concern that PET imaging provides false-positive results in lung cancer patients, particularly if inflammatory processes are involved [13]. Unnecessary additional testing, noninvasive or invasive, or both, would most likely be the consequence. In our study, we found a similar proportion of false-positive findings with both imaging procedures (22% in the PET-CT group and 17% in the CE-CT group). In a retrospective analysis, Lou and colleagues [1] reported a false-positive rate of 25% with CT screening (with or without contrast enhancement) after curative NSCLC treatment. We believe that the relatively small numbers of false-positive findings in the PET-CT and CE-CT groups are the result of our practice to discuss all surveillance investigations in a standardized fashion at our interdisciplinary board. For example, Gorenberg and colleagues [14] analyzed ^{18}F-FDG uptake in postthoracotomy scars and found particular patterns in cases of local cancer recurrence compared with ^{18}F-FDG uptake in regular scar areas. This, in our opinion, underlines the importance of having detailed knowledge of the surgical site and the need for interdisciplinary involvement when surveillance images are interpreted.

We found no evidence of PET-CT being more suitable for the detection of small and potentially curable lesions than CE-CT: 14% (PET-CT) and 20% (CE-CT) of patients had a potentially curable stage of recurrence. This means that approximately half of the detected cancer recurrences were potentially curable, irrespective of the imaging technique. In a randomized trial that compared conventional versus ^{18}F-FDG–coincidence imaging-based follow-up of resected NSCLC patients, more recurrences were detected at an early, still asymptomatic (and potentially curable) stage in the ^{18}F-FDG–coincidence imaging group than in the group in which conventional imaging techniques were used, including chest CT [15]. This may be attributed to the fact that ^{18}F-FDG–coincidence imaging was not performed in all patients during the initial cancer staging.

Considering that in the current study we performed 130 PET-CTs to detect 7 potentially curable recurrences and 138 CE-CTs to detect 9 potentially curable recurrences, the routine use of PET-CT as the primary imaging surveillance modality after curative-intent treatment of NSCLC appears unjustified in view of the high costs of PET-CT.

In only 3 of 96 patients did symptomatic recurrence occur between scheduled surveillance imaging procedures. Interestingly, in retrospective trials, symptomatic recurrence between surveillance imaging occurred in up to 30% of patients [1]. These higher proportions may result from the retrospective design of the earlier studies with heterogeneous initial staging modalities and ill-defined and inconsistent surveillance procedures. It further underscores the importance of prospective randomized studies in this field.

Our study has several limitations. Firstly, the sample size of the current study was small, and thus, the detection of minor differences in performance between the two imaging procedures was not possible. Results from larger studies are required to ultimately assess the role of PET-CT versus CE-CT in posttreatment surveillance of NSCLC patients.

Secondly, the sample size justification was based on the assumption that sensitivities of PET-CT and CE-CT

for detecting cancer recurrence are similar to those for mediastinal nodal staging of NSCLC; this is currently unproven.

Thirdly, because our study population included all patients treated curatively for NSCLC, the latter was heterogeneous across cancer stage and treatment approach. Sensitivity analysis restricted to patients treated by surgical resection yielded test variables for PET-CT and CE-CT imaging that were overall comparable to those of the main analysis. Thus, there is some evidence that findings are valid for the most common treatment given with curative intent.

Fourthly, we did not subdivide cancer recurrence into cancer relapse and second primary lung cancer because allocation to one specific group was not always possible based on the established criteria of Martini and Melamed [16] for diagnosis of second primary lung cancer.

Lastly, the follow-up period of our study was limited to 2 years. Studies with a longer observational time and with survival as the primary end point are warranted to further evaluate the clinical relevance of the two imaging procedures in posttreatment surveillance of NSCLC patients.

In summary, the results of our randomized pilot study suggest that PET-CT is not superior to CE-CT in detecting cancer recurrence during the 2 years after curative-intent treatment of NSCLC. Sensitivity, specificity, and positive predictive value were comparable between the two imaging procedures. In addition, the number of potentially curable recurrences was similar in the two groups. If imaging investigations are discussed at an interdisciplinary board, both methods may thus have a similar performance in posttherapeutic surveillance of lung cancer. Considering the substantially higher costs associated with PET-CT compared with CE-CT, the latter appears to be the preferred option for routine surveillance (at least short-term) after curative-intent treatment of NSCLC. However, some patients with a specific tumor stage or histopathology may require PET-CT follow-up based on their individual characteristics.

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