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Long-Term Follow-Up Results From PET/CT Surveillance After Surgical Resection of Lung Adenocarcinoma Manifesting as Ground-Glass Opacity

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Abstract: The purpose of our study was to retrospectively evaluate the value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for postoperative surveillance of lung adenocarcinoma manifesting as ground-glass opacity (GGO).

From May 2003 to December 2007, 111 patients with surgically resected lung adenocarcinoma manifesting as GGO were included. Clinical findings of recurrence and survival, CT features, and maximum standardized uptake value (SUVmax) were reviewed and compared among 3 groups according to GGO proportion: Group I, GGO 100%; Group II, GGO $\geq$50%; Group III, GGO $<$ 50%. Disease-free survival (DFS) was estimated using the Kaplan–Meier method. Diagnostic performances of CT and PET/CT for recurrence were compared during a long-term follow-up period of $>$5 years.

Recurrence was identified in Group III (18 of 53, 34%) but not in Groups I (n = 25) or II (n = 33) over a mean follow-up period of 74 months. Group showed significant differences in GGO proportion, SUVmax, and DFS duration ($P < 0.001$). PET/CT led to 6 false-positive and 5 false-negative interpretations of recurrence. For surveillance CT, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 94.4%, 98.6%, 98.2%, 94.4%, and 98.9%, respectively; for PET/CT, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 72.2%, 92.3%, 88.5%, 68.4%, and 93.5%, respectively. CT showed significantly higher accuracy than PET/CT ($P = 0.0188$).

FDG-PET/CT showed no clear advantage for postoperative surveillance of lung cancer with predominant GGO because of low incidence of recurrence and frequent false-positive and false-negative results.

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Abbreviations: CT = computed tomography, DFS = disease-free survival, FDG = fluorodeoxyglucose, GGO = ground-glass opacity, NSCLC = nonsmall cell lung cancer, PET = positron emission tomography, SUVmax = maximum standardized uptake value.

INTRODUCTION

Despite recent advances in lung cancer screening and targeted therapies, lung cancer is still the leading cause of cancer mortality worldwide.[1] Curative surgical resection remains the best treatment option for nonsmall cell lung cancer (NSCLC), but reported recurrence rates after curative surgical resection are 20% to 75%, depending on the final pathological stage.[2–7] Postoperative surveillance for recurrence is therefore a crucial element of cancer survivorship care and selection of optimal treatment. Several guidelines cover for follow-up and surveillance of lung cancer resected with curative intent.[8] Although the guidelines do not include ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in surveillance imaging protocols, it is currently part of clinical follow-up in many institutions based on studies demonstrating the value of PET/CT in surveillance for patients with NSCLC.[3,6,9–13] However, these studies did not consider the radiological and pathological characteristics of primary tumors such as internal density or histologic subtypes.

Recent studies demonstrated that imaging features of lung cancer are closely related to genomic characteristics and prognosis.[14–16] In particular, lung cancer manifesting as predominantly ground-glass opacity (GGO) represent adenocarcinoma with lepidic subtype. PET/CT frequently shows negative results for these lesions and is unlikely to detect lymph nodes or distant metastasis because of their low prevalence.[17,18] Thus, the value of PET/CT for surveillance of resected GGO-dominant lung cancer might be different from the value for solid lung cancers. PET/CT should therefore be evaluated in detail for diagnostic performance and potential limitations for this type of cancer. To our knowledge, no study has specifically evaluated the diagnostic utility of PET/CT surveillance for lung adenocarcinoma manifesting as GGO after curative surgery. The purpose of our study was to determine the value of ^{18}F-PET/CT for postoperative surveillance of lung cancer manifesting as GGO.

METHODS

Study Population

Our Institutional Review Board approved this retrospective study and informed consent was waived. Given that lung cancer manifesting as GGO may progress very slowly, the study population was confined to patients followed for $>$5 years after surgical resection at the time of medical record review. From

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May 2003 to December 2007, 574 consecutive patients underwent curative surgery for primary NSCLC at our institution. One author (K.B.N.) reviewed the electronic medical records to obtain clinical and pathological information. Of 574 patients, 315 had pathologically confirmed lung adenocarcinoma. In these patients, preoperative CT scans were screened by 1 thoracic radiologist (T.J.K. with 15 years of experience in chest CT interpretation) and categorized into 2 groups: solid lung cancer and lung cancer with GGO, according to internal density of the primary tumor on CT.[19] Lung cancer with GGO was defined as a primary tumor containing GGO. After exclusion of 193 patients with solid lung cancer, 6 patients without postoperative PET/CT, and 5 patients lost to follow-up, the final study population was 111 patients with lung adenocarcinoma with GGO. The same radiologist mentioned above measured tumor size and GGO proportion from preoperative CTs. GGO proportion was calculated as (1 − maximum diameter of the solid component/total maximum diameter) × 100. The study population was classified into 3 groups according to GGO proportion: Group I, pure GGO (GGO 100%); Group II, GGO ≥50%; and Group III, GGO < 50%. The final pathological stages were assessed according to the seventh edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM classification.[20]

Image Acquisition: CT and PET/CT

CT scans were performed using 1 of 3 CT scanners (iCT, Brilliance 64, or Mx-8000 IDT; Philips Medical Systems, Best, the Netherlands) with following parameters: 120 kVp, 100 to 150 mAs, pitch 0.75 to 1.75, and collimation 0.625 to 1.5 mm. Images were reconstructed using a lung reconstruction algorithm as 1 mm (thin section) or 3 mm (thick section). Postcontrast CT scans using the same parameters were performed from the lower cervical area to the lower limit of the kidney after intravenous injection of 80 to 100 mL iopromide (Ultravist 370; Schering, Berlin, Germany).

PET/CT used a dedicated PET/CT scanner (Gemini, Philips Medical Systems, Cleveland, OH). All patients fasted for at least 6 h before the PET scan to peripheral blood glucose < 140 mg/kg. ^{18}F-FDG (5.18 MBq/kg; 0.14 mCi/kg) was injected intravenously and patients rested for 50 min before whole-body scanning. Low-dose CT scan for coregistration with PET images was from the skull base to the pelvis (120 kV, 35 mA, pitch 0.8, slice thickness 5 mm). To analyze FDG accumulation, a circular region of interest was drawn on transaxial images on a slice-by-slice basis to cover whole-lesion volumes. Maximum standardized uptake value (SUVmax) was considered representative of FDG uptake.

Postoperative Surveillance

The standard surveillance regimen in our institution includes history, physical examination, and a baseline CT scan 3 months after resection with follow-up CT every 6 months for the first 2 years and annually thereafter for 5 years, which conforms to recent guidelines. Use of contrast media in surveillance CT was decided by surgeon's preference. Postoperative CT scans were interpreted for evidence of recurrence by 2 thoracic radiologists (T.J.K. and K.W.L., with 15 and 20 years' experience in chest image interpretation, respectively) that were blinded to clinical information and PET/CT findings. Recurrence decisions were made by consensus based on findings such as new pulmonary nodules, lymphadenopathy, pleural effusion, and extrathoracic mass. Lymph node assessment was based on the size criterion with short axis diameter > 10 mm defined as abnormal. Necrosis within lymph nodes was defined as a sign of malignancy, regardless of size.

Surveillance PET/CT was typically performed when recurrence was suspected, either by new symptoms or abnormal findings on conventional imaging studies. If recurrence was not suspected in routine surveillance, PET/CT was performed as surveillance ~12 months after resection, then annually for 3 to 5 years by surgeon's direction. Postoperative PET/CT scans were interpreted by a nuclear medicine physician in our hospital for evidence of recurrence. PET/CT was interpreted as positive for recurrence if new hypermetabolic areas were detected compared to prior PET/CT exams with sufficient activity to suggest neoplastic disease, or if biopsy was requested for a suspicious lesion. All suspicious hypermetabolic areas were measured quantitatively. No focal uptake or faint uptake of surrounding soft tissue was defined as negative.

If brain metastases were suspected, brain magnetic resonance imaging was performed. Final diagnosis of recurrence was confirmed by biopsy or relevant imaging studies with a follow-up period of at least 12 months. The presence of metachronous tumors was defined according to the Martini–Melamed criteria.[21]

Statistical Analysis

Clinical findings, CT features including lesion size and GGO proportion, and SUVmax were compared using 1-way analysis of variance followed by Student–Newman–Keuls post hoc test. The diagnostic value of surveillance CT and PET/CT for recurrence were calculated on a per-patient basis and compared using McNemar's test. Disease-free survival (DFS) after curative-intent surgery was analyzed and compared using the Kaplan–Meier method and log-rank test. Multivariate logistic regression analysis was performed to identify independent factors predicting recurrence. Forward stepwise selection logistic analysis was used with iterative variable entry based on test score P value < 0.05, removing variables with a probability likelihood of 0.10. P values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the MedCalc, ver. 14 commercial software package (MedCalc Software, Mariakerke, Belgium).

RESULTS

Demographics and Preoperative Imaging Features

Preoperative characteristics and surveillance results for 111 patients are summarized in Table 1. Among the patients, 56 were men (mean age, 60 ± 10 years; range, 27–81 years) and 55 were women (mean age, 60 ± 10 years; range, 28–82 years). Standard lobectomy was performed in 81 patients, segmentectomy in 9, and wedge resection in 21. The final pathological stages included stage IA in 80 patients (72.1%), stage IB in 23 (20.7%), stage IIA in 3 (2.7%), stage IIB in 1 (0.9%), and stage IIIA in 4 (3.6%). Preoperative CT scans were performed on all patients with preoperative PET/CT on 102. All preoperative CT and PET/CT scans were performed within 30 days before surgery (range, 1–25 days, median 13 for CT; range, 1–24 days, median 12 for PET/CT). No differences were seen in sex and age among groups. Tumor size, GGO proportion, and SUVmax were significantly larger in Group III (GGO < 50%) 50%) than in Groups I or II ($P < 0.001$, respectively). All Group I patients had stage IA disease. Incidences of stage IA disease

TABLE 1. Demographics, Preoperative Ground-Glass Opacity Proportion and SUVmax, and Surveillance Results for 111 Patients With Resected Lung Adenocarcinoma

	Group I (GGO 100%)	Group II (GGO ≥ 50%)	Group III (GGO < 50%)	*P* Value
Number (%)	25 (22)	33 (30)	53 (48)	
Sex				
Men	12	15	28	
Women	13	18	25	
Age	61 ± 8.6 (44–78)	59 ± 9.5 (41–74)	61 ± 9.9 (35–79)	*0.534
Tumor size (cm)	1.5 ± 0.6 (0.6–2.9)	2.0 ± 0.6 (1.0–4.0)	2.6 ± 0.9 (0.8–5.2)	*<0.001
GGO proportion	100	66.2 ± 9.8 (52–85)	29.6 ± 11.9 (6–48)	*<0.001
SUVmax	0.6 ± 0.7 (0–2.4)	1.2 ± 1.3 (0–6.6)	2.9 ± 2.1 (0–8.4)	*<0.001
Pathologic stage				
IA	25	29	26	†<0.001
IB	0	3	20	
IIA	0	1	2	
IIB	0	0	1	
IIIA	0	0	4	
DFS (months)	78.1 ± 10.0 (60–96)	76.1 ± 12.1 (61–109)	60.1 ± 28.0 (6–106)	*<0.001
OS (months)	78.1 ± 10.0 (60–96)	76.1 ± 12.1 (61–109)	70.2 ± 31.0 (17–106)	*0.094
Recurrence	0	0	18	†<0.001

Data are numbers, with range in parentheses.
DFS = disease free survival; OS, overall survival, GGO = ground-glass opacity, SUVmax = maximum standardized uptake value.
* *P* values based on 1-way analysis of variance with Student–Newman–Keuls posthoc test.
† *P* values based on comparisons between Groups I and III and Groups II and III by Fisher's exact test. *P* values <0.017 were regarded as statistically significant considering multiple comparison setting.

were significantly higher in Groups I and II than Group III ($P < 0.001$, respectively).

Postoperative Surveillance and Survival

The median postoperative follow-up duration was 74 months (range, 17–109 months). Postoperative CT surveillance was performed with noncontrast (n = 212) or postcontrast (n = 545) CT scans. Mean number of follow-up CT scans was 7.7 ± 2.7 times (range, 4–12). Mean number of follow-up PET/CT was 4.6 ± 1.4 times (range, 1–8). Mean time interval between surgery and initial follow-up PET/CT scan was 9.7 ± 2.3 months (range, 3–13 months).

Recurrence was diagnosed in 18 of 53 patients (34.0%) in Group III with no recurrence in Group I or II ($P < 0.001$, respectively). DFS was significantly longer in Groups I and II than Group III (Figure 1) ($P < 0.001$, respectively), but overall survival was not significantly different among groups ($P = 0.094$). Recurrence was diagnosed by histological examination in 8 patients and by serial imaging follow-up in 10. Recurrences were found in 4 patients with stage IA disease, 8 with stage IB, 2 with stage IIA, and 4 with stage IIIA. Locoregional recurrences were found in 9 lesions in 9 patients, including regional lymph nodes in 4, ipsilateral lung in 4, and staple line in 1. Distant recurrences were found for 15 lesions in 9 patients, including pleural disease in 4, contralateral lung in 4, spine in 2, and liver, kidney, adrenal gland, spleen and brain in 1, respectively. Recurrence sites, detection methods and treatment for recurrent diseases are in Table 2.

CT and PET/CT scans were available within 1 month of recurrence diagnosis for all patients. In 13 patients, recurrence was diagnosed by both CT and PET/CT scans. In 1 patient with neurological symptoms, brain metastasis was not detected by PET/CT and was diagnosed with brain MRI. One false-positive result due to reactive lymph node enlargement and 1 false-negative result due to brain metastasis occurred for surveillance CT. Six false-positive results and 5 false-negative results occurred for surveillance PET/CT. Reasons for PET/CT false-positive results were lung inflammation in 3 patients, reactive lymph node in 2 (Figure 1), and degenerative arthritis in 1. In these patients, the primary tumor had a mean SUVmax in preoperative PET/CT of 1.1 (range, 0–1.8), whereas mean SUVmax for false-positive results in surveillance PET/CT was 4.0 (range, 2.2–4.6). All 5 false-negative results were in Group III. Reasons for false-negative results in PET/CT were pulmonary (n = 3) and pleural seeding (n = 1) nodules measuring <5 mm in diameter (Figure 2) and brain metastasis (n = 1). Detailed information on false-positive and false-negative results for PET/CT is in Table 3. For surveillance CT, sensitivity was 94.4%, specificity was 98.9%, accuracy was 98.2%, positive predictive value was 94.4%, and negative predictive value was 98.9%; for PET/CT, sensitivity was 72.2%, specificity was 93.5%, accuracy was 90.1%, positive predictive value was 68.4%, and negative predictive value was 94.6%. CT showed significantly higher accuracy than PET/CT ($P = 0.0188$).

Predictors of recurrence were identified in multivariate logistic regression analysis using the variables of pathological stage (I vs II–III), GGO proportion, and preoperative SUVmax. GGO proportion was the only independent predictor of recurrence (odds ratio, 0.913; 95% confidence interval, 0.861–0.967; $P = 0.002$). Pathological stage (odds ratio, 9.680; 95% confidence interval, 0.918–102.1; $P = 0.059$) and SUVmax (odds ratio, 1.006; 95% confidence interval, 0.669–1.513; $P = 0.977$) were not significant predictors.

During the follow-up period, 2 patients with metachronous lung adenocarcinomas in Group II were diagnosed by both CT

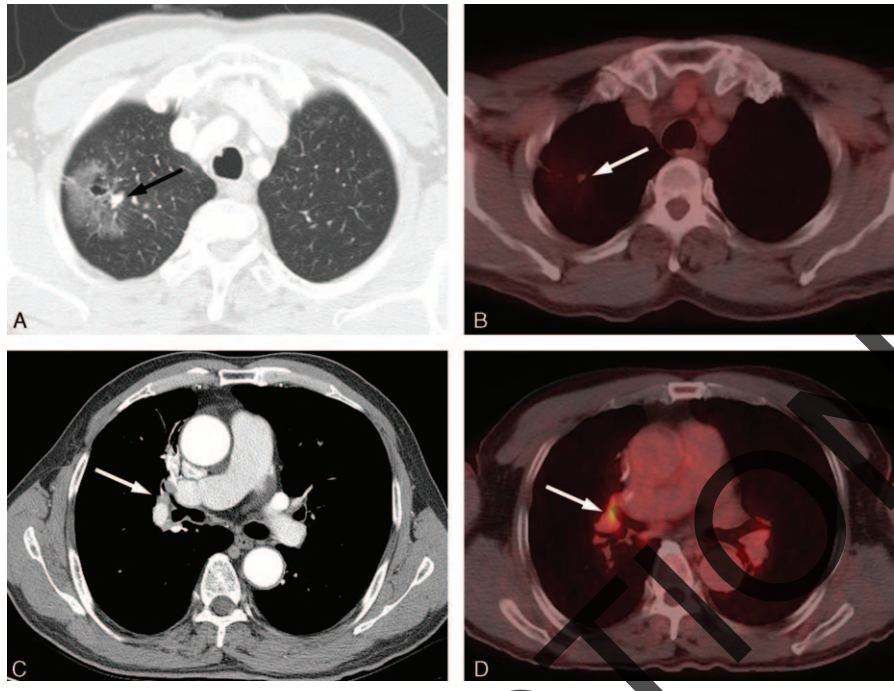

FIGURE 1. False-positive finding in PET/CT in a 57-year-old male patient with lung adenocarcinoma who underwent right upper lobectomy. (A) CT image shows a ground-glass opacity (GGO) lesion with solid portion (arrow) in the right upper lobe (GGO proportion: 83%, Group II). (B) PET/CT image shows a GGO lesion with faint fluorodeoxy glucose (FDG) uptake (arrow) with an SUVmax of 1.8. (C) Surveillance CT scan performed 12 months after lobectomy shows several right peribronchial lymph nodes measuring <1 cm in short diameter (arrow). (D) Surveillance PET/CT scan performed at the same day with surveillance CT shows right peribronchial lymph node (arrow) with an SUVmax of 4.8. Endobronchial ultrasound-guided aspiration biopsy for peribronchial lymph nodes revealed no tumor involvement. The patients are followed postoperatively for >7 years without evidence of recurrence. FDG = fluorodeoxy glucose, GGO = ground-glass opacity, PET/CT = positron emission tomography/computed tomography, SUVmax = maximum standardized uptake value.

and PET/CT scans, at 6 and 71 months after surgery. Extrapulmonary malignancies were diagnosed in 7 patients: thyroid (n = 3), prostate (n = 2), breast (n = 1), and rectum (n = 1). In these patients, thyroid (n = 2) and prostate (n = 1) cancers were initially detected on follow-up PET/CT.

DISCUSSION

In our study, ^{18}F-FDG-PET/CT demonstrated no advantage for postoperative surveillance of lung cancer manifesting as predominant GGO. The reasons for the lack of advantage were the low incidence of recurrence and more frequent false-positive and false-negative results than surveillance CT. In our cohort of patients with surgically resected lung adenocarcinoma followed <5 years postoperatively, no recurrence was found for lung cancer with GGO ≥50%; recurrence was diagnosed in patients with lung cancer with GGO < 50% (18 out of 53, 34.0%). Compared with surveillance CT, which detected all instances of recurrent diseases except for a single brain metastasis, PET/CT resulted in 6 false-positive and 5 false-negative results.

The incidence of recurrence in our study population, which was enriched for patients with lung adenocarcinoma with a GGO dominant lesion was 16.2% (18 of 111), which was lower than rates (24–30%) in the studies on resected stage I NSCLC [22,23] but comparable to rates (11–15%) in studies on resected stage IA NSCLC.[24–26] In addition to a lower incidence of recurrence, all recurrences in our study occurred in patients with GGO < 50% (Group III). Our results are consistent with previous studies that reported the GGO proportion in lung adenocarcinoma correlates well with recurrence, nodal metastasis, and overall survival.[27–31] Pretest probability is important in determining appropriate use of imaging modality for diagnostic workup. Therefore, the value of surveillance PET/CT might be limited in GGO dominant lung cancer because of the low incidence of recurrence after curative surgical resection.

Several studies reported that PET/CT is useful for lung cancer surveillance after surgery and has better sensitivity and specificity than conventional imaging modalities.[3,9–13] In contrast to these results, in our cohort of patients with surgically resected adenocarcinoma manifesting as GGO, PET/CT resulted in more frequent false-positive and false-negative results than CT. False-negative results in our study might be explained by following reasons. First, PET/CT examinations have limited detection of small pulmonary or pleural nodules because of spatial resolution.[32] Second, FDG uptake values of GGO dominant lung cancer are not high, making accurately detecting less FDG-avid recurrent disease difficult. In addition to false-negative findings, PET/CT examinations are sensitive to nonspecific inflammation which frequently results in false-positive findings, especially in a tuberculosis-endemic area.[33,34] False-positive PET/CT results in our study were mainly due to nonspecific inflammation in the lungs or benign mediastinal lymph nodes, resulting in lower specificity for PET/CT than for CT.

TABLE 2. Recurrence Characteristics in 18 Patients

Characteristic	Number
Recurrence location	
Locoregional	9
Regional lymph nodes	4
Ipsilateral lung	4
Staple line	1
Distant	15
Pleural disease	4
Contralateral lung	4
Liver	1
Kidney	1
Adrenal gland	1
Spleen	1
Spine	2
Brain	1
Detection method	
Surveillance CT	17
PET/CT	13
Brain MRI	1
Methods by diagnosis	
Histologic diagnosis	8
Serial imaging follow-up	10
Treatment of recurrence	
Surgery	3
Chemotherapy	9
Radiation therapy	2
Chemo + RT	1
Others	3

Chemo = chemotherapy, MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography, RT = radiation therapy.

TABLE 3. Reasons for False-Positive and False-Negative Results of PET/CT Scans

	False-Positive Results	False-Negative Results
Causes	Lung inflammation (n = 3)	Pulmonary nodules (n = 3)
	Reactive lymph node (n = 2)	Pleural seeding (n = 1)
	Degenerative arthritis (n = 1)	Brain metastasis (n = 1)
Group I	2	0
Group II	3	0
Group III	1	5

PET/CT = positron emission tomography/computed tomography.

Preoperative SUVmax is reported to be a predictor of recurrence in resected NSCLC.[9–13] However, SUVmax was not useful in predicting recurrence in GGO-dominant lung cancers, which frequently show negative or less-avid FDG uptake. Recurrent disease from these non-FDG-avid primary tumors also showed negative findings. In contrast to SUVmax, in our study, GGO proportion, an imaging biomarker derived from thin-section CT, was an independent predictor of recurrence in GGO dominant lung cancer. We believe that thin-section CT is an important surveillance method, along with preoperative evaluation of GGO dominant lung cancer.

Our study results suggested that personalized surveillance protocols based on individual patient risk factors and tumor characteristics should be implemented in clinical practice. Recent studies reported the value of PET/CT for diagnosis of postoperative recurrence in lung cancer,[3,9–13] and many institutions now use PET/CT in routine surveillance protocols.

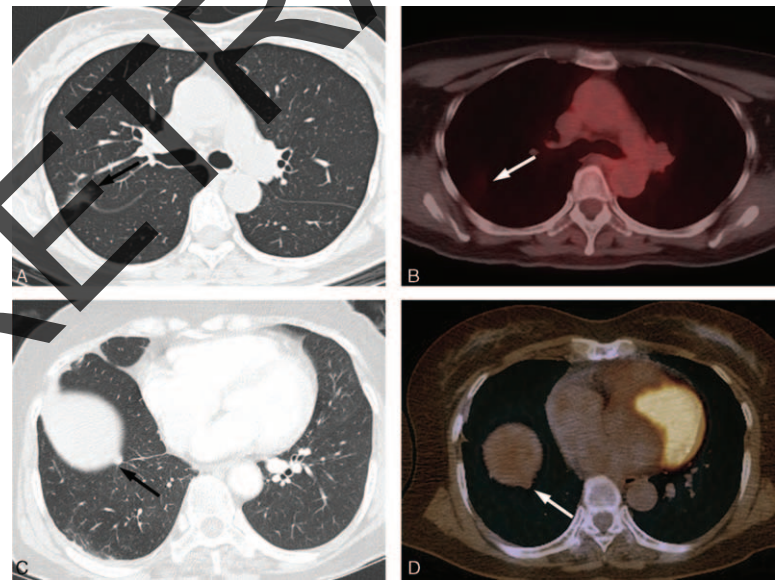

FIGURE 2. False-negative finding in PET/CT in a 65-year-old female patient with lung adenocarcinoma who underwent right upper lobectomy. (A) CT image shows a mixed GGO lesion (arrow) with fissural retraction in the right upper lobe (GGO proportion: 38%, Group III). (B) PET/CT image shows a GGO lesion with faint FDG uptake (arrow) with an SUVmax of 1.7. (C) Surveillance CT scan performed 9 months after lobectomy shows a pleural based nodule suggesting pleural seeding (arrow). (D) Surveillance PET/CT scan performed at the same day with surveillance CT shows no FDG uptake within the nodule. Pleural seeding was confirmed by the disease progression on follow-up imaging studies. FDG = fluorodeoxy glucose, GGO = ground-glass opacity, PET/CT = positron emission tomography/computed tomography, SUVmax = maximum standardized uptake value.

However, these studies and current surveillance guidelines do not consider the radiogenomic characteristics of lung cancer. Primary tumor imaging characteristics such as internal density are closely related to biological and clinical behavior and patient prognosis. Typically, GGO dominant lung cancer represents lepidic-predominant adenocarcinoma, which has a low probability of lymph node or distant metastasis and excellent prognosis after curative surgery. Therefore, the utility of PET/CT for surveillance of GGO-dominant lung cancer may be different from the utility for solid lung cancer. Radiogenomic features of the primary tumor, including GGO or solid internal density, could be a promising imaging biomarker for future, tailored surveillance protocols.

Our study has several limitations. First, the retrospective design unavoidably introduces the issue of inherent bias. To our knowledge, no prospective randomized control study has evaluated the clinical utility of PET/CT for surveillance of lung cancer after surgical resection. A regimen tailored to the characteristics of the primary tumor should be considered and evaluated in future prospective studies. Second, the number of recurrences in our study population might not be large enough to evaluate the diagnostic accuracy of surveillance imaging modalities including CT and PET/CT. Further large-scale studies are warranted. Third, the recurrence sites in our study were mainly intrathoracic, and so the recurrences might have been adequately detected with chest CT. Fourth, we used low-dose CT protocol with thick-section reconstruction for coregistration with PET images. The diagnostic quality CT with full-dose and thin-section reconstruction might reduce the false-negative PET findings for small pulmonary or pleural nodules.

CONCLUSION

In conclusion, FDG-PET/CT showed no clear advantage for postoperative surveillance of lung cancer with predominant GGO because of the low incidence of recurrence and frequent false-positive and false-negative results. Further studies are required to evaluate the utility of tailored surveillance protocols with PET/CT for patients with resected lung cancer.

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