

## Original Article

# PET/CT vs. non-contrast CT alone for surveillance 1-year post lobectomy for stage I non-small-cell lung cancer

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**Abstract:** <sup>18</sup>F-FDG PET/CT was compared with non-contrast chest CT in monitoring for recurrence 1-year after lobectomy of stage 1 non-small-cell lung cancer (NSCLC). For surveillance after treatment with curative intent, current (April 2012) National Comprehensive Cancer network guidelines recommend chest CT with or without contrast every 6-12 months for 2 years, then non-contrast chest CT annually. PET/CT is not currently indicated for routine follow-up. One hundred patients receiving surveillance PET/CT 1-year after lobectomy for the treatment of stage 1a or 1b NSCLC were included in the study. Exclusion criteria included the presence or interval diagnosis of a second malignancy, or surgical treatment more radical than single lobectomy. The non-contrast CT obtained from the 1-year PET/CT was interpreted by an experienced chest radiologist blinded to the PET/CT for evidence of recurrence using the following findings: pulmonary nodule, pleural effusion, pleural mass, adenopathy, and extrathoracic mass. The decision about recurrence was made solely from the non-contrast CT without PET/CT findings. This was compared with the determination made with PET/CT. The reference standard for determination of recurrence was the multi-disciplinary tumor board who had access to all imaging and clinical data. Recurrence at 1 year was documented in 16 of 90 patients. All 16 recurrences were documented with PET/CT and 9 were found with non-contrast CT. Five of the 7 recurrences missed with non-contrast CT were extrathoracic metastases. Sensitivity of CT and PET/CT for recurrence was 56.3% and 100%, respectively ( $p = 0.015$ ). Specificity of CT and PET/CT for recurrence was 95.9% and 93.2%, respectively ( $p = 0.62$ ).

**Keywords:** Lung cancer, PET/CT, non-small cell, CT, lobectomy, stage 1, lung cancer surveillance

## Introduction

Lung cancer is the most common cause of cancer related mortality and second most frequently diagnosed malignancy in the United States. In 2007, there were 203,536 new diagnoses of lung cancer in the United States of which 109,643 were males and 93,893 were females. In the same year there were 158,683 deaths from lung cancer, 88,329 of which were men and 70,354 were women [1].

According to the 7<sup>th</sup> edition of the TNM staging system for non-small cell lung cancer (NSCLC), stage 1A cancers are isolated to the lung and  $\leq 3$  cm in maximum diameter. Stage 1B tumors have one or more of the following: a) tumor size greater than 3 cm and  $\leq 5$  cm, b) tumor involving main bronchus  $\geq 2$  cm distal to carina, c) tumor invading visceral pleura, and/or d) associated obstructive pneumonitis or atelectasis

extending to hilar region but not including the entire lung. Median survival for patients with clinical stage 1A is 60 months, clinical stage 1B is 43 months, pathologic stage 1A is 119 months, and pathologic stage 1B is 81 months [2, 3]. The clinical stage is determined by the initial imaging prior to obtaining a pathologic diagnosis. Pathologic stage is determined after surgery based upon the histological characteristics of the tumor.

The treatment of choice for patients with stage 1 NSCLC is surgery. Lobectomy is preferred to limited pulmonary resection because the latter has a 75% higher locoregional recurrence rate exclusive of second primaries and 30% higher overall death rate compared with lobectomy [4-6]. According to the lung cancer study group, the 5-year incidence of local recurrence after lobectomy for stage I and II disease is 23% [4, 7, 8].

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For surveillance after treatment with curative intent, current (April 2012) National Comprehensive Cancer network (NCCN) guidelines are for chest CT with or without contrast every 6-12 months for the first 2 years, then non-contrast chest CT annually (category 2B recommendation). Positron emission tomography (PET) is not currently indicated for routine follow-up [5, 9] ([http://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)). Nevertheless, PET/CT is becoming accepted as the standard for staging and monitoring for recurrence in oncology.

A postoperative PET/CT 1 year after curative resection of NSCLC can be used for early detection of recurrence in asymptomatic patients [10]. The prior study by Cho et al was not intended to compare PET/CT with non-contrast CT. As such, non-contrast CT findings were not examined for comparison. Our study compares PET/CT and non-contrast CT with each patient serving as their own control for comparison. PET/CT may also be useful in distinguishing recurrence from scarring, pleural thickening, and mediastinal fibrosis, which is commonly found after surgical resection [11]. PET/CT has been shown to be at least as accurate as CT alone in detecting postoperative recurrence [10, 12, 13]. However, a limitation of the study by Onishi et al is that it utilized brain MR imaging, contrast enhanced whole-body CT and bone scintigraphy for comparison with PET/CT to make a decision about recurrence [14]. These examinations are not currently recommended in the NCCN guidelines for surveillance. Our study addresses this limitation by using non-contrast chest CT for comparison, which is detailed in the NCCN guidelines.

As PET/CT is becoming accepted as the standard for surveillance despite a paucity of support in the literature, this study aims to provide evidence for or against the use of PET/CT over non-contrast CT. The purpose of this study is to compare the effectiveness of PET/CT versus non-contrast CT in monitoring for recurrence 1 year after lobectomy for stage 1 NSCLC.

### Methods

#### *Patients*

One hundred patients with clinical stage 1 NSCLC as determined by PET/CT who received

a surveillance PET/CT between November 2007 and 2010 1 year after lobectomy for the treatment of stage 1 (including 1a and 1b) NSCLC were included in the study. Exclusion criteria included the presence or interval diagnosis of a second malignancy, or surgical treatment more radical than a single lobectomy. Ten patients were excluded from the study for these reasons so there were 90 total patients included. Twenty-one of the 90 patients included in the study (23.3%) were upstaged to stage 2 or 3 based on the results of the pathology from their lobectomy. Sixty-nine patients were confirmed to be pathologically stage 1 after lobectomy. The Institutional Review Board at Stony Brook University Hospital approved this study.

#### *PET/CT image acquisition and interpretation*

PET/CT images were obtained on a Siemens Biograph 40 scanner 60 minutes after receiving an intravenous injection of  $^{18}\text{F}$ -FDG. Patients fasted for at least 6 hours prior to the time of injection. The PET/CT workstation software used was MIM 4.2.2 and 5.1 (MIM Software, 2009, 2010). Maximum standardized uptake value (SUVmax) was used with a 3D region of interest for all measurements. Foci of activity were compared with lung background and blood pool. Three experienced board-certified nuclear radiologist interpreted PET/CT images at the time of image acquisition and a decision was made about recurrence using the PET/CT.

The nuclear medicine physician made the determination of a positive PET/CT qualitatively. A PET/CT was considered positive for recurrence if there were new hypermetabolic areas compared to prior PET/CT exams with activity (measured by standardized uptake value, SUV) elevated enough to suggest neoplastic disease. Alternatively, the PET/CT was determined to be positive if tissue sampling was requested for a suspicious lesion. However, all suspicious hypermetabolic areas were measured quantitatively, with SUVmax for proven recurrences ranging from 3.9 to 10.1, mean of  $6.1 \pm 2.6$ . A standard SUV cutoff value was not utilized, as the final determination of recurrence was qualitative. Both qualitative and quantitative measurements were necessary because of the comparative nature of PET/CT. For example, an area of mild hypermetabolic activity with SUV 3.5 would not be concerning if it appeared sta-

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**Table 1.** This table summarizes the recurrences and remissions identified with PET/CT and non-contrast CT alone. Cases were determined to be recurrences by the multidisciplinary tumor board, who had access to all imaging and clinical information. "Remission" describes cases that were not deemed to be recurrences by the multidisciplinary tumor board. All 16 true recurrences were identified with PET/CT, resulting in a sensitivity of 100%. Nine of the 16 recurrences were identified with non-contrast CT alone, so the sensitivity of non-contrast CT was 56.3%. There were 3 false positive non-contrast CT reads and 5 false positive PET/CT reports resulting in a specificity of 95.9% and 93.2%, respectively.

	Recurrence	Remission	Total
Non-contrast CT Pos.	9	3	12
Non-contrast CT Neg.	7	71	78
Total	16	74	90
Sensitivity Non-contrast CT: 56.3%			
Specificity Non-contrast CT: 95.9%			
	Recurrence	Remission	Total
PET/CT Pos.	16	5	21
PET/CT Neg.	0	69	69
Total	16	74	90
Sensitivity PET/CT: 100%			
Specificity PET/CT: 93.2%			

ble from a prior study. However, a new hypermetabolic nodule would be suspicious for recurrence.

### *Non-contrast CT image acquisition and interpretation*

The non-contrast CT interpreted for this study was a series of the PET/CT scan obtained 1 year after lobectomy including both soft tissue and edge enhanced algorithms. All CT images were obtained at respiratory arrest. Scan time was approximately 7 seconds. The patient was then instructed to slowly exhale. The non-contrast CT was interpreted for evidence of recurrence by an experienced academic chest radiologist who was blinded to the PET/CT findings and clinical information. A decision about recurrence was made based on the presence or absence of the following: pulmonary nodule, pleural effusion, pleural mass, adenopathy, and extrathoracic mass [15]. The determination of recurrence was made solely from the non-contrast CT, without PET/CT findings.

### *Final determination of recurrence*

The decision about recurrence from the non-contrast CT alone was compared with that made from the PET/CT. The final determination of recurrence was made by the multidisciplinary tumor board, who had access to all imaging and clinical data. Readers of the PET/CT and non-contrast CT were blinded to the board's determination.

### *Statistical analysis*

The sensitivity and specificity of both PET/CT and non-contrast CT were calculated. They were then compared using McNemar's chi-squared test. Chi-square and Fischer's exact tests are only appropriate when the values compared are independent [16, 17]. However, the data points in this study were paired as each PET/CT and CT pair analyzed was of the same patient. Therefore, McNemar's chi-squared test was used to compare sensitivities and specificities of PET/CT versus CT versus the reference decision of the multidisciplinary tumor board.

## **Results**

### *True recurrences*

There were 16 true recurrences as determined by the multidisciplinary tumor board out of 90 total patients included in the study (17.8%). Six of these recurrences were in the group of patients confirmed to have stage 1 disease after lobectomy and ten recurrences were in the group of patients upstaged to stage 2 or 3 after surgery. The recurrence rate of stage 1 NSCLC 1 year after lobectomy was 8.7%. The recurrence rate of patients upstaged to stage 2 or 3 disease 1 year after lobectomy was 47.6%.

### *PET/CT: all stages*

All of the 16 recurrences were found with PET/CT (100%). Twenty-one of the 90 (23.3%) PET/CTs performed 1 year after lobectomy were called positive using the criteria detailed in the methods. The multidisciplinary tumor board determined that 16 of that 21 actually had recurrent disease and 5 of the 21 patients (23.8%) were false positives without recurrent disease. Three of the 5 false positive patients had a negative lymph node biopsy. The other

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**Table 2.** Table 2 shows the non-contrast CT findings stratified by result. It is important to note that many patients had pleural effusions and pulmonary nodules. Of the 90 total patients, 30 had pleural effusions and 50 had pulmonary nodules. A large percentage of patient's with these findings were read correctly as a negative CT without evidence of recurrence (22 pleural effusions and 37 pulmonary nodules). Additionally, few extrathoracic masses were identified. No extrathoracic masses were identified in the false negative CT reads (missed recurrences).

	Adenopathy	Pleural Effusion	Pleural Mass	Pulmonary Nodule	Extrathoracic Mass
True positive CT	5	4	3	7	2
False negative CT	0	3	0	3	0
False positive CT	2	1	0	3	0
True negative CT	2	22	3	37	2
Total CT	9	30	6	50	4

two patients did not have a biopsy at the discretion of their clinician. However, follow-up PET/CT exams were negative for disease up to one year later. There were no false negative PET/CT exams. The sensitivity and specificity of PET/CT for recurrence was 100% and 93.2%, respectively. See **Table 1** for a summary of this data. The PET/CT findings described as hypermetabolic in the official imaging report of the 16 confirmed recurrences are as follows. Pulmonary nodules were identified as hypermetabolic in 11/16 recurrences. Extrathoracic masses were hypermetabolic in 9/16 recurrences. Hypermetabolic adenopathy was found in 6/16 recurrences. Hypermetabolic pleural effusions and pleural masses were each noted in 2/16 recurrences. There were 2 false positive examples of adenopathy. One false positive PET/CT had a negative lymph node biopsy. The other example of false positive adenopathy was correctly identified as benign by PET/CT based on the SUV uptake.

### *Non-contrast CT: all stages*

Nine of the 16 recurrences were found with non-contrast CT (56.3%). Each non-contrast CT was evaluated for the presence of extra-thoracic masses, adenopathy, pleural effusion, pleural mass, and pulmonary nodules to make a decision about recurrence. Twelve of the 90 CTs (13.3%) were called positive using the non-contrast CT alone. The multidisciplinary tumor board agreed that 9 of those 12 CTs represented recurrences (true positive). Therefore, there were 3 false positives (25%) and 7 false negatives (44%). The sensitivity and specificity of CT in detecting recurrence was 56.3% and 95.9%, respectively. This is summarized in **Table 1**.

The 3 false positive CTs are the same three cases described above with a negative lymph node biopsy. The 7 recurrences missed with non-contrast CT alone (false negatives) were 5 extrathoracic metastases (71%), one anterior mediastinal mass and one new hypermetabolic pulmonary nodule in a patient with countless pulmonary nodules. The extrathoracic metastases missed by CT were to the anterior chest wall in one patient, to the neck in two patients, to the sacrum and T4 vertebra in another patient, and to the liver below the adrenals in the last patient (not normally imaged on a chest CT).

**Table 2** summarizes the non-contrast CT findings using the 5 data points listed above. Pulmonary nodules were found in 50 of the 90 patients enrolled in the study. Thirty-seven of the pulmonary nodules were in true negative CT reads. Pleural effusions were identified in 30 patients, 22 of which were true negative CT cases. Non-contrast CT identified pulmonary nodules in 10/16 recurrences, pleural effusions in 7/16 recurrences, adenopathy in 5/16 recurrences, pleural masses in 3/16 recurrences, and extrathoracic masses in 2/16 recurrences. No extrathoracic masses were identified in false negative CT reads or missed recurrences.

### *Stage 1*

Sixty-nine patients were confirmed to have stage 1 NSCLC pathologically after lobectomy. There were 6 recurrences in this group of patients, yielding a one-year recurrence rate of 8.7%. All six recurrences were identified with PET/CT and one recurrence was not identified with non-contrast CT alone. The missed recur-

rence was a hypermetabolic pulmonary nodule in a patient with many pulmonary nodules. This can be seen in **Figure 1**.

#### Stage 2/3

Twenty-one of the initial 90 patients were upstaged to stage 2 or 3 after lobectomy. In this group of patients there were ten recurrences producing a 1-year recurrence rate of 47.6%. All ten recurrences were identified with PET/CT and 6 recurrences were missed using non-contrast CT alone. Five of the missed recurrences were the extrathoracic metastases described earlier to the neck in two patients, liver below the adrenals, anterior rib and vertebral bodies. The sixth missed recurrence was the anterior mediastinal mass. See **Figures 2** and **3** for examples of recurrences missed with non-contrast CT but identified with PET/CT.

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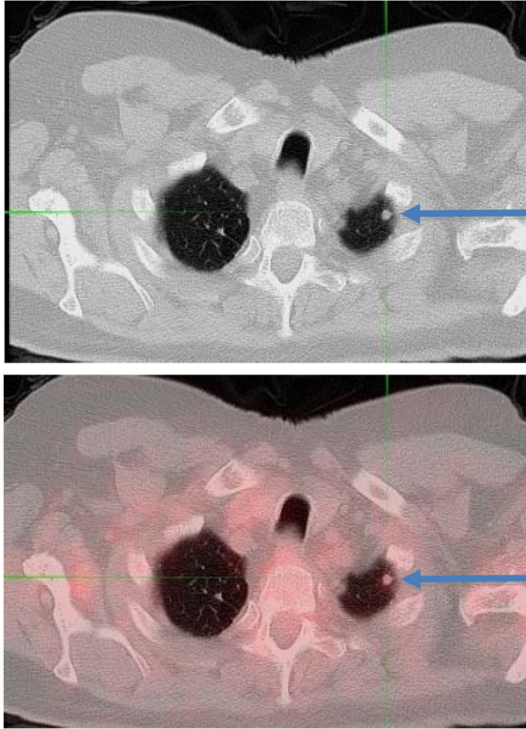
All of the 16 recurrences were found with PET/CT (100%) and 9 were found with non-contrast CT alone (56.3%). Using McNemar's chi-squared test, CT is 56.3% as sensitive as PET/CT in detecting recurrence 1 year after lobectomy for all patients included in the study ( $p = 0.016$ , 95% confidence interval 37-87%). There was no significant difference in the specificity of PET/CT and non-contrast CT ( $p = 0.62$ , 95% confidence interval 22-165%). For patients confirmed to be stage 1 after lobectomy, there was no statistically significant difference in the sensitivity or specificity between PET/CT and non-contrast CT. For patients upstaged to stage 2 or 3 disease after lobectomy, the sensitivity of CT and PET/CT were 40% and 100% respectively. Using McNemar's chi squared test, CT is 40% as sensitive as PET/CT with a  $p$ -value of 0.03, which is statistically significant. There was no statistically significant difference in the specificity between PET/CT and non-contrast CT for this group of patients. **Table 3** compares the results of PET/CT versus non-contrast CT in monitoring for recurrence 1 year after lobectomy for patients with clinical stage 1 NSCLC.

#### Discussion

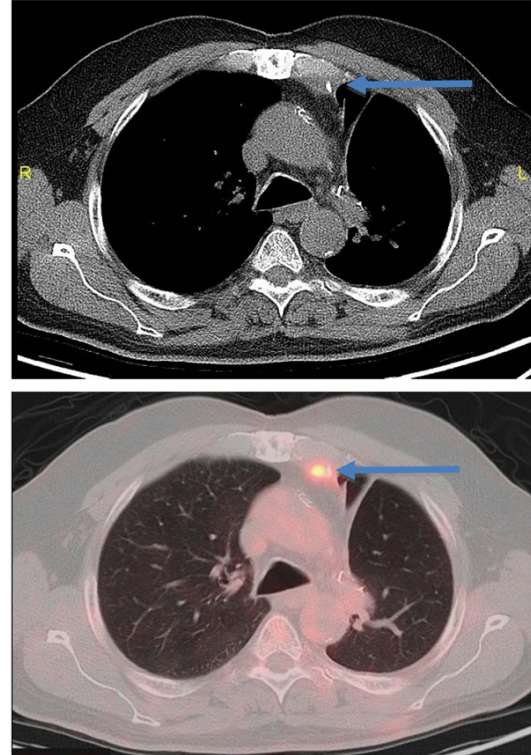
PET/CT found all of the true recurrences and non-contrast CT alone found slightly more than half. There was no statistically significant difference in the specificity of PET/CT and non-contrast CT. The major limitation of non-contrast

CT was the difficulty in identification of extrathoracic masses. Not surprisingly, a small soft tissue lesion in the neck or anterior ribs was difficult to identify without contrast or  $^{18}\text{F}$ -FDG. These unidentified extrathoracic masses resulted in three false negative CT reads. Another missed extrathoracic mass was in the liver below the adrenals, which is not normally imaged on a chest CT. The last extrathoracic mass missed by non-contrast CT was metastases to the sacrum and T4 vertebrae. If not meticulously searched for, osseous metastases can be easily missed. All of these extrathoracic masses were identified with PET/CT and were called recurrence. Interestingly, none of the false negative CTs noted extrathoracic masses (**Table 1**). Missing the extrathoracic mass was the reason for the false negative most of the time (71%). The ease of localizing a hypermetabolic extrathoracic mass with PET/CT certainly contributes to its superiority over non-contrast CT in monitoring for recurrence. Further, based on the results of this study, it is likely the greatest benefit of PET/CT.

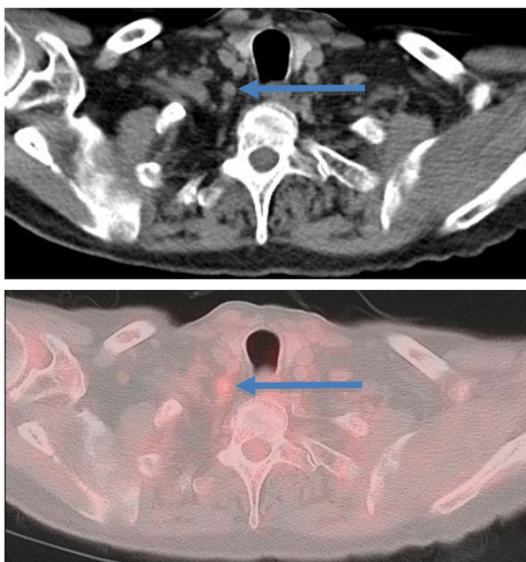
Another benefit of PET/CT over non-contrast CT is in identifying a hypermetabolic nodule in a patient with many pulmonary nodules. The 7<sup>th</sup> missed recurrence by CT was such a case in a patient with countless pulmonary nodules. It is nearly impossible to account for all of these nodules in a non-contrast CT alone. However, missing a new hypermetabolic lesion with  $^{18}\text{F}$ -FDG PET/CT is difficult. The difficulty in identifying a malignant nodule with non-contrast CT stems, in part, from the frequency that pulmonary nodules occur. Pulmonary nodules were found in more than half of the patients enrolled in the study. Most of the pulmonary nodules were identified in patients without evidence of recurrent disease (**Table 2**). As such, the presence of a pulmonary nodule is not very suggestive of recurrence and subsequently, was not useful in identifying recurrence with non-contrast CT. It is not surprising, therefore, that pulmonary nodules were present in the false negative CT cases. A similar trend was seen with pleural effusions. Pleural effusions were identified in a third of patients in this study, nearly all of which were true negative CT cases (**Table 2**). Ultimately, the presence of a pulmonary nodule or pleural effusion was not useful in identifying recurrence with CT. PET/CT was able to successfully identify the one recurrence resulting from a pulmonary nodule and non-contrast CT was not for these reasons.



**Figure 1.** This slice through the upper lung fields shows a hypermetabolic pulmonary nodule not identified with non-contrast CT but found with PET/CT (see arrow). Note that this nodule had previously been stable in size on multiple CTs, but had developed interval hypermetabolic activity seen only on the PET/CT. This patient had countless pulmonary nodules on the CT scan.



**Figure 3.** This cross-sectional view of the upper lung fields shows a recurrence to the anterior mediastinum missed with non-contrast CT but identified with PET/CT. The arrows in the figures identify the recurrence. A difficult to spot lesion on non-contrast CT was identified on PET/CT.



**Figure 2.** This cross-sectional view of the neck shows a recurrence to right side of neck identified on PET/CT but missed with non-contrast CT. The arrows identify pathology.

Interestingly, there were no missed adenopathy recurrences with non-contrast CT. It is often stated that non-contrast CT limits the ability to detect lymphadenopathy [18]. However, in this study, all recurrences with adenopathy were identified on non-contrast CT. None of the false negatives or missed recurrences resulted from failing to identify malignant adenopathy. Therefore, using non-contrast CT rather than contrast CT was not a limitation of this study.

The presence of adenopathy on CT was likely to be called a recurrence as 7 of the 9 cases with adenopathy were called “positive” by the chest radiologist. Although 5 of these were true positives, 2 were false positives. This is a possible benefit of PET/CT, however, it did not matriculate to any superiority in this study.

As expected, the recurrence rate was much higher for patients upstaged to stage 2 or 3 disease 1 year after lobectomy than for those confirmed to have stage 1 disease. Nearly half of the patient’s upstaged to stage 2 or 3 disease

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**Table 3.** This shows the sensitivity and specificity of PET/CT versus non-contrast CT in monitoring for recurrence 1 year after lobectomy for clinical stage 1 NSCLC. **Table 3A** shows the sensitivity of PET/CT and non-contrast CT for all patients included in this study. For all patients included in this study, PET/CT is more sensitive than non-contrast CT alone in monitoring for recurrence 1 year after lobectomy. **Table 3B** compares the sensitivity of PET/CT and non-contrast CT for the subset of patients confirmed to have stage 1 NSCLC after surgery. For these patients, there was no difference in the sensitivity of PET/CT and non-contrast CT in monitoring for recurrence. **Table 3C** shows the sensitivity and specificity of PET/CT and non-contrast CT monitoring for recurrence in the subset of patients up-staged to stage 2 or 3 after surgery. PET/CT is more sensitive than non-contrast CT in monitoring for recurrence in this subset of patients. There was no statistically significant difference in the specificity of PET/CT and non-contrast CT in all subsets of patients.

A. All pathologic stages, clinical stage 1			
	CT	PET/CT	CT Relative to PET/CT
Sensitivity (%)	56.3	100	56.3 (p = 0.016, 95% CI: 37-87)
Specificity (%)	96	93.2	103 (p = 0.62, 95% CI: 22-165)
B. Pathologic Stage 1			
	CT	PET/CT	CT Relative to PET/CT
Sensitivity (%)	83.3	100	83.3 (p = 0.31, 95% CI: 52-124)
Specificity (%)	95.2	93.7	102 (p = 0.56, 95% CI: 15.7-188)
C. Pathologic Stage 2/3			
	CT	PET/CT	CT Relative to PET/CT
Sensitivity (%)	40	100	40 (p = 0.03, 95% CI: 18.7-85.4)
Specificity (%)	100	90.9	110 (p = 0.31, 95% CI: 58.8-285)

recurred at one year while few confirmed to be stage 1 recurred at that time.

There are a few limitations of this study. A major limitation is that there is not a complete electronic medical record at the institution where the research was performed. Subsequently, it is possible that patients free of disease at the time of the PET/CT presented soon after the yearly follow-up with symptoms suggestive of recurrence (false negative PET/CT). Similarly, there is no true data on recurrence in the two patients in whom lymph node biopsy was declined by the clinician. These patients were called false positive PET/CT reads in this study. Another limitation of the study is that it only analyzed the PET/CT performed 1 year after lobectomy. Patients presenting with symptoms prior to this time period were excluded from the study. There was one such patient who presented with a seizure less than 1-year after surgery and was excluded. The seizure was found to be a consequence of a brain metastasis. Another limitation is that there was only one radiologist interpreting the non-contrast CTs. It would be beneficial to have another radiologist confirm the results in a future study. Further, this is a single institution study. A final limitation to this

study is that the sensitivity of PET/CT is 100%. This suggests that the multidisciplinary tumor board used PET/CT data heavily in making a decision about recurrence. However, it could not have been the only criteria used, as the specificity of PET/CT is not 100%.

We chose to perform the PET/CT one year after lobectomy because it was felt that imaging any sooner would cause the false positive rate due to surgical damage to be exceedingly high and not justifiable for an expensive test [10, 14, 19, 20].

It remains an unanswered question if any surveillance after lung cancer resection prolongs survival. The NCCN guidelines are based on weak, category 2B evidence. This study did not test whether PET/CT surveillance prolonged survival. The results of this study do not apply to patients treated with alternative therapy such as stereotactic ablative radiotherapy, percutaneous cryablation therapy or radiofrequency ablation.

### Conclusion

PET/CT is more sensitive than non-contrast CT alone in monitoring for recurrence one-year sta-

tus post lobectomy for all patients included in this study, specifically those upstaged to stage 2 or 3 disease. According to this study, it is postulated that this is due to the superiority of PET/CT in identifying extrathoracic masses and a new hypermetabolic nodule in patients with many pulmonary nodules. There is no statistically significant benefit of PET/CT in monitoring for recurrence for those with pathologic stage 1 NSCLC. However, PET/CT may be helpful for those with advanced disease because of their increased risk of having distant metastases. Although this is not a surprising conclusion given the increased sensitivity and whole-body nature of PET/CT, the rationale for this study is that current treatment guidelines do not recommend PET/CT for routine follow-up. This study demonstrates that the routine use of PET/CT could have significant prognostic implications for current lung cancer patients given its increased sensitivity. It is hoped that future studies similar can help change the screening guidelines to include PET/CT for surveillance after treatment with curative intent for patients with advanced disease.

**Disclosure of conflict of interest**

None.

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