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Original article

The Role of Fluorodeoxy-D-glucose Positron Emission Tomography/Computed Tomography in Nodal Staging of Nonsmall Cell Lung Cancer in Sequential Surgical Algorithm

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Abstract

With nonsmall cell lung cancer (NSCLC), accurate mediastinal nodal staging is crucial to determine whether a patient is or is not a surgical candidate. Traditionally, computed tomography (CT) and fluorodeoxy-D-glucose (FDG) positron emission tomography (PET)/CT are the initial steps followed by tissue sampling through mediastinoscopy and/or thoracotomy, which are invasive procedures. There is controversy regarding the possibility of omission of the invasive diagnostic procedures and solely relying on noninvasive presurgical staging CT and FDG PET/CT results. Eighty-three patients who had PET/CT, mediastinoscopy, and thoracotomy for NSCLC were analyzed. For all lymph nodes that may be sampled by mediastinoscopy, PET/CT sensitivity was 80%, specificity was 86%, positive predictive value was 47%, and negative predictive value (NPV) was 97%; and for those in this group whose clinical stage was T1/T2 M0, sensitivity was 100% and specificity was 84%. For lymph nodes accessible only at thoracotomy, sensitivity was 42% and specificity was 88%. FDG PET/CT is accurate in assessing stations 2R/L, 4R/L, and 7 nodes and has the potential to replace mediastinoscopy in the treatment algorithm of T1/T2 M0 disease. A negative PET/CT may potentially prevent the patient from invasive mediastinoscopy given its high NPV. However, a patient with positive PET/CT should undergo tissue biopsy with pathology confirmation.

Keywords: Fluorodeoxy-D-glucose positron emission tomography/computed tomography, mediastinoscopy, nonsmall cell lung cancer, staging

Introduction

Lung cancer is the leading cause of cancer-related mortality in North America with approximately 157,300 persons dying of lung cancer in the United States of America (USA) in the year 2010. The majority of lung cancer is nonsmall cell lung cancer (NSCLC). Depending on the staging of NSCLC, treatment options include surgery, chemotherapy, radiation, or combined therapy, with the best outcome from surgical resection.[1] The surgical approaches of NSCLC include segmentectomy, lobectomy, and less commonly, pneumonectomy in eligible patients. The selection of surgical approach depends on tumor size and accurate mediastinal nodal staging [Supplement 1, definition of tumor, node, and metastasis stage of lung cancer]. Accumulating evidence has demonstrated that the presence of mediastinal lymph node disease (N2 and N3) is a contraindication to surgery as initial therapy given that the goal of surgery is to provide potential curative treatment for medically fit patients, though

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in some institutions surgical resections are performed after chemotherapy for patients with N2 disease.[2] The mediastinal nodal staging workup for NSCLC is composed of noninvasive modalities, computed tomography (CT) and (^{18}F) fluorodeoxy-D-glucose positron emission tomography/CT (FDG PET/CT), and invasive diagnostic approaches, mediastinoscopy, and/or thoracotomy. FDG-PET/CT plays an important role for both metastatic (M) and nodal (N) staging of NSCLC with higher sensitivity and specificity than CT alone (for N staging 70% and 91% vs. 57% and 82% for CT).[3,4] Cervical mediastinoscopy has long been considered the "gold standard" of nodal staging, though with limitations. Minimally invasive techniques, such as endobronchial and endoesophageal ultrasound, are increasingly being used for this purpose.[5,6] There is a significant controversy in literature on the indications for obtaining mediastinoscopy: Only for patients with positive CT and PET/CT finding or on every patient planning for NSCLC resection.[7-9] To address this question, we analyzed operable NSCLC patients between 2003 and 2013 in our institution retrospectively to evaluate the roles of FDG PET/CT and mediastinoscopy on mediastinal nodal staging.

Materials and Methods

Retrospectively, we analyzed all the presumably operable cases between 2003 and 2013 at the Medical College of Georgia, Augusta, Georgia, USA, with a tissue diagnosis of NSCLC. The project was approved by the Institutional Review Board of Medical College of Georgia. Our inclusion criteria were (1) PET/CT within 3 months prior to surgery, (2) all preoperative workup done in our institution, and (3) all patients underwent mediastinoscopy and/or thoracoscopy/thoracotomy prior to definitive resection. The exclusion criteria were (1) PET/CT done in an outside institution, (2) patient did not qualify for lung resection, (3) presence of other malignancy in addition to primary NSCLC, and (4) poor follow-up or follow-up done in an outside institution. Of all the 180 patients, 83 patients were included in the final analysis after applying the inclusion and exclusion criteria. The patient population included 42/83 female (50.6%) and 41/83 male (49.4%); 47/83 (56.6%) Caucasian and 35/83 (42.2%) African–American. Staging FDG PET/CT (Gemini TF PET/CT, Philips Medical Systems, with 16-slice Brilliance CT scanner, Phillips Medical Systems, Bothell, Washington, USA) was obtained for each of the 83 patients with a standardized protocol and images were interpreted by board-certified nuclear medicine physicians. Based on the institutional policy, patient underwent a standard cervical mediastinoscopy for assessment of nodal station 2 R, 2L, 4R, 4L, and 7 (Group A) regardless of CT and PET/CT staging. No mediastinoscopy was performed for 8/83 patients due to negative PET/CT and intravenous-contrast CT (Group A nodes were sampled by thoracotomy or thoracoscopy instead). In the same operative session, if the mediastinoscopy was negative, patients proceeded to exploratory thoracoscopy and/or thoracotomy. Group B nodes were sampled at thoracotomy (stations 3, 5, 6, 8, 9, and 10). If curative resection was considered likely, lobectomy/segmentectomy or pneumonectomy was performed depending on the tumor (T) staging of cancer. Intrapulmonary nodes 11, 12, 13, and 14 (Group C) were sampled during lobectomy/segmentectomy. SAS 9.3 was used for all statistical analyses (SAS Institute, Cary, NC, USA). Descriptive statistics were calculated for all variables. Sensitivity and specificity (with 95% confidence intervals) of PET for detection nodal involvement were calculated separately for nodal Groups A (PET A), B (PET B), and C (PET C) using respective pathology results as the gold standard.

Results

For the 83 patients, the surgical sampling rates of Group A, B, and C mediastinal nodes were 90%, 72%, and 35%, respectively. Lung primary tumors were distributed in all lobes but predominantly in the upper lobes (63/83). Tumor histology was adenocarcinoma (40/83), squamous (22/83), and other (21/83). Eighty of 83 patients had no evidence of distant metastases (M0), whereas three patients were found to have solitary M1 disease. T staging of tumor was T1 or T2 in 76%, T3 or T4 in 21%. The predominant nodal status was N0 [Table 1]. By comparing to pathology results, for Group A nodes PET sensitivity was 80%, specificity was 86%, positive predictive value (PPV) was 47%, and negative predictive value (NPV) was 97%; for Group B nodes sensitivity was 42%, specificity was 88%, PPV was 46%, and NPV was 86%. In Group A, 9/17 (53%) of PET-positive nodes were false positive, whereas 2/58 (3.4%) PET-negative nodes were false negative [three patients with false-positive, false-negative, and true-positive PET/CT are shown as examples on [Figures 1-3]. In Group B, 6/11 (53%) of PET-positive nodes were false positive, whereas 7/49 (14%) of PET-negative nodes were false negative [Table 2]. Because of the low surgical sampling rate and lack of significant contribution to tumor staging, data of Group C (level 11, 12, 13, and 14) were not further analyzed. The two false-negative PET cases had a T3 stage. When dividing Group A based on T staging and calculate the sensitivity, specificity, PPV, and NPV separately. T0 + T1 + T2 (n = 56): Sensitivity 100%, specificity 84%, PPV 33%, and NPV 100%; T3 (n = 8): Sensitivity 33%, specificity 100%, PPV 100%, and NPV 71%; T4 (n = 9): Sensitivity 100%, specificity 83%, PPV 0.75, and NPV 100%; M1 (n = 3): Sensitivity 100%, specificity 100%, PPV 100%, and NPV 100%.

Discussion

The goal of mediastinal staging is to exclude with highest

Table 1: Descriptive statistics

Variable	*n* (%)
Location of tumor	
LLL	6 (7.23)
LUL	30 (36.14)
RLL	8 (9.64)
RML	6 (7.23)
RUL	33 (39.76)
Stage of tumor	
T0	2 (2.50)
T1a	27 (33.75)
T1b	5 (6.25)
T2a	27 (33.75)
T2b	2 (2.50)
T3	8 (10.00)
T4	9 (11.25)
Nodal stage	
N0	61 (74.39)
N1	7 (8.54)
N2	12 (14.63)
N3	1 (1.22)
Nx	1 (1.22)
Metastasis	
M0	80 (96.39)
M1	3 (3.61)
Histology tumor	
Adeno	40 (48.19)
Squamous cell	22 (26.51)
Other	21 (25.3)

LLL: Left lower lobe; LUL: Left upper lobe; RLL: Right lower lobe; RML: Right middle lobe; RUL: Right upper lobe

Table 2: Sensitivity and specificity of positron emission tomography (A, B, and C)

	Value	LCL[a]	UCL[b]	Number of matches	Number of different	Total
PET A						
Sensitivity[c]	0.80	0.49	0.94	8	2	10
Specificity[d]	0.86	0.76	0.93	56	9	65
PPV[e]	0.47	0.26	0.69			
NPV[f]	0.97	0.88	0.99			
PETB						
Sensitivity	0.42	0.19	0.68	5	7	12
Specificity	0.88	0.75	0.94	42	6	48
PPV	0.46	0.21	0.72			
NPV	0.86	0.73	0.93			
PET C						
Sensitivity	0.00	0.00	0.56	0	3	3
Specificity	1.00	0.87	1.00	26	0	26
PPV	-	-	-			
NPV	0.90	0.74	0.96			

[a]LCL: Lower (95%) confidence limit, [b]UCL: Upper (95%) confidence limit, [c]Sensitivity: Of those who have pathology+, percent who have a PET+. [d]Specificity: Of those who have pathology−, the percent who have a PET−. [e]PPV: Of those who have PET+, percent who have pathology+. [f]NPV: Of those who have PET−, percent who have pathology−. PPV: Positive predictive value; NPV: Negative predictive value; PET: Positron emission tomography

certainty and lowest morbidity patients with mediastinal nodal disease since these patients are not the surgical

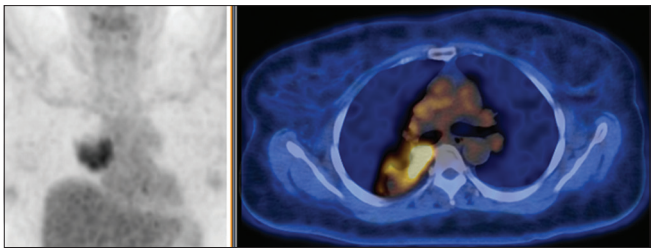

Figure 1: False-negative lymph nodes: A 55-year-old female who presented with epigastric pain. Computed tomography revealed a 7.4 cm superior segment right lower lobe lung mass, no pathologically enlarged lymph nodes within the mediastinum or left hilum, no distant metastasis. Positron emission tomography/computed tomography revealed the right lower lobe lung tumor, standardized uptake value 5.5; no active lymphadenopathy; no distant metastasis. Surgical right middle and lower lobectomies, moderately differentiated lung adenocarcinoma, pT3; lymph node metastases ipsilateral stations 2R (5/6), 4R (4/5), and 7-subcarinal (2/3), sizes 0.4 cm and smaller, pN2

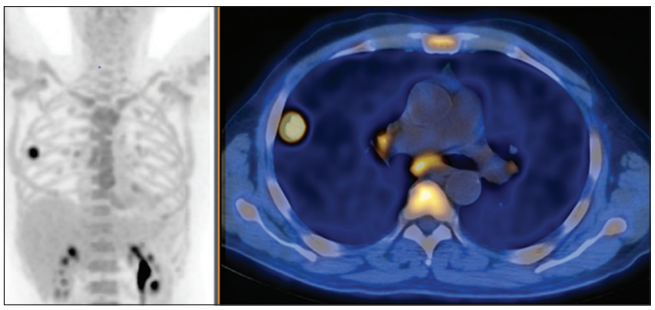

Figure 2: False-positive lymph nodes: A 65-year-old male with abnormal chest X-ray showing a right lung nodule, needle biopsy revealed adenocarcinoma. Positron emission tomography/computed tomography revealed a 2.7 cm right upper lobe lung tumor, standardized uptake value 9.6; active lymphadenopathy (arrowheads) in the right lung hilum standardized uptake value 3.1, subcarinal standardized uptake value 3.7, left hilum standardized uptake value 3.2; no distant metastasis. Surgical right upper lobe wedge resection, moderate to poorly differentiated lung adenocarcinoma, pT2; lymph nodes right and left hilar, station 7-subcarinal, benign, chronic inflammation, anthracotic changes, pN0

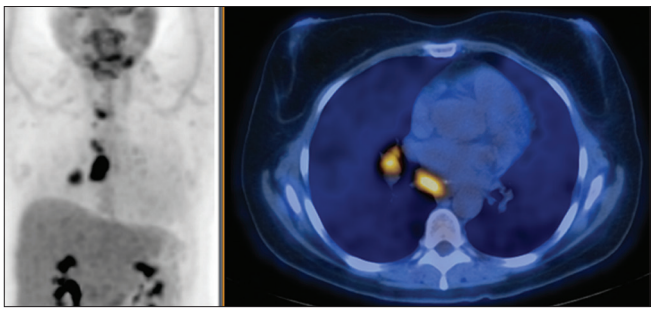

Figure 3: True-positive lymph nodes: A 47-year-old female with chronic cough and weight loss, chest X-ray showed right hilar lung mass. Positron emission tomography/computed tomography revealed a 2.4 cm right hilar lung tumor, standardized uptake value 5.4; active lymphadenopathy (arrowheads) right mediastinum and subcarinal, standardized uptake value 12. Mediastinoscopy sampled stations 4R (benign), 2R and 7 positive for metastatic nonsmall cell carcinoma

candidates for surgical resection.[10,11] Mediastinoscopy is traditionally the gold standard for mediastinal staging to evaluate potential N2 and N3 node involvement. As an invasive diagnostic procedure, a small risk of complications including serious ones such as pneumothorax, recurrent laryngeal nerve injury, hemorrhage, and tracheal laceration do exist even for experienced thoracic surgeons. A review of 2000 cases from Duke University revealed 1.07% complication rate and 0.05% date rate associated with cervical mediastinoscopy.[12]

In addition to its definite role in searching for distant metastatic disease (M staging), another potential role of FDG PET/CT on lung cancer staging is to evaluate mediastinal metastases. Darling *et al*. reported FDG PET/CT to have sensitivity of 70% and specificity of 94% for mediastinal metastasis. Our results of Group A are in agreement with the published data in the previous literature with the slight difference presumably due to patient selection, subtype of lung cancer, type of scanner, or prevalence of inflammatory or other metabolically active benign pulmonary disease.[1,13] False positive and false negative results do occur on FDG PET/CT lung cancer staging presumably due to incapability of FDG PET differentiating uptake of lung cancer from that of infection/inflammation, such as fungal infection and sarcoidosis, and the spatial and contrast resolution limitations of PET/CT, which would miss very small sites of metastatic disease.[2]

Although the PPV of FDG PET is poor, only 47% in our study, the NPV of FDG PET of 97% (Group A) is striking which is again similar to results reported by others.[1,14,15] When only T1 and T2 cases are analyzed, the NPV is 100%. Therefore, positive PET/CT findings in the mediastinal lymph nodes should be used with caution. Patients should undergo invasive nodal staging to exclude benign etiology of positive uptake and failure to do so would deny patients from potential curative resection. In the case of negative PET and CT, direct surgical resection with the omission of invasive mediastinoscopy should be considered. In our study, for patient with negative PET/CT only 2/58 (3.4%) of mediastinal metastatic lung cancer are missed regardless of the nodal size on CT and T staging. When T stage is limited to T1 and T2, no mediastinal metastases are missed. Similar conclusions are also drawn by other groups through meta-analysis and clinical research.[16,17] On the other hand, Gonzalez–Stawinski *et al*. prospectively compared the efficacy of PET/CT to mediastinoscopy in 202 NSCLC cases. Of the 137 patients with negative PET, 16 (11.7%) were demonstrated to have N2 or N3 disease. Therefore, authors concluded that negative PET/CT cannot exclude the mediastinal involvement of lung cancer, and mediastinoscopy should be performed on every patient with pathology confirmation.[18] Similar results were also reported by Daniels *et al*.[19]

The 2014 European Society of Thoracic Surgeons algorithm for preoperative mediastinal staging updated the role of FDG PET on NSCLC mediastinal staging: (1) Direct surgery can be performed if all of the three criteria apply: No suspected lymph node on CT or PET, a tumor <3 cm, and located in the outer third of the lung and (2) In case of enlarged node on CT or PET-positive nodes, tissue confirmation is indicated.[20] Our current results provide additional evidence to support this algorithm.

Due to the limited evidence available and with accumulating results from large ongoing clinical trials, criteria revision will likely occur. For example, our patient population includes T3 (n = 8) and T4 (n = 9) which are traditionally considered locally aggressive with poor prognosis. With the inclusion of T3 and T4, the NPV decreases only from 100% to 97%. Should these patients be considered for potentially curative resection without invasive procedure? In the future, the guideline could potentially be generalized to cT4 N0 M0 cases or even to patients with solitary M1 disease based on our limited evidence.

An unfortunate reality is that in a large USA survey among 11,668 patients received lung resection for lung cancer, only 27% underwent mediastinoscopy and lymph nodes were sampled in only 47% of these procedures.[21] Therefore, most of the patients in the US with lung cancer resection only undergo imaging staging alone which is at least partially due to the invasive nature of mediastinoscopy. Therefore, it is critical to triage patients based on CT and PET findings for the optimal outcome. The NPV of FDG PET is a promising parameter for patients to proceed to resection without an invasive staging procedure, though large prospective clinical trials are still warranted.

There are several limitations of our study: (1) It is a retrospective single institution study, (2) after the application of inclusion and exclusion criteria, 83 patients were included in the analysis, a comparably small sample size, and (3) there is literature showing that adenocarcinoma and squamous cell lung cancer have different rate of mediastinal metastases with higher rate for adenocarcinoma.[7] In the current study, they were not analyzed separately.

Conclusion

Mediastinoscopy remains the gold standard for mediastinal staging of NSCLC with low risk of complication. FDG-PET is an accurate noninvasive staging modality with excellent NPV. A negative PET could prevent unnecessary invasive diagnostic staging procedure, such as mediastinoscopy. However, in the case of positive PET, tissue biopsy with pathology

confirmation should be obtained given the suboptimal PPV of PET. In the future, potentially operable cT4 N0 M0 or M1 cases may be considered for curative direct resection based on imaging staging with the omission of mediastinoscopy.

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Conflicts of interest
There are no conflicts of interest.

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Supplement 1: Definition of tumor, node, and metastasis stage of lung cancer

Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. In: American Joint Committee on Cancer, Cancer Staging Manual. 7th ed. New York: Springer-Verlag; 2010.

Nonsmall Cell Lung Cancer Staging

T1 Tumor ≤3 cm greatest dimension, surrounded by lung or visceral pleura, without invasion more proximal than the lobar bronchus.
T1a Tumor ≤2 cm.
T1b – Tumor >2 cm but ≤3 cm.
T2 Tumor >3 cm but ≤ 7 cm or less or tumors with any of the following features: involves main bronchus ≥2 cm distal to the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T2a Tumor >3 cm but ≤5 cm.
T2b – Tumor >5 cm but ≤7 cm.
T3 Tumor >7 cm or one that directly invades any of the following: parietal pleural, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium;; or tumor in the main bronchus <2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe.
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, and separate tumor nodule(s) in a different ipsilateral lobe.
N0 No regional lymph node metastases.
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
M0 No distant metastasis.
M1 Distant metastasis.
M1a Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion.
M1b Distant metastasis (in extrathoracic organs).