Diagnostic Performance of Dual-time ^{18}F-FDG PET in the Diagnosis of Pulmonary Nodules: A Meta-analysis

Richard L. Barger, Jr., MD, Kiran R. Nandalur, MD

Rationale and Objective: Perform a comprehensive meta-analysis evaluating the diagnostic performance of dual time point deoxy-2-[^{18}F] fluoro-D-glucose positron emission tomography (FDG-PET) in the diagnosis of pulmonary nodules.

Materials and Methods: MEDLINE, EMBASE, and PUBMED were queried between January 2000 and January 2011. Studies were included if they: 1) used dual time point FDG-PET as a diagnostic test for pulmonary nodules, 2) used pathology or clinical follow-up as the reference standard, and 3) reported absolute number of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results or stated sufficient data to derive these values. Summary sensitivity (SN), summary specificity (SP), positive and negative likelihood ratios (LR+) and (LR−), and diagnostic odds ratio were calculated. Heterogeneity of the results was assessed using Forest plots and the value of inconsistency index (I^2).

Results: Inclusion criteria were fulfilled by 10 articles with a total of 816 patients and 890 pulmonary nodules. The summary sensitivity was 85% (82%–89% at 95% confidence interval [CI]) and summary specificity was 77% (CI: 72%–81%), with a LR+ of 2.7 (CI: 1.4–5.2) and a LR− of 0.26 (CI: 0.14–0.49). Diagnostic odds ratio was 11 (CI: 3.8–32.2). Significant heterogeneity was found in the sensitivity (I^2 = 77%) and specificity (90.3%).

Conclusion: Dual time point FDG-PET demonstrates similar sensitivity and specificity to single time point FDG-PET in the diagnosis of pulmonary nodules. The additive value of the dual time point FDG-PET is questionable, primarily because of the significant overlap of benign and malignant nodule FDG-PET characteristics and lack of consensus criteria for quantitative thresholds to define nodules as malignant.

Key Words: Pulmonary nodule; FDG-PET; meta-analysis.

2-deoxy-2-[^{18}F]-fluoro-D-glucose positron emission tomography (FDG-PET) is well established in the management of pulmonary malignancy, primarily as a staging imaging modality (1). FDG-PET has also been used as a diagnostic problem-solving tool. One of the most common diagnostic indications for FDG-PET is for the determination of benign versus malignant pulmonary nodules. Approximately 150,000 new pulmonary nodules are found in the United States annually, with 60%–70% of these being benign (2). Furthermore, recently published data from the National Lung Screening Trial showed that screening low-dose computed tomography (CT) decreased mortality of lung cancer, but 96.4% of the positive results in the CT group and 94.5% of the positive results in the radiography group were false-positive (FP) results (3). Currently, the gold standard for diagnosing pulmonary nodules is pathology, with tissue obtained either surgically or by percutaneous biopsy, but both of these techniques are invasive and may involve significant risk to the patient (4). Using FDG-PET as a diagnostic tool could reduce the number of unwanted interventions on benign pulmonary nodules. As determined in a previous meta-analysis, the sensitivity and specificity of single time point FDG-PET for characterizing pulmonary nodules is 96.8% and 77.8%, respectively (5). Primary speculations regarding the low specificity for determining nature of pulmonary nodules are the wide ranges of standardized uptake values (SUV) and sizes of both malignant and benign pulmonary nodules (6).

Dual time point FDG-PET has been investigated as a potential technique to improve the specificity of FDG-PET in the diagnosis of pulmonary nodules (7). The theoretical reasoning is based on the fact that in vitro malignancy demonstrates deranged glucose metabolism, higher surface glucose receptor expression, and different glycolysis enzyme production compared to inflammation/infection (8,9). Based on this, the hypothesis is that on delayed imaging, malignant nodules will demonstrate increased FDG avidity, whereas a benign process should demonstrate a plateau or decreasing FDG avidity. Multiple studies have been done investigating the clinical application of dual time point FDG-PET in the diagnosis of pulmonary nodules.

Acad Radiol 2012; 19:153–158

From the Department of Radiology, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, MI 48073 (R.L.B., K.R.N.) Received June 28, 2011; accepted October 7, 2011. Presented at the American Roentgen Ray Society Annual Meeting May 1-6, 2011 Chicago, IL. **Address correspondence to:** R.L.B. e-mail: richard.barger@beaumont.edu

doi:10.1016/j.acra.2011.10.009

The current data show mixed results in the diagnosis of pulmonary nodules using dual time point FDG-PET with publications demonstrating arguments for, against, and neutral to its usage. Given that the diagnostic capabilities have only been examined by studies of limited sample size, leading to wide confidence intervals for sensitivity and specificity and potentially unreliable estimates of performance, we have performed a comprehensive meta-analysis of dual time point FDG-PET in the diagnosis of pulmonary nodules. The goal was improve the statistical power of the published data and further evidence-based medicine insight of the usage of dual time point FDG-PET.

MATERIALS AND METHODS

Execution of Data Collection and Statistical Analysis

Execution of data collection and the statistical calculations was decided on before the start of the study. The statistical analyses were performed independently by the authors of this study and compared. Inconsistencies were resolved by discussion and consensus.

Data Sources and Searches

MEDLINE, EMBASE, and PUBMED databases were searched for English and non-English literature published between January 2000 and January 2011 evaluating pulmonary nodules using dual time point FDG-PET. The medical subject headings queried included *pulmonary nodule, pulmonary malignancy, FDG-PET,* and *dual time point FDG-PET.* The bibliographies of retrieved publications and textbooks were evaluated for additional possible pertinent references. The retrieved literature was reviewed for duplications and overlapping data. Meeting abstracts, because they do not provide sufficient detail with regards to data and results, were excluded.

Study Selection

Publications were included if it fulfilled the following criteria: 1) used dual time point FDG-PET as a diagnostic test for pulmonary nodules, 2) used pathology or clinical follow-up as the reference standard, and 3) reported absolute number of true positive (TP), true negative (TN), FP, and false negative (FN) results, or stated sufficient data to derive these values. Publications were eligible regardless of the dual time point FDG-PET technique. Animal studies, phantom studies, studies with <10 patients, and healthy volunteer-only studies were excluded from the analysis. Any data that involved normal healthy volunteers or pathology outside the lung parenchyma were excluded from the analysis if the publication was included for its pulmonary nodule data.

Data Extraction and Quality Assessment

The following data were extracted: first author, journal title, year of publication, total number of patients, mean age, scanner brand, type of study (retrospective or prospective), dual time technique, patient selection, imaging assessment and definitions of benign versus malignant pulmonary nodule, numbers and sizes of pulmonary nodules, early and delayed pulmonary nodule SUV values, and type of follow-up reference standard(s). With regard to the dual time technique, extracted data included radiotracer doses, time delay until initial scan, time delay between initial and delayed scan, and determination of regions of interest (ROI) for maximal SUV. The statistical data was derived from the numbers of TP, TN, FP, and FN given in the individual studies. All data, as available, were recorded at the patient level. Study quality and applicability was assessed by a modified checklist based on the Quality Assessment Tool for Diagnostic Accuracy (QUADAS) (10). Because all data were taken from publications, institutional review board approval was waived.

Data Synthesis and Statistical Analysis

Statistical analyses described here were performed using Meta-DiSc 1.4 (11). The primary analysis was performed at the patient data level because most publications focused on this level of information. A secondary analysis was performed assessing overall average nodule sizes and average early and delayed maximum SUV values of pulmonary nodules. Inter-study variability was assessed assuming correlated, normally distributed random effects for logit (sensitivity) and logit (specificity). Summary sensitivity and specificity was derived as functions of the estimated model parameters with associated 95% confidence intervals.

Likelihood ratios (LR) are metrics that express how much the odds change for the presence of malignant pulmonary nodule in a positive (abnormal) dual time FDG-PET scan (positive likelihood ratio: LR+) and for the presence of malignant pulmonary nodule with a negative (normal) dual time FDG-PET scan (negative likelihood ratio: LR−). A LR+ greater than 10 and a LR− less than 0.1 implies a large and often conclusive increase or decrease in the likelihood of disease, respectively (12). The diagnostic odds ratio (dOR) is a measure of how much greater the odds of having disease are with a positive test rather than a negative test (13). This test is not dependent on prevalence and can be used as a lone test for diagnostic performance. The higher the value, on a scale of 0 to infinity, the better the test is at discriminating between those with and without the disease. A value of 1 is indicative of no discrimination. A value less than 1 indicates tests were interpreted incorrectly (more negative tests among those with disease).

Heterogeneity of the results was assessed graphically using Forest plots, and statistically using the value of inconsistency index (I^2), which describes the percentage of total variability across studies attributable to heterogeneity rather than chance. The value of I^2 is calculated using the equation:

$$I^2 = 100[(Q - df)/Q] \quad (1)$$