Extrapulmonary benign and malignant lesions avid for 18F-fluoro-deoxyglucose by multivariate regression model identification (Postprint)

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Abstract

Whether extrapulmonary lesions are avid for 18F-fluorodeoxyglucose (18F-FDG) could help differentiate benign from malignant lung lesions. In this trial, 199 consecutive patients with newly diagnosed lung lesions (169 malignant and 36 benign lesions) underwent whole-body 18F-FDG PET/CT imaging. Histopathology and clinical results served as the reference standard. Malignancy likelihood was assessed by CTscores, the maximum standardized uptake value (SUVmax) of lung lesions, PET on FDG negative or positive, and metastasis index (MI), using PET combined with CT findings. The data were analyzed by stepwise logistic regression and receiver-operating-characteristic analysis. The malignancy predictive probability (P) was obtained by P =ex/(1+ex), where x = -1.16 + 0.87(CTscore) + 0.15(SUVmax) + 0.27(MI). The area under curve (AUC) for the fitted logistic model was 0.82$±0.04, *whichwassuperiorandsignificantlydifferentfromSUVmax*(*AUC*, 0.73±0.05)*andCTscores*(*AU*
The fitted logistic model could improve diagnostic performance. The MI could help with differential diagnosis.

Full Text

Identification of Extrapulmonary Benign and Malignant Lesions with 18F-Fluorodeoxyglucose Avidity Using a Multivariate Regression Model

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Abstract

Whether extrapulmonary lesions demonstrate avidity for 18F-fluorodeoxyglucose (18F-FDG) could help differentiate benign from malignant lung lesions. In this study, 199 consecutive patients with newly diagnosed lung lesions (169 malignant and 36 benign lesions) underwent whole-body 18F-FDG PET/CT imaging. Histopathology and clinical results served as the reference standard. Malignancy likelihood was assessed using CT scores, the maximum standardized uptake value (SUVmax) of lung lesions, PET findings (FDG negative or positive), and a metastasis index (MI) derived from PET combined with CT findings. Data were analyzed using stepwise logistic regression and receiver operating characteristic analysis. The malignancy predictive probability (P) was obtained by P = e /(1+e), where x = -1.16 + 0.87(CTscore) + 0.15(SUVmax) + 0.27(MI). The area under the curve (AUC) for the fitted logistic model was 0.82 $\pm$ 0.04, which was superior and significantly different from SUVmax alone (AUC, 0.73 $\pm$ 0.05) and CT scores alone (AUC, 0.71 $\pm$ 0.05). The fitted logistic model could improve diagnostic performance, and the MI could aid in differential diagnosis.

Key words: Lung neoplasm, 18F-fluorodeoxyglucose, Positron-emission tomography and computed tomography, Logistic models, Receiver-operating-characteristic

Introduction

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) has been established for the differential diagnosis of pulmonary nodules and mass lesions in many countries. According to a meta-analysis of published data on 18F-FDG-PET scanning from January 1996 to September 2000, the average sensitivity and specificity for detecting malignancy was 97% and 78%, respectively [1]. However, 18F-FDG-PET does not offer benefit for evaluating pulmonary nodules with low 18F-FDG avidity [2]. Combining 18F-FDG-PET with diagnostic CT scanning without intravenous contrast can improve sensitivity from 69% to 97% without changing specificity [3]. The diagnostic accuracy of 18F-FDG PET/CT without high-quality CT of lung nodules was similar to that of 18F-FDG-PET alone [4,5]. Nie et al. [6] reported a semiautomatic computer-assisted diagnostic (CAD) scheme, indicating that combining 18F-FDG-PET with CT can differentiate benign from malignant pulmonary nodules better than either modality alone. In that study, we excluded two nodules with extrathoracic malignancy and focused on whole-body 18F-FDG-PET. Lesions outside the lung that are avid for 18F-FDG were considered metastasis. The presence of extrapulmonary lesions avid for 18F-FDG indicates that the newly diagnosed lung lesion is malignant.

2.1 Patient Cohort

Patients with newly diagnosed lung lesions identified through conventional chest radiography or X-ray CT suspicious for a malignant primary underwent whole-body 18F-FDG PET/CT between February 2005 and January 2009. We selected patients with pathological confirmation or suspicious infection cured by antibiotics, and excluded those with recent malignancy history or diabetes mellitus. Institutional Review Board approval was obtained without requiring patient informed consent.

A total of 199 consecutive patients (63 women and 136 men, aged 25–88 years, mean age $\pm$ SD: 58.8 $\pm$ 12.4) met the criteria for further analysis. Among 205 lung lesions, biopsy or surgery confirmed 169 as malignant and 32 as benign by pathology; 4 were infections cured by antibiotics (Table 1).

2.2 PET/CT Image Acquisition

To ensure blood glucose levels remained below 8.3 mmol/dL, patients were asked to fast for over 6 hours and rest for 15 minutes before administration of 5 MBq/kg 18F-FDG. Images were acquired using a whole-body PET/CT scanner (Discovery DST 8; GE Healthcare, USA) 60 minutes after injection, with whole-body scans extending from the mid-thighs to the skull roof. CT scans without intravenous contrast were performed using a protocol of 140 kV, 150 mA, 0.8 s tube rotation, and 3.75-mm slice thickness. PET scans were performed with 3.27-mm section thickness, 3.5 minutes per table position, and two-dimensional acquisitions. Patients were asked to maintain normal shallow respiration during image acquisition. 18F-FDG-PET images were reconstructed using CT attenuation correction and an ordered subset expectation maximization algorithm. The maximum standardized uptake value (SUVmax) was determined according to Ref. [7].

2.3 CT Image Acquisition

All patients underwent breath-hold spiral CT scanning of lung lesions without intravenous contrast after PET/CT scanning, using parameters of 120 kV, 170 mA, 0.8 s tube rotation, 2.5-mm slice thickness, and 1.35 pitch.

2.4 CT Image Interpretation

CT images were interpreted by two radiologists unaware of each patient’ s history and PET findings. Each lesion was described by its site, size, attenuation, characteristics, consolidation, cavitation, margin shape, and invasion. Established criteria were applied for lesion interpretation [5]. Consensus readings were performed in cases of differing results.

2.5 PET/CT Image Interpretation

18F-FDG-PET criteria for malignancy were applied as cited in [8]. Locations of abnormal tracer uptake were recorded, and the metastasis index (MI) was scored on a 5-point scale (Table 2). PET/CT images were analyzed by two physicians with 5 years of experience in 18F-FDG PET/CT, with consensus readings conducted in cases of differing results.

2.6 Statistical Analysis

Patient characteristics were compared using Student's t-test and chi-squared test. When expected values in any contingency table cells were below five, Fisher' s exact test was conducted. Variables reaching significance could be included in a multivariate logistic regression model. Selection method with entry testing was based on the significance of the score statistic, and removal testing used a probability threshold ($P > 0.15$) of the likelihood ratio test [9]. Odds ratios (OR) and 95% confidence intervals were computed using unconditional logistic regression. Receiver operating characteristic (ROC) analysis was performed for CT characteristics, lesion SUVmax uptake, and the predicted malignancy probability (P) calculated by the fitted multivariate logistic regression model. Differences in area under the curve (AUC) were tested using Z statistic. Two-tailed p-values ≤ 0.05 indicated statistically significant differences. Diagnostic OR for a test was defined as sensitivity/(1−sensitivity) × specificity/(1−specificity) [10].

3.1 CT and PET/CT Results

Patient and lesion characteristics are shown in Table 2. Lesion size could not be determined in 58 lesions due to local atelectasis with associated obstruction and parahilar location. In the remaining 147 lesions, sizes ranged from 4–143 mm (mean 36 ± 21 mm). Locations of distant lesions avid for 18F-FDG are listed in Table 3 .

Non-contrast CT showed that 62% (104/169) of malignant lesions were classified as positive, 29% (59/205) of all lesions were equivocal, and 44% (16/36) of benign lesions were negative (Table 2). Taking equivocal lesions as malignancy yielded a diagnostic OR of 8.2; taking them as benign yielded an OR of 3.6.

As shown in Table 2, 18F-FDG PET/CT had a sensitivity of 95% (161/169) and specificity of 25% (9/36) at a diagnostic OR of 6.7. No significant differences were observed in sex, age, or lesion size between benign and malignant lesions, but CTscore, SUVmax, 18F-FDG score, and MI showed highly significant differences ($p < 0.01$).

3.2 Multivariate Logistic Regression Analysis

Stepwise selection included CTscore, SUVmax, and MI in the fitted multivariate logistic regression model, while excluding 18F-FDGscore. In this model, increasing CTscore, SUVmax, or MI served as malignancy predictors. The probability P was calculated by P = e /(1+e), where x = -1.16 + 0.87(CTscore) + 0.15(SUVmax) + 0.27(MI) (Table 4).

Table 4 shows variables in the fitted multivariate logistic model of 205 lung lesions (dependent variable: malignancy/benignancy) selected by stepwise analysis. The model estimated $P > 50\%$ when $x \geq 0$, which corresponded to a CTscore of 2 at $x > 0$. In other words, at positive CT scan, the lung lesion should be considered malignant regardless of SUVmax. For example, a right upper lobe adenocarcinoma had CTscore = 2, SUVmax = 1.5, MI = 0, and P = 69.1%, as shown in Fig. 1 [Figure 1: see original paper].

When CTscore = 1 and SUVmax $\geq$ 2, x was larger than zero. At indeterminate CT scan, SUVmax = 2.0 was used as the cutoff for malignancy [3,11], thus helping distinguish benign from malignant lesions. When CTscore = 0, x was larger than zero only when SUVmax > 7.7, suggesting the lung lesion should be considered malignant regardless of morphological information. When CTscore results contradicted SUVmax, MI could aid differential diagnosis. For example, an inflammatory lesion in the left lower lobe had CTscore = 0, SUVmax = 5.0, MI = 0, and P = 39.9% (Fig. 2 [Figure 2: see original paper]).

3.3 ROC Analysis

ROC analysis was performed for CTscore, SUVmax, and P (Fig. 3 [Figure 3: see original paper]). The SUVmax curve based on lung lesions had cutoffs from initial 1.5 to end 8.0 in steps of 0.5, intersecting the CTscore curve. The model showed additional value over CTscore and SUVmax across the entire range of sensitivity and specificity. AUC was 0.83 ± 0.04 for the model, 0.71 ± 0.05 for CTscore, and 0.74 ± 0.05 for SUVmax. Statistical analysis of AUC showed the model was superior and significantly different from SUVmax ($p = 0.01$) and CTscore ($p < 0.01$). No significant difference existed between SUVmax and CTscore ($p = 0.64$). At the cutoff value of 0.50 for malignancy, sensitivity was 96% (163/169), specificity was 31% (11/36), and diagnostic OR for P was 12.0.

4 Discussion

In the 18F-FDG-PET model, SUVmax was associated with lung malignancy at OR = 1.16 ($p < 0.01$). The finding that increased SUVmax served as a significant malignancy predictor aligns with Grgic' s report [10]. The 95% sensitivity of 18F-FDG PET/CT for detecting malignancy in our study was equivalent to the 97% sensitivity reported in meta-analyses [1] and the 92% sensitivity from a prospective multicenter study [8]. However, our 25% specificity was lower than reported values of 44%–85% [1,3-5,8,11-13]. False-positive readings in 18F-FDG-PET are mainly caused by low specificity in benign lesions including tuberculosis, bacterial pneumonia, organized pneumonia, active sarcoidosis, infectious granulomas, and acute pyogenic abscesses [14].

CT morphological information was an effective predictor for malignancy at OR = 2.41 ($p < 0.01$), though its sensitivity and specificity in this study were not as accurate as in a multicenter contrast-enhanced CT study (98% sensitivity, 58% specificity) [15]. As we know, CT diagnosis of suspicious lung lesions usually depends on morphological information and enhancement [16]. Some equivocal lesions may be reclassified as definitely malignant or definitely benign based on enhancement characteristics, improving CT sensitivity and specificity. The lower accuracy in our study was likely due to the absence of contrast-enhanced CT [15].

MI was included in the model at OR = 1.31 ($p = 0.05$). To our knowledge, this is the first evidence that whether lesions outside the lungs are avid for 18F-FDG might help distinguish malignant lung lesions. Based on the score statistic probability ($p = 0.05$), we should be cautious when drawing conclusions from MI alone.

The 18F-FDGscore was excluded from the model because its information was already included in SUVmax. Stepwise logistic regression was designed to identify the most parsimonious set of predictors for malignancy. ROC curves show the model lies above the curves for CT diagnosis and SUVmax alone, indicating superior model accuracy regardless of threshold setting. Furthermore, AUC statistical testing confirms the model' s superiority over CTscore and SUVmax individually. Compared with diagnostic OR values of 3.7 or 8.3 for different CT and 18F-FDG diagnosis protocols (6.3), our model achieved the highest diagnostic OR of 12.0 at the 0.50 P cutoff, suggesting it performs better than CT or SUVmax alone. This model has potential for development into a semiautomatic CAD system to aid and improve physician diagnostic skills, which should be tested in a multicenter study in the future.

5 Limitation

This retrospective clinical study selected patients from a larger pool who were referred for 18F-FDG PET/CT because of pathologic verification of their lung lesions, inducing a selection bias. The malignancy rate was 82% (169/205). Regardless of influencing factors such as serum glucose level, respiration, partial-volume effects, and noise [17], SUVmax was used as the de facto standard [18].

6 Conclusion

In this study, extrapulmonary lesions avid for 18F-FDG could help distinguish malignancy from benignancy. Our logistic model incorporating CTscore, SUVmax, and MI information for predicting malignancy probability P was superior to CT or 18F-FDG alone, thus improving physician diagnostic performance.

Acknowledgments

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