

Original Research Article

Using positron emission tomography - computed tomography imaging to distinguish of metastatic disease from second primary lung tumours in patients with non-small cell lung cancer

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ABSTRACT

Background: In NSCLC patients with multiple lesions, the differentiation between metastases and second primary tumours has significant therapeutic and prognostic implications. The aim of this retrospective study was to investigate the potential of 18F-FDG PET to discriminate metastatic disease from second primary lung tumours.

Methods: Of 318 NSCLC patients between November 2015 and October 2018 at Bach Mai hospital, patients with a synchronous second primary lung cancer were selected. Patients with metastatic disease involving the lungs served as the control group. Maximum standardized uptake values (SUVs) measured with 18F-FDG PET were determined for two tumours in each patient. The SUVmax was determined and compared between the second primary group and metastatic disease group. Receiver-operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of the SUVmax for an optimal cut-off value.

Results: A total of 81 NSCLC patients (44 metastatic disease, 37 second primary cancer) were included for analysis. The SUVmax was significantly higher in patients with second primary cancer than in those with metastatic disease (7.53 ± 4.33 vs 4.35 ± 2.58 , respectively, $p < 0.001$). The area under the ROC curve was 0.81 and the odds ratio for the optimal cut-off was 7.52.

Conclusions: SUVmax from 18F-FDG PET images can be helpful in differentiating metastatic disease from second primary tumours in patients with synchronous pulmonary lesions. Further studies are warranted to confirm the consistency of these results.

Keywords: Metastatic disease, Non-small cell Lung cancer, Second primary tumour, SUVmax

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality.¹ Although the incidence of lung cancer is decreasing, the number of patients presenting with a second primary cancer has dramatically increased in the last decades.¹ A simultaneous second primary lung carcinoma occurs in 1-8% of lung cancer patients.² The occurrence of multiple primary cancers may be attributed to shared aetiological factors. For non-small cell lung cancer patients 18F-fluorodeoxyglucose positron

emission tomography (FDG PET) is recommended according to the American College of Chest Physicians (ACCP) guidelines as standard work-up in potentially curable lung cancer based on conventional imaging. The rate of detection of unanticipated metastasis by FDG PET has been reported as 1-18% in patients with clinical stage I or II disease.³ When an FDG PET scan is made for lung cancer staging, both metastases as well as synchronous primary tumours can be visualized. While multiple lung nodules of varying sizes are usually classified as metastases, it is a much greater challenge to distinguish a

lung metastasis from a second primary lung carcinoma when only one additional pulmonary lesion is detected.⁴

This retrospective study evaluated the potential of SUVmax measured with FDG PET to discriminate metastatic disease from second primary lung tumours in patients with non-small cell lung cancer.

METHODS

Patients

A total of 318 patients (220 men and 98 women) between November 2015 and October 2018 at Bach Mai hospital were retrospectively screened. First, patients were included in the ‘second primary group’ when they presented with two primary tumours, including any index tumour and a synchronous pulmonary tumour, defined as a tumour diagnosed within 6 months of diagnosis of the index tumour.⁵ Second, patients with lung cancer metastasized to the same lobe (stage IIIB) or to different lobes or other organs (stage IV) were consecutively searched for and included to form the control group (or ‘metastatic disease group’), until a similar sample size as of the second primary group was reached.

Inclusion criteria

- The lung tumors must have been solitary lesions as determined by PET/CT.
- The patients must have undergone FNA biopsy and/or surgical resections of their lung tumor.

Patients who histology could not be confirmed or was confirmed as other than NSCLC were excluded from the study.

When FDG uptake is measured in small tumours, bias can be introduced by the partial volume effect resulting in underestimation of the tumour SUV. To prevent bias by partial volume effects, patients with a tumour smaller than 15 mm were excluded from analysis.

FDG-PET-CT imaging

All patients underwent diagnostic and/or staging FDG-PET-CT prior to biopsy or therapy. Patients were asked to fast at least 6 h before the FDG-PET-CT scan. All patients had a glucose level below 180 mg/dl and were injected intravenously with 0.15-0.20 mCi /kg (7-12mCi) FDG. At 45-60 min after the injection, data were acquired from the vertex to the upper thigh. Immediately after CT, a PET scan (PET/CT Biograph True Point - Siemens, Germany) was performed for about 25 min, with seven to eight bed positions and 3 min/position. PET images were reconstructed iteratively with CT data for attenuation correction, using an inline integrated Siemens Esoft Workstation system. Computerized tomography integrated positron emission tomography fusion images in transaxial, sagittal, and coronal planes were evaluated

visually, and the SUVmax of lesions was obtained from transaxial images.

Standardized uptake values

The maximum SUV (SUVmax, the activity from the maximum-valued pixel within the tumour volume of interest (VOI); hereafter referred to as SUV) normalized to injected activity and patient body weight was calculated at approximately 60 min after tracer injection for each primary lesion and the chosen metastatic lesion with use of the following equation: $SUV = \frac{\text{maximum activity concentration in the VOI [kBq/ml]}}{\text{injected dose [MBq/ml]} / \text{patient body weight [kg]}}$. In patients with multiple metastatic lesions, the lesion with the largest diameter was chosen to prevent partial volume effects.

Area under the receiver-operating characteristic curve and cut-off value

After constructing a receiver-operating characteristic (ROC) curve of the SUVmax, the area under the curve (AUC) was assessed, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and odds ratio (OR) were determined for an optimal cut-off of the SUVmax.

Statistical analyses

Since the SUVmax was normally distributed in both groups, an independent samples one-tailed ANOVA test was used to compare the mean SUVmax between the second primary tumour and metastatic disease group. Mean age were compared using a two-sided t test.

RESULTS

Patient characteristics

A total of 81 eligible patients with synchronous malignancies (44 metastatic disease and 37 second primary cancer, respectively) were included.

Table 1: Patients with metastatic disease and a second primary tumour.

Patient characteristics	Second primary group (n=37)	Metastatic disease group (n=44)	p value
Mean age (range)	62.5±10.7	62.8±8.9	>0.05
Sex (men/women)	26/11	35/9	>0.05
Histopathology			
ACC	32	41	
SCC	3	1	
LCC	2	2	

The mean age of the patients (57 men and 24 women) was 62.7 years (range: 26-87 years). Other patient

discriminating metastases from second primary tumours in cases of synchronously presenting lesions. A significantly larger SUVmax between two tumours was found in patients presenting with two primary tumours as compared to patients with metastatic disease involving the lungs. The moderately high accuracy, as measured with the AUC, as well as the good sensitivity and specificity of the SUVmax support the use of FDG PET as a modality for discriminating second primary lung tumours from metastases.

Previously, multiple case reports and studies have been published presenting cases of unexpected synchronous primary lung tumours detected by FDG PET.⁶ On the contrary, only few reports exist in which FDG PET contributes in determining the clonal origin of synchronous tumours. The current available literature further supports this hypothesis that SUVs can differentiate tumours of common origin and with common biological behaviour (i.e. metastases) from those of separate clonal origin (i.e. multiple primary tumours). That is, FDG uptake has been reported to relate to several tumour characteristics, including histological subtype and tumour aggressiveness.⁷

FDG PET imaging is already extensively being used in patients with lung cancer for several purposes, including the diagnosis of recurrent disease, staging, prognostic stratification and radiotherapy planning.⁸⁻¹⁰ Also, it has been shown to be an accurate modality to differentiate benign from malignant solitary pulmonary lesions. Furthermore, FDG PET can be used to monitor the response of non-small cell lung cancer to chemotherapy, radiotherapy and potentially to targeting of cell signalling pathways.^{11,12} The results presented implicate that the use of FDG PET might be expanded to the identification of early stage second primary tumours in patients with synchronous pulmonary lesions.

The population studied was carefully defined by stringent inclusion criteria. By including only those patients for whom sufficient data for a definite diagnosis of second primary cancer were available, the validity of this study was strengthened. Additionally, conditions between the patient groups studied were equalized as much as possible by choosing one reconstruction method for all PET images, since this is known to affect the SUV.

Several limitations to this study should be noted. First, this study has a small sample size. Because of the retrospective nature of the study. Second, diagnosis was made without histological confirmation in most cases of metastatic disease. In these patients, histopathology of the metastatic lesion was lacking, because the clinical presence of multiple lesions in a pattern typical for metastatic spread was considered sufficient for diagnosis of metastatic disease. If this study had been prospectively conducted, however, tissue for immunohistochemical and mutation analyses could have been sampled for all

tumours, thereby assuring validity of diagnoses of both patient groups studied.

CONCLUSION

The results of this study suggest that measurement of the SUVmax using FDG PET images can be useful in differentiating metastatic disease from second primary cancer in patients presenting with synchronous pulmonary lesions.

This non-invasive technique, which is standardly available in pre-surgically staged lung cancer patients, may increase cost-effectiveness due to less cumbersome diagnostic procedures and more efficient identification of potentially curable second primary cancer patients.

However, larger and prospectively conducted studies are warranted to confirm the consistency of these results and to test the accuracy of the SUVmax at the cut-off value proposed in this study.

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Ethical approval: The study was approved by the Institutional Ethics Committee Board of Bach Mai Hospital

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