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Original article

FDG uptake of pulmonary lesions in synchronous primary lung cancers and lung metastases

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ABSTRACT

Purpose: In lung cancer patients, the distinction between synchronous primary lung cancer and intrapulmonary metastasis can be challenging. The intensity of FDG uptake in pulmonary lesions has been shown to be potentially useful in classifying synchronous lung cancer. The aim of this retrospective study is to investigate the effectiveness of FDG uptake in differentiating metastases from synchronous primary lesions in the setting of lung cancer.

Methods: Consecutive patients with primary lung cancer with two or more malignant lung lesions referred for (^{18}F)-FDG PET-CT imaging between 2010 and 2019 were reviewed and classified into synchronous and metastasis groups. Lesional maximum standardized uptake values (SUV_{max}), relative differences in SUV_{max} and SUV_{max} ratios were calculated and compared using receiver operating characteristic (ROC) curve analysis. Intra-group correlation in SUV_{max} between lesion pairs was examined using Pearson's and Spearman's correlation analysis.

Results: 94 patients were included for analysis, divided into synchronous (n = 62; 68 lesion pairs) and metastasis (n = 32; 33 lesion pairs) groups. The correlation of FDG uptake between lesions in the metastasis group was strong (r = 0.81). A significant difference in mean relative difference in SUV_{max} (synchronous: 0.50±0.23 metastasis: 0.34±0.17, p = 0.001) and mean SUV_{max} ratio (synchronous: 2.6 ± 1.7 metastasis: 1.7 ± 0.6, $p < 0.001$) was observed. ROC analysis revealed a fair AUC (0.71–0.72) for these parameters, with an associated sensitivity of 59 % and specificity of 82 % at optimal cut-off values.

Conclusion: Differences in FDG uptake intensity among multiple synchronously presenting malignant nodules may be helpful to distinguish second primary lung tumours from metastatic spread.

1. Introduction

Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography (F)-FDG PET-CT) imaging is routinely performed for initial staging of primary lung cancer, which assesses the glucose metabolism of tumors [1,2]. In patients with more than one hypermetabolic lung lesion suspected to be malignant, the lung lesions could represent either synchronous primary lung cancers or a primary cancer with metastatic spread [3]. According to the American Joint Committee on Cancer (AJCC) cancer staging system [4], tumors may be considered second primaries if they are clearly of a different histologic type on biopsy. Based on time of presentation, multiple discrete tumours may further be designated as synchronous (if an additional tumour appears within 6 months of an initial index tumour) or metachronous (if a new tumour emerges beyond this timepoint) [5]. The gold standard for differentiation includes immunohistochemistry and P53 gene mutation analyses [6,7], which may not be routinely performed or feasible.

In cases of equivocal histopathological findings or in situations where patients are unable to tolerate a biopsy or it being infeasible due to lesion location, FDG PET-CT may be helpful. The criteria favoring separate tumors include differences in radiological appearance or metabolic uptake on FDG PET-CT [4]. In addition, it may be easier to differentiate two primary cancers if they have different histopathology. The challenge is when tumors show similar histopathological features wherein it remains difficult to determine whether the tumor is a second primary lung cancer or a metastasis.

The distinction of synchronous primary lung cancer from intrapulmonary metastasis affects staging and management, underlying its clinical significance. If the second lesion represents metastasis, TNM staging based on the 8th edition of the AJCC staging system

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classifies a separate tumor in a different lobe of the ipsilateral lung as T4 (stage III) while a tumor in the contralateral lung is considered as M1a (stage IV) [4]. Patients with lung metastases may not be suitable surgical candidates and thus, are typically treated with palliative intent [8]. In contrast, aggressive surgical intervention has been proven to be safe and effective in patients with synchronous primary lung carcinoma and negative nodal involvement [9,10].

Standardized uptake value (SUV) is a semiquantitative measure of FDG uptake, which serves as a proxy for tumor metabolic activity. It is known that poorer tumour differentiation and higher tumour aggressiveness correspond to higher FDG uptake [11–13]. It has also been shown that the difference in FDG uptake between two lung nodules could be helpful in differentiating metastatic disease from second primary tumours in patients with synchronously presenting pulmonary lesions [14,15].

Tumours with a shared clonal origin often behave similarly and have common histological features. We hypothesized that the SUVs of clonally related tumours (i.e., metastases) would be more similar in FDG uptake than tumours possessing a different clonal origin, and, consequently, that a larger difference in FDG uptake would potentially infer the presence of synchronous primary lung cancers rather than metastatic disease. The primary objective of the study is to assess the diagnostic value of FDG uptake intensity for differentiating synchronous lung cancer from metastasis in patients with multiple malignant lung lesions. The secondary objective is to assess the correlation of FDG uptake parameters of lung lesions between the synchronous and metastasis patient groups.

2. Materials and methods

2.1. Study design

A single-centre retrospective study was performed to examine the use of maximum SUV (SUV_{max}) parameters to reliably distinguish between second primary lung tumours and lung metastases in the setting of primary lung cancer. For the purposes of this study, two groups were defined, analyzed, and compared: the “synchronous group”, representing patients presenting with multiple primary lung cancers, and the “metastasis group”, representing patients presenting with intrapulmonary metastasis from a primary lung cancer.

2.2. Patients

Consecutive patients with lung cancer (confirmed or suspected) referred for FDG PET-CT imaging between January 2010 to December 2019 with two or more hypermetabolic lung nodules were included. Most patients were referred for diagnosis and initial staging. Patients with prior treatment for lung cancer were excluded and therefore only patients for initial staging were included. In addition, patients with tumours of unknown or uncertain clonal origin, small lesion sizes (<8 mm), ground glass opacities, metastases from extrapulmonary malignancies, and active inflammatory or infectious conditions were excluded.

2.3. ^{18}F-FDG PET data acquisition and reconstruction

All patients underwent whole-body FDG PET-CT imaging as part of their routine preoperative staging procedure. Before FDG administration, patients fasted for 6 h. Patients’ glucose level was subsequently verified (≤9.0 mmol/L was considered acceptable before 2015, which was relaxed to 11.0 mmol/L based on the current guidance document [16]). Images were acquired at 60 min following radiotracer administration.

FDG PET images were acquired with the GE Discovery 710 Scanner (GE Healthcare) after administration of 2-(^{18}F)-fluoro-2-deoxy-D-glucose with three-dimensional (3D) acquisition. The administered dose was weight-based (5 MBq/kg) and the spatial resolution of the PET scanner was 5 mm. Images were acquired over 2.5 min intervals per bed position using typical image acquisition parameters on the GE Discovery 710 PET-CT scanner. Images were reconstructed by ordered subset expectation maximization (OSEM) with correction for attenuation and scattering on the GE Discovery 710 scanner and subsequently interpreted on HERMES workstation. For each pulmonary nodule, the SUV_{max} (defined as the maximum uptake value of a lesion taken as the voxel with the highest activity level within the volume of interest) was measured by a nuclear medicine fellow and subsequently verified by a nuclear medicine physician with 20 years of FDG PET experience.

2.4. Histopathological data

A tumour was considered a second primary tumour if histopathological or immunohistochemical features differed from those of the index tumour, demonstrating separate clonal origin. The relevant pathology report was accessed and reviewed from each patient’s chart in the hospital and provincial electronic medical record. Patients without conclusive diagnosis of second primary cancer due to the impossibility of gaining adequate tissue samples for confirmation were excluded. Metastatic disease was concluded based on identical histopathological findings and immunohistochemical staining of the lesions pointing toward a shared clonal origin or clinical suspicion involving tumour morphological and spatial characteristics consistent with metastatic spread (metastasis group). In patients with multiple primary lung cancers, further distinguishing between synchronous and metachronous lesions (based on aforementioned differences in time of lesion detection) is difficult due to the lack of sequential imaging studies. For simplicity, we grouped these patients together (synchronous group).

2.5. Statistical method

In addition to SUV_{max}, the absolute difference in SUV_{max} (ΔSUV_{max}) between hypermetabolic pulmonary nodules was calculated in each patient, where SUV_{max}^1 corresponded to the lesion with the higher uptake value ($\Delta SUV_{max} = SUV_{max}^1 - SUV_{max}^2$). Relative difference in SUV_{max} (relative ΔSUV_{max}) was calculated using ΔSUV_{max} relative to SUV_{max}^1 ($\Delta SUV_{max}/SUV_{max}^1$), while SUV_{max} ratio was expressed in terms of SUV_{max}^1 to SUV_{max}^2. In the case of patients presenting with more than two synchronous lung lesions, pairwise comparisons were conducted for all possible permutations in the synchronous group such that the SUV_{max} of the less FDG-avid lesion was subtracted from the SUV_{max} of the more FDG-avid lesion. For instance, in a patient presenting with 3 synchronous pulmonary nodules, the values SUV_{max}^1, SUV_{max}^2 and SUV_{max}^3 were recorded, and the differences in SUV_{max} were calculated as $\Delta SUV_{max} = SUV_{max}^1 - SUV_{max}^2$, $SUV_{max}^1 - SUV_{max}^3$ and $SUV_{max}^2 - SUV_{max}^3$ (where $SUV_{max}^1 > SUV_{max}^2 > SUV_{max}^3$). In the metastasis group, pairwise comparisons were conducted using the primary tumour as the index tumour 1, which was taken as the lesion with the highest SUV_{max} measurement, where $\Delta SUV_{max} = SUV_{max}^1 - SUV_{max}^2$.

The imaging parameters between the synchronous and metastasis groups were analysed using the Mann–Whitney U test as none of the parameters followed a normal distribution based on the Shapiro-Wilk test. Correlation of FDG PET uptake (given by SUV_{max} measurements) between lesion pairs in the metastasis group (expected linear relationship) was performed by Pearson’s analysis and the synchronous group (expected non-linear relationship) was examined using Spearman’s correlation analysis. For discrete histopathological types, receiver operating characteristic (ROC) analysis was performed to determine the area under the curve (AUC), optimal cut-off value, and corresponding sensitivity and specificity of SUV_{max} ratio and relative difference in SUV_{max} as suitable parameters to differentiate between

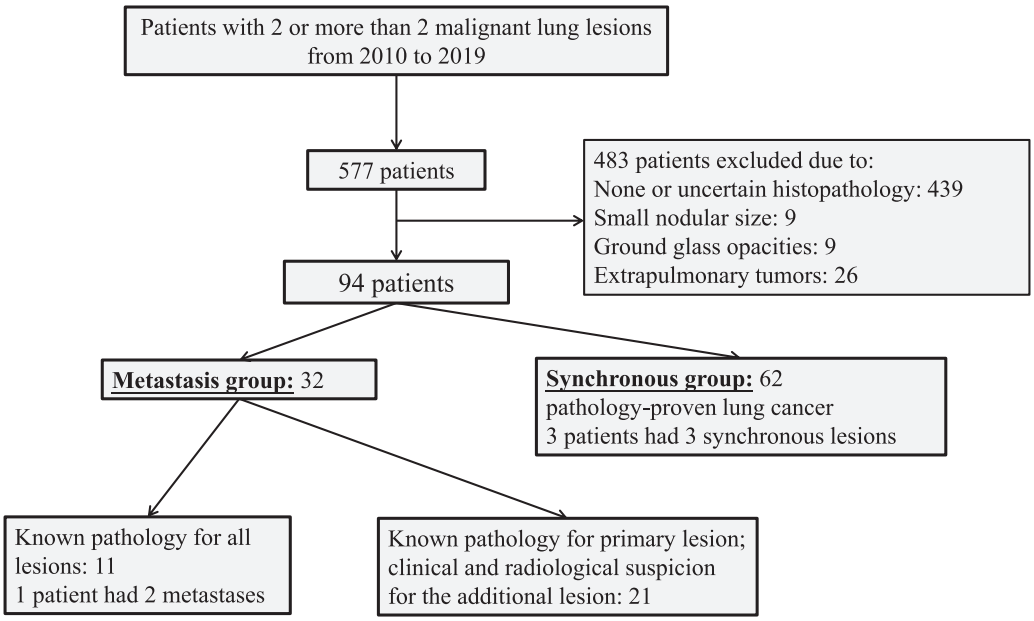

Fig. 1. Flow chart of selecting patients with lung cancer.

second primary lung tumours and metastasis. All statistical tests were two-tailed and a *p*-value below 5 % was considered statistically significant. All analyses were performed with IBM SPSS Statistics (version 26, IBM, USA).

3. Results

3.1. Patient distribution

Upon reviewing patient chart records, a total of 577 patients with two or more hypermetabolic lung lesions were identified. After exclusion of patients with lesions of unknown or uncertain tumour histopathology (n = 439), small lesion size (n = 9), ground glass opacity appearance (n = 9), and metastatic disease originating from extrapulmonary tumours (n = 26), 94 patients (age: 69±9, F: M = 55:39) remained for analysis. Of those patients, 62 patients comprised the synchronous group, where 59 patients had two lesions and three patients had three lesions, with all lesions confirmed by histopathology to be of different clonal origin and thus, represented separate primary lung tumours. In terms of histological subtype, the majority of lesions represented adenocarcinoma (43 of the first lesions and 52 of the second lesions), followed by squamous cell carcinoma (15 of the first lesions and 7 of the second lesions). The metastasis group, consisting of 32 patients, was further sub-divided based on whether the metastatic tumour was confirmed by histopathology (n = 11) or suspected due to imaging features and clinical information suggesting metastatic disease (n = 21) (Fig. 1). One patient in the metastasis group had two biopsy-proven metastases. In contrast to the synchronous group, a larger proportion of lesions corresponded to squamous cell carcinoma [15] in the metastasis group, followed by adenocarcinoma [10] and others.

3.2. Tumour characteristics

In comparing nodule size between the two lesions in each patient, the first lesion was taken as the one with the more intense FDG uptake. The mean lesion volume of the two lesions in the synchronous group was 23 ml (±45 ml) and 5 ml (±13 ml), while the mean volume of the two lesions was 59 ml (±63 ml) and 4 ml (±7 ml) in the metastasis group. In terms of nodule distribution, the majority of metastatic tumours (84 %) were found in the same lobe as the primary cancer whereas second primary tumours tended toward a more variable distribution pattern, with only 20 % of tumours presenting in an intra-lobar manner.

3.3. Tumour SUV parameters

For the synchronous group, mean SUV_{max} was 11.6 ± 7.4 for lesion 1 and 5.0 ± 3.0 for lesion 2, and for the metastasis group it was 14.2 ± 6.9 for lesion 1 and 9.0 ± 4.5 for lesion 2 (Table 1). The

Table 1
Patient characteristics and imaging parameters.

	Synchronous primary group		Metastatic group		*p* values
Total patients	62		32		
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	
Age (years)	69.3 ± 9.0	71 (46, 88)	69.0 ± 9.3	68 (53,89)	0.90
Tumor volume (ml)					
Tumor 1	21.0 ± 42.4	6.1 (0.5, 204.1)	55.9 ± 63.4	30.2 (1.2, 204.8)	0.001
Tumor 2	5.0 ± 12.4	1.6 (0.3, 94.5)	5.9 ± 12.9	1.2 (0.4, 66.6)	0.65
FDG uptake					
SUV_{max}^1	11.6 ± 7.4	10.2 (2.7, 42,2)	14.2 ± 6.9	11.7 (6.4, 33.5)	0.026
SUV_{max}^2	5.0 ± 3.0	4.2 (1.5, 16.7)	9.0 ± 4.5	8.2 (3.5, 26.2)	<0.001
SUV_{max}^1 - SUV_{max}^2	6.6 ± 6.3	4.1 (0.3, 32.4)	5.2 ± 4.3	4.1 (0.6, 20.8)	0.67
SUV_{max}^1/SUV_{max}^2	2.6 ± 1.7	1.9 (1.1, 10.2)	1.7 ± 0.6	1.5 (1.1, 3.5)	<0.001
$(SUV_{max}^1/SUV_{max}^2)/SUV_{max}^1$	0.50±0.23	0.49 (0.06, 0.90)	0.34±0.17	0.34 (0.08, 0.71)	0.001

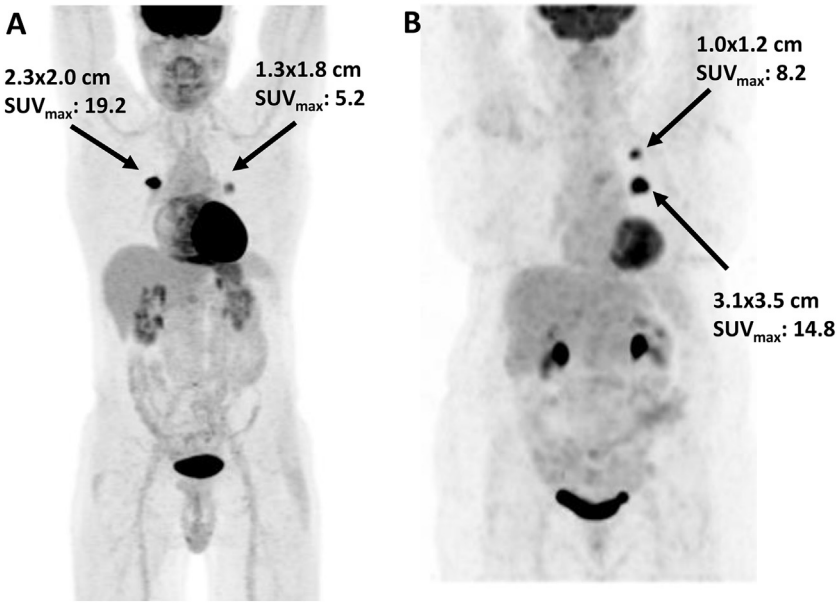

Fig. 2. A. 62 year old male with biopsy proven SCC in the RUL and adenocarcinoma in the LLL (Synchronous group). B. 78 year old female with two hypermetabolic lung lesions status post LUL lobectomy with pT3pN0 staging (Metastasis group).

difference in FDG uptake in both index (SUV_{max}^1) and second lesions (SUV_{max}^2) between the synchronous and metastasis groups was significant (p = 0.026 for the index lesion and $p < 0.001$ for the second lesion). Representative cases from the synchronous and metastasis groups with imaging results and FDG uptake values are shown in Fig. 2.

Although the mean absolute difference in SUV_{max} (ΔSUV_{max}) was not found to be statistically significant (synchronous: 6.6 ± 6.3; metastasis: 5.2 ± 4.3; p = 0.67), the mean relative difference in SUV_{max} (synchronous: 0.50±0.23; metastasis: 0.34± 0.17) and mean SUV_{max} ratio (synchronous: 2.6 ± 1.7 metastasis: 1.7 ± 0.6) both differed significantly (p = 0.001 for relative ΔSUV_{max} and $p < 0.001$ for SUV_{max} ratio) between patients with synchronous primary lung cancer and metastatic pulmonary disease (Table 1).

3.4. Correlation analysis

The relationship of SUV_{max} between the index lesion and the additional lesion(s) for each group is illustrated in Fig. 3. Intra-group correlation in SUV_{max} between the index tumour and the additional lesion(s) was analyzed using Pearson's (metastasis group) and Spearman's (synchronous group) correlation analysis, which exhibited a strong correlation of lesional uptake within the metastasis group (r = 0.81) and fair correlation in the synchronous group (ρ=0.53) [17].

3.5. ROC analysis

The area under the curve (AUC) for relative ΔSUV_{max} and SUV_{max} ratio were determined to be 0.72 and 0.71, respectively (Fig. 4). A sensitivity of 59 % and a specificity of 82 % were achieved from the optimal cut-off values for both parameters (0.41 for relative ΔSUV_{max} and 1.85 for SUV_{max} ratio) in predicting metastatic disease in patients presenting with two or more hypermetabolic pulmonary lesions, showing that both parameters exhibited fair discriminative ability.

4. Discussion

Assessment of multifocal lung tumors and the distinction of synchronous primary tumors from intrapulmonary metastases is crucial in determining staging and subsequent treatment approaches. Utilization of recent advances in imaging may be helpful. In this study, we demonstrated that the difference in FDG uptake intensity between lung lesions could be helpful in inferring whether an additional lesion represents synchronous primary lung cancer or metastasis in some patients.

FDG uptake can be affected by multiple factors including histologic subtype, cell differentiation, proliferative rate, microvasculature density, and hypoxia, as well as the imaging technology itself [18,19]. Regardless, if the additional lesion corresponds to a metastatic

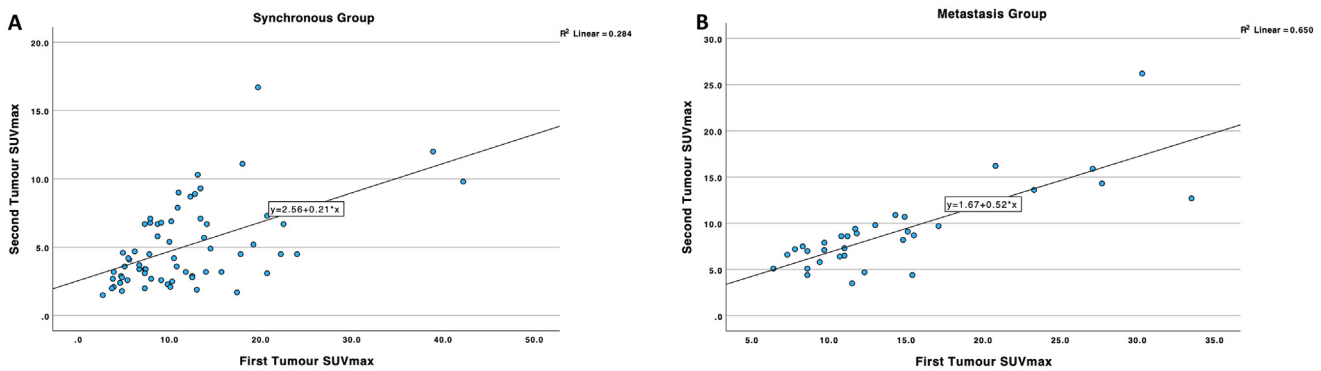

Fig. 3. Relationship between SUV_{max} measurements of the index/first tumour (SUV_{max}^1) and secondary lesion (SUV_{max}^2), where each datapoint represents an individual lesional pairing in the synchronous (A) and metastasis (B) groups respectively.

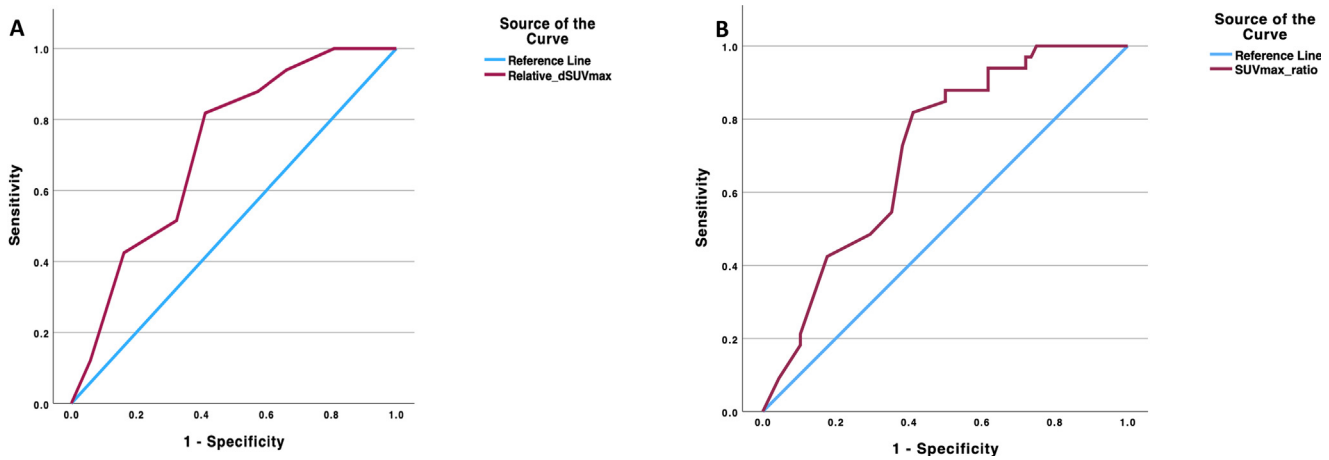

Fig. 4. ROC curve analysis for relative ΔSUV_{max} (A) and SUV_{max} ratio (B), with optimal cut-off values of 0.41 and 1.85 corresponding to an AUC of 0.72 and 0.71, respectively (sensitivity = 59 % and specificity = 82 % for both parameters in differentiating metastatic disease from synchronous primary cancer in the lungs).

nodule, its FDG intensity is expected to mirror the activity of the index lesion due to a shared histologic origin. Consequently, if the difference in FDG uptake intensity is large, the additional lesion is unlikely to be a metastasis (and therefore, more likely to represent a synchronous primary cancer). Nonetheless, the opposite may not be true: if the lesions in a pair have similar FDG uptake intensity, the additional lesion could either be a synchronous primary lung cancer (with similar histological type and tumor grade) or a metastasis. As a result, the use of FDG intensity in differentiating metastatic disease from synchronous primary cancer may only be helpful in a subset of patients where the relative ΔSUV_{max} or ratio between the two lesions is large and may not be predictive when the ΔSUV_{max} is small.

The study demonstrated a statistically significant difference in SUV_{max} ratio (2.6 ± 1.7 vs. 1.7 ± 0.6, $p < 0.001$) and relative ΔSUV_{max} (0.50±0.23 vs. 0.34±0.17, $p = 0.001$) between the synchronous primary cancer and metastasis groups, which agrees with and builds upon findings reported in previous retrospective studies [14,15,20,21]. Dijkman et al. [14] studied 37 patients with metastases (n=21) and second primary lung cancer (n=16) and found that ΔSUV_{max} was significantly higher in patients with second primary cancer than in those with metastatic disease (58% vs. 28 %, respectively, $p < 0.001$). In our study, however, we did not find a statistically significant difference in absolute ΔSUV_{max} between the two groups. Instead, we found that the ratio of FDG uptake between two lesions and relative ΔSUV_{max} were better predictive parameters. By using the optimal cut-off value of 1.85 for SUV_{max} ratio in our study, more patients from the synchronous group (57 %) were identified than from the metastasis group (18 %). A prior study [15] analyzed SUV_{max} ratio by examining 59 patients with synchronously presenting primaries and 23 patients with metastatic disease and found a significant difference in SUV_{max} ratio between the synchronous and intrapulmonary metastasis groups (2.3 ± 1.6 vs. 1.5 ± 0.4, $p < 0.01$). Another study [22] found that synchronous primary tumours were more likely than metastatic spread if SUV_{max} differences between two lesions fell outside of the range of 50 % to 200 %. Relative ΔSUV_{max} has also been studied where tumours with the same clonal origin (i.e., metastases) demonstrate similar FDG uptake [14,20,21]. Optimal cut-off values of 41 % [14] and 35 % [21] for relative ΔSUV_{max} have been reported, with one study correctly predicting almost 75 % of all histopathologically-confirmed synchronous multiple primary cancers using the former recommendation [20]. Nonetheless, these studies included comparisons involving extrapulmonary tumours in their analysis, whereas the current study examined SUV_{max} relationships among lung malignancies only. With an optimal cutoff value of 41 % for relative ΔSUV_{max} determined from our study, there were more patients classified from the synchronous group (65 %) than the metastasis group (27 %).

To assess the association of FDG uptake between lung lesions, we excluded metastases from extrapulmonary tumors. A stronger linear relationship was observed in the metastasis group than the synchronous group as demonstrated in Fig. 3 (R^2=0.65 vs. R^2=0.28), which shows a strong correlation between $SUV_{max}{}^1$ and $SUV_{max}{}^2$ in the metastasis group ($r = 0.81$). Such a relationship is logically consistent, as both lesions being compared within the metastasis group share the same clonal origin and therefore, are expected to show similar patterns of tumour proliferation, tumor grade and metabolism as reflected in FDG uptake. On the other hand, there was a fair correlation between $SUV_{max}{}^1$ and $SUV_{max}{}^2$ in the synchronous group (ρ=0.53), which was not expected. The more variable intra-group differences in SUV_{max} pairings highlights the increasing divergent origin of these tumours presenting as independent synchronous primary cancers; however, a relatively weak correlation does still exist, perhaps partly because of the possibility of two synchronous primary cancers of different histological subtype exhibiting similar patterns of tumour metabolic activity and thus, FDG uptake.

The area under the ROC curves in our study (0.71−0.72) is comparable to other studies [14,15], with a sensitivity of 59 % and a specificity of 82 % at the optimal cut-off ratio and relative ΔSUV_{max} values. The FDG uptake is predictive only when the difference in intensity between two lesions is large (for example, a ratio of at least 1.85 in our study); therefore, AUC is unlikely to be close to 1. Consequently, due to this inherent limitation, using FDG uptake as a marker to distinguish a synchronous lung cancer from a metastasis for an additional lesion may only be helpful in a subset of patients with multiple malignant pulmonary nodules, where the difference in lesional FDG uptake is large enough that synchronous primary cancer is strongly suggested.

In terms of patient exclusion, ground glass nodular opacities usually form a distinct group of lung malignancies so patients with this pattern of presentation were excluded. Patients with biopsy-proven metastases from other primaries, including breast cancer and melanoma, were likewise excluded. Aside from states of malignancy, high SUV values are also observed in certain benign conditions involving inflammatory or infectious processes [23]. As such, patients with suspected active underlying inflammatory or infectious disease were excluded to minimize confounding. A possible source of error in the case of small tumours is the partial volume effect, which results in an underestimation of SUV_{max} [24]. To account for inaccuracies introduced by the effect, lesions whose shortest axis was less than 8 mm in diameter were excluded from analysis, which aligned with the National Comprehensive Cancer Network (NCCN) guideline [25] of performing FDG PET for solid nodule(s) larger than 8 mm in size. Employing this recommendation reduces, but may not completely

eliminate, the partial volume effect; nevertheless, using this cut-off is consistent with our clinical practice.

Of the 577 patients with two or more hypermetabolic lesions, the majority (n = 439) had incomplete or uncertain histopathological data. In the original study by Dijkman et al. [14], only 37 patients were identified for analysis from 1396 patients evaluated by the thoracic oncology group over a five-year period. Our sample size is relatively small (n = 94), as it is exceedingly challenging to obtain a large sample size of patients with unequivocal histopathology for at least two hypermetabolic pulmonary lesions.

FDG uptake can be semi-quantified as SUV_{max}, SUV_{mean}, or SUV_{peak}. SUV_{max} was used in this study due to its robust nature and routine use in clinical practice. SUV_{mean} is dependent on the definition of the region of interest and therefore, may be reader-dependent and less accurate in lesions with central necrosis. SUV_{peak} (maximum average SUV within a 1 cm^3 spherical volume) has often been used in research studies and was considered to be a reliable parameter for FDG quantification [26]. We have measured SUV_{peak} values in lung lesions in our study and found similar results to that of SUV_{max} and therefore, did not present the results using SUV_{peak}. Other metabolic parameters, such as total lesion glycolysis and metabolic volume, were not evaluated in the current study and could be explored in the future.

Morphological features of pulmonary nodules on CT may be helpful in distinguishing synchronous from metastatic lung cancer. Certain features, such as spiculation of the nodule anatomical margins, pleural indentation, vascular convergence and air bronchograms, have been shown to correlate with an increased risk of lung cancer [27]. The nodule growth rate and the location of the nodule (the majority of which occur in the upper lobes) have been identified as predictors of malignancy as well [28,29]. Although CT findings were not included in the current study, combining and correlating FDG uptake and CT findings will likely improve diagnostic accuracy and could likewise be considered in a future study.

In light of more recent developments in AI deep-learning algorithms designed to assist clinicians in detecting and classifying lung nodules including the classification of lung nodules as malignant or benign [30], new opportunities exist in leveraging this technology to further improve the differentiation between synchronous primary lung cancer and intrapulmonary metastasis. AI tools may prove to be indispensable in further characterizing the relationship between synchronously presenting malignant lesions by both complementing and further integrating findings reported on FDG PET imaging with salient radiomics imaging features.

Some limitations apply to the current study. Firstly, the conclusions that can be drawn are limited by the study's retrospective nature and relatively small sample size for the metastasis group. Furthermore, the metastasis group was sub-divided based on whether the tumour was confirmed histopathologically or assumed based on a high index of clinical suspicion related to imaging findings suggestive of metastatic spread. Although we attempted to account for the partial volume effect by excluding patients presenting with smaller lesion sizes, adopting a threshold of 8 mm may not fully eliminate all possible discrepancies or variation in SUV_{max} introduced by the effect. Since FDG uptake is correlated with tumour aggressiveness, similarities in FDG uptake may be found when comparing tumours of different clonal origin (and either similar or different histological subtype) that show similar metabolic behaviour; thus, it is likely that larger differences in SUV_{max} (suggesting the presence of synchronous primary cancers) may confer a greater clinical benefit than comparatively smaller differences (where the distinction between synchronous primary cancers and metastatic disease is far less clear). Consequently, the study (and the clinical utility of reported findings) is limited by this inherent nature of uncertainty when the FDG uptake among multiple lesions is similar, which likely explains the low sensitivity observed during ROC analysis [3].

5. Conclusion

Our results demonstrated a strong correlation in FDG uptake between the index and additional pulmonary lesion(s) in patients with known pulmonary metastasis, supporting the notion that tumours of the same clonal origin (i.e., metastases) exhibit more similar FDG uptake when compared to tumours of separate clonal origin (i.e., second primary cancers). This observation is further supported by differences reflected in relative ΔSUV_{max} and SUV_{max} ratio in comparing FDG uptake between lesions representing either synchronous primary lung cancer or intrapulmonary metastasis. The FDG uptake intensity among multiple pulmonary lesions may thus be helpful to distinguish second primary tumours from metastatic disease in a subgroup of patients with primary lung cancer.

Ethical statement

This is a retrospective review of molecular imaging data. The study has received approval from the regional Research Ethic Board. We have followed The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Sebastian Karpinski: Formal analysis, Writing – review & editing. **Zamzam AL Bimani:** Data curation, Writing – review & editing. **Jessica L. Dobson:** Data curation, Writing – review & editing. **Wanzhen Zeng:** Data curation, Writing – review & editing.

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