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IMPACTS OF CLINICOPATHOLOGICAL FACTORS ON METABOLIC PARAMETERS OF ^{18}F FLUORODEOXYGLUCOSE PET/CT IN THE STAGING OF BREAST CANCER

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Abstract: This study aims to evaluate the impact of clinicopathological factors on metabolic parameters of ^{18}F-FDG PET/CT in the different staging of breast cancer. 15 histopathologically confirmed breast cancer lesions on patients who underwent whole-body FDG-PET/CT for staging were retrospectively reviewed. Three PET/CT metabolic parameters including semiquantitative maximum standardised uptake value (SUV_{max}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were quantified over the primary lesions of the breast. The parameters were statistically correlated with clinicopathological factors including patients' age, body mass index (BMI) and tumour size. Multivariate regression was performed to determine the significant factors that best predicted those metabolic parameters. Tumour size was significantly correlated to all metabolic parameters ($p < 0.001$) and was a significant predictor of those parameters ($p < 0.001$). Tumour size accounted for 77.5%, 94.3% and 96.2% of the $SUV_{max,}$ MTV and TLG variances, respectively. Tumour size significantly affects the metabolic parameters of ^{18}F-FDG PET/CT (SUV_{max}, MTV and TLG) in the staging of breast cancer. Therefore, tumour size has a prognostic value for the staging of breast cancer in a ^{18}F-FDG PET/CT study for improved clinical management.

Keywords: Breast cancer, clinicopathological factors, metabolic parameters, positron emission tomography.

Introduction

World Health Organisation (WHO) has revealed that breast cancer is the most prevalent cancer affecting more than one million women worldwide (Taghipour *et al.*, 2016). Breast cancer has been reported as being the most prevalent cancer type among females in Malaysia (Azizah *et al*., 2015) and the second highest cause of deaths in the country (Chen *et al.*, 2018). The high mortality rate makes breast cancer a major health problem (Jiménez-Ballvé *et al*., 2018). Thus, accurate clinical decision-making is vital to prevent any delay where urgent treatment is required (Groheux *et al*., 2016). As a result, non-invasive diagnostic tools that predict tumour behaviour are essential for breast cancer treatment (Kitajima *et al*., 2018).

^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) has been extensively employed in clinical practices to characterise and stage tumours non-invasively. This integrated modality could identify the early stage of breast cancer, demonstrate the glycolytic changes of tumours and concurrently assess the whole body's response to the tumours in vivo (Chen *et al.*, 2018). Moreover, it has improved the effectiveness of imaging in the staging of breast cancer patients (Ulaner, 2019). PET/CT provides quantitative biomarkers which reflect the tumour receptor status, degree of tumour heterogeneity and treatment response (Bailly *et al.*, 2019). Semiquantitative standardised uptake values (SUV) have been widely used as a PET parameter for estimating the metabolic activity of tumours. However, SUV has been reported to cause overestimations in obese patients as this parameter is estimated based on the whole-body weight metric, including the patient's body fat (Chen *et al.*, 2018). Thus, the role of

volumetric parameters derived from FDG PET/CT including metabolic tumour volume (MTV) and total lesion glycolysis (TLG) have been explored as these parameters determine the metabolic burden of the whole tumour (Park *et al*., 2015).

An integration of clinical examination and imaging with a confirmation of pathological assessment is used for the diagnosis of breast cancer (Huszno & Kolosza, 2019). The clinicopathological features such as tumour size, axillary node metastasis and clinical stage are the considering factors for the clinical and pathological assessment of breast cancer. Several clinicopathological factors of breast cancer have been linked with the ^{18}F-FDG uptake and PET/CT metabolic parameters describe the uptake in the volume of interest (Kajáry *et al.*, 2015). Integrating clinicopathological data and metabolic parameters would be useful to improve diagnostic efficiency and prognosis (Yang *et al.*, 2019). Several studies have reported the association of FDG PET/CT image-derived parameters and clinicopathological factors to determine the prognosis and treatment plan of breast cancer patients; however, highly inconsistent findings have been reported (Chang *et al.*, 2019). Furthermore, the impact of those factors on the volumetric-based PET/CT parameters including MTV and TLG is not well-reported (Myssayev *et al*., 2019). Therefore, this study aims to evaluate the impact of clinicopathological factors on metabolic parameters of ^{18}F-FDG PET/CT in the staging of breast cancer.

Materials and Methods

Samples

This retrospective study was granted by the Research Ethics Committee of our institution (UiTM REC/03/2020 UG/MR/93). Patients who underwent whole-body ^{18}F-FDG PET/CT examination for breast cancer staging between April 2015 to March 2017 have been reviewed. Only PET/CT examinations for staging and histopathologically confirmed breast cancer patients were included in the study. Patients' data with the PET/CT examination for monitoring treatment responses were excluded. PET/CT images were selected based on the inclusion and exclusion criteria.

PET/CT Images Acquisition

PET/CT images were acquired using GE Healthcare Discovery 610 PET/CT system. Patients with a blood glucose level of more than 130 mg/dL prior the ^{18}F-FDG injection were excluded. The scanning was acquired 60 minutes (min) after an intravenous administration of ^{18}F-FDG. The patients were positioned in supine and the scans were acquired being immobilised using six to eight bed positions with an image acquisition time of 2.0 - 2.5 minutes per bed position. Non-contrast enhanced CT imaging was started at the vertex and extended to the upper thigh; subsequently, PET scanning was performed over the same body region. CT-based attenuation correction and a standard ordered-subset expectation-maximisation (OSEM) reconstruction algorithm were employed.

Quantification of PET/CT Metabolic Parameters

The PET/CT images were assessed at a workstation using fusion software (Syngo. Via, Siemens Medical Solutions). Tumour mapping was performed using manual contouring of the lesions under the supervision of a nuclear medicine physician. Standard circular regions of interest (ROI) were placed over the increased pathological uptakes of the primary breast cancer lesions on the PET/CT images to obtain the SUV_{avg} and SUV_{max}. A volumetric ROI around the outline of the primary lesions in the breast was put on the axial PET/CT images. Tumour size was depicted by the maximum diameter of the MTV measured by contouring margins defined with the threshold of SUV of 2.5. The TLG was estimated as the product of SUV_{avg} and MTV of the primary lesion (TLG = SUV_{avg} × MTV).

Statistical Analysis

The variables were expressed as the median and interquartile range (IQR). Two-tailed Spearman's correlation test was performed to determine the association between metabolic parameters (SUV_{max}, MTV and TLG), patients' age, body mass index (BMI) and tumour size. The analysis was further extended with multivariate analysis to determine the predictor of breast cancer lesion uptake as signified by the metabolic parameters. The data was analysed using SPSS version 21.0 with $p < 0.05$ and was deemed to be statistically significant.

Results and Discussion

A total of 15 lesions from 10 patients with a median (IQR) age of 51 (10) years old were evaluated in this study. The clinicopathological factors and metabolic parameters characteristics are presented in Table 1.

The correlation of clinicopathological factors and metabolic parameters is demonstrated in Table 2. BMI and tumour size show a significant correlation with all the metabolic parameters (SUV_{max}, MTV and TLG) ($p < 0.05$). Tumour size shows a remarkable strong correlation with SUV_{max} ($r = 0.817$), MTV ($r = 0.954$) and TLG ($r = 0.971$).

After modifying for all other covariates in the final model of multivariate regression analysis, it was demonstrated that tumour size was significantly correlated with all the metabolic parameters ($p < 0.001$) (Table 3). This covariate accounted for 77.5%, 94.3% and 96.2% of the $SUV_{max,}$ MTV and TLG variances, respectively. The MTV and TLG have stronger correlations (adjusted standardised beta coefficient, $\beta = 0.934$ and 0.970, respectively) as compared with SUV_{max} ($\beta = 0.545$).

The present study explored the impacts of clinicopathological factors on ^{18}F-FDG PET/CT metabolic parameters in the staging of breast cancer. Our results demonstrated that tumour size has a significant correlation to SUV_{max}, MTV and TLG. This finding is consistent with the previously reported studies (Vatankulu *et al*., 2016; Kitajima *et al*., 2018; Chang *et al*., 2019; Önner *et al*., 2019). Tumour size is one of the criteria used in the staging of various

Table 1: Clinicopathological factors and metabolic parameters characteristics

Parameter	Median (IQR)
Age (41 - 68 years old)	51 (10)
BMI (17.63 - 29.13)	18.94 (8.95)
Tumour size (cm^2) (0.87 - 20.90)	2.58 (5.17)
Metabolic parameters	
SUV_{max}	8.90 (5.87)
MTV	5.96 (22.62)
TLG	21.68 (128.15)

Table 2: Correlation of clinicopathological factors and FDG PET/CT metabolic parameters of breast cancer

Metabolic Parameter	Age		BMI		Tumour Size	
	r	*P*	r	*P*	r	*P*
SUV_{max}	0.187	0.504	0.848	< 0.001	0.817	< 0.001
MTV	0.246	0.376	0.602	0.018	0.954	< 0.001
TLG	0.244	0.380	0.597	0.019	0.971	< 0.001

Table 3: Multivariate linear regression analysis of clinicopathological factors and PET/CT metabolic parameters

Variables	SUV_{max}			MTV			TLG		
	Unstandardized Beta Coefficient	Standardised Beta Coefficient	*P*	Unstandardized Beta Coefficient	Standardized Beta Coefficient	*P*	Unstandardized Beta Coefficient	Standardized Beta Coefficient	*P*
Age	-0.016	-0.018	0.869	-0.735	-0.113	0.212	-2.526	-0.055	0.468
BMI	0.745	0.521	0.002	0.847	0.079	0.476	1.913	0.025	0.788
Tumour size	0.576	0.545	< 0.001	7.361	0.934	<0.001	54.638	0.970	< 0.001

cancers and has a well-known prognostic role (Kasangian *et al*., 2017; Önner *et al*., 2019). Tumour size may influence patients' staging status and have an impact on subsequent surgical and oncological treatment including the type of treatments. Indeed, tumour size is a valuable parameter for categorising tumours in the event of limited information on the primary tumour status (T stage) (Paner *et al*., 2018). Furthermore, a significant correlation between an increase in metabolic activity with an increase in tumour size has been reported in several studies (Kitajima *et al*., 2018; Huang *et al*., 2019). Larger tumour sizes or higher grade of malignancy were typically signified by higher glucose uptakes (Wellberg *et al*., 2016; Zhang & Wang, 2020). The SUV was dependent on tumour size with increased uptake seen in larger tumour sizes, tumour grades and the stage of the breast cancer lesions (Ayaz *et al*., 2017; Jain *et al*., 2017) that demonstrates increased tumour aggressiveness.

In this study, a higher correlation magnitude has been observed in MTV and TLG as compared with SUV_{max} concerning tumour sizes. These findings are in accordance with the available literature on the subject (Vatankulu *et al*., 2016; Önner *et al*., 2019) where MTV reflects the metabolic volume of the tumour instead of size of the mass (Chen *et al*., 2018). Accordingly, TLG and MTV may more precisely reflect the tumour's activity and grade of malignancy as compared with SUV_{max} (Son *et al*., 2014; Chen *et al*., 2018). The whole tumour metabolic uptake is not signified by SUV_{max} because this parameter is limited to one voxel (Im *et al*., 2018). SUV_{max} is limited for providing area information from the high metabolic uptake of a particular lesion area which can make it difficult to identify the expansion of active lesions within malignant tumours accurately based on this parameter alone and it is difficult to assess how much-measured volume reflects on the viable tumour region (Ogawa *et al*., 2015). As the present study shows a wide range of breast tumour sizes, the disparity of the result may be explained by the underestimation of SUV_{max} due to the partial volume effect expressed

by the small-sized tumours (Takahashi *et al*., 2016). The underestimation of SUV_{max} may have a crucial impact on the patients' prognosis (Sahiner *et al*., 2013). Therefore, MTV and TLG are superior metabolic parameters correlating with the tumour size relative to SUV_{max}. Hence, both parameters are useful PET indexes to signify the aggressiveness of the lesions.

Furthermore, our findings demonstrate no significant correlation between the patient's age and all PET/CT metabolic parameters which are consistent with the previous reports (Lahmann *et al*., 2004; Sparano *et al*., 2012; Minicozzi *et al*., 2013). Therefore, age is not the main clinicopathological factor that could influence the PET/CT metabolic parameters. On the other hand, this study reveals a good correlation between a patient's BMI and SUV_{max}. High BMI numbers have been linked with worse outcomes in hormone receptor-positive of breast cancer (Sparano *et al*., 2012; Minicozzi *et al*., 2013). Obesity is suggested as a risk factor for breast cancer development (Ursin *et al*., 1995; Lahmann *et al*., 2004). BMI status integrated with SUV data of the tumour has been reported to improve risk-stratification of breast cancer, independent of clinical stage and tumour subtypes. Weight as a dependent factor of SUV would explain its good correlation as presented in the current study.

FDG PET/CT may provide metabolic information about the tumour but it may be insufficient in determining lesion size, specifying the infiltration boundaries and the surrounding tissue invasion for tumour staging (Ceylan *et al*., 2018). PET/CT has a limited role in detecting early-stage cancer with small tumour volume, superficial tumours with a depth of less than four millimetres and low stage tumours due to its restrictive spatial resolution (Groheux *et al*., 2016; Huang *et al*., 2017). Small lesions will result in limited spatial resolution and affect the heterogeneity of radiotracer uptake by the primary tumours as the high prevalence of false-negative results for tumour smaller than one centimetre in diameter (Kutluturk *et al*., 2019). Thus, the smaller the lesion, the more significant the underestimation of the uptake via PET imaging (Sarikaya *et al*., 2019). Measuring the FDG uptake is important when interpreting the result of PET/CT where the metabolic parameters reflect the cellular FDG uptake (Kim *et al*., 2020).

The glucose uptake within the whole tumour was comprehensively signified by MTV and TLG instead of single-pixel value of SUV_{max} (Chen *et al*., 2018). It provides valuable information about the whole tumour body's metabolic activity volume (Cetin *et al*., 2018). MTV is the sum of all voxels in a volume which represents the amount of metabolically active tumour tissue. TLG is the product of SUV_{mean} and MTV which integrates the volumetric and metabolic information of the tumour and metastasis. Yet, SUV_{max} is limited for providing area information from the high metabolic uptake of a particular lesion area which can make it difficult to identify the expansion of active lesions within malignant tumours accurately based on this parameter alone.

Conclusion

Tumour size significantly affects the metabolic parameters of ^{18}F-FDG PET/CT including SUV_{max}, MTV and TLG in the staging of breast cancer. Hence, tumour size has a prognostic value for the breast cancer staging in ^{18}F-FDG PET/CT study for improved further clinical management. For future studies, an investigation of the impact of other clinicopathological factors such as histopathology and molecular pathological profiles on the metabolic parameters of ^{18}F-FDG PET/CT would be recommended. Large prospective studies on various type of cancers would benefit for further improvement in the management of oncological patients.

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