RESEARCH ARTICLE

Association of ^{18}F-FDG PET/CT imaging metabolic parameters with tumour size in breast carcinoma

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Abstract:

Tumour size is a well-known independent prognostic factor that plays an important role in the management and diagnosis of cancer. ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT) has been widely used in oncology which their metabolic parameters including maximum standardized uptake value (SUV_{max}) and metabolic tumour volume (MTV) are important PET indexes to signify the degree of tumour aggressiveness. The correlation of SUV_{max} with tumour size has been widely reported in the literatures, however such correlation with MTV was not well reported. This study aims to evaluate the association between tumour size and PET/CT metabolic parameters in breast carcinoma. PET/CT images of breast cancer patients (n = 10) who underwent ^{18}F-FDG PET/CT examination for staging were reviewed. The patients were histopathologically confirmed with breast carcinoma. PET/CT derived metabolic parameters (SUV_{max} and MTV) of the primary breast carcinoma lesions (n=15) were quantified. The parameters were associated with the tumour size of the primary lesions using Spearman Rho Correlation. All the metabolic parameters have positive statistically significant association with tumour size where SUV_{max} ($p < 0.001$, $r = 0.817$) and MTV ($p < 0.001$, $r = 0.954$). ^{18}F-FDG PET/CT-derived metabolic parameters (SUV_{max} and MTV) are valuable imaging markers associating with tumour size of the breast lesions in which better association is demonstrated in volume based metabolic parameter (MTV) as compared to SUV_{max}. Therefore, both parameters have prognostic value for the evaluation of breast carcinoma.

Keywords: ^{18}F-FDG PET/CT, breast carcinoma, metabolic tumour volume, standardized uptake value

1. INTRODUCTION

World Health Organization (WHO) has revealed that breast cancer is the most prevalent cancer among females in the world, and it is the second major cause of death from cancer among women [1]. Breast cancer has been reported as the major cancer among females in Malaysia [2]. Its high incidence and mortality make breast cancer is a major health problem [3] as it affects more than one million women all over the world [4]. Thus, accurate staging of breast cancer is vital for clinical management decisions to prevent delayed urgent treatment [5]. As a result, non-invasive diagnostic tools for staging and tumour behaviour prediction are becoming increasingly crucial for breast cancer management [6].

An advanced hybrid molecular imaging, ^{18}F-fluorodeoxyglucosepositron-emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely used in clinical practice to characterize and stage tumours non-invasively. It can identify breast cancer in its early stage, reflect the glycolytic changes of tumours, and simultaneously evaluate the whole body's responses to the tumours in vivo [1]. Besides, it has improved the effectiveness of imaging in staging patients with breast cancer [7]. PET/CT can provide quantitative biomarkers or known as metabolic parameters such as standardized uptake value (SUV) and metabolic tumour volume (MTV), which reflect tumour receptor status, the degree of tumour heterogeneity, and treatment response [8]. SUV has been widely used as PET parameter for estimating the metabolic activity of tumours. However, SUV has been reported to cause overestimation in obese patients as this parameter is calculated based on the whole-body weight metric including fat contribution of the patients [1]. Thus, accurate staging of the cancer will be affected. To compensate this limitation, the role of volumetric parameter derived from FDG PET/CT such as MTV has been explored as this parameter measures the metabolic burden of the whole tumour [9]. This parameter has been shown to be independent prognostic factors in several oncological studies [10].

Generally, the diagnosis of breast cancer is based on clinical examination in combination with imaging and is confirmed by pathological assessment [11]. The clinicopathological features such as tumour size are one of the important factors in making the clinical and pathological assessment of breast cancer. Tumour size is one of the staging criteria for various types of cancer and has a well-known prognostic role [12, 13]. Tumour size may influence patients' staging (T) status, thus having an impact on subsequent surgical and oncological management, including the type of treatment. The accuracy of preoperative tumour measurement is great importance in deciding patients' eligibility for conserving their breasts [14], as more accurate tumour staging can be achieved, and a correct treatment protocol can be followed.

Combining clinicopathological data with metabolic parameters may further improve diagnostic efficiency and evaluation prediction of the prognosis of the patient with cancer [15]. Significant correlation of SUV_{max} and tumour size have been reported in the previous literatures [6, 10, 16, 17]. However, such impact on MTV parameter is not well reported [18, 19]. Therefore, this study aims to evaluate the association between tumour size and PET/CT metabolic parameters in breast carcinoma.

2. MATERIALS AND METHODS

2.1 Study Population

This retrospective study was approved by the Research Ethics Committee of Faculty of Health Sciences Universiti Teknologi MARA (UiTM REC/03/2 UG/MR/93) and informed consent was waived due to the retrospective design. Breast cancer patients who underwent whole-body ^{18}F-FDG PET/CT examination between April 2015 to March 2017 has been reviewed. Only PET/CT examinations for staging were included in the study. All the cases have been confirmed with histopathological examination. The PET/CT images were selected using purposive sampling method based on the inclusion and exclusion criteria.

2.2 ^{18}F-FDG PET/CT Image Acquisition

PET/CT images were acquired using an integrated PET/CT system (GE HEALTHCARE DISCOVER). None of the patients had a blood glucose level >130 mg/dL before ^{18}F-FDG injection. The scanning was acquired 60 min following intravenous ^{18}F-FDG administration. All patients were placed in the supine position and the scans were acquired with the patients immobilized. Six-to-eight-bed positions were used, and the acquisition time was 2–2.5 min per 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 data were used for attenuation correction, and images were reconstructed using a standard ordered-subset expectation-maximization algorithm.

2.3 Imaging and Data Analysis

The PET/CT images were reviewed using a workstation (Syngo. Via, Siemens Medical Solutions, Chicago, IL) that provided multiplanar reformatted images in transverse, coronal, and sagittal planes. The images of the same patient were analysed frame by frame. Tumour mapping was performed by manual contouring of the lesions guided by a nuclear medicine physician. Areas of abnormally intense tracer uptake were recorded. Standard spherical regions of interest (ROI) were placed over the increased pathological uptakes of the primary lesions on PET/CT images to obtain the SUV_{avg} and $SUV_{max.}$ These parameters were determined automatically by the Syngo software following the delineation of the ROI on the selected lesions in the PET/CT images. A volumetric ROI around the outline of primary tumour in the breast was placed on the axial PET/CT images and the borders of the ROI were adjusted manually by visual inspection of the primary lesions outline to avoid overlapping on adjacent FDG-avid structures or lesions (Figure 1). Tumour size was expressed by the maximum diameter of the MTV measured by contouring margins defined with threshold of SUV of 2.5.

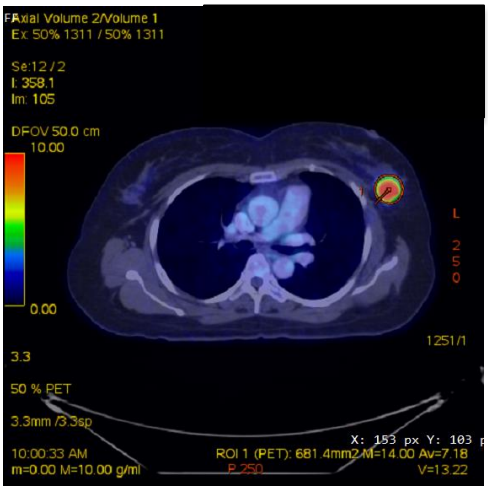


Figure 1. Tumour mapping of breast lesion in ^{18}F-FDG PET/CT image. Note the breast lesion margin was delineated by the red line.

2.4 Statistical Analysis

SPSS 21.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous variables were expressed as median (interquartile range) (IQR). Two-tailed Spearman's rho correlation test was performed to evaluate association between tumour size and metabolic parameters with p-value < 0.05 was considered as statistically significant.

3. RESULTS AND DISCUSSION

A total of 15 lesions from 10 patients with the median (IQR) age of 51 (10) years old were quantified in this study. Tumour and metabolic parameters characteristics are presented in Table 1.

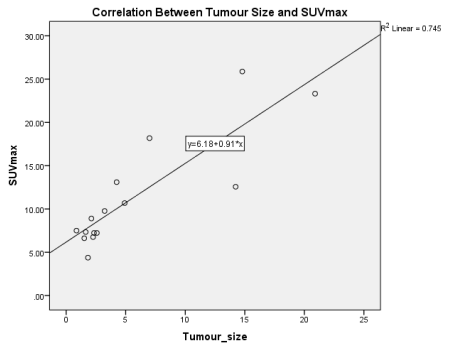
Table 1. Patients, tumour characteristics and metabolic parameters

Variable	Median (IQR)
Age	51.00 (10.00)
Tumour size, cm^2	2.58 (5.17)
Metabolic parameters	
SUV_{max}	8.90 (5.87)
MTV	5.96 (22.62)

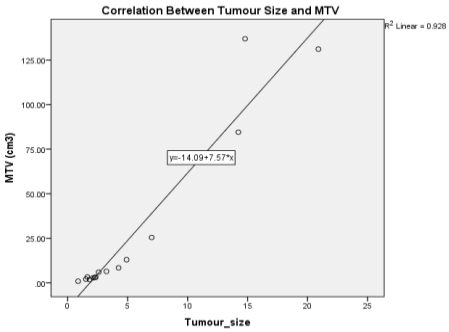
Association of metabolic parameters and tumour size of the breast lesion is demonstrated in Table 2. Both parameters show strong association with tumour size (SUV_{max}, r = 0.817; MTV, r = 0.954) and are significantly associated ($p < 0.001$). These associations are expressed in the scatter plot graphs, as shown in Figure 2.

Table 2. Spearman rho correlation analysis between FDG PET/CT metabolic parameters and tumour size of breast carcinoma

Variable	Tumour Size	
	r	*p value*
SUV_{max}	0.817	< 0.001
MTV	0.954	< 0.001



(a)



(b)

Figure 2. Association between tumour size and metabolic parameters (a) SUV_{max} and (b) MTV, respectively ($p < 0.001$).

In this study, significant associations have been observed between tumour size of breast carcinoma and metabolic parameters (SUV_{max} and MTV). The findings of the present study are in accordance with the previous literatures [6, 10, 13, 24]. Kitajima et al. [6] and Chang et al. [10] reported a significant association between SUV_{max} and MTV with tumour size and grade. Furthermore, several studies have reported association in increased metabolic activities with an increase of tumour size [6, 20]. Higher glucose uptake usually reflects larger tumour sizes or worse malignancy, so that the higher FDG signals around the advanced stage of tumour [21, 22]. Ayaz et al. [16] and Jain et al. [23] claimed SUV was dependent on tumour size with increased uptake seen in larger tumour size, tumour grade and stage of breast lesions. This is probably because of the increased aggressivity of breast cancer and unfavourable changes in tumour behaviour as the time proceeds and tumour grows further [16].

In the present study, higher correlation magnitude (r) is observed in MTV and TLG as compared to SUV_{max} in relation to tumour size. This finding is supported by several previous literatures. Önner *et al.* [13] and Vatankulu *et al.* [24] reported the tumour size showed stronger positive association with MTV than $SUV_{max.}$ MTV can reflect the metabolic volume, which is the FDG-avid volume in the tumour, rather than the size of the mass. MTV associates with the size of the mass and provide more accurate measurement than the maximum or minimum diameters, especially for lesions with non-FDG uptake necrosis inside [1]. Thus, MTV may more accurately reflect the tumour activity and grade of malignancy as compared to SUV_{max} [1, 25]. SUV_{max} does not represent the whole tumour metabolic burden because the value is generated from only one voxel [26]. SUV_{max} is limited to provide area information from the high metabolic uptake of a particular lesions area, which can make it difficult to identify the expansion of active lesions within malignant tumours accurately based on this parameter alone and difficult to assess how much measured volume reflects the viable tumour region [27]. MTV has been proven to be more accurate because they highly correlate with the tumour size of the breast lesion. Therefore, MTV is a superior metabolic parameter associating with the tumour size in relative to SUV_{max}. Hence this parameter is useful PET index to signify the aggressiveness of the lesions.

4. CONCLUSION

^{18}F-FDG PET/CT-derived metabolic parameters (SUV_{max}, and MTV) are valuable imaging markers associating with the tumour size of the breast lesions. MTV as a volume based metabolic parameter demonstrates better association with tumour size in breast lesions as compared to SUV_{max}. Therefore, both parameters have prognostic value for the evaluation of breast carcinoma.

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REFERENCES

[1] W. Chen, L. Zhu, X. Yu, Q. Fu, W. Xu, and P. Wang, "Quantitative assessment of metabolic tumor burden in molecular subtypes of primary breast cancer with FDG PET/CT," *Diagnostic Interv. Radiol.*, vol. 24, no. 6, pp. 336–341, 2018.

[2] I. P. Gopal Ram, "Vital Role of Water Treatment in Energy Management.," *Energy Manag. (New Delhi)*, vol. 7, no. 1, pp. 45–51.

[3] A. Jiménez-Ballvé *et al.*, "Prognostic value of metabolic tumor volume and total lesion glycolysis in 18F-FDG PET/CT scans in locally advanced breast cancer staging," *Rev. Española Med. Nucl. e Imagen Mol. (English Ed.*, vol. 35, no. 6, pp. 365–372, 2016.

[4] M. Taghipour, R. Wray, S. Sheikhbahaei, J. L. Wright, and R. M. Subramaniam, "FDG avidity and tumor burden: Survival outcomes for patients with recurrent breast cancer," *Am. J. Roentgenol.*, vol. 206, no. 4, pp. 846–855, 2016.

[5] D. Groheux, A. Cochet, O. Humbert, J. L. Alberini, E. Hindié, and D. Mankoff, "18F-FDG PET/CT for staging and restaging of breast cancer," *J. Nucl. Med.*, vol. 57, p. 17S–26S, 2016.

[6] K. Kitajima, Y. Miyoshi, T. Yamano, S. Odawara, T. Higuchi, and K. Yamakado, "Prognostic value of FDG-PET and DWI in breast cancer," *Ann. Nucl. Med.*, vol. 32, no. 1, pp. 44–53, 2018.

[7] D. M. Schuster, "Clinical Utility of PET Scanning in Breast Cancer Management," *Am. J. Hematol. Oncol.*, vol. 11, no. June, pp. 20–25, 2015.

[8] C. Bailly *et al.*, "Exploring tumor heterogeneity using PET imaging: The big picture," *Cancers (Basel).*, vol. 11, no. 9, pp. 1–17, 2019.

[9] S. Y. Park *et al.*, "Prognostic value of total lesion glycolysis by 18F-FDG PET/CT in surgically resected stage IA non-small cell lung cancer," *J. Nucl. Med.*, vol. 56, no. 1, pp. 45–49, 2015.

[10] C. C. Chang, C. J. Chen, W. L. Hsu, S. M. Chang, Y. F. Huang, and Y. C. Tyan, "Prognostic Significance of Metabolic Parameters and Textural Features on 18F-FDG PET/CT in Invasive Ductal Carcinoma of Breast," *Sci. Rep.*, vol. 9, no. 1, pp. 1–11, 2019.

[11] J. Huszno and Z. Kolosza, "Molecular characteristics of breast cancer according to clinicopathological factors," *Mol. Clin. Oncol.*, vol. 11, no. 2, pp. 192–200, 2019.

[12] A. A. Kasangian *et al.*, "The prognostic role of tumor size in early breast cancer in the era of molecular biology," *PLoS One*, vol. 12, no. 12, pp. 1–12, 2017.

[13] H. Önner *et al.*, "Which of the fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography parameters are better associated with prognostic factors in breast cancer?," *Medicine (Baltimore).*, vol. 98, no. 22, p. e15925, 2019.

[14] Y. Z. Jiang, C. Xia, W. T. Peng, K. Da Yu, Z. G. Zhuang, and Z. M. Shao, "Preoperative measurement of breast cancer overestimates tumor size compared to pathological measurement," *PLoS One*, vol. 9, no. 1, pp. 1–5, 2014.

[15] B. Yang *et al.*, "Correlations Study Between 18F-FDG PET/CT Metabolic Parameters Predicting Epidermal Growth Factor Receptor Mutation Status and Prognosis in Lung Adenocarcinoma," *Front. Oncol.*, vol. 9, no. July, pp. 1–9, 2019.

[16] S. Ayaz, S. S. Gültekin, Ü. Y. Ayaz, and A. Dilli, "Initial fludeoxyglucose (18F) positron emission tomography-computed tomography (FDG-PET/CT) imaging of breast cancer - Correlations with the primary tumour and locoregional metastases," *Polish J. Radiol.*, vol. 82, pp. 9–16, 2017.

[17] O. C. Guler, N. Torun, B. A. YılDıRım, and C. Onal, "Pretreatment metabolic tumour volume and total lesion glycolysis are not independent prognosticators for locally advanced cervical cancer patients treated with chemoradiotherapy," *Br. J. Radiol.*, vol. 91, no. 1084, 2018.

[18] A. Myssayev *et al.*, "Usefulness of FDG PET/CT derived parameters in prediction of histopathological finding during the surgery in patients with pancreatic adenocarcinoma," *PLoS One*, vol. 14, no. 1, pp. 1–15, 2019.

[19] K. Pak *et al.*, "Original article Prognostic value of metabolic tumor volume and total lesion glycolysis in breast cancer : a meta-analysis," no. June, 2020.

[20] Z. Huang, S. Chen, and J. Li, "Correlation between 18F-FDG PET/CT Metabolic Parameters and Lymph Node Metastasis of Esopageal Cancer," Int. J. Clin. Exp. Med., vol. 12, no. 3, pp. 2690–2696, 2019.

[21] E. A. Wellberg et al., "The glucose transporter GLUT1 is required for ErbB2-induced mammary tumorigenesis," Breast Cancer Res., vol. 18, no. 1, pp. 1–15, 2016.

[22] Y. Zhang and J. Wang, "Targeting uptake transporters for cancer imaging and treatment," Acta Pharm. Sin. B, vol. 10, no. 1, pp. 79–90, 2020.

[23] A. Jain et al., "Tumor characteristics and metabolic quantification in carcinoma breast: An institutional experience", Indian Journal of Cancer, vol. 54, no. 1, p. 333, 2017.

[24] B. Vatankulu et al., "Do 18F-FDG PET/CT findings have a relationship with histopathological and immunohistochemical factors of breast cancer in men?," *Nucl. Med. Commun.*, vol. 37, no. 12, pp. 1273–1281, 2016.

[25] S. H. Son *et al.*, "Prognostic implication of intratumoral metabolic heterogeneity in invasive ductal carcinoma of the breast," *BMC Cancer*, vol. 14, no. 1, p. 585, 2014.

[26] H. J. Im, T. Bradshaw, M. Solaiyappan, and S. Y. Cho, "Current Methods to Define Metabolic Tumor Volume in Positron Emission Tomography: Which One is Better?," *Nucl. Med. Mol. Imaging (2010).*, vol. 52, no. 1, pp. 5–15, 2018.

[27] S. Ogawa, M. Itabashi, C. Kondo, M. Momose, S. Sakai, and S. Kameoka, "Prognostic value of total lesion glycolysis measured by 18F-FDG-PET/CT in

patients with colorectal cancer," *Anticancer Res.*, vol. 35, no. 6, pp. 3495–3500, 2015.