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Asian Journal of Oncology

Original Article

Role of SUV and ADC values as a predictors of grade and molecular subtypes of breast malignancy

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ABSTRACT

Objectives: The purpose of the study is to evaluate the role of Standardized Uptake Value (SUV) and Apparent Diffusion Coefficient (ADC) values as a predictor of histologic grade and molecular subtype of breast malignancy and to evaluate the correlation of grade of malignancy with background parenchymal uptake, background parenchymal enhancement and fibroglandular tissue of the contralateral normal breast.

Material and Methods: 53 patients with unilateral breast cancer were included in the study. Images from Computed Tomography (CT) and Positron Emission Tomography (PET) were analyzed measuring maximum SUV and background SUV from the contralateral normal breast by placing a single Region of interest (ROI). From Diffusion-weighted magnetic resonance imaging (DWI-MRI) images ADC values were calculated with b value 0–1200 s/mm^2 and single ROI placed in an area corresponding to the ROI placed to obtain maximum SUV of the mass. Type of fibroglandular tissue and background parenchymal enhancement was categorized based on Breast Imaging-Reporting and Data System (BI-RADS)–lexicon on T1 weighted and Dynamic Contrast-Enhanced (DCE) images respectively. Necrotic and hemorrhagic areas within the mass were excluded in both positron emission tomography–computed tomography (PET-CT) and Magnetic resonance imaging (MRI) while calculating SUV and ADC.

Results: A positive correlation was found between grade and Mean SUV_{max} with higher values in grade 3 malignancy (11.41 ± 4.76) (p-value – 0.003). Statistically significant variation in SUV_{max} was seen among estrogen receptor/progesterone receptor (ER/PR) status with low values in ER/PR positive tumors (p-value < 0.05). There was significant correlation between the molecular subtypes with higher SUV_{max} in triple-negative tumors (12.27 ± 4.22) (p-value – 0.02). Significant variation in ADC values among different molecular subtypes was seen with higher values in human epidermal growth factor receptor (HER2)-Enriched tumors (1.032 ± 0.25) and low values in luminal A subtype (0.798 ± 0.13).

Conclusion: Therefore, PET-CT and MRI can be used as a complementary imaging tool in assessing the aggressiveness and biological characteristics of tumors.

Keywords: Breast carcinoma, Tumor grades, Molecular subtypes, Receptor status, Prognostic factors, Imaging, MRI, PET-CT, SUV, DWI, ADC values, Background parenchymal uptake, Background parenchymal enhancement, Fibroglandular pattern, Fibroglandular tissue (FGT)

INTRODUCTION

Breast cancer has ranked number one among Indian females with an age-adjusted rate of 25.8 per 1,00,000 women and mortality of 12.7 per 1,00,000 women.[1] Multiple risk factors, such as age, parity, family history, BReast CAncer (BRCA) gene mutation, sedentary lifestyle, hormonal replacement therapy, and radiation exposure that are involved in the development of breast cancer have been studied.[2–7] Several clinico-pathological factors have been studied and correlated with the prognosis of breast cancer.

Predicting the prognosis of breast cancer is important for determining the treatment protocol. Currently histopathological grading is the most commonly used factor for assessing the aggressiveness of the lesion and is a strong predictor of prognosis[8,9] that needs invasive procedure such as incision or excision biopsy for evaluation. Nottingham Histologic Score system is used to classify the tumor as Grade 1, 2, or 3 by taking into consideration the amount of gland formation (cell "differentiation"), nuclear features (degree of "pleomorphism"), and mitotic activity (how much the tumor cells are dividing, or proliferating).

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Received: 16 August 2022 **Accepted:** 23 January 2023 **Published:** 27 November 2023 **DOI** 10.25259/ASJO-2022-56-(412)

Another recently used factor for predicting prognosis is the receptor status that is also proved to be useful in determining targeted therapy. Immunohistochemical (IHC) techniques are utilized to measure the expression of receptors such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[10–12]

Based on the receptor status molecular subtyping (luminal and non-luminal) is done.

- Luminal subtype:
  - Luminal A: A high expression of ER-related genes and low expression of HER2 and proliferation-related genes (ki67 index). ER+ PR+ HER2–, usually low grade. Most common among the luminal types and have the best prognosis
  - Luminal B: A lower expression of ER-related genes, variable expression of HER2 gene clusters, and higher expression of proliferation-related genes (ki67 index) ER+ PR+ HER2+, usually intermediate to high grade
- Non-luminal subtypes
  - HER2-Enriched: A high expression of HER2 and low expression of ER and PR, usually mid to high grade
  - Triple-negative: ER-negative, PR-negative, and HER2-negative. These tumors have worse prognosis among all subtypes[13]; with higher proliferation rates, and predominantly high-grade tumors.

Imaging plays an important role in screening, diagnosis, and staging of breast cancer. Commonly used modalities are mammography, ultrasound, positron emission tomography–computed tomography (PET-CT), and Magnetic Resonance Imaging (MRI). Few imaging features have been correlated with the risk and prognosis of breast cancer. For example, there is increased risk of breast cancer in patients with increased parenchymal density.[14,15] Poor prognosis is seen in patients with larger lesion, nodal involvement, tumor necrosis, extensive intraductal component, lymphovascular invasion, and multifocal or multicentric disease.[16–21]

Functional imaging techniques such as MRI and PET are used primarily for staging, but were found to have a role to play in assessing the tumor aggressiveness.

18F-fluorodeoxyglucose (FDG) PET-CT is used for the staging, assessment of recurrence and treatment response.[22] FDG avidity reflects the cellularity of the lesion and glucose metabolism in cancer cells. It also helps in predicting the prognosis of primary breast cancer as it is associated with few histopathological and immunohistochemical prognostic factors,[23,24] such as the grade of malignancy in breast carcinoma.

MRI is known to be a highly sensitive, noninvasive technique for the detection and local staging of breast cancer. The diffusion-weighted image (DWI) in MRI is used to evaluate the microstructural characteristics of water diffusion in biological tissues.[25] As malignant mass has increased the cell proliferation, it shows restricted diffusion as a result of inhibition of water diffusion. The apparent diffusion coefficient (ADC) is a quantitative measure of the diffusion of water molecules within the tissues. Several studies have shown that the ADC value is useful for differentiating benign and malignant breast lesions.[26,27] Recently, various studies have evaluated the relationship between tumor prognostic factors and DWI or ADC values.[28–32] Thus, it can help us identify tumors with high malignant potential and can provide preoperative prognostic information.

Additionally, information about background parenchymal uptake, background parenchymal enhancement, and fibroglandular tissue can serve as an important imaging biomarker in breast cancer, which has to be further evaluated.[33]

In this study, we intend to correlate these imaging findings with histological and immunohistochemical prognostic factors. By studying all these factors, imaging can have a better role to perform as a non-invasive tool in predicting the aggressiveness of the tumor and thus the prognosis.

MATERIAL AND METHODS

This is a prospective observational study including patients with biopsy-proven breast carcinoma who were referred for PET-CT. The study has been approved by the Institutional Ethics Committee (IEC) of Apollo Hospitals, Chennai; the approval reference number being - ECR/37/Inst/TN/2013/RR-16.

Inclusion criteria

- All adult patients with newly diagnosed biopsy-proven breast carcinoma who were referred for PET-CT

Exclusion criteria

- Patients with bilateral breast carcinoma
- Patients who had undergone surgery, chemotherapy, or radiotherapy
- Recurrent breast carcinoma
- Patients with contraindication for MRI
- Patients not willing to consent

Imaging technique

Every patient underwent a whole-body PET-CT imaging using a combined PET-CT scanner (SIEMENS BIOGRAPH MCT 42 slice) at least 2 weeks after the invasive biopsy. Spiral CT was acquired first in a craniocaudal direction, with 200–360 mas, 90–120 kvp. Subsequently, the PET scan was performed in a reverse longitudinal direction. Field of the scan was from vertex of skull to mid-thigh. A nonionic intravenous contrast

agent (1 mL/kg body weight with saline bolus chasing) was given to improve the CT diagnostic accuracy.

CT image was used for attenuation correction and lesion localization. Displayed data includes maximum intensity projection (MIP), three plane PET, three plane CT, and PET-CT fusion images.

MRI was performed for every patient using a 1.5 Tesla Philips Achieva MRI scanner within 1–6 days after PET-CT acquisition. Following the patient's informed consent and exclusion of contraindications, imaging was done in a prone position using a dedicated 8-channel breast coil. T1, multiphase dynamic post-contrast, and diffusion-weighted sequences were obtained.

Image analysis

The CT and PET images were analyzed by the principal investigator. Maximum SUV of the mass was calculated by placing a single ROI in an area with the highest FDG uptake within the mass (10–60 mm^2). Background SUV from the contralateral normal breast was calculated by placing ROI in the fibroglandular tissue of approximate area 50 mm^2.

From DWI-MRI images, ADC values were calculated with "b value" of 0–1,200 s/mm^2. Single ROI was placed in an area (10–60 mm^2) within the lesion corresponding to the ROI placed to obtain maximum SUV of the mass, and ADC values were measured. With T1-weighted image type of fibroglandular tissue and with DCE images background parenchymal enhancement of contralateral normal breast was categorized based on BIRADS–lexicon. Necrotic and hemorrhagic areas within the mass were excluded in both PET-CT and MRI while calculating SUV and ADC.

The histopathological report including the grade of malignancy, immunohistochemical analysis, and molecular subtypes were assessed. Molecular subtypes were classified based on receptor status ER, PR, and HER2. Imaging findings of MRI and PET-CT were compared with the histopathological findings and were documented for each patient.

RESULTS

In our prospective study, 53 patients with biopsy-proven unilateral breast cancer were included. Clinical, histopathological, and imaging characteristics of the patient are provided in Table 1. There is a significant difference in mean SUV_{max} values between the grades of malignancy ($P = 0.003$) [Figure 1], positive and negative estrogen receptor tumors [$P = 0.04$], positive and negative progesterone receptor tumors [$P = 0.001$] and among different molecular subtypes ($P = 0.018$) [Figure 2 and Table 2]. Higher mean SUV_{max} values were seen in Grade 3 tumors (11.41 ± 4.76) [Figure 1], ER negative (10.64 ± 4.37), PR negative tumors (11.64 ± 4.12), and triple-negative molecular subtype (12.27 ± 4.22) [Figure 2]. No significant difference was observed between SUV values of positive and negative HER2 receptor tumors.

Statistically significant difference was seen in ADC values between positive and negative estrogen receptor tumors

Table 1: Clinical, histopathological and imaging characteristics.

Variables	Number	Percentage (%)
Clinical characteristics		
Age		
<40 years	14/53	26.4
>40 years	39/53	73.6
Menstrual status		
Premenopausal	20/53	37.7
Post-menopausal	33/53	62.3
Histopathological characteristics		
Grade		
Grade 1	3	6
Grade 2	26	49
Grade 3	24	45
Histological type		
Invasive ductal carcinoma	46	87
Invasive lobular carcinoma	3	5
Mucinous	2	4
Invasive medullary carcinoma	1	2
Metaplastic carcinoma	1	2
ER status		
Positive	31	58.5
Negative	22	41.5
PR status		
Positive	32	60.4
Negative	21	39.6
HER2 status		
Positive	19	35.8
Negative	34	64.2
Molecular subtypes		
Luminal A	21	40
Luminal B	14	26
HER2-Enriched	5	9
Triple negative	13	25
Imaging characteristics		
Fibroglandular pattern		
Almost entirely fat	10	19
Scattered	18	34
Heterogenous	20	38
Extreme	5	9
Background parenchymal enhancement		
Minimal	20	38
Mild	18	34
Moderate	10	19
Marked	5	9

ER: Estrogen receptor, PR: Progesterone receptor PR, HER2: Human epidermal growth factor receptor 2

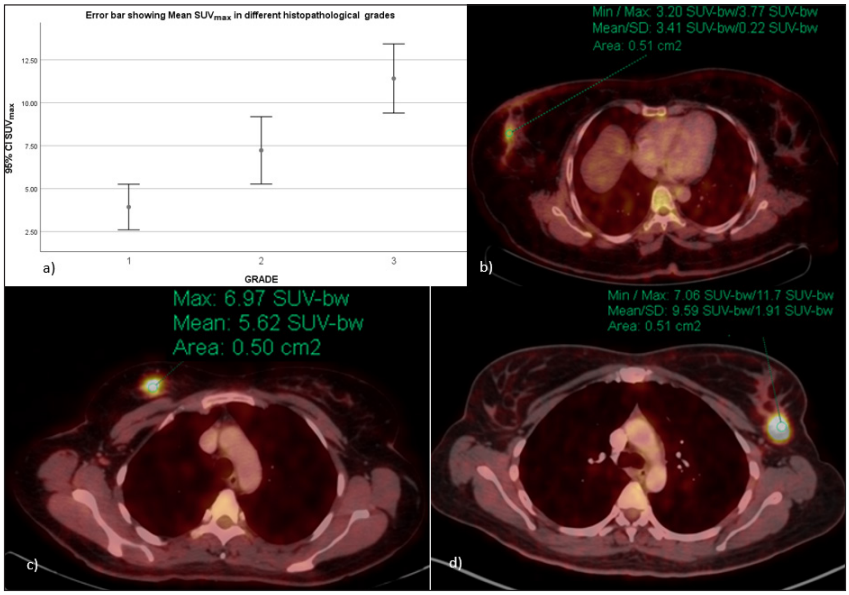

Figure 1: (a) Error bar showing difference between SUV_{max} and histopathological grades [p value - 0.003]. (b) Examples: Grade 1 invasive ductal carcinoma in right breast with minimal FDG uptake (SUV ~ 3.77). (c) Grade 2 carcinoma in right breast with moderate FDG uptake (SUV ~ 6.97). (d) Grade 3 carcinoma in left breast with marked FDG uptake (SUV ~ 11.7). SUV: Standardized Uptake Value, FDG: fluorodeoxyglucose.

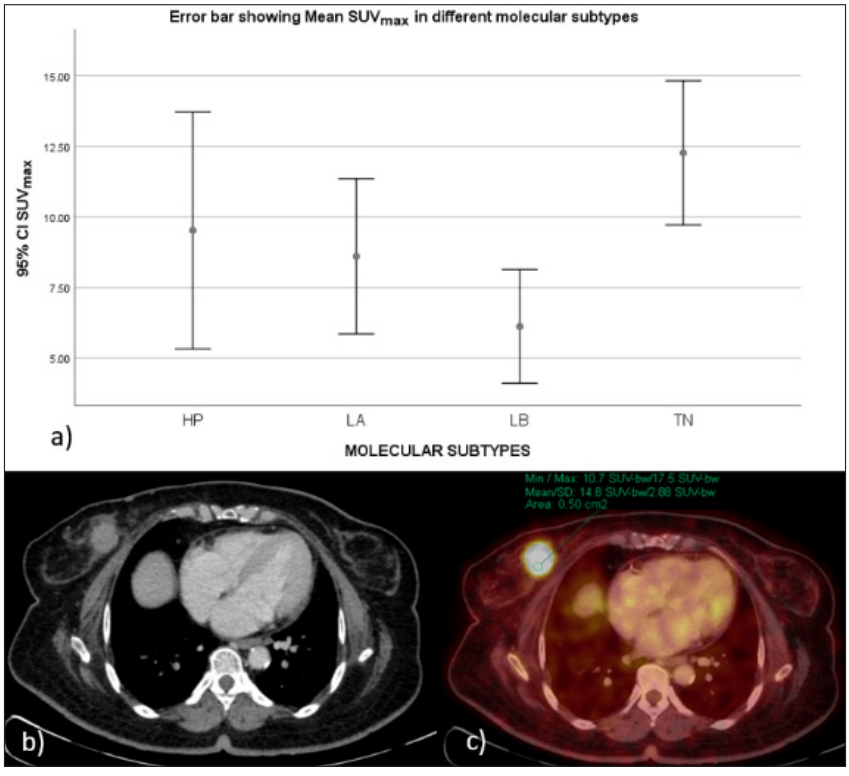

Figure 2: (a) Error bar showing difference between SUV_{max} in different molecular subtypes [p value - 0.018]. Example: Patient with Triple negative molecular subtype – CT (b) and fused PET-CT (c) images showed markedly FDG avid irregular lesion with microlobulated margins in inner quadrant of right breast (SUV ~ 17.5) HP: HER2-Enriched, LA: Luminal A, LB: Luminal B, TN: Triple negative molecular subtype, SUV: Standardized Uptake Value, CT: Computed Tomography, PET-CT: positron emission tomography–computed tomography, FDG: fluorodeoxyglucose.

Table 2: Comparison of histopathological factors with Standardized Uptake Value and Apparent Diffusion Coefficient values.

Histopathological factor	Number	SUV_{max}	*P*	ADC ($\times 10^{-3}$ mm^2/s)	*P*	Background SUV of contralateral breast	*P*
Grade							
Grade 1	3	3.93 ± 0.53	0.003	0.79 ± 0.19	0.597	0.86 ± 0.22	0.200
Grade 2	26	7.23 ± 4.84		0.91 ± 0.19		1.28 ± 0.64	
Grade 3	24	11.41 ± 4.76		0.90 ± 0.19		1.04 ± 0.43	
ER status							
Positive	31	7.72 ± 5.46	0.043	0.85 ± 0.16	0.025	1.13 ± 0.54	0.792
Negative	22	10.64 ± 4.37		0.97± 0.21		1.17 ± 0.56	
PR status							
Positive	32	7.15 ± 5.11	0.001	0.86 ± 0.16	0.100	1.14 ± 0.55	0.981
Negative	21	11.6 ± 4.12		0.95 ± 0.22		1.15 ± 0.55	
HER2 status							
Positive	19	7.48 ± 3.92	0.130	0.94 ± 0.15	0.229	1.07 ± 0.56	0.431
Negative	34	9.74 ± 5.68		0.88 ± 0.21		1.19 ± 0.54	
Molecular subtypes							
Luminal A	21	8.60 ± 6.04	0.018	0.79 ± 0.14	0.009	1.16 ± 0.50	0.652
Luminal B	14	6.12 ± 3.48		0.95 ± 0.15		1.06 ± 0.58	
HER2-Enriched	5	9.52 ± 3.37		1.03 ± 0.26		0.95 ± 0.63	
Triple negative	13	12.27 ± 4.22		0.97± 0.23		1.28 ± 0.56	

ER: Estrogen receptor, PR: Progesterone receptor PR, SUV: Standardized Uptake Value, ADC: Apparent Diffusion Coefficient, HER2: Human epidermal growth factor receptor 2

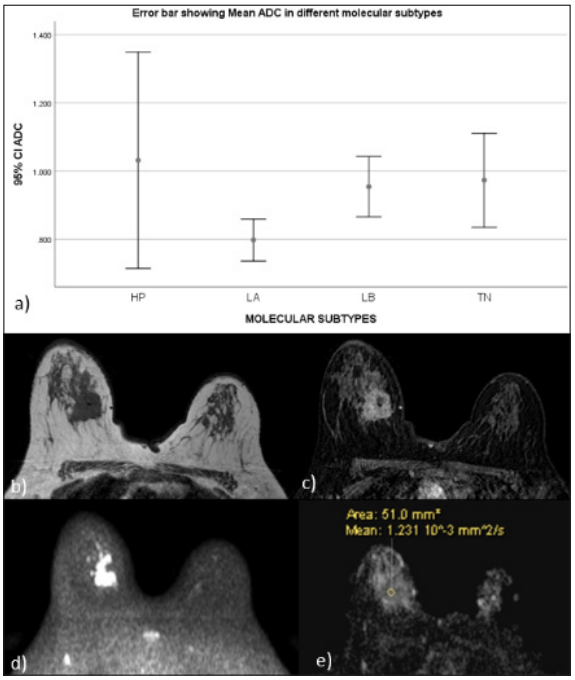

Figure 3: (a) Error bar showing difference between ADC values in different molecular subtypes [p value - 0.009]. Example: 58-year-old postmenopausal female with HER2-Enriched molecular subtype AxT1. HP: HER2-Enriched, LA: Luminal A, LB: Luminal B, TN: Triple negative molecular subtype. (b) and post contrast (c) sequences show heterogeneous fibroglandular tissue with malignant lesion in inner quadrant of right breast showing heterogeneous enhancement, central non-enhancing areas and restricted diffusion (ADC values, 1.231 × 10^{-3} mm^2/s) (d & e). ADC: Apparent Diffusion Coefficient, HER2: Human epidermal growth factor receptor 2.

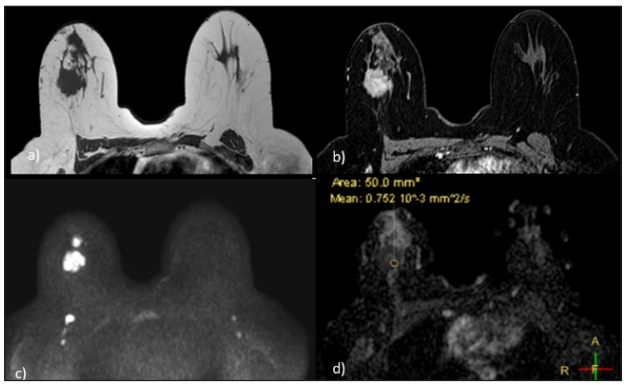

Figure 4: 52-year-old female with Luminal A (ER+, PR+) molecular subtype and grade 2 invasive ductal carcinoma in right breast. Ax T1 (a) and post contrast (b) sequences shows malignant lesion in right breast with heterogeneous enhancement and satellite lesion anterior to the index lesion. The index lesion and the satellite nodule show restricted diffusion with low ADC values, 0.752 × 10^{-3} mm^2/s (c & d). Also note the metastatic right axillary node with restricted diffusion (c). ER+: estrogen receptor-positive, PR+: progesterone receptor-positive, ADC: Apparent Diffusion Coefficient.

(*P* = 0.02) and different molecular subtypes (*P* = 0.009) [Figures 3–5; and Table 2]. Higher mean ADC values were seen in HER2-Enriched molecular subtype (1.03 ± 0.25) [Figure 3]. Lower mean ADC values were seen in ER-positive tumors (0.85 ± 0.16) and luminal A molecular subtype (0.79 ± 0.13) [Figure 4]. There was no statistically significant correlation between ADC values of different grades of malignancy, PR, and HER2 receptor status [Table 2].

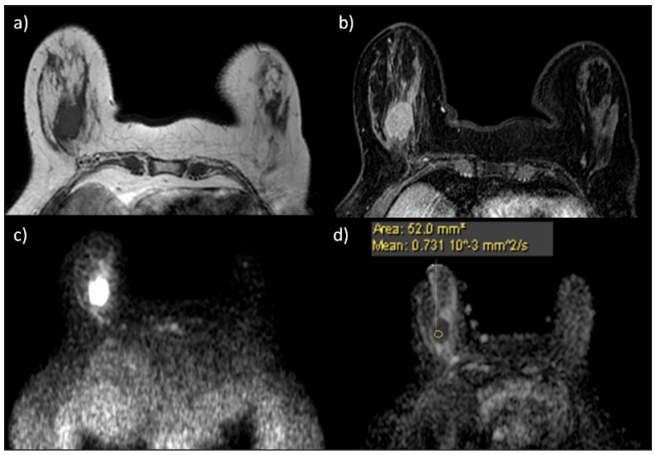

Figure 5: 53-years-old female with Triple negative molecular subtype and grade 3 carcinoma, Ax T1 (a) and post contrast (b) sequences show heterogeneous fibroglandular tissue with heterogeneously enhancing irregular micro lobulated lesion in 6 O' clock position of right breast. The lesion shows restricted diffusion with low ADC values, 0.731 × 10^{-3} mm^2/s (c&d). ADC: Apparent Diffusion Coefficient.

Twenty-five out of 53 patients in our study had heterogenous or extreme fibroglandular pattern in which 24 patients (95%) had a higher grade of malignancy. Among the patients with marked background parenchymal enhancement (5 out of 53), 80% of them had Grade 3 malignancies. There was no statistically significant correlation between background SUV of the contralateral breast, with the grades of malignancy, receptor status, or molecular subtypes.

DISCUSSION

Tumor grade, receptor status, and molecular subtypes are important histological prognostic factors. Higher grade of malignancy and triple negative molecular subtype are aggressive with poor prognosis.

18F-fluorodeoxyglucose PET detects enhanced glycolysis of cancer cells, which is primarily used for staging, response assessment and identifying disease recurrence. FDG uptake is expressed in a quantitative parameter, that is, SUV_{max}, and it carries clinical as well as biological information. In our study, higher SUV values were seen in tumors with Grade 3, ER or PR negative and triple negative molecular subtype. These results are similar to those of few previously published studies such Groheux *et al*,[13] Nakajo *et al*,[22] Ueda *et al*,[34] Choi *et al*,[35] Abubakar *et al*.[36]

In our study, no correlation was found between grade of tumors and ADC values. In accordance with Yoshikawa *et al*.,[37] the ADC value depends on a number of factors including cell density, the spatial organization, and characteristics of the cells such as wall or nuclear size and the type of the stroma. It is not unusual to find high-grade invasive tumors with ADC values higher than expected. It is likely that these types of tumors have a microstructure that promotes water diffusion. Kim *et al*.,[25] concluded that the ADC value was a helpful parameter in detecting malignant breast tumors, but it could not predict patient prognosis.

In our study, statistically significant variation in ADC values among various molecular subtypes. Higher ADC values were seen in HER2-Enriched tumors. Similar results were seen in Horvat *et al*.[38] and Kim *et al*.[32] Kim *et al*.[32] stated, it is known that HER2 expression increases angiogenesis which leads to increase in tumor vascularity. These new vessels are larger and discontinuous that increases the extracellular fluid volume thereby increasing the ADC values.[19] Low ADC values were seen in luminal A subtype and ER-positive tumors were consistent with the results of Horvat *et al*.[38] as these tumors have low neovascularity and high cellularity. It is important to differentiate luminal and non-luminal tumors for the reason that the luminal tumors require endocrine therapy rather than a cytotoxic chemotherapy. Horvat *et al*.[38] expressed that in future the improvements in DWI technology may increase the accuracy of ADC metrics and it can have clinical applicability in the preoperative classification of tumor subtypes.

However, there was no statistically significant variation in ADC values between progesterone/HER2 receptor-positive and negative lesions in our study. Similar results were also observed with Nakajo *et al*.[22] and Kim *et al*.[25]

Larger number of patients with heterogeneous fibroglandular pattern had higher grade of malignancies. These results were in agreement with the previously published studies by McCormack *et al*.,[14] and Boyd *et al*.,[15] which proved that the risk of malignancy is higher in patients with denser breast.

This study has some limitations. It was a short-duration prospective study with a relatively low number of patients. Heterogeneous sample of patients were examined that showed uneven distribution of histologic (low number of lobular carcinoma and Grade 1 tumors) and molecular subtypes (low number of HER2-Enriched type) which can influence the significance of the results

CONCLUSION

PET-CT and MRI can be used as a complementary imaging tool in evaluating the patient with breast carcinoma for noninvasive assessment of the aggressiveness, and biological characteristics of tumor such as grade, hormone receptor status, and to differentiate molecular subtypes.

Our study showed higher SUV values in Grade III, ER- or PR-negative and triple-negative tumors. Therefore, in essence, the SUV values obtained from 18F-FDG PET-CT shows a positive correlation with the aggressiveness of the tumor. ADC values

helps to analyze the cellularity and neo angiogenesis of the tumor

Ethical Approval

The author(s) declare that they have taken the ethical approval from IEC (ECR/37/Inst/TN/2013/RR-16).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Ramakrishnan B, Sivaramalingam G, Raghavan B, Govindaraj J, Viswanathan S, Umretiya N. Role of SUV and ADC values as a predictor of grade and molecular subtypes of breast malignancy. Asian J Oncol. 2023;9:16. doi: 10.25259/ASJO-2022-56-(412)