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Relationship Between FDG Uptake and Neutrophil/Lymphocyte Ratio in Patients with Invasive Ductal Breast Cancer

TAKAAKI FUJII, KEIKO YANAI, SHOKO TOKUDA, YUKO NAKAZAWA, SASAGU KUROZUMI, SAYAKA OBAYASHI, REINA YAJIMA, TOMOKO HIRAKATA and KEN SHIRABE

Division of Breast and Endocrine Surgery, Department of General Surgical Science, Graduate School of Medicine, Gunma University, Gunma, Japan

Abstract. *Background: ^{18}F-Fluorodeoxyglucose-positron-emission tomography (FDG-PET) is used to evaluate the glucose metabolic rates of tumors. Several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer. FDG uptake is influenced by many factors, including inflammation. In this study, the relationship between FDG uptake and neutrophil/lymphocyte ratio (NLR), which is an indicator of systemic inflammation, was investigated. Patients and Methods: A retrospective investigation of the cases of 143 consecutive patients with invasive ductal carcinoma who had undergone surgery and FDG-PET preoperatively. PET was evaluated using standardized uptake value max (SUV_{max}). The median SUV_{max} was 2.5 (range=0-10.5). The cases were divided into two groups based on the value of SUV_{max}: low (<2.5) and high (≥2.5). The relationships between SUV_{max} and clinicopathological features, including NLR, were investigated. Results: Among the 143 patients, 73 (51.0%) had high SUV_{max} in the primary tumor. The analysis revealed that large tumor size ($p<0.001$), high nuclear grade ($p<0.001$), the presence of lymphovascular invasion ($p<0.001$), high C-reactive protein ($p=0.046$) and high NLR ($p<0.001$) were significantly associated with high SUV_{max} in the primary tumor. SUV_{max} and NLR were significantly positively correlated ($r=0.323$, $p<0.001$). Among the 70 cases with low SUV_{max}, there was no recurrent disease, while out of the 73 cases with high SUV_{max} had disease recurrence. It is interesting to note that the group with high SUV_{max} and low NLR had no recurrent disease. Conclusion: The present study demonstrated that the finding of high preoperative FDG uptake in breast cancer may be reflective of poor prognosis and that a high NLR may be predictive of aggressive features among patients with breast cancer. On the other hand, among patients with breast cancer with high SUV_{max} in the primary tumor, it will be useful to identify those with a low NLR in order to improve prognostic accuracy.*

Correspondence to: Takaaki Fujii, MD, Ph.D., FACS, Department of General Surgical Science, Graduate School of Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81 0272208224, Fax: +81 0272208230, e-mail: ftakaaki@gunma-u.ac.jp

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There is increasing evidence to show that the presence of a systemic inflammatory response is associated with poor survival in multiple types of cancers (1-7). Cancer progression and prognosis are affected by the patient's inflammatory response in the tumor microenvironment (1, 2). Recently, the neutrophil/lymphocyte ratio (NLR) was found to be a prognostic factor in breast cancer. It is of interest that the presence of a systemic inflammatory response, as evidenced by an elevated NLR, has been shown to predict recurrence and overall survival in patients with breast cancer (2, 8-12).

In recent years, the clinical applications of positron-emission tomography (PET) have grown explosively. PET using ^{18}F-fluorodeoxyglucose (FDG) is a non-invasive whole-body imaging technique used to evaluate different kinds of malignancies, including breast cancer, for tumor staging and restaging, detecting recurrence, and monitoring treatment responses (13-21). FDG-PET measures glucose metabolism, which reflects the biological aggressiveness of tumors (21-26). Several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer (21-26). FDG uptake is influenced by many factors, including inflammation, yet no published study, to our knowledge, has assessed the association between FDG uptake and NLR in breast cancer cases, even though both these measures represent inflammation.

In this study, we investigated the relationship between FDG uptake and the NLR at baseline in patients with breast cancer.

Patients and Methods

Patients. We retrospectively investigated the cases of 143 consecutive patients with primary breast cancer who had undergone FDG-PET preoperatively at Gunma University between January 2010 and October 2015. All patients subsequently underwent radical breast surgery. Patients with synchronous bilateral breast cancer or clinical signs of infection or other inflammatory conditions preoperatively, including pneumonia or articular rheumatism, were excluded from the study. Patients with incomplete clinical information and male patients were excluded. Patients underwent FDG-PET/computed tomography (CT) as part of the routine standard of care without deviating from the main protocol. The maximum standardized FDG uptake value (SUV_{max}) of primary tumors was calculated in a routine clinical fashion. Written consent was obtained from all patients for the use of their records and imaging in future studies.

The details extracted from the database were age, histological type, size of invasive primary tumor, size of ductal spread, lymphatic or vascular invasion, nuclear grade, estrogen receptor (ER) and progesterone receptor (PgR) expression status, human epidermal growth factor receptor 2 (HER2) score of the primary tumor, axillary lymph node status, serum C-reactive protein (CRP), serum carcinoembryonic antigen (CEA), hemogram parameters (neutrophils and lymphocytes), and SUV_{max} of the primary tumor and visibility of detected lesion by FDG-PET. The ER and PgR statuses were assessed by ALLRED scores, with an ALLRED score of 3 or higher indicating ER and PgR positivity (27). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The relationships between SUV_{max} and clinicopathological features, including NLR, were investigated. The median SUV_{max} was 2.5 (range=0-10.5). Therefore, the cases were divided into two groups based on SUV_{max} value: low (<2.5) and high (≥2.5).

Statistical analysis. The breast cancer cases were divided into two groups on the basis of FDG uptake in the primary tumor. A univariate statistical analysis was carried out using Fisher's exact test or the chi-squared test with Yates' correction. To compare the two groups, Student's *t*-test was used. Differences were considered significant when $p<0.05$. Relapse-free survival (RFS) was calculated using the Kaplan–Meier method. The log-rank test was used to evaluate differences in overall survival and the recurrence-free interval. Differences were considered significant when $p<0.05$.

Results

In total, 143 cases were included in the analysis. The median SUV_{max} was 2.5 (range=0-10.5). Among the143 patients, 73 (51.0%) had high SUV_{max} in the primary tumor. The 143 cases with breast cancer were divided into two groups based on SUV_{max} in the primary tumor. Table I shows the patient characteristics and summarizes the results of the univariate analysis conducted to determine the relationships between SUV_{max} in the primary tumor and clinicopathological variables.

The univariate analysis revealed that large tumor size ($p<0.001$), high nuclear grade ($p<0.001$), the presence of lymphovascular invasion ($p<0.001$), high CRP ($p=0.046$) and high NLR ($p<0.001$) were significantly associated with high SUV_{max} in the primary tumor. SUV_{max} and NLR were positively correlated (r=0.323, $p<0.001$).

The RFS shown by the Kaplan–Meier curves was significantly shorter for patients with high SUV_{max} ($p=0.013$) (Figure 1). Among the 70 cases with low SUV_{max}, there was no recurrent disease, while six out of the 73 cases with high SUV_{max} had disease recurrence. The overall median follow-up period was 48.9 months (range=9.6-94.7 months).

It is interesting to note that the group with high SUV_{max} and low NLR (NLR<1.8) had no recurrent disease, although there were no differences in any clinicopathological features between the group with high NLR and high SUV_{max} and that with low NLR with high SUV_{max} (Table II).

Discussion

Inflammation in patients with cancer is a significant problem due to a variety of mechanisms involving the tumor and the host response to the tumor. Several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer (21-26). FDG-PET provides biological information about a tumor's growth potential and shows inflammation. Recently, NLR was reported to be a prognostic factor in breast cancer. NLR is considered as important as CRP in the inflammatory assessment. It is of interest that some authors have reported that NLR reflects systemic inflammation and prognosis in patients with cancer (2, 8-12). The key observations of the present study can be summarized as follows: i) among various clinicopathological characteristics, high SUV_{max} was associated with high NLR; ii) high SUV_{max} was associated with disease recurrence in patients with operable breast cancer; iii) the group with high SUV_{max} and low NLR had no recurrent disease. Our results suggest that FDG uptake may be predictive of inflammation in addition to aggressive features among patients with breast cancer. These findings provide evidence that high SUV_{max} is a useful predictor of disease recurrence in patients with operable breast cancer, but cases with low NLR despite high SUV_{max} in the primary tumor may have a lower risk of recurrent disease.

SUV_{max} is used as a semi-quantitative indicator of FDG uptake as it is influenced by many factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells (14, 18, 28). FDG-PET measures local glucose metabolism and may reflect local inflammation of cancer. For the evaluation of breast cancer, it is important to understand not only systemic inflammatory response but also local inflammatory response represented by FDG avidity. As components of systemic inflammatory response, lymphocytes and neutrophils are increasingly being recognized as having an important role in cancer progression. NLR is determined to indicate systemic inflammation. From our findings, high SUV_{max} with high NLR may reflect aggressive tumor features

Table I. *Patient characteristics and clinicopathological features associated with ^{18}F-fluorodeoxyglucose (FDG) uptake in primary breast cancer.*

	FDG uptake		
	Low (n=70)	High (n=73)	*p*-Value
Age, mean±SD (years)	60.3±11.3	57.6±12.5	0.906
Tumor size (mm)	14.4±9.1	23.0±9.9	<0.001
Nodal metastasis-positive (n)	11	21	0.095
ER-positive (n)	63	58	0.064
PgR-positive (n)	53	55	0.886
HER2-positive (n)	8	17	0.049
Nuclear grade 3 (n)	14	42	<0.001
Lymphatic invasion-positive (n)	17	41	<0.001
Vascular invasion-positive (n)	5	23	<0.001
NLR, mean±SD	2.08±0.91	2.83±1.65	<0.001
CEA (ng/mI), mean±SD	2.26±1.67	2.61±2.97	0.191
CRP (mg/mI), mean±SD	0.05±0.06	0.20±0.73	0.046

n, Number of patients; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NLR, neutrophil:lymphocyte ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen.

Table II. *Patient characteristics and clinicopathological features associated with neutrophil:lymphocyte ratio (NLR) in patients with high ^{18}F-fluorodeoxyglucose (FDG) uptake.*

	NLR		
	Low (n=16)	High (n=57)	*p*-Value
Age, mean±SD (years)	57.6±11.6	57.7±12.8	0.519
Tumor size (mm)	22.4±8.8	23.1±10.2	0.600
Nodal metastasis-positive (n)	2	19	0.090
ER-positive (n)	15	43	0.100
PgR-positive (n)	14	41	0.173
HER2-positive (n)	2	15	0.210
Nuclear grade 3 (n)	12	30	0.093
Lymphatic invasion-positive (n)	6	35	0.079
Vascular invasion-positive (n)	5	18	0.617
SUV_{max}	5.04±2.06	5.19±2.70	0.587
CEA (ng/ml), mean±SD	3.06±3.41	2.48±2.69	0.273
CRP (mg/ml), mean±SD	0.06±0.10	0.24±0.82	0.934

n, Number of patients; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NLR, neutrophil:lymphocyte ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen.

and systemic inflammation, which strongly predict poor prognosis in patients with breast cancer. On the other hand, a high SUV_{max} without a high NLR may predict local inflammation at the tumor, which may reflect immunoreaction to the tumor.

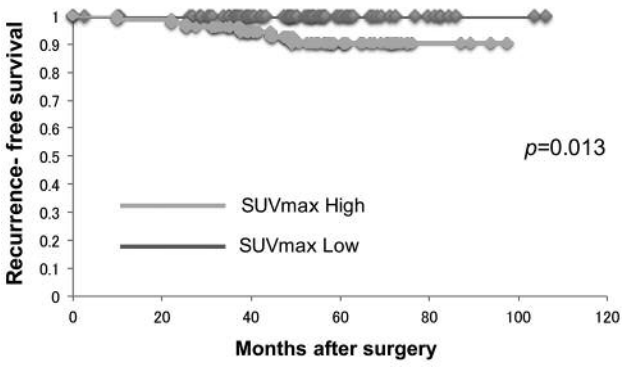

Figure 1. *Recurrence-free survival curves according to standardized uptake value max (SUV_{max}) of the primary tumor. The recurrence-free interval for the group with high SUV_{max} was significantly shorter than that with low SUV_{max} (p=0.013). The overall median follow-up period was 48.9 months (range=9.6-94.7 months).*

An elevated NLR is associated with adverse survival probabilities in multiple cancer types, including breast cancer. However, evidence of the prognostic role of NLR in breast cancer is relatively controversial (12, 29). Inflammation is associated with many factors, and an elevated NLR is not only induced by the cancer environment. In our study, there was no recurrence in patients with low SUV_{max} with high NLR. Therefore, an elevated NLR without FDG uptake in the primary tumor may not pose an increased risk of recurrent disease.

Cancer progression and prognosis are affected by many factors, including the host's inflammatory response or immunological response in the tumor microenvironment (1, 2). From our findings, SUV_{max} represents the local reaction of the tumor and NLR predicts the systemic inflammatory reaction, including the response to the tumor; it is considered that the combination of SUV_{max} and NLR findings is effective for predicting local and systemic tumor microenvironments and predicting prognoses of patients with breast cancer.

This study had several potential limitations, the major ones being that it was a retrospective analysis and that the number of cases was relatively small. Additional research is needed to explore other benefits and drawbacks of NLR and FDG-PET evaluation of primary breast cancer. However, to the best of our knowledge, this is the first report to describe the relationship between FDG uptake and NLR in breast cancer. NLR as a predictor in patients with primary breast cancer with high SUV_{max} may indicate a lower risk of recurrent disease.

In conclusion, we demonstrated that the finding of a high preoperative SUV_{max} in primary breast cancer is effective for predicting poor prognosis among patients. On the other hand, among those with high SUV_{max} in the primary tumor, it will be useful to identify the subset of patients with low NLR to improve prognostic accuracy. Analyses from large

randomized trials are warranted to evaluate the relationship between the combination of these two factors and disease recurrence.

Competing Interest

The Authors declare that they have no competing financial interests in regard to this study.

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