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Meme Kanserinde SUVmax ile Tümör-Stroma Oranı Arasındaki İlişki: Patolojik Bir Korelasyon Çalışması

Association Between SUVmax and Tumour-Stroma Ratio in Breast Cancer: A Pathological Correlation Study

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ÖZ

Amaç: Çalışmamızda, birçok kanser türünde prognostik bir belirteç olarak kabul edilen tümör-stroma oranı ile yarı kantitatif bir parametre olan lezyon maksimum standardize uptake volüm değeri (SUVmax) arasındaki korelasyonu araştırmak ve eğer anlamlı bir ilişki saptanırsa, SUVmax değerlerinin çok merkezli çalışmalarla desteklendiğinde prognostik bir belirteç olarak da kullanılabileceğini göstermeyi amaçladık.

Yöntem: Tamamı kadın olan, meme kanseri tanısı almış ve ikincil primeri bulunmayan toplam 42 hasta çalışmaya dahil edildi. Kemoterapi veya radyoterapi almış hastalar çalışma dışı bırakıldı. Patolojik preparatlar ve evreleme amacıyla çekilmiş F-18 FDG PET/BT arşiv görüntüleri retrospektif olarak incelendi. Tüm hastalar için patolojik tümör-stroma oranı ile PET/BT incelemesinde tümör tracking yöntemiyle hesaplanan SUVmax değerleri elde edildi.

Bulgular: Tamamı kadın olan bu çalışmada, hastaların ortalama yaşı 55.86±14.11 (30–79) yıl, ortalama SUVmax değeri 8.18±5.05 (1.26–20.26) ve ortalama tümör-stroma oranı 0.70±0.42 (0.16–1.93) olarak hesaplandı. SUVmax değerleri ile tümör-stroma oranı arasında düşük düzeyde anlamlı pozitif bir korelasyon saptandı (r=0.277, p=0.042).

Sonuç: Çalışmamızda, birçok kanser türünde önemli bir prognostik belirteç olarak kabul edilen tümör-stroma oranı ile lezyon SUVmax değerleri arasında düşük düzeyde anlamlı pozitif bir korelasyon olduğu gösterilmiştir. Bu bulguya göre, yeterli hasta sayısı ve çok merkezli çalışmalarla desteklendiği takdirde, SUVmax değerlerinin de prognostik belirteç olarak kullanılabileceği öngörülmektedir. Meme kanserinde SUVmax ile tümör-stroma oranı arasındaki ilişkiyi araştıran başka bir çalışmaya literatürde rastlanmamıştır.

Anahtar Kelimeler: Meme Kanseri, SUVmax, Tümör-stroma oranı.

ABSTRACT

Objective: In our study, we purposed to investigate the correlation between tumour-stroma ratio, which is considered a prognostic marker in many types of cancer, and lesion maximum standardized uptake values (SUVmax), which is a semiquantitative parameter, and to show that, if significant, SUVmax values can also be used as a prognostic marker when supported by multicenter studies.

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Yazar Katkıları: A) Fikir/Kavram, B) Tasarım, C) Veri Toplama ve/veya İşleme, D) Analiz ve/veya Yorum, E) Literatür Taraması, F) Makale Yazımı, G) Elestirel İnceleme

Method: A total of 42 patients, all female, who were diagnosed with breast cancer, had no secondary primary. The patient who had received chemotherapy or radiotherapy treatments, were excluded. Pathological preparations and staging F-18 FDG PET/CT archive images were examined retrospectively. The pathological tumour-stroma ratio and SUVmax calculated by the tumour tracking method in the PET/CT examination were obtained for all patients.
Results: In this all-female study, the mean age was calculated as 55.86±14.11(30-79) years, mean SUVmax was 8.18±5.05 (1.26-20.26) and mean tumour-stroma ratio was 0.70±0.42 (0.16-1.93). There was a poor level significant positive correlation between the SUVmax values and tumour-stroma ratio (r=0.277, p=0.042).
Conclusion: In our study the tumour stroma ratio, which is considered as an important prognostic marker in many cancer types, correlates with the lesion SUVmax values. According to this information, it is predicted that we can foresee that SUVmax values can be used as prognostic markers when supported by appropriate patient number and multi-center studies. No other studies have examined the correlation between SUVmax and tumour stroma ratio in the breast cancer.

Key words: Breast cancer, SUVmax, Tumour-stroma ratio.

1. INTRODUCTION

Positron emission tomography-computed tomography with F-18 fluorodeoxyglucose (F-18 FDG PET/CT) is one of the most preferred imaging methods in the diagnosis of malignancy. F-18 FDG PET/CT, which has become an indispensable diagnostic tool for clinical oncology, is useful in the diagnosis of almost all advanced stage cancers.

The most widespread type of cancer in women is breast cancer, and it ranks second in cancer-related death after lung cancer. Mammography and ultrasonography are the main methods used in breast cancer screening. Tc-99m MIBI mammoscintigraphy, F-18 FDG and F-18 estradiol PET can be used as more specific imaging methods for MRI and USG in the differential diagnosis of malignancy.

All malignant epithelial tumours consist of epithelial cells admixed with supporting tissue, called “stroma”, which is not only containing vascular-lymphatic channels and inflammatory cells, but also contains some type of fibrous tissue named desmoplasia. Desmoplastic stroma, known to play an important role in progression, invasion and metastasis of the tumourin question (1,3,4) is a structure that contains new extracellular matrix and activated fibroblast-like cells induced by the invasion of malignant cells (1,2). Tumour-stroma ratio is considered a prognostic factor in some types of carcinomas, including breast, colorectal, prostate and esophageal adenocarcinomas (5-10).

In our study; the correlation between the lesion maximum standardized uptake values (SUVmax) and the tumour stroma ratio, which is calculated by the tumour tracking method, is investigated for the first time in the patients who have breast cancer.

2. METHODS

In our study, the records of 42 female patients who underwent mastectomy and positron emission tomography-computed tomography (PET/CT) scans at the Department of Nuclear Medicine between November 2012 and March 2017, were retrospectively analyzed for preoperative staging of breast cancer. Both pathological preparations and archival imaging data were included in the evaluation. Patients who received neoadjuvant chemotherapy prior to mastectomy were excluded from the study. The aim was to investigate the correlation between SUVmax values, derived from lesions visually assessed in each section using the Tumour Tracking method, and the tumour-stroma ratio (TSR), calculated from corresponding pathological preparations.

PET/CT imaging

3.7 MBq/kg F-18 FDG was injected via intravenous (IV) against the upper extremity in patients with serum glucose levels below 180 mg/dL after at least 6 hours of fasting rest for 1 hour before imaging. The upper extremities are removed from the field of view of the cameras when the patient is in the supine position. Image taken from the base of the head to the upper femoral region with a 3-minute / bed position. A PET / CT device with integrated LYSO crystal, TOF technology (Philips Tru Flight Select, Ohio, 2011) was used as a PET / CT device.

Whole-body PET imaging (in 3D mode) was performed immediately after low-dose (120 keV, 10-90 mAs) IV non-contrast whole-body CT imaging. PET images with recorded CT images attenuation correction was performed and the images were processed to create 5mm thick sections in three orthogonal planes; axial, coronal and sagittal. SUVmax values were calculated automatically by tumour tracking method by determining the area of interest from the lesions detected in each section evaluated visually (Figure 1).

Figure 1. Calculation of SUVmax values by tumour tracking method

Histopathological evaluation

Three digital images were recorded at x20 magnification from tumour-sampling sections of hematoxylin eosin (H&E) stained preparations of mastectomy material from 42 patients included in the study. Tumour stroma ratio was measured with a new software tool called ARACHNE. Histopathological Image Atlas Editor (HIAE), a Windows operating

system, was used during measurement. The measurements were made by the pathologists by marking the square blocks, and the ratio of the marked areas was automatically calculated by the ARACHNE software (11) (Figure 2).

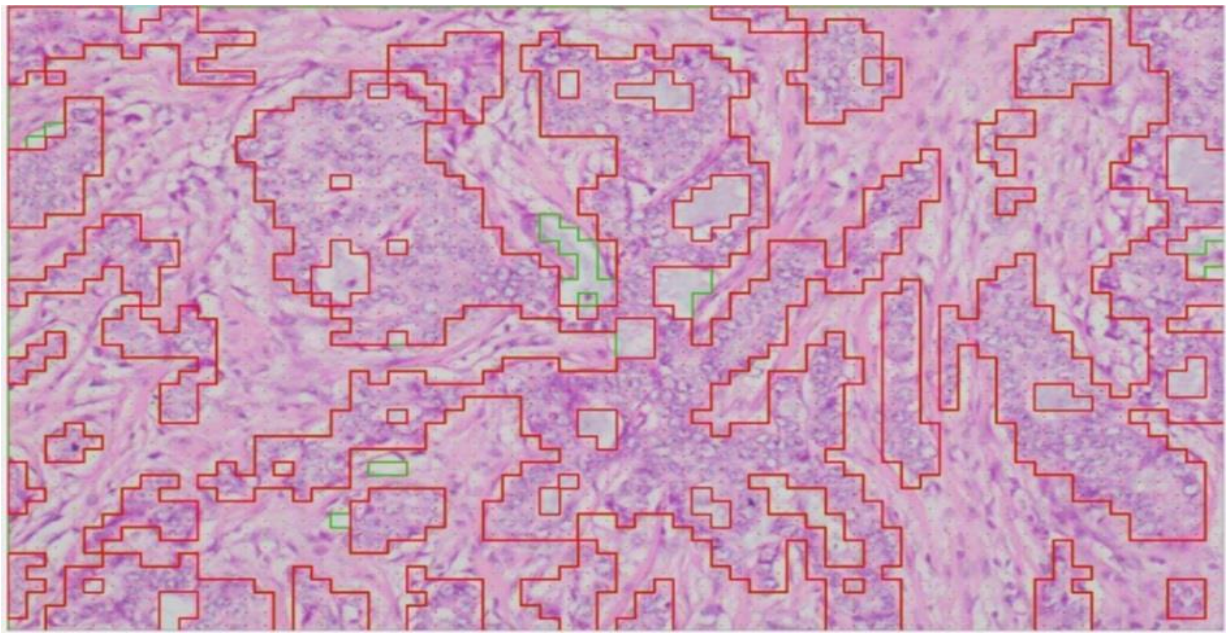

Figure 2. Tumour-stroma ratio calculation with ARACHNE program

Statistical analysis

All statistical analyzes were performed using SPSS software version 15.0. The relationship between tumour-stroma ratio and quantitative PET / CT parameters in breast was evaluated using Pearson Correlation test. Descriptive statistics were showed as mean±standard deviation (minimum-maximum values). Statistical significance was accepted as $p<0.05$.

3. RESULTS

In this all-female study, the average age was calculated as 55.86±14.11(range:30-79) years, the average SUVmax was 8.18±5.05 (range:1.26-20.26) and the average tumour-stroma ratio was 0.70±0.42 (range:0.16-1.93).

Although 2 (4.76%) of the patients in the study were diagnosed with tru-cut biopsy and F-18 FDG uptake was calculated higher than the surrounding tissue on PET / CT imaging, no invasive tumour tissue was detected in mastectomy material.

There was a poor level significant positive correlation between the SUVmax values and the tumour-stroma ratio ($r=0.277$, $p=0.042$) (Figure 3).

4. DISCUSSION

Recent findings emphasize the prognostic significance of tumour-stroma ratio in some cancer types (12-18). It has been shown that tumour stromal cells are introduced into the Warburg effect in a reverse manner by stimulating the production of hydrogen peroxide inducing pseudohypoxia from tumour cells in the tumour microenvironment. Stromal cells produce and supply L-lactate and ketone as well as amino acids such as glutamine, fatty acids, and nucleotides to tumour cells by aerobic glycolysis and mitophagy. The data mentioned above

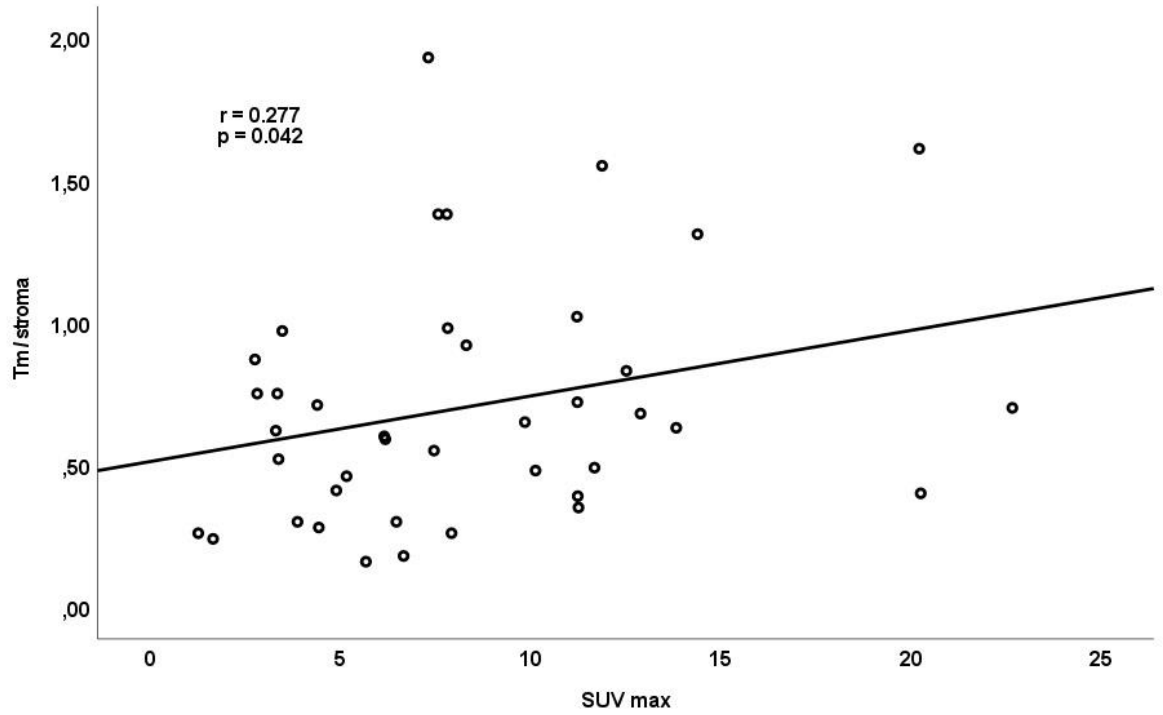

Figure 3. Tumour-stroma ratio and SUVmax correlation graphic

support that stromal cells are an important determinant of tumour behavior. Based on these findings, morphological quality and quantity of stroma is evaluated as prognostic marker in various cancer types (19,20).

de Kruijf et al in a study of 574 patients in 2010 demonstrated that tumour-stroma ratio is an independent prognostic factor in breast cancer patients. Stromal-rich tumours associated with an increased risk of relapses. Importantly, the rate of tumour stroma in the triple negative breast cancer group compared to the group with no definitive prognostic biomarker; it has emerged as a prognostic parameter that shows a significant correlation when compared with stroma-poor tumours with a better 5-year relapse-free survival rate of 81%, and stroma-rich tumours with a 5-year relapse-free survival rate of 56% (15).

FDG activity, is the SUVmax value, is a semiquantitative value indicating the glucose uptake of the lesion. The exact mechanism for FDG uptake is still unknown (21,22). The SUVmax is the most widely used and the most reproducible parameter for estimating the metabolic activity of FDG uptake. The SUVmax value of a tumour is the product of many essential factors, including the number of cells / cell type and glucose metabolism within the tumour. A higher SUVmax may result from increased FDG uptake due to a higher number of inflammatory cells, such as lymphocytes and macrophages, competing for glucose uptake, or higher mitotic activity of tumour cells. Conversely, a lower number of high metabolic activity tumour cells or a low number of high metabolic activity tumour cells may be present (21).

Köksal et al. in a study of 81 patients in 2013, demonstrated that tumour size and presence of necrosis were the factors affecting SUVmax value of the tumour. Several previous studies have reported that SUVmax was positively correlated with tumour diameter (23-26). At the same time, the increase in tumour diameter is associated with increased expression of glucose transporter-1 (GLUT-1) on the surface of tumour cells, thereby increasing FDG uptake

(27). No correlation was found between the degree of necrosis and SUVmax. This can be explained by calculating the SUVmax value from the area of the tumour showing the highest FDG uptake (28).

What Jiayuan Wu et al.in a comprehensive electronic data including 4238 patients investigating the relationship between prognosis of solid tumours (breast cancer, ovarian cancer, extracellular lung cancer, hepatocellular cancer, cervical cancer, colorectal cancer, nasopharyngeal cancer) and in a meta-analysis of 14 studies, including a comprehensive electronic database study of 4238 patients, who investigated the relationship between tumour stroma ratio; showed that tumour-rich stroma was associated with overall survival (14 studies, 4238 patients) and disease-free survival (9 studies, 2235 patients). In the same study, high stroma in tumour tissue; advanced clinical stage (p=0.012), the existence of lymph node metastasis (p = 0.008) and advanced invasion depth (p=0.006) showed significant correlation with some phenotypes of tumour aggression (29).

Some limitations of this study should be acknowledged. In particular, the relatively small sample size may have limited the generalizability of the findings. According to this information, SUVmax values can be used as prognostic markers when supported by appropriate patient numbers and multi-center studies.

The manual selection of stroma-rich areas for tumor–stroma ratio assessment is a standard procedure; however, it is inherently subject to inter-observer variability. To minimize this limitation, all evaluations were performed by a single pathologist, and the tumor–stroma ratio was automatically calculated using an artificial intelligence–based software program, ARACHNE.

Although numerous studies have evaluated breast cancer patients, the correlation between tumour-stroma ratio and SUVmax has not been reported before.

In conclusion, in our study, SUVmax and pathologic tumour stroma ratio showed a poor level significant positive correlation. In many studies; SUVmax value of primary tumour has been associated with certain pathological characteristics such as mitosis, histology, maximum diameter.

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