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The expression of miR-22, miR-140, and miR-328 in breast cancer tissues: Implications for PET/CT imaging biomarkers

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Abstract

Aim: To evaluate the correlation between microRNA (miRNA) expression and 18F-fluorodeoxyglucose (18F-FDG) uptake in breast cancer patients, focusing on the tumor-suppressor miRNAs miR-22, miR-140, and miR-328, and their potential as diagnostic biomarkers.

Material and Methods: Biopsies from 14 female breast cancer patients were analyzed, including both tumor and adjacent healthy tissues. The expression levels of miR-22, miR-140, and miR-328 were quantified using real-time PCR. SUVmax values from PET/CT imaging were obtained to assess metabolic activity in tumor tissues. Statistical analyses were performed to explore correlations between miRNA expression and PET/CT results.

Results: Our patients' ages ranged from 38 to 74 years, with a mean of 59.5 years. The levels of miR-22, miR-328, and miR-140 were significantly lower in breast cancer tissues compared to healthy tissues. However, no statistically significant correlations were found between miRNA values and 18-FDG PET/CT SUVmax values.

Discussion: While miR-22, miR-140, and miR-328 show promise as potential diagnostic biomarkers for breast cancer due to their significant downregulation in tumor tissues, their expression does not correlate with metabolic activity as measured by SUVmax in PET/CT imaging. Further research is needed to explore the clinical applications of miRNAs in breast cancer diagnosis and prognosis.

Keywords

Breast Cancer, Glut, Mir-22, Mir-328, Mir-140, PET/CT

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Introduction

Breast cancer represents a significant public health issue, with a lifetime risk of one in eight women developing the disease. Its development and progression are influenced by various factors, including genetics and environmental influences [1]. Biomarkers play a crucial role in distinguishing cancerous cells from normal cells; however, existing tumor markers in serum have limitations in specificity and sensitivity [2].

Various biochemical markers, including enzyme and hormone levels, as well as mRNA and microRNA (miRNA) expression, are associated with different cancer types. miRNAs are short, non-coding RNA molecules crucial for post-transcriptional gene regulation in nearly all biological processes. Dysregulation of the miRNA pathway is closely linked to cancer development and progression [3, 5]. Specifically, the up- or down-regulation of miRNAs can influence the initiation and advancement of breast cancer and other malignancies. The deletion of tumor-suppressor miRNAs or the overexpression of oncogenic miRNAs can promote tumorigenesis and metastasis, thus positioning miRNAs as potential diagnostic, prognostic, and therapeutic targets [6].

Glucose metabolism and uptake are increased in breast cancer. Moreover, the expression of metabolic enzymes, such as glucose transporter (GLUT) and hexokinase, modulates miRNA involvement in cell metabolism. The expression of glucose transporter-1 (GLUT-1) is elevated in poorly differentiated breast cancer [7], and GLUT-1 expression is influenced by tumor suppressor microRNAs, specifically miR-22, miR-140, and miR-328, which are decreased in breast cancer [8, 10].

Combining the glucose equivalent 18F-fluorodeoxyglucose (18-FDG) with positron emission tomography (PET) is a valuable tool in the assessment and management of many malignancies [11]. 18-FDG-PET relies on FDG uptake into the tumor cell by metabolic enzymes, including GLUT-1. The XbaI G>T single-nucleotide polymorphism in the GLUT-1 gene leads to higher 18-FDG uptake, which is linked to the stage of breast cancer [12]. 18-FDG-PET/X-ray computed tomography (PET/CT) is well-studied in breast cancer [13]. The standardized uptake value (SUV) in PET/CT images represents the radioactivity accumulated by 18-FDG uptake in tissue.

Numerous studies have investigated the etiology and prognosis of microRNAs (miRNAs) in breast cancer alongside various imaging techniques aimed at enhancing the detection and monitoring of the disease. However, no research has yet examined the relationship between these imaging modalities and miRNA expression profiles, which are linked to the biological mechanisms underlying imaging. The identification of novel biomarkers related to imaging biology presents intriguing opportunities for breast cancer detection. Notably, the downregulation of tumor-suppressor miR-22, miR-140, and miR-328 has been observed in breast cancer, influencing GLUT-1 expression. Positron emission tomography/computed tomography (PET/CT) scans measure cellular metabolic activity by assessing the uptake of 18-FDG, a glucose analog, which increases with heightened metabolic activity in cancer cells. We hypothesize that alterations in miRNA levels in cancerous tissue may affect GLUT protein levels, thereby influencing 18-FDG uptake and the maximum standardized uptake value (SUVmax) in tumor tissue. This study aims to evaluate the correlation between 18F-FDG uptake and the effects of tumor-suppressor miRNAs on GLUT-1 expression in breast cancer.

Material and Methods

Design and Patients

This comparative study involved biopsies from 14 female breast cancer patients aged 18 years and older, all eligible for surgery and capable of providing written consent. Fresh tumors and adjacent normal tissues were collected during surgery, ensuring clear surgical margins [14]. RNA extraction and miRNA measurements were conducted on both tissue types, and SUVmax values of the cancerous tissues were obtained from the patients' PET/CT reports.

Sample Preparation and RNA Extraction

Samples were homogenized with ceramic beads for 45 seconds, vortexed, and incubated on ice for 5 minutes, then at room temperature. To facilitate phase separation, 200 µL of chloroform was added after centrifuging at 12,000 rpm for 20 minutes at 4°C. The RNA-containing aqueous phase was transferred to a new tube, and 500 µL of isopropanol was added for precipitation and incubated for 10 minutes, followed by centrifuging at 12,000 rpm. The RNA pellet was washed with 75% ethanol and centrifuged at 7,500 × g for 5 minutes at 4°C. After removing the supernatant, the ethanol was evaporated at 60°C, and the pellet was resuspended in 50-100 µL of RNase-free water.RNA quality and quantity were assessed via gel electrophoresis and spectrophotometric analysis (Thermo Scientific, USA), with total RNA standardized to 2 ng for qPCR. PET/CT.

Before surgery, all patients underwent standardized PET/CT imaging. To minimize external influences, patients were instructed to avoid physical activity and cold exposure for two days before imaging and to fast for at least six hours. After confirming appropriate blood glucose levels with a capillary test, 8-12 mCi of FDG was administered via an angiocath. Patients then rested for 45-60 minutes to optimize biodistribution and tumor uptake. Following this resting period, they were asked to empty their bladders and lie supine with their arms positioned overhead on the PET/CT scanner bed. Initial guide tomograms were obtained, followed by non-contrast computed tomography (CT) scans, and then PET images captured at 2 mm intervals. The entire imaging procedure took approximately 25 minutes.

Complementary DNA (cDNA) procedure

A commercial kit (abmPoly-A Polymerase) was utilized to add a poly(A) tail to the microRNAs. Selected miRNAs were then reverse transcribed to cDNA using the OneScript® Plus cDNA Synthesis Kit. RNA samples were mixed with the provided reagents on ice and incubated at 25 °C for 10 minutes, followed by 50 °C for 15 minutes, and 85 °C for 5 minutes to ensure proper primer denaturation. The synthesized cDNA was stored at -20 °C for further analysis.

Real-time quantitative PCR

Real-time PCR was performed to assess miR-22, miR-140, and miR-328 expression in 28 samples (14 healthy, 14 cancerous). RNU6 was used as a normalization control [15-16]. The qPCR assays were conducted using the SensiFast Probe No-Rox kit on the Thermo Scientific™ PikoReal™ Real-Time PCR System, with

triplicate reactions. Amplification conditions included initial denaturation at 94°C for 15 minutes, followed by 45 cycles of 94°C for 30 seconds, 59°C for 15 seconds, and 72°C for 30 seconds. Melting curve analysis confirmed product specificity. Expression levels were calculated using the 2^-ΔΔCt method (Livak ve Schmittgen 2001), and diagnostic potential was assessed with ROC curves and cluster analysis.

Statistics

Data were presented as mean ± standard deviation. Statistical significance was determined using Student's t-test or ANOVA, while the Mann-Whitney U test was applied to evaluate PET/CT values. Changes in miRNA expression between healthy and cancerous tissues were assessed using the t-test, followed by ROC analysis for diagnostic grouping. Cluster analysis further explored the diagnostic potential of miRNAs. Pearson correlation analysis was used to examine the relationship between miRNA expression and PET/CT results, with p-values <0.05 considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (Date: 2021-10-20, No: 2021-07). Informed consent was obtained from all participants.

Results

Baseline information on study subjects

This study comprised 14 patients with a median age of 59.5 years (range: 38–74 years). Tumor staging was conducted using the TNM classification based on postoperative pathological data. According to this system, four patients (28.57%) were classified as Stage IA, six patients (42.85%) as Stage IB, two patients (14.28%) as Stage IIA, and one patient each as Stage IIB and IIIB (7.14% each). The median tumor size was 29.42 mm, with a range of 11 to 130 mm. Of the patients, nine had right-sided tumors, and five had left-sided tumors. Axillary metastases were present in six patients (Table 1).

PET/CT

FDG/PET is a method that has proven its sensitivity in palpable breast masses undergoing PET/CT, with SUVmax values related not only to the malignancy of the tumor but also to the size of the lesion. The average SUVmax value of healthy breast tissue was 0.8, based on previous studies [17], and this was used as the reference value for our analysis. In this study, the highest tumor SUVmax value observed was 17.3 in a Stage IB breast cancer patient, while the lowest was 1.2 in a Stage IA patient. The median SUVmax value for the tumors was 5.58. Tumor tissue SUVmax values were compared with the reference value of 0.8 for normal breast tissue. Statistical analysis using the Mann-Whitney U test indicated a significant difference, with a z-score of -2.40067 and p = 0.0164 (p < 0.05). Patient demographics, tumor staging, and SUVmax values are summarized in Table 1.

Expression profiling of select miRNAs

The study examined the expression levels of miR-22, miR-140, and miR-328 in breast cancer tissues compared to healthy tissues, revealing significant downregulation of all three miRNAs in cancerous samples. The median log values for miR-22, miR-140, and miR-328 in healthy tissues were -0.125, 0.78, and 0.03, respectively, while tumor tissues exhibited lower

Table 1. Patient staging, Tumor SUVmax values, and demographics

No	Size (mm)	Grade	Ax. met	HER2	ER	PR	T	N	M	Stage	SUV max Tumor	Age
1	16	2	0	-	+	+	1	0	0	IA	3,3	47
2	13	2	0	-	+	+	1	0	0	IA	1,2	74
3	13	2	1	-	+	+	1	1	0	IB	1,5	66
4	30	2	1	-	+	+	2	1	0	IIA	8,2	61
5	25	2	0	-	+	+	2	0	0	IB	2,24	63
6	130	2	1	+	-	-	4	1	0	IIIB	2,52	45
7	30	2	0	-	-	-	2	0	0	IIB	3,82	69
8	30	2	0	+	+	+	2	0	0	IB	17,3	40
9	17	2	2	+	-	-	1	1	0	IA	1,92	38
10	11	2	2	-	-	-	1	1	0	IB	3,3	74
11	15	2	1	+	+	+	1	1	0	IB	6,91	52
12	12	2	0	-	+	+	1	0	0	IA	4,66	65
13	30	2	0	+	-	-	2	0	0	IIA	11,4	64
14	40	3	0	+	+	+	2	0	0	IB	9,9	75

T: Tumor classification, N: Lymph node involvement, M: Presence of metastasis HER2: Epidermal growth factor 2, ER: Estrogen receptor PR: Progesterone receptor, Ax Met: Axillary metastasis, SUVmax: maximum standardized uptake value

Table 2. Statistical analysis of miR-22, miR-140, and miR-328 expression in healthy and cancer tissues

Micro RNA Type	Pathology Group	Average (S. Deviation)	T Value	P Value (miRNA)	Correlation with PET/CT	P Value (SUV max)	Correlations between miRNAs
miR-22	Healthy	-0.0007 (1.06)	10.523	<0.001	0.049	0.049	miR-22 & miR-140
	Cancer	-4.5086 (1.20)					0.429
miR-140	Healthy	0.000 (1.14)	12.219	<0.001	-0.175	0.049	miR-22 & miR-328
	Cancer	-4.8971 (0.97)					0.012
miR-328	Healthy	0.000 (2.57)	6.903	<0.001	-0.219	0.049	miR-140 & miR-328: -0.341
	Cancer	-5.2414 (1.19)					

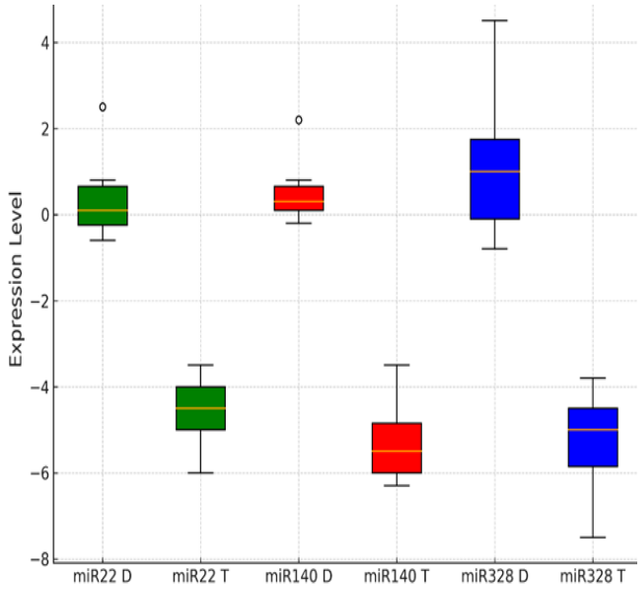

Figure 1. Box plot showing the expression levels of miR-22, miR-140, and miR-328 in healthy (D) and tumor (T) tissues. T

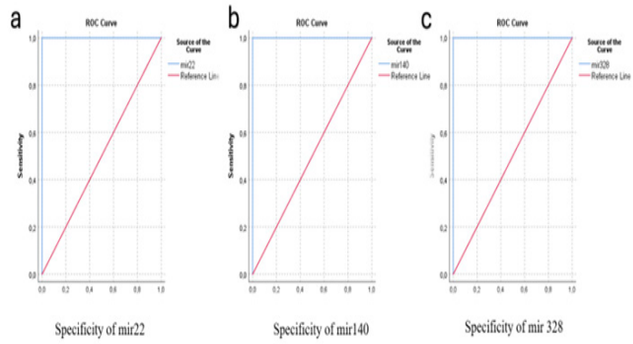

Figure 2. Distribution of mir22(a), mir140(b), and miR-328(c) in healthy and tumor tissue

medians of -4.86, -2.85, and -4.91 (Figure 1).

ROC analysis identified cut-off values of -1.975, -2.780, and -3.535 for miR-22, miR-140, and miR-328, respectively, highlighting their potential as diagnostic biomarkers (Figure 2). Cluster analysis further validated the diagnostic relevance of miR-22 and miR-140, although miR-328 showed some variability in differentiating between healthy and cancerous tissues (Table 2).

All miRNAs showed significant downregulation in cancer tissues ($P < 0.001$). Correlations between miRNAs are provided, indicating moderate relationships between miR-22 and miR-140 ($r = 0.429$) and a weaker relationship between miR-22 and miR-328 ($r = 0.012$). Negative correlations are observed between miR-140 and PET/CT SUVmax ($r = -0.175$) as well as miR-328 and SUVmax ($r = -0.219$).

Discussion

Our study highlights the significant downregulation of miR-22, miR-140, and miR-328 in breast cancer tissues, supporting their potential role as diagnostic biomarkers. Consistent with previous studies, miR-22 was significantly reduced in cancer tissues compared to healthy tissues. This miRNA targets GLUT-1. A key regulator of glucose metabolism and its downregulation has been associated with inhibited cancer cell proliferation and invasion [4], as well as enhanced metastasis potential [18]. We identified a diagnostic cut-off value of -1.975 for miR-22, reinforcing its potential to distinguish between healthy and cancerous tissues.

Similarly, miR-140 showed substantial downregulation in tumor tissues, with a cut-off value of -2.780 established through ROC analysis. miR-140 is known to exert antiglycolytic and antiproliferative effects by targeting GLUT-1 [9], and its downregulation has been linked to poor prognosis in breast cancer [5]. Our cluster analysis supported miR-140's diagnostic value, showing clear differentiation between healthy and cancerous tissues.

miR-328 also exhibited significant downregulation, though it demonstrated some variability in cluster analysis, with a subset of healthy tissues misclassified as cancerous. This miRNA also directly targets GLUT-1[19] and plays a critical role in breast cancer. ROC analysis for miR-328 revealed a cut-off value of -3.535, indicating its potential as a diagnostic marker, although its clustering performance was less precise than miR-22 and miR-140.

Both miR-22 and miR-140 showed strong concordance with pathology results, while miR-328 exhibited variability in differentiating between healthy and cancerous tissues, as revealed by cluster analysis (Figure 4, Table 2). The expression levels of miR-22, miR-140, and miR-328 were significantly reduced in tumor tissues compared to healthy tissues (Figure 2, Table 2). The bar plot illustrates the relative expression ratios of miR-22 to miR-140 and miR-22 to miR-328 in both healthy and tumor tissues. In tumor samples, these ratios significantly altered, with a notable decrease in the miR-22/miR-140 and miR-22/miR-328 ratios, indicating dysregulation of these miRNAs in cancer. ROC analysis for all three miRNAs demonstrated that a greater distance between the blue line (representing miRNA expression) and the red line (representing pathology results) indicates higher diagnostic capability. The ROC plots showed the blue line forming an outer frame, highlighting their potential as diagnostic markers. Additionally, the expression levels of miR-22, miR-140, and miR-328 were correlated with tumor tissue SUVmax values.

PET/CT and miRNA expression

Our study demonstrated a significant downregulation of miR-22, miR-140, and miR-328-3p in breast cancer tissues, consistent with findings in the literature. Despite this, we did not observe a significant correlation between the expression levels of these miRNAs and SUVmax values from PET/CT scans. While glucose metabolism and FDG uptake are closely related to GLUT-1 expression [20], prior studies have reported mixed results regarding the relationship between GLUT-1 and FDG retention, suggesting that other proteins may influence FDG uptake [20, 21].

In this study, we aimed to explore whether miRNA expression changes in healthy and cancerous tissues correlate with PET/CT findings. Although significant downregulation of miR-22, miR-140, and miR-328 was observed in tumor tissues compared to healthy controls ($p<0.05$) (Table 3), Pearson correlation analysis revealed no statistically significant association between miRNA expression levels and PET/CT results ($p>0.05$). This suggests that while these miRNAs are downregulated in tumor tissues,

their expression does not directly correspond with PET/CT imaging data in this context.

Conclusion

Identifying a correlation between miRNA expression and PET/CT data could facilitate the development of novel tumor markers for cancer monitoring and diagnosis. Our study found decreased expression of miR-22, miR-328, and miR-140 in malignant tissues compared to healthy tissues; however, no correlation was established with PET/CT scan results. The majority of our patients had early-stage breast cancer, with only two patients at Stage IIB and IIIB. This may explain the lack of correlation, as more advanced stages typically show higher metabolic activity and SUVmax values. Additionally, SUVmax can be influenced by various factors, including patient body mass index, blood glucose levels, and differences in PET/CT protocols [22]. Furthermore, the complexity of metabolic processes in tumors may involve additional regulatory mechanisms beyond miRNA expression, which could account for the lack of correlation between miRNA levels and 18F-FDG uptake. Breast tissue density directly affects SUV values, with denser tissues resulting in higher SUV values [17].

In conclusion, our findings corroborate the significant downregulation of miR-22, miR-140, and miR-328 in tumor tissues. However, the absence of a correlation with PET/CT SUVmax values suggests a need for further research to understand the complex interactions between miRNA expression, glucose metabolism, and imaging biomarkers in breast cancer. MiRNAs may serve as valuable diagnostic and prognostic tools, warranting exploration of larger sample sizes with diverse tumor stages and consideration of additional oncogenic or tumor-suppressive miRNAs in future studies.

Study Limitations

This study is limited by a small and heterogeneous sample size, predominantly consisting of participants with early-stage breast cancer, which may restrict the generalizability of the findings. Specifically, only one patient was at Stage IIB and another at Stage IIIB, limiting the applicability of the results to advanced breast cancer, where miRNA expression and metabolic activity may vary. The cross-sectional design further restricts causal inferences between miRNA expression levels and PET/CT SUVmax values, underscoring the need for longitudinal studies to elucidate this relationship. Additionally, variations in PET/CT imaging protocols and patient preparation factors, such as fasting state and body mass index, could affect SUVmax measurements. Lastly, potential confounding variables, including hormonal status and treatment history, were not controlled for, which may influence both miRNA expression and PET/CT outcomes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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