BMC Cancer

RESEARCH Open Access

Exploring the role of tumor to background parenchymal ratio of the [18F]FLT PET/CT measures in determining response to neoadjuvant chemotherapy in breast cancer: a multicenter study

Alisa Mohebbi[1,2], Fatemeh Asli[1,2], Saeed Mohammadzadeh[1,2], Ali Abbasian Ardakani[3], Seyed Mohammad Tavangar[4,5] and Afshin Mohammadi[6*]

Abstract

Objective To investigate the potential of 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography computed tomography ([18F]FLT PET/CT) in predicting locally advanced breast cancer response to neoadjuvant chemotherapy (NAC), focusing on the role of tumor to background parenchymal ratio (TBR) of the standardized uptake value (SUV) ratios.

Methods This retrospective analysis utilized prospectively collected data from the multicenter ACRIN 6688 observational trial. It used a dataset of 90 patients from 17 centers with confirmed breast cancer who planned to receive NAC followed by surgery as part of their treatment. Three [18F]FLT PET/CTs were scheduled for each participant at three time points to obtain serial tumor dimensions and TBR values of SUV ratios: before therapy initiation, after completion of the first cycle, and after the termination of chemotherapy.

Results Tumor size, TBRmean, and TBRmax all showed poor diagnostic performance in predicting pathological response in all three scans, with the highest AUC of 0.682. The combined model of PET and CT parameters exhibited the best diagnostic performance, significantly improving the diagnostic values of the first and third PET/CT scans, with AUCs of 0.731 and 0.833 for each scan and 0.875 for their percentage change. The mid-NAC scan did not seem to show any considerable diagnostic value in either of the models, with the highest AUC being 0.626.

Conclusion The combined model, having both tumor size and uptake values as its components, performed well in predicting the tumor's pathological response to chemotherapy, particularly when compared to each component's performance alone, which suggests the complementary role of functional (i.e., TBR) and anatomical (i.e., size) parameters.

*Correspondence:
Afshin Mohammadi
mohammadi.a@umsu.ac.ir

Full list of author information is available at the end of the article

Keywords Breast cancer, Computed tomography (CT), Positron emission tomography/computed tomography (PET/CT), 18F-fluorothymidine ([18F]FLT), Neoadjuvant chemotherapy (NAC), Diagnostic test accuracy (DTA)

Introduction

Breast cancer, accounting for 23% of cases of all cancer diagnoses worldwide, represents the most prevalent cancer diagnosed in females and the fifth leading cause of cancer-related death among this population [1, 2]. Locally advanced breast cancer (LABC) is commonly defined as tumors inoperable at presentation with no signs of distant metastases. In other words, these lesions seem to have a poor prognosis with only loco-regional treatments [3, 4]. The gold standard therapy in LABC is neoadjuvant chemotherapy (NAC) combined with surgical resection. Patients undergoing NAC are proven to have higher chances of breast-conserving surgery due to down-staging of the primary lesions [5]. The ideal response to NAC is pathologic complete response (pCR), which is thought to be a strong indicator of improved survival and desirable prognosis. The challenge with pCR for response assessment of NAC is bi-fold; first, it can only be confirmed after surgical resection, and second, only a proportion of patients will reach pCR after receiving NAC and surgery [5, 6]. Bearing in mind the low rates of achieving pCR after chemotherapy, response monitoring early after initiation of the treatment can lead to discontinuation of ineffective and potentially toxic agents, making room for treatment adjustments, and switching to alternative options for non-responders.

Currently, tumor response to therapy is routinely evaluated by measuring changes in tumor size. When exposed to chemotherapeutic agents, changes in tumor dimensions may occur long after the molecular response [6, 7]. Molecular imaging modalities have gained attention regarding their established role in detecting tumor responses. 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography/computed tomography ([18F]FLT PET) is among these methods. Using [18F]FLT, a thymidine kinase substrate, as the radiotracer can quantify cellular proliferation and act as a promising tool in early response assessment. Early changes found by [18F]FLT are shown to correlate more with longer-term treatment outcomes than other parallel radiotracers, such as 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG) [8]. Serving as a promising non-invasive tool, several studies investigated the possible role of different parameters of [18F]FLT PET/CT in predicting long-term treatment outcomes. Changes in standardized uptake values (SUVs) throughout the course of treatment have been widely studied as an indicator of tumor response to chemotherapy for different types of cancers as well as breast cancer [5–7]. SUV, however, tends to be affected by various factors, including imaging protocols, equipment variability, and some patient characteristics. Therefore, some clinicians may consider this ratio a relative value that is subjected to variability based on different conditions. To solve the problem with SUV and in order to compensate for the effects of some non-adjustable variables, the relative ratio of varying SUV measures (e.g., SUVmax, SUVmean) of the tumor to normal parenchyma refered to as tumor to background parenchymal ratio (TBR) can be used as an alternative [9, 10].

To our knowledge, no studies have investigated the role of TBR of different SUV parameters for [18F]FLT in response assessment of breast cancer. Accordingly, this study is designed with the main objective of exploring the role of TBR of the SUV of [18F]FLT radiotracer in monitoring tumor response to NAC in locally advanced breast cancer using [18F]FLT PET/CT imaging and comparing it with CT measure performances.

Materials and methods

Patients in this analysis were drawn from the ACRIN 6688 dataset, which originated from a multicenter, prospective, observational phase II clinical trial. Our study is a retrospective analysis of these prospectively collected data. The protocol of the present study has been registered in advance at https://osf.io/fvg5u/) on the Open Science Framework (OSF) platform (Appendix A). As for reporting our findings, we employed the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines. The study is approved by the institutional review board of each of the contributory centers. A written informed consent form was signed by all participants. Patients were studied and analyzed from the ACRIN 6688 dataset, a multicenter prospective observational study [6].

Study design and patient selection

Ninety histologically confirmed breast cancer patients with locally advanced breast cancer or primary tumor size ≥ 2 cm, eligible for NAC and subsequent surgical resection, were recruited in this study. Patients with stage IV breast cancer were omitted. In participants with multiple primary lesions, the maximum number of three primary tumors was included per patient, giving the total number of 118 primary tumors. Three [18F]FLT PET/CT studies were planned for each individual: [18F]FLT1 or pre-NAC, at baseline, within 4 weeks before chemotherapy initiation; [18F]FLT2 or mid-NAC, performed within 5–10 days after initiating the first cycle and before starting the second one; and [18F]FLT3 or post-NAC,

planned after termination of chemotherapy and within 3 weeks before surgical resection.

Pre-NAC PET/CT scans were successfully completed for 81 (90.0%) enrolled patients. Of these, 66 patients (73.3%) underwent the mid-NAC PET/CT, and 52 patients (57.7%) completed the post-NAC PET/CT scan. The reduction in the number of patients with complete imaging at each time point was due to loss to follow-up, which we defined as failure to undergo the scheduled PET/CT scan within the specified acquisition window. The reasons for loss to follow-up were documented and included: (1) voluntary withdrawal of consent by the patient for personal or medical reasons; (2) disease progression or clinical deterioration necessitating a change in the planned treatment regimen before the scheduled imaging; (3) logistical constraints, such as scheduling conflicts, transportation difficulties, or inability to attend appointments; and (4) technical failure during image acquisition, including scanner malfunction or incomplete data capture.

Imaging protocol and interpretation

[18F]FLT was utilized with the approval of the National Cancer Institute. A whole body image (5-7 bed positions) was acquired 60 min (mean 70 min; range 50–101 min) after the administration of 2.6 MBq/kg (mean 167 MBq; range 110–204 MBq) of radiotracer. PET/CT scanners were all calibrated and validated by ACRIN by reviewing the images and testing the SUVs applying a uniform phantom. In addition to whole-body static [18F]FLT PET/CT imaging, a regional dynamic acquisition was performed in a subset of individuals. According to the original ACRIN 6688 protocol, dynamic imaging was initially required for all participants and consisted of a 60-min dynamic scan of the primary tumor region immediately following tracer injection. However, after a protocol amendment to facilitate recruitment and reduce patient burden, dynamic imaging became optional and was performed only in the first approximately 20 participants or at sites with the necessary technical capability and patient consent. The rationale for including dynamic acquisitions was to enable kinetic modeling of [18F]FLT uptake, such as calculation of the influx constant (Ki), which may provide additional information about tumor proliferation beyond static SUV measurements. As dynamic imaging was not performed in the majority of patients, no separate results from these acquisitions are reported, and all primary analyses in this study are based on static PET data. As mentioned before, three [18F]FLT PET/CT scans were in order. All consecutive imaging sessions for each participant were obtained by the same or technically equivalent PET/CT scanners. Surgical resection of the primary tumor by either segmental or total mastectomy and evaluation of axillary lymph nodes were performed after completing NAC.

After transferring to the ACRIN Core Laboratory, quality control, archiving, and analysis of all [18F]FLT PET/CT images were performed. The supervision of image review and region placement was undertaken by two nuclear medicine board-certified physicians experienced in PET/CT analysis blinded to patients' outcomes and characteristics. Afterward, for both primary and non-primary tumors at the [18F]FLT1 scan, the volume of interests (VOIs) were placed over the area having the highest activity. For every identified site on [18F]FLT1, on [18F]FLT2 and [18F]FLT3 scans, VOIs were constructed with the guidance of CT localization and residual tumor uptake, if present. Then, two independent experts reviewed the VOIs for [18F]FLT1, [18F]FLT2, and [18F]FLT3 blindly. Subsequently, corresponding values of TBRmax, and TBRmean were recorded for the SUV components as the ratio of tumor to normal breast parenchyma uptakes. Considering the difficulties regarding determining tumor boundaries from CT scans and the variation in employed scanners, partial volume corrections of the SUVs were not attempted. Tumor size defined as the largest tumor diameter, was assessed using the low-dose CT component of the [18F]FLT PET/CT scan, which was acquired for anatomical localization and attenuation correction during each PET/CT session.

Histopathology analysis

The paraffin specimens from diagnostic and post-surgical tissue samples were all collected and delivered to the Core Pathology Laboratory at Virginia Commonwealth University for further evaluation. A representative sample was considered satisfactory in cases of present residual tumors on post-therapy specimens. However, if no residual tumor was discovered either on original pathology reports or post-surgical samples, the entire tumor bed had to be sectioned to confirm a pCR. A pCR was only documented if no signs of viable or residual tumor were found after analysis of all sections. An absence of viable invasive tumors in histopathologic samples of post-surgical sections was regarded as pCR. Residual cancer burden (RCB) was also determined at the pathology laboratory as described in detail by Symmans et al. [11]. Partial response was defined as a reduction of more than 50% in the product of the two largest perpendicular dimensions of the breast mass. If the tumor demonstrated chemoresistance or substantial residual disease, it was categorized as a no response tumor.

Statistical analysis

STATA 17.0 and MedCalc 22.0 were employed to perform the statistical analyses. A pairwise Pearson correlation analysis was used to check for the associations

between different variables. The percentage change was defined as the percentage reduction of the imaging parameter from baseline to final divided by the baseline level. Models' performances were examined using receiver operating characteristic (ROC) curve analysis. The optimal cut-point values and corresponding sensitivities and specificities were determined using Youden's index. Regarding ROC curve analysis, true positive and false positive were respectively defined as a complete response based on imaging modality in a patient with a pCR and without a pCR. True negative and false negative, on the other hand, were delineated as incomplete responses as determined by imaging findings in patients with pCR and non-pCR pathological results. Finally, a combined role of PET parameters (i.e., TBRmean and TBRmax) and tumor size were also created using binary logistic regression and were compared to PET and CT parameters alone. A p-value of < 0.05 was considered statistically significant.

Results

Patients characteristics

A total of 90 female patients with 118 primary tumors from 17 centers fulfilled the primary eligibility criteria. Of 118 tumors, 97 underwent histopathological assessment, with 20 showing pCR and 77 non-pCR. To avoid the bias effects of a limited number of patients with a high number of primary tumors constituting a large portion of overall included tumors, only up to three tumors were included per patient. Details on patients' characteristics are provided in Table 1. While the PET/CT scan findings were available for all participants for pre-NAC, as for the mid-NAC and post-NAC scans, a rather smaller number of patients had the required data due to loss to follow-up.

Correlation findings

Figure 1 demonstrates the pairwise Pearson correlation coefficients between different [18F]FLT PET/CT derived features, including tumor size, TBRmean, and TBRmax values, as well as clinical variables such as pathology response and the number of involved lymph nodes. Altogether, it could be stated that CT-derived size measures were weakly correlated with both TBR-related values, potentially suggesting their complementary and additive roles to each other in predicting tumor response to treatment. Pre-NAC tumor size was weakly correlated with [18F]FLT uptake findings, with the best correlation coefficient being 0.393. For mid-NAC and post-NAC, these values were 0.466 and 0.422.

Regarding the involved lymph nodes, CT-derived tumor size at the third scan showed moderate associations with nodal status, with a correlation coefficient of 0.583. Additionally, tumor size percentage change correlated with lymph node status (coefficient of 0.351).

Participants' residual cancer burden demonstrated moderate correlations with CT findings (i.e., mainly post-NAC tumor size and percentage change in tumor size with respective values of 0.561 and 0.376). Moderate association was also observed with [18F]FLT uptake findings, mainly with post-NAC TBRmean and TBRmax and the percentage change of TBRmean and TBRmax (coefficients of 0.494 to 0.586).

Tumor size analysis

As illustrated in Fig. 2A, the ROC curve analysis for CT-derived tumor size in predicting tumor response to therapy showed an area under the curve (AUC) of 0.615, 0.626, and 0.606 for baseline, mid-NAC, and post-NAC [18F]FLT PET/CTs, respectively, and the AUC for tumor size percentage change was 0.642. Thus, tumor size demonstrates poor diagnostic value in predicting pCR. Table 2 also presents the t-test results for CT parameters for pCR vs. non-pCR, with the p-values being mainly non-significant, confirming the results by ROC analysis.

TBRmean analysis

Regarding the ROC analysis for TBRmean, the AUC for the three scheduled [18F]FLT PET/CT scans and the percentage change of TBRmean were as follows: 0.558 for pre-NAC, 0.566 for mid-NAC, 0.682 for post-NAC, and 0.666 for the percentage change of TBRmean (Fig. 2B). Based on these findings, TBRmean proved to be of poor diagnostic value in predicting pCR after chemotherapy in patients with breast cancer. The TBRmean t-test results in Table 2 were also non-significant, supporting these findings.

TBRmax analysis

Figure 2C shows the ROC curves for TBRmax. Based on ROC analysis, the AUC levels for baseline, mid-NAC, post-NAC, and percentage change of TBRmax hovered between 0.526 and 0.662, indicating poor diagnostic performance in predicting pathological response for TBRmax as well. The TBRmax independent t-test results in Table 2 also had non-significant p-values, supporting these findings.

Combined CT and PET performance

A combined model integrating TBRmean, TBRmax, and tumor size substantially improved AUCs compared to the abovementioned models (Fig. 2D). The AUCs for the combined model were as follows: 0.731 for pre-NAC, 0.591 for mid-NAC, 0.833 for post-NAC, and 0.875 for percentage change of the values, showing good to excellent diagnostic performance, especially for post-NAC scan and the percentage change. Details regarding the diagnostic performance of each TBRmean, TBRmax,

Table 1 Patient characteristics

Variable			
Age (mean (CI)) ($n=90$)			51.2 (48.9 to 53.4)
Menopausal status ($n=90$)	Pre-menopausal		42 (46.7%)
	Post-menopausal		47 (52.2%)
	Unknown menopausal status		1 (1.1%)
Surgical procedure ($n=90$)	Lumpectomy		16 (17.8%)
	Simple mastectomy		11 (12.2%)
	Modified radical mastectomy		33 (36.7%)
	Other surgical procedures		6 (6.7%)
	Unknown surgical status		24 (26.7%)
Involved side ($n=90$)	Right		44 (48.9%)
	Left		45 (50%)
	Bilateral		1 (1.1%)
Receptor status ($n=90$)	ER ($n=90$)	Negative	40 (44.4%)
		Positive	49 (54.4%)
		Unknown receptor status	1 (1.1%)
	PR ($n=90$)	Negative	51 (56.7%)
		Positive	38 (42.2%)
		Unknown receptor status	1 (1.1%)
	HER2 ($n=90$)	Negative	54 (60%)
		Positive	32 (35.5%)
		Unknown receptor status	4 (4.4%)
Primary cancer type at diagnosis ($n=90$)	Invasive ductal		71 (78.9%)
	Ductal carcinoma in situ		5 (5.5%)
	Invasive lobular		4 (4.4%)
	Mixed invasive ductal and lobular		4 (4.4%)
	Poorly differentiated adenocarcinoma		1 (1.1%)
	Infiltrating lobular carcinoma		1 (1.1%)
	Metastatic lobular carcinoma		1 (1.1%)
	Invasive high grade carcinoma		1 (1.1%)
	Invasive mammary carcinoma with associated focal ductal carcinoma in-situ		1 (1.1%)
	Unknown histological subtype		1 (1.1%)
Primary Nottingham grade ($n=90$)	Grade 1		2 (2.2%)
	Grade 2		19 (21.1%)
	Grade 3		44 (48.9%)
	Not assessed		25 (27.8%)
Stage at entry ($n=90$)	I		2 (2.2%)
	II		43 (47.8%)
	III		44 (48.9%)
	Not assessed		1 (1.1%)
Post-treatment pathology response ($n=90$)	Invasive breast carcinoma		83 (92.2%)
	Inflammatory breast carcinoma		2 (2.2%)
	Ductal carcinoma in situ		2 (2.2%)
	Breast carcinoma, NOS		3 (3.3%)

CI confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *NOS* not otherwise specified

tumor size alone, and their combined model are presented in Table 3.

Discussion

Over the past decade, functional imaging modalities, mainly PET scans by various radiotracers, have been the focus of many studies regarding their role in early tumor response assessments in various types of cancers [12–15]. Of these, PET/CT with [18F]FLT radiotracer particularly attracted attention regarding its ability to quantify cellular proliferative function. [18F]FLT acts as a substrate for thymidine kinase 1, a key enzyme involved in DNA synthesis. As the most distinctive feature of malignant cells is believed to be their high rates of proliferation, [18F]FLT is arguably considered to be one of the main radiotracers in assessing tumor response to treatments [16, 17].

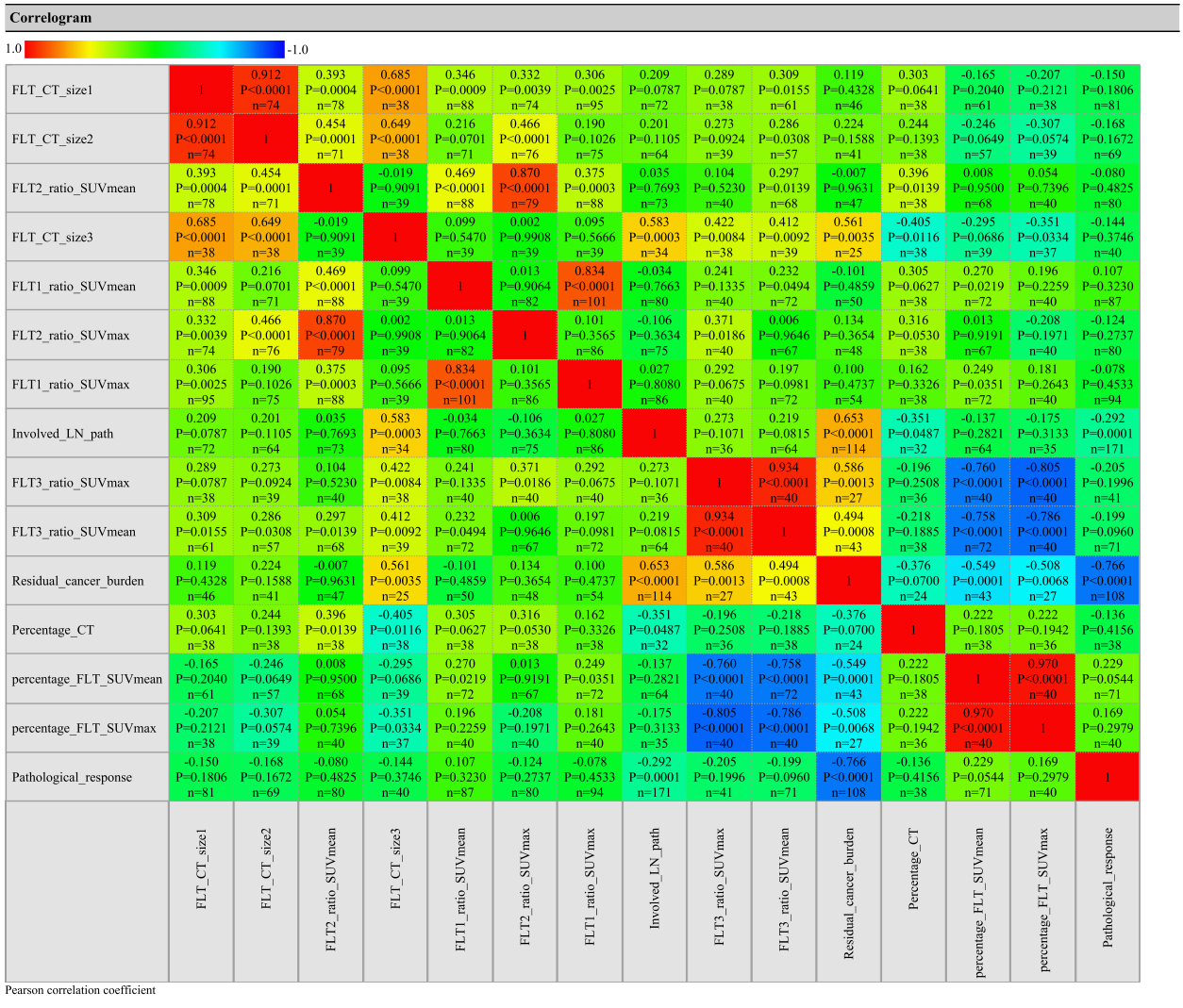

Fig. 1 Pairwise Pearson correlation analysis

Exploring the literature, several studies investigated the utility of [18F]FLT in assessing breast cancer response to treatment, especially NAC, by evaluating both short- and long-term outcomes. The findings altogether are somewhat controversial and variable. Not to mention, most of the studies admitted to several limitations, mostly having relatively small sample sizes (i.e., < 10 patients) held in common among almost all of them, which can greatly influence the results [5, 7, 12, 18, 19]. Also, none of the previous studies evaluated the different adjusted TBR roles in response assessment and sufficed to assess SUV parameters only [5–7, 12, 18, 19]. In our study, we tried to address and overcome these limitations.

SUVs are proven to be widely affected by several variables, including patients'body composition and imaging protocols and equipment, making them impossible to rely on as an absolute value. To address this concern, many clinicians propose the use of a reference tissue, most commonly surrounding normal tissue and, in this case, normal breast parenchyma, to obtain a ratio of tumor to normal parenchyma uptake, which can be used as a substitute for relative values of SUV [9, 10]. In our investigation, for the first time, we decided to use TBR (SUV ratios) as an alternative to the previously used SUV when assessing tumor response to NAC in [18F]FLT. Our findings regarding mean values of TBRmean and TBRmax showed no statistically significant differences between pCR and non-pCR groups. Changes in either TBR values did not seem to correlate significantly with pCR either. Although a marginally significant ($p = 0.0544$) difference was observed between the two groups with the percentage change in TBRmean levels, the mean reduction in TBRmean was 79.2% in the pCR group compared to 57.9% in the non-pCR group. In line with our findings,

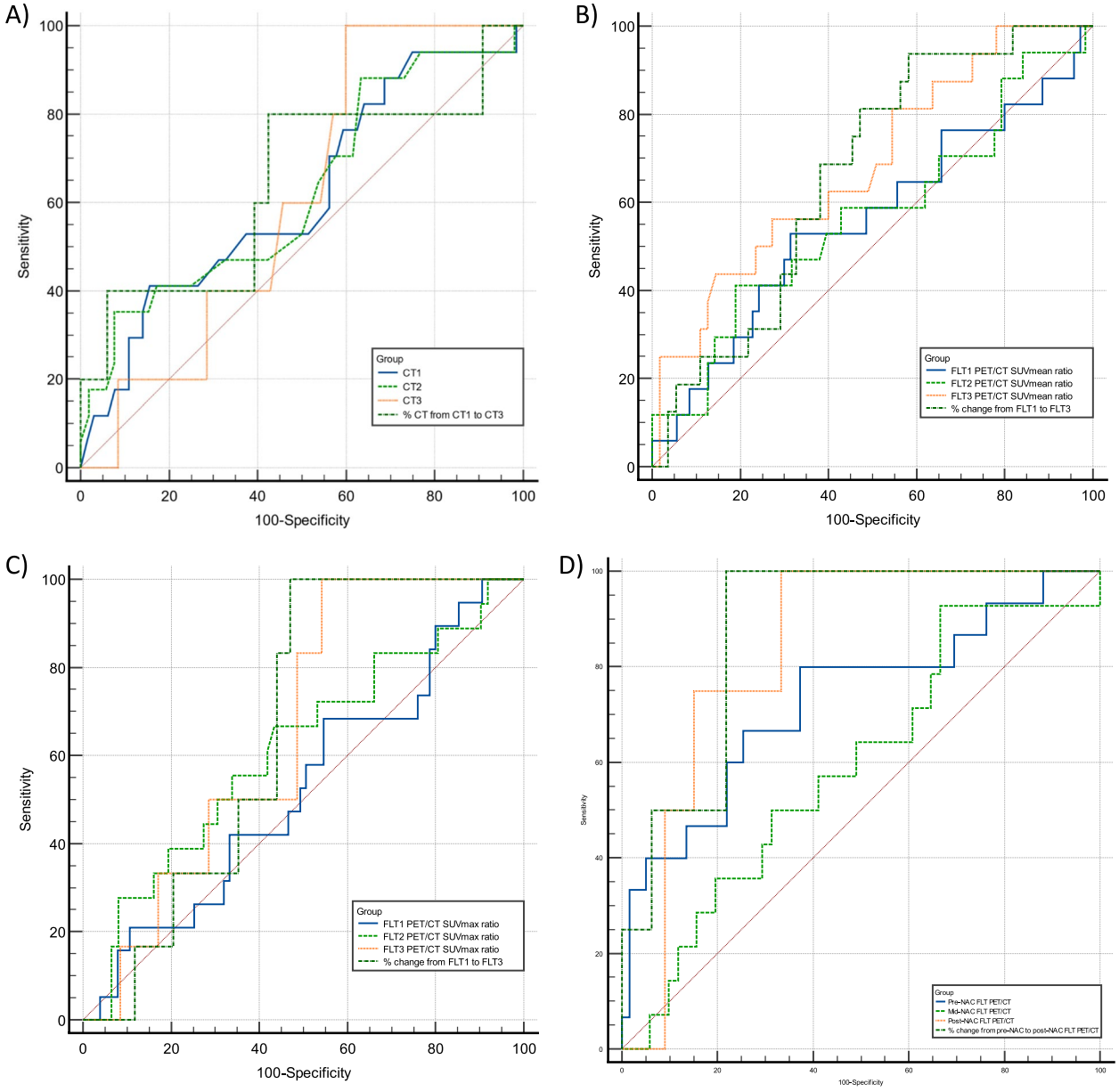

Fig. 2 **A** Receiver operating characteristic (ROC) curve for tumor size. **B** ROC curve for TBRmean. **C** ROC curve for TBRmax. **D** ROC curve for the combined model

a study by Woolf et al. [20] failed to prove a significant relation between baseline, post-chemotherapy, and change in SUVmax levels with pathological response to NAC in patients with primary breast cancer.

As explained before, the changes in tumor dimensions, commonly measured by serial CT scans, have been widely used in tumor response assessment, particularly since the establishment of the Response Evaluation Criteria in Solid Tumors (RECIST) in 2000 [21]. Our findings showed no significant differences regarding tumor size in either time points or the percentage change of the tumor size in the pCR group compared to the non-pCR group (Table 2). Reviewing the ROC curves for each of the variables alone (Fig. 2A-C), it can be deduced that neither the size, TBRmean, TBRmax, nor their percentage change could acceptably predict pCR in patients, with the AUCs hovering between 0.526 and 0.682. As displayed in Fig. 2D, merging all the variables in a unified model substantially improved the AUCs. This model yielded AUCs of 0.731, 0.591, and 0.833 for pre-NAC, mid-NAC, and post-NAC [18F]FLT PET/CT scans, indicating fair to good diagnostic values in predicting pathologic response except for the mid-NAC scan. Regarding the percentage change of the variables, this model gave an AUC of 0.875, exhibiting the best performance in predicting pathological response. Therefore, it seems more efficient to bring

Table 2 [18F]FLT PET/CT findings based on pathological response

		Complete tumor response	Non-complete tumor response	T-test *p*-value	Best cut point
Mean tumor size	Baseline [18F]FLT PET/CT	3.0 (CI = 1.8 to 4.2)	3.9 (CI = 3.3 to 4.5)	0.180	≤ 1.8 (CI = ≤ 1.3 to ≤ 5.7)
	Mid-NAC [18F]FLT PET/CT	2.7 (CI = 1.6 to 3.8)	3.6 (CI = 2.9 to 4.2)	0.167	≤ 1.2 (CI = ≤ 0.8 to ≤ 2.8)
	Post-NAC [18F]FLT PET/CT	1.6 (CI = 0.9 to 2.3)	2.3 (CI = 1.7 to 2.9)	0.374	≤ 1.7 (CI = ≤ 1.6 to ≤ 1.8)
	Percent change %	32.3 (CI = −10.9 to 75.5)	44.1 (CI = 33.7 to 54.5)	0.415	≥ 38.2 (CI = ≥ 4.1 to ≥ 84.3)
Mean TBRmean	Baseline [18F]FLT PET/CT	14.8 (CI = 8.9 to 20.6)	12.3 (CI = 10.2 to 14.3)	0.323	≤ 13.7 (CI = ≤ 2.4 to ≤ 25.2)
	Mid-NAC [18F]FLT PET/CT	6.6 (CI = 3.8 to 9.3)	7.7 (CI = 6.2 to 9.2)	0.482	≤ 3.2 (CI = ≤ 1.4 to ≤ 11.1)
	Post-NAC [18F]FLT PET/CT	1.9 (CI = 1.2 to 2.6)	4.5 (CI = 2.9 to 6.2)	0.096	≤ 1.2 (CI = ≤ 0.9 to ≤ 2.3)
	Percent change%	79.2 (CI = 71.0 to 87.3)	57.9 (CI = 46.4 to 69.4)	0.054	> 60.2 (CI = > 25.3 to > 73.6)
Mean TBRmax	Baseline [18F]FLT PET/CT	10.5 (CI = 7.0 to 14.0)	12.3 (CI = 10.0 to 14.6)	0.453	≤ 10.5 (CI = ≤ 5.3 to ≤ 30.0)
	Mid-NAC [18F]FLT PET/CT	6.8 (CI = 4.1 to 9.5)	12.8 (CI = 7.0 to 18.5)	0.273	≤ 7.1 (CI = ≤ 3.1 to ≤ 19.4)
	Post-NAC [18F]FLT PET/CT	2.2 (CI = 1.1 to 3.3)	6.5 (CI = 3.8 to 9.1)	0.199	≤ 2.7 (CI = ≤ 2.4 to ≤ 3.6)
	Percent change %	68.9 (CI = 51.5 to 86.2)	46.1 (CI = 27.9 to 64.2)	0.297	> 54.8 (CI = > 51.7 to > 85.8)

TBR tumor to background parenchymal ratio, *FLT* 18F-fluorothymidine, *NAC* neoadjuvant chemotherapy, *CI* confidence interval, *PET* positron emission tomography, *CT* computed tomography

Table 3 Diagnostic findings of [18F]FLT PET/CT measures

		Sensitivity	Specificity	AUC
Tumor size	Baseline [18F]FLT PET/CT	41.1 (CI = 18.4 to 67.1)	84.3 (CI = 73.1 to 92.2)	0.615 (CI = 0.501 to 0.721)
	Mid-NAC [18F]FLT PET/CT	35.2 (CI = 14.2 to 61.7)	92.3 (CI = 81.5 to 97.9)	0.626 (CI = 0.501 to 0.739)
	Post-NAC [18F]FLT PET/CT	60.0 (CI = 14.7 to 94.7)	54.2 (CI = 36.6 to 71.2)	0.606 (CI = 0.439 to 0.756)
	Percent change %	57.5 (CI = 39.2 to 74.5)	80.0 (CI = 28.4 to 99.5)	0.642 (CI = 0.471 to 0.791)
TBRmean	Baseline [18F]FLT PET/CT	68.5 (CI = 56.4 to 79.1)	52.9 (CI = 27.8 to 77.0)	0.558 (CI = 0.447 to 0.664)
	Mid-NAC [18F]FLT PET/CT	41.1 (CI = 18.4 to 67.1)	80.9 (CI = 69.1 to 89.8)	0.566 (CI = 0.451 to 0.677)
	Post-NAC [18F]FLT PET/CT	43.7 (CI = 19.8 to 70.1)	85.4 (CI = 73.3 to 93.5)	0.682 (CI = 0.561 to 0.787)
	Percent change %	93.7 (CI = 69.8 to 99.8)	41.8 (CI = 28.7 to 55.9)	0.666 (CI = 0.544 to 0.773)
TBRmax	Baseline [18F]FLT PET/CT	68.4 (CI = 43.4 to 87.4)	45.3 (CI = 33.8 to 57.3)	0.526 (CI = 0.421 to 0.630)
	Mid-NAC [18F]FLT PET/CT	66.6 (CI = 41.0 to 86.7)	56.4 (CI = 43.3 to 69.0)	0.613 (CI = 0.498 to 0.720)
	Post-NAC [18F]FLT PET/CT	83.3 (CI = 35.9 to 99.6)	51.4 (CI = 34.0 to 68.6)	0.657 (CI = 0.493 to 0.798)
	Percent change %	100.0 (CI = 54.1 to 100.0)	52.9 (CI = 35.1 to 70.2)	0.662 (CI = 0.495 to 0.803)
Combined model	Baseline [18F]FLT PET/CT	80.0 (CI = 51.9 to 95.7)	62.7 (CI = 49.1 to 75.0)	0.731 (CI = 0.615 to 0.828)
	Mid-NAC [18F]FLT PET/CT	92.8 (CI = 66.1 to 99.8)	33.3 (CI = 20.8 to 47.9)	0.591 (CI = 0.462 to 0.711)
	Post-NAC [18F]FLT PET/CT	75.0 (CI = 19.4 to 99.4)	84.8 (CI = 68.1 to 94.9)	0.833 (CI = 0.675 to 0.935)
	Percent change%	100.0 (CI = 39.8 to 100.0)	78.1 (CI = 60.0 to 90.7)	0.875 (CI = 0.722 to 0.961)

TBR tumor to background parenchymal ratio, *[18F]FLT* 18F-fluorothymidine, *AUC* area under the curve, *CI* confidence interval, *NAC* neoadjuvant chemotherapy, *PET* positron emission tomography, *CT* computed tomography

together the anatomical findings from CT scans and the results of functional imaging modalities to boost the diagnostic values rather than completely abandoning anatomical methods or replacing them with functional modalities. To further support this hypothesis, we can refer to our correlogram findings (Fig. 1), representing the correlation coefficients of imaging and pathological findings. As mentioned before, the overall correlation between tumor size and [18F]FLT uptake values was altogether considered weak, possibly suggesting complementary roles for these variables.

As for the mid-NAC [18F]FLT PET/CT scan performed around one week after the commencement of chemotherapy, based on our findings, all three variables (TBRmean, TBRmax, and tumor size), alone and integrated into the combined model, failed to provide acceptable diagnostic performance, with the highest AUC being 0.626. Therefore, it would be reasonable, based on our findings, to consider omitting the mid-NAC scans, liberating the patients from the cost and radiation of a futile PET/CT scan. Additionally, much similar to our results, Woolf et al. [20] reported no diagnostic values for their second [18F]FLT PET scan, obtained 7–14 days after initiation of chemotherapy, which can be regarded as the equivalent to our mid-NAC scan. Furthermore, Kostakoglu and colleagues [6] only found marginal predictive values for percentage change in SUVmax between their baseline and second [18F]FLT scans (performed around one week before and after starting chemotherapy) concerning differentiating pCR from non-pCR groups, further questioning the need for an early scan after the initiation of chemotherapy. Although our findings weren't able to support the role of [18F]FLT PET scan in early response assessment of primary breast cancer to NAC, obtaining the scan later in the course of treatment might still show promising results, considering most patients may receive at least three cycles of NAC before undergoing surgery. Looking at AUCs for tumor size, there was no significant improvement over time when compared to the previous ones; while both TBR values showed improvement in AUCs over time, suggesting the possibility for a later mid-NAC scan to perform well as an early indicator of tumor response. Therefore, we would suggest that future studies consider performing their mid-NAC scan at a different time point later in the treatment. Also, investigating the role of combined PET/MRI scans would be suggested for future directions, as MRI is considered as the modality of choice in assessing breast tumors' anatomical features. Furthermore, the findings from our combined model showed good performance in predicting pathological response to treatment for both pre- and post- therapy scans and their percentage change, which can guide clinicians in selecting individuals benefiting from a more extensive and potent course of chemotherapy before surgical management. So, in order to outline our key findings, we should emphasize integrating tumor size and [18F]FLT uptake indicators, which led to significant improvement in AUCs in predicting pathological response based on our findings. Finally, a comprehensive

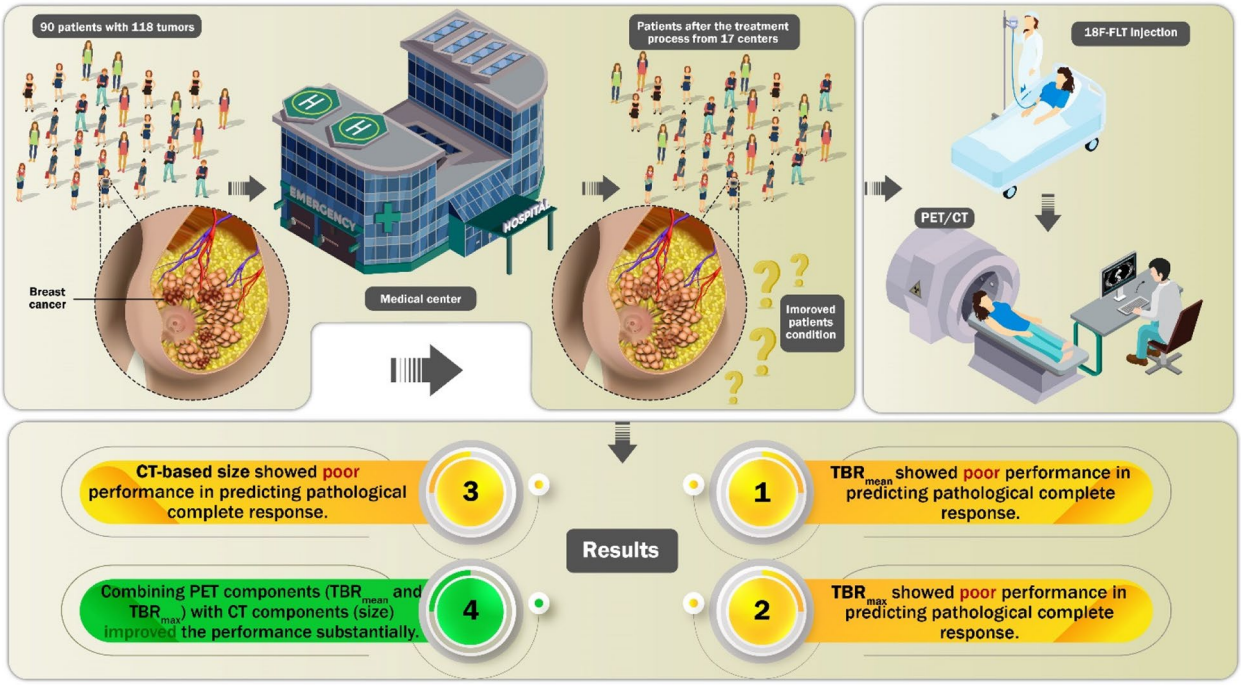

Fig. 3 Graphical summary presenting the main findings of the study

graphical summary displays the key findings of our study in Fig. 3.

There are some limitations to this study that need to be mentioned: 1) The primary source of variability in this study was the lack of a uniform treatment plan and irregularities in chemotherapy regimens applied by different participating centers. 2) The broader use of [18F]FLT PET/CT modality may be hampered by factors including the limited availability (e.g., pending for Food and Drug Administration approval) and high financial costs. 3) The third limitation concerns attrition between imaging time points, with 24 patients (26.7%) not completing the mid-NAC scan and 38 patients (42.3%) not completing the post-NAC scan. Loss to follow-up was defined as absence of imaging within the study window due to patient withdrawal, clinical progression, logistical barriers, or technical factors. Although we documented reasons for missing scans, differential attrition related to disease severity or treatment tolerance may have introduced bias. 4) As opposed to our primary objectives, considering the lack of data regarding normal breast parenchyma SUVpeak, we have not been able to include the results of TBRpeak in our final analysis.

Conclusion

While the results regarding tumor size and uptake values failed to adequately anticipate pathological response to chemotherapy and demonstrated poor diagnostic performance, using a combined model led to remarkable improvements in the diagnostic performance by fully exploiting the potential of each variable. In conclusion, it could be stated that our findings advocate the use of both anatomical and functional imaging modalities in assessing breast cancer response to chemotherapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14534-w.

Supplementary Material 1.

Acknowledgements
We would like to acknowledge all those who contributed to gathering the dataset.

Animal study
N/A.

Authors' contributions
All authors contributed significantly to this article. A.Mohebbi: statistical analysis, data collection, and data interpretation. F.A: primary writer of manuscript. S.M: providing revision for writing of manuscript. A.A.A: methodology. S.M.T: study design, providing revision for writing of manuscript. A.Mohammadi: Manager and principal investigator.

Funding
None.

Data availability
The data that support the findings of this study are openly available in The Cancer Imaging Archive (TCIA) at https://doi.org/10.7937/K9/TCIA.2017.ol20zmxg.

Declarations
All authors contributed significantly to this article.

Ethics approval and consent to participate
We adhered to the principles outlined in the Declaration of Helsinki. Each contributary center must obtain initial local IRB approval to participate in ACRIN trials. Also, the study is approved by IRB of Virginia Commonwealth University in cooperation with American College of Radiology Imaging Network (ACRIN).
All participants provided written informed.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

Author details
[1]Universal Scientific Education and Research Network (USERN), Tehran, Iran
[2]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Radiology Technology, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Pathology, Dr. Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[5]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[6]Head of Radiology Department, Faculty of Medicine, Urmia University of Medical Science, Urmia, Iran

Received: 2 March 2025 / Accepted: 17 June 2025
Published online: 03 July 2025

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
2. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk factors and preventions of breast cancer. Int J Biol Sci. 2017;13(11):1387–97.
3. Aebi S, Karlsson P, Wapnir IL. Locally advanced breast cancer. Breast. 2022;62 Suppl 1(Suppl 1):S58-s62.
4. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. J Clin Oncol. 2008;26(5):786–90.
5. Ueberroth BE, Lawhorn-Crews JM, Heilbrun LK, Smith DW, Akoury J, Ali-Fehmi R, et al. The use of 3'-deoxy-3'-(18)F-fluorothymidine (FLT) PET in the assessment of long-term survival in breast cancer patients treated with neoadjuvant chemotherapy. Ann Nucl Med. 2019;33(6):383–93.
6. Kostakoglu L, Duan F, Idowu MO, Jolles PR, Bear HD, Muzi M, et al. A phase II study of 3'-deoxy-3'-18F-fluorothymidine PET in the assessment of early response of breast cancer to neoadjuvant chemotherapy: results from ACRIN 6688. J Nucl Med. 2015;56(11):1681–9.
7. Kenny L, Coombes RC, Vigushin DM, Al-Nahhas A, Shousha S, Aboagye EO. Imaging early changes in proliferation at 1 week post chemotherapy: a pilot study in breast cancer patients with 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography. Eur J Nucl Med Mol Imaging. 2007;34(9):1339–47.
8. Zhang J, Liu X, Knopp MI, Ramaswamy B, Knopp MV. How long of a dynamic 3'-deoxy-3'-[(18)F]fluorothymidine ([(18)F]FLT) PET acquisition is needed for robust kinetic analysis in breast cancer? Mol Imaging Biol. 2019;21(2):382–90.
9. Utsunomiya T, Ogawa K, Funamizu N, Sakamoto K, Watanabe J, Otani H, et al. The tumor-to-liver ratio of the standardized uptake value is a useful FDG-PET/CT parameter for predicting malignant intraductal papillary mucinous neoplasm of the pancreas. Ann Gastroenterol Surg. 2022;6(5):695–703.

10. Keyes JW Jr. SUV: standard uptake or silly useless value? J Nucl Med. 1995;36(10):1836–9.
11. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007;25(28):4414–22.
12. Marti-Climent JM, Dominguez-Prado I, Garcia-Velloso MJ, Boni V, Peñuelas I, Toledo I, et al. [1^{8}F]fluorothymidine-positron emission tomography in patients with locally advanced breast cancer under bevacizumab treatment: usefulness of different quantitative methods of tumor proliferation. Rev Esp Med Nucl Imagen Mol. 2014;33(5):280–5.
13. Groheux D, Hindié E, Giacchetti S, Hamy AS, Berger F, Merlet P, et al. Early assessment with 18F-fluorodeoxyglucose positron emission tomography/computed tomography can help predict the outcome of neoadjuvant chemotherapy in triple negative breast cancer. Eur J Cancer. 2014;50(11):1864–71.
14. Romine PE, Peterson LM, Kurland BF, Byrd DW, Novakova-Jiresova A, Muzi M, et al. (18)F-fluorodeoxyglucose (FDG) PET or (18)F-fluorothymidine (FLT) PET to assess early response to aromatase inhibitors (AI) in women with ER+ operable breast cancer in a window-of-opportunity study. Breast Cancer Res. 2021;23(1):88.
15. Marcus C, Tajmir SH, Rowe SP, Sheikhbahaei S, Solnes LB. (18)F-FDG PET/CT for response assessment in lung cancer. Semin Nucl Med. 2022;52(6):662–72.
16. Pio BS, Park CK, Pietras R, Hsueh WA, Satyamurthy N, Pegram MD, et al. Usefulness of 3'-[F-18]fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy. Mol Imaging Biol. 2006;8(1):36–42. https://doi.org/10.1007/s11307-005-0029-9.
17. Crippa F, Agresti R, Sandri M, Mariani G, Padovano B, Alessi A, et al. 1^{8}F-FLT PET/CT as an imaging tool for early prediction of pathological response in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy: a pilot study. Eur J Nucl Med Mol Imaging. 2015;42(6):818–30.
18. Pio BS, Park CK, Pietras R, Hsueh WA, Satyamurthy N, Pegram MD, et al. Usefulness of 3'-[F-18]fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy. Mol Imaging Biol. 2006;8(1):36–42.
19. Contractor KB, Kenny LM, Stebbing J, Rosso L, Ahmad R, Jacob J, et al. [18F]-3'deoxy-3'-fluorothymidine positron emission tomography and breast cancer response to docetaxel. Clin Cancer Res. 2011;17(24):7664–72.
20. Woolf DK, Beresford M, Li SP, Dowsett M, Sanghera B, Wong WL, et al. Evaluation of FLT-PET-CT as an imaging biomarker of proliferation in primary breast cancer. Br J Cancer. 2014;110(12):2847–54.
21. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-update and clarification: from the RECIST committee. Eur J Cancer. 2016;62:132–7.

Publisher's Note