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RESEARCH

Real-world, multicenter assessment of 18 F-FDG PET/CT prognostic value in triple-negative breast cancer (TRINE-PET): the study protocol

Luca Urso[1,2] · Stefano Panareo[3] · Antonella Iudicello[2] · Domenico Albano[4] · Luca Filippi[5] · Laura Evangelista[6,7]

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Abstract

Purpose Triple-negative breast cancer (TNBC) represents a highly aggressive subtype of breast cancer with limited therapeutic options. [^{18}F]FDG PET/CT has shown potential in evaluating disease extension and treatment response in breast cancer, but its prognostic role and the impact on treatment management in TNBC remains unclear. Therefore, a large experience is highly desired to solve some clinical needs in this subset of breast cancer.

Methods A retrospective, multicenter, real-world observational study will be conducted, enrolling TNBC patients from various nuclear medicine centers across Italy, supported by the Italian Association of Nuclear Medicine, Molecular Imaging and Therapy. Imaging and clinical data will be collected and analyzed. Statistical analysis will be performed in accordance with the distribution of the study population. MedCalc software will be used for computing each collected variables and for testing all the endpoints.

Expected results [^{18}F]FDG PET/CT may provide valuable prognostic insights, particularly in stratifying TNBC patients according to their risk of progression and death and aiding treatment decisions.

Conclusion Understanding the prognostic implications of [^{18}F]FDG PET/CT in TNBC may contribute to personalize treatment strategies.

Keywords 18F-FDG · PET · PET/CT · Breast cancer · Triple negative breast cancer · Prognosis

Introduction

Breast cancer (BC) is a highly prevalent malignancy and its diagnostic and therapeutic management is quickly evolving [1]. The overexpression of glucose transporters (GLUT) 1–3 has been well described in the literature in BC patients, mostly in aggressive molecular subtypes, including triple-negative breast cancer (TNBC) and Human Epidermal growth factor Receptor 2 (HER-2) enriched BC [2, 3]. Therefore, imaging with 2-deoxy-2-[18F]fluoro-D-glucose ([^{18}F]FDG) Positron Emission Tomography/Computed Tomography (PET/CT) is currently used in several clinical scenarios in patients affected by BC. Indeed, the latest European Society of Medical Oncology (ESMO) guidelines suggest performing [^{18}F]FDG PET/CT for staging – in cases of high risk neoplasms, or inconclusive conventional imaging findings – or restaging metastatic disease, as an alternative to bone scan and thorax and abdomen contrast enhanced CT [4, 5]. Recently, the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) have released their own

✉ Luca Urso
luca.urso@unife.it

1 Department of Translational Medicine, University of Ferrara, Via Aldo Moro n.8, 44124 Ferrara, Italy

2 Nuclear Medicine Unit, Onco-Hematology Department, University Hospital of Ferrara, Ferrara, Italy

3 Nuclear Medicine Unit, Oncology and Hematology Department, University Hospital of Modena, Modena, Italy

4 Nuclear Medicine Unit, University of Brescia, Brescia, Italy

5 Nuclear Medicine, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Rome, Italy

6 Department of Biomedical Science, Humanitas University, Pieve Emanuele, Milan, Italy

7 Nuclear Medicine Unit, IRCCS Humanitas Research Hospital, Milan, Italy

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guidelines, that reaffirm the indication of [^{18}F]FDG PET/CT for staging, from stage IIB disease onwards. Additionally, they expand the role of metabolic PET in treatment response assessment of [^{18}F]FDG-avid BC subtypes and in patients with bone metastases [6].

Although the increasing relevance of [^{18}F]FDG PET/CT in BC is undeniable, some open questions remain unanswered. Considering TNBC, which accounts for about 15% of all BC, [^{18}F]FDG PET/CT is a valuable tool to define the real extent of disease since this subtype of BC is highly [^{18}F]FDG-avid [2, 7]. However, despite existing evidence supporting its utility, its prognostic role remains insufficiently explored [8–10].

It is within this context that the Italian Association of Nuclear Medicine, Molecular Imaging and Therapy (AIMN) promoted the study "18F-FDG PET/CT in triple negative breast cancer: a multicenter real-world experience (TRINE-PET)".

Methods

The TRINE-PET trial is a retrospective real-world, multicenter, observational, no profit trial involving Nuclear Medicine Department from Italian Centers. The study was approved by the local ethical committee of the promoting center (Azienda Ospedaliero-Universitaria di Modena, Modena, Italy) on February 13, 2024 (656/2023/OSS/AOUMO – SIRER ID: 6869). Every participant center has been invited to obtain ethical approval by its local ethical committee. In some cases, a sponsorship agreement has been established between the promotor and the collaborators.

Objectives

Primary objective will be to analyze the prognostic role, in terms of survival (progression-free survival – PFS; overall survival – OS), of [^{18}F]FDG PET/CT at different stages of disease in patients with TNBC.

Secondary objectives will be (a) to compare [^{18}F]FDG PET/CT with conventional imaging (bone scintigraphy and contrast-enhanced CT of the chest and abdomen) in terms of diagnostic accuracy; (b) to define the impact of [^{18}F]FDG PET/CT on the therapeutic management of patients with TNBC at different disease stages; (c) to investigate potential correlations between [^{18}F]FDG PET/CT findings and tumor marker trends, in relation to patient outcomes.

Finally, an exploratory objective will be to analyze potential correlations between therapy responses assessed by [^{18}F]FDG PET/CT and clinical outcomes in patients with metastatic TNBC.

Study design and population

Patients have been directly enrolled by the Nuclear Medicine Units of each participant center. Enrolment has been active from 01 April 2024 to 31 December 2024. For the enrolment, the following inclusion criteria were established: (a) age > 18 years old at the diagnosis of BC; (b) histologically confirmed TNBC; (c) at least one available [^{18}F]FDG PET/CT scan (additional [^{18}F]FDG PET/CT scans from the same patient, even if acquired in various clinical settings, were also included); (d) availability of the main clinical-histological, diagnostic and therapeutic data; and (e) a follow-up period of at least two years. Patients who refuse to sign informed consent will be excluded from the study.

TNBC patients enrolled will be further subdivided into 4 settings according to the clinical stage in which [^{18}F]FDG PET/CT was performed: (a) *Baseline*, including all [^{18}F]FDG PET/CT in newly diagnosed, treatment naïve TNBC; (b) *Post neoadjuvant chemotherapy* (NAC): in case [^{18}F]FDG PET/CT was performed after NAC and before surgery; (c) *Restaging for suspect of recurrence*, when [^{18}F]FDG PET/CT was made in case of suspicious of recurrence at conventional imaging or in case of increase in tumor markers, before to start any treatment approach; (d) *Restaging in advanced metastatic setting*, performing [^{18}F]FDG PET/CT to monitor the efficacy of systemic therapy or in case of restaging in metastatic TNBC. Figure 1 represents a schematic representation of the diverse selected settings of disease.

Data collection and image analysis

Patient data, including clinical history and laboratory markers, imaging and follow-up data, will be gathered from institutional databases. The following variables will be collected for each patient regarding TNBC: date of diagnosis, familiarity, histological type and grade, tumor-node-metastasis (TNM) stage, proliferation index, oncological comorbidities, achievement of pathological complete response (pCR) after NAC. Considering imaging, the following data will be collected: date and clinical setting of the [^{18}F]FDG PET/CT, ongoing systemic therapy including the type at the time of [^{18}F]FDG PET/CT, acquisition time after the injection of agent, presence of [^{18}F]FDG-avid breast lesions [named T stage – comprehending mono vs. multifocal disease, breast quadrant involved, lesion size at co-registered CT and maximum standardized uptake value (SUVmax)], presence of [^{18}F]FDG-avid lymph node [named N stage – comprehending the number (up to 5; 5–10; more than 10) and the site] and distant metastases [named M stage – comprehending the number (up to 5; 5–10; more than 10) and the site]. The same data will be also collected for conventional imaging

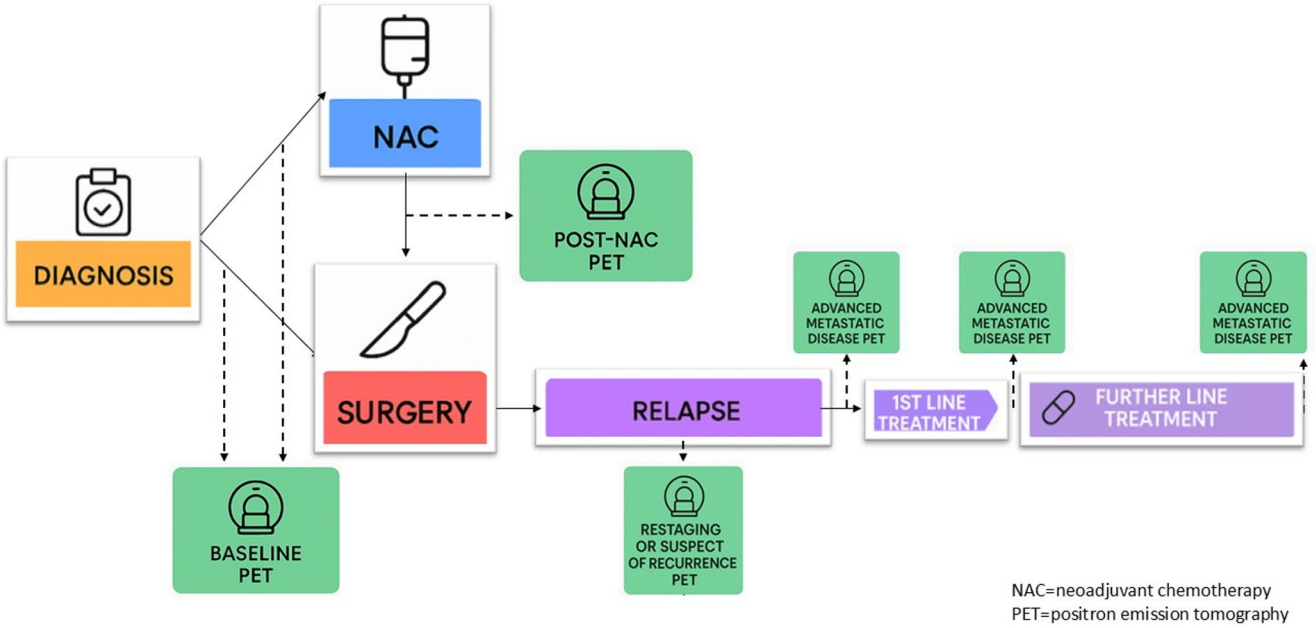

Fig. 1 Clinical settings (a-d) of [^{18}F]FDG PET/CT considered in the TRINE-PET study

(including CT, bone scan and breast magnetic resonance imaging - MRI), to be compared to [^{18}F]FDG PET/CT results. Moreover, for each [^{18}F]FDG PET/CT scan, the following parameters will be collected: SUVmean of the liver and the mediastinum blood pool (obtained by drawing a circular volume of interest of, respectively, 3 and 1 cm of diameter); reference lesion: considered the most relevant [^{18}F]FDG-avid lesion in terms of uptake intensity and extension. In patients with multiple scans available, the reference lesions will be compared between baseline and post treatment scans to obtain Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0 response, according to previously published literature [11]. Researchers will be also asked to assess and record doubtful findings and the impact of [^{18}F]FDG PET/CT in changing the management. For the latter, the researchers will be asked to reply "yes" in case the results of [^{18}F]FDG PET/CT have induced the clinicians to change the planned, or ongoing treatment strategy. Finally, for each patient, the date of the last follow-up, clinical and/or radiological evidence of disease progression and death will be collected.

Sample size

Based on current scientific evidence published in the literature [9], an increase in OS of at least 20% will be assumed in TNBC patients with negative [^{18}F]FDG PET/CT, compared with those who will show positive scans. Therefore, considering a type I error (alpha) of 0.05 and a type II error (beta) of 80%, a minimum of 153 patients will be required for assessing the prognostic value of [^{18}F]FDG PET/CT in this cohort of patients.

Statistical analysis

A descriptive analysis will be performed by using a parametric or non-parametric analysis, depending on the distribution of the data (normal vs. non-normal). The normality test will be assessed according to Shapiro-Wilk test. Categorical variables will be expressed as numbers (percentages). Continuous variables will be expressed as median (range) or mean (standard deviation).

For the primary endpoint, a survival analysis will be used by applying Kaplan Meyer analysis (log rank test will compare the curves) and univariate and multivariate Cox-regression analysis. PFS and OS will be calculated from the date of [^{18}F]FDG PET/CT, until, respectively, the dates of clinical/radiological evidence of disease progression, or death from any cause.

For secondary endpoints, sensitivity, specificity, positive and negative predictive value and accuracy will be calculated by applying the standard method with 95% confidence interval. The comparison of categorical data will be made by 2×2 contingency tables and applying the Chi-square test. Continuous variables will be compared by applying Student's T-test or Mann-Whitney analysis. In the case of multiple variables, ANOVA test or Kruskal-Wallis test will be used, in accordance with the distribution of the data. A post-hoc analysis will be done for the various disease settings. The significance level will be set for $p < 0.05$

Table 1 List of participating centers and relative details.

		Principal Investigator	Name of the Center	City	Number of scans
Promoter		Stefano Panareo	A.O.U. Policlinico di Modena	Modena	34
Co-investigator	1	Luca Urso	A.O.U. di Ferrara	Ferrara	65
	2	Laura Evangelista	Istituto Clinico Humanitas Rozzano	Rozzano (Milan)	125
	3	Lucia Setti	Istituto Clinico Humanitas Gavazzeni	Bergamo	69
	4	Demetrio Aricò	Istituto Clinico Humanitas Catanese	Catania	22
	5	Federico Garrou	A.O.U Maggiore della Carità di Novara	Novara	30
	6	Alberto Miceli	A.O.U. SS. Antonio e Biagio e Cesare Arrigo	Alessandria	8
	7	Rosa Sciuto	IRCCS Regina Elena - IRCCS Istituti Fisioterapici Ospitalieri	Roma	26
	8	Angela Spanu	A.O.U di Sassari	Sassari	14
	9	Angelica Mazzoletti	Istituto ospedaliero Fondazione Poliambulanza di Brescia	Brescia	47
	10	Angelina Filice	AUSL – IRCCS Reggio Emilia	Reggio Emilia	7
	11	Domenico Albano	Spedali civili di Brescia - Azienda Ospedaliera	Brescia	56
	12	Gianluca Cassarino	Ospedale Giovanni Paolo II di Ragusa	Ragusa	18
	13	Maria Lucia Calcagni	Policlinico Universitario Agostino Gemelli	Roma	31
	14	Maria Luisa De Rimini	Azienda Ospedaliera Specialistica dei Colli	Napoli	5
	15	Massimo Castellani	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Milano	25
	16	Guido Rovera	Ospedale Molinette	Torino	21
	17	Pasquale Reccia	Istituto Oncologico Veneto – IRCCS	Padova	12
	18	Salvatore Ialuna	Azienda Ospedaliera Ospedali Riuniti Villa Sofia - Cervello	Palermo	17
	19	Cristina Ferrari	Policlinico di Bari Ospedale Giovanni XXIII	Bari	32
	20	Federica Matteucci	Istituto Tumori della Romagna IRST- IRCCS	Meldola	22
	21	Anna Margherita Maffione	Presidio Ospedaliero Santa Maria della Misericordia-AULSS 5 POLESANA	Rovigo	7
	22	Davide Donner	Ospedale Santa Chiara di Trento	Trento	14

All data collected from participating centers have been analyzed, and the comprehensive results of the study are expected to be finalized and submitted for publication in early 2026

(two-tailed test). Statistical analysis will be performed by using MedCalc® software.

Status of the study

From April 01, 2024, to December 31, 2024, data from 389 patients in 23 centers have been collected. The full list of centers involved, and the relative local principal investigators can be found in Table 1. Overall, 707 [^{18}F]FDG PET/CT scans have been retrieved. Among those, 257, 111, 144 and 195 scans were collected in the baseline, post-NAC, restaging for suspect of recurrence and advanced metastatic settings, respectively.

Every active centre has contributed to the study with at least 5 [^{18}F]FDG PET/CT scans. Details can be found in Table 1.

Discussion

Current evidence highlights [^{18}F]FDG PET/CT utility in TNBC management, yet its prognostic potential remains under-investigated [8]. By analysing real-world data, this study seeks to bridge the gap in knowledge and support the integration of metabolic imaging into clinical decision-making. Previous studies suggest that metabolic imaging may

stratify TNBC patients based on disease aggressiveness and, consequently, prognosis [8, 9, 12]. We anticipate that [^{18}F]FDG PET/CT will show significant prognostic value in identifying high-risk patients throughout the different clinical settings. We believe that [^{18}F]FDG PET/CT might have an increasing relevance as we go through to the late stages of disease, with an expected prognostic impact higher in metastatic patients in systemic treatments. We firmly believe that the real-world data of this study will have an impact in guiding treatment strategies.

This study is not without limitations. Its retrospective nature may introduce potential selection biases, particularly given the multicenter design and variability in local clinical practices. However, we believe that this real-world framework also offers a unique opportunity to capture the current indications for which [^{18}F]FDG PET/CT is currently requested in routine clinical settings. Moreover, the use of different scan protocols across participating institutions may introduce heterogeneity in semi-quantitative parameters (e.g., SUV measures). To address this, we collected SUVmean values of the liver and mediastinum to calculate tumor-to-background ratios, which help reduce variability. Moreover, data about EARL certification across the centers will be collected. Finally, these metrics are used solely for exploratory purposes.

Conclusions

Results from TRINE-PET will be published in the next year. The results have been presented as a poster and oral presentation at the European Association of Nuclear Medicine Congress, held on 4-8th October 2025 in Barcelona.

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Author contributions Luca Urso and Laura Evangelista contributed to the study conception and design. Ethical approval and study management were performed by Luca Urso, Stefano Panareo and Antonella Iudicello. Material preparation and data collection were performed by Luca Urso, Laura Evangelista, Domenico Albano and Luca Filippi. Data analysis was performed by Laura Evangelista. The first draft of the manuscript was written by Luca Urso and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Datasets are available upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate The study was approved by the local ethical committee of the promoting center (Azienda Ospedaliero-Universitaria di Modena, Modena, Italy) on February 13, 2024 (656/2023/OSS/AOUMO – SIRER ID: 6869). Every participant center has been invited to obtain ethical approval by its local ethical committee. In some cases, a sponsorship agreement has been established between the promotor and the collaborators. Consent to participate and for publication was obtained from patients at each participating center.

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