OSPEDALE SAN RAFFAELE

PET-RM e ricerca clinica

Dr. Rosa Di Micco, MD, PhD, MSc
UO Chirurgia della mammella
IRCCS Ospedale San Raffaele, Milano

Overview

1. Background
2. PET/MRI in breast cancer (BC) staging
3. Ongoing trials with 18F-fluorodeoxiglucose (FDG) PET/MRI
4. Rationale of a new trial with PET/MRI with 18F-fluorestradiol (FES)
5. Conclusions

1. Background

- PET/MRI is a hybrid imaging technique introduced in 2011 in the USA and UE that combines metabolic information from PET and high contrast morphological images with the potential to unite the specificity obtained by the functional imaging of PET with the superior sensitivity of MRI.
- This integrated system with an accurate spatial and temporal co-registration of PET and MR data has provided the best of the two imaging techniques and could potentially improve the diagnostic accuracy in breast cancer.
- It offers the dual advantage of minimizing radiation exposure, while simultaneously evaluating locoregional extent and metastatic spread of the disease.

Catana, Magn Reson Imaing Clin N Am, 2017; Jafari, J Cell Physiol, 2018; Di Micco, Cancers, 2021; de Mooij, Nucl Med Commun, 2020

2. PET/MRI in breast cancer staging

- The reliability of PET/MRI seemed to be **comparable or even superior to PET/CT** in systemic staging.
- Considering the BC lesions, the axillary nodes and the metastatic lesions, PET/MRI showed an equivalent performance in terms of qualitative lesion detection to PET/CT, but it had a superior sensitivity and lower specificity in the lesion-per-lesion analysis, with a more accurate definition of **brain, bone and liver metastases.**
- PET/MRI has demonstrated to be more accurate (82% vs. 68%) and more sensitive in detecting **smaller lesions** than whole-body PET/CT (89% vs. 77%).
- In the assessment of **distant metastasis**, PET/MRI has been reported to have a higher sensitivity (0.87 vs. 0.81) and AUC value (0.98 vs. 0.95) compared to PET/CT.
- In terms of therapeutic **response prediction**, combined PET/MRI parameters (SUVmax, total lesion glycolysis, ADCmin), have been more accurate than individual PET and MRI parameters, offering a possibility for tailoring treatment plans and early identification of non-responding tumors.

Di Micco R, Cancers, 2021; de Moy, J Nucl Med, 2007. Samarin, Nucl Med Commun, 2015; de Mooij, Cancers (Basel), 2023

Review of PET/MRI studies

Category group	Reference	Tot-.BC/tot (%)	Study design	Patient position	Type of acquisition	Axillary detection sensitivity	Axillary detection specificity
STAGING	Catalano, O.A. 2013 (6)	35/134 (26.1%)	retrospective	supine	simultaneous	NA	NA
	Huellner, M. W. 2014 (7)	5/106 (4.8%)	prospective	supine	sequential	NA	NA
	Drzezga, A. 2012 (8)	3/32 (9.4%)	prospective	supine	simultaneous	NA	NA
	Appenzeller, P. 2013 (9)	7/63 (11.1%)	prospective	supine	sequential	NA	NA
	Wiesmuller, M. 2013 (10)	2/46 (6.5%)	prospective	supine	simultaneous	NA	NA
	Kirchner, J. 2018 (11)	38/38 (100%)	prospective	supine WB, prone B	simultaneous	93%	95%
	Botsikas, D. 2019 (13)	80/80 (100%)	retrospective	supine WB, prone B	sequential	89%	96%
	Pace, L. 2014 (14)	36/36 (100%)	prospective	supine	simultaneous	NA	NA
	Kong, E. 2014 (15)	42/42 (100%)	prospective	NA	simultaneous	NA	NA
	Melsaether, A. N. 2016 (16)	51/51 (100%)	prospective	supine	simultaneous	100-88% (CI 69, 97)	95% (CI 88,98)
	van Nijnatten, T. J. 2018 (17)	12/12 (100%)	prospective	prone	simultaneous	NA	NA
	Taneja, S. 2014 (18)	36/36 (100%)	retrospective	supine WB, prone B	simultaneous	60-93.3%	91%
	Grueneisen, J. 2015 (19)	49/49 (100%)	prospective	prone	sequential	78% (CI 52 ,94)	90% (CI 74, 98)
	Botsikas, D. 2016 (20)	58/58 (100%)	retrospective	supine WB, prone B	simultaneous	79%	100%
	Catalano, O.A. 2017 (21)	51/51 (100%)	retrospective	NA	simultaneous	NA	NA
	Goorts, B. 2017 (22)	40/40 (100%)	prospective	prone	simultaneous	NA	NA
FOLLOW UP	Grueneisen, J. 2017 (12)	36/36 (100%)	prospective	supine	sequential	96%	91%
	Sawicki, L. M. 2017 (23)	21/21 (100%)	retrospective	NA	simultaneous	NA	NA
	Pujara, A. C. 2016 (24)	35/35 (100%)	prospective	prone	simultaneous	NA	NA
	Beiderwellen, K. 2013 (25)	10/70 (14%)	prospective	NA	simultaneous	NA	NA
	Chandarana, H. 2013 (26)	10/32 (31.2%)	prospective	NA	simultaneous	70.3%	NA
	Rauscher, I. 2014 (27)	4/40 (10%)	prospective	NA	simultaneous	NA	NA
	Catalano, O.A. 2015 (28)	109/109 (100%)	retrospective	NA	simultaneous	96% (CI 87, 99)	98% (CI 95, 99)
	Raad, R. A. 2016 (29)	15/208 (7.2%)	retrospective	NA	simultaneous	NA	NA
	Ishii S., 2016 (30)	33/123 (26.8%)	prospective	NA	simultaneous	NA	NA
	Kirchner, J. 2017 (31)	2/41 (5%)	prospective	NA	simultaneous	NA	NA
	Schiano, C. 2019 (32)	40/217 (18.4%)	retrospective	NA	simultaneous	NA	NA
	Sonni, I. 2019 (33)	23/74 (31%)	prospective	NA	simultaneous	NA	NA
PROGNOSIS	Margolis, N. E. 2016 (34)	12/12 (100%)	prospective	prone	simultaneous	NA	NA
	Catalano, O.A. 2017 (35)	21/21 (100%)	retrospective	supine WB, prone B	simultaneous	NA	NA
	Jena, A. 2017 (36)	69/69 (100%)	prospective	supine WB, prone B	simultaneous	NA	NA
	Jena, A. 2017 (37)	70/98 (71.4%)	prospective	prone	simultaneous	NA	NA
	Kong, E. 2018 (38)	46/46 (100%)	prospective	NA	simultaneous	NA	NA
	Incoronato, M. 2018 (39)	50/50 (100%)	prospective	NA	simultaneous	NA	NA
	Inglese, M. 2019 (40)	46/46 (100%)	prospective	NA	simultaneous	NA	NA
	Incoronato, M. 2019 (41)	77/155 (49.7%)	prospective	NA	simultaneous	NA	NA
	Leithner, D. 2019 (42)	100/141 (70.9%)	prospective	prone	sequential	NA	NA
RESPONSE	Andreassen, M.M.S.2019 (43)	24/24 (100%)	prospective	NA	simultaneous	NA	NA
	Jena, A. 2017 (44)	50/50 (100%)	prospective	supine WB, prone B	simultaneous	NA	NA
	Wang, J. 2017 (45)	14/14 (100%)	prospective	prone	simultaneous	NA	NA
	Romeo, V. 2017 (46)	4/4 (100%)	prospective	NA	simultaneous	NA	NA
	Cho, N. 2018 (47)	26/26 (100%)	prospective	prone	simultaneous	NA	NA

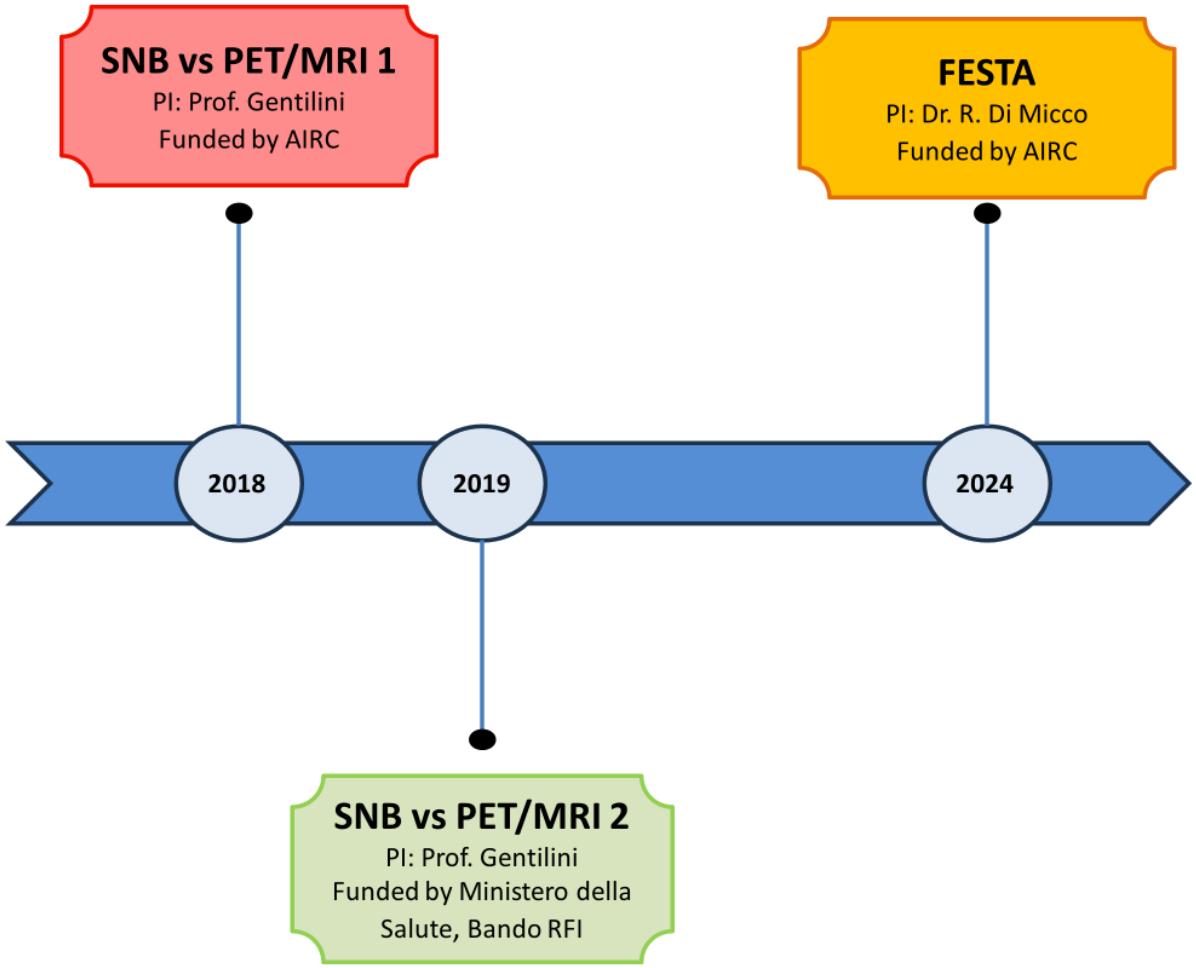
Di Micco R., Cancers 2021

Previous studies on PET/MR evaluating the axillary status

Authors	Total number of patients	Study design	Patient position	Type of acquisition	Axillary node detection sensitivity	Axillary node detection specificity
Grueneisen, J. 2017	36	prospective	supine	sequential	96%	91%
Chandarana, H. 2013	10	prospective	NA	simultaneous	70.3%	NA
Catalano, O.A. 2015	109	retrospective	NA	simultaneous	96% (CI 87, 99)	98% (CI 95, 99)
Kirchner, J. 2018	38	retrospective	supine WB, prone B	sequential	93%	95%
Botsikas, D. 2019	80	prospective	supine WB, prone B	simultaneous	89%	96%
Melsaether, A. N. 2016	51	retrospective	supine	simultaneous	100-88% (CI 69, 97)	95% (CI 88,98)
Taneja, S. 2014	36	prospective	supine WB, prone B	sequential	60-93.3%	91%
Grueneisen, J. 2015	49	retrospective	prone	simultaneous	78% (CI 52 ,94)	90% (CI 74, 98)
Botsikas, D. 2016	58	prospective	supine WB, prone B	simultaneous	79%	100%

Di Micco R. et al., Cancers 2021

PET/MRI trials over time



STUDY HYPOTHESIS

Hybrid PET/MRI might be a non-invasive, one-stage, operator-independent imaging modality to accurately define nodal status

SNB vs PET/MRI 1

Targeting the future of axillary staging in node positive breast cancer patients receiving primary systemic therapy. A comparative study between axillary surgery vs PET/MRI

PI: Oreste D.Gentilini
ClinicalTrials.gov Identifier: NCT04826211

Inclusion criteria:

- Proven diagnosis of early BC of any size;
- Patients candidate to primary systemic therapy (PST);
- Positive axillary nodes at diagnosis

PRIMARY AIM:

Compare the staging power of SNB/lymphadenectomy vs PET/MRI in detecting axillary lymph node macro-metastases (>2 mm)

SECONDARY AIMS:

- comparison with axillary US
- PPV, NPV
- cut-off size of missed nodal involvement on imaging
- diagnostic performance of PET/MRI in the different BC molecular subtypes, value of PET in the characterization of MRI additional findings, correlations between PET/MRI parameters and tumor biology.

SAMPLE SIZE: 110 patients

SNB vs PET/MRI 2

Targeting the future of axillary staging in early breast cancer. A comparative study: sentinel lymph node biopsy vs PET/MRI

PI: Prof. O.D. Gentilini
ClinicalTrials.gov Identifier: NCT04829643

PET/MRI

Ministero della Salute

Inclusion criteria:

- T≤3 cm
- cN0(no palpable nodes)
- iN0 (no metastatic nodes on preoperative ultrasound)
- Candidates to BCS or mastectomy plus SNB

PRIMARY AIM:

Compare the staging power of SNB vs PET/MRI in detecting axillary lymph node macro-metastases (>2 mm)

SAMPLE SIZE: 247 patients

UNPLANNED PRELIMINARY ANALYSIS on 205 pts.

to evaluate the impact of PET/MRI on the management of early breast cancer

PRIMARY ENDPOINT

Changes in treatment strategies

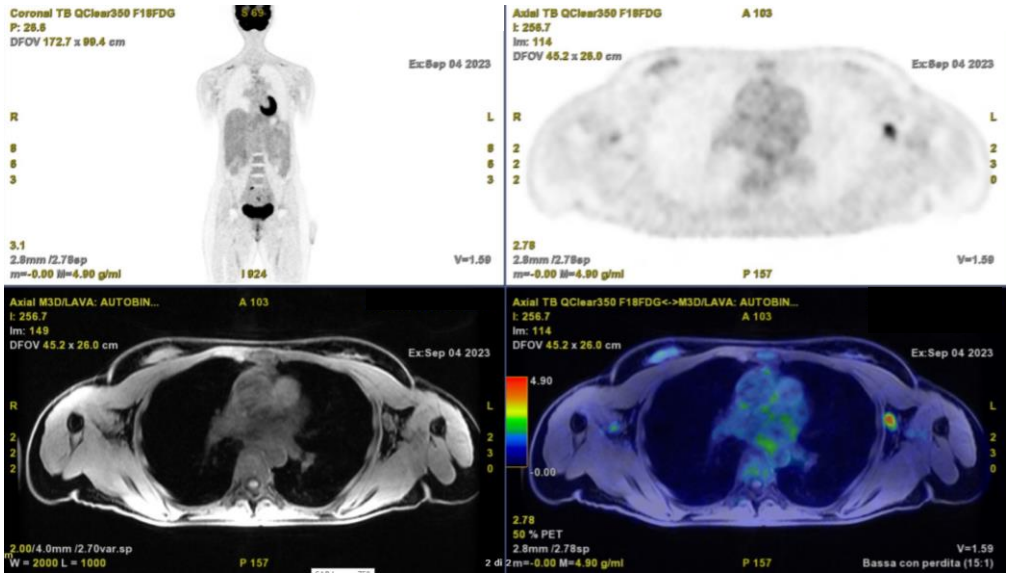
due to new findings discovered on PET/MRI

CHANGES IN TREATMENT STRATEGY

27.8% (57/205)

- 25% (n=14) primary systemic therapy
- 7% (n=4) systemic therapy
- 16.7% (n=9) mastectomy
- 10.5% (n=6) oncoplastic surgery
- 21.1% (n=12) bilateral surgery
- 21.1% (n=12) axillary dissection/node sampling

21.1% (n=12) identification of non-cancerous lesions



SECONDARY ENDPOINTS

POSITIVE PREDICTIVE VALUE
OF NEW BREAST LESIONS VISIBLE ON PET/MRI ONLY

Accuracy In Detecting New Foci Of Disease

PPV: 58.3% in the same breast
PPV: 45.5% in the contralateral breast

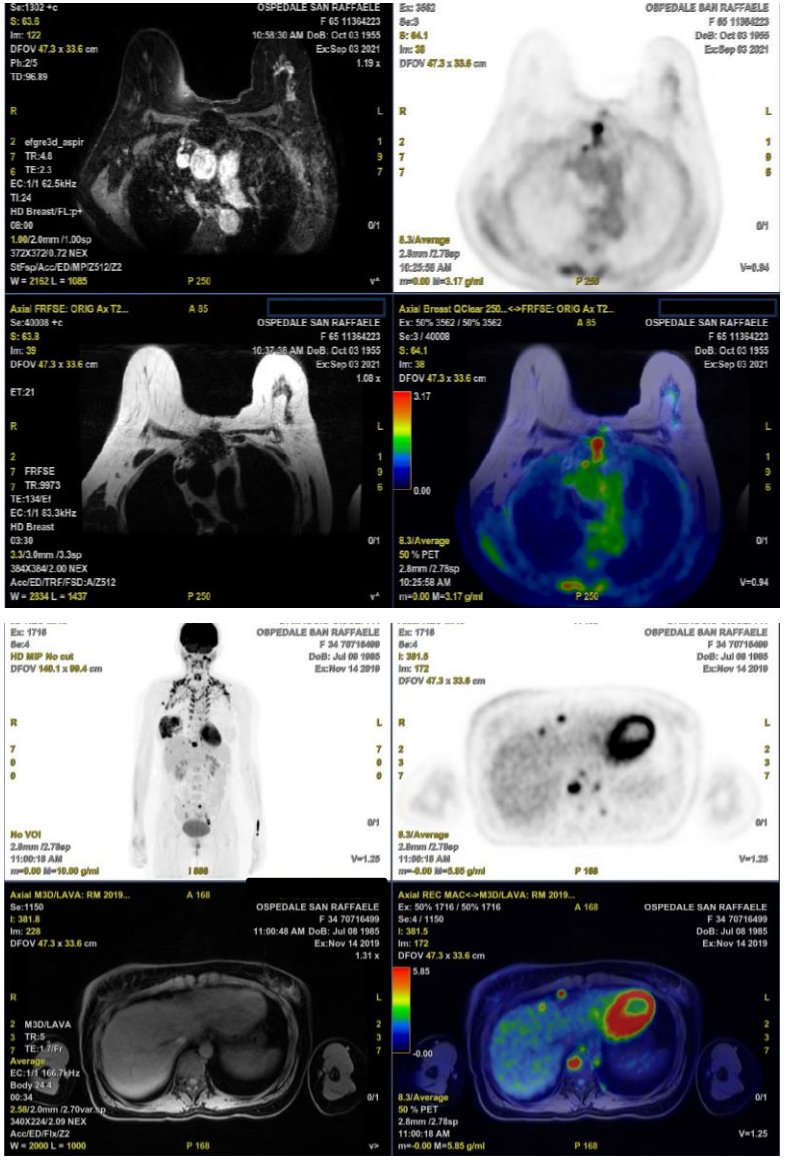
Analysis Of Multifocal Breast Lesions

Sensitivity: 68.4%
Specificity: 88.9%

NEW FINDINGS IN OTHER SITES

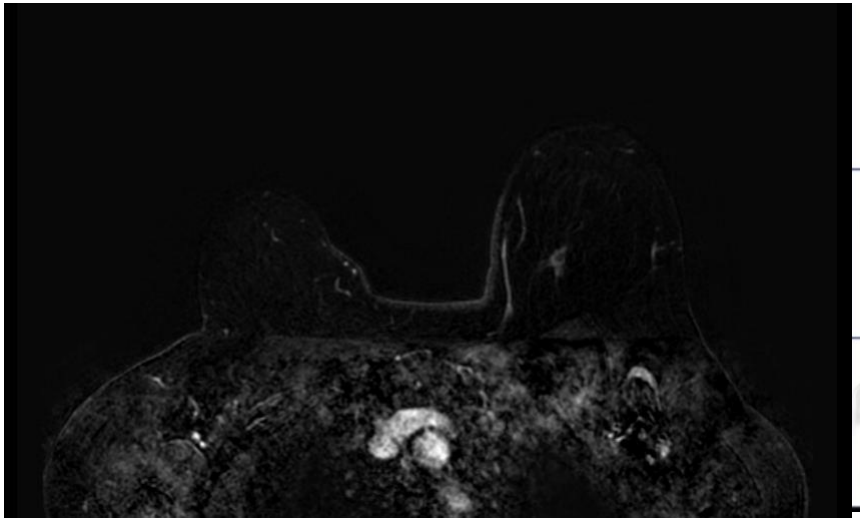
Of **55 patients** identified with new lesions after further exams we found:

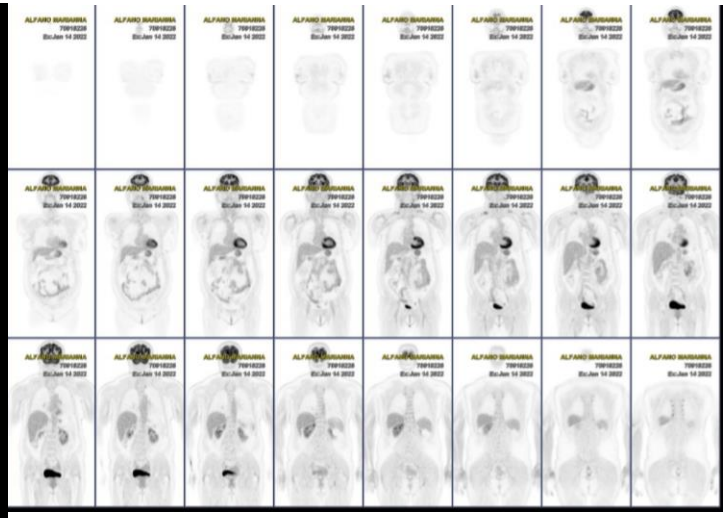
- 4 (7.3%) metastatic breast cancers
- 1 (1.8%) metastatic lung cancer
- 10 (18.2%) benign tumors
- 10 (18.2%) benign conditions



ADDITIONAL FINDINGS

25 out of 210 breasts (11.9%) presented poorly visible tumors
(84%Lum A 20% Lob)

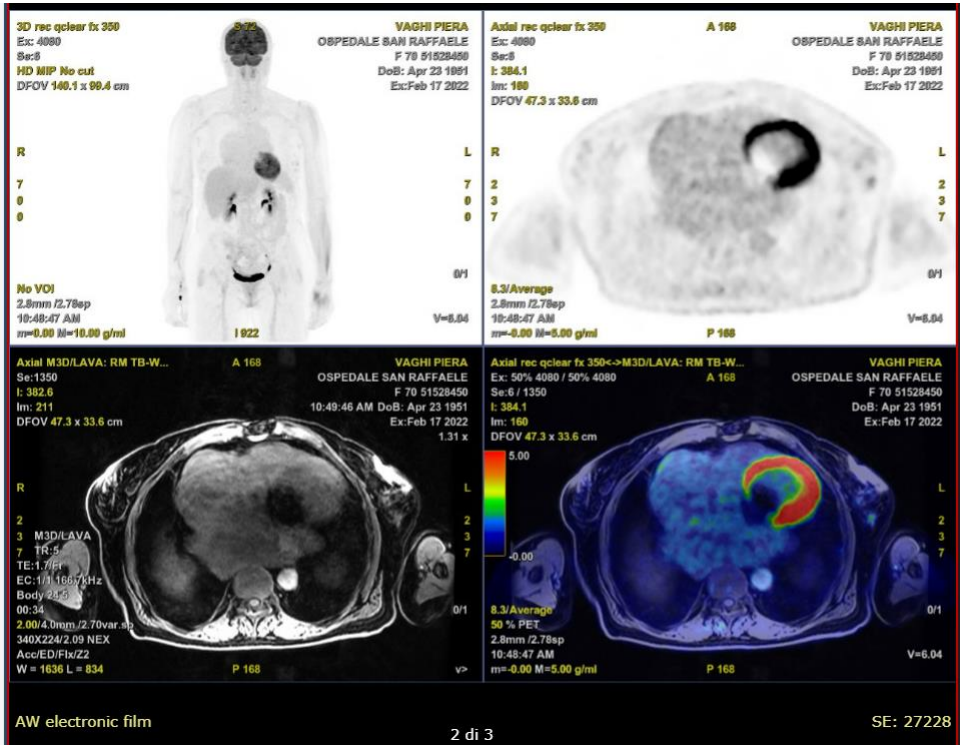


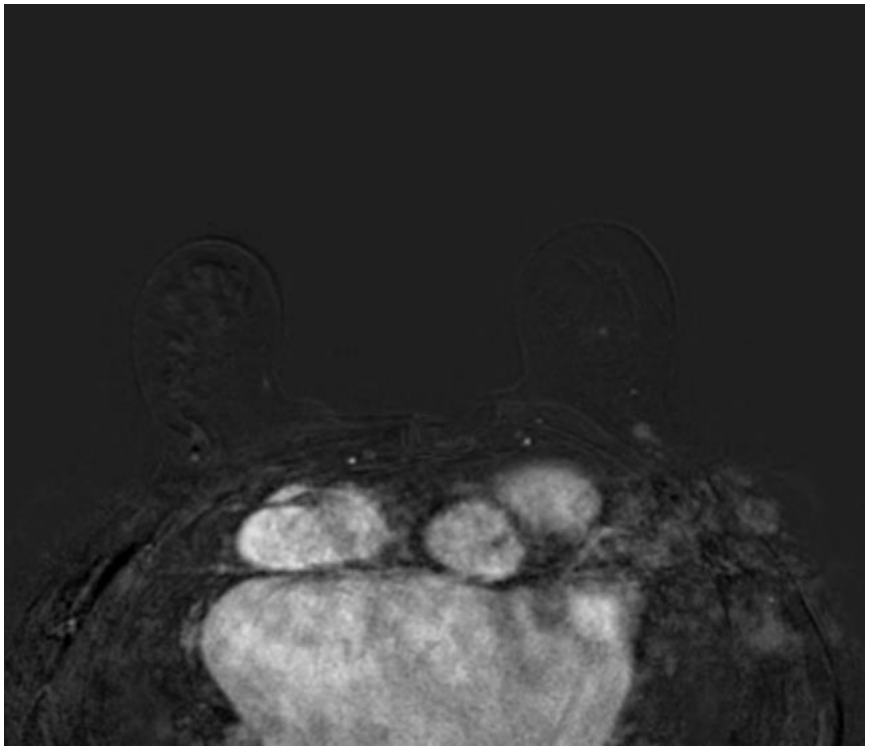


L UIQ ILC ER 90% PgR90% ki67 10% Grade 2

Stage: pT1c (m) N0

ADDITIONAL FINDINGS





L UOQ IDC ER 90% PgR90% ki67 11% Grade 1

Stage: pT1cN0

18F-FES PET/MRI for Tailoring treatment of luminal A and lobular breast cancer: FESTA trial

PI: R.Di Micco

ClinicalTrials.gov ID NCT05982496

AIRC

Next Gen Clinician Scientist Grant

UPFRONT SURGERY	**COHORT A** LumA and ER+ Lob candidates to primary surgery	**FES PET/MRI at baseline**
INDUCTION ENDOCRINE THERAPY	**COHORT B** ER-positive BC treated with induction ET	**1st FES PET/MRI at diagnosis** **2nd FES PET/MRI after ET**
NEOADJUVANT CHEMOTHERAPY	**COHORT C** LumA and ER+ Lob candidates to neoadjuvant chemotherapy	**1st FES PET/MRI + FDG PET at baseline** **2nd FES PET/MRI after two cycles of therapy**
METASTATIC SETTING	**COHORT D** Metastatic LumA and ER+Lob treated with systemic therapy	**1st FES PET/MRI + FDG PET at baseline** **2nd FES PET/MRI after two cycles of therapy**
TRANSLATIONAL ANALYSIS	Patients from cohorts A-B-C-D with large (>2 cm) and heterogeneous tumor	**Additional genomic analysis**

STUDY RATIONALE

- Luminal A BC (Lum A) and Lobular BC (Lob) constitute more than 50% of BC cases.
- Standard imaging has limited accuracy in these cancer types.

- Improving detection and staging could allow to ameliorate prognosis in the vast majority of BC patients and impact on:
  - ✓ **SURGERY**→choice of surgery vs neoadjuvant, SNB vs AD, axillary staging
  - ✓ **SYSTEMIC THERAPY**→ choice of genomic testing and targeted drugs, prediction and monitoring of response to therapy
  - ✓ **RADIOTHERAPY**→extension of irradiation fields
  - ✓ **PATIENTS**→non-invasive assessment of ER-status
  - ✓ **HEALTHCARE SYSTEM**→potential reduction in costs for biopsies, further exams, recurrences and their treatment
  - ✓ **RESEARCH**→promising field of research for future studies on heterogeneity and omics approaches

RESEARCH PLAN

Prospective interventional phase II cohort study on the use of 18F-fluoro-17-beta-estradiol (FES) in hybrid PET/MRI to study luminal A BC (LumA) and ER-positive lobular BC (Lob) in different settings.

- **Primary endpoint:**

ability of FES PET/MRI to detect macrometastatic axillary lymph nodes in BC patients with LumA or Lob who are candidates to primary surgery.

- **Secondary endpoint:**

potential correlation between FES uptake and ki67 after induction endocrine therapy (ET) in luminal BC.

- **Tertiary endpoints:**

additional value of FES PET/MRI compared with standard imaging in patients with LumA or Lob who are candidates to systemic therapy for neoadjuvant purposes or for metastatic disease; exploring the biological determinants of tumor heterogeneity.

FES PET/MRI vs Axillary surgery

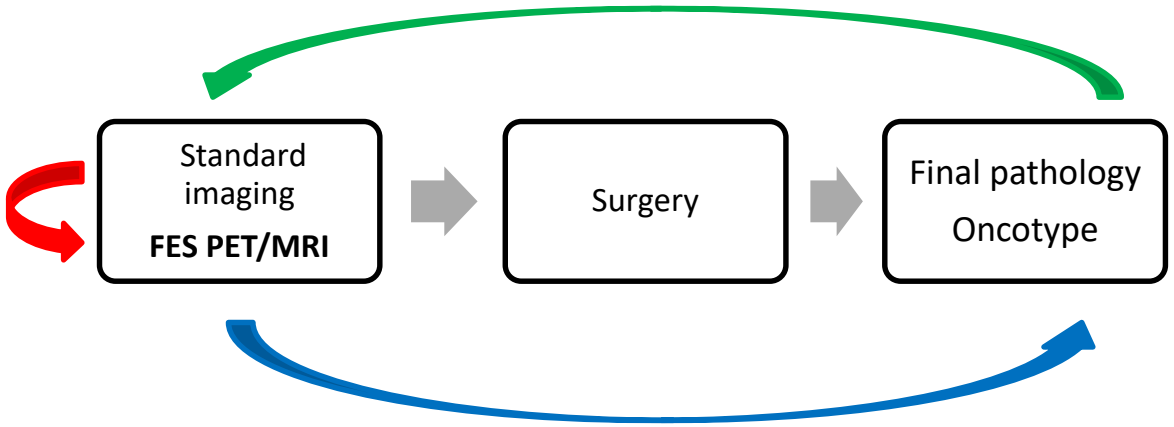
RESEARCH QUESTION 1:
Is FES PET/MRI able to predict macrometastatic axillary nodes?

Cohort A:

LumA or ER+ Lob candidates to **SURGERY** as first treatment regardless of cN

- **Task 1.1** FES PET/MRI vs axillary surgery
- **Task 1.2** FES PET/MRI vs standard imaging
- **Task 1.3** FES PET/MRI parameters and Recurrence Score

SAMPLE SIZE: 119 pts



FES uptake vs proliferation index after induction therapy

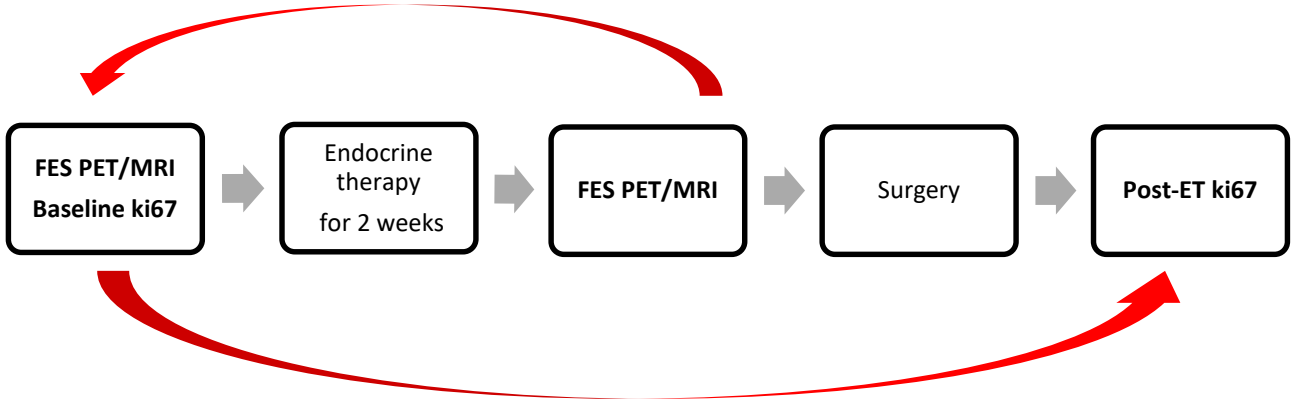
RESEARCH QUESTION 2:
Does FES uptake correlate with proliferation index after induction endocrine therapy?

Cohort B:
ER+ Her2 negative BC with ki67>10%

candidates to surgery as first treatment and **INDUCTION ET**

- **Task 2.1** FES uptake changes and ki67 changes
- **Task 2.2** In vivo pharmacodynamic response

SAMPLE SIZE: 52 pts



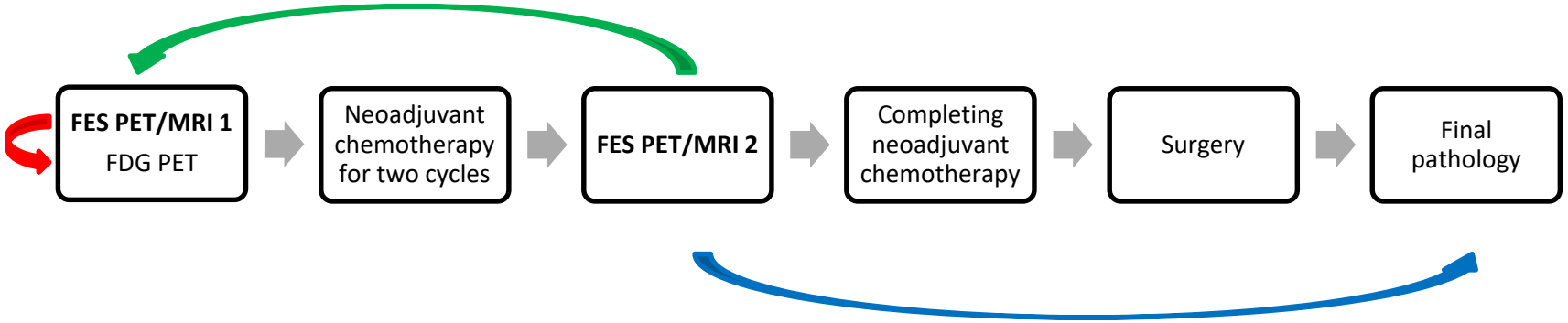
FES PET/MRI vs FDG PET in neoadjuvant setting

RESEARCH QUESTION 3:
Is the FES PET/MRI able to detect more lesions than FDG PET and to predict response to chemotherapy?

Cohort C:
LumA or ER+ Lob BC candidates to **NEOADJUVANT** chemotherapy

- **Task 3.1** FES PET/MRI vs FDG PET
- **Task 3.2** FES PET/MRI to predict early response
- **Task 3.3** FES PET/MRI to predict pCR

SAMPLE SIZE: 20 pts



FES PET/MRI vs FDG PET in metastatic setting

RESEARCH QUESTION 4:

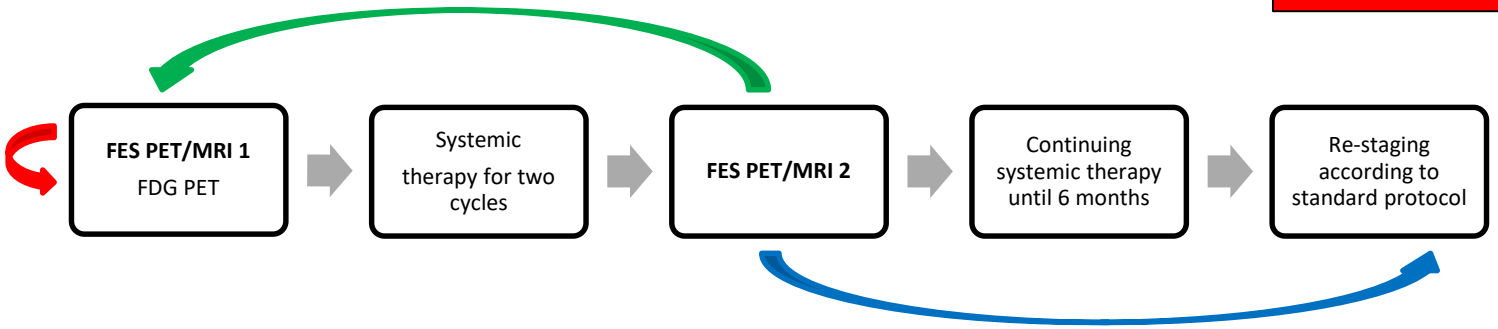
Is the FES PET/MRI able to detect more lesions than FDG PET and to predict response to therapy?

Cohort D:

METASTATIC LumA or ER-positive Lob BC, at first diagnosis or in progression

- **Task 4.1** FES PET/MRI vs FDG PET
- **Task 4.2** FES PET/MRI to predict early response
- **Task 4.3** FES PET/MRI to predict response after 6 month follow-up
- ***Task 4.4*** Elucidating the differences in FES PET/MRI changes after chemotherapy or chemo-free therapy

SAMPLE SIZE: 30 pts



Biological determinants of tumor heterogeneity

RESEARCH QUESTION:

Does intra- and inter-lesion heterogeneity correlate with biological tumor features?

Translational cohort:

SELECTED CASES of large (<2cm) tumors from all cohorts showing heterogeneity on PET/MRI

- The PI and involved researchers will select cases of heterogeneous tumor on imaging. Samples deriving from surgery or biopsy of these tumors will be analyzed by the OSR Center for Omics Sciences through RNA sequencing.

No sample size

IMAGING
Cohorts C-D

- Task 5.1 FES PET vs FDG PET

PATHOLOGY
Cohorts A-B-C-D

- Task 5.2 Pathological features - FES uptake

GENE EXPRESSION
Cohorts A-B-C-D

- Task 5.3 Tumor gene expression - FES PET/MRI parameters

Study site

I.R.C.C.S. Ospedale San Raffaele

IRCCS OSPEDALE SAN RAFFAELE

SCIENTIFIC RESEARCH

DIVISIONS INSTITUTES CENTERS CORE FACILITIES CLINICAL RESEARCH CENTERS

A RESEARCH HOSPITAL

UniSR

Università Vita-Salute San Raffaele

RESEARCH TEAM

Breast Surgery Unit

- 1. Oreste D. Gentilini
- 2. Veronica Zuber
- 3. Sara Baleri
- 4. Giovanni Cisternino (PhD candidate)
- 5. Silvia Paola Corona
- 6. Mario Rampa
- 7. Nicole Rotmensz
- 8. Manuela Morgante

Medical Oncology Unit

- 9. Giampaolo Bianchini
- 10. Giulia Viale
- 11. Stefania Zambelli
- 12. Zucchinelli Patrizia

Nuclear Medicine Department

- 13. Luigi Gianolli
- 14. Carla Canevari
- 15. Patrizia Magnani
- 16. Michela Olivieri
- 17. Paola Scifo
- 18. TBD

Breast Imaging Unit

- 19. Pietro Panizza
- 20. Elena Venturini

Pathology Department

- 21. Isabella Sassi
- 22. TBD

Statistician

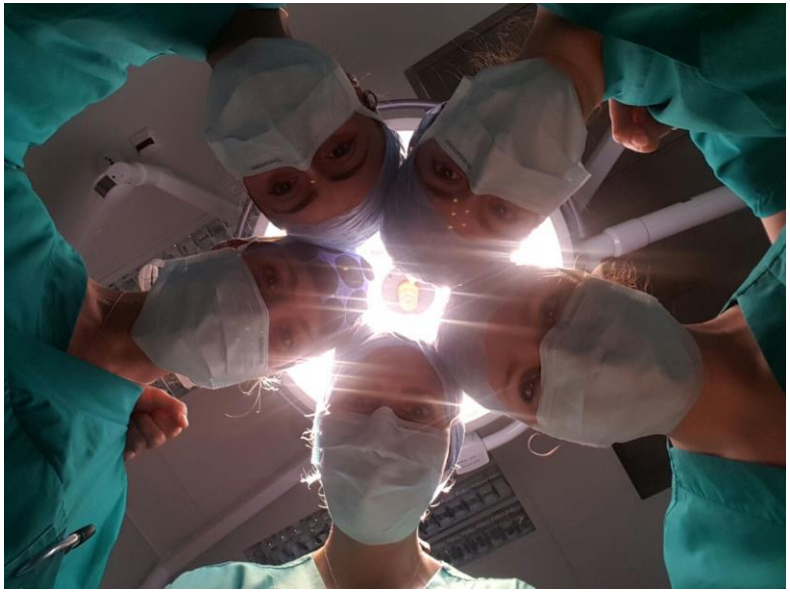
- 23. Vincenzo Bagnardi

External collaborators

24. Francesca Gallivanone
25. Maria Giulia Cangi
26. Marjolein Smidt
27. Thiemo Van Nijnatten

Omics Center

28. Giovanni Tonon
29. Marco Morelli
30. Lazarevic Dejan



Consiglio Nazionale delle Ricerche

Maastricht UMC+

5. Conclusions

- The advantages PET/MRI are a **lower radiation dose** when compared to PET/CT, **better inter-observer agreement**, a **one-stage exam** and more accurate **detection of brain, bone and liver metastases**.
- PET/MRI is still an **expensive and time-consuming** imaging method; despite the attractiveness of performing a single exam when both PET and MR imaging are indicated, PET/MRI still exhibits limitations and a high number of **false positive results**.
- Preliminary results showed that PET/MRI **may have an impact** on treatment strategy but false positive results may lead to overtreatment so any new finding should be confirmed by further biopsy.
- To date, evidence available is not sufficient to define which patient cohort could benefit from a staging with PET/MRI. Ongoing studies will help tailoring **molecular imaging** on the basis of tumor biology and if PET/MRI achieves a higher diagnostic accuracy it might play a role in BC management.

OSPEDALE
SAN RAFFAELE

THANKS FOR THE ATTENTION!