

Progetto CANOA

CARCINOMA MAMMARIO: QUALI NOVITA' PER IL 2024?

"Saper leggere" uno studio clinico per migliorare la pratica clinica



Coordinatori scientifici:

Stefania Gori
Giovanni L. Pappagallo

Verona, 22-23 Marzo 2024
Hotel Leon d'Oro

**Stadiazione nel carcinoma
mammario localmente avanzato:
è raccomandabile PET-TC-FDG?**

Contro:

Gaia Griguolo

*DiSCOG, Università di Padova
UOC Oncologia 2, IOV - IRCCS*



Definition of LABC

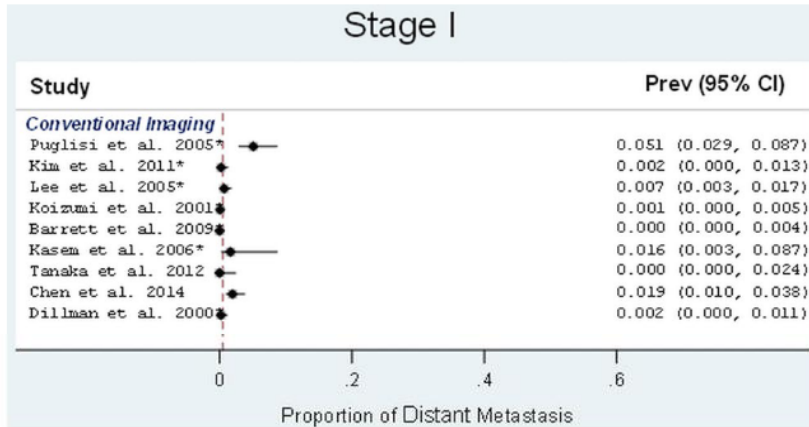
- Stage IIIA to IIIC disease
- Stage IIB disease (T3N0) - ? large operable

Breast carcinoma TNM anatomic stage group AJCC UICC 2017

When T is...	And N is...	And M is...	Then the stage group is...
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC

BC Staging: What do we know?

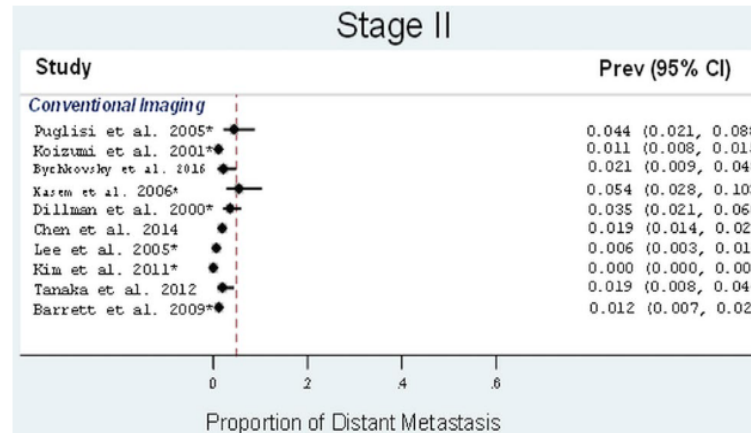
Retrospective, observational, and single-institution studies



Conventional Imaging

(mainly CE CT scan+ bone scan; in some cases chest Rx + abdomen ultrasound)

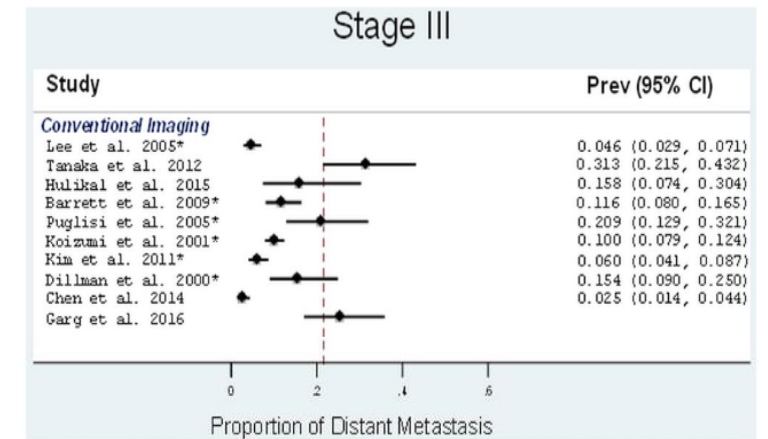
Prevalence of distant metastasis: 1.0% (0%-5%)



Conventional Imaging

(mainly CE CT scan+ bone scan; in some cases chest Rx + abdomen ultrasound)

Prevalence of distant metastasis: 1.9% (0%-5.4%)



Conventional Imaging

(mainly CE CT scan+ bone scan; in some cases chest Rx + abdomen ultrasound)

Prevalence of distant metastasis: 21% (3%-31%)

**ROUTINE SYSTEMIC
IMAGING IS RECOMMENDED**

Staging for LABC

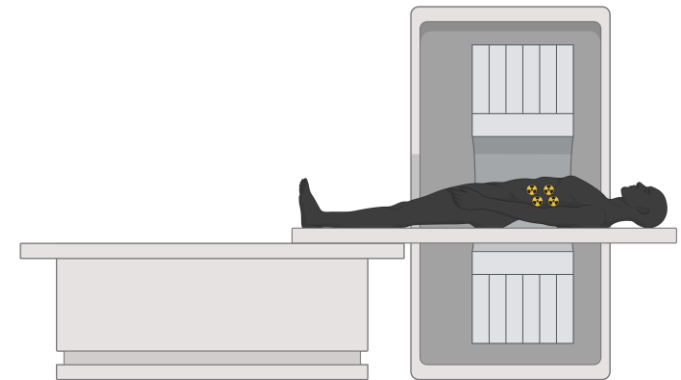
Traditional Staging

- CE Thorax/abdomen CT scan
- Bone scan

VS

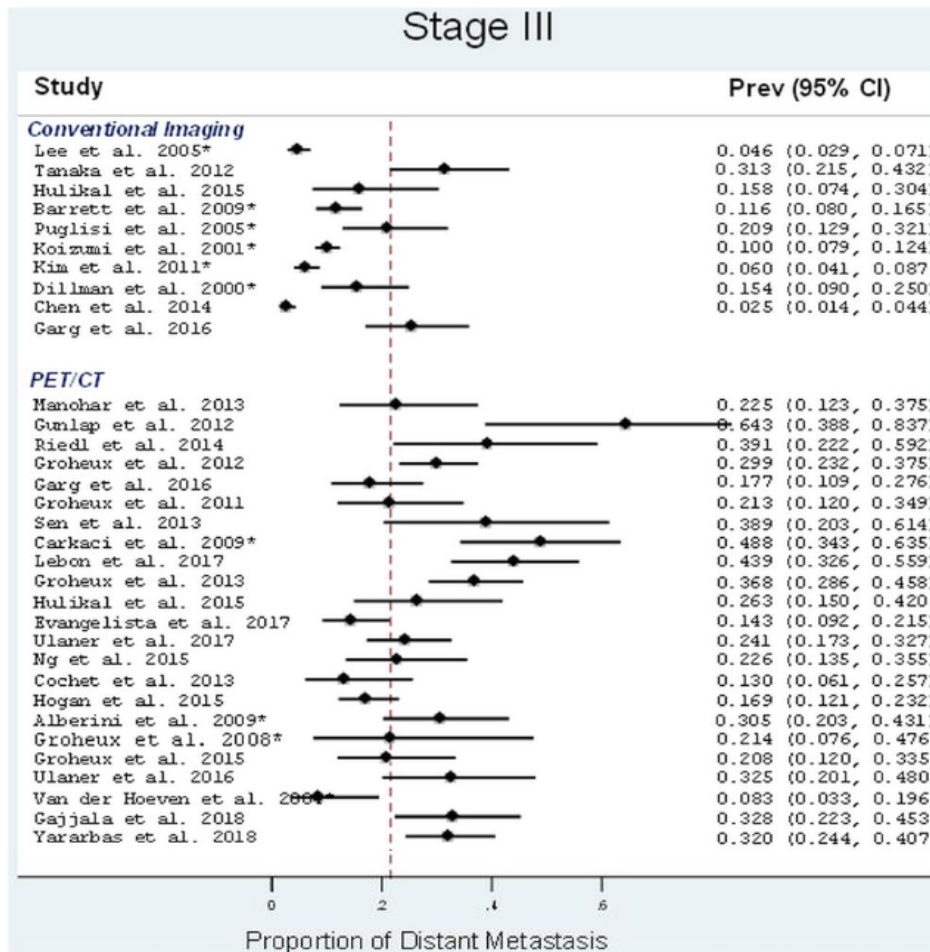
FDG PET/CT scanning when conventional staging studies yield nondiagnostic or suspicious results

FDG PET/CT Scan



BC Staging: What do we know about PET/CT?

Retrospective, observational, and single-institution studies



Prevalence of distant metastasis: 21% (3%-31%)

Prevalence of distant metastasis: 26% (8%-64%)

Staging for LABC

- **CE Thorax/abdomen CT scan**
- **Bone scan**






*FDG PET/CT scanning **can** be performed for high risk patients or when conventional staging studies yield non-diagnostic or suspicious results*

Traditional Staging vs FDG PET/CT Scan for LABC Staging

Original Reports | Breast Cancer

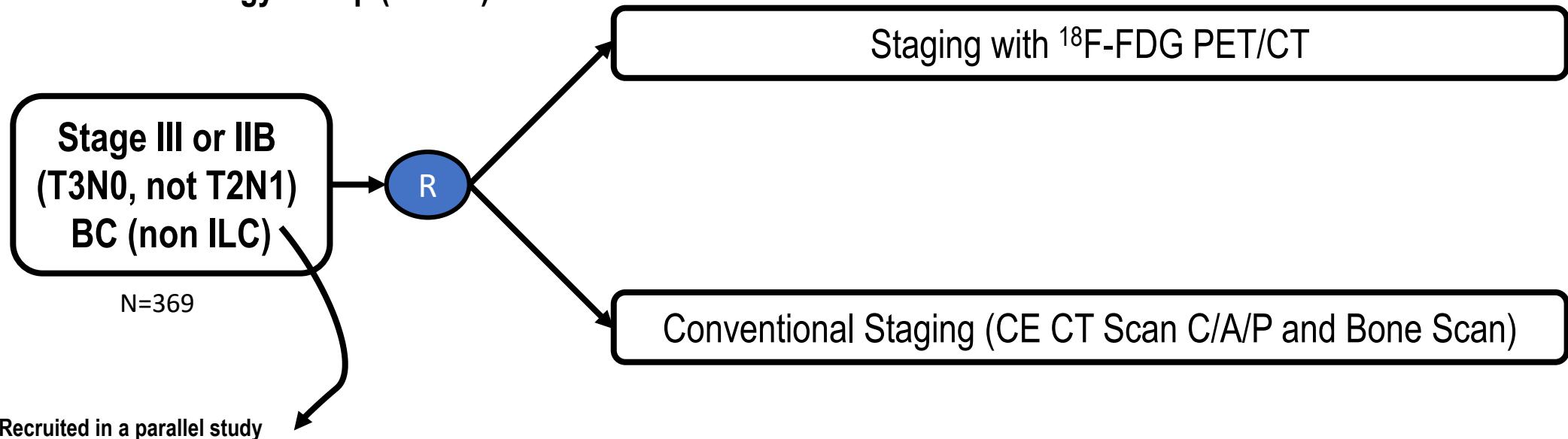
Journal of Clinical Oncology®

Impact of ¹⁸F-Labeled Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography Versus Conventional Staging in Patients With Locally Advanced Breast Cancer

Ian S. Dayes, MD, MSc^{1,2,3,4} ; Ur Metser, MD^{5,6} ; Nicole Hodgson, MD, MSc⁷; Sameer Parpia, PhD^{1,3,4}; Andrea F. Eisen, MD^{8,9,10}; Ralph George, MD^{11,12} ; Phillip Blanchette, MD, MSc^{13,14}; Tulin D. Cil, MD^{5,11} ; Angel Arnaout, MD^{15,16}; Adrien Chan, MD, MPH^{17,18}; and Mark N. Levine, MD, MSc^{1,2,3,4} 

DOI <https://doi.org/10.1200/JCO.23.00249>

Ontario Clinical Oncology Group (OCOG)



Traditional Staging vs FDG PET/CT Scan for LABC Staging

TABLE 1. Baseline Characteristics

Characteristic	PET-CT (n = 184)	Conventional (n = 185)
ECOG, No. (%)		
0	165 (90)	166 (90)
1	15 (8)	17 (9)
2	1 (<1)	1 (<1)
Missing	3 (2)	1 (<1)
Stage, No. (%)		
IIB	52 (28)	42 (23)
IIIA	93 (50)	104 (56)
IIIB	36 (20)	35 (19)
IIIC	3 (2)	4 (2)
Grade, No. (%)		
I	7 (4)	5 (3)
II	88 (48)	86 (46)
III	76 (41)	86 (46)
Unknown	13 (7)	8 (4)
ER status, No. (%)		
Positive	129 (70)	132 (72)
Negative	55 (30)	52 (28)
PR status, No. (%)		
Positive	96 (52)	99 (54)
Negative	87 (47)	84 (45)
Unknown	1 (<1)	2 (1)
Her2Neu, No. (%)		
Positive	65 (35)	58 (32)
Negative	119 (65)	120 (65)
Missing	0 (0)	7 (3)
Age, years: mean, SD	53 (13)	53 (13)
Primary tumor size, cm: mean, SD	6.6 (2.7)	7.0 (3.5)

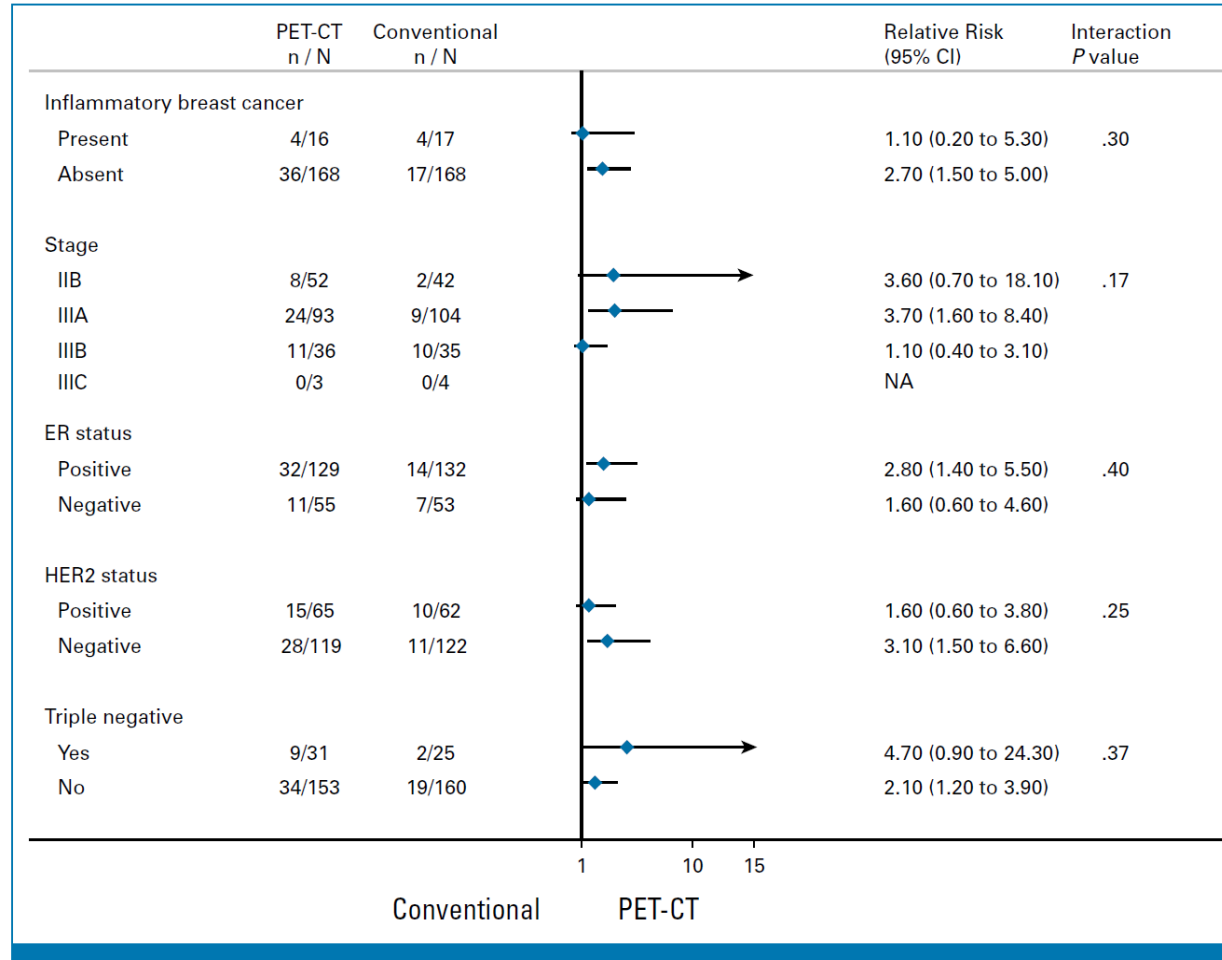
More than twice as many PET-CT pts were upstaged to stage IV than conventionally staged pts

% pts upstaged to stage IV	
PET-CT	Conventional Staging
23% (N=43)	11% (N=21)
RR 2.4 (95% CI, 1.4 to 4.2) P=0.002	

Fewer patients in the PET-CT group received combined modality therapy

81 % (149/184) PET-CT staged pts vs
89% (165/185) conventional staged pts
P=0.03

Traditional Staging vs FDG PET/CT Scan for LABC Staging



**No significant interaction
with other
clinical/pathological factors**

FIG 2. Relationship between subgroups and upstaging. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not available; PET-CT, positron emission tomography-computed tomography.

Traditional Staging vs FDG PET/CT Scan for LABC Staging

TABLE 3. Sites of Metastases for Upstaged Patients

Distant Site	PET-CT, No. (n = 184)	Conventional, No. (n = 185)
Bone only	14	6
Bone, liver	6	1
Bone, lung	0	5
Mediastinal nodes only	3	0
Lung only	3	2
Liver only	2	0
Bone, mediastinal nodes	2	0
Bone, lung, liver	2	2
Bone, lung, mediastinal nodes	2	0
Mediastinal nodes, neck nodes	1	0
Lung, mediastinal nodes	1	0
Lung, mediastinal nodes, contralateral, ^a neck nodes	1	0
Liver, ovary	1	0
Liver, mediastinal nodes	1	0
Lung, liver	1	2
Bone, mediastinal nodes, neck nodes	1	0
Bone, mediastinal nodes, contralateral, ^a pleura	1	0
Bone, mediastinal nodes, retroperitoneal nodes	1	0
Lung, bladder	0	1
Liver, adrenal	0	1
Pancreas	0	1

The percent agreement between the local reader and central reader was 92%, and kappa was 0.78 (95% CI, 0.68 to 0.88).

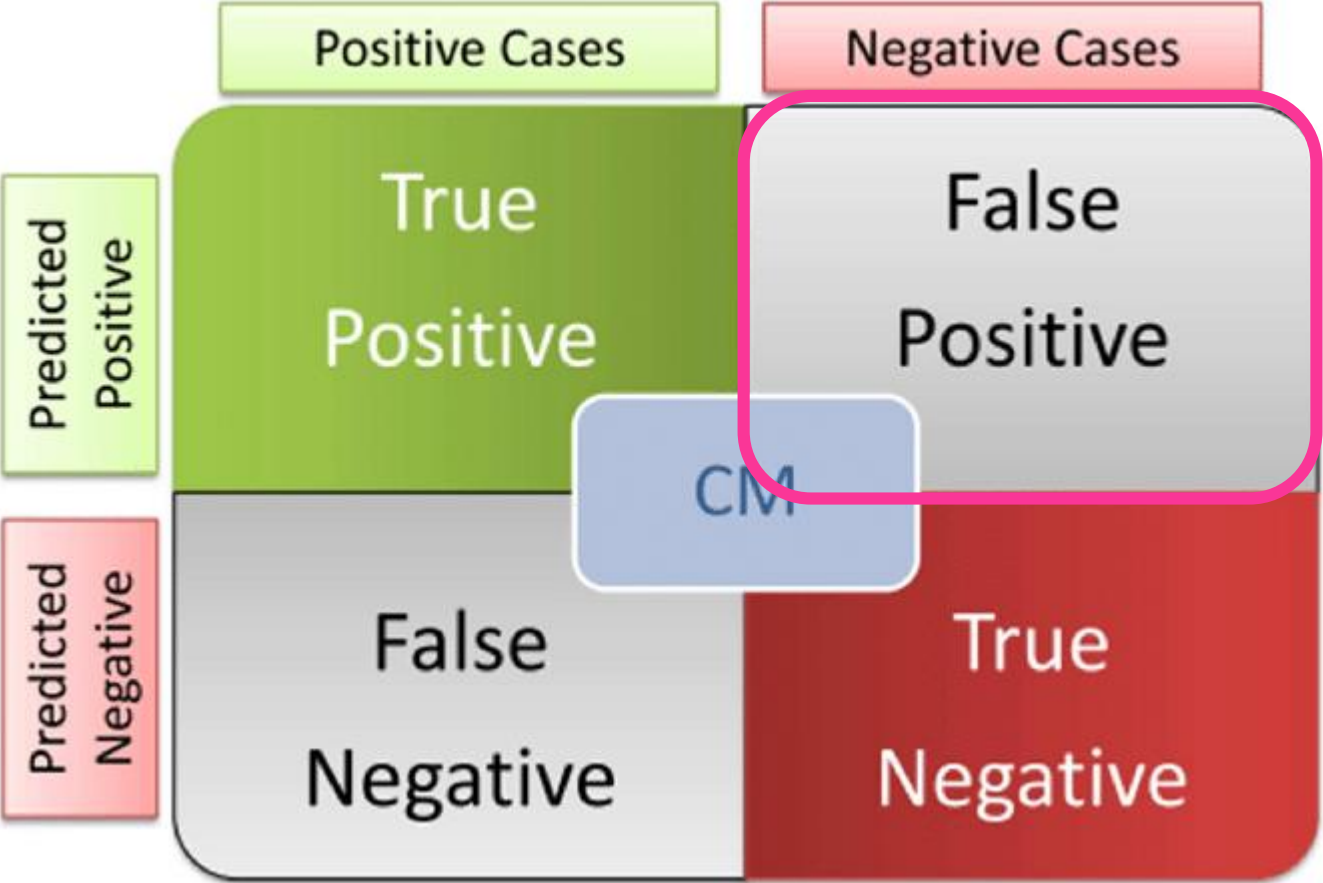
TABLE A3. Diagnostic Tests for Patients Upstaged Within 6 Weeks of Random Assignment

Diagnostic Test	PET-CT (n = 43)	Conventional (n = 21)
Patients with diagnostic tests, No.	22	5
Diagnostic tests, ^a No.	35	7
Bone scan	11	0
CT scan	9	0
MRI	4	2
Mediastinoscopy	1	0
Needle aspirate	1	1
US	4	2
X-ray	5	2

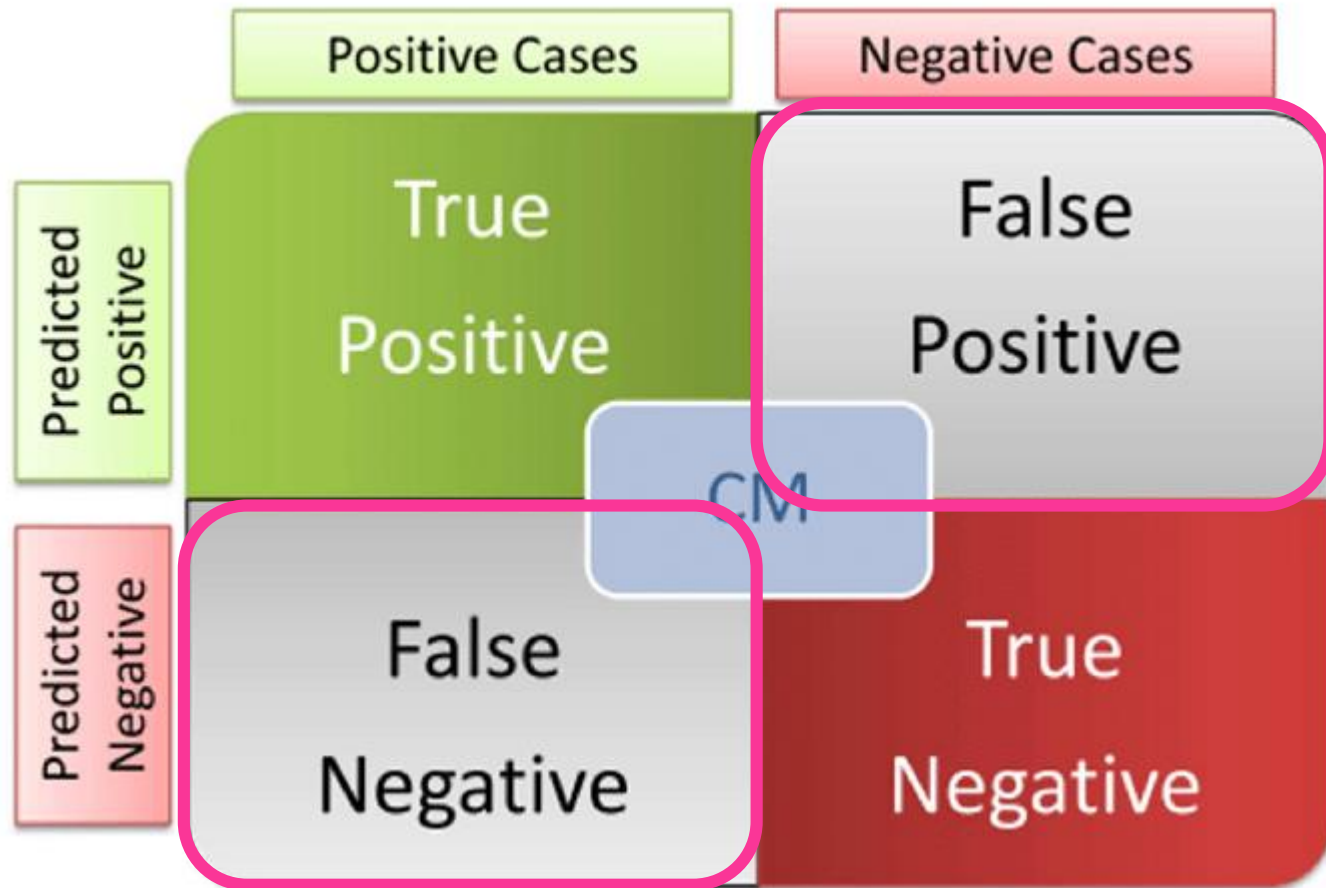
Only 2 cases of distant metastases were histologically confirmed

Consistent risk of false positive results

FDG PET/CT for LABC Staging: Potential risks



FDG PET/CT for LABC Staging: Potential risks



Factors known to have an impact on FDG captation:

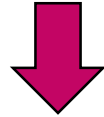
- Histological grade (G1-2G vs G3)
 - Histotipe (Lobular vs NST)
 - Proliferation (low ki67 vs high ki67)
 - Hormone receptors (HR+ vs HR-)
 - PgR (PgR + vs PgR-)
 - Phenotype (other phenotypes vs TNBC)
- Among HR+ tumors, Luminal A vs Luminal B

FDG PET/CT for LABC Staging: which is the real impact?

In LABC, staging with PET-CT detects more distant metastases than conventional staging (bone scan, CT of the chest/abdomen and pelvis)



Fewer PET-CT staged patients receive combined modality therapy



Fewer PET-CT staged patients are treated with curative intent

Is this the correct endpoint?

FDG PET/CT for LABC Staging: which is the real impact?

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Is this the correct endpoint?

These patients were not treated in pivotal clinical trials for MBC

Beyond diagnostic accuracy: The clinical utility of diagnostic tests

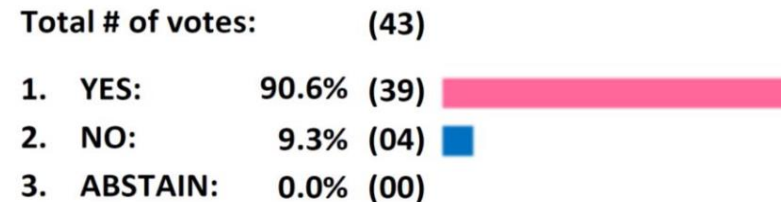
“...standard use of a test in routine clinical practice should be recommended only if the marker reliably adds to the clinician’s judgment during clinical decision-making, resulting in a more favorable clinical outcome for the patient.”

These favorable outcomes are increased overall survival, increased disease-free survival, improved quality of life, and/or reduced cost of care....”

Is Stage IV BC always incurable? There might be exceptions

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)

A small but very important subset of patients with ABC, for example those with **oligo-metastatic disease or low volume metastatic disease** that is highly sensitive to systemic therapy, can achieve complete remission and a long survival. A multimodal approach, including local-regional treatments with curative intent, should be considered for these selected patients (LoE: Expert opinion).



Cardoso F et al, Ann Oncol 2020











Around 50% of patients diagnosed with Stage IV in the PETABC trial might have these characteristics

Is Stage IV BC always incurable?

Comments and Controversies

Journal of Clinical Oncology®

De Novo Oligometastatic Breast Cancer

Lajos Pusztai, MD, DPhil¹ ; Mariya Rozenblit, MD¹ ; Peter Dubsy, MD, PhD² ; Thomas Bachelot, MD³ ; Anna M. Kirby, MB BChir, MD⁴ ; Barbro K. Linderholm, MD, PhD⁵; Julia R. White, MD⁶ ; Steven J. Chmura, MD, PhD⁷ ; Lisa A. Carey, MD⁸ ; Boon H. Chua, MB BS, PhD⁹ ; and Kathy D. Miller, MD¹⁰ 

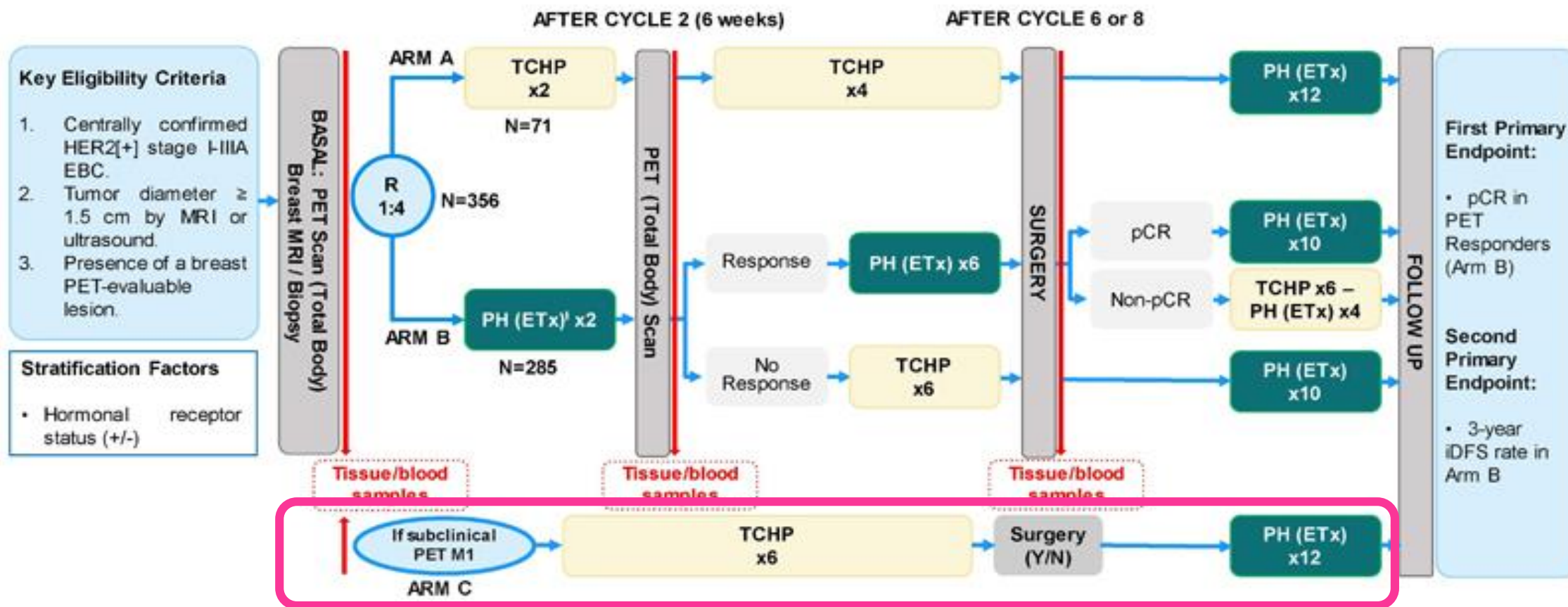
DOI <https://doi.org/10.1200/JCO.23.00911>

De novo metastatic breast cancers ... distant metastases often share molecular similarities with the primary tumor...among these patients, those with oligometastatic disease represent a unique subset that could be rendered NED. This clinical setting resembles patients with stage IIIC disease after surgical resection and radiation therapy; in both settings, macroscopic disease was eliminated, but the presence of micro metastasis is very likely, or certain...

Until 2002, supraclavicular lymph node involvement at presentation was considered M1 (stage IV) metastatic disease, and these patients were considered incurable and often received systemic therapies only with palliative intent. However, clinical data indicated that this group of patients when treated with combined modality therapy had long-term survival similar to stage III breast cancers, eventually leading to reclassification to N3c (stage IIIC) disease (AJCC edition 7), and today they all receive multimodality therapy with curative intent.

Might in one day we consider oligometastatic stage IV breast cancer as stage IIID disease?

PHERGAIN Trial Design



Preventing a TNBC or HER2+ pt for receiving multiagent chemotherapy and immunotherapy or anti-HER2 treatment due to subclinical M1 might not be the best treatment option
 (CE CT scan and bone scan are usually used to confirm staging in most EBC and LABC clinical trials)

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20% of pts upstaged by PET/CT continued to receive combined modality therapy

Conclusions: Contra

- Diagnosing metastatic disease is not enough
- We need to demonstrate that this results in a more favorable clinical outcome for the patient
- If we want to widely use PET/CT for disease staging, we need to know how to treat these patients to obtain the best clinical outcomes

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