SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

OECI CLINICAL Cancer Centre

X-ray medical imaging at Azienda USL-IRCCS Reggio Emilia

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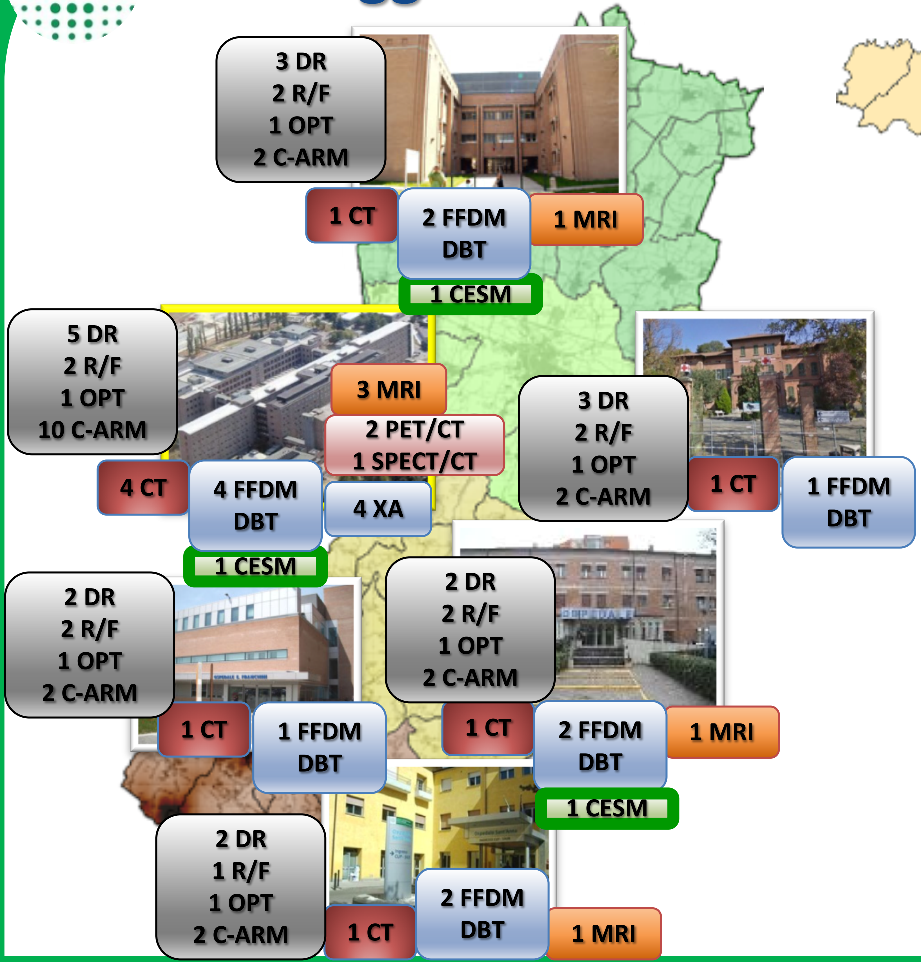
Advanced Medical Imaging with Synchrotron and Compton X-ray Sources

21-22 November 2019
Bologna

Reggio Emilia's Province Public Healthcare System



Azienda USL – IRCCS di Reggio Emilia

	S. Maria Nuova Hospital	**Ex-AUSL**
Beds	890	750 (5 hospitals)
Inpatient access	50,000/y	39,000/y
Outpatient access	>1,500/d	2,000/d
Employees	2,400	3,700
Radiology exams	> 180,000/y	> 220,000/y

AUSL-IRCCS di Reggio Emilia catchment area comprises a population of approximately **530,000** people

Mammography at AUSL-IRCCS Reggio Emilia

- Breast screening can reduce mortality
- However, sensitivity is not optimal → it limits screening efficacy
- The same intervention is proposed to all women independently from their inherent risk

→New strategies should be considered to improve Breast screening and x-ray mammography in general

Breast Cancer Screening: state of the art

NIH NATIONAL CANCER INSTITUTE

- **Mammography** is the most widely used screening modality

Benefits

- **Decreases breast cancer mortality in women 50 to 69 y/o**
- **Increases breast cancer incidence** in a given population
- **Changes the characteristics of cancers detected**, with increased incidence of
  - lower-risk cancers
  - premalignant lesions
  - DCIS

Potential harms:

- ***Overdiagnosis*** *and resulting treatment of insignificant cancers*
- ***False Positives*** *with additional testing and anxiety*
- ***False Negatives*** *with false sense of security and potential delay in diagnosis*
- *Radiation-Induced Breast Cancer*

Physical characteristics: FFDM

Mammography system	GE Senographe SenoClaire	GE Senographe Pristina
x-Ray tube Anode/filter (mm)	Mo/Mo (0.03)	Mo/Mo (0.03)
	Mo/Rh (0.025)	Rh/Ag (0.03)
	Rh/Rh (0.025)	
Detector type	(CsI:Tl)/a-Si	(CsI:Tl)/a-Si
Pixel size (µm)	100	100
FOV (cm^2)	23.9 x 30.6	24 x 28.9
Pixel array	2394 x 3062	2394 x 2850
Source to table distance	635 mm	637 mm
Source to detector distance	658 mm	660 mm
AEC Modes	Standard, Contrast, Dose	Dose +, Standard, Dose

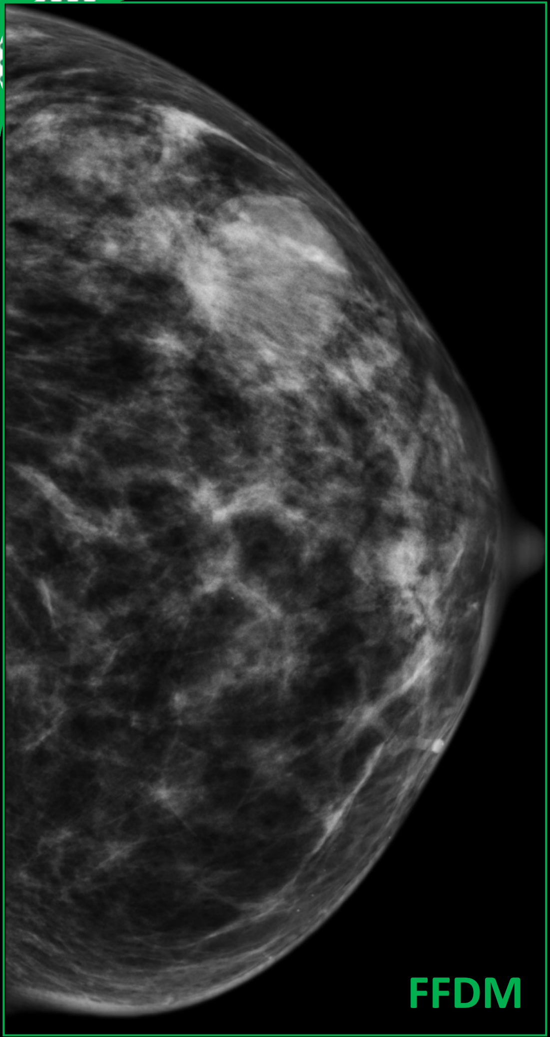
10 units

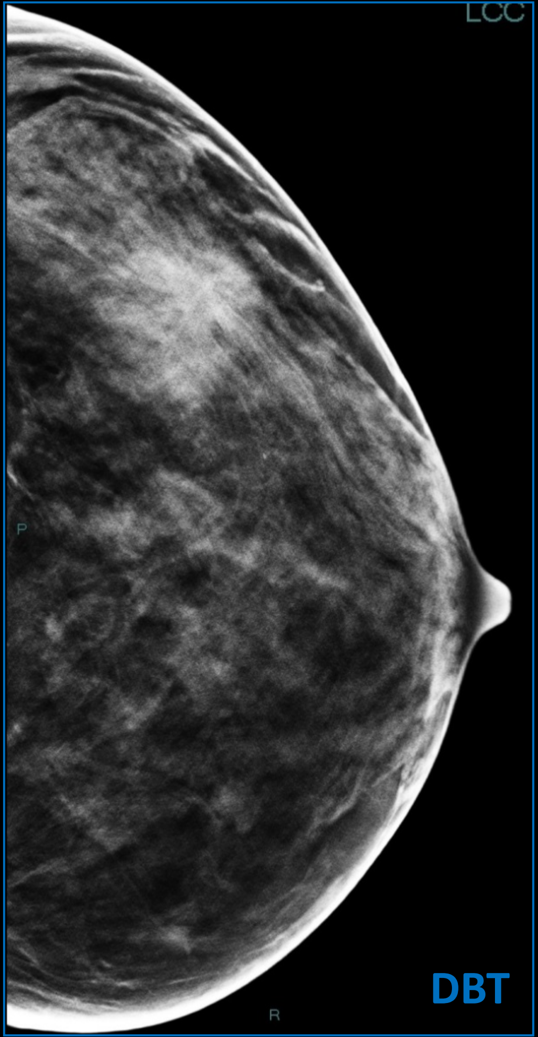
1 unit

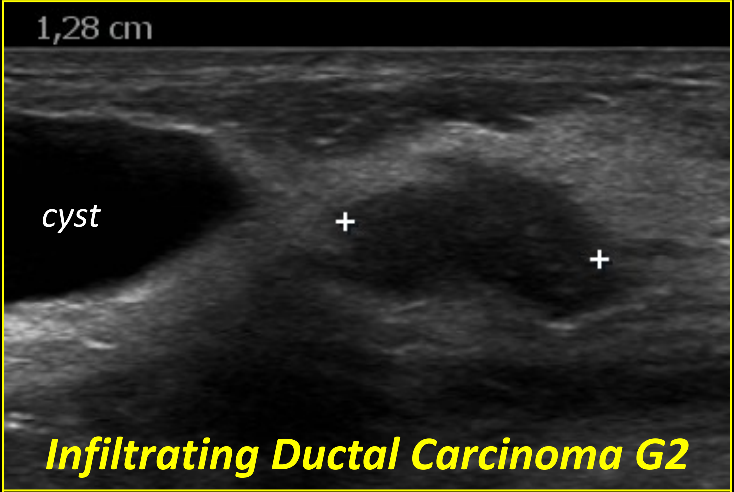
Physical characteristics: DBT

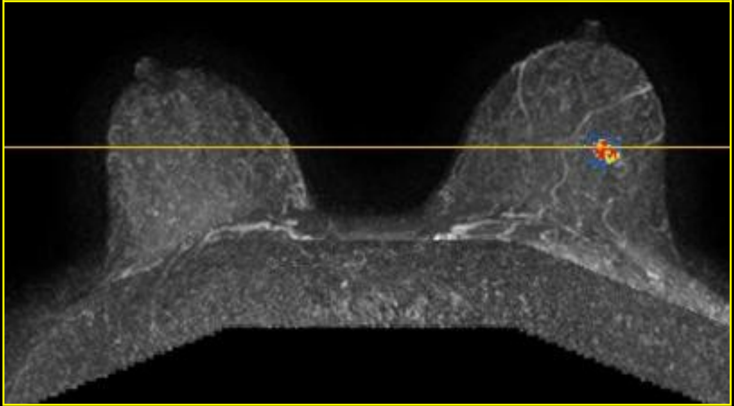
Mammography system	GE Senographe SenoClaire	GE Senographe Pristina
x-ray tube Anode/filter (mm)	Mo/Mo (0.03)	Mo/Mo (0.03)
	Mo/Rh (0.025)	Rh/Ag (0.03)
	Rh/Rh (0.025)	
Detector type	(CsI:Tl)/a-Si	(CsI:Tl)/a-Si
Pixel size (µm)	100 no binning	100 no binning
FOV (cm^2)	23.9 x 30.6	24 x 28.9
Pixel array	2394 x 3062	2394 x 2850
Grid	Yes/static	Yes/static
Angular range / # of projections	25° / 9	25° / 9
Acquisition time (s)	7	5
Reconstruction algorithm	Iterative	Iterative

DBT overcomes superimposition!



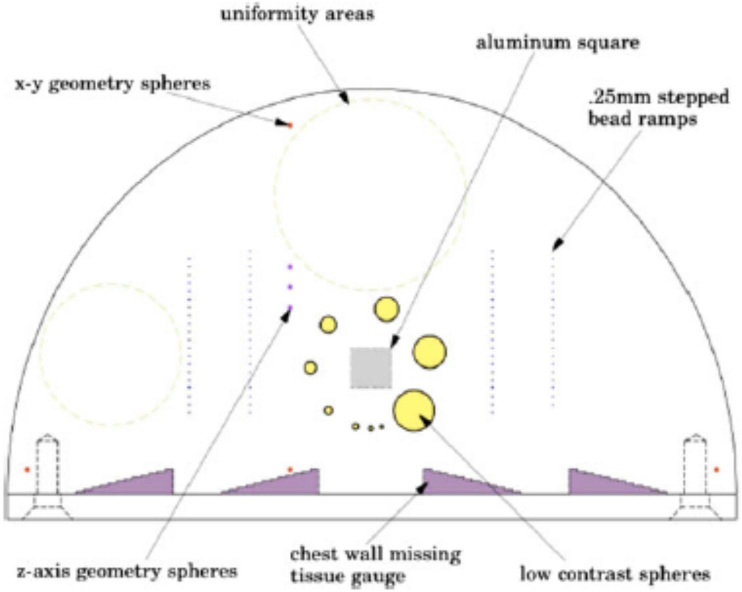






DBT quality evaluation

- We evaluated DBT quality using metrics such as:
  - Planar MTF (f)
  - Planar NNPS
  - Signal difference to noise ratio (SDNR)
  - Artifact spread function (ASF)
  - Uniformity



Radiation Protection Dosimetry (2018), pp. 1–13
doi:10.1093/rpd/ncy024

PHYSICAL CHARACTERISATION OF FOUR DIFFERENT COMMERCIAL DIGITAL BREAST TOMOSYNTHESIS SYSTEMS

O. Ortenzia[1,*], R. Rossi[1], M. Bertolini[2], A. Nitrosi[2] and C. Ghetti[1]
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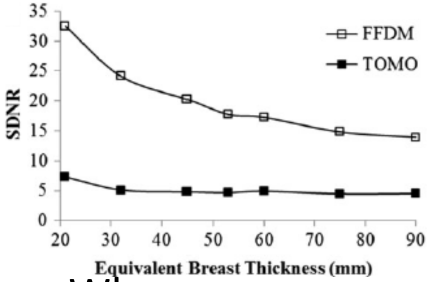
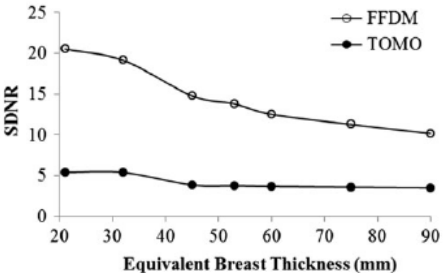
[2]Department of Medical Physics, Santa Maria Nuova Hospital of Reggio Emilia, Reggio Emilia, Italy

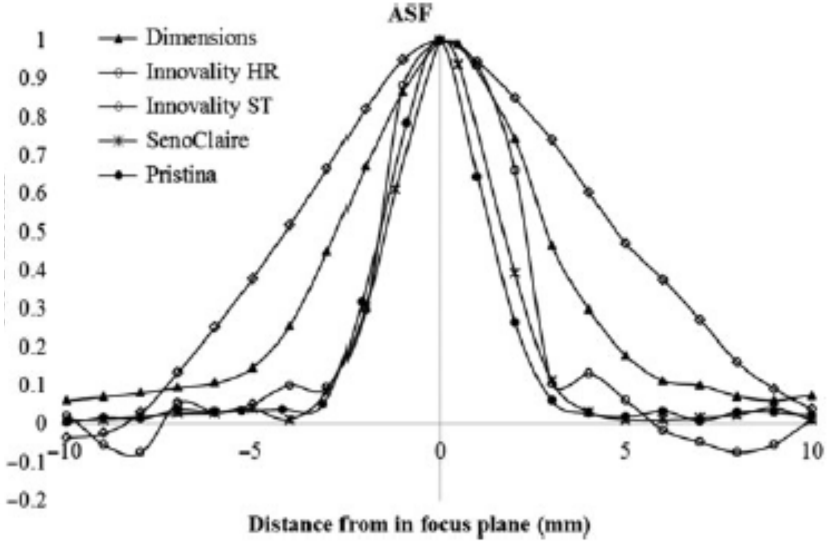
DBT: Average Glandular Dose (AGD)

SenoClaire					
Equivalent breast thickness (mm)	Anode / filter	kVp	mAs	AGD 3D	3D vs 2D AGD ratio
21	Mo/Mo	26	40	0.95	1.66
32	Rh/Rh	29	33	1.03	1.28
45	Rh/Rh	29	50	1.4	1.17
53	Rh/Rh	29	56	1.51	0.91
60	Rh/Rh	29	75	1.91	1.48
75	Rh/Rh	31	83	2.52	1.2
90	Rh/Rh	31	128	3.51	1.43
Pristina					
Equivalent breast thickness (mm)	Anode / filter	kVp	mAs	AGD 3D	3D vs 2D AGD ratio
21	Mo/Mo	26	23.1	0.6	0.95
32	Mo/Mo	26	54.4	1.02	0.99
45	Rh/Ag	34	28.2	1.22	0.95
53	Rh/Ag	34	33.7	1.33	0.98
60	Rh/Ag	34	41.1	1.5	0.98
75	Rh/Ag	34	60.1	1.91	0.97
90	Rh/Ag	34	90.7	2.56	0.97

DBT: image quality results

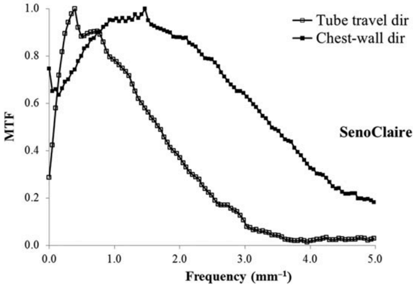


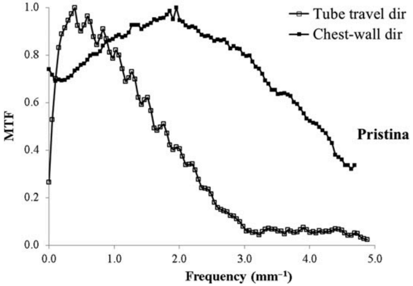




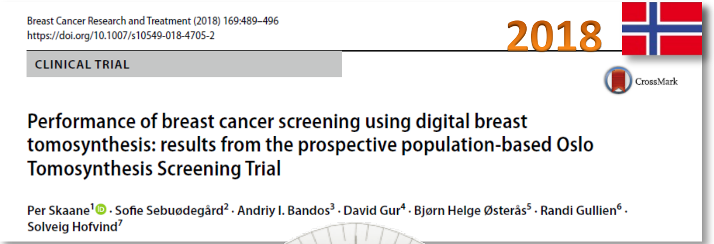
Where

- PV_{Al} is the mean value within an ROI of





DBT & Screening


Breast Cancer Research and Treatment (2018) 169:489–496
https://doi.org/10.1007/s10549-018-4705-2

2018

CLINICAL TRIAL

CrossMark

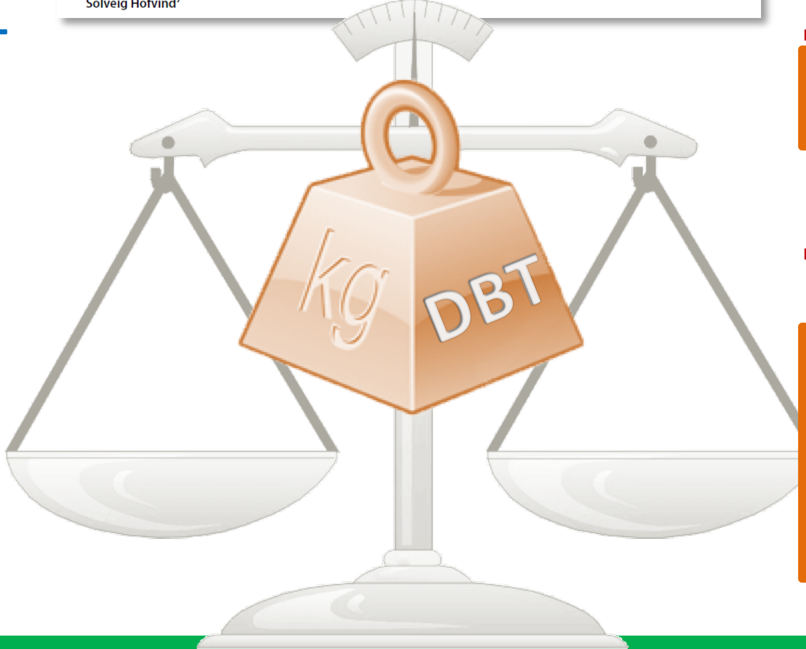
Performance of breast cancer screening using digital breast tomosynthesis: results from the prospective population-based Oslo Tomosynthesis Screening Trial

Per Skaane[1] · Sofie Sebuødegård[2] · Andriy I. Bandos[3] · David Gur[4] · Bjørn Helge Østerås[5] · Randi Gullien[6] · Solveig Hofvind[7]

Screening using FFDM + **DBT** as compared to FFDM-only demonstrated a

- significantly **higher DR**
- significantly **lower RR**
- significantly **improved specificity**

importantly in terms of reducing potential harms



- **No reduction in interval**

Interval Cancers

post-DBT screening

- Most of the additionally detected cancers were

Prognostic Characteristics of detected cancers

DBT Current Trials & Screening: DBT + FFDM

RETomo Trial

Clinical trial to evaluate the efficacy of Tomosynthesis in Breast Cancer Screening program of Reggio Emilia's province

Regional Health System Funds

Randomization

Purpose: to evaluate the clinical accuracy of **Tomosynthesis** in

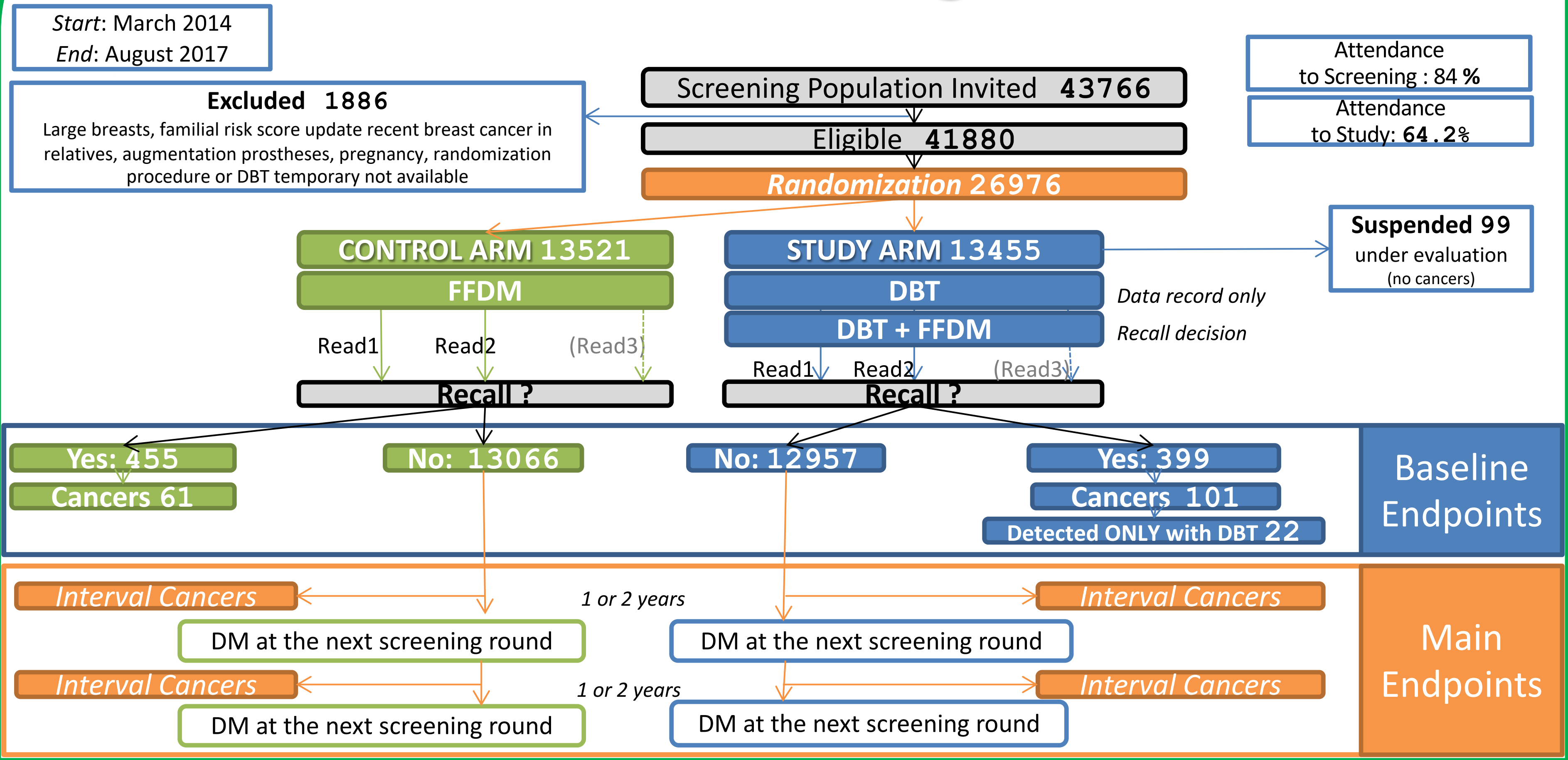
- **Interval cancers**
- **T2+ incidence** at 1st and 2nd subsequent rounds
- **Recall Rate**
- **Detection Rate**
- **Reading time**

Secondary:

- Dose levels
- Diagnostic performance index (accuracy, sensitivity, specificity, PPV, NPV, FN, FP)
- Inter-reader and intra-reader agreement
- DBT and FFDM agreement
- DR of invasive vs non-invasive cancers
- Histological cancer characteristics
- Negative biopsies incidence
- 2D CC-MLO vs DBT CC-MLO agreement
- Synthetic 2D / Volumetric CAD
- Subgroup analysis according to radiological variables (density, breast thickness..)

RE Tomo Screening Trial

european society of breast imaging
EUSOBI Annual Scientific Meeting 2018
October 11-13, 2018



II Interim Analysis
March 2016

ORIGINAL RESEARCH • BREAST IMAGING

Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial

Pierpaolo Pattacini, MD • Andrea Nitrosi, MMP • Paolo Giorgi Rossi, PhD • Valentina Iotti, MD • Vladimiro Ginocchi, MD • Sara Ravaioli, MD • Rita Vacondio, MD • Luca Braglia, MSc • Silvio Cavuto, MSc • Cinzia Campari, MSc • for the RETomo Working Group

From the Radiology Unit (P.P., V.I., V.G., S.R., R.V.), Medical Physics Unit (A.N.), Epidemiology Unit (P.G.R.), Scientific Directorate (L.B., S.C.), and Screening Coordinating Centre (C.C.), AUSL Reggio Emilia, IRCCS, Via Amendola 2, Reggio Emilia 42122, Italy. Received September 24, 2017; revision requested November 8; revision received January 24, 2018; accepted January 24. **Address correspondence to** P.G.R. (e-mail: *mailto:paolo.giorgirossi@ausl.re.it*).

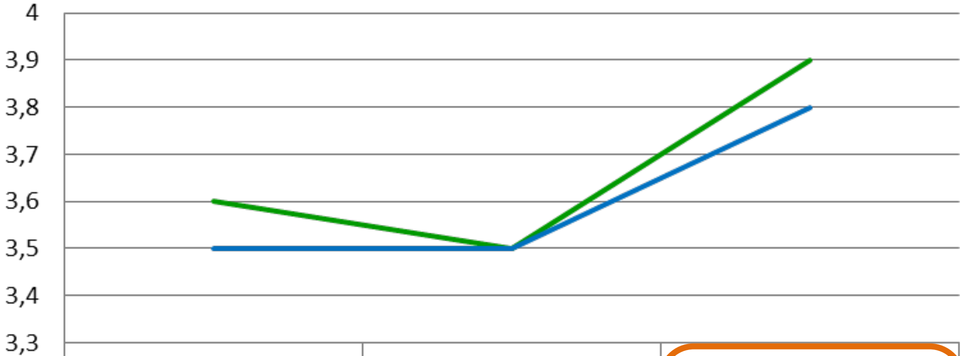
Supported in part by the Emilia-Romagna Regional Health Authority (Bando Modernizzazione 2012). Supported by the institutional funds of the Azienda Unità Sanitaria locale Reggio Emilia and the Arcispedale S. Maria Nuova, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, and by GE Healthcare, which provided part of the breast tomosynthesis equipment.

Conflicts of interest are listed at the end of this article.

Radiology 2018; ■:1–10 • https://doi.org/10.1148/radiol.2018172119 • Content code: BR

Recall Rate

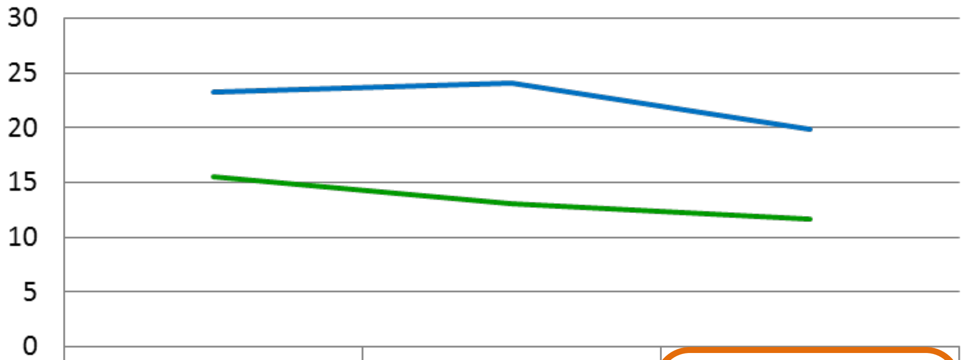
CONTROL ARM	STUDY ARM
3.9 %	3.8 %



	I interim	II interim	Final data
Control Arm	3,6	3,5	3,9
Study Arm	3,5	3,5	3,8

Positive Predictive Value

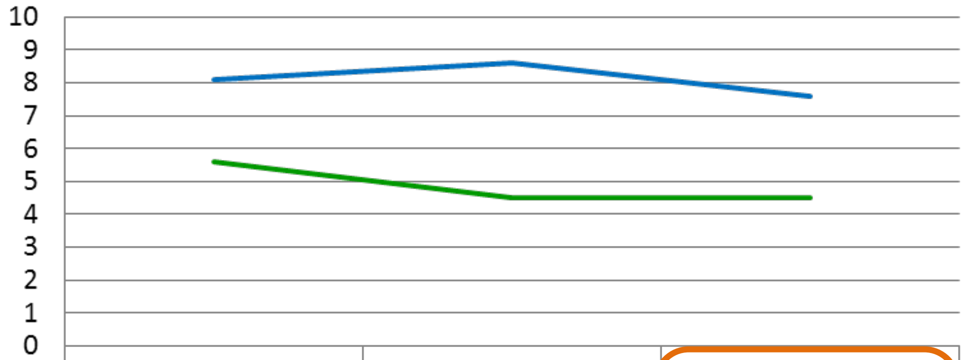
CONTROL ARM	STUDY ARM
11.7 %	**19.8 %**



	I interim	II interim	Final data
Control Arm	15,5	13	11,7
Study Arm	23,3	24,1	19,8

Detection Rate

CONTROL ARM	STUDY ARM
4.5 ‰	7.6 ‰



	I interim	II interim	Final data
Control Arm	5,6	4,5	4,5
Study Arm	8,1	8,6	7,6
	+ 45 %	+ 78 %	+ 68 %

DBT Current Trials & Screening: Risk

MyPEBS

2018 / 26

Not yet recruiting in Italy (probably form Dec 2019!)

My Personalized Breast Screening *UNICANCER*

- Randomized, open-label, multicentric, study assessing the effectiveness of a **risk-based breast cancer screening strategy** compared to **standard screening** (according to the current national guidelines in each participating country) in detecting stage 2 or higher breast cancers
- Follow up data will be collected for 15 years from study entry for evaluation of **long-term cumulative breast cancer incidence** and **breast cancer-specific survival**

INT: Randomized

85 000 (40/70 yo)

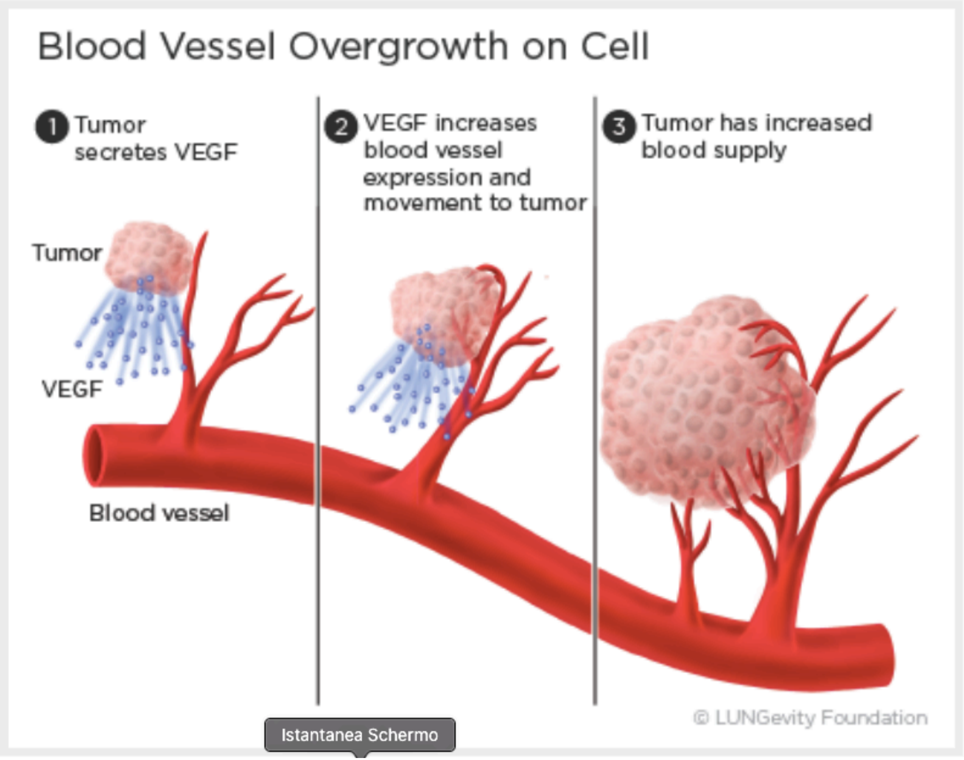
DBT alternative to FFDM

DEDICATED CENTRALIZED RISK-EVALUATION SOFTWARE *(Mammorisk / Tyrer-Cuzick)*

- family history
- previous history of benign breast biopsy
- personal hormonal and reproductive history
- breast mammographic **density**
- genotyping results (polygenic risk score - SNPs)

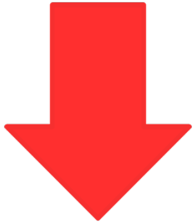
M/DBT | M/DBT | M/DBT | M/DBT +/- US | M/DBT | M/DBT + US | MRI +/- US | M/DBT | M/DBT

From morphological to functional x-ray mammography



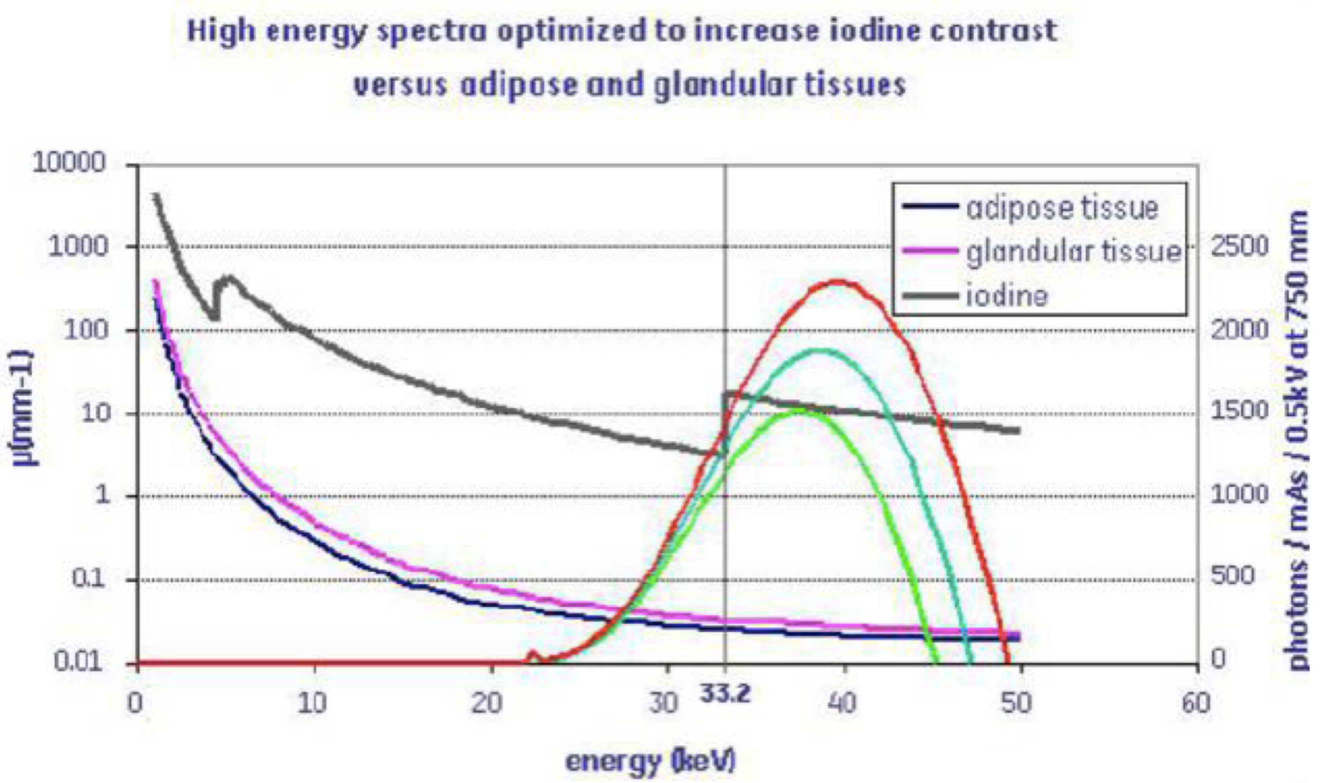
How to:

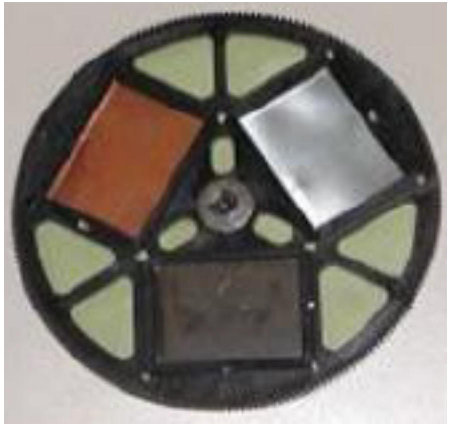
- Solve diagnostic doubts ?
- Assess the extent of disease ?
- Monitor response to therapy ?
- Screen high risk women ?



CESM

CESM: realization (GE Healthcare solution)





- Dual Energy solution (Mo and Cu filters)
- Iodinated contrast medium (peak @ 33.2 keV)

How to select better energies?

- The knowledge of optimal monoenergetic spectra is a good indicator for the design of optimal spectra by standard sources

Aerial view of the ESRF (courtesy of ESRF/D. Morel)

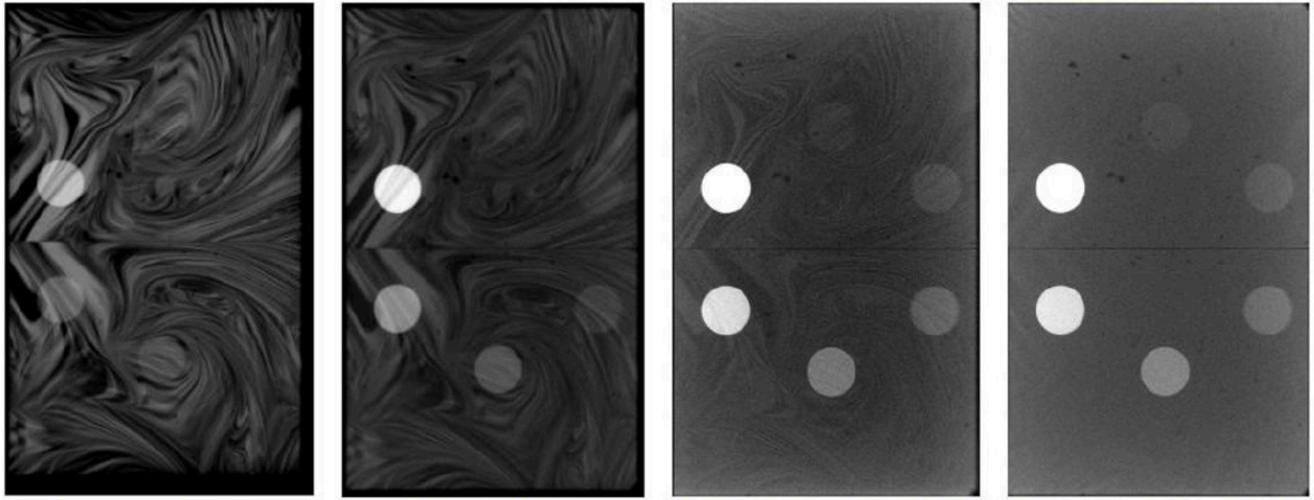
- GE Healthcare validated its spectra at the European Synchtrotron Radiation Facility (ESFR) in Grenoble (France), using monoenergetic radiations.

X-ray spectra selection for CESM

- As a result, two spectra were selected:
  - Low energy spectrum
    - 26-32 kVp Mo filter → like a standard mammography (without contrast medium) – FDA and CE diagnostic
  - High energy spectrum
    - 45-49 kVp Cu filter → to maximize SDNR of the iodinated contrast agent (K-edge @ 33.2 keV)
- The chosen kVp selection depends on the breast thickness and density

Dual energy image combination

- Low and high-energy images are combined using a quadratic function instead of a the usual linear one
  - Linear combination is accurate only in the monoenergetic case!



low-energy image (Rh/Rh, 28kV) | high-energy image (Rh/Cu, 44kV) | iodine image recombined with log-subtraction | iodine image recombined with quadratic algorithm

(courtesy of GE Healthcare)

CESM protocol

CESM examination consisted in a pair of low and high energy exposures for each mammographic view, combined to visualize lesions with contrast up-take

0 min — **2 min** — **4 min**

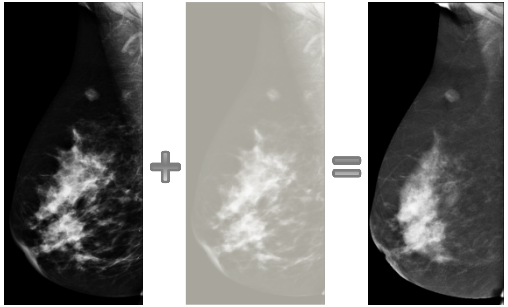
MLO
Breast compression

CC
Breast compression

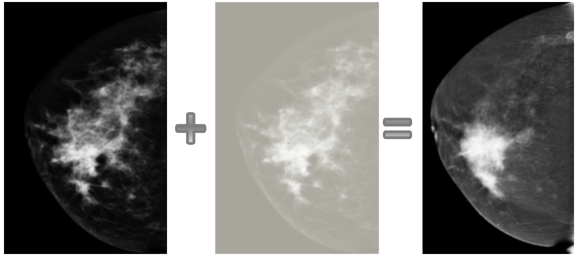
Contrast Medium
IV Injection

1.5 ml/Kg 350 mg/ml iodine

Low Energy — *High Energy* — ***Contrast Uptake***



Low Energy — *High Energy* — ***Contrast Uptake***



Dromain C et al., Eur Radiol, 2009

Methods and Material

- 54 consenting women (age range 33–72 y/o; mean age 54 y/o) with breast cancer and indication of **neoadjuvant chemotherapy** (**NAC**) were enrolled into this prospective study between October 2012 and December 2014
- 46 patients completed NAC and underwent surgery
- 8 excluded because of premature NAC interruption

Inclusion criteria

✓ Diagnosis of breast cancer at stage II or III, with indication of *NAC*
✓ Over 18 years old
✓ Agreement to participate

Exclusion criteria

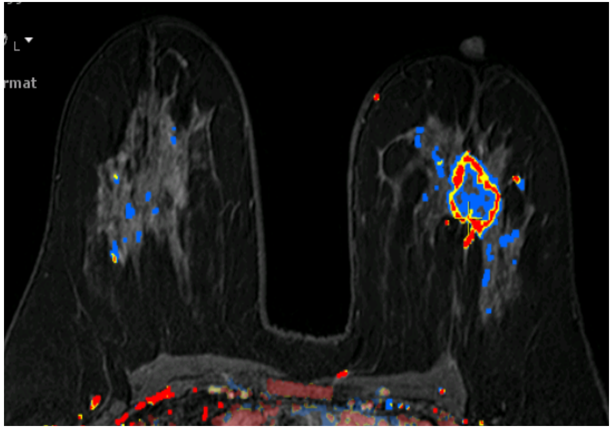
- Known BRCA mutation
- General MRI contraindications (e.g. PM)
- Contraindications to the administration of iodine or gadolinium contrast agent
- Pregnancy

Breast Contrast-Enhanced MRI protocol - 1.5 T

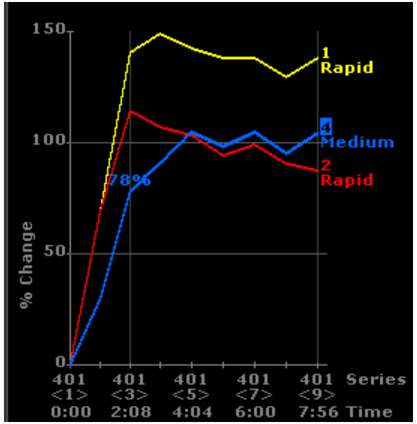
- **T2w Fat suppresed**
- **T1w Dynamic contrast enhanced** (1+8 acquisitions, temporal resolution ~ 1')
- **DWI**
- **CAD** post processing

During NAC | Post - NAC

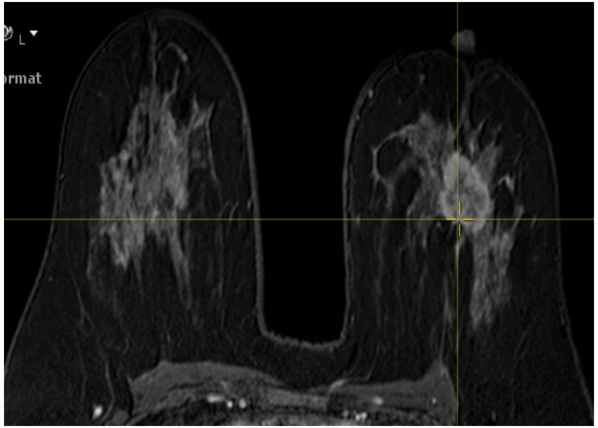
CAD processing



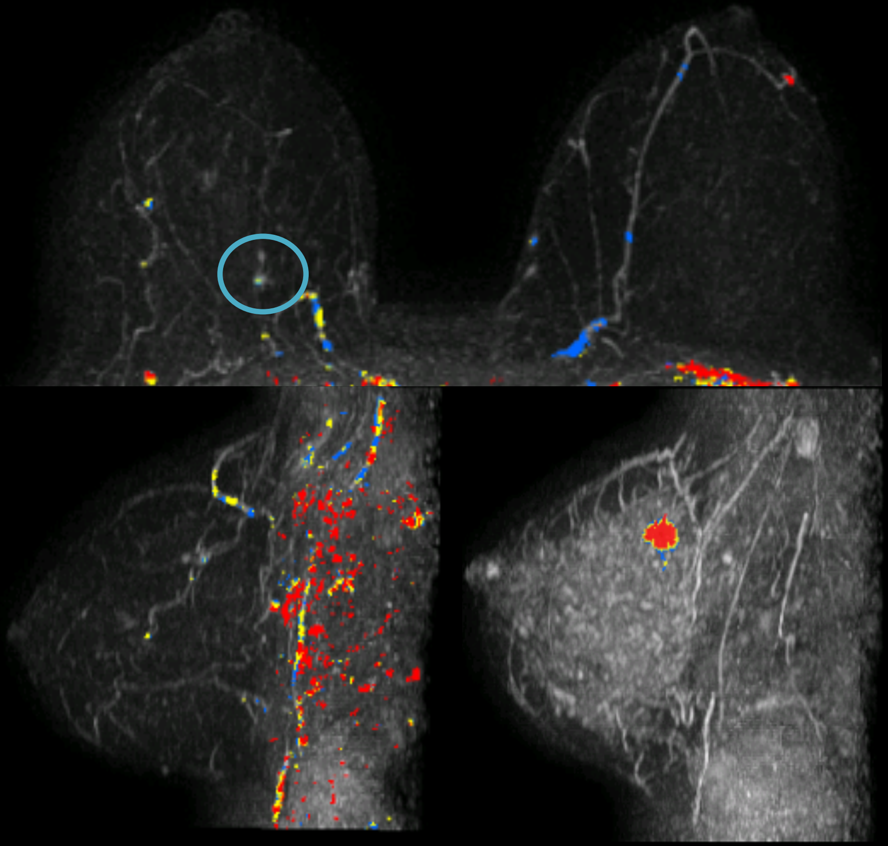
Enhancement Kinetics Curves

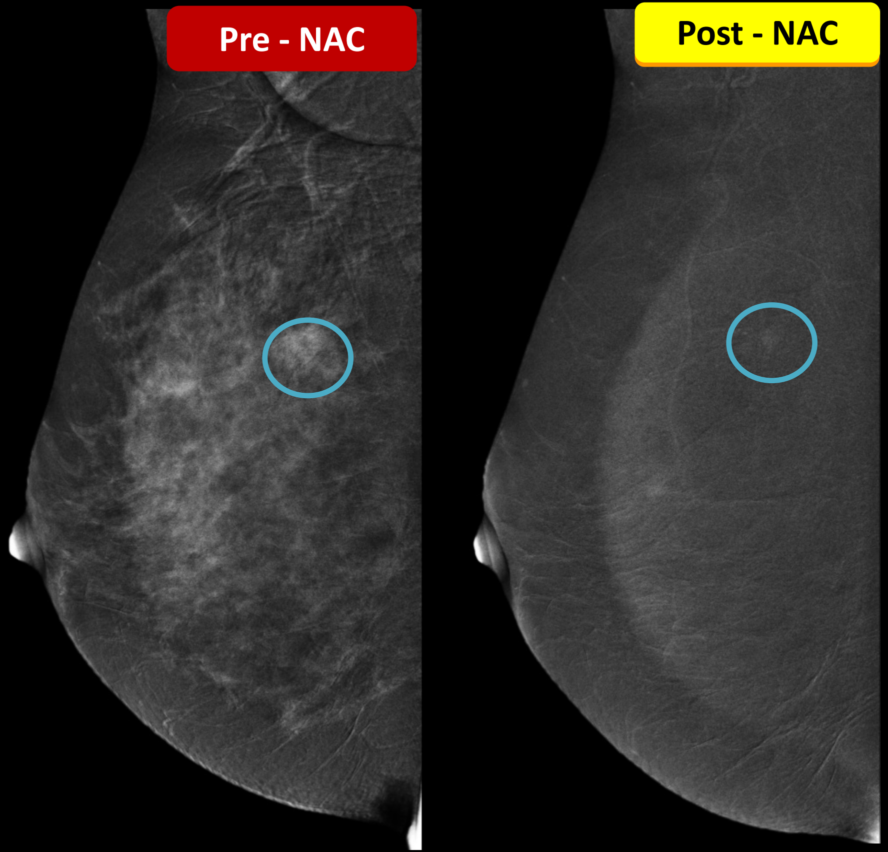


peak of enhancement

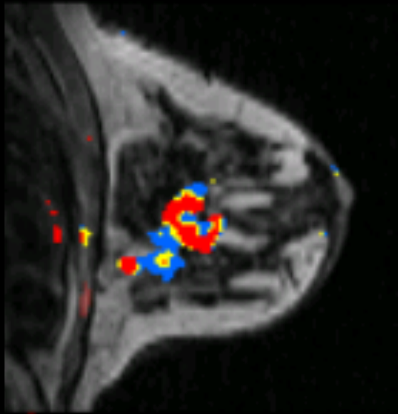


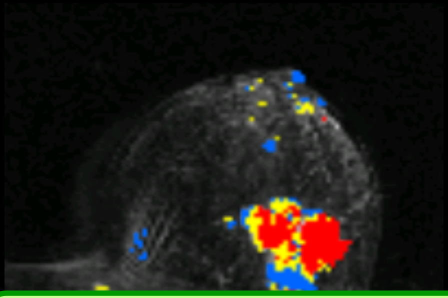
Background Parenchymal Enhancement?

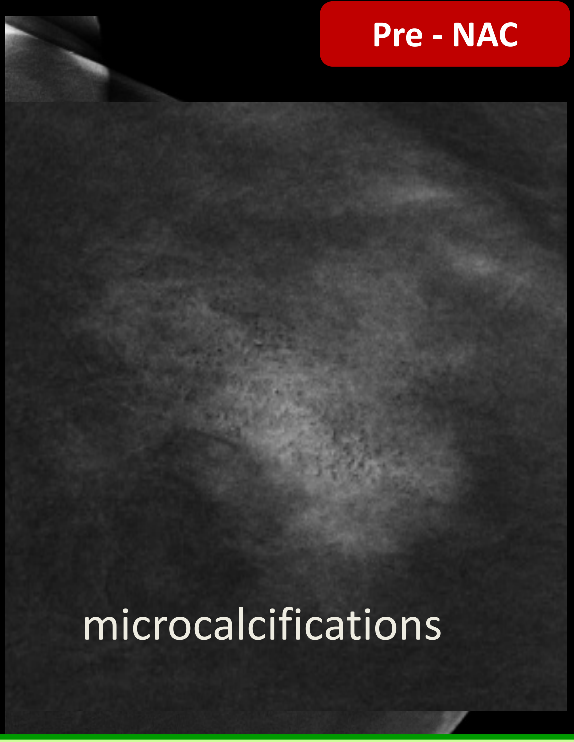


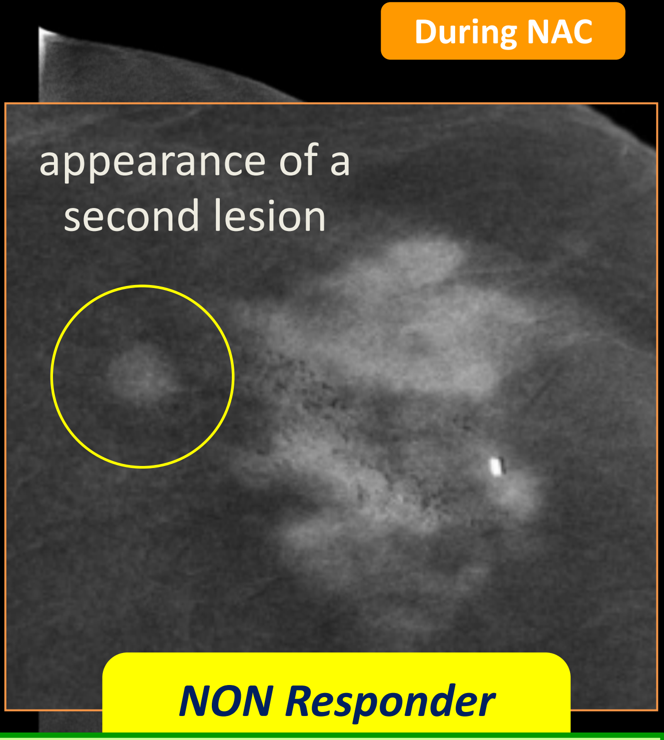


Microcalcifications







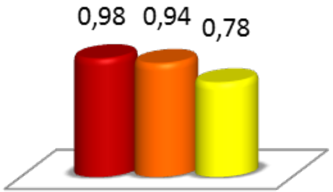


CESM more precisely correlates the response with the “enhancing” **microcalcifications**

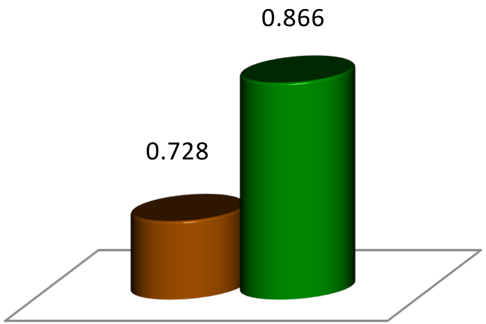
Results

- Quantifying the diagnostic performance of both methods, using *post-operative histopathology* as gold standard:

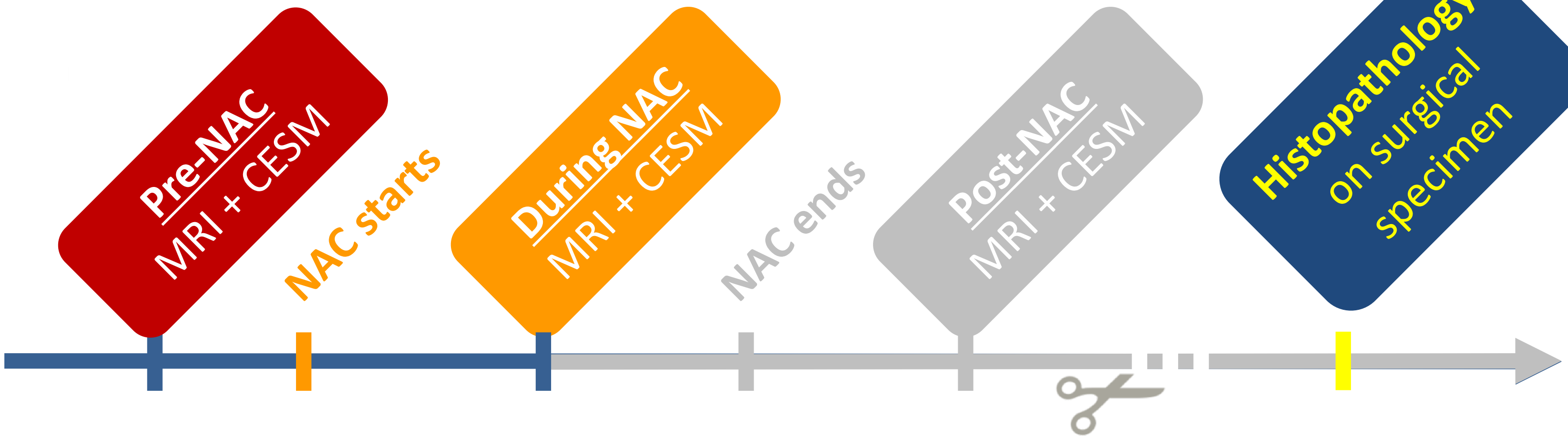
MRI vs CESM	Pre – NAC	During NAC	Post - NAC
CORRELATION *(Pearson)*	r = 0.98	r = 0.94	r = 0.78



	Post -NAC	
Histopathology vs	MRI	CESM
CORRELATION *(Pearson)*	r = 0.728	r = **0.866**
Mean underestimation	*7.5 mm*	*4.1 mm*

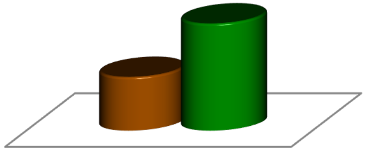


Early Assessment

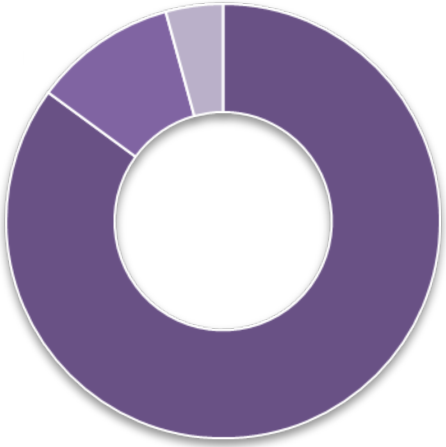


	Correct Prediction of Response	Incorrect Prediction of Response	
		SD (excess)	PD (excess)
CESM	**79 %**	18 %	3 %
MRI	**77 %**	14 %	9 %

Percentage of tumour shrinkage *3 months* after NAC

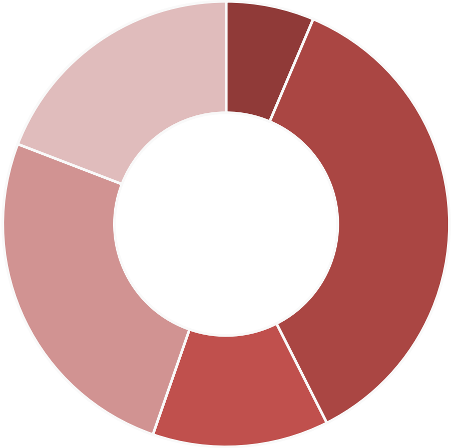


Breast Cancer Subtypes



Histology

- 40 Infiltrating Ductal Carcinoma
- 4 Infiltrating Lobular Carcinoma
- 2 Metaplastic Carinoma



Biology

- 3 Luminal A
- 16 Luminal B
- 6 Luminal B HER2+
- 12 Triple Negative
- 9 Her2+

The *accuracy* of breast imaging techniques to **assess the response to NAC** ***depends on breast cancer subtypes***

Bufi E et al, Clin Breast Cancer 2015; Cortazar P et al, Cancer Res 2012

Discussion

- Both MRI and CESM tend to *underestimate* the extension of residual tumor
- Main limitations in assessing tumor response evaluating ***dimension*** and ***vascularization***:
  - changes in tumor ***micro-vessel functionality*** after NAC
  - loss of cellularity vs persistent ***fibrous stroma***
  - scattered residual neoplastic cells spread throughout the tumor bed receive nutrients via ***diffusion*** and not from vascular perfusion

- **CESM** vs **MRI**: technical differences
  - Resolving power ***(CESM >10times MRI!!)***
  - Iodinated contrast vs Gadolinium
  - Acquisition Timing

Fallenberg EM et al, Eur Radiol 2014
Tomida K et al, Mol Clin Oncol 2014
Kim TH et al, J Comput Assist Tomogr 2012
Ogston KN et al, Breast 2003

Therapy Monitoring

CESM may be an *alternative* to MRI in assessing response to NAC

CESM	Breast - **MRI**
• Higher spatial resolution *(10 times!!)* • Faster • Cheaper • Well-accepted by patients	• Wide field of view (nodes, peripheral lesions..)

Journal of Medical Imaging and Radiation Oncology **59** (2015) 300–305

MEDICAL IMAGING—ORIGINAL ARTICLE

Contrast-enhanced spectral mammography (CESM) and contrast enhanced MRI (CEMRI): Patient preferences and tolerance

Max M Hobbs,[1] Donna B Taylor,[1,2] Sebastian Buzynski[1] and Rachel E Peake[2]

Conclusion

- In evaluating a new technology we need
  - High productivity
  - Relative hi[illegible] of exam execution
  - Reliability
  - Logistics

Cost-effectiveness

- Contrast Enhanced Mammography using monoenergetic X-ray beams??
- Or why not CE DBT using monoenergetic X-ray beams?

TAKE HOME MESSAGE

- Now, monoenergetic x-ray beams are very good to validate diagnostic technology

Thanks for your kind attention
and keep exploring!

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Sunrise from Monte Cusna - RE