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

<table>
<thead>
<tr>
<th></th>
<th>S. Maria Nuova Hospital</th>
<th>Ex-AUSL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beds</strong></td>
<td>890</td>
<td>750 (5 hospitals)</td>
</tr>
<tr>
<td><strong>Inpatient access</strong></td>
<td>50,000/y</td>
<td>39,000/y</td>
</tr>
<tr>
<td><strong>Outpatient access</strong></td>
<td>&gt;1,500/d</td>
<td>2,000/d</td>
</tr>
<tr>
<td><strong>Employees</strong></td>
<td>2,400</td>
<td>3,700</td>
</tr>
<tr>
<td><strong>Radiology exams</strong></td>
<td>&gt; 180,000/y</td>
<td>&gt; 220,000/y</td>
</tr>
</tbody>
</table>

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

• 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

<table>
<thead>
<tr>
<th>Mammography system</th>
<th>GE Senographe SenoClaire</th>
<th>GE Senographe Pristina</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-Ray tube Anode/filter (mm)</td>
<td>Mo/Mo (0.03)</td>
<td>Mo/Mo (0.03)</td>
</tr>
<tr>
<td></td>
<td>Mo/Rh (0.025)</td>
<td>Rh/Ag (0.03)</td>
</tr>
<tr>
<td>Detector type</td>
<td>(CsI:Tl)/a-Si 100</td>
<td>(CsI:Tl)/a-Si 100</td>
</tr>
<tr>
<td>Pixel size (μm)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>FOV (cm²)</td>
<td>23.9 x 30.6</td>
<td>24 x 28.9</td>
</tr>
<tr>
<td>Pixel array</td>
<td>2394 x 3062</td>
<td>2394 x 2850</td>
</tr>
<tr>
<td>Source to table distance</td>
<td>635 mm</td>
<td>637 mm</td>
</tr>
<tr>
<td>Source to detector distance</td>
<td>658 mm</td>
<td>660 mm</td>
</tr>
<tr>
<td>AEC Modes</td>
<td>Standard, Contrast, Dose</td>
<td>Dose +, Standard, Dose</td>
</tr>
</tbody>
</table>

10 units

1 unit
## Physical characteristics: DBT

<table>
<thead>
<tr>
<th>Mammography system</th>
<th>GE Senographe SenoClaire</th>
<th>GE Senographe Pristina</th>
</tr>
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<tr>
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</tr>
<tr>
<td>Detector type</td>
<td>(CsI:Tl)/a-Si</td>
<td>(CsI:Tl)/a-Si</td>
</tr>
<tr>
<td>Pixel size (μm)</td>
<td>100 no binning</td>
<td>100 no binning</td>
</tr>
<tr>
<td>FOV (cm²)</td>
<td>23.9 x 30.6</td>
<td>24 x 28.9</td>
</tr>
<tr>
<td>Pixel array</td>
<td>2394 x 3062</td>
<td>2394 x 2850</td>
</tr>
<tr>
<td>Grid</td>
<td>Yes/static</td>
<td>Yes/static</td>
</tr>
<tr>
<td>Angular range / # of projections</td>
<td>25° / 9</td>
<td>25° / 9</td>
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<tr>
<td>Acquisition time (s)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Reconstruction algorithm</td>
<td>Iterative</td>
<td>Iterative</td>
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</tbody>
</table>
DBT overcomes superimposition!

Infiltrating Ductal Carcinoma G2
We evaluated DBT quality using metrics such as:

• Planar MTF (f)
• Planar NNPS
• Signal difference to noise ratio (SDNR)
• Artifact spread function (ASF)
• Uniformity
## DBT: Average Glandular Dose (AGD)

### SenoClaire

<table>
<thead>
<tr>
<th>Equivalent breast thickness (mm)</th>
<th>Anode / filter</th>
<th>kVp</th>
<th>mAs</th>
<th>AGD 3D</th>
<th>3D vs 2D AGD ratio</th>
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</thead>
<tbody>
<tr>
<td>21</td>
<td>Mo/Mo</td>
<td>26</td>
<td>40</td>
<td>0.95</td>
<td>1.66</td>
</tr>
<tr>
<td>32</td>
<td>Rh/Rh</td>
<td>29</td>
<td>33</td>
<td>1.03</td>
<td>1.28</td>
</tr>
<tr>
<td>45</td>
<td>Rh/Rh</td>
<td>29</td>
<td>50</td>
<td>1.4</td>
<td>1.17</td>
</tr>
<tr>
<td>53</td>
<td>Rh/Rh</td>
<td>29</td>
<td>56</td>
<td>1.51</td>
<td>0.91</td>
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<tr>
<td>60</td>
<td>Rh/Rh</td>
<td>29</td>
<td>75</td>
<td>1.91</td>
<td>1.48</td>
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<tr>
<td>75</td>
<td>Rh/Rh</td>
<td>31</td>
<td>83</td>
<td>2.52</td>
<td>1.2</td>
</tr>
<tr>
<td>90</td>
<td>Rh/Rh</td>
<td>31</td>
<td>128</td>
<td>3.51</td>
<td>1.43</td>
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</tbody>
</table>

### Pristina

<table>
<thead>
<tr>
<th>Equivalent breast thickness (mm)</th>
<th>Anode / filter</th>
<th>kVp</th>
<th>mAs</th>
<th>AGD 3D</th>
<th>3D vs 2D AGD ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Mo/Mo</td>
<td>26</td>
<td>23.1</td>
<td>0.6</td>
<td>0.95</td>
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<tr>
<td>32</td>
<td>Mo/Mo</td>
<td>26</td>
<td>54.4</td>
<td>1.02</td>
<td>0.99</td>
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<tr>
<td>45</td>
<td>Rh/Ag</td>
<td>34</td>
<td>28.2</td>
<td>1.22</td>
<td>0.95</td>
</tr>
<tr>
<td>53</td>
<td>Rh/Ag</td>
<td>34</td>
<td>33.7</td>
<td>1.33</td>
<td>0.98</td>
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<tr>
<td>60</td>
<td>Rh/Ag</td>
<td>34</td>
<td>41.1</td>
<td>1.5</td>
<td>0.98</td>
</tr>
<tr>
<td>75</td>
<td>Rh/Ag</td>
<td>34</td>
<td>60.1</td>
<td>1.91</td>
<td>0.97</td>
</tr>
<tr>
<td>90</td>
<td>Rh/Ag</td>
<td>34</td>
<td>90.7</td>
<td>2.56</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Where

- $PVAI$ is the mean value within an ROI of

- $PV_{bg}$ is the mean value within an ROI $200\mu m$ thick
DBT & Screening

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 post-DBT screening

\textbf{Interval Cancers}

- Most of the additionally detected cancers were

\textbf{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**

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

- Interval cancers
- T2+ incidence at 1\(^{st}\) and 2\(^{nd}\) 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

**Start:** March 2014  
**End:** August 2017

**Excluded 1886**  
Large breasts, familial risk score update recent breast cancer in relatives, augmentation prostheses, pregnancy, randomization procedure or DBT temporary not available

**Screening Population Invited 43766**

**Eligible 41880**

**Randomization 26976**

**CONTROL ARM 13521**
- FFDM
  - Read1
  - Read2
  - (Read3)
  - **Recall?**
    - Yes: 455  
    - Cancers 61
    - No: 13066

**STUDY ARM 13455**
- DBT
  - Read1
  - Read2
  - (Read3)
  - **Recall?**
    - Yes: 399  
    - Cancers 101
    - Detected ONLY with DBT 22
    - No: 12957

**Baseline Endpoints**

- Interval Cancers
  - DM at the next screening round

**Main Endpoints**

- Interval Cancers
  - DM at the next screening round

**Attendance to Screening:** 84%

**Attendance to Study:** 64.2%

**Suspended 99 under evaluation (no cancers)**

- **Data record only**
- Recall decision

**Cancers 61**

**Cancers 101**
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 Cavato, 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@auel.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; 18:1–10 • https://doi.org/10.1148/radiol.2018172119 • Content code: BR
Recall Rate

CONTROL ARM

3.9%

STUDY ARM

3.8%

<table>
<thead>
<tr>
<th></th>
<th>I interim</th>
<th>II interim</th>
<th>Final data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Arm</td>
<td>3.6</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Study Arm</td>
<td>3.5</td>
<td>3.5</td>
<td>3.8</td>
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</table>
Positive Predictive Value

<table>
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<th></th>
<th>I interim</th>
<th>II interim</th>
<th>Final data</th>
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<tbody>
<tr>
<td>Control Arm</td>
<td>15,5</td>
<td>13</td>
<td>11,7</td>
</tr>
<tr>
<td>Study Arm</td>
<td>23,3</td>
<td>24,1</td>
<td>19,8</td>
</tr>
</tbody>
</table>
Detection Rate

<table>
<thead>
<tr>
<th></th>
<th>I interim</th>
<th>II interim</th>
<th>Final data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Arm</td>
<td>5,6</td>
<td>4,5</td>
<td>4,5</td>
</tr>
<tr>
<td>Study Arm</td>
<td>8,1</td>
<td>8,6</td>
<td>7,6</td>
</tr>
</tbody>
</table>

+ 45%  + 78%  + 68%
DBT Current Trials & Screening: Risk

My Personalized Breast Screening

- 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.

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)

INT: Randomized
85 000 (40/70 yo)

DBT alternative to FFDM

Low Risk
Moderate Risk
High Risk
Very high Risk

Annual M/DBT + US
Annual M/DBT + annual MRI +/- US
No M/DBT
2-3-yearly M/DBT

Choice
>50y
<50y

Density
CD
Density
AB

Risk-based Breast Cancer Screening

UNICANCER

MyPEBS

2018 / 26

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

Blood Vessel Overgrowth on Cell

1. Tumor secretes VEGF
2. VEGF increases blood vessel expression and movement to tumor
3. Tumor has increased blood supply

© LUNGevity Foundation

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.

• GE Healthcare validated its spectra at the European Synchrotron Radiation Facility (ESFR) in Grenoble (France), using monoenergetic radiations.
• 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 the usual linear one.
  - Linear combination is accurate only in the monoenergetic case!
CESM examination consisted in a pair of low and high energy exposures for each mammographic view, combined to visualize lesions with contrast up-take.

 CESM protocol

Contrast Medium IV Injection

1.5 ml/Kg 350 mg/ml iodine

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 suppressed
- T1w Dynamic contrast enhanced (1+8 acquisitions, temporal resolution ~ 1’)
- DWI
- CAD post processing

During NAC

Post - NAC
Background Parenchymal Enhancement?
Microcalcifications

CCESSM 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

<table>
<thead>
<tr>
<th></th>
<th>Pre – NAC</th>
<th>During NAC</th>
<th>Post - NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORRELATION (Pearson)</td>
<td>r = 0.98</td>
<td>r = 0.94</td>
<td>r = 0.78</td>
</tr>
</tbody>
</table>

### Histopathology vs MRI, CESM

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>CESM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORRELATION (Pearson)</td>
<td>r = 0.728</td>
<td>r = 0.866</td>
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<tr>
<td>Mean underestimation</td>
<td>7.5 mm</td>
<td>4.1 mm</td>
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</table>

- Results showing significant correlation between MRI/CESM and histopathology during NAC and post-NAC treatment.
Early Assessment

Percentage of tumour shrinkage 3 months after NAC

<table>
<thead>
<tr>
<th>Correct Prediction of Response</th>
<th>Incorrect Prediction of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CESM</td>
<td>SD (excess) 18 %</td>
</tr>
<tr>
<td>MRI</td>
<td>SD (excess) 14 %</td>
</tr>
</tbody>
</table>
The accuracy of breast imaging techniques to assess the response to NAC depends on breast cancer subtypes.

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

- 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*

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

Max M Hobbs,1 Donna B Taylor,1,2 Sebastian Buzynski1 and Rachel E Peake2
Conclusion

• In evaluating a new technology we need
  • High productivity
  • Relative high speed of exam execution
  • Reliability
  • Logistics

• Contrast Enhanced Mammography using monoenergetic X-ray beams??

• Or why not CE DBT using monoenergetic X-ray beams?
• Now, monoenergetic x-ray beams are very good to validate diagnostic technology
Thanks for your kind attention and keep exploring!

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