The global burden of cancer and the role of imaging modalities

Lale Umutlu

Department of Diagnostic and Interventional Radiology and Neuroradiology
1. Get familiar with current global cancer statistics and their effects on patient population

2. Understand the diagnostic capacity and potential benefits of different imaging modalities in screening and early diagnosis of cancer

3. Assess the advantages/disadvantages of PET/CT and PET/MRI for whole-body staging
Overview

- The global burden of cancer
  - Statistics

- The role of imaging
  - Introduction of modalities
  - Screening & early diagnosis
    - Breast cancer
    - Lung cancer
  - Therapy monitoring
  - Whole-body Staging
Overview

- The global burden of cancer
  - Statistics
Worldwide cancer spread

[Torre et al, CA Cancer J Clin, 2015]

14,090,100
Worldwide cancer spread

Estimated New Cases

**Male**
- Lung, bronchus, & trachea: 1,241,600
- Prostate: 1,111,700
- Colon & rectum: 746,300
- Stomach: 631,300
- Liver: 554,400
- Urinary bladder: 330,400
- Esophagus: 323,000
- Non-Hodgkin lymphoma: 217,600
- Kidney: 213,900
- Leukemia: 200,700
- All sites*: 7,427,100

**Female**
- Breast: 1,676,600
- Colon & rectum: 614,300
- Lung, bronchus, & trachea: 583,100
- Cervix uteri: 527,600
- Stomach: 320,300
- Corpus uteri: 319,600
- Ovary: 238,700
- Thyroid: 229,900
- Liver: 228,100
- Non-Hodgkin lymphoma: 168,100
- All sites*: 6,663,000

Estimated Deaths

**Male**
- Lung, bronchus, & trachea: 1,098,700
- Liver: 521,900
- Colon & rectum: 469,000
- Cervix uteri: 373,600
- Stomach: 307,500
- Prostate: 281,200
- Esophagus: 224,500
- Urinary bladder: 151,900
- Non-Hodgkin lymphoma: 115,400
- All sites*: 4,653,400

**Female**
- Breast: 521,900
- Lung, bronchus, & trachea: 491,200
- Colon & rectum: 320,300
- Cervix uteri: 265,700
- Stomach: 254,100
- Prostate: 224,500
- Pancreas: 156,600
- Ovary: 151,900
- Esophagus: 119,000
- Leukemia: 114,200
- All sites*: 3,548,200

[Torre et al, CA Cancer J Clin, 2015]
Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. (Jemal et al, CA Cancer J Clin 2011)

Cancer is the leading cause of death in both more and less economically developed countries. (Torre et al, CA Cancer J Clin 2015)
Cancer burden expected to grow worldwide due to:

- Growth and aging population (part. in less developed countries, in which 82% of the world’s pop. resides)
- Adoption of lifestyle behaviors that are known to increase cancer risk:
  - Smoking
  - Poor diet & physical inactivity
  - Reproductive changes

[Torre et al, CA Cancer J Clin, 2015]
What is the role of imaging?
Overview

- The global burden of cancer
  - Statistics

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  - Whole-body Staging
Imaging modalities
Overview

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  - Statistics

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    - Lung cancer
"Breast cancer is currently the most common cancer type among women, leading to the (second) most common cause of cancer death"

NICE and ACS
Breast cancer

- Primary prevention restricted
- Aetiology remains unknown
  - progressive age
  - familial and genetic predisposition
  - reproductive and hormonal aspects
- Primary prevention impeded
- Mortality depends on time of first detection

High-quality screening to enable early diagnosis
How Do I Screen Patients for Breast Cancer?

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Out of the commonly applied breast imaging techniques (US, XRM, bMRI), breast MRI is known to provide highest sensitivity and specificity.
Prospective Multicenter Cohort Study to Refine Management Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial

Christiane Kuhl, Stefanie Weigel, Simone Schrading, Birke Arand, Heribert Bieling, Roy König, Bernd Tombach, Claudia Leutner, Andrea Rieber-Brambs, Dennis Nordhoff, Walter Heindel, Maximilian Reiser, and Hans H. Schild

See accompanying editorial on page 1441

ABSTRACT

Purpose
We investigated the respective contribution (in terms of cancer yield and stage at diagnosis) of clinical breast examination (CBE), mammography, ultrasound, and quality-assured breast magnetic resonance imaging (MRI), used alone or in different combination, for screening women at elevated risk for breast cancer.
The EVA Trial

![Bar chart showing cancer yield with different imaging modalities.

- Mx: 5.4
- US: 6.0
- Mx+US: 7.7
- MRI: 14.9
- MRI+US: 14.9
- MRI+Mx: 16.0
- MRI+Mx+US: 16.0

[Kuhl, J Clin Oncol; 2010]
The EVA Trial

[Kuhl, J Clin Oncol; 2010]
• Neither mammography nor US or CBE provide significant addition to cancer yield achieved by MRI alone

[Kuhl, J Clin Oncol; 2010]
• Three important questions:

1. What about cost effectiveness of MRI screening?

2. Should every woman undergo bMRI for screening?

3. Should everybody be able to perform and read bMRI?
Cost effectiveness of breast MRI

- Numerous studies have demonstrated the cost-effectiveness of breast MRI as a screening tool for high-risk women.
- Correlation of costs with diagnosis, therapy, additional care, patient utilities, life expectancy, and quality-adjusted life-years (QALYs).
- Cost effectiveness of screening breast MRI increases with increasing risk.
  - Highest benefit in BRCA1 mutation carriers.

[Berg WA, Am Journ. Roentgenol; 2009]
[Mainiero M, Jour. Am Coll Radiol; 2013]
• Three important questions:

1. What about cost effectiveness of MRI screening?

2. Should every woman undergo bMRI for screening?
Personalized (breast cancer) screening

- Accurate stratification of breast cancer risk
- Optimized screening recommendations

Screening imaging techniques

Patient risk classification
• Three important questions:

1. What about cost effectiveness of MRI screening?

2. Should every woman undergo bMRI for screening?

3. Should everybody be able to perform and read bMRI?
Preoperative breast MRI

- MONET trial
- COMICE trial
Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial

Lindsay Turnbull, Sarah Brown, Ian Harvey, Catherine Olivier, Phil Drew, Vicky Napp, Andrew Hanby, Julia Brown

Summary
Background MRI might improve diagnosis of breast cancer, reducing rates of reoperation. We assessed the clinical efficacy of contrast-enhanced MRI in women with primary breast cancer.

Methods We undertook an open, parallel group trial in 45 UK centres, with 1623 women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment. Patients were randomly assigned to receive either MRI (n=816) or no further imaging (807), with use of a minimisation algorithm incorporating a random element. The primary endpoint was the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation. Analysis was by intention to treat. This study is registered. ISRCTN number 57474502.

Findings 816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0.96, 95% CI 0.75–1.24; p=0.77).

Interpretation Our findings are of benefit to the NHS because they show that MRI might be unnecessary in this population of patients to reduce repeat operation rates, and could assist in improved use of NHS services.

Funding National Institute for Health Research’s Health Technology Assessment Programme.

Introduction
The quality-assurance standard for the UK National Health Service Breast Screening Programme (NHS BSP) has set a target for reoperation rates for incomplete tumour excision of less than 10%. In 2001, when the COMICE protocol was written, the actual rate was 14.2% and has not reduced over time. According to the 2006–07 UK audit of screen-detected breast cancers, 17% of two observational studies\textsuperscript{5,22} of the role of dynamic contrast-enhanced MRI in clinical management of patients scheduled for breast-conservation surgery have shown management to be altered in 14–18% of patients because of detection of disease that was more extensive than was first diagnosed, although neither study reported factors predictive of alteration in outcome.

Cost-effectiveness of MRI in this clinical setting is...
COMICE trial

- COMICE = Comparative effectiveness of MRI in breast cancer
- Goal: compare the efficacy of MRI and standard triple assessment with triple assessment alone in reduction of re-operation rates
- 1623 patients (MRI n= 816; no MRI = 807)
- Results:
  - Total re-operation rates equivalent in both groups (19%)
  - Additional wide local excision rates almost equal (MRI group 10.4%; no-MRI group 11.2%)
Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial

Lindsay Turnbull, Sarah Brown, Ian Harvey, Catherine Olivier, Phil Drew, Vicky Napp, Andrew Hanby, Julia Brown

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Findings We assessed the MRI images for two interpreters, who jointly determined the population of patients to reduce repeat operation rates, and could assist in improved use of NHS services.

Funding National Institute for Health Research's Health Technology Assessment Programme.

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Really no benefit based on breast MRI??
Should we dispense with preoperative breast MRI?

Prof. Elizabeth Morris
Discussion points:

1. Re-excision rates
2. Expertise of participating centers
3. MR guided biopsy
4. Limited evaluation of data
Expertise of participating centers

- Centers defined as „large recruiters“, if 1 patient / month was recruited!
- 86% of the patients recruited by surgeons with 10 patients over 6 years -> very small patient cohort

Lack of expertise of the centers?
MR guided biopsy

- Unavailability of MR guided biopsy
  1. COMICE started several years before MRI biopsy devices available
  2. MRI biopsy or wire marking not available / performed at all centers after suspicious MRI finding
     • 1/3 of all mastectomies (16/58) were performed without pathological verification of disease

Potentially unnecessary mastectomies performed?
Learning points based on the COMICE trial

- Caution when it comes to study set up
- Expertise and high-quality imaging are inevitable
- Prospective multicenter trials with state of the art imaging, biopsy capability, experienced readers, consistent evaluation of pathological tissue
Preoperative Breast MRI in Clinical Practice:
Multicenter International Prospective Meta-Analysis (MIPA) of Individual Woman Data
An EIBIR-EuroAIM/EUSOBI Study

Managing structure: EIBIR/EuroAIM
Principal Investigator: Francesco Sardanelli, University of Milan, EuroAIM Director
Data manager at the Central Unit in Milan: Rubina M. Trimboli
Statistical Analysis at the Central Unit in Milan: Giovanni Di Leo
Scientific Advisor: Nehmat Houssami, University of Sydney
The study was endorsed by the European Society of Breast Imaging (EUSOBI)
Steering Committee: Francesco Sardanelli, Thomas Helbich, Fiona J. Gilbert, Nehmat Houssami, Giovanni Di Leo

The MIPA study is supported by a research grant by Bayer Healthcare-Medical Care-Radiology and Interventional

Study Outline
Overview

- The global burden of cancer
  - Statistics
- The role of imaging
  - Introduction of modalities
  - Screening & early diagnosis
    - Breast cancer
    - Lung cancer
Targeting of Low-Dose CT Screening According to the Risk of Lung-Cancer Death

Stephanie A. Kovalchik, Ph.D., Martin Tammemagi, Ph.D., Christine D. Berg, M.D., Neil E. Caporaso, M.D., Tom L. Riley, B.Sc., Mary Korch, M.Sc., Gerard A. Silvestri, M.D., Anil K. Chaturvedi, Ph.D., and Hormuzd A. Katki, Ph.D.

ABSTRACT

BACKGROUND
In the National Lung Screening Trial (NLST), screening with low-dose computed tomography (CT) resulted in a 20% reduction in lung-cancer mortality among participants between the ages of 55 and 74 years with a minimum of 30 pack-years of smoking and no more than 15 years since quitting. It is not known whether the benefits and potential harms of such screening vary according to lung-cancer risk.
National Lung Screening Trial (NLST)

- Patient cohort:
  - 55-74 years, 30 pack years
  - 53,454 part. -> 26,604 low-dose CT versus 26,554 chest X-ray

- Results:
  - 20% reduction in lung cancer mortality
  - Screening with low-dose CT prevented the greatest number of deaths in participants who were at highest risk and prevented very few deaths among those at lowest risk.

[New England Journal of Medicine, 2013]
Cum. Screening Outcomes in Low-Dose CT

A. Prevented Lung-Cancer Deaths

B. Number Needed to Screen

C. False Positive Results

D. False Positive Results per Prevented Lung-Cancer Death

[New England Journal of Medicine, 2013]
Personalized (lung cancer) screening

Accurate stratification of breast cancer risk

Optimized screening recommendations

Screening imaging techniques

Patient risk classification
Personalized cancer screening

Accurate stratification of breast cancer risk

Optimized screening recommendations

Screening imaging techniques

Patient risk classification
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    - Lung cancer
- Therapy monitoring
Response assessment: RECIST limitations

RECIST - READING:

Baseline: 17 + 15 = 32 mm
Control: 11 + 12 = 23 mm
Change: -28% = SD

+ 6 weeks
Response assessment: RECIST limitations

Metastases of GIST under Sunitinib

-> pseudo-progression under therapy

Baseline

1. Restaging
PERCIST 1.0 - response assessment

- Measurement of percentage change in $SUL_{\text{peak}}$ compared to baseline
  - **CMR** = Complete metabolic response
  - **PMR** = Partial metabolic response ($\downarrow$30% & $\downarrow$0.8)
  - **SMD** = Stable metabolic disease
  - **PMD** = Progressive metabolic disease ($\downarrow$30% & $\downarrow$0.8)
Soft tissue sarcoma under ILP

Pre - ILP

Post - ILP
Overview

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    - Lung cancer
  - Therapy monitoring
- Whole-body staging
Hybrid imaging for whole-body staging

- PET/CT provides excellent sensitivity and specificity for detection of metastases and/or tumor relapse
- Better diagnostic ability over conventional imaging techniques
- Well-established in oncologic imaging
PET/CT versus PET/MRI
PET/CT or PET/MRI for whole-body staging?
Soft tissue contrast
Soft tissue contrast

CT PET/CT

T2w PET/MRI ADC

T1 w/c PET/MRI DWI
**[18F]FDG PET/MRI vs. PET/CT for whole-body staging in patients with recurrent malignancies of the female pelvis: initial results**

Karsten Beiderwellen • Johannes Grueneisen • Verena Ruhlmann • Paul Buderath • Bahriye Aktas • Philipp Heusch • Oliver Kraff • Michael Forsting • Thomas C. Lauenstein • Lale Umutlu

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**Abstract**

*Purpose* To evaluate the diagnostic potential of PET/MRI with [18F]FDG in recurrent ovarian and cervical cancer in comparison to PET/CT.

*Methods* A group of 19 patients with suspected recurrence of pelvic malignancies (ovarian cancer, 11 patients; cervical cancer, 8 patients) scheduled for an [18F]FDG PET/CT were subsequently enrolled for a PET/MRI. The scan protocol consisted of T1W with VIBE, T2W with VIBE, T1W contrast-enhanced. The numbers of metastatic lesions were counted, lesion localization, lesion conspicuity (four-point scale), lesion characterization (benign/malignant/indeterminate) and diagnostic confidence (three-point scale). All available data (histology, prior examinations, PET/CT, PET/MRI, follow-up examinations) served as standard of reference. Median values were compared using the Wilcoxon rank sum test.

*Results* Metastatic lesions were present in 16 of the 19 patients (87.1%). Similar to PET/CT, 18/19 patients had metastatic lesions on PET/MRI.
Results

Detection of tumor relapse

- PET/MRI: 100%
- PET/CT: 100%
Lesion conspicuity

<table>
<thead>
<tr>
<th>Modality</th>
<th>Lesion Conspicuity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/MRI</td>
<td>3.9</td>
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<tr>
<td>PET/CT</td>
<td>3.7</td>
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</tbody>
</table>

Diagnostic confidence

<table>
<thead>
<tr>
<th>Modality</th>
<th>Diagnostic Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/MRI</td>
<td>2.9</td>
</tr>
<tr>
<td>PET/CT</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Whole-body staging

100% tumor detection
19.6 mSV
18.0 min
PET/CT

100% tumor detection
4.7 mSV
44 min
PET/MRI
Implementation of FAST-PET/MRI for whole-body staging of female patients with recurrent pelvic malignancies: A comparison to PET/CT

Johannes Grueneisen\textsuperscript{a,\textdagger}, Benedikt Michael Schaarschmidt\textsuperscript{b}, Martin Heubner\textsuperscript{c}, Saravanabavaa Suntharalingam\textsuperscript{a}, Ines Milk\textsuperscript{a}, Sonja Kinner\textsuperscript{a}, Antonia Heubner\textsuperscript{c}, Michael Forsting\textsuperscript{a}, Thomas Lauenstein\textsuperscript{a}, Verena Ruhlmann\textsuperscript{d}, Lale Umutlu\textsuperscript{a}

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\textbf{ABSTRACT}

Objectives: To compare the diagnostic competence of FAST-PET/MRI and PET/CT for whole-body staging of female patients suspect for a recurrence of a pelvic malignancy.

Methods: 24 female patients with a suspected tumor recurrence underwent a PET/CT and subsequent PET/MRI examination. For PET/MRI readings a whole-body FAST-protocol was implemented. Two readers separately evaluated the PET/CT and FAST PET/MRI datasets regarding identification of all tumor lesions and qualitative assessment of visual lesion-to-background contrast (4-point ordinal scale).
Implementation of a FAST-protocol for wholebody-staging

Reduction of applied MR sequences from 9 to 3:
- HASTE
- DWI
- post contrast VIBE

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Bed positions</th>
<th>Scan duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT</td>
<td>5-6 (2 min/bp)</td>
<td>18.0 ± 1.0</td>
</tr>
<tr>
<td>PET/MRI (standard protocol)</td>
<td>4-5 (8 min/bp)</td>
<td>44.0 ± 4.0</td>
</tr>
<tr>
<td>PET/MRI (fast protocol)</td>
<td>4-5 (4 min/bp)</td>
<td>26.5 ± 2.0</td>
</tr>
</tbody>
</table>
PET/CT | FAST-PET/MRI
---|---
100% tumor detection | 100% tumor detection
18,0 min | 26 min
19,4 mSV | 4,5 mSV
Limitation 1: Pulmonary metastases
Limitation 1: Pulmonary metastases
Limitation 2: Attenuation correction

SUV=7,7

SUV=7,1
Conclusion?

**PET/CT**
- 100% tumor detection
- 18.0 min
- 19.4 mSV

**FAST-PET/MRI**
- 100% tumor detection
- 26 min
- 4.5 mSV
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  - Whole-body Staging

05.10.2015 Lale Umutlu  The global burden of cancer and the role of imaging modalities, IPET 2015
Screening for Cancer with PET and PET/CT: Potential and Limitations

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Certainty? In this world nothing is certain but death and taxes.

Benjamin Franklin

Screening for cancer remains a very emotional and hotly debated issue in contemporary medical practice. An analysis of published data reveals a multitude of opinions based on a limited amount of reliable data. Even for breast cancer screening, which is now widely practiced in the United States and many European countries, there is continuing controversy regarding the appropriate age limits for screening mammography and, in fact, concerning the value of mammography itself. Similarly, there is no agreement as to whether screening for lung or prostate cancer is meaningful as currently practiced. Recommendations and decisions regarding cancer screening should be based on reliable data, not good intention, assumptions, or speculation. Therefore, we first explain the underlying principles and premises of screening and then briefly discuss current controversies regarding completed curative treatment, but who remain at high risk for recurrent disease.

Key Words: cancer screening; PET; PET/CT


In 2005, an estimated 1,373,000 people in the United States were diagnosed with cancer, and about 570,000 died of cancer (1). Over the years, there has been considerable interest in screening as a means for reducing cancer-related mortality for a number of malignancies, including cancers of the breasts, colon, prostate, lungs, uterine cervix, and ovaries. In fact, screening has become popular in the United...
PET/MRI for screening?
PET/MRI instead of PET/CT for screening?
Imaging, Diagnosis, Prognosis

Improved Differentiation of Benign and Malignant Breast Tumors with Multiparametric $^{18}$Fluorodeoxyglucose Positron Emission Tomography Magnetic Resonance Imaging: A Feasibility Study

Katja Pinker¹, Wolfgang Bogner², Pascal Baltzer¹, Georgios Karanikas³, Heinrich Magometschnigg¹, Peter Brader¹, Stephan Gruber², Hubert Bickel¹, Peter Dubsky⁴, Zsuzsanna Bago-Horvath⁵, Rupert Bartsch⁶, Michael Weber², Siegfried Trattnig², and Thomas H. Helbich¹

Abstract

**Purpose:** To assess whether multiparametric $^{18}$fluorodeoxyglucose positron emission tomography magnetic resonance imaging (MRI) (MP $^{18}$FDG PET-MRI) using dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted imaging (DWI), three-dimensional proton MR spectroscopic imaging (3D $^{1}$H-MRSI), and $^{18}$FDG-PET enables an improved differentiation of benign and malignant breast tumors.

**Experimental Design:** Seventy-six female patients (mean age, 55.7 years; range, 25–86 years) with an imaging abnormality (BI-RADS 0, 4–5) were included in this Institutional Review Board (IRB)-approved study. Patients underwent fused PET-MRI of the breast with $^{18}$FDG-PET/CT and MP MRI at 3T. The likelihood of malignancy was assessed for all single parameters, for MP MRI with two/three parameters, and for MP $^{18}$FDG PET-MRI. Histopathology was used as the standard of reference. Appropriate statistical tests were used to assess sensitivity, specificity, and diagnostic accuracy for each assessment combination.

**Results:** There were 53 malignant and 23 benign breast lesions. MP $^{18}$FDG PET-MRI yielded a significantly higher area under the cure (AUC) of 0.935 than DCE-MRI (AUC, 0.86; $P = 0.044$) and the combination of DCE-MRI and another parameter (AUC, 0.761–0.826; $P = 0.013–0.020$). MP $^{18}$FDG PET-MRI showed slight further improvement to MP MRI with three parameters (AUC, 0.925; $P = 0.317$). Using MP $^{18}$FDG PET-MRI there would have been a reduction of the unnecessary breast biopsies recommended by
Multifocal versus multicentric breast cancer
Multifocal versus multicentric breast cancer
The global burden of cancer and the role of imaging modalities

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