LUND UNIVERSITY

Evaluation of absorbed dose and image quality in mammography

Hemdal, Bengt

2009

Medical Radiation Physics
Department of Clinical Sciences, Malmö
Lund University
Malmö University Hospital

Evaluation of absorbed dose and image quality in mammography

Bengt Hemdal

Malmö 2009

Cover: A screening mammogram (left) of the left breast in mediolateral oblique projection acquired with screen-film technique. White dots at the top and bottom of the film are images of lead markers for estimation of compressed breast thickness. In the enlarged part of the central region of the mammogram (right), two dosemeters are visible, one attached to the compression paddle on top of the breast (lower part of image), the other to the breast support at the bottom of the breast (upper part of image).

The cover illustration have been reproduced with kind permission of the publishers:
The British Journal of Radiology, 78, 328 - 334 (2005) (paper IIIa in this thesis) and
Radiation Protection Dosimetry, 114 (1-3), 444 - 449 (2005) (paper IIIb in this thesis).

Thesis for the Degree of Doctor of Philosophy
Faculty of Science at Lund University
Medical Radiation Physics
Department of Clinical Sciences, Malmö (IKVM)
Malmö University Hospital
SE-205 02 Malmö, Sweden

ISBN 978-91-628-7747-7
Printed in Sweden by Media-Tryck, Lund, 2009

With a lot of help from my friends

Abstract

Mammography refers to the X-ray examination of the human breast, and is considered the single most important diagnostic tool in the early detection of breast cancer, which is by far the most common cancer among women. There is good evidence from clinical trials, that mammographic screening can reduce the breast cancer mortality with about 30%. The side effects include a small and age related risk of carcinogenesis due to the exposure of the glandular tissues in the breast to ionising radiation. As for all X-ray examinations, and of special importance when investigating large populations of asymptomatic women, the relationship between radiation risk and diagnostic accuracy in mammography must be optimised. The overall objective of this thesis was to investigate and improve methods for average glandular dose (AGD) and image quality evaluation in mammography and provide some practical guidance.

Dose protocols used for so-called reference dose levels in Sweden 1989 (Nordic) and 1998 (European) were compared in a survey of 32 mammography units. The study showed that the AGD values for a "standard breast" became 5±2% (total variation 0-9%) higher at clinical settings, when estimated according to the European protocol.

For the Sectra MDM, a digital mammography (DM) unit with a scanning geometry, it was impossible to follow procedures for characterisation of the X-ray beam (HVL=half value layer) specified in the European protocol. In an experimental setup, it was shown that non-invasive measurements of HVL can be performed accurately with a sensitive and well collimated semiconductor detector with simultaneous correction for the energy dependence. AGD values could then be estimated according to 3 different dose protocols.

A dosimetry system based on radioluminescence and optically stimulated luminescence from Al_2O_3:C crystals was developed and tested for in vivo absorbed dose measurements. It was shown that both entrance and exit doses could be measured and that the dosemeters did not disturb the reading of the mammograms. A Monte Carlo study showed that the energy dependence could be reduced, primarily by reducing the diameter of the crystal.

It is proposed that radiation scattered forward towards the breast from the compression paddle, a scanning device etc, should be considered with greater clarity in the breast dosimetry protocols, and be described with a forward-scatter factor, FSF, for the various geometries and conditions proposed.

Low contrast-detail (CD) phantoms of simulated glandularity 30, 50 or 70%, and thickness 3, 5 or 7 cm, were used to compare three different mammography systems. The same number of perceivable objects was visible for the full-field DM system at 20-60% of the AGD necessary for the screen-film (SFM) system, with the largest dose

reduction potential for the thickest phantoms with the highest glandularity. However, more recent research shows that CD phantoms with a homogeneous background, as used here, must be used with care due to the presence of "anatomical noise" in the real clinical situation.

Image quality criteria (IQC) recommended in a European Guideline 1996 for SFM were adjusted to be relevant also for DM images. The new set of IQC was tested in two different studies using clinical images from DM and SFM, respectively. The results indicate that the new set of IQC has a higher discriminative power than the old set. The results also suggest that AGD for the DM system used may be reduced.

Abbreviations, acronyms and symbols

2D	Two-dimensional
3D	Three-dimensional
ACR	American College of Radiology
AEC	Automatic exposure control
AGD	Average glandular dose (see MGD)
BSF	Backscatter factor
BT	Breast tomosynthesis
c	Correction factor to AGD for glandularity other than 50%
CC	Cranio-caudal
CAD	Computer-aided detection
CD	Contrast-detail (phantom)
CR	Computed radiography (imaging plate)
CT	Computed tomography
DM	Digital mammography
DQE	Detective quantum efficiency
EC	European Commission
ESAK	Entrance surface air kerma
ESD	Entrance surface dose
EUREF	European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services
FFDM	Full field digital mammography
FSF	Forward-scatter factor
g	K to AGD conversion factor for 50% glandularity
HVL	Half value layer
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
ICS	Image criteria score
IQC	Image quality criteria
IPEM	Institute of Physics and Engineering in Medicine
K	Incident air kerma
K_{air}	Kerma free-in-air
MGD	Mean glandular dose (see AGD)
MLO	Mediolateral oblique
Mo/Mo	Anode/filter combination molybdenum/molybdenum
MOSFET	Metal oxide semiconductor field effect transistor
MRI	Magnetic resonance imaging
MTF	Modulation transfer function
NPS	Noise power spectrum
NRPA	Nordic Radiation Protection Authorities
OD	Optical density
OSL	Optically stimulated luminescence

PMMA	Polymethyl methacrylate (plexiglas or acrylic glass)
QA	Quality assurance
QC	Quality control
RL	Radioluminescence
ROC	Receiver operating characteristics
s	Correction factor to AGD for spectrum other than from Mo/Mo
SD	Standard deviation
SF	Screen-film
SFM	Screen-film mammography
T	Compressed breast thickness
TLD	Thermoluminescense dosemeters
VGA	Visual grading analysis
VGAS	Visual grading analysis score
VGC	Visual grading characteristics
W/Al	Anode/filter combination tungsten/aluminium

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Hemdal B, Bengtsson G, Leitz W, Andersson I, Mattsson S. Comparison of the European and Nordic protocols on dosimetry in mammography involving a standard phantom. *Radiat Prot Dosim 90 (1-2), 149-154 (2000).*

IIa Hemdal B, Herrnsdorf L, Andersson I, Bengtsson G, Heddson B, Olsson M. Average glandular dose in routine mammography screening using a Sectra microdose mammography unit. *Radiat Prot Dosim 114 (1-3), 436-443 (2005).*

IIb Hemdal B, Herrnsdorf L, Andersson I, Bengtsson G, Heddson B, Olsson M. Average Glandular Dose According to American and European Dose Protocols Using a Sectra MicroDose Mammography Unit. *Biomedizinische Technik 50 (Suppl vol 1, Part 2) 1116-1117 (2005).*

IIIa Aznar M C, Hemdal B, Medin J, Marckmann C J, Andersen C E, Bøtter-Jensen L, Andersson I, Mattsson S. *In vivo* absorbed dose measurements in mammography using a new real-time luminescence technique. *Brit J Radiol, 78, 328–334 (2005).*

IIIb Aznar M C, Medin J, Hemdal B, Thilander Klang A, Bøtter-Jensen L, Mattsson S. A Monte Carlo study of the energy dependence of Al_2O_3:C crystals for real-time *in vivo* dosimetry in mammography. *Radiat Prot Dosim 114 (1-3), 444–449 (2005).*

IV Hemdal B, Bay T H, Bengtsson G, Gangeskar L, Martinsen A C, Pedersen K, Thilander Klang A, Mattsson S. Comparison of screen-film, imaging plate and direct digital mammography using a low contrast-detail phantom. *In: Digital Mammography. Edited by H-O Peitgen, Springer Verlag, Berlin, pp 105-107 (2003).*

Va Hemdal B, Andersson I, Grahn A, Håkansson M, Ruschin M, Thilander Klang A, Båth M, Börjesson S, Medin J, Tingberg A, Månsson L G, Mattsson S. Can the average glandular dose in routine digital mammography screening be reduced? A pilot study using revised image quality criteria. *Radiat Prot Dosim 114 (1-3), 383–388 (2005).*

Vb Grahn A, Hemdal B, Andersson I, Ruschin M, Thilander-Klang A, Börjesson S, Tingberg A, Mattsson S, Håkansson M, Båth M, Månsson L G, Medin J, Wanninger F, Panzer W. Clinical evaluation of a new set of image quality criteria for mammography. *Radiat Prot Dosim 114 (1-3), 389–394 (2005).*

The papers have been reproduced with kind permission of the following publishers:

Radiation Protection Dosimetry (Papers I, IIa, IIIb, Va and Vb)
VG Wort, Biomedizinische Technik (Paper IIb)
The British Journal of Radiology (Paper IIIa)
Springer Verlag, Berlin (Paper IV)

My contribution to the papers

Paper I	I had the main responsibility for planning and conducted the experimental work together with Gert Bengtsson. I had the main responsibility for evaluation of the results and writing of the paper.
Paper IIa	I had the main responsibility for planning and took active part in all the experimental work. I had the main responsibility for evaluation of the results and writing of the paper.
Paper IIb	I had the main responsibility for planning and took active part in all the experimental work. I had the main responsibility for the evaluation of the results and writing of the paper.
Paper IIIa	I participated in all the planning and took active part in all the experimental work. I took active part in evaluation of the results with main responsibility for radiation dose measurements and wrote part of the paper.
Paper IIIb	I participated in the planning and took active part in the evaluation of the results. I wrote part of the paper.
Paper IV	I had the main responsibility for planning and took active part in all the experimental work. I had the main responsibility for evaluation of the results and writing of the paper.
Paper Va	I planned and conducted the experimental work largely together with Ingvar Andersson. I had the main responsibility for evaluation of the results and writing of the paper.
Paper Vb	I participated in the planning and took active part in the experimental work and evaluation of the results. I wrote part of the paper.

Preliminary reports have been presented at the following international meetings

First Malmö Conference on Medical X-ray Imaging, Malmö June 13-15 1999. Hemdal B, Bengtsson G, Verdun F, Andersson I, Mattsson S. Evaluation of new screen/film systems for mammography.

First Malmö Conference on Medical X-ray Imaging, Malmö June 13-15 1999. Hemdal B, Bengtsson G, Leitz W, Andersson I and Mattsson S. Comparison of the European and Nordic protocols on dosimetry in mammography involving a standard phantom.

The 6th International Workshop on Digital Mamography, Bremen, Germany, June 22-25 2002. Hemdal B, Bay T H, Bengtsson G, Gangeskar L, Martinsen A C, Pedersen K, Thilander Klang A and Mattsson S. Comparison of screen-film, imaging plate and direct digital mammography with CD phantoms.

Second Malmö Conference on Medical X-Ray Imaging, April 23-25 2004. Hemdal B, Herrnsdorf L, Andersson I, Bengtsson G, Heddson B, Olsson M. Average glandular dose in routine mammography screening using a Sectra microdose mammography unit.

Second Malmö Conference on Medical X-Ray Imaging, April 23-25 2004. Aznar M C, Medin J, Hemdal B, Thilander Klang A, Bøtter-Jensen L, Mattsson S. A Monte Carlo study of the energy dependence of Al_2O_3:C crystals for real-time *in vivo* dosimetry in mammography.

Second Malmö Conference on Medical X-Ray Imaging, April 23-25 2004. Hemdal B, Andersson I, Grahn A, Håkansson M, Ruschin M, Thilander Klang A, Båth M, Börjesson S, Medin J, Tingberg A, Månsson L G, Mattsson S. Can the average glandular dose in routine digital mammography screening be reduced? A pilot study using revised image quality criteria.

Second Malmö Conference on Medical X-Ray Imaging, April 23-25 2004. Grahn A, Hemdal B, Andersson I, Ruschin M, Thilander-Klang A, Börjesson S, Tingberg A, Mattsson S, Håkansson M, Båth M, Månsson L G, Medin J, Wanninger F, Panzer W. Clinical evaluation of a new set of image quality criteria for mammography.

47th AAPM Annual Meeting, Washington State Convention and Trade Centre, Seattle, Washington SU-FF-I-36, July 24-28 2005. Hemdal B, Herrnsdorf L, Martin M, Andersson I, Bengtsson G, Heddson G, Olsson M. Average Glandular Dose According to American and European Dose Protocols Using a Sectra MicroDose Mammography Unit. *Med Phys* **32** (6) 1912 (2005).

14th International Conference of Medical Physics of the International Organization for Medical Physics (IOMP), Nuremberg, Germany, September 14-17 2005. Hemdal B, Herrnsdorf L, Martin M, Andersson I, Bengtsson G, Heddson G, Olsson M. Average Glandular Dose According to American and European Dose Protocols Using a Sectra MicroDose Mammography Unit.

Australasian Conference for Medical Physics and Bio-Engineering, Adelaide, Australia, October 23-27 2005. Hemdal B, Andersson I, Mattsson S (invited). Digital mammography – Experiences, optimisation and QA aspects.

Other related publications by the author

Aznar M, Hemdal B 2008 Absorbed dose measurement in mammography. In: Cancer Imaging: Lung and Breast Carcinomas. (Ed by M A Hayat), Elsevier, pp 493-501

Bengtsson G, Hemdal B 1997 Survey of Mammographic Equipment in the Southern Health Care Region. *National Board of Health and Welfare, Public Service, Stockholm*, Article No. 1997-00-31 (in Swedish) (50 pages)

Börjesson S, Håkansson M, Båth M, Kheddache S, Svensson S, Tingberg A, Grahn A, Ruschin M, Hemdal B, Mattsson S, Månsson L G 2005 A software tool for increased efficiency in observer performance studies in radiology Radiat Prot Dosim **114** (1-3) 45-52

Hemdal B, Andersson I, Thilander Klang A, Bengtsson G, Leitz W, Bjurstam N, Jarlman O, Mattsson S 2002 Mammography – recent technical developments and their clinical potential. *Swedish Radiation Protection Authority, Stockholm*, SSI Report 2002:08 Available at: http://www.stralsakerhetsmyndigheten.se/Publikationer/Rapport/Stralskydd/2002/200208-Mammography-recent-technical-developments-and-their-clinical-potential/

Ruschin M, Tingberg A, Båth M, Grahn A, Håkansson M, Hemdal B, Andersson I 2005 Using simple mathematical functions to simulate pathological structures - input for digital mammography trial *Radiat Prot Dosim* **114** (1-3) 424-431

Ruschin M, Hemdal B, Andersson I, Börjesson S, Håkansson M, Båth M, Grahn A, Tingberg A 2005 Threshold pixel size for shape determination of microcalcifications in digital mammography: a pilot study *Radiat Prot Dosim* **114** (1-3) 415-423

Ruschin M, Båth M, Hemdal B, Tingberg A 2005 Shape determination of microcalcifications in simulated digital mammography images with varying pixel size In: Medical imagning 2005: Image perception, observer performance and technology assessment (Ed by M P Eckstein, Y Jiang) *Proc SPIE* **5749** 288-299

Ruschin M, Timberg P, Båth M, Hemdal B, Svahn T, Saunders R, Samei E, Andersson I, Mattsson S, Chakraborty D P, Tingberg A 2007 Dose dependence of mass and microcalcification detection in digital mammography: Free response human observer studies *Med Phys* **34(2)** 400-407

Ruschin M, Timberg P, Svahn T, Andersson I, Hemdal B, Mattsson S, Båth M, Tingberg A 2007 Improved in-plane visibility of tumors using breast tomosynthesis In: Medical imaging 2007: Physics of medical imaging (Ed by J Hsieh, M J Flynn) *Proc SPIE* **6510** 65104R

Svahn T, Hemdal B, Ruschin M, Chakraborty D, Andersson I, Tingberg A, Mattsson S 2007 Dose reduction and its influence on diagnostic accuracy and radiation risk in digital mammography: an observer performance study using an anthropomorphic breast phantom *Br J Radiol* **80** 557-562

Svahn T, Ruschin M, Hemdal B, Nyhlén L, Andersson I, Timberg P, Mattsson, S Tingberg A 2007 In-plane artifacts in breast tomosynthesis quantified with a novel contrast-detail phantom. In: Medical imaging 2007: Physics of medical imaging (Ed by J Hsieh, M J Flynn) *Proc SPIE* **6510** 65104R

Timberg P, Ruschin M, Båth M, Hemdal B, Andersson I, Mattsson S, Chakraborty D, Saunders R, Samei E, Tingberg A 2006 Potential for lower absorbed dose in digital mammography: A JAFROC experiment using clinical hybrid images with simulated dose reduction. In: Medical Imaging 2006: Image perception, observer performance, and technology assessment (Ed by Y Jiang, M P Eckstein) *Proc SPIE* **6146** 614614

Timberg P, Ruschin M, Båth M, Hemdal B, Andersson I, Svahn T, Mattsson S, Tingberg A 2007 Optimization of image quality in breast tomosynthesis using lumpectomy and mastectomy specimens. In: Medical imagning 2007: Physics of medical imaging (Ed by J Hsieh, M J Flynn) *Proc SPIE* **6510** 651032

Timberg P, Båth M, Andersson I, Svahn T, Ruschin M, Hemdal B, Mattsson S, Tingberg A 2008 Impact of dose on observer performance in breast tomosynthesis using breast specimens. In: Medical Imaging 2008: Physics of medical imaging (Ed by J Hsieh, E Samei) *Proc SPIE* **6913** 69134J

Contents

1. Preface

1.1 Introduction

Mammography refers to the X-ray examination of the human breast and has been used for more than half a century (Leborgne 1951) in the diagnosis of breast diseases, and for several decades also for mass screening of asymptomatic women. Mammography is one of the most frequent X-ray examinations, considered the single most important diagnostic tool in the early detection of breast cancer, which is the woman's by far most common cancer. There is evidence from clinical trials, like that in Malmö from 1978 to 1986 (Andersson *et al.* 1988) and the two-county study (Tabar *et al.* 1985), that mammographic screening can reduce the breast cancer mortality with about 30% (Nyström *et al.* 1993, 2002).

One of the main reasons for the expansion of mammography is the introduction of high volume screening programs. There has been doubts about the efficiency of so-called service screening, i.e. routine screening programs (Sjönell and Ståhle 1999), but there is evidence suggesting a reduction of breast cancer mortality similar to that observed in the randomised trials (Duffy et al. 2002).

The main positive effects are prevented deaths, prevented cases of metastatic disease and increased possibility of breast conserving surgery. However, there are also several negative effects (Andersson and Janzon 1997, Mattsson *et al.* 2000, Andersson 2001). False positive tests result in further examinations and occasionally surgery for benign disease. Some true positive tests lead to detection of clinically insignificant breast cancer. As with any X-ray examination, there is a small risk of carcinogenesis involved with irradiating the breast tissue, a risk that is clearly related to the age of the women exposed (UNSCEAR 2000). Radiation risk with mammography has been analysed in more detail elsewhere (Law and Faulkner 2002, Svahn *et al.* 2007).

Most expert groups have concluded that the advantages outweigh the disadvantages and that screening should be recommended for women aged 50 to 70. Although the balance between positive and negative effects is less favourable for the younger age group 40-50 (Moss *et al.* 2006), several expert committees recommend screening also for this age group, e.g. the National Board of Health and Welfare (1998) in Sweden. According to Svahn *et al.* (2007), the estimated number of radiation induced breast cancer fatalities because of an AGD of 1.3 mGy for one image (Reference level in Sweden, SSI 2002) is of the order of 7-18 cases for a screening involving 100 000 women (40-49 years, 80% participation rate) in two-view mammography. A linear dose-response relationship and age-specific relative riskmodels were used in the risk calculations with derived data from three populations; atomic bomb survivors and women that received medical high-dose exposures in Northamerica and Sweden. At the same time the number of deaths prevented as a result of screening mammography,

according to the Malmö Mammographic Screening Trial (Andersson and Janzon, 1997) is 200, which means a very clear net benefit with the screening programme.

In a screening programme, the specificity should be high, about 97% (National Board of Health and Welfare 1998), in order to avoid an unacceptable number of recalls. To justify screening, the positive cases must be found to a large extent, i.e. the sensitivity must also be high. In this case there is room for improvement, since sensitivity of mammography has been reported to be about 70% (Poplack *et al.* 2000, Rosenberg *et al.* 2000, Pisano *et al.* 2005). In more than half of the cancer cases not found, mammographic signs of breast cancer can be identified retrospectively (Laming and Warren 2000). This indicates that several conditions from the origin of the X-ray photons in the focus of the X-ray tube to the decision of the radiologist can be improved.

Screen-film mammography (SFM), developed for decades, is fast and cost-efficient, but there are also limitations such as a limited dynamic range, a fixed display scale with low image contrast in the dense breast parenchymal area and environmental problems from chemicals in the processor. Introduction of digital mammography (DM) and spin-off techniques such as computer-aided detection (CAD) and breast tomosynthesis (BT) may represent improvements that will increase sensitivity in mammography screening.

Detectors for DM have generally higher detective quantum efficiency (DQE) than SFM, i.e. the efficiency in information transfer from the spatial distribution of X-ray quanta behind the breast to an image is improved. This indicates a potential for improvement of the image quality and/or a reduction of the dose with digital systems compared to SFM. Further improvements can be expected from increased dynamic range, a linear response to incident radiation, improved contrast and image processing. There is also an increased possibility for optimisation, since each part of the imaging chain can be treated separately. The technical development and its clinical potential were discussed in a study supported by the Swedish Radiation Protection Authority (Hemdal *et al.* 2002). Further details of technical developments can be found elsewhere (Pisano and Yaffe 2005, Fischer *et al.* 2006). In randomised trials comparing screen-film mammography with digital mammography, the sensitivity of mammography for cancer detection was equal or increased in DM (Levin *et al.* 2001, Skaane and Skjennald A 2004, Pisano *et al.* 2005, Skaane *et al.* 2007), although the difference was not statistically significant in most of the studies.

A problem with SFM and DM is that structures are projected on a two-dimensional (2D) image. Thus, the resulting "anatomical noise" can obscure relevant lesions. Also, normal structures can be superimposed in a way to be mistaken for a tumour. Breast tomosynthesis (BT) is a technique to produce three-dimensional (3D) digital images of the breast (Grant 1972, Niklason *et al.* 1997, Wu *et al.* 2003, Bissonnette *et al.* 2005,

Ruschin 2006). Several projection images (typically 10-25), each acquired from a different direction (angular range about 15-50 degrees), are reconstructed mathematically to a 3D breast volume, or rather 2D image planes with lower spatial resolution between the planes (distance approximately 1 mm) than within planes. The total radiation dose is comparable to the dose from 1-2 ordinary DM images. This is expected to reduce the influence of "anatomical background", particularly in dense breasts. Studies using test objects (Smith *et al.* 2006), computer simulation (Gong *et al.* 2006) hybrid images (simulated structures in normal clinical images) (Ruschin *et al.* 2007) or clinical images (Varjonen 2006, Andersson *et al.* 2008) indicate a potential for increased sensitivity and specificity of BT compared to DM.

There are a number of alternative or complementary techniques to mammography (Karellas and Vedantham 2008), but mammography is presently the only realistic technique for screening on a large scale, at present with SFM or DM techniques, in the near future probably also with BT technique. For breast diagnosis, ultrasound is also a standard technique. The main complementary imaging technique to mammography and ultrasound is MRI. Both ultrasound and MRI have the advantage of not using ionising radiation and works well also for dense breasts where mammography has difficulties.

1.2 Optimisation in mammography

In an attempt to standardise the imaging techniques and other procedures involved in mammography, quality assurance (QA) protocols have been developed. Such protocols provide guidelines for image quality and absorbed dose in mammography (NRPA 1991, Hendrick *et al.* 1999, EC 2006, IPEM 2005) or concentrate on dosimetry in mammography (Zoetelief *et al.* 1996, IAEA 2007). There are also guidelines on quality criteria for diagnostic radiographic images, including mammography (EC 1996).

In SFM and DM a screening examination usually includes two exposures of each breast, in medio-lateral oblique (MLO) and in cranio-caudal (CC) projections. The image quality must enable the detection of clusters of so-called microcalcifications (each with an extension of only 0.1-0.5 mm in diameter) and of tumours with low contrast compared to their surroundings, even in dense and large breasts. However, the absorbed dose delivered to the breast must not be higher than needed for this purpose. In other words, the relationship between dose and image quality must be optimised, as for all X-ray examinations (ICRP 2004). This is of special importance when screening large populations of asymptomatic women. For optimisation in mammography, efficient tools are needed for estimation of both image quality and dose.

1.3 Objectives of the present study

The overall objective of this thesis was to investigate and improve methods for radiation absorbed dose and image quality evaluation in mammography and provide some practical guidance. The hope is to help sharpen the tools for the optimisation of the relationship between absorbed dose and image quality in mammography. The specific objectives are:

- To compare the Nordic and European dose protocols in an attempt to harmonise methods for radiation absorbed dose measurements in mammography within Europe (Paper **I**)

- To find a method to perform accurate radiation dose estimates on a new type of mammography equipment and to analyse special conditions in technical developments regarding both mammography systems and dosemeters (Papers **IIa** and **IIb**)

- To develop and test a small size optical fibre dosemeter, both for breast simulating phantoms and for *in vivo* entrance and exit dose measurements in real mammography examinations (Papers **IIIa** and **IIIb**)

- To evaluate a method based on contrast/detail phantoms to compare the image quality of digital mammography techniques and that of screen-film technique (Paper **IV**)

- To adjust and sharpen present image quality criteria and perform preliminary evaluation studies of the new set of quality criteria with clinical images based on both digital and screen-film technique (Papers **Va** and **Vb**)

2. Background

2.1 Absorbed dose

The average (or mean) absorbed dose to the glandular tissues within the breast, here called AGD (alternatively MGD), is the recommended radiation risk related quantity for mammography (ICRP 1987, 1996). AGD can not be determined directly, but conversion factors for estimation of AGD from incident air kerma, K, can be used. Such factors can be determined by the use of thin thermoluminescence dosemeters (TLDs) in breast-like phantoms, and through Monte Carlo calculations, which can be made with better flexibility (Alm Carlsson and Dance 1992). Determination of AGD for an individual woman is uncertain, as it depends not only on tissue composition, but also on tissue distribution within the breast. It has been shown (Dance *et al.* 2005) that changes in the distribution of glandular tissue can result in around 60% deviation from AGD estimated using a simple breast model. Instead, AGD is usually determined for groups of women or for "standard" breasts simulated with a suitable material, generally polymethyl methacrylate (PMMA). AGD estimated for groups of women provide more realistic data in risk estimates, while AGD for standard breasts are especially useful for quality control (QC) and comparisons, over time and between units/centra/countries.

2.1.1 Average glandular dose estimation

In this thesis, average glandular dose, AGD, is determined (Dance *et al.* 2000) as

$$AGD = K\,g\,c\,s$$

where K is the incident air kerma att the upper surface of the breast (or at the upper surface of a PMMA phantom that simulate a standard breast), measured without backscatter but with forward-scattered X-ray photons from the compression paddle included (this will be commented further in Chapter 4). The g-factor is the incident air kerma to average glandular dose conversion factor for breasts with a glandularity of 50%. The c-factor corrects for any difference in breast composition from 50% glandularity and the s-factor corrects for any difference in the X-ray spectrum used from the molybdenum anode, molybdenum filter, Mo/Mo, combination.

The g- and c-factors are tabulated as a function of breast thickness and air kerma half-value layer, HVL, of the X-ray beam, while the s-factor varies with the anode/filter combination used (Dance 1990, Dance *et al.* 2000, Dance *et al.* 2009). These g- and c-factors are tabulated for breasts, but also for standard breasts simulated with PMMA.

Consequently, the quantities K, HVL and (for breasts) compressed breast thickness, T, has to be estimated in order to determine AGD. As mentioned in Chapter 1.2, QA

protocols provide guidelines for absorbed dose estimations in mammography. The dose protocols discussed in this thesis are the Nordic (NRPA 1991), European (Zoetelief *et al.* 1996), Euref (van Engen *et al.* 2003 and EC 2006) and American (Hendrick *et al.* 1999) protocols, cf. Table 2.1. There are also other dose protocols, both international (IAEA 2007) and national. The one from the United Kingdom (IPEM 2005) is perhaps the most used national protocol, with reference position 4 cm from the table edge. Otherwise the conditions are as for the Euref dose protocol in Table 2.1.

A summary and comparison of factors g, c and s published by various authors has been presented recently (ICRU, 2005). Notably, the conversion factors by Dance *et al.* (2000) are used in all the dose protocols mentioned (in the American protocol among other factors), except for the Nordic protocol, which uses other g factors (Rosenstein *et al.* 1985).

It should also be mentioned that the quantity K used here is equivalent to the quantity Entrance Surface Air Kerma, ESAK, that is used for instance in the European dose protocol (Zoetelief *et al.* 1996) and in the papers of this thesis. However, ESAK is elsewhere (ICRU 2005) defined as air kerma including backscatter.

The equivalent thickness of PMMA phantoms used for simulating the exposure of breasts have been calculated by several authors (Thilander-Klang 1997, Dance *et al.* 2000, Dance *et al.* 2009).

Table 2.1: Dose protocols tested and discussed in this thesis; column 1) the name as used in the text, essentially also in the papers, 2-3) the reference position and its distance from the film edge and the breast support edge at the chest wall side, respectively, 4) the thickness and glandularity of the standard breast, 5) the PMMA thickness used to simulate the standard breast and 6) the type of conversion factors used.
Note 1: For the Nordic protocol is HVL measured without the compression paddle in the X-ray beam, otherwise with.
Note 2: For the American (or ACR) protocol the standard breast is simulated with the so-called accreditation (or ACR) phantom, with 44 mm thickness of which 7 mm is a dental vax layer with embedded test objects.

Name of protocol	**Ref position**	**From edge of**	**Standard breast thick-ness and glandularity**	**PMMA thickness**	**Conv factors**
Nordic	3 cm	Film	Not specified	45 mm	g
European	6 cm	Support	50 mm, 50%	45 mm	g
Euref	6 cm	Support	21 mm, 97% - 103 mm, 3%	20-80 mm	g, c, s
American	4 cm	Support	42 mm, 50%		g

2.1.2 Dosemeters

Dosemeters for indirect as well as for direct measurement of K, must fulfill specific requirements. As an example Zoetelief *et al.* (1996) state that they should have a dynamic range covering at least 0.5 to 100 mGy, a total accuracy of less than ±10% including the energy response for the beam qualities involved and a precision better than ±5%. Because of these or stricter requirements, as discussed in Paper **IIa** and Chapter 4, but also because of other factors like user-friendliness and cost, to date only ionisation chambers and semiconductors are in widespread use for output and HVL measurements in mammography.

DeWerd *et al.* (2002) evaluated ten commercially available ionisation chambers, which were found to vary considerably in volume (0.2-15 cm^3), composition and geometry. Their energy response allowed AGD determination within about 2% for a wide range of beam qualities. Ionisation chambers are fragile and the measurements have to be corrected for variation in atmospheric pressure and temperature, but they provide valuable tools for accurate dosimetry.

Semiconductor systems are sturdy, sensitive and can be relatively easy to handle. However, they are usually much more energy-dependent than ionisation chambers and must be calibrated for air kerma free-in-air, K_{air}, with care (Witzani et al., 2004). In the last decade, instruments have been developed with several semiconductors. With suitable selection of materials and thicknesses to filter incident radiation to at least two of these semiconductors, such instruments can also be used for accurate dosimetry (Paper **IIa**).

When dosemeters are used for direct *in vivo* measurements, i.e. when they are present during the acquisition of a breast image, it is fundamental that the reading of the mammogram is not disturbed by the dosemeters. Warren-Forward and Duggan (2004) have used TLDs made thin enough not to degrade the diagnostic quality of the mammogram (they should not mask a lesion or be mistaken for one). The results are promising, but yet not quite convincing that the reading of mammograms cannot be affected under any circumstances. Normally TLDs are clearly visible and therefore their position might be specified as e.g. "on the upper inner quadrant of the breast" (Zoetelief *et al.* 1996) in order to minimise the interference with the reading of the mammogram. The European dose protocol also specify requirements, e.g. the accuracy and precision are both to be better than ±10% and provide procedures for sending TLDs to a central laboratory for calibration and reading. This procedure has been used for inter-institute comparison studies such as the one reported by Gentry and DeWerd (1996), which involved 4400 women in 170 mammography facilities across the United States. This is one of many studies using small TLDs with a characteristic shape that are visible in the mammogram. However, they can as well be used to expose a phantom (Table 2.1) that simulates a standard breast. One of the

limitations of TLDs is that they are relatively cumbersome to use with a complicated procedure of heating in an oven under specified conditions both before and after the reading of the dosemeters.

In the past years, some dosimetry systems other than TLDs have shown a potential for measurements involving a phantom that simulate a standard breast and for *in vivo* measurements in mammography. They differ mainly from TLDs in terms of increased sensitivity and/or potential user-friendliness. Though those novel techniques are not yet evaluated and commercially available in the way TLDs are and hence, far from widespread in clinical application, a short review is given here.

Metal Oxide Semiconductor Field Effect Transistor (MOSFET) is a silicon semiconductor to which a voltage is applied. Exposure to radiation will result in a shift in voltage, directly proportional to the amount of energy absorbed in the detector. Though their clinical use is at present limited, MOSFETs have gained popularity because of their small size and the possibility of immediate read-out. Applications in mammography (Dong at al., 2002; Benevides and Hintenlang, 2006) are encouraging in terms of sensitivity. However, in the direct measurements used, the detectors were not positioned on the breast surface (Dong at al., 2002) or phantom surface (Benevides and Hintenlang, 2006), but substantially further from the edge of the breast support than the prescribed distance (4-6 cm, Table 2.1) in various dose protocols. This was done in order to minimize the degradation of the diagnostic quality of the image. Consequently, no "true" *in vivo* measurements are made and the impact of this discrepancy on dose results should be evaluated further. Other potential pitfalls of MOSFET detectors include their limited lifetime (they have to be replaced regularly as they accumulate dose) and that proper correction must be performed for the energy dependence of the signal, when measuring the kerma value.

There are also dosemeters based on the phenomenon of radioluminescence (RL) and optically stimulated luminescence (OSL). Most crystalline materials produce luminescence when exposed to ionising radiation, and RL is emitted promptly during irradiation, while OSL is emitted when the crystal is stimulated by laser light (in analogy with TLDs, that are stimulated by heat). The RL signal is then proportional to the dose rate while the OSL signal is proportional to the absorbed dose in the crystalline detector. It has been shown (Aznar 2005, Yukihara and McKeever 2008) that instruments using an aluminum oxide (Al_2O_3:C) crystal linked to an optical fibre are well suited for radiotherapy. A prototype instrument has been evaluated for *in vivo* measurements in mammography (Papers **IIIa** and **IIIb**).

2.2 Image quality

Image quality can be quantified with basic physical characteristics, contrast, spatial resolution (Modulation Transfer Function, MTF) and noise (Wiener spectrum or Noise Power Spectrum, NPS), each representing a specific characteristic of the imaging system. These measures can be combined and for instance the overall performance can be described with the Detective Quantum Efficiency (DQE). All these physical measures are tools for objective quantification and comparison of imaging systems and are described elsewhere (Cunningham 2000, Dobbins III 2000, Båth 2003). If the imaging task is not limited by physical noise (quantum noise or system noise), but by anatomical noise, i.e. fluctuations in the appearance of the projected anatomical structures, the DQE may not be a relevant measure of image quality (Båth 2003).

Another way of describing the overall system performance is to use a contrast-detail (CD) phantom (de Paredes *et al.* 1998). The phantom can be made of PMMA or of a more breast equivalent material as the one used in Paper **IV**. The CD structures can be holes or objects of different diameter and depth, e.g. gold discs (EC 2006). Human observers are usually used for the evaluation of the smallest visible object for a given contrast (or the smallest visible contrast for a given diameter), thereby including the whole imaging chain, as in Paper **IV**. As human observers are subjective, can get tired and have limited time, methods for objective computer-assisted evaluation have been developed (Young *et al.* 2008a). A problem with CD phantoms is their homogeneous background. According to the Rose model (Rose 1948), the contrast must increase when the diameter decrease for a CD object to be visible. This is normally found in practice with phantoms of homogeneous background. However, in observer performance studies of lesion detection in an anatomical background it has been shown (Burgess *et al.* 2001) that this is not valid for structures with an extension of about 1 mm or larger. Instead, larger objects may be more difficult to see than smaller due to the anatomical background. It is likely that this applies to detection of masses (i.e. tumours) in mammograms, a detection task for which the anatomical background dominates. It has been shown (Ruschin *et al.* 2007) that masses as structures in hybrid images were only marginally affected by a dose reduction (increase in random noise), because the anatomical noise remained virtually unchanged. On the other hand simulated microcalcifications with an extension much below 1 mm were harder to see when the dose was reduced. A conclusion by Månsson *et al.* (2005) is that CD phantoms with a homogeneous background are questionable as tools for optimisation. However, their use as a tool for image quality control on a regular basis is well justified (EC 2006, Young *et al.* 2008b). It has been shown (Young *et al.* 2008a) that evaluation with computer aid can be made both efficiently and with results comparable to those from human observers.

In Receiver Operating Characteristics (ROC) analysis, a widely used and well accepted method (Chakraborty 2000), a number of images with known pathology and others without pathology are used. The structure (e.g. a tumour) used for the imaging task must be known and also be subtle enough not always to be visible with full confidence, as the visibility of a structure should be stated with different degrees of confidence. ROC methods are then generally very time-consuming in the set-up and implementation of a study, although more effective variants like free-response ROC (FROC) techniques have been developed (Chakraborty and Berbaum 2004).

Visual Grading Analysis (VGA) can be performed with relative gradings (using one or several images as references and a 3-, 5- or 7-step scale) or with absolute gradings (using no references), as described by Månsson (1994). Both relative and absolute gradings are used in the study presented in Paper **Va**, absolute gradings (two alternatives, yes or no) also in the study in Paper **Vb**. In both these studies the detection task regarded fulfilment of image quality criteria (IQC) in normal mammograms. As such criteria are related to reproduction of structures in normal mammograms, the set-up and implementation of a study is generally much less time consuming compared to ROC studies. The results can be quantified by calculating the Visual Grading Analysis Score (VGAS) and Image Criteria Score (ICS), i.e. the fraction of fulfiled criteria, respectively (Tingberg 2000). The fulfilment of image quality criteria can be stated with different degrees of confidence in a similar way as the visibility of structures are stated in an ROC study. Results from a VGA study with absolute gradings and use of a rating scale (with e.g. 5 steps) regarding the degree of fulfilment for each criteria, can be analysed with a method called Visual Grading Characteristics (VGC), as described by Båth and Månsson (2007). The rating data is analysed in a similar way as in ROC analysis.

3. Evaluation of absorbed dose and image quality

An overview of the studies presented in this thesis, Table 3.1, shows that AGD was evaluated in most of the studies with four different dose protocols applied. Image quality was evaluated in three of the studies, with the use of images from breast equivalent phantoms (Paper **IV**) or of women (Paper **Va** and **Vb**). In one study (Paper **IIIb**), Monte Carlo technique was used, with no need for any imaging technique or image object. Three different imaging techniques were used, screen-film (SF), computed radiography (CR) and full field digital mammography (FFDM). Three different image objects were used, standard phantoms, breast equivalent phantoms and breasts. In one study (Paper **IV**), all three imaging techniques were used and compared with breast equivalent phantoms.

Table 3.1: Overview of the imaging techniques and the type of objects used for imaging, the dose protocols applied for AGD evaluation (cf. Table 2.1), and the type of image quality evaluation performed in the studies presented in the papers of this thesis. The notation + means that also the s-factor was used, ++ that both the s- and c-factors were used in addition to the g-factor specified in the European or American dose protocol.

	Paper							
	I	**IIa**	**IIb**	**IIIa**	**IIIb**	**IV**	**Va**	**Vb**
Imaging techniques								
Screen-film	x			x		x		x
Computed radiography						x		
Full Field Digital Mammogr.		x	x			x	x	
Objects								
Standard phantoms	x			x				
Breast equivalent phantoms						x		
Breasts				x			x	x
Dose protocols applied								
Nordic	x							
European	x	x+	x+	x		x++	x+	
Euref		x	x					
American			x+					
Image quality evaluation								
Perceivable objects (score)						x		
VGA, relative gradings							x	
VGA, absolute gradings							x	x

3.1 Comparison of Nordic and European dose protocols (Paper I)

AGD for a standard breast simulated with a 45 mm PMMA phantom has been a quantity used in Swedish reference dose levels since routine screening programs started in 1986 (National Board of Health and Welfare 1986, 1990). At first, the Swedish dose protocol (Leitz 1989) was used. This protocol was adopted by the other Nordic countries (NRPA 1991), and was called the Nordic dose protocol. In order to harmonise with the other European countries, the authorities in Sweden instead adopted, from 1998 (National Board of Health and Welfare 1998, Leitz 1998), the concept of the European dose protocol (Zoetelief *et al.* 1996). A few years later this protocol was also implemented in the Swedish legislation (SSI 2002) and is still valid. The purpose of the study in Paper **I** was to compare the Nordic and European dose protocols before the change of protocols in 1998. Differences in measuring procedures and calculations and their implications on the results were to be analysed.

The AGD was derived according to both the European and the Nordic protocol from measurements on thirty-two SFM systems in southern Sweden. The exposure of the standard phantom at clinical settings was performed as clinically used for a standard-sized breast according to the local staff, including the selection of X-ray beam quality and position of the automatic exposure control, AEC, detector. This lead to the selection of the molybdenum anode, molybdenum filter, Mo/Mo, combination in all cases, while the tube voltage varied from 25 kV to 30 kV. The same test equipment was used during the whole study by the same two medical physicists (BH and GB) working together. The practical arrangements considered to be the most suitable, e.g. the positioning of the compression paddle at the HVL measurement according to the European protocol, were identified and documented with a digital camera.

A consequence of the heel effect is that the tube output values, measured 24-28 mm more distant from the chest wall side of the cassette table edge, were 3±2% lower. The most important difference between the two dose protocols is that the air kerma half value layer, HVL, of the X-ray beam is evaluated including the compression paddle in the European protocol and without it in the Nordic protocol. Mainly due to this, but to some extent also due to the heel effect, the HVL values from use of the European protocol were considerably higher, 0.32-0.39 mm Al compared to 0.28-0.35 mm Al, although the X-ray beams were the same. When the European protocol is used instead of the Nordic protocol to estimate the standard AGD, the estimates differ so that the value is increased by 5±2% (total variation 0–9%) at clinical settings and by 9±3% (4–17%) at a standardised net optical density, OD, of 1.00.

The European protocol predicted that the output should be the same, while the AGD values should be 1-2% lower (Tables A4.2 and A4.3, respectively, in Zoetelief *et al.* 1996). In the case of output, the agreement with the results in Paper **I** was fairly good, and the difference can be explained by a neglection of the small heel effect in the

European protocol prediction. However, regarding AGD, the difference between predicted 1-2% lower and measured 5±2% higher can be explained if the prediction in the European protocol did not consider the difference in HVL results regarding the two protocols. This illustrates that careful evaluation of AGD differences with measurements according to different protocols should be undertaken. Results as those presented in Paper **I** should be considered in quality control programmes and optimisation procedures as well as in interpretation of trends and in future legislation programmes.

3.2 Dosimetry for a scanning technique (Papers IIa and IIb)

One of the new DM techniques, Sectra MDM (MicroDose Mammography) was developed in Stockholm, Sweden (Lundqvist *et al.* 2003). The first unit used in routine mammography screening was installed at the hospital of Helsingborg, Sweden, in 2003. Different from other DM units, it had a scanning geometry with a multi-slit pre-collimator, which scanned at a distance of only 115 mm above the breast support. It was for instance then not possible to follow usual procedures for HVL measurements (Zoetelief et al. 1996). The purpose of the study in Paper **IIa** was to find a method to perform accurate HVL measurements and analyse other possible obstacles in order to estimate AGD for standard breasts according to the European and Euref dose protocols.

In an experimental setup (Paper **IIa**), the same type of X-ray tube as in the mammography unit was used. Also the same type of compression paddle was used and the multi-slit pre-collimator was simulated. Thus, it was possible to simulate HVL measurements according to both usual procedures for HVL measurements and the simulated geometry of the mammography unit. In this study, exposures of standard phantoms were not needed, since the exposure parameter settings was determined by the breast thickness only, and this was anticipated to work properly. AEC was not introduced for this mammography system until later (Åslund *et al.* 2005).

The study in Paper **IIa** has demonstrated that non-invasive measurements of HVL can be performed accurately with a sensitive and well-collimated semiconductors detector ionisation chamber (23344, PTW, Freiburg, Germany)with simultaneous correction for the energy dependence of the kerma value.

The purpose of Paper **IIb** was to evaluate the AGD also according to the American dose protocol. In this case the reference position is 4 cm from the table edge and not 6 cm as for the European and Euref protocols (Table 2.1). Therefore, the air kerma profile in the anode-cathode direction was investigated also.

Results in Paper **IIb** from measurements at the same occasion showed AGD values for the standard breast, cf. Table 2.1, according to the European protocol (50 mm

thick with 50% glandularity) of 0.29 mGy, for the most similar standard breast (53 mm thick with 29% glandularity) according to the Euref protocol of 0.32 mGy and for the standard breast according to the American protocol (42 mm thick with 50% glandularity) of 0.28 mGy, respectively. It was also demonstrated that the air kerma profile in the anode-cathode direction showed discontinuities due to the construction of the multi-slit pre-collimator.

It was concluded from Papers **IIa** and **IIb** that the accuracy of absorbed dose measurements for this unit could be increased, if the existing dose protocols were revised to account also for the tungsten anode, aluminium filter, W/Al, combination, scattered radiation from the multi-slit pre-collimator device and the occurrence of a dose profile in the scanning direction (Paper **IIa**) as well as discontinuities of the air kerma profile in the anode-cathode direction (Paper **IIb**). A preliminary s-value of 1.05 for W/Al (the same as used in Paper **IIa**) was presented in the European guidelines (EC 2006), but a value of about 1.15 seems to be closer to the truth (Dance *et al.* 2009). Because of this, the AGD values presented in Papers **IIa** and **IIb** may be underestimated with about 10%. However, until the issues mentioned about scattered radiation and dose profiles are properly accounted for, AGD values from this mammography unit are less accurate that AGD values from units with a conventional geometry.

3.3 A new dosemeter using luminescence (Papers IIIa and IIIb)

In Paper **IIIa**, a dosimetry system based on RL and OSL from carbon doped aluminium oxide (Al_2O_3:C) crystals was developed and tested for *in vivo* absorbed dose measurements in mammography. A probe consists of one small cylindrical crystal of Al_2O_3:C (diameter 0.48 mm and length 2 mm) coupled to the end of a 1 mm diameter optical fibre cable (Radiation Research Department, Risoe National Laboratory for Sustainable Energy, Technical University of Denmark, Roskilde, Denmark). Owing to their small size and characteristic shape, it was expected that these probes could be placed on the breast surface in the field of view during the examination, without compromising the reading of the mammogram. Our new technique was tested with a mammography unit (Siemens Mammomat 3000) and SF technique over a range of clinically relevant X-ray energies using the molybdenum anode, molybdenum filter, Mo/Mo, combination. The results were compared with those obtained from an ionisation chamber (23344, PTW, Freiburg, Germany) usually used for the determination of absorbed dose in mammography.

The reproducibility of measurements was around 3% (1 SD) at 4.5 mGy for both RL and OSL data. The dose response was found to be linear between 4.5 mGy and 30 mGy. The energy dependence of the kerma value was around 18% between tube voltages 23 kV and 35 kV for the system. *In vivo* measurements were performed during examinations of three women. Figures 6 (Paper **IIIa**) and 1 (Paper **IIIb**), as well as the

illustration on the front cover of this thesis, shows an example of *in vivo* measurements where the presence of the small and characteristic probes did not significantly interfere with the diagnostic quality of the images. Both probes were positioned about 6 cm from the edge of the breast support according to the European protocol (Table 2.1), one attached underneath the compression paddle and the other on the breast support. It was shown that entrance and exit doses could be measured. Entrance doses estimated by RL/OSL results agreed within 3% with entrance surface dose (ESD) values calculated from the ionisation chamber measurements. These results indicate a potential for use in routine control and *in vivo* dose measurements in mammography.

For Al_2O_3:C crystals there is a large difference in atomic composition between the detector material and the breast tissue. This causes relatively large energy dependence at measurements of absorbed dose to the crystal in the low-energy X-ray beams used in mammography. In Paper **IIIb** the energy dependence of the system was modelled with the Monte Carlo code EGSnrc using three types of X-ray spectra. The results obtained between tube voltages 25 kV and 31 kV (5.6–7.3%) agree with the previously determined experimental result in Paper **IIIa** (9% in this case) within the combined standard uncertainty of the two methods. The influence of the size of the crystal on the energy dependence was investigated together with the effect of varying the thickness of the surrounding light-protective material. The results obtained indicate a minor effect owing to the thickness of the light-protective material, and a somewhat larger effect from reducing the diameter of the crystal. The outcome of this study can be used to improve the future design of the RL/OSL dosimetry system for use in mammography.

3.4 Comparison of imaging techniques (Paper IV)

The technique shift from SFM to DM was since long expected, but DM was still in very limited use around the year 2000 due to much higher investment costs and doubt about performance. At that time we evaluated the recent technical developments of DM and their clinical potential (Hemdal *et al.* 2002). The present study (Paper **IV**) was a natural follow-up of that project in order to compare the performance of DM and that of the current SFM.

A series of CD phantoms of simulated glandularity 30, 50 and 70%, and thickness 3, 5, and 7 cm respectively, were imaged. Three mammography systems (SFM, CR, and FFDM) were studied. Images were acquired for a range of anode/filter/tube voltage/dose combinations. The images were read in a randomised order by six observers and the number of perceivable objects (score) was recorded. The AGD was determined according to the European protocol, but in addition both c- and s-factors (Dance *et al.* 2000) was used (the Euref protocol was not published when this study was performed).

For the FFDM system, image scores similar to those with the SFM system can be achieved at 20-60% of the AGD necessary for the SFM system. The largest dose reduction potential was found for the thickest phantoms with the highest glandularity. With the CR system, the results were similar to those of the SFM system, although results of a t-test indicated a significantly better result for the CR system at a specific AGD level.

As mentioned in Chapter 2.2, recent research shows that CD phantoms with a homogeneous background, as used here, must be used with care. The results rather reflect the detector performance, as DQE measurements do, than the real clinical situation, as there is no "anatomical noise" in the images.

3.5 New image quality criteria (Papers Va and Vb)

In Paper **Va**, the current European image quality criteria (IQC) for screen-film mammography (EC 1996) were adjusted to be relevant also for digital mammography images. The aim was to use as simple and as few criteria as possible. An evaluation of the new set of criteria was made with mammograms of 28 women from a FFDM system (Senographe 2000D, General Electric). One breast was exposed using the standard automatic exposure mode, the other with the same anode/filter combination and tube voltage, but with about half of the absorbed dose for the breast exposed first. The lower absorbed dose level was arrived at in a previous pilot study by incremental reductions of the dose level and continuous evaluation of the image quality. Three experienced radiologists evaluated the images using the new set of IQC and visual grading analysis, VGA, technique. Relative gradings and a 5-step scale were used with the right image in each pair as the reference (recalculated as if the image with standard dose had been the reference image in each case). VGA with absolute grading (yes or no for 1 or 0) was also used for the images aquired with reduced dose. The results indicate that the new quality criteria can be used for the evaluation of image quality related to clinical requirements in digital mammography in a simple way. The results also suggest that absorbed doses for the mammography system used may be substantially reduced.

In Paper **Vb**, the new set of IQC for mammography developed in Paper **Va** was further evaluated in a trial. Screen-film mammograms have been digitised, manipulated to simulate different image quality levels, and reprinted on film. Nine expert radiologists have evaluated these manipulated images using both the original and the new criteria. A trial was performed using VGA technique with absolute grading (yes or no for 1 or 0). An image criteria score, ICS, was calculated for the old and new set of criteria, respectively. The results suggest that the new set of criteria may be a better tool for the evaluation of image quality based on different dose levels than the old set since, according to this study they have a stronger separating power. Whether they are clinically relevant remains to be investigated.

4. General discussion, summary and conclusions

4.1 Absorbed dose (Papers I, IIa, IIb, IIIa and IIIb)

Recent technical developments, regarding both mammography systems and dosemeters, have raised the question if present dose protocols in mammography account for the new situation.

4.1.1 Attempts to harmonise AGD estimations (Paper I)

By initiative of the Swedish radiation protection authority a dose protocol was established in Sweden (Leitz 1989) and other Nordic countries (NRPA 1991). A review of national dose protocols in Europe and a proposal of a common European dose protocol (Zoetelief *et al.* 1996), both demonstrated the difficulties of dose comparisons and proposed a method to solve the problem. A 50 mm standard breast with 50% glandularity should be simulated by 45 mm PMMA and only conversion factor g (Dance 1990) should be used. After a comparison of the Nordic and European dose protocols (Paper **I**), the latter was adopted in Swedish legislation (National Board of Health and Welfare 1998). The hope was that the equivalent move would be made in all other European countries. According to the former European guidelines for quality assurance in mammography screening (EC 2001), AGD estimations should follow the European dose protocol. However, in an addendum on digital mammography to this guideline (van Engen *et al.* 2003) and later verified (EC 2006), the 50 mm standard breast with 50% glandularity was abandoned and replaced with multiple standard breasts with thicknesses 21-103 mm and glandularities 97% - 3% to be simulated by 20-80 mm PMMA with the use of g-, c- and s-factors. Furthermore, one of these standard breasts (53 mm thick with 29% glandularity) was adopted as a new standard breast in the United Kingdom (IPEM 2005). As the standard breast according to the European dose protocol, it was simulated with 45 mm PMMA. It can be concluded that the attempts described to harmonise AGD measurements in Sweden with all other European countries did not succeed.

Under the circumstances I suggest that AGD measurements be performed according to both the European and Euref dose protocols. For modern mammography units, especially of DM type, beam quality varies with the object thickness, possibly also with object density. Exposures of PMMA phantoms with thicknesses in a range of about 20-80 mm (including 45 mm) should be performed to check the automatic exposure control of the mammography unit in routine QC measurements. Results from this procedure, complemented with output and HVL measurements, will provide data for AGD estimations according to the Euref dose protocol (EC 2006). An extra exposure of the 45 mm PMMA phantom might be needed if AGD should be estimated also according to the European dose protocol, as a 50 mm thick breast is simulated (53 mm in the Euref case). This fulfils not only requirements in Swedish legislation,

but provides also AGD results that can be compared with other results from SFM and DM systems over time (in Sweden since around 1998) and with other mammography centra, also in other countries that follow the European dose protocol. In comparisons between AGD results obtained for different anode/filter combinations, the s-factor could be applied. If comparisons are made with AGD values estimated according to the Nordic dose protocol, a correction could be made also with a factor 1.05±1.02 (range 1.00-1.09) according to Paper **I**. In this way, it is possible to compare AGD values over the last twenty years in Sweden with reasonable accuracy and relevance.

It should be noted that it happens quite often that PMMA phantoms used to simulate standard breasts are used incorrectly. The settings of the mammography unit should be done as for the standard breast (for example 50 or 53 mm thickness) and not as for the phantom (45 mm thickness in this example). However, the incident air kerma value should refer to the PMMA phantom (45 mm above the breast support).

It is also very important to specify how AGD values have been estimated, the dose protocol used and possible deviations from the procedures specified in the dose protocol, for instance use of a factor s although not specified in the particular dose protocol, as in Paper **IIb** regarding the American and European dose protocols.

4.1.2 A forward-scatter factor (FSF) for incident air kerma (K) estimations? (Paper IIa)

The incident air kerma, K, should be determined without influence of backscattered radiation, i.e. primarily radiation scattered in the breast in case of direct *in vivo* measurement or in the detector itself and the detector support in case of direct measurement. This is evident from papers on conversion factors (Dance 1990, Dance *et al.* 2000) and all dose protocols mentioned in Chapter 2.1.1. It is also clear that the compression paddle should be present, i.e. in place between the focus of the X-ray tube and the dosemeter, but where? With no information on this, it is not clear to what degree forward-scattered radiation from the compression paddle should be included in K. When direct *in vivo* measurements are performed, the dosemeter has to be in close contact with the compression paddle, if the measurement is properly done, as the dosemeter must be positioned on a compressed breast (preferably at 4-6 cm distance from the table edge, depending on the dose protocol, cf. Table 2.1). Also in case of indirect measurements, the American dose protocol (Hendrick *et al.* 1999) specifies that the compression paddle must be "in contact with or slightly above" the ionisation chamber. In other dose protocols tested in this thesis (Zoetelief *et al.* 1996, EC 2006) or papers on conversion factors (Dance 1990, Dance *et al.* 2000) there is no information available regarding the position of the compression paddle in case of indirect measurements. However, it was recently confirmed (Dance 2009) that the model of the Monte Carlo calculations of the g conversion factor (Dance 1990) had

the dosemeter (ionisation chamber) in contact with the compression paddle and that photons scattered forward from the paddle then should be included in K, although one dose protocol is in contradiction to that (IPEM 2005).

At the time when the calculations were made of the g-factors mentioned, the ionisation chamber was the natural choice as a dosemeter. Also more recently, some dose protocols (Hendrick *et al.* 1999, IPEM 2005) specify that an ionisation chamber should be used, while others (Zoetelief *et al.* 1996) only mention a "dosemeter". However, during the past 20 years it has been more common to use other types of dosemeters, primarily semiconductors (Chapter 2.1). Such dosemeters can be more or less collimated regarding incident radiation and in that way measure more or less of the forward-scattered radiation mentioned above. In this work (Paper **IIa**) comparison was made between an ionisation chamber (23344, PTW, Freiburg, Germany) and a dosemeter with several well-collimated semiconductors (MPD detector in a Barracuda, RTI Electronics AB, Mölndal, Sweden). The former recorded a scatter contribution of about 6% from the compression paddle alone, the latter about 1/10 of that value. This indicates not only that forward-scattered radiation should be considered in K estimates, but also that difference in sensitivity to such radiation between dosemeters should be accounted for, as suggested in Paper **IIa**.

Backscatter factors (BSF) are usually tabulated as a function of HVL, for instance BSF of 1.07-1.13 for HVL values from 0.25 mm Al to 0.65 mm Al (Zoetelief *et al.* 1996). The BSF dependence on phantom material is <5% between PMMA, the "breast equivalent" material BR12, fat and water (ICRU 2005). It is suggested that a corresponding forward-scatter factor (FSF) be used in mammography, e.g. 1.06 as a preliminary value for the ionisation chamber mentioned above. Besides the type of dosemeter used, the FSF will depend on the X-ray beam quality as well as the material and thickness of the compression paddle and its distance to the dosemeter.

There could also be other sources of forward-scattered radiation than the compression paddle, for example a multi-slit pre-collimator scanning device (Paper **IIa**). It is proposed that radiation scattered forward towards the breast from the compression paddle, a scanning device etc, should be considered with greater clarity in the breast dosimetry protocols, and be described with a FSF for the various situations given. However, due to different origin of the scattered radiation, as discussed in Paper **IIa**, the use of a FSF might differ, which for instance could be accounted for in Monte Carlo calculations of g-factors.

4.1.3 Dosemeters for indirect measurements (Papers IIa and IIb)

The ionisation chamber has been regarded to be the standard dosemeter for output and HVL measurements in mammography for several decades and is still the recommended equipment (IAEA 2007). The reason for this is mainly that an

ionisation chamber can be constructed to have a relatively low energy dependence of the signal, when measuring kerma in air, compared to other types of dosemeters. There is also a long tradition of using ionisation chambers for accurate dose measurements in general radiology, both therapeutic and diagnostic. However, other types of dosemeters with other characteristics are also available as discussed in Chapter 2.1.2. Of these instruments, semiconductors are most important for output and HVL measurements in mammography. Initially, their much larger energy dependence of the signal when measuring kerma in air compared to ionisation chambers tended to be insufficiently compensated for. However, today instruments are available with several semiconductors that each can have different filters and collimation properties. It has been demonstrated in this work (Paper **IIa**) that such instruments can be used for accurate estimates of HVL in a situation where it is impossible to follow usual procedures for HVL measurements. This was possible due to a well-collimated semiconductor for air kerma measurement, simultaneous quantification of the X-ray beam quality (in this case the tube voltage) with other semiconductors and proper correction for the energy dependence of the kerma value, all done after one single X-ray exposure.

Ionisation chambers should be positioned in close contact with the compression paddle to account for forward-scattered radiation from the paddle, as discussed in Chapter 4.1.2. An alternative is to measure in a "good geometry", as in HVL measurements, and apply a standard FSF of e.g. 1.06, although the value could have been different in the actual situation with respect to the thickness of the compression paddle, for instance. For a well-collimated semiconductor the signal is usually about the same, regardless of the compression paddle position. Then there is no alternative than to use a standard FSF, unless a calibration has been made for the actual situation with an ionisation chamber in close contact with the compression paddle.

It should also be noted, that a dynamic range of 0.5 to 100 mGy (Zoetelief *et al.* 1996), as discussed in Chapter 2.1.2, is not sufficient for all types of mammography units. The Sectra MDM unit (Paper **IIa**) requires a dynamic range at least from 0.05 mGy. This is fulfilled for the semiconductor instrument used in Paper **IIa** (MPD detector in a Barracuda, RTI Electronics AB, Mölndal, Sweden), but not for the ionisation chamber (23344, PTW, Freiburg, Germany) with a volume of 0.2 cm^3.

4.1.4 Dosemeters for direct in vivo measurements (Papers IIIa and IIIb)

In vivo dose measurements can be performed in different ways, as discussed in Chapter 2.1.1. One strategy is to use thin dosemeters (in direction from focus to image detector) with a similar atomic composition as normal breast tissue making them virtually invisible (Warren-Forward and Duggan 2004). Nevertheless, the radiologist must be informed about their presence, because they may still be seen in women with thin, adipose breasts, or with the use of a low X-ray beam energy, an image detector

with high contrast resolution or an extreme window setting in digital mammography. Such dosemeters are likely to have a relatively large surface in order to be sensitive enough, which increases the risk of interfering with the reading of the mammogram. Another strategy is simply to locate the dosemeter away from the breast (Dong *et al.* 2002). The obvious disadvantage is that it is no longer a "true" *in vivo* measurement close to the position prescribed by the dose protocol used. It is then necessary to correct for differences in the X-ray beam (e.g. the heel effect), focus-detector distance (due to e.g. the X-ray beam geometry and the flexure of the compression paddle) and scatter conditions.

The strategy used in this work (Paper **IIIa**) is to use dosemeters small enough that relevant structures, e.g. clusters of microcalcifications or small tumours, are not obscured, and with shapes that are characteristic enough not to be mistaken for such structures or any other structure of the breast. Even if these conditions are fulfilled, the radiologist has to get used to and accept the presence of dosemeters in the mammogram.

In vivo measurements were performed (Paper **IIIa**) during three examinations of women with four images each. A probe consists of one small cylindrical crystal of Al_2O_3:C (diameter 0.48 mm and length 2 mm) coupled to the end of a 1 mm diameter optical fibre cable (Radiation Research Department, Risoe National Laboratory for Sustainable Energy, Technical University of Denmark, Roskilde, Denmark). It was concluded that the presence of the small and characteristic probes did not significantly interfere with the diagnostic quality of the images, nor did the lead markers used for estimation of compressed breast thickness. One potential drawback of this system is the significant energy dependence due to the fact that the crystals are not tissue equivalent (Paper **IIIb**). However, the first results indicate a potential for use in routine quality control and *in vivo* absorbed dose measurements in mammography.

4.2 Image quality (Papers IV, Va and Vb)

There is a continuous need to improve the image quality and doing so requires reliable methods to evaluate image quality related to clinical requirements in mammography. In this thesis, this has been done using CD phantoms representing various degrees of glandularity and thickness as well as using real X-ray mammograms. Results from two different studies (Papers **IV** and **Va**) have indicated that the AGD for a particular kind of FFDM system (Senographe 2000D, General Electric) may be reduced. CD phantom with a homogenous background was used in one of the studies (Paper **IV**). As discussed in Chapter 2.2, such results must be used with care. They reflect rather physical characteristics than clinical requirements, as there is no "anatomical noise" in the images. This question has also been discussed by Gennaro *et al.* (2005). A reasonable conclusion regarding methods for evaluation of clinical image quality is therefore not to use such CD phantoms. However, they can be reliable and efficient

tools for constancy checks and basic intercomparisons between various mammography units (EC 2006, Young *et al.* 2008b). The results can be used in a similar way as physical characteristics to compare for instance the effect of different X-ray beam qualities on image quality as a baseline for further studies. Phantoms producing clinically realistic background images (Svahn *et al.* 2007) or real clinical images — possibly modified with respect to e.g. quantum noise levels (Timberg *et al.* 2006, Ruschin *et al.* 2007) — are preferred for such studies.

In Paper **Va** and **Vb** clinical images have been evaluated using visual grading methods. The results indicate that the new image quality criteria, adjusted in this work (Paper **Va**), may be a better tool for the evaluation of image quality based on different dose levels than the old set since they may have a stronger separating power (Paper **Vb**). The results also indicate that they can be used for the evaluation of image quality related to clinical requirements also in DM in a simple way (Paper **Va**). The presence of "anatomical noise" in the images indicates an improved clinical relevance compared to the study in Paper **IV**. Improved methods, with the new concept VGC, have also been introduced recently (Båth and Månsson 2007). Efficient tools for reading of images and analysing the results have also been developed (Börjesson *et al.* 2005). As mentioned in Chapter 2.2, there are advantages with studies using IQC, since normal mammograms that are readily available can be used. However, this is also a disadvantage, since the clinical tasks in mammography are related to malignancy. Therefore, VGA studies with IQC can be used as relatively fast and efficient tools for comparisons and preliminary optimisation work, but finally the clinical relevance should be checked with ROC related metods. Clinical images, possibly modified, with real or simulated structures that are subtle and relevant, should be used.

4.3 Concluding remarks concerning optimisation in mammography

The overall objective of this thesis was to investigate and improve methods for radiation absorbed dose and image quality evaluation in mammography and provide some practical guidance. The hope was to help sharpen the tools for the optimisation of the relationship between absorbed dose and image quality in mammography.

This thesis has contributed with improved knowledge regarding the different methods used for AGD estimation according to the Nordic and European dose protocols. However, AGD measurements in mammography within Europe are not yet harmonised, which is discussed in Chapter 4.1.1. (Paper **I**)

A method was found to perform accurate HVL measurements and estimate AGD on a new type of mammography equipment according to three different dose protocols. However, it has been demonstrated that some conditions for this type of mammography equipment should be accounted for in order to increase the accuracy in AGD estimates. A difference between an ionisation chamber and a dosemeter with

several well-collimated semiconductors regarding the sensitivity for scattered radiation has also been analysed. It is for instance proposed that radiation scattered forward towards the breast from the compression paddle, a scanning device etc, should be considered with greater clarity in the breast dosimetry protocols, and be described with a forward-scatter factor, FSF, for the various geometries and conditions proposed. Forward-scattered radiation from the compression paddle should be included in the estimation of incident air kerma. This is discussed in Chapter 4.1.2 and 4.1.3. (Papers **IIa** and **IIb**)

A small size optical fibre dosemeter was developed and tested. It was shown that both entrance and exit doses could be measured *in vivo* and that the dosemeters did not disturb the reading of the mammograms. A Monte Carlo study showed that the energy dependence could be reduced, primarily by reducing the diameter of the crystal. This is discussed in Chapter 4.1.4. (Papers **IIIa** and **IIIb**)

A method based on CD phantoms was used to compare the image quality of digital mammography techniques and that of screen-film technique. The same number of perceivable objects was visible for the full-field DM system at 20-60% of the AGD necessary for the screen-film (SFM) system, with the largest dose reduction potential for the thickest phantoms with the highest glandularity. However, more recent research shows that CD phantoms with a homogeneous background, as used here, must be used with care due to the presence of "anatomical noise" in the real clinical situation. This is discussed in Chapter 4.2. (Paper **IV**)

The present image quality criteria (IQC) recommended in a European Guideline 1996 for SFM was adjusted to be relevant also for DM images. The new set of IQC was tested in two different studies using clinical images from DM and SFM, respectively. The results indicate that the new set of IQC has a higher discriminative power than the old set (SFM images) and that they can be used for the evaluation of image quality related to clinical requirements also in DM in a simple way. The results also suggest that AGD for the DM system used may be reduced. The presence of "anatomical noise" in the images indicates an improved clinical relevance compared to the method with CD phantoms. The set-up and implementation of a study based on visual grading methods as VGA or VGC with IQC related to reproduction of structures in normal mammograms is generally much less time consuming compared to ROC studies. This is discussed in Chapter 4.2. (Papers **Va** and **Vb**)

References

Alm Carlsson G and Dance D R 1992 Breast absorbed doses in mammography: evaluation of experimental and theoretical approaches *Radiat Prot Dosim* **43** (1/4) 197-200

Andersson 2001 Current status of breast screening programmes *Proceedings of the 9th Asian Oceanian Congress of Radiology* 71-75

Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, Ljungberg O, Ranstam J, Sigfusson B 1988 Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial *BMJ* **297** 943-948

Andersson I, Janzon L 1997 Reduced breast cancer mortality in women under age 50: updated results from the Malmo Mammographic Screening Program. *J Natl Cancer Inst Monogr* **22** 63–67

Andersson I 2000 Mammographic screening under age 50: a review *Breast* **9** 125-129

Andersson I, Ikeda D M, Zackrisson S, Ruschin M, Svahn T, Timberg P and Tingberg A 2008 Breast tomosynthesis and digital mammography: a comparison of breast cancer visibility and BIRADS classification in a population of cancers with subtle mammographic findings." *Eur Radiol* **18** (12) 2817-25

Aznar M 2005 Real-time *in vivo* luminescence dosimetry in radiotherapy and mammography using Al_2O_3:C (PhD Thesis, Risø National Laboratory: Roskilde, Denmark)

Benevides L A and Hintenlang D E 2006 Characterization of metal oxide semiconductor field effect transistor dosimeters for application in clinical mammography *Med Phys* **33** 514-520

Båth M 2003 *Imaging properties of digital radiographic systems: development, application, and assessment of evaluation methods based on linear-systems theory* (PhD Thesis, Göteborg University: Göteborg)

Båth M and Månsson L G 2007 Visual grading characteristics (VGC) analysis: a non-parametric rank-invariant statistical method for image quality evaluation *Br J Radiol* **80** 169-176

Bissonnette M, Hansroul M, Masson E, Savard S, Cadieux S, Warmoes P, Gravel D, Agopyan J, Polischuk B, Haerer W, Mertelmeier T, Lo J Y, Chen Y, Dobbins III J T, Jesneck J L, Singh S 2005 Digital breast tomosynthesis using an amorphous selenium flat panel detector *Proc SPIE* **5745** 529-540

Börjesson S, Håkansson M, Båth M, Kheddache S, Svensson S, Tingberg A, Grahn A, Ruschin M, Hemdal B, Mattsson S, Månsson L G 2005 A software tool for increased efficiency in observer performance studies in radiology *Radiat Prot Dosim* **114** (1-3) 45-52

Burgess A E, Jacobson F L, Judy P F 2001 Human observer detection experiments with mammograms and power-law noise *Med Phys* **28** 419-437

Chakraborty D P. 2000 The FROC, AFROC and DFROC variants of the ROC analysis. In: Beutel J, Kundel HL, Van Metter RL, eds. *Handbook of Medical Imaging. Volume 1. Physics and Psychophysics.* Bellingham: SPIE Press 771-796.

Chakraborty D P, Berbaum K S 2004 Observer studies involving detection and localization: modeling, analysis, validation *Med Phys* **31** 2313-2330

Cunningham I A. 2000 Applied linear-systems theory. In: Beutel J, Kundel HL, Van Metter RL, eds. Handbook of Medical Imaging. Volume 1. Physics and Psychophysics. Bellingham: *SPIE Press* 79-159.

Dance D R 1990 Monte Carlo calculation of conversion factors for the estimation of mean glandular breast dose *Phys Med Biol* **35** 1211-1219

Dance D R 2009 Personal communication

Dance D R, Hunt R A, Bakic P R, Maidment A D A, Sandborg M, Ullman G, Alm Carlsson G 2005 Breast Dosimetry using a high-resolution voxel phantom *Radiat Prot Dosim* **114** (1-3) 359-363

Dance D R, Skinner C L, Young K C, Beckett J R, Kotre C J 2000 Additional factors for the estimation of mean glandular breast dose using the UK mammography dosimetry protocol *Phys Med Biol* **45** 3225-3240

Dance D R, Young K C and van Engen R E 2009 Further factors for the estimation of mean glandular dose using the United Kingdom, European and IAEA breast dosimetry protocols *To be published in Phys Med Biol*

Dobbins III J T. 2000 Image quality metrics for digital systems. In: Beutel J, Kundel HL, Van Metter RL, eds. *Handbook of Medical Imaging. Volume 1. Physics and Psychophysics*. Bellingham: SPIE Press 161-222.

Dong S L, Chu T C, Lee J S, Lan G Y, Wu T H, Yeh Y H and Hwang J J 2002 Estimation of mean glandular dose from monitoring breast entrance skin air kerma using a high sensitivity metal oxide semiconductor field effect transistor (MOSFET) dosimeter system in mammography *Appl Radiat Isot* **57** 791-799

Duffy S W, Tabar L, Chen H H, Holmqvist M, Yen M F, Absalah S et al. 2002 The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties *Cancer* **95**(3) 458-469

EC 1996 European guidelines on quality criteria for diagnostic radiographic images *European Commission, Brussels, Office for Official Publications of the European Communities* EUR 16260

EC 2001 European guidelines for quality assurance in mammography screening (third edn.) *European Communities, Luxembourg, Office for Official Publications of the European Communities*

EC 2006 European guidelines for quality assurance in breast cancer screening and diagnosis (fourth edn.) *European Commission, Luxembourg, Office for Official Publications of the European Communities*

Eckstein M P, Abbey C K, Bochud F O. 2000 A practical guide to model observers for visual detection in synthetic and natural noisy images. In: Beutel J, Kundel HL, Van Metter RL, eds. *Handbook of Medical Imaging. Volume 1. Physics and Psychophysics*. Bellingham: SPIE Press 593-628.

van Engen R, Young K, Bosmans H and Thijssen M 2003 Addendum on digital mammography to chapter 3 of the European guidelines for quality assurance in mammography screening, ver 1.0 EUREF

Fischer U, Hermann K P and Baum F 2006 Digital mammography: current state and future aspects *Eur Radiol* **16** (1) 38-44

Gennaro G, Katz L, Souchay H, Alberelli C, di Maggio C 2005 Are phantoms useful for predicting the potential of dose reduction in full-field digital mammography? *Phys Med Biol* **50** 1851-1870

Gentry J R, and DeWerd L A 1996 TLD measurements of *in vivo* mammographic exposures and the calculated mean glandular dose across the United States *Med Phys* **23** 899-903

Gong X, Glick S J, Liu B, Vedula A A, Thacker S 2006 A computer simulation study comparing lesion detection accuracy with digital mammography, breast tomosynthesis, and cone-beam CT breast imaging *Med Phys* **33** 1041-1052

Grant D G 1972 Tomosynthesis: A three-dimensional radiographic imaging technique IEEE *Trans Biomed Eng* BME **19** (1) 20-28

Hemdal B, Andersson I, Thilander Klang A, Bengtsson G, Leitz W, Bjurstam N, Jarlman O, Mattsson S 2002 Mammography – recent technical developments and their clinical potential. *Swedish Radiation Protection Authority, Stockholm*, SSI Report 2002:08, Available at: http://www.stralsakerhetsmyndigheten.se /Publikationer/Rapport/Stralskydd/2002/200208-Mammography-recent-technical-developments-and-their-clinical-potential/

Hendrick R E, Basset L, Botsco M A et al. 1999 Mammography Quality Control Manual *American College of Radiology, ACR, Reston*

IAEA 2007 Dosimetry in diagnostic radiology: an international code of practice *International Atomic Energy Agency, Technical Reports Series*, no. 457, Vienna, Austria

ICRP 1987 Statement from the 1987 Como meeting of the ICRP, *International Commission on Radiological Protection* ICRP Publication 52. Oxford: Pergamon Press *Ann ICRP* **17** (4)

ICRP 1996 Radiological protection and safety in medicine ICRP Publication 73. Pergamon Press, Oxford and New York *Ann ICRP* **26** (2) 1-47

ICRP 2004 Managing patient dose in digital radiology ICRP Publication 93. Pergamon Press, Oxford and New York *Ann ICRP* **34** (1) 1-73

ICRU 2005 International Commission on Radiation Units and Measurements. Patient dosimetry for x-rays used in medical imaging. ICRU Report 74. Oxford, University Press

IPEM 2005 The commissioning and routine testing of mammographic X-ray systems *Institute of Physics and Engineering in Medicine, IPEM Report 89*, York, United Kingdom

Karellasa A and Vedantham S 2008 Breast cancer imaging: A perspective for the next decade *Med Phys* **35** 11 4878-4897

Laming D and Warren R 2000 Improving the detection of cancer in the screening of mammograms *J Med Screen* **7** 24-30

Law J, Faulkner K 2002 Concerning the relationship between benefit and radiation risk, and cancers detected and induced, in a breast screening programme *Br J Radiol* **75** 678-684

Leborgne R 1951 Diagnosis of tumors of the breast by simple roentgenography *AJR* **65** 1-11

Leitz W 1989 Quality Assurance in mammography - performance and constancy tests *Swedish Radiation Protection Institute, SSI* Stockholm Report 89-19 (in Swedish)

Leitz W 1998 Reference (Target) Levels for mammography in Sweden *Radiat Prot Dosim* **80** 181-182

Lewin J M, Hendrick R E, D'Orsi C J, Isaacs P K, Moss L J, Karellas A, Sisney G A, Kuni C C, Cutter G R 2001 Comparison of full-field digital mammography with screen-film mammography for cancer detection: results of 4,945 paired examinations *Radiology* **218** 873-880

Lundqvist M, Danielsson M, Cederstroem B, Chmill V, Chuntonov A, Aslund M 2003 Measurements on a full-field digital mammography system with a photon counting crystalline silicon detector *Proc SPIE* **5030** 547-552

Månsson L G 1994 *Evaluation of radiographic procedures: Investigations related to chest imaging* (PhD thesis, Göteborg University: Göteborg)

Månsson L G, Båth M and Mattsson S 2005 Priorities in optimisation of medical X-ray imaging - a contribution to the debate *Radiat Prot Dosim* **114** (1-3) 298-302

Mattsson A, Leitz W, Rutqvist L E 2000 Radiation risk and mammographic screening of women from 40 to 49 years of age: effect on breast cancer rates and years of life *Brit J Cancer* **82** (1) 220-226

Moss S M, Cuckle H, Evans A, Johns L, Waller M and Bobrow L 2006 Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years´ follow-up: a randomised controlled trial *Lancet* **368** 2053-2060

National Board of Health and Welfare 1986 Screening with Mammography *The National Board of Health and Welfare* Stockholm Advice and recommendations 1986:3 (in Swedish)

National Board of Health and Welfare 1990 Screening with Mammography, follow-up and Quality Assurance of the mammographic technique *The National Board of Health and Welfare* Stockholm Advice and recommendations 1990:3 (in Swedish)

National Board of Health and Welfare 1998 Screening with Mammography for early detection of breast cancer *The National Board of Health and Welfare* Stockholm SoS-report 17 (in Swedish)

Niklason L T, Christian B T, Niklason L E, Kopans D B, Castleberry D E, Opsahl-Ong B H, Landberg C E, Slanetz P J, Giardino A A, Moore R, Albagli D, DeJule M C, Fitzgerald P F, Fobare D F, Giambattista B W, Kwasnick R F, Liu J, Lubowski S J, Possin G E, Richotte J F, Wei C Y, Wirth R F 1997 Digital tomosynthesis in breast imaging *Radiology* **205** 399-406

NRPA 1991 Quality Assurance in Mammography − Quality Control of Performance and Constancy *Nordic Radiation Protection Authorities, NRPA, Stockholm* Report 1

Nyström L, Rutqvist L E, Wall S, Lindgren A, Lindqvist M, Ryden S, Andersson I, Bjurstam N, Fagerberg G, Frisell J, et al. 1993 Breast cancer screening with mammography: overview of Swedish randomised trials *Lancet* **341** 973-978

Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B and Rutqvist L E 2002 Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* **359** (9310) 909-919

de Paredes E S, Fatouros P P, Thunberg S, Cousins J F, Wilson J and Sedgwick T 1998 Evaluation of a digital spot mammographic unit using a contrast detail phantom. In Digital Mammography. The 4th International Workshop on Digital Mammography, IWDM 1998, Nijmegen, the Netherlands. Edited by Karssemeijer N, Thijssen M, Hendriks J and van Erning L Kluwer Academic Publishers, Dordrecht, The Netherlands 47-50

Pisano E D, Gatsonis C, Hendrick E, Yaffe M, Baum J K, Acharyya S, Conant E F, Fajardo L L, Bassett L, D'Orsi C, Jong R, Rebner M 2005 Diagnostic performance of digital versus film mammography for breast-cancer screening *N Engl J Med* **353** 1773-1783

Pisano E D, Yaffe M J 2005 Digital mammography *Radiology* **234** 353-362

Poplack S P, Tosteson A N, Grove M R, Wells W A, Carney P A 2000 Mammography in 53,803 women from the New Hampshire mammography network *Radiology* **217** 832-840

Rose A 1948 The sensitivity performance of the human eye on an absolute scale *J Opt Soc Am* **38** 196–208

Rosenberg R D, Yankaskas B C, Hunt W C, Ballard-Barbash R, Urban N, Ernster V L, Kerlikowske K, Geller B, Carney P A, Taplin S 2000 Effect of variations in operational definitions on performance estimates for screening mammography *Acad Radiol* **7** 1058-1068

Rosenstein M, Andersen L W, Warner G G 1985 Handbook of Glandular Tissue Doses in Mammography. US Department of Health and Human Services, HHS Publication FDA85-8239 (Rockville, Md., USA: CDRH)

Ruschin M 2006 *The role of projected anatomy, random noise, and spatial resolution on clinical image quality in digital mammography* (PhD thesis, Lund University: Malmö)

Ruschin M, Timberg P, Svahn T, Andersson I, Hemdal B, Mattsson S, Båth M, Tingberg A 2007 Improved in-plane visibility of tumors using breast tomosynthesis In: Medical imaging 2007: Physics of medical imaging (Ed by J Hsieh, M J Flynn) *Proc SPIE* **6510** 65104R

Sjönell G and Ståhle L 1999 Hälsokontroller med mammografi minskar inte dödlighet i bröstcancer *Läkartidningen* **96** 904-913 (in Swedish)

Skaane P, Hofvind S, Skjennald A 2007 Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based

screeningprogram: Follow-up and final results of OsloII study *Radiology* **244** 708–717

Skaane P, Skjennald A 2004 Screen-film mammography versus full-field digital mammography with soft-copy reading: randomized trial in a population-based screening program--the Oslo II Study *Radiology* **232** 197-204

Smith A P, Niklason L, Ren B, Wu T, Ruth C, Jing Z 2006 "Lesion visibility in low dose tomosynthesis." In: Eds. Astley SM, Brady M, Rose C, Zwiggelaar R, Proceedings of the 8th international workshop on digital mammography, IWDM. Manchester, UK: Springer Verlag Berlin, 160-166

Svahn T, Hemdal B, Ruschin M, Chakraborty D, Andersson I, Tingberg A, Mattsson S 2007 Dose reduction and its influence on diagnostic accuracy and radiation risk in digital mammography: An observer performance study using an anthropomorphic breast phantom. *Br J Radiol*, **80**, 557-562

SSI 2002 Regulations and general advice on diagnostic standard doses and reference levels within medical X-ray diagnostics. *Swedish Radiation Protection Authority,* Stockholm SSI FS 2002:2 (in Swedish) Non-authorised translation to English available at http://www.ssi.se/forfattning/eng_forfattlista.html

Tabar L, Fagerberg C J, Gad A, Baldetorp L, Holmberg L H, Grontoft O, Ljungquist U, Lundstrom B, Manson J C, Eklund G, et al. 1985 Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare *Lancet* **1** 829-832

Thilander Klang A 1997 *Diagnostic quality and absorbed dose in mammography: Influence of X-ray spectra and breast anatomy* (PhD Thesis, Göteborg University: Göteborg)

Thunberg S, Francke T, Egerström J, Eklund M, Ericsson L, Kristoffersson T, Peskov V, Rantanen J, Sokolov S, Svedenhag P, Ullberg C, Weber N 2002 Evaluation of a photon counting mammography system *Proc SPIE* **4682** 202-208

Timberg P, Ruschin M, Båth M, Hemdal B, Andersson I, Mattsson S, Chakraborty D, Saunders R, Samei E, Tingberg A 2006 Potential for lower absorbed dose in digital mammography: A JAFROC experiment using clinical hybrid images with simulated dose reduction. In: Medical Imaging 2006: Image perception, observer performance, and technology assessment (Ed by Y Jiang, M P Eckstein) *Proc SPIE* **6146** 614614

Tingberg A 2000 *Quantifying the quality of medical X-ray images: An evaluation based on normal anatomy for lumbar spine and chest radiography* (PhD thesis, Lund University: Malmö)

UNSCEAR 2000 United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionising radiation. Report to the General Assembly, with scientific annexes. Vol. **I** (Vienna: UNSCEAR) 306–400

Varjonen M 2006 "Three-dimensional digital breast tomosynthesis in the early diagnosis and detection of breast cancer." In: Eds. Astley SM, Brady M, Rose C, Zwiggelaar R, Proceedings of the 8th international workshop on digital mammography, IWDM. Manchester, UK: Springer verlag Berlin, 152-159

Warren-Forward H M and Duggan L 2004 Towards in vivo TLD dosimetry in mammography *Br J Radiol* **77** 426-432

DeWerd L A, Micka J A, Laird R W and Pearson D W 2002 The effect of spectra on calibration and measurement with mammographic ionization chambers. *Med Phys* **29** 2649-2654

Witzani L, Bjerke H, Bochud F, Csete I, Denoziere M, de Vries W, Ennow K, Grindborg J E, Hourdakis C, Kosunene A, Kramer H M, Pernicka F and Sander T 2004 Calibration of dosemeters used in mammography with different x-ray qualities: EU-ROMET project no. 526. *Radiat Prot Dosim* **108** 33-45

Wu T, Stewart A, Stanton M, McCauley T, Phillips W, Kopans D B, Moore R H, Eberhard J W, Opsahl-Ong B, Niklason L, Williams M B 2003 Tomographic mammography using a limited number of low-dose cone-beam projection images *Med Phys* **30** 365-380

Young K C, Alsager A, Oduko J M, Bosmans H, Verbrugge B, Geertse T and van Engen R 2008a Evaluation of software for reading images of the CDMAM test object to assess digital mammography systems. In: Medical Imaging 2008: Physics of medical imaging (Ed by J Hsieh, E Samei) *Proc SPIE* **6913** 69131C

Young K C, Oduko J M, Gundogdu O and Alsager A 2008b "Comparing the performance of digital mammography systems." In: Eds. Krupinski EA, Proceedings of the 9th international workshop on digital mammography, IWDM. Tucson, Arizona, USA: Springer verlag Berlin, 732-739

Yukihara E G and McKeever S W S 2008 Optically stimulated luminescence (OSL) dosimetry in medicine, Topical review *Phys Med Biol* **53** R351-R379

Zoetelief J, Fitzgerald M, Leitz W, Säbel M 1996 European protocol on dosimetry in mammography *European Commission, Luxembourg, Office for Official Publications of the European Communities* EUR 16263

Åslund M, Cederström B, Lundqvist M, Danielsson M 2005 AEC for scanning digital mammography based on variation of scan velocity *Med Phys* **32** (11) 3367-3374

Summary in Swedish (Sammanfattning på svenska)

Utvärdering av stråldos och bildkvalitet i mammografi

Bröstcancer är den cancerform som är vanligast hos kvinnor. Genom tidig upptäckt med bröströntgen, mammografi, kan man behandla sjukdomen i ett tidigare stadium och därmed minska dödligheten. Det är också möjligt att behandla på ett skonsammare sätt vid tidig upptäckt. Därför har man startat hälsokontroller, screening, med mammografi. I början genomfördes detta i form av kontrollerade studier; i Malmö t.ex. under åren 1978-1986. Dessa har visat att dödligheten i bröstcancer kan reduceras. Efter utvärdering av Socialstyrelsen 1986 har sjukvårdshuvudmännen startat allmän screening. Motsvarande har skett i en rad andra europeiska länder. Förutom minskad dödlighet minskas även antalet fall med spridd sjukdom och behandling kan i större utsträckning ske med bröstbevarande kirurgi.

Det finns också problem med mammografiscreening. Studier tyder på att ca. 30% av tumörerna inte upptäcks, särskilt svårt är det i täta bröst, d.v.s. med stor andel körtelvävnad. En del av de kvinnor, som återkallas för vidare utredning vid misstanke om bröstcancer, visar sig efter kompletterande bildtagning, ultraljudsundersökning och ibland biopsi inte ha bröstcancer, s.k. falskt positiva resultat. En annan aspekt är, att man vid screeningen upptäcker en bröstcancer, som annars inte skulle ha upptäckts p.g.a kvinnans död i annan sjukdom, men risken för detta är liten. Vidare finns en - för den enskilda kvinnan visserligen liten - risk för att strålningen kan inducera en bröstcancer senare i livet. Under lång tid har man samlat och analyserat data från ett stort antal kvinnor, som utsatts för strålning med jämförelsevis höga stråldoser, t.ex. vid kärnvapenattackerna mot Japan under andra världskriget. Man har då kunnat påvisa ett samband mellan strålning och bröstcancer och även kunnat konstatera att ju yngre man är, desto större är risken för strålinducerad cancer. Det är detta förhållande och att förekomsten av bröstcancer är mycket lägre bland yngre kvinnor samt att tätare bröst gör det svårare att upptäcka den, som gör att man är restriktiv med mammografi bland yngre och inte rekommenderar screening före 40 års ålder, såvida inte kvinnan tillhör en högriskgrupp.

Stor samstämmighet råder om uppfattningen att stråldoserna vid all diagnostik med joniserande strålning ska hållas så låga som överhuvudtaget är möjligt utan att äventyra den diagnostiska säkerheten. Detta är särskilt angeläget vid mammografiscreening, eftersom ca 90% av kvinnorna aldrig kommer att besväras av bröstcancer under sin livstid. Utrustningen måste fortlöpande kontrolleras, så att undersökningens bildkvalitet tillåter upptäckt av bröstcancer i så stor utsträckning och så tidigt som möjligt. Metoder för bestämning av stråldos och bildkvalitet finns beskrivna i den vetenskapliga litteraturen. Olika myndigheter, i Sverige t ex Strålsäkerhetsmyndigheten, SSM (förut SSI), och Socialstyrelsen, har gett ut författningar, som reglerar detta.

Det övergripande syftet med denna avhandling är att undersöka och förbättra metoder för bestämning av stråldos och bildkvalitet vid mammografiundersökningar samt ge viss praktisk vägledning. Följande studier presenteras i avhandlingen:

Strax efter att Sverige gått med i EU, ville SSI ändra metoden att mäta stråldos från den nordiska till den nyutkomna europeiska rekommendationen. Vi gjorde därför jämförande dosmätningar enligt båda metoderna på 32 st mammografiutrustningar i Sydsverige för att kartlägga metodskillnaderna. Vi fann bl.a. att den beräknade stråldosen för ett s.k. standardbröst simulerat med 45 mm plexiglas blev 5±2% högre om man gjorde mätningar enligt den Europeiska rekommendationen. Därmed blev gällande riktvärde något svårare att underskrida, när metoden strax därefter infördes.

En ny typ av mammografiutrustning med digital bilddetektor strålar på bröstet med tunna strålfält i en scannande rörelse. Det gick inte att mäta stråldos på det sätt som var föreskrivet i nyss nämnda europeiska rekommendation, helt enkelt för att scanningenheten var i vägen. I en experimentell uppställning med samma typ av röntgenrör, kunde vi visa att ett nyutvecklat instrument kunde användas vid mätning på mammografiutrustningen med noggrant resultat.

Ett annat dosmätningssystem med en liten kristall av aluminiumoxid, Al_2O_3:C, sänder spontant ut ljus vid bestrålning och även om man efteråt belyser den med laserljus genom en tunn (ca. 1 mm diameter) kabel. Ett sådant system utvecklades och testades för dosmätning vid mammografi både med bröstsimulerande s.k. fantom och vid in vivo mätning av stråldos. I den senare studien placerades två kristaller på ovan- resp. undersidan av bröstet vid screeningundersökning av tre kvinnor (bilder kan ses på avhandlingens omslag). Studien visade att både in- och utgångsdos kunde mätas och att avbildningen av objekten inte störde granskningen av bilderna.

Fantom med olika tjocklek och täthet, innehållande objekt med olika diameter och tjocklek, användes för att jämföra 3 st mammografiutrustningars bildkvalitet. För den med digital bilddetektor kunde samma antal objekt ses vid 20-60% av den stråldos som behövdes när ett filmbaserat (skärm-film) system användes. Störst potential för dosminskning fann vi för fantom med störst tjocklek och täthet. Vår senare erfarenhet visar att resultat från mätningar med denna typ av fantom med homogen bakgrund måste tolkas med försiktighet, eftersom ”anatomiskt brus” saknas i bilden. Med anatomiskt brus menas bl.a. den oregelbundenhet i den projicerade bildens bakgrund som uppkommer genom att vävnaden är heterogen med avseende på täthet och atomär sammansättning. Detta anatomiska brus är i många situationer begränsande för möjligheten att iaktta de subtila förändringar som den radiologiska diagnostiken bygger på.

En noggrann utvärdering av bildkvalitet i röntgenbilder med s k ROC-metoder kräver kända och inte alltför tydliga tumörer i bilderna. Det är därför ett omfattande arbete

att samla in bilder och genomföra en sådan studie. Vanliga röntgenbilder utan tumörer finns lätt tillgängliga och kan användas för att bestämma bildkvalitet med s.k. bildkvalitetskriterier, som definierar krav på synbarhet av normala strukturer i bilden. De kriterier som fanns i en europeisk anvisning för skärm-film teknik utvecklades i syfte att göra dem mer effektiva och även passa digital teknik. En studie med skärm-film bilder visade att man kunde mäta skillnad i bildkvalitet vid mammografiundersökningar säkrare med de nya kriterierna. Resultat från en motsvarande studie med digitala bilder visade att kriterierna var användbara även för digital teknik samt antydde att en dosminskning för denna utrustning var möjlig.

Acknowledgements

During the years I have had the privilege to work with a large number of professionals, each with extensive knowledge in his or her field. I thank you all and I would particularly like to express my sincere gratitude to:

My supervisor, Sören Mattsson, for professional guidance and enthusiastic support over the years with never-ending ideas, patience and valuable criticism of manuscripts.

Ingvar Andersson for sharing your great knowledge and skilfulness in mammography and in writing papers.

Gert Bengtsson for not only sharing your knowledge in e.g. screen-film and processing, but also being a nice companion in experimental work and travelling.

Anne Thilander-Klang for always being a sounding board and support in mammography physics.

Wolfram Leitz for being a perfect representative of the radiation protection authority and especially for sharing your knowledge in valuable discussions.

Joakim Medin for fruitful cooperation, support in physics and valuable criticism of manuscripts.

Marianne Aznar for sharing your knowledge in physics and English until the last minute.

Lars Herrnsdorf for enthusiastic and creative support in measurements and sharing your technical know-how.

David Dance for sharing your great knowledge in breast dosimetry and for valuable discussions.

Ken Young, Ruben van Engen and Martin Thijssen for being available when needed with support and discussions.

Mats Nilsson for valuable support and criticism on manuscripts.

Anders Tingberg, Mark Ruschin, Anna Grahn, Tony Svahn, Pontus Timberg and Daniel Förnvik from the Malmö DM and BT team; Magnus Båth, Lars-Gunnar Månsson, Sara Börjesson, Markus Håkansson and Patrik Sund from Göteborg; Magnus Olsson and Boel Heddson from Helsingborg; Kristin Pedersen, Jan B Olsen, Tonje Holter Bay, Line Gangeskar and Anne-Catrine Martinsen from Oslo in

Norway; Lars Bøtter-Jensen, Claus Andersen and Carl-Johan Marckmann from Risø in Denmark for a fruitful and stimulating cooperation in various projects and matters.

Nils Bjurstam and Olof Jarlman for your cooperation in the project on digital mammography and the SSI-report.

Marianne Löfgren, Cecilia Wattsgård, Lars Bååth, Annika Lindahl and Anita Strömbeck from Malmö; Sture Götberg from Lund; Claes-Göran Lindberg from Landskrona; Isabelita Berlin, Jan Johansson and Roland Johansson from Göteborg for valuable input to the studies on quality criteria.

Ann-Christin Persson, Karin Martling, Gunilla Dinnetz, Agneta Landgren, Laila Löfdahl, Katarina Ovin, Marina Björk and a number of other people at the mammography section, Malmö University Hospital, for sharing your knowledge and providing support, not least in various studies.

The staff att all mammography departments in southern Sweden for sharing your knowledge and providing support.

Peter Wallenius, Jan Ilver and Jonas Svensson for support when computers were a problem.

A lot of people, not directly involved in the projects related to this thesis, but still providing valuable support and perspectives.

Representatives of a large number of commercial companies for sharing your technical know-how.

A special thanks to Sören Mattsson, Ingvar Andersson, Anne Thilander-Klang, Anders Tingberg, Mats Nilsson, Marianne Aznar, Wolfram Leitz, Tony Svahn and Gert Bengtsson for constructive criticism and valuable support regarding this manuscript.

Finally, I want to thank my wife Ulla-Karin and my children Amanda and Julia for their love and understanding.

Financial support has been given by the Swedish radiation protection authority (P 934.96 and P 1062.98), the Cancer foundation at Malmö University Hospital and the EU 5th framework programme (contract no. FIGM-CT-2000-00036).