ISBN 978-82-471-2012-5 (printed ver.)
ISBN 978-82-471-2013-2 (electronic ver.)
ISSN 1503-8181

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Printed by Tapir Uttrykk

Evaluering av behandlingseffekt i kreft ved MR avbildning og spektroskopi

Arbeidet i denne avhandlingen presenterer et sett utfyllende MR metoder som kan brukes for å studere effekt av kreftbehandling. Motivasjonen er blant annet å kunne tilby skreddersydd behandling for hver enkelt pasient. Pasienter med lokalavansert brystkreft får ofte behandling med kjemoterapi i forkant av kirurgi for å redusere tumorstørrelse og utbredelse av såkalt primær inoperabel sykdom. Det er stor variasjon i behandlingsrespons for denne pasientgruppen, og det er derfor behov for metoder som kan forutsi eller tidlig detektere behandlingseffekt, slik at behandlingen kan tilpasses individuelt. Arbeidet i denne avhandlingen viser at effekter av kreftbehandling kan detekteres med MR allerede etter en behandling, og fremstår dermed som et lovende verktøy ved kreftbehandling.

I dette arbeidet ble forandringer i blodgjennomstrømningen i tumor påvist med dynamisk kontrastoppladet MR avbildning, både i tumormodeller for brystkreft behandlet med kjemoterapi og i tumormodeller for tykktarmkreft påvirket av fettsyren TTA. Forandringer ble også funnet for brystkreftpasienter behandlet med kjemoterapi. I tillegg ble det funnet en sammenheng mellom dynamisk kontrastoppladet MR ved diagnosetidspunktet og 5 års overlevelse for brystkreftpasienter, noe som viser at MR også kan ha prognostisk verdi for denne pasientgruppen. I dynamisk kontrastoppladet MR avbildning brukes økningen i signalintensiteten i en serie MR–bilder før og etter intravenøs injeksjon av kontrastmiddel til å studere vev med økt blodgjennomstrømning, som tumorvev.

Videre ble det observert lavere relative nivåer av metabolitten kolin målt med MR spektroskopi av behandlede tumormodeller for brystkreft, sammenlignet med ubehandlede tumorer. Metabolitter er små molekyler som inngår i cellenes stoffskifte, og kan studeres med MR spektroskopi både før og etter tumoren er operert bort. Kolinforbindelser blir ofte brukt som tumormarkør,

og kan gi viktig informasjon om mekanismer ved behandlingsrespons.

Den tilsynelatende diffusjonskoeffisienten i tumor ble beregnet fra diffusjonsvektede MR bilder i brystkreftpasienter, og økte etter kjemoterapi. Dette ble også vist i en studie av tumormodeller i brystkreft. Diffusjonsvektet MR avbildning utnytter de naturlige bevegelsene til vannmolekyler, og kan brukes til å studere egenskaper i tumor på cellulært nivå. Diffusjon av vannmolekyler i vev er begrenset av strukturer som cellemembraner og makromolekyler, og kan brukes til å detektere forandringer i for eksempel celletetthet.

Forskningsarbeidet består av fire deler, to studier av tumormodeller i mus, og to studier av brystkreftpasienter. Både MR protokoller og metoder for analyse av data ble etablert, og prinsipper fra dyreforsøkene ble overført til pasientstudiene. Dynamisk kontrastoppladet MR ble analysert ved hjelp av en farmakokinetisk modell for kontrastmiddelet, og MR spekter ble analysert med multivariate analysemetoder. Tre av studiene er publisert i internasjonale tidsskrifter, og den siste er innsendt for vurdering.

Kandidat: Line Rørstad Jensen
Institutt: Institutt for sirkulasjon og bildediagnostikk
Veiledere: Ingrid S. Gribbestad og Steinar Lundgren

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden Philosophiae Doctor i medisinsk teknologi. Disputas finner sted i Seminarrom, 1902-bygget, St. Olavs Hospital fredag 12. mars 2010, kl. 12:15.

Acknowledgements

The work presented in this thesis has been performed at the MR center, Department of Circulation and Medical Imaging, NTNU, with financial support from Norwegian Women's Public Health Association in Trondheim.

I started on the work for this thesis in 2005, with encouragement from my supervisor Professor Ingrid S. Gribbestad. She has always been optimistic and believed in me, and her contributions has been crucial for my work. I'm deeply grateful for our collaboration and for her interest in my work and my future. I'm also thankful for the many interesting discussions with my co–supervisor Professor Steinar Lundgren, reminding me of all the patients behind the MR images.

I have enjoyed an enthusiastic working environment at the MR center, with a close collaboration between colleagues and co-authors. Medical technology is an interdisciplinary research field, thus I'm thankful to all my co–authors that has contributed on my projects. I'm grateful to Dr. Tone F. Bathen for important collaboration on the animal experiments and for being available for discussions and with suggestions. I would also like to thank Dr. Beathe Sitter, who introduced me to MR spectroscopy during my Master's degree, and for her unique expertise on HR MAS MRS. Further, I would like to thank my fellow PhD students Mariann G. Heldahl, who has organized the patient recruitment and MR examinations of my last work, and Else Marie Huuse who has been a valuable collaborator on the animal studies and on image analysis. My thanks also goes to Trond Singstad and Emil Veliyulin for technical assistance at the beginning of the projects, Dr. Pål Erik Goa for programming the basis for the image analysis tool in Matlab, and Benjamin Garzon for introducing me to bash-scripting and joining my last clinical project. I'm grateful to Tina B. Pedersen for her contributions on the animal projects, and for always being helpful with practical issues, the staff at the animal facility for taking care of the animals, and the radiographers

at St. Olav's Hospital, assisting at the patient MR examinations. My deepest gratefulness goes to the women participating in the MR examinations, making the clinical studies possible.

Finally, I would like to thank my family, especially my mom and dad for always encouraging words and love. And most important, I'm deeply grateful to my best friend and husband Dr. Gullik Anthon Jensen, for giving me the opportunity to do this thesis, showing understanding for my work and contributing with his skills. And last but not least, thanks to my adorable children Marthine, Gullik and Oda Natalie for reminding me that life is so much more than magnetic resonance.

Line Rørstad Jensen
Trondheim, February 2010

Summary

Breast cancer patients with locally advanced disease are often treated with chemotherapy prior to surgery, to downstage primary inoperable disease. There is a large variation in treatment response between patients, and methods that can predict or early detect treatment effects are needed to optimize therapy individually.

Magnetic resonance (MR) has evolved as an important diagnostic tool in oncology, both for detection and follow–up in the course of treatment. Several MR methods are often used during one examination, providing both detailed anatomical images and functional images of perfusion, water diffusion or metabolic information. In dynamic contrast enhanced (DCE) MRI a series of images are acquired before and after intravenous injection of a contrast agent, demonstrating an increase in signal intensity of highly perfused tissues as in tumors. The formation of new blood vessels is an important step in tumor progression, and aggressive tumors are often highly vascularized. Thus DCE–MRI has potential for *in vivo* imaging of tumor blood supply, and functional changes may be assessed. Diffusion weighted (DW) MRI exploits the natural diffusion of water molecules, and may be used to study tumor properties at a cellular level. The motion of water molecules in tissue is restricted by structures such as cell membranes and macromolecules, and DW–MRI may be used to detect changes in e.g. cell density. Metabolic information can be studied both with *in vivo* MR spectroscopy (MRS) before the tumor is resected, and with *ex vivo* MRS of tumor biopsies. MR signals from small metabolites as choline compounds are used to study tumor metabolism, and may give important information on treatment response mechanisms.

The aim of this work was to use a combination of MR methods to assess treatment response both in pre–clinical human tumor models in mice and in breast cancer patients undergoing neoadjuvant chemotherapy (NAC). Both

in vivo MR protocols and methods for analysis of the data were established during this work. Overall, differences in tumor vascularity were detected with DCE–MRI, both in breast cancer xenografts treated with chemotherapy and in colon cancer xenografts influenced by the fatty acid TTA. Changes in response to chemotherapy were also found with DCE–MRI in breast cancer patients, in addition to a correlation between parameters after DCE–MRI before treatment with overall survival. The apparent diffusion coefficient derived from DW–MRI in breast cancer patients appeared to increase after one cycle of chemotherapy, as was also found in a study of breast cancer xenografts. In addition, treated breast tumor models had lower levels of choline compounds when compared to controls, as measured with MRS.

Overall, the work in this thesis presents a useful set of complementary MR methods, well suited for treatment monitoring.

Symbols and abbreviations

α	flip angle
ADC	apparent diffusion coefficient
AIF	arterial input function
AUC	area under the curve
b	diffusion weighting factor
C	contrast agent concentration
C_p	plasma concentration
C_t	tissue concentration
D	dose of contrast agent
DCE	dynamic contrast enhanced
DW	diffusion weighted
EES	extravascular extracellular space
FEC	5–fluorouracil, epirubicin and cyclophosphamide
FLASH	fast low angle shot
FOV	field of view
HR MAS	high resolution magic angle spinning
IAUC	initial area under the curve
IDC	infiltrating ductal carcinoma
ILC	infiltrating lobular carcinoma
ICA	independent component analysis
K^{trans}	transfer constant
KNN	kohonen neural network
LDA	linear discriminant analysis
MRI	magnetic resonance imaging

MRS	magnetic resonance spectroscopy
NAC	neoadjuvant chemotherapy
PCA	principal component analysis
PLS	partial least squares regression
PNN	probabilistic neural network
ppm	parts per million
PRESS	point resolved spectroscopy
r_1	relaxivity
RSI	relative signal intensity
SE	spin echo
SI	signal intensity
T_1	longitudinal relaxation time
T_2	transversal relaxation time
TE	echo time
TR	repetition time
TTA	tetradecylthioacetic acid
TTP	time to peak
v_e	volume fraction of extravascular extracellular space
v_p	volume fraction of plasma

List of papers

Paper I
Effect of dietary tetradecylthioacetic acid on colon cancer growth studied by dynamic contrast enhanced MRI
LR Jensen, K Berge, TF Bathen, H Wergedahl, SA Schønberg, AM Bofin, RK Berge and IS Gribbestad
Cancer Biology & Therapy. 2007 Nov;6(11):1810–1816.

Paper II
Assessment of early docetaxel response in an experimental model of human breast cancer using DCE–MRI, ex vivo HR MAS and in vivo ^{1}H MRS
LR Jensen, EM Huuse, TF Bathen, PE Goa, AM Bofin, TB Pedersen, S Lundgren and IS Gribbestad
NMR in Biomedicine. 2010 Jan;23(1):56–65.

Paper III
Predicting survival and early clinical response to primary chemotherapy for patients with locally advanced breast cancer using DCE–MRI
R Johansen, LR Jensen, J Rydland, PE Goa, KA Kvistad, TF Bathen, DE Axelson, S Lundgren and IS Gribbestad
Journal of Magnetic Resonance Imaging. 2009 Jun;29(6):1300–1307.

Paper IV
Diffusion weighted and dynamic contrast enhanced MRI in evaluation of early treatment effects during neoadjuvant chemotherapy in breast cancer patients
LR Jensen, B Garzon, MG Heldahl, TF Bathen, PE Goa, S Lundgren and IS Gribbestad
Submitted Paper

Contents

Chapter 1

Introduction

1.1 Cancer

In Norway, more than 25.000 patients are diagnosed with cancer each year, and one fourth of all deaths are caused by cancer[1]. Optimal treatment of the disease is important both for patients and for socio–economic reasons. The trend moves toward individualized therapy, where each patient receive tailored treatment for their disease. In this setting, tumor markers of both predictive and prognostic value are important, and also methods to monitor treatment response are needed.

Cancer is thought of as a monoclonal disease, i.e. a tumor has developed from a single cell. An accumulation of mutations in DNA affecting proliferation and anti proliferation genes, is transforming human cells into immortal, rapidly growing cancer cells that show little cell–to–cell interactions. Generally, cells need blood supply to grow, thus for solid tumors, growth is restricted by the diffusion distance of oxygen in tissue. The ability to recruit new blood vessels is crucial in tumor progression, and is termed the neoagniogenic switch (Folkman, 1971; Carmeliet and Jain, 2000). This results in formation of a chaotic and abnormal vascular network, where vessels can lack basement membrane and are highly permeable. Tumors often have high cell density, high fluid pressure, and permanent or fluctuating hypoxia, which makes treatment challenging, and tumors become lethal when developing to infiltrating and metastatic disease.

[1] Statistics Norway, `http://www.ssb.no`

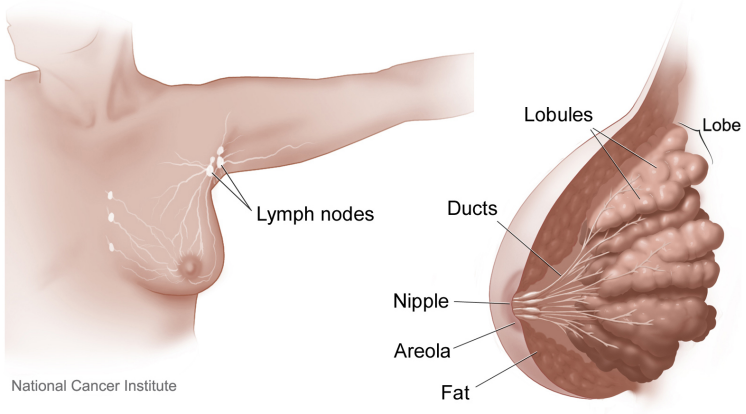

Figure 1.1: Anatomy of the breast, showing lobes and ducts inside the breast. The lymph nodes near the breast are also shown. Adapted from Don Bliss, National Cancer Institute (NCI).

1.2 Breast cancer

Breast cancer is the most frequent cancer type in women, with more than 2700 reported cases in Norway each year (Bray, 2008). The most common type of breast cancer is carcinomas, developing from epithelial cells in the ducts of the breast as infiltrating ductal carcinoma (IDC), or the lobules of the breast as infiltrating lobular carcinoma (ILC), see Figure 1.1 for the anatomy of the breast. Clinical examination, mammography and pathologic examination of fine needle aspiration cytology or core biopsy defines the basis for diagnosis of breast cancer. In addition, important prognostic factors are tumor size and grade, lymph node metastases, estrogen and progesterone receptor status, and proliferative index (Ki–67/MIB–1). Following the TNM system for malignant tumors, the disease is classified by tumor size (T), grade of axillary lymph node involvement (N) and distant metastases (M), as described in Sobin and Wittekind (2009). Combinations of these factors defines the tumor stage, from small primary tumors ($<$ 2cm, Stage I) to locally advanced disease (Stage III) and distant metastases (Stage IV).

Approximately 10% of breast cancer patients are diagnosed with locally advanced disease, which is defined as primary inoperable cancer. This diagnosis includes large tumors and/or involvement of axillary lymph nodes. The 5–year progression free survival for these patients is around 30%, however substansial better prognosis is expected for stage III compared to stage IV

(Figure 1.2). The last decades there has been an increase in relative survival for breast cancer patients in general, however, for metastatic disease (stage IV) this is not the case. A combination of better treatment and a national program for mammography screening are possible explanations for the trend to improved survival.

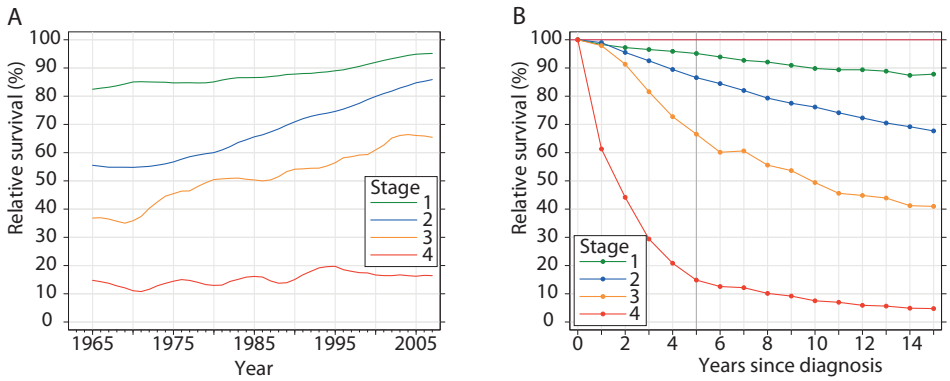

Figure 1.2: Survival for breast cancer patients by stage. (A) Trends in 5–year relative survival, and (B) Long–term relative survival. From Småstuen et al. (2008).

1.2.1 Neoadjuvant chemotherapy

Patients with locally advanced breast cancer are treated with chemotherapy before surgery, termed neoadjuvant chemotherapy (NAC). It has been shown that this is equivalent with traditional adjuvant chemotherapy administered after surgery, when comparing disease free and overall survival (Rastogi et al., 2008). Furthermore, the treatment effect can be evaluated and optimized, and early systemic treatment would also benefit treatment of micro–metastatic disease. The trend moves toward including patients with tumors of lower stage for NAC as well, to increase the possibility for breast conservation surgery.

In Norway, the standard therapy is a combination of the cytostatic agents 5–fluorouracil, epirubicin and cyclophosphamid (FEC). After four cycles, the treatment effect is evaluated by measurement of tumor size, and treatment is changed to taxane–based treatment when tumor response is insufficient.[2] The taxane docetaxel is produced from the needles of the European yew tree, an important group of cytostatica developed in the 1990s.The mechanism

[2]Norwegian breast cancer group, `http://www.nbcg.no`

of action is binding to and impairing the dynamics of microtubuli, causing apoptosis and cell death. Docetaxel has been shown to enhance response to NAC in breast cancer patients (Smith et al., 2002), however there is large variations between patients in response rates and there is a need for predictive factors to identify tumors that are sensitive to this agent (Noguchi, 2006).

1.3 Colon cancer

The most common type of colon cancer is adenocarcinoma, originating from epithelial cells in mucosa in the colon (Figure 1.3). The initial stage is often manifested as adenomatous polyps. In Norway a total of 3400 new cases of colorectal cancer were diagnosed in 2007, and the incidence has increased the last 50 years (Bray, 2008). Colonoscopy with biopsy is the most important method for diagnosis, however CT, ultrasound and MRI are often used in the further diagnostic assessment. Early stages and localized cancer is treated with surgery, while locally advanced disease is treated with NAC followed by surgery, and radiotherapy.[3]

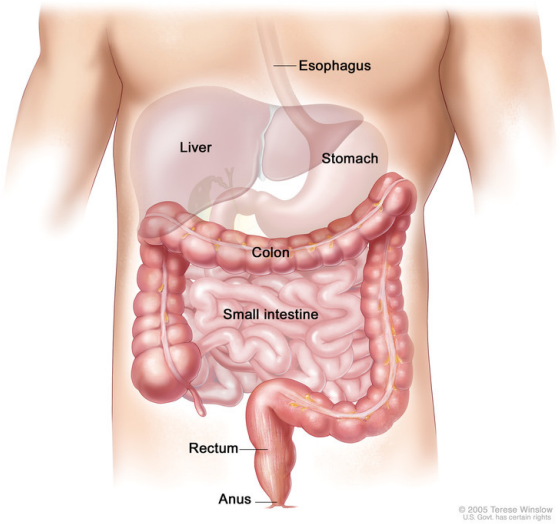

Figure 1.3: Anatomy of the colon and rectum. Printed with permission. (©2005 Terese Winslow, U.S. Govt. has certain rights.)

[3] Oncolex, `http://www.oncolex.no`

1.3.1 Dietary fatty acids

Diet has been proposed as an important risk factor in the development of colon cancer. A diet high on animal fat and low on fiber, fruit and vegetables is thought to increase the risk. Special attention has been given n–3 poly-unsaturated fatty acids found e.g. in marine oils, as protective agents for development of cancer (Bartsch et al., 1999; Tsubura et al., 2009). Studies of the synthetic fatty acid tetradecylthioacetic acid (TTA) has also shown growth inhibitory effect on malignant cancer cell lines from breast, glioma and leukemia (Berge et al., 2003; Abdi-Dezfuli et al., 1997; Tronstad et al., 2002; Berge et al., 2001). The metabolic effects of TTA has been reviewed (Berge et al., 2002).

1.4 Human tumor xenografts

Commonly used model systems for human cancer is transplanting human tumor cells or tissue to immunodeficient mice, to form a xenograft. Often the tumor is transplanted under the skin of the animal, but methods for transplantation to the site of origin has also been developed. The implanted tumor cells will trigger neoangiogenesis from the host tissue, and continue to grow into a tumor mass, as an 'animal culture' (Frese and Tuveson, 2007). The model systems retain many characteristics from its native tumor, as histological properties and response characteristics. However, the stromal tissue is of mouse origin, and care has to be taken when generalizing to human tumors. Nevertheless, the number of publications based on tumor mouse models has increased exponentially the last two decades (Krupke et al., 2008), showing the importance of such models for several research areas like development of new treatments, understanding molecular mechanisms, and developing methods for characterizing and monitoring tumor progression.

1.5 Magnetic resonance imaging

Magnetic resonance imaging (MRI) emerged as a clinical available method in the early 1980s, however the principles of magnetic resonance was discovered as early as 1946 by Bloch (1946) and Purcell et al. (1946). By use of a strong external magnetic field, magnetic gradients and radio frequent

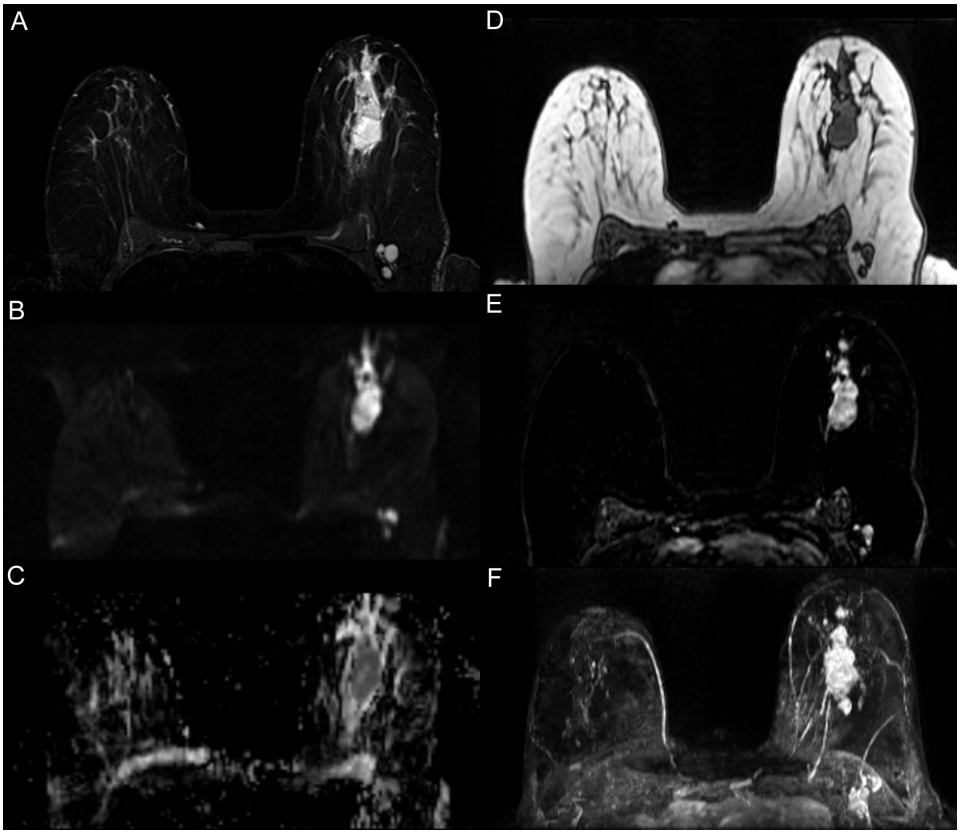

Figure 1.4: MR images from a breast cancer patient, a T_2–weighted image (A), diffusion weighted image (B) and an ADC–map calculated from the diffusion–weighted images (C). On the right side, a T_1–weighted image (D), a subtraction image after contrast agent injection (E), and a projection of the maximum signal intensity of the subtraction image volume (F).

electromagnetic radiation, protons in the body is stimulated to release signals detectable by coils. There is no documented biological side effects, and MRI has evolved as an important method for diagnostic assessment of solid cancer. With MRI, different type of contrast of the tissue can be obtained by exploiting different magnetic properties of protons, as proton density, longitudinal relaxation rate (T_1) and transversal relaxation rate (T_2). An example of the difference in contrast of T_1– and T_2–weighted images from a breast cancer patient is demonstrated in Figure 1.4.

In addition to superior anatomical images, functional images can also be obtained by MRI. The most important techniques for imaging of malignancies

are dynamic contrast enhanced MRI (DCE–MRI), diffusion weighted MRI (DW–MRI) and chemical shift imaging.

1.5.1 Dynamic contrast enhanced MRI

In T_1–weighted dynamic contrast enhanced MRI a series of identical images is acquired before and after intravenous injection of a contrast agent. The paramagnetic contrast agent is distributed through the blood, and leaks out in highly vascularized tissue, especially cancer tissue. An example of a series of contrast–enhanced images in a breast cancer patient are shown in Figure 1.5, with signal intensity variation over time. Dynamic contrast enhanced MRI has been used for imaging in breast cancer since late 1980s (Kaiser and Zeitler, 1989), and was early used to differentiate between benign and malignant disease, and correlated well to pathologic tumor size (Gribbestad et al., 1992). It is generally accepted that injection of a contrast agent is essential to differentiate tumor tissue from parenchyma, and it is therefore included in standard MRI–protocols for breast cancer. DCE–MRI is used to differentiate benign from malignant disease, staging, screening of patients at high risk, monitoring treatment response, and follow–up after surgery and radiotherapy (Turnbull, 2009). Guidelines for breast MRI have been proposed by the European Society of Breast Imaging (Mann et al., 2008). For colon cancer, DCE–MRI has been of minor use in detection and staging. However, more attention has been paid to the evaluation of treatment effect, in particular to antiangiogenic agents (Goh et al., 2007). In addition, DCE–MRI has been shown to correlate to immunohistochemical markers for tumor angiogenesis (Zhang et al., 2008).

Contrast agents used in the clinics are often paramagnetic Gadolinium complexes, as the extracellular tracer gadodiamide (Omniscan$^{\text{TM}}$, GE Healthcare), which operates by shortening of the longitudinal relaxation rate (T_1), hence increasing the signal in T_1–weighted images. Several imaging sequences can be used for dynamic contrast enhanced imaging, of these the spin echo sequence has the advantage of a linear relationship between signal intensity and contrast agent concentration (Larsson et al., 1990), although this is a time consuming method. The signal intensity (SI) for a spin–echo sequence follows the equation

$$\text{SI} \propto \rho \cdot (1 - \mathrm{e}^{-\text{TR}/T_1}) \cdot \mathrm{e}^{-\text{TE}/T_2}, \tag{1.1}$$

where ρ is the proton density, TR the repetition time, TE the echo time, and T_2 is the transverse relaxation rate. By choosing a short echo time, the

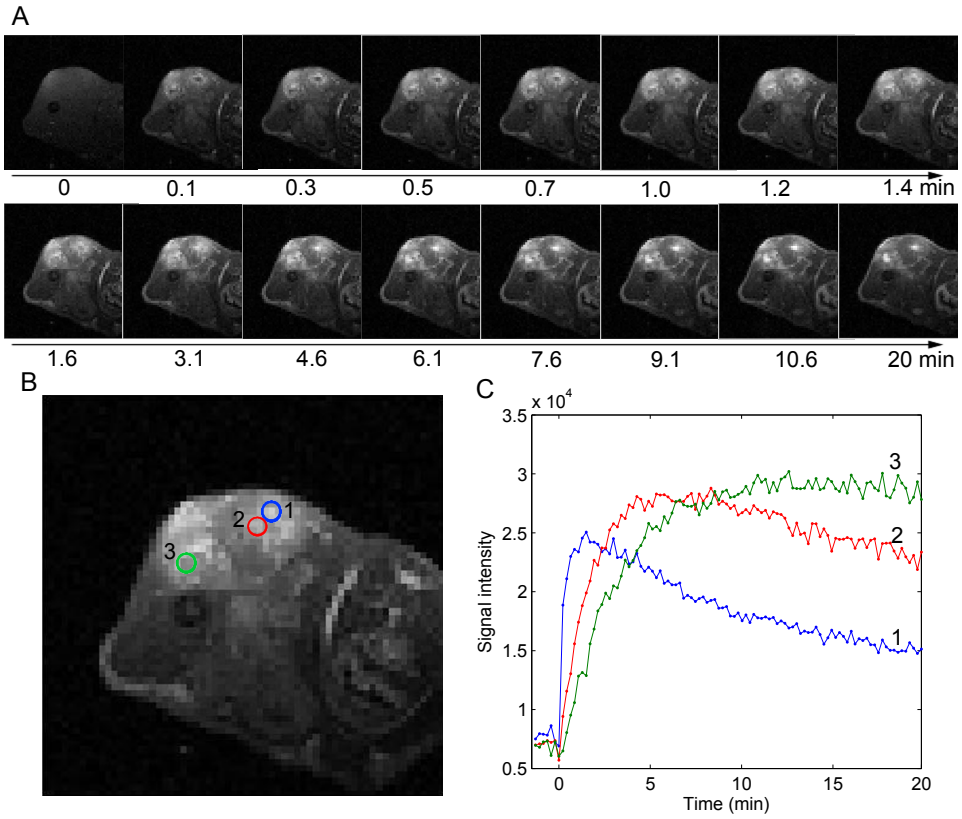

Figure 1.5: (A) Dynamic contrast enhanced MRI series of an MCF7 xenograft at 7 Tesla. The first T_1–weighted image has low contrast, however after contrast agent injection the vascular tumor tissue lightens up. At the end of the sequence contrast agent has diffused into necrotic areas, which can be seen as high intensity areas. (B) A contrast enhanced image 1.6 min. after contrast agent injection. Three voxels are encircled, with corresponding enhancement curve in (C), showing viable tumor tissue (1 and 2) and necrotic tissue (3).

sequence will be T_1–weighted. To improve temporal resolution and increase the imaging matrix, the Fast Low Angle Shot (FLASH) sequence has been used frequently in the clinical setting, with signal intensity described by

$$\mathrm{SI} \propto \rho \sin\alpha \cdot \frac{1 - \mathrm{e}^{-\mathrm{TR}/T_1}}{1 - \cos\alpha \cdot \mathrm{e}^{-\mathrm{TR}/T_1}} \cdot \mathrm{e}^{-\mathrm{TE}/T_2^*}, \tag{1.2}$$

where α is the flip angle and T_2^* is the apparent transverse relaxation rate. When the echo time is sufficiently lower than T_2^*, this sequence will also be T_1–weighted. This is especially well suited for fast imaging of 3D volumes. For a fixed TR and T_1 the sequence has its highest signal intensity at Ernst angle. However, to maximize sensitivity to changes in T_1, the optimal flip angle, α_1 can be found from the relationship

$$\cos(\alpha_1) = \frac{2\mathrm{e}^{-\mathrm{TR}/T_1} - 1}{2 - \mathrm{e}^{-\mathrm{TR}/T_1}}. \tag{1.3}$$

The T_1 relaxation rate after injection of contrast agent is related to the contrast agent concentration (C) and relaxivity (r_1) by

$$\frac{1}{T_1} = \frac{1}{T_{10}} + r_1 \cdot C, \tag{1.4}$$

where T_{10} is the longitudinal relaxation rate without contrast agent. This precontrast relaxation rate can be measured in several ways, e.g. by varying the repetition time in the spin echo sequence (1.1) or varying the flip angle in the FLASH sequence (1.2). Thus the concentration of contrast agent in tissue can be derived.

1.5.2 Analysis of DCE-MRI

Dynamic contrast enhanced imaging has been used to assess the vascularity of tumor tissue, by using pharmacokinetic modeling of the contrast agent concentration (Larsson et al., 1990; Tofts and Kermode, 1991). These methods have been derived from studies using freely diffusible tracers to measure blood flow (Kety, 1960), where tissue is modeled by two compartments, the intravascular space and the extravascular extracellular space (EES). When the contribution to the contrast agent concentration in an MRI voxel is assumed to come from both tissue (C_t) and blood plasma (C_p), the two–compartment model can be expressed as

$$C_t(t) = v_p C_p(t) + K^{\mathrm{trans}} \int_0^t C_p(t') \mathrm{e}^{K^{\mathrm{trans}}(t-t')/v_e} \mathrm{d}t', \tag{1.5}$$

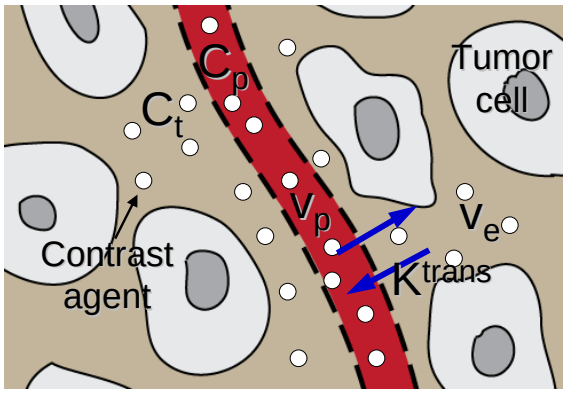

Figure 1.6: The pharmacokinetic model assumes two compartments in a MRI voxel: The plasma (v_p) and the extracellular extravascular space (v_e). The concentration of contrast agent is C_p and C_t, respectively. The extraction fraction of contrast agent over the vessel wall is given by K^{trans}.

where v_p is the volume fraction of blood plasma, v_e is the volume fraction of tissue space available for contrast agent (EES for the extracellular tracer gadodiamide), and K^{trans} is the transfer constant between blood plasma and EES, see Figure 1.6. The transfer constant is dependent on several physiological conditions, e.g permeability and blood flow. In tumors, we assume the model is limited by both flow and permeability surface area product, giving the relation $K^{\text{trans}} = EF\rho(1 - \text{Hct})$, where E is the extraction ratio, F is the flow of whole blood per unit mass of tissue, and Hct is Hematocrit. A consensus for pharmacokinetic analysis of DCE–MRI was proposed by Tofts et al. (1999).

The concentration in blood plasma, the arterial input function (AIF), is often assumed to follow a bi–exponential decay, as described by

$$C_p(t) = D \cdot (a_1 \mathrm{e}^{-m_1 t} + a_2 \mathrm{e}^{-m_2 t}), \tag{1.6}$$

where D is the injected contrast agent dose, a_1 and a_2 are the amplitudes of the components, and m_1 and m_2 are their rate constants. The fast component of the function comes from the exchange of contrast agent between plasma and EES, while the slow component is renal secretion of contrast agent. The AIF may be derived from arteries in the DCE–MRI series directly, and provides the best input to the analysis. However, population based AIF parameters are widely used, especially on clinical data, due to difficulties with definition of arteries, partial volume effects and other practical considerations.

In clinical practice, a DCE–MRI examination can be subjectively evaluated by review of the signal intensity time curves. Each curve may be classified based on curve shape, as proposed by Daniel et al. (1998). Other empirical methods with no assumptions are also frequently used for analyzing DCE–MRI. The relative signal intensity (RSI) is calculated as the fraction of signal intensity at a specified time after contrast agent injection, to the baseline. The area under the signal enhancement curve is often calculated for the first two minutes after contrast agent injection (initial area under the curve, IAUC), or for the total time series (AUC). The time to peak (TTP) is the time from contrast agent injection to the maximum signal intensity, and is also a parameter used for characterizing the contrast enhancement curves. Multivariate methods has also been proposed as a model–free tool for DCE–MRI analysis, in combination with curve types as a diagnostic tool (Eyal and Degani, 2009; Eyal et al., 2009).

1.5.3 Diffusion weighted MRI

Diffusion weighted MRI (DW–MRI) exploits the natural random motion of water molecules. In tissue, this motion is restricted by cellular packing, intracellular elements, membranes and macromolecules (Figure 1.7). The method is extensively used for assessment of intracranial disease, where early changes are detected before visibly abnormality can be seen. The method has also evolved as promising in oncology, and technological developments has made DW–MRI of the body available (Koh and Collins, 2007). Solid tumors often separates from normal tissue with high cellularity and macromolecular structure, thus water is more restricted and gives higher intensities in DW–MRI. Structures at the cellular level can be assessed using diffusion sensitizing gradients (Stejskal and Tanner, 1965; Bammer, 2003). The MR signal (SI) in a diffusion weighted image can be expressed by

$$\mathrm{SI} = \mathrm{SI}_0 \cdot \mathrm{e}^{-b \cdot \mathrm{ADC}}, \tag{1.7}$$

where SI_0 is MR signal without diffusion sensitization, ADC is the apparent diffusion constant (s/mm^2), and b is termed the b–value, reflecting the grade of diffusion weighting. The b–value depends on the strength and the duration of the gradients in the sequence. The diffusion gradients are usually applied in three orthogonal directions to average potential anisotropy, a measurement termed "trace". A consensus on DW–MRI in cancer has been proposed, but the need for more work for standardizing and validating the method is emphasized (Padhani et al., 2009).

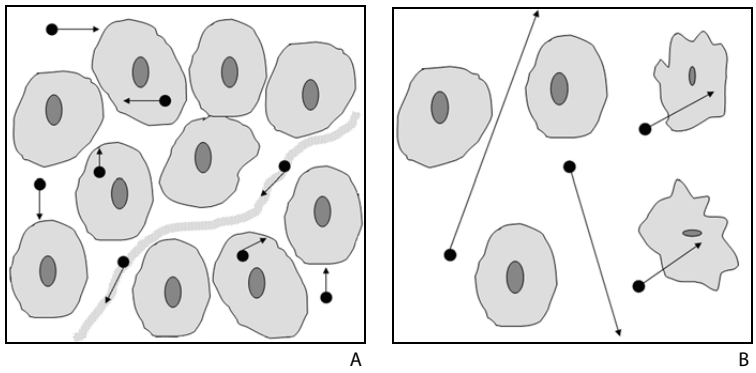

Figure 1.7: Principles of diffusion of water in tissue. (A) In tissue with high cellularity, as in tumors, there is a high grade of restricted diffusivity of water molecules (black dots). (B) After an effective treatment the cellularity is reduced from apoptosis and necrosis, and the diffusivity increases. (Koh and Collins, 2007)

1.6 Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a method used to obtain information about molecules. The most common nucleus used for MRS is ^{1}H, however ^{13}C, ^{19}F and ^{31}P are also frequently used in analysis of cell cultures, tissue biopsies, animals and humans. The natural abundance and the appearance in biological tissue is of importance when choosing nucleus of interest, together with high sensitivity, which makes ^{1}H a good candidate for MRS. When placed in a high magnetic field, protons have a resonance frequency proportional to the magnetic field. In addition, the chemical environment will also influence this frequency, thus protons from different chemical compounds can be separated in a spectrum. Furthermore, protons closely located can influence each other, resulting in splitting of the peaks. After acquiring a spectrum from a sample, the frequency of the peaks are calculated as parts per million (ppm) of the frequency of a standard, and the peaks are assigned to molecules. In biological tissue, amino acids, glucose, lactate, creatine and choline are available with ^{1}H MRS. The metabolic fingerprint of a wide range of cancers has been investigated, and "metabolomics" has evolved as a current and potential method for diagnosis, prognosis and therapeutic evaluation in oncology (Spratlin et al., 2009).

1.6.1 *In vivo* MRS

In vivo MRS can be performed in the same imaging session as MRI. The most common method is single voxel point resolved spectroscopy (PRESS), which uses three slice selective pulses ($90°-180°-180°$) to localize the signal from a defined volume. For spectroscopy, it is crucial with a homogeneous magnetic field, thus a good shim is important when acquiring spectra. In addition, moving to higher field strengths especially benefits *in vivo* MRS, as the separation between metabolites is proportional to the magnetic field. The resolution is limited for *in vivo* MRS, however metabolites such as the total choline peak and lactate may be detected and used as biomarkers for breast cancer (Figure 1.8). The poor resolution is also a consequence of aniotropic interactions between molecules in tissue, where molecular motion is restricted. In solutions, the effect of these interactions are averaged by random molecular motion.

1.6.2 *Ex vivo* high resolution magic angle spinning MRS

MRS examinations of tumor biopsies can be performed with high magnetic field spectrometers, however the defined structures in the samples will reduce the spectral resolution as for *in vivo* MRS. By spinning the sample at a magic angle to the external magnetic field ($54.7°$) the anisotropic interactions is canceled out, producing peaks that are comparable with the resolution for liquids. This has become a valuable method for analyzing biological tissue like tumor samples (Sitter et al., 2009), and is termed high resolution magic angle spinning (HR MAS). The tissue preparation is simple, the biopsy is cut to fit the MAS rotor, and a buffer with a reference compound is added for shimming and chemical shift referencing. A single spectrum may contain information from more than 30 metabolites (Sitter et al., 2002), and spectra are often analyzed with multivariate analysis methods.

1.7 Multivariate analysis methods

Multivariate analysis methods are frequently used to analyze data consisting of many variables. In MRS, the number of variables is often equal to the number of points describing the spectra, often thousands. A large degree of redundancy is expected for such data sets, and multivariate methods can reduce the number of variables significantly without loosing information.

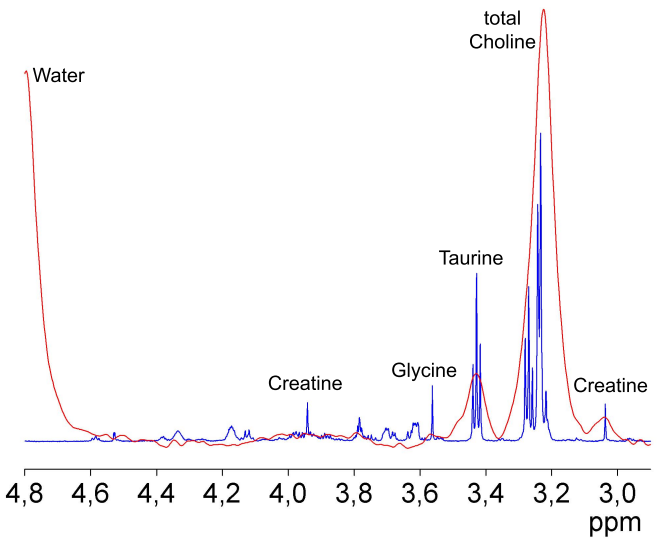

Figure 1.8: Spectra from *ex vivo* HR MAS MRS (blue line) and *in vivo* MRS (red line) of the same MCF–7 breast cancer xenograft. The intensities are individually scaled for the two spectra.

Principal component analysis (PCA) and independent component analysis (ICA) are examples of unsupervised methods that decomposes the data matrix into a set of components with associated score values for each sample. The natural variation in a dataset can then be assessed without adding a priori information. In supervised methods, information on e.g. class assignment is used as input to the analysis, to emphasize the difference between the classes. Methods as partial least squares regression (PLS), kohonen neural networks (KNN), probabilistic neural networks (PNN) and linear discriminant analysis (LDA) are methods frequently used in chemometrics (Brereton, 2003).

Chapter 2

Objectives

The main objective of the research presented in this thesis are to apply MR methods in the evaluation of treatment effects in tumors. More specifically, to:

- Establish a protocol for MR imaging and spectroscopy for experimental tumor xenografts in mice.
- Investigate the feasibility of the MR methods for evaluating therapy response in the tumor xenograft models.
- Implement similar methods for evaluation of tumor response during neoadjuvant chemotherapy in breast cancer patients.

Chapter 3

Materials and methods

An overview of the experimental setup and methods are given in Figure 3.1. The methods will be shortly presented, additional descriptions can be found in the publications I–IV.

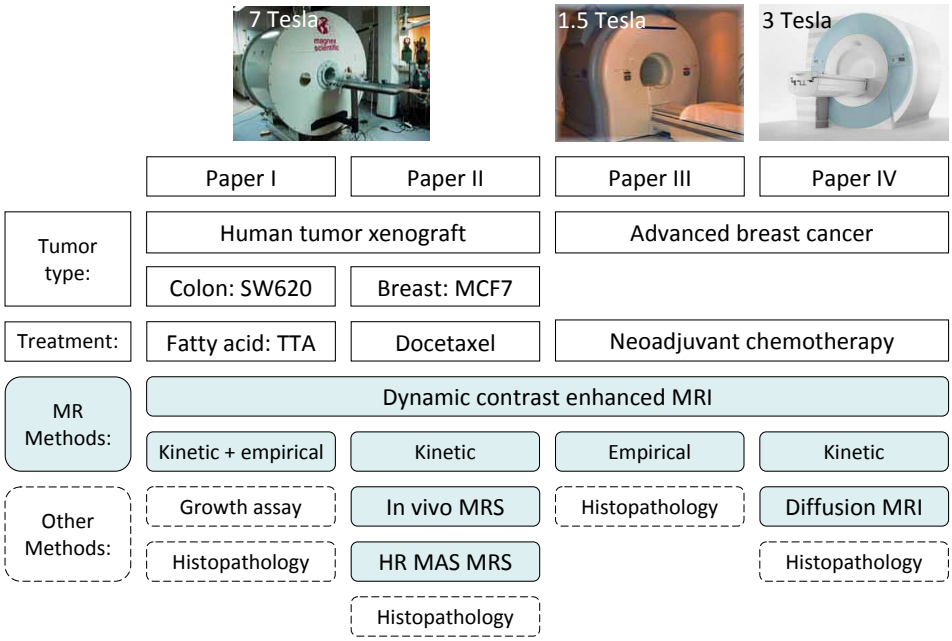

Figure 3.1: Schematic presentation of methods used in the papers presented in this thesis.

3.1 Tumor model systems

Model systems for colon and breast cancer was established in this thesis, and were initiated by subcutaneously injection of the human tumor cells on the hind leg of immunodeficient mice (BalbC nu/nu). The breast cancer cell line MCF–7 was originally isolated from pleural effusion in a woman with malignant adenocarcinoma in 1970 (Soule et al., 1973), and was used as a model system for breast cancer in Paper II. The colon cancer cell line used in Paper I, SW620, was originally isolated from a lymph node metastasis in a male patient diagnosed with colorectal adenocarcinoma in the early 1970's (Leibovitz et al., 1976). This cell line consists of individual small spherical and bipolar cells lacking microvilli, and are highly tumorigenic in nude mice. The cell lines used in the studies were purchased from the American Type Culture Collection (ATCC), and cultured according to the manufacturers recommendation. The colon cancer cell line was cultured at the Department of Laboratory Medicine, Children's and Woman's Health, NTNU. The animal experiments were approved by The National Animal Research Authority.

The *in vitro* cell culture experiments in Paper I were done at the Section of Medical Biochemistry, Institute of Medicine, University of Bergen.

3.2 Patients

Patients with primary inoperable breast cancer, undergoing neoadjuvant chemotherapy at St Olavs Hospital, Trondheim, Norway, were enrolled in the clinical studies. All patients signed written informed consent, and the studies were approved by the institution's human ethics committee. Patients included in paper III were enrolled in the period 1998–2001 and were followed in minimum 5 years after diagnosis. For paper IV, patients were enrolled in the period 2008–2009. Additional clinical information as tumor size, age, and treatment, were obtained from the patient journals.

3.3 Preclinical MR protocols

For the tumor model systems in paper I and II, the MRI and in vivo MRS were performed on a 7 Tesla Bruker BioSpec Avance 70/20 (Bruker Biospin, Ettlingen, Germany) with a volume coil for transmitting and an actively

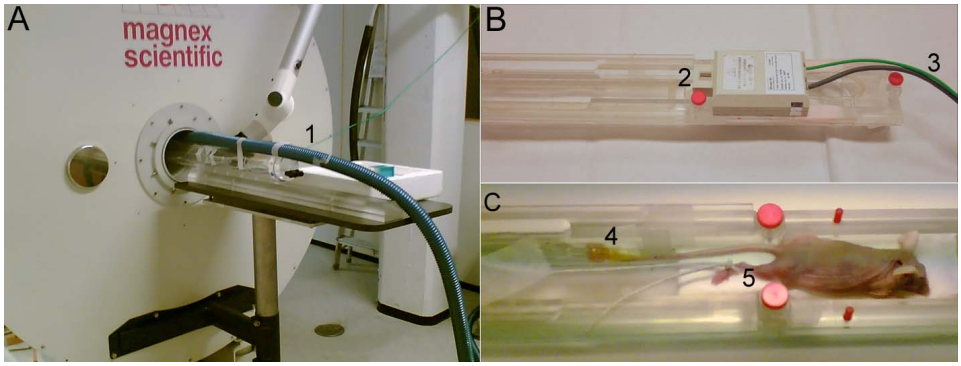

Figure 3.2: (A) Image from a pre–clinical experiment on the 7 Tesla, with the animal bed inside the magnet, and the tube for heated air fastened (1). (B) The animal bed with coil, the tumor was placed under the surface coil (2), and the coil was connected to the system with cables (3). (C) A mouse ready for scanning with intravenous catheter placed in the tail vein (4), and the tumor bearing leg stabilized in a stretched–out position (5).

decoupled quadrature surface coil (rat or mouse head) for receiving. The mice were anastesized and an intravenous canule placed in the tail vein. The mice were then fixed on a dedicated animal bed with the surface coil placed over the tumor on the leg, and then positioned in the isocenter of the magnet. Body temperature was maintained by heated air flow. The experimental set–up is shown in Figure 3.2. The MR protocols were optimized by use of phantoms, four tubes filled with agarose gel doped with different concentrations of gadodiamide. A series of spin–echo images with 5 different repetition times were acquired to calculate precontrast T_1–maps. Only three slices were chosen to reduce the scan time. The T_1–weighted sequence for DCE–MRI was also a spin–echo sequence, with identical geometry as the T_1–maps. Finally, the *in vivo* MRS in Paper II was acquired with a PRESS sequence after automatic shimming. Water suppression was optimized manually, and signal from outside the voxel was suppressed by adding six suppression slices parallel to the surfaces of the voxel. Detailed description of the MR protocols are given in Table 3.1.

The *ex vivo* HR MAS MRS was performed on a Bruker Avance DRX600 spectrometer (600 MHz) equipped with a $^{1}H/^{13}C$ MAS probe with gradient aligned with the magic angle axis. The HR MAS protocol for *ex vivo* MRS was adopted from work with breast cancer biopsies at our institution (Sitter et al., 2002).

Table 3.1: MR protocols used in the studies.

	Paper I & II	Paper III	Paper IV
Field strength	7 Tesla	1.5 Tesla	3 Tesla
DW–MRI			2D EPI
b–values			50, 200, 500, 800
TR (ms)			5400
TE (ms)			86
NA			2
FOV			127×340
Matrix			72×192
Res. (mm^2)			1.77×1.77
Slice (mm)			3–3.5
T_1–map	2D SE		3D FLASH
TR (ms)	150, 400, 1000, 2500, 4000		6
TE (ms)	7		2.45
α			2, 6, 10, 15
FOV (cm)	3×3 & 2×2*		18.7×25
Matrix	64×64		144×192
Res. (mm^2)	0.47×0.47 & 0.31×0.31*		1.3×1.3
Slice (mm)	0.5 & 0.7*		2
DCE–MRI	2D SE	3D FLASH	3D FLASH
TR (ms)	200	9	3.5
TE (ms)	7	3.8	1.14
α		30	10
FOV (cm)	3×3 & 2×2*	25×25	18.7×25
Matrix	64×64	256×256	144×192
Res. (mm^2)	0.47×0.47 & 0.31×0.31*	0.98×0.98	1.3×1.3
Slice (mm)	0.5 & 0.7*	3–4	2
Temp. res. (s)	12.8	57	18.2
Repetitions	100	9	24

*Parameter in Paper I and II, respectively.

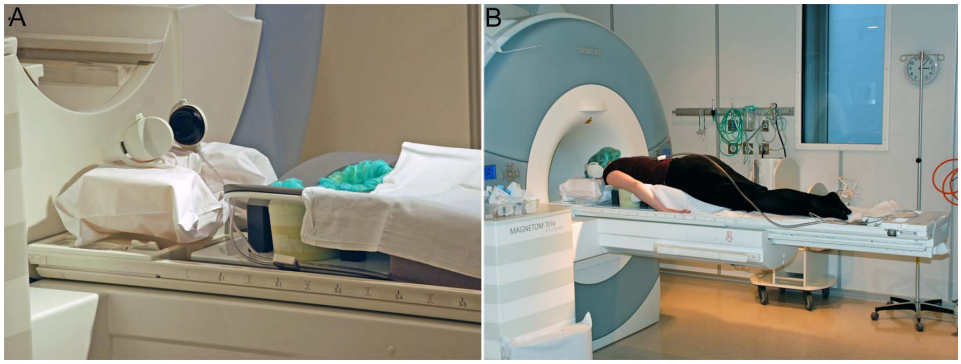

Figure 3.3: (A) The breast coil made ready for clinical examination, with padding, green disposable covers, and a pillow to rest the head. (B) A volunteer is lying on the patient bed, ready to be placed in the magnet.

3.4 Clinical MR protocols

The MRI examinations in paper III were acquired on a 1.5 Tesla Picker Edge system (Picker Edge EPI II, Cleveland, OH, USA) with a receive only double breast coil. These examinations were data available from earlier projects at our institution, and only the DCE–MRI was analyzed. There was no T_1–measurements from these examinations.[1]

In Paper IV, a MAGNETOM Trio Tim 3 Tesla system (Siemens, Erlangen, Germany) was used for MRI, with a dedicated bilateral 4–channel breast array coil for receiving. A canule was placed in the antecubital vein in the patient's arm at arrival. The patients were lying in prone position during the examinations with the breasts in the coil (Figure 3.3). The MR protocol was optimized by use of water–filled phantoms with gadodiamide, and volunteers. Four b–values were chosen for the DW–MRI, 50, 200, 500 and 800 mm2/s. A 3D FLASH sequence with four different flip angles was chosen for precontrast T_1–measurements, and this was also the sequence for DCE–MRI. In addition, a high resolution 3D volume was acquired before and after the dynamic sequence. Detailed description of the clinical MR protocol is given in Table 3.1.

[1] Projects by Kjell Arne Kvistad and Jana Rydland, Dept. of Radiology, St. Olav's Hospital, Trondheim, Norway.

3.5 Motion correction of DCE–MRI

In Paper IV there were some severe cases of patient motion during DCE–MRI, probably caused by contraction of the pectoral muscle. To correct for this, the misaligned images were registered to a chosen reference image by use of FNIRT, a non–linear image registration tool from the software package FSL (Smith et al., 2004). Remaining misalignment was then removed by use of independent component analysis using MELODIC 3.09 from the same software package.

3.6 Data analysis

The image analysis was performed by use of in–house analysis program developed in Matlab (The MathWorks Inc, Natick, MA, USA). DCE–MRI data in paper I, II and IV were analyzed with the two–compartment model described in 1.5.2, while the empirical methods RSI and AUC were used in paper I, II and III. Statistical analyses were performed in SPSS (SPSS Inc, Chicago, IL, USA).

3.7 Histopathology

The histopathological examinations for paper I and II were done in collaboration with the Department of Laboratory Medicine, Children's and Woman's Health, NTNU. Staining for proliferation was done using Ki–67, apoptotic cells were stained with M30 cytodeath and endothelial cells were stained with CD31 to detect blood vessels. In paper III and IV, standard clinical histopathology was obtained from the patient journals.

Chapter 4

Summary of papers

Paper I

Effect of dietary tetradecylthioacetic acid on colon cancer growth studied by dynamic contrast enhanced MRI.

The purpose of this study was to evaluate the effects of diets supplemented with the modified fatty acid TTA and fish protein hydrolysate (FPH) on tumor growth of the human colon cancer cell line SW620, and to investigate the properties of tumor vasculature by dynamic contrast enhanced MRI in a human tumor xenograft. In addition, MR protocol for imaging of tumor xenografts was established.

SW620 cells were grown in vitro in presence of TTA and palmitic acid and proliferation was measured by thymidine incorporation. The xenograft study in mice was performed with four distinct diets: control diet, diet with TTA, diet with TTA and FPH, and diet with FPH. SW620 cells were injected subcutaneously, and dynamic contrast enhanced MRI was performed on a Bruker BioSpec 7 Tesla system. The data was analyzed by two–compartment modeling of the contrast enhancement, initial area under the curve and by use of relative signal intensity distributions.

The in vitro cell studies revealed that TTA reduced tumor cell proliferation as a function of both dose and time. The in vivo tumor growth was significantly reduced for the two groups fed TTA, as compared to the control group. The mean 10^{th} percentile RSI, v_e and IAUC for the TTA group were significant higher than for the control group. This study confirms the growth inhibitory effects of TTA, both in vitro and in vivo, in a colon cancer model.

The analysis of DCE–MRI data showed that TTA influences the vascular properties of the tumor in addition to the growth.

Paper II

Assessment of early docetaxel response in an experimental model of human breast cancer using DCE–MRI, ex vivo HR MAS and in vivo ^{1}H MRS.

The purpose of this study was to evaluate the use of dynamic contrast–enhanced MRI, in vivo ^{1}H MRS and ex vivo high resolution magic angle spinning MRS of tissue samples as methods to detect early treatment effects of docetaxel in a breast cancer xenograft model (MCF–7) in mice.

MCF–7 cells were implanted subcutaneously in athymic mice and treated with docetaxel (20, 30 and 40 mg/kg) or saline six weeks later. DCE–MRI and in vivo ^{1}H MRS were performed on a 7 Tesla MR system three days after treatment. The dynamic images were used as input for a two–compartment model, yielding the vascular parameters K^{trans} and v_e. HR MAS MRS, histology and immunohistochemical staining for proliferation (Ki67), apoptosis (M30 cytodeath) and vascular/endothelial cells (CD31) was performed on excised tumor tissue. Both in vivo spectra and HR MAS spectra were used as input for multivariate analysis (principal component analysis and partial least squares regression analysis) to compare controls to treated tumors.

Tumor growth was suppressed in docetaxel treated mice compared to the controls. The antitumor effect led to changes in the distributions of K^{trans} and v_e in all the treated groups. Furthermore, in vivo MRS and HR MAS MRS revealed a significant decrease in choline metabolite levels for the treated groups, in accordance with reduced proliferative index as seen on Ki67 stained sections. In this study DCE–MRI, in vivo MRS and ex vivo HR MAS MRS have been used to demonstrate that docetaxel treatment of a human breast cancer xenograft model results in changes in the vascular dynamics and metabolic profile of the tumor. This indicates that these MR methods could be used to monitor intra–tumoral treatment effects.

Paper III

Predicting Survival and Early Clinical Response to Primary Chemotherapy for Patients with Locally Advanced Breast Cancer using DCE–MRI.

The purpose of this study was to evaluate dynamic contrast–enhanced MRI as a tool for early prediction of response to neoadjuvant chemotherapy and 5–year survival in patients with locally advanced breast cancer.

DCE–MRI was performed in patients scheduled for NAC (n = 24) before and after first treatment cycle. Clinical response was evaluated after completed NAC. Relative signal intensity and area under the curve were calculated from the DCE curves and compared to clinical treatment response. Kohonen and probabilistic neural network (KNN and PNN) analysis were used to predict 5–year survival.

RSI and AUC were reduced after only one cycle of NAC in patients with clinical treatment response (P = 0.02 and P = 0.08). The mean and 10^{th} percentile RSI value before NAC were significantly lower in patients surviving more than 5 years compared to non–survivors (P = 0.05 and 0.02). This relationship was confirmed using KNN which demonstrated that patients who remained alive clustered in separate regions from those that died. Calibration of contrast enhancement curves by PNN for patient survival at 5 years yielded sensitivity and specificity for training and testing ranging from 80% to 92%. In conclusion, DCE–MRI in locally advanced breast cancer could predict 5–year survival in a small patient cohort. In addition, changes in tumor vascularization after one cycle of NAC can be assessed.

Paper IV

Diffusion weighted and dynamic contrast enhanced MRI in evaluation of early treatment effects during neoadjuvant chemotherapy in breast cancer patients.

The purpose of this study was to use MRI at 3 Tesla for early evaluation of treatment effects in breast cancer patients undergoing neoadjuvant chemotherapy, and to identify MRI parameters that correlate to treatment response. In addition, the reproducibility of diffusion weighted MRI was assessed.

Diffusion weighted and dynamic contrast enhanced MRI of breast cancer patients were performed before and after the first cycle of NAC. The apparent diffusion coefficient was calculated from the DW–MRI, and the parameters K^{trans} and v_e were calculated from two–compartment analysis of the DCE–MRI. ADC values from two baseline examinations prior to NAC were used in a reproducibility analysis, and the intraclass correlation coefficient (ICC) was calculated. Changes in statistical features derived from the distributions of MRI parameters, the tumor diameter and the volume after one cycle of NAC was assessed. In addition, the same features were used as input for a linear discriminant analysis (LDA) to find the best predictors for pathologic response.

The ADC values from two baseline examinations showed very good reproducibility, with ICC ranging from 0.75 – 0.84. A reduction in both MRI defined longest tumor diameter and tumor volume were found after only one cycle of NAC. In addition, the treatment resulted in increased ADC mean, ADC maximum and v_e mean, and a reduction in v_e skewness. The best predictors from the LDA among the baseline features were the entropy and skewness of ve. After the first treatment, the decrease in the longest diameter measured on MRI was the best predictor of treatment response, followed by mean and skewness of ADC, and K^{trans} entropy.

ADC measurements were highly reproducible, and increased significantly after only one cycle of NAC. The change in longest tumor diameter from DCE–MRI was the best predictor for tumor response, while changes in kinetic parameters were more moderate. Further investigations on early evaluation of treatment effects should focus on a combination of change in DCE–MRI derived tumor size combined with changes in ADC after one cycle of NAC.

Chapter 5

Discussion and conclusion

5.1 Main findings

In this thesis, different MR methods have been used to assess tumor properties and treatment effects. The main focus has been on breast cancer, however a xenograft study of colon cancer was performed initially, to establish MR protocols on the newly installed 7 Tesla animal scanner. In this paper (Paper I), the growth of a colon cancer model was inhibited by the synthetic fatty acid TTA, both *in vitro* and *in vivo*. The restricted tumor growth influenced the microenvironment and vascularity, and differences between TTA tumors and control tumors were detected with DCE–MRI. In Paper II, the established MRI protocol was extended with *in vivo* MRS, and used for the breast cancer xenograft models treated with docetaxel. Kinetic analysis of DCE–MRI revealed similar differences in vascularity between treated and control tumors as in Paper I. In addition, multivariate analysis of both *in vivo* and *ex vivo* MRS found changes in the metabolic pattern between treated and control tumors. For the clinical breast cancer studies the pattern were more complex, however changes in vascularity were detected using empirical analysis of DCE–MRI after only one cycle of NAC, as shown in Paper III. In addition, DCE–MRI parameters were correlated to overall survival. Multivariate analysis was also used to analyze the data, and confirmed the findings. In Paper IV, ADC values from DW–MRI were measured in addition to kinetic parameters from DCE–MRI. After one cycle of NAC the tumor size decreased and the ADC mean values increased for all the patients. Overall, the MR–methods used in this thesis can detect treatment effects, both with DCE–MRI, MRS and DW–MRI. The methods used

in the pre–clinical studies were transferred and used in the clinical studies.

5.2 Dynamic contrast enhanced MRI

DCE–MRI has become a widely used tool for imaging of tumor vascularity. The nature of the tumor vascular network is chaotic, highly permeable and heterogeneous, thus designing MRI experiments sensitive to both structural and functional properties may be a challenge. There are often conflicting interests when deciding parameters for DCE–MRI, on one side a high spatial resolution is needed for imaging of heterogeneous tumors, while on the other side, high temporal resolution is essential when studying contrast enhancement dynamics. In addition, adequate signal to noise ratio (SNR) and sufficient dynamic range for signal intensity change after contrast agent injection has to be ensured.

Gadodiamide (Omniscan) is a widely used contrast agent used in clinical contrast enhanced MR examinations, and was chosen for both the preclinical and the clinical studies in this thesis. By choosing a commonly used contrast agent, results are easily comparable to other studies, and knowledge from the preclinical studies can be transfered to the clinics. However, this intermediate sized extracellular contrast agent is not optimal for imaging of vascular properties. For measuring perfusion, a freely diffusible tracer would be a better choice combined with pharmacokinetic analysis. On the other side, to assess the permeability of blood vessels, a high molecular weight tracer would be appropriate, with more specific leakage in tumor areas.

The choice of MR sequences for the preclinical studies were based on experiments with phantoms and excess mice from the Department of Comparative Medicine, NTNU. The protocol was also based on earlier studies on a Bruker Biospec 24/40 2.35 Tesla magnet. A 2D spin–echo sequence with short echo time was chosen both for measuring pre–contrast T_1–values and for the dynamic sequence. Other sequences were also considered, as gradient echo (FLASH), but SE was found to be more robust, and the signal equation is simple (1.1). It has been shown later that the FLASH sequence implemented at the 7 Tesla scanner is not optimal, and may not be used for quantification.[1] Experiments with agarose phantoms were used to measure T_1–values for different concentrations, and to convert signal intensities from the SE scan used in the dynamic sequence for calculation of T_1–values. In these ex-

[1] Huuse, E. M., unpublished work, Dept. of Circulation and Medical Imaging.

periments the volume coil was used to avoid sensitivity variations between the phantoms, such that the signal intensity in the phantom without contrast agent could be used as precontrast value. As shown in Figure 5.1A, the calculated T_1–values were in good agreement with the measured values. Furthermore, the calculated relaxation rate ($1/T_1$) showed a linear relationship to the actual contrast agent concentration, and the relaxivity (r_1) for the contrast agent was estimated by linear regression to 4.5 $(\text{mMs})^{-1}$ ($r^2 = 0.995$, Figure 5.1B). In Paper I and II, a literature value was used for the contrast agent relaxivity, $r_1 = 3.6$ $(\text{mMs})^{-1}$ (Yankeelov et al., 2005). Studies have shown that the relaxivity for a contrast agent may vary between different tissues, buffers and temperatures (Xie et al., 2001).

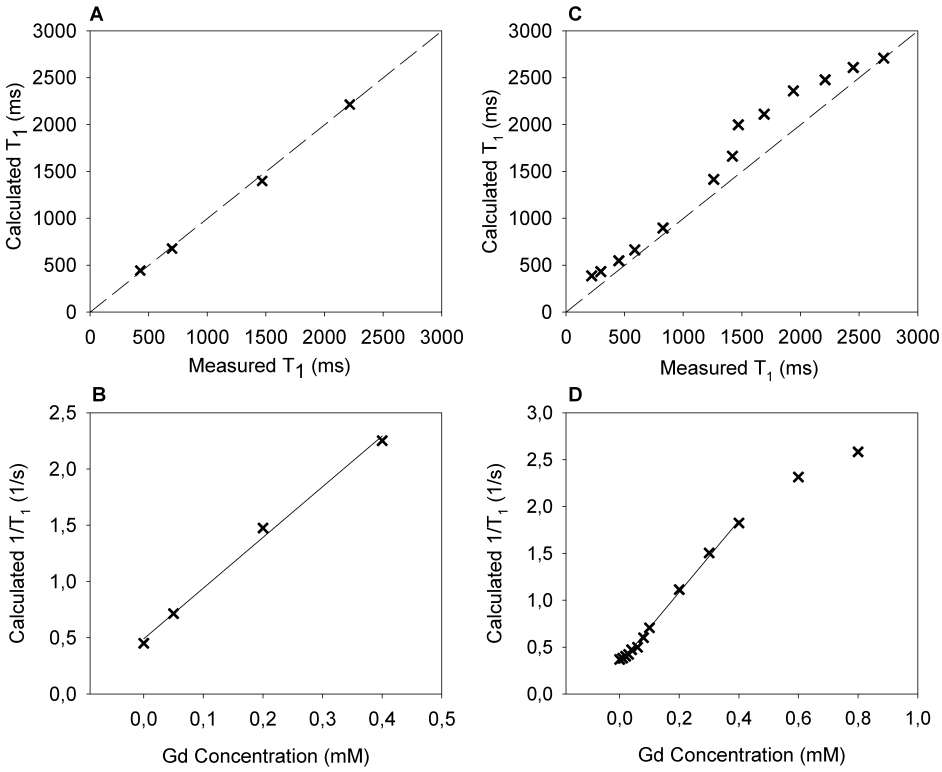

Figure 5.1: Results from work with phantoms on 7 Tesla and 3 Tesla. (A) Measured T_1 using several TR–values vs. calculated T_1, and (B) contrast agent concentration vs. calculated relaxation rate ($1/T_1$) with linear regression curve from the 7 Tesla scanner. (C) Measured T_1 using four flip angles vs. calculated T_1, and (D) the contrast agent concentration vs. relaxation rate ($1/T_1$) with linear regression curve from the clinical 3 Tesla scanner.

In the preclinical studies, the DCE–MRI sequence was analyzed both with two–compartment kinetic modeling and empirical methods. The two–compartment model was based on the consensus from Tofts et al. (1999), and the terming of parameters was adapted from this paper. For the calculation of contrast agent concentration, fast water exchange between tissue water compartments was assumed, a phenomenon described by Donahue et al. (1994). Water in tissue is distributed between intracellular, interstitial and intravascular space, and is moving between them. The spaces may contribute with different MR properties, and the degree of water exchange is defined as the ratio of motion relative to the difference in relaxation rates between the spaces. Although this topic is debated, a fast exchange regime is often assumed with clinical relevant contrast agent doses, however this may introduce a source of error to the calculations. Other methods for pharmacokinetic analysis have also been proposed, as Brix et al. (1991) and Su et al. (1994), with slightly different conditions and parameters. However, the consensus paper was chosen as a basis, to enable comparison with other studies (Tofts et al., 1999). Furthermore, a global AIF was chosen of practical reasons, measured at our lab with similar mice. Individual AIF's should optimally be used, however this is challenging and was not the main focus of this work. Better temporal resolution could also improve the results, however for the tumor models, the enhancement curves is described well, with several points at the initial increasing part.

For the clinical studies, a 3D FLASH sequence was used for DCE–MRI. In Paper III, MRI data from earlier examinations were analyzed, thus optimization of the protocol was not a part of this thesis. For Paper IV the MRI protocol was optimized with aim to improve the temporal resolution compared to a standard clinical examination. In breast cancer patients it is difficult to define the tumor borders before injection of contrast agent, thus imaging of the whole breast is necessary. The choice of MRI sequences were based on standard protocols on the Trio 3 Tesla system, and refined through phantom measurements and imaging of healthy volunteers. The 3D FLASH sequence has several advantages including fast imaging, large volume of interest, and high SNR. Furthermore, good agreement with the theoretical signal equation was found when varying flip angle and repetition time on the system. A short TR was chosen to reduce scan time, and the flip angle was calculated to be sensitive to T_1–changes in the actual range (1.3). The echo time was chosen as short as possible to reduce T_2^*–effects. No standard sequence for T_1–measurement was available, and several methods were tested with varying results. By using the FLASH sequence, identical geometry with the DCE–MRI were possible, and calculations of

contrast agent concentration in each voxel were then simplified. The TR was increased to increase SNR and increase TE to avoid negative fat–shift artifacts. Four flip angles were chosen to increase the accuracy of the calculations. Phantom studies from the 3 Tesla scanner were performed with water–filled tubes doped with different concentrations of contrast agent. The T_1–values from a T_1–measurement were compared to calculated T_1–values from signal intensities in an image identical to the dynamic sequence, and a nice agreement was found (Figure 5.1C). When comparing calculated relaxation rates ($1/T_1$) with the actual contrast agent concentrations, there was a linear relationship up to 0.4 mM (Figure 5.1D). The relaxivity of contrast agent on 3 Tesla was estimated to $r_1 = 3.8$ $(\text{mMs})^{-1}$ from linear regression ($r^2 = 0.996$). This is in agreement with values from the manufacturer (3.9 $(\text{mMs})^{-1}$ at 0.5 Tesla, from the Product Characteristics of Omniscan, GE Healthcare), and is identical to the relaxivity used for calculations in Paper IV.

Pharmacokinetic analysis was implemented in Paper IV, using the same principles as for the preclinical models. A population based arterial input function previously published was used in the analysis (Fritz-Hansen et al., 1996; Schmid et al., 2009), as signal from arteries in the DCE–MRI were difficult to achieve. However, individual AIF measurements in the aorta has previously been implemented for breast cancer DCE–MRI (Port et al., 2001).

5.3 Diffusion weighted MRI

Diffusion weighted MRI was implemented in the patient study protocol at 3 Tesla in Paper IV. The method used for imaging was a twice–refocused spin–echo sequence with EPI read–out, designed to reduce spatial distortions due to eddy–currents. Signal attenuation for low b–values is expected to be highly influenced by intravascular water and blood flow, thus b–values close to zero was omitted. Diffusion of water in tissue may be of complex character, as water is distributed in different tissue compartments. Nevertheless, a mono–exponential fit was considered relevant, as signal from the intravascular compartment was suppressed. The range of b–values chosen (b = 50 – 800 s/mm^2) is in accordance with the recommendations for DW–MRI in oncologic imaging (Padhani et al., 2009). The diffusion time will also influence the measured ADC values, depending on the range of the corresponding diffusion distance. In paper IV, the diffusion time was roughly

estimated to 40 ms, giving a diffusion distance of 20 μm, which is of the same magnitude as human cells. Changes in ADC values after treatment is therefore assumed to reflect cellular changes, as cell damage.

DW–MRI was also implemented on the preclinical scanner (7 Tesla) and used for treatment monitoring of MCF–7 xenografts.[2] A diffusion weighted spin–echo sequence was used with EPI read–out as described by Stejskal and Tanner (1965), with b–values in the range 0–1000 s/mm^2. The diffusion time was 14 ms, giving a diffusion distance of 13 μm, also of the same magnitude as the cell size.

5.4 MR spectroscopy

The PRESS sequence for *in vivo* MRS at 7 Tesla adapted a clinical relevant echo time for breast cancer to reduce signal from fatty acids (TE = 135 ms). However, this was reduced in later work with MCF–7 xenograft tumor models, as there was very little signal from fatty acids.[2] The PRESS–sequence has limitations in choice of low TE–values, but higher SNR compared to e.g. the Stimulated Echo Acquisition Mode (STEAM). This sequence is suitable for experiments with low TE, however this was not emphasized in this study. For the HR MAS MRS study, the pulse acquired spectra were not dominated by signals from fatty acids, and were used in the analysis.

The MR spectra in Paper II were analyzed using multivariate methods. One of the advantages with such methods is the ability to analyze all data in one operation, and to extract important features from complex data. These methods are not quantitative, thus only relative content and variation in metabolites can be assessed. Both the unsupervised method PCA and the supervised method PLS were used to analyze spectra. A careful selection of the spectrum region of interest and mean normalization were done to form a good basis for the analysis, however other choices may yield other results. Generally, preprocessing of data is important when using multivariate analysis, as differences in SNR and large variation in signals between samples may contribute to the result. Work has been done to implement absolute quantification both *in vivo* and *ex vivo* with internal or external standards. In high resolution MRS of solutions, quantification is routinely done, however for tissue samples the concentration of internal standards has

[2]EM Huuse, LR Jensen et al. Monitoring docetaxel response in MCF7 xenografts using multimodal *in vivo* and *ex vivo* magnetic resonance methods, histopathology, and gene expression. Submitted 2009

to be assumed, and external standards may bind to proteins or structures in tissue. The method ERETIC was developed for *in vivo* quantification of MRS by Barantin et al. (1997), and this method has been implemented for HR MAS MRS the last years (Sitter et al., 2010). However, this method was not implemented for the experiments in Paper II.

5.5 Tumor model systems

In this thesis, model systems were used to assess tumor characteristics and therapy induced changes. The use of xenografts may be a powerful tool in cancer research, and mimics the whole tumor system, in contrast to cell cultures. The tumors in a xenograft study are very similar, which increases the power of the studies. In addition, the tumors grow fast, and optimization of treatment regimens and timing of the experiments may be carefully designed. For MRI and MRS, the availability of higher field strengths and smaller volumes of interest is a great advantage. However, care has to be taken when translating results to the clinics. The properties of the injected human tumor cells are retained, but the stroma, including the blood vessels, are from the host. Complex interactions between cancer cells and stroma are contributing to the development of tumors. Neoangiogenesis is crucial for invasive growth and tumor development (Vargo-Gogola and Rosen, 2007), thus the assessment of tumor vascularity might not be directly transferable to the clinics. However, subcutaneously tumor models were established in Paper I and II to implement MR protocols for the assessment of treatment response. To reflect the great biological diversity in a patient population, the MR methods should be implemented for other tumor models. Studies of gene expression profiles in breast cancer biopsies suggest at least five distinct diseases, with different treatment response and prognosis (Perou et al., 2000; Sørlie et al., 2003). Two of these are established as orthotopic tumor models and are currently being used with the MR–methods implemented in this thesis (Bergamaschi et al., 2009; Huuse et al., 2009) .

Several conditions have to be considered when comparing animal studies to clinical studies. In this thesis, the imaging of the breast cancer xenografts was done only three days after the administration of chemotherapy. In patients, the imaging is of practical reasons usually done three weeks after chemotherapy, at the timing of the next treatment cycle. DCE–MRI of the tumor models detected changes after treatment, although the parameters related to vascularity increased, while in many clinical studies of treatment

response a decrease in these parameters are often detected (Pickles et al., 2005; Ah-See et al., 2008). This could be explained by the timing of the imaging. However, despite the limitations, MRI and MRS of tumor models is a powerful tool for understanding response mechanisms of chemotherapy, and also to develop methods transferable to the clinics.

5.6 Assessment of treatment response

During the administration of NAC to breast cancer patients the tumor response can be monitored *in situ*, a great advantage to adjuvant therapy where the primary tumor is resected. MRI is a powerful tool for this task, and has been shown superior for monitoring of treatment when compared to clinical evaluation, mammography and ultrasound (Zakhireh et al., 2008). Currently, MRI is recommended as a tool for evaluation of treatment response halfway during treatment in the guidelines from the European Society of Breast Imaging (Mann et al., 2008). However, early treatment evaluation with functional MRI is a field that still needs validation.

Results from the DCE–MRI experiments in the pre–clinical studies showed differences in vascular parameters between treated and control tumors. The shift in the distributions to higher values could be explained by reduced proliferation for the treated tumors, leading to an increased EES and vascular surface area. Numerous pre–clinical studies have used DCE–MRI to assess tumor vascularity, of colon (de Lussanet et al., 2003), melanoma (Benjaminsen et al., 2004) and breast (Dadiani et al., 2004) as examples. With the development of new vascular targeted therapies, DCE–MRI is a valuable tool for treatment monitoring and understanding therapeutic effects (Checkley et al., 2003; McIntyre et al., 2004; de Lussanet et al., 2004). DCE–MRI uses signal intensity change caused by indirect effects of a contrast agent to assess vascularity, which is often indirectly affected by chemotherapy. Thus this might be a more important tool for monitoring anti–angiogenic agents, that more directly affects the vascular system of tumors. Nevertheless, therapy of tumors in general will influence the vascularity, directly or indirectly, and the observed effects could also be vascular "normalization", which would benefit further treatment (Jain, 2005). In the colon cancer xenograft study, differences in vascularity were also detected with DCE–MRI, showing the diversity of mechanisms influencing neoangiogenesis, and that the method can be used in several model systems.

Several clinical studies of NAC in breast cancer have used DCE–MRI to

Table 5.1: Selected publications on early treatment evaluation with MRI in breast cancer patients undergoing NAC.

Publication	Patients	Response	MRI method	Parameters correlated to response
Martincich et al. (2004)	n = 30	Clinical & pathological	DCE–MRI	↓ Tumor volume (↓ early enhancement rate)
Chang et al. (2004)	n = 13	MRI volume	DCE–MRI kinetic analysis	↓ Peak enhancement to homogeneous distr. of amplitude
Pickles et al. (2005)	n = 68	MRI volume	DCE–MRI kinetic analysis	↓ Tumor size ↓ K^{trans} and v_e*
Padhani et al. (2006)	n = 25	Clinical & pathological	DCE–MRI	↓ Tumor size after 1 and 2 cycles ↓ K^{trans} range after 2 cycles
Manton et al. (2006)	n = 22	Pathological	DCE–MRI & ADC	↓ Tumor volume after 2 cycles ↓ Water T_2
Pickles et al. (2006)	n = 8	none†	ADC	↑ ADC after 1 and 2 cycles ↓ Tumor size after 2 cycles
Loo et al. (2008)	n = 54	Pathological	DCE–MRI	↓ Tumor size after 2 cycles
Ah-See et al. (2008)	n = 28	Clinical & pathological	DCE–MRI kinetic analysis	↓ median kinetic param. after 2 cycles ↓ Tumor size‡
Sharma et al. (2008)	n = 11 (24)⋆	Clinical	ADC	↓ Tumor volume ↑ ADC after 1 and 2 cycles
Iacconi et al. (2009)	n = 21	MRI volume	ADC	low ADC_{pre} ↑ ADC after 3 cycles
Craciunescu et al. (2009)	n = 20	Pathological	DCE–MRI	↑ Morpho–physiological tumor score
Paper III	n = 24	Clinical	DCE–MRI	↓ RSI and AUC ↓ Tumor volume for all patients
Paper IV	n = 14	Pathological	DCE–MRI & ADC kinetic analysis	↓ Tumor diameter ↑ ADC for all patients

* Hot spot analysis; †Findings presented as changes in tumor properties for all patients; ‡Only 3 slices through tumor;
⋆ Patients after one cycle (after two cycles in parentheses). ↓↑ Reduced or increased parameter after treatment.

assess early treatment effects. An accurate measurement of change in tumor size is an important measure for response, in addition to a valuable tool for distinguishing between malign and benign disease of the breast (Kuhl, 2000). The MRI measured tumor size or volume from DCE–MRI has shown good correlation to pathologic measured tumor size. The decrease in MRI measured tumor size was the most significant change after only one cycle of NAC in the clinical studies, however no significant difference was seen between responders and non–responders. In addition to tumor size, quantitative vascular or empirical parameters have been investigated as predictive parameters to response, however the results are diverse. Some find a clear correlation of kinetic parameters to response (Pickles et al., 2005; Ah-See et al., 2008; Wasser et al., 2003), while others show more moderate results (Padhani et al., 2006; Loo et al., 2008). In Paper III, a decrease in RSI and AUC were found for responders after only one cycle, which can be explained as reduced perfusion in tumor as an indirect effect of treatment. In Paper IV an increase in v_e was found for all patients after treatment which is similar to the results in the pre–clinical studies. This could also be interpreted as increased EES after cell death. For an overview of selected publications on early treatment evaluation with MRI, see Table 5.1. Large variation can be found in study design, MR system used, imaging methods and analysis methods. There are also variations in the definition of response, from clinical evaluation to pathologic confirmed response, and this will have a great impact on the results in the different studies.

DW–MRI was used for treatment monitoring in the clinical study, and also in MCF7 xenografts as shown in Figure 5.2. Three days after treatment with docetaxel the ADC median values increased significantly compared to control tumors. Measurement of water diffusion during therapy has been proposed as a more direct measure of treatment response, as diffusivity is restricted by e.g cell membranes, and may be correlated to cellularity (Lyng et al., 2000). Thus the increase in ADC may be explained as degradation of cell membranes due to cell death, and reduced cell density caused by inhibition of proliferative cells.

DW–MRI of breast cancer patients also showed a significant increase in ADC values after treatment (Paper IV). This result is in agreement with other published studies, that also propose a correlation to degree of tumor response (Pickles et al., 2006; Sharma et al., 2008; Iacconi et al., 2009). As for the pre–clinical study (Figure 5.2) the ADC measurements reflects direct effects as cell damage and death after chemotherapy. Despite challenging imaging of the breast with EPI sequences sensitive for eddy current artifacts and fat

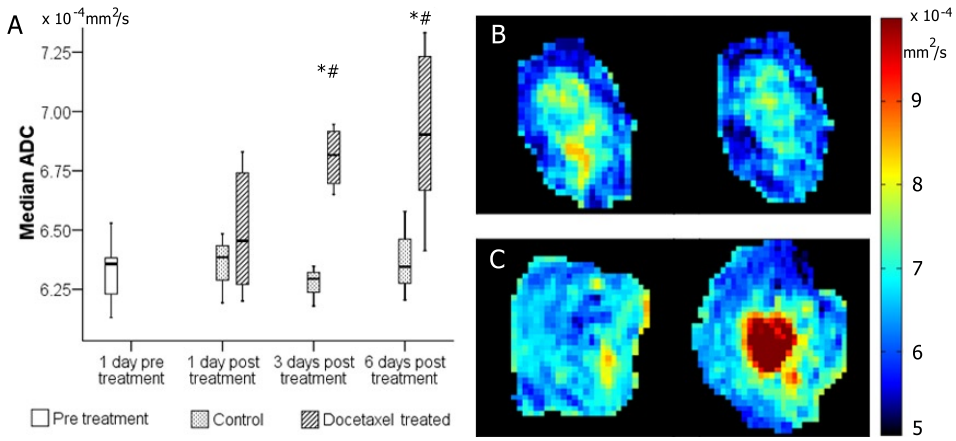

Figure 5.2: A, Progress in median ADC 1 day before treatment and 1, 3, and 6 days post treatment. # significantly different (Dunnet) compared to before treatment, * significant difference (t–test) between treated and control on the same day. B and C: ADC maps from a control tumor and a treated tumor 1 day before treatment and 3 days post–treatment. Note the higher ADC values in the treated tumor. From Huuse, Jensen et al., submitted 2009

shift, this seems like a promising tool for evaluating treatment response in breast tumors.

MRS is a promising method for monitoring metabolism *in vivo* at the same session as MRI. In the pre–clinical study of MCF7 xenografts in Paper II, a change in the metabolic profile after docetaxel treatment was demonstrated, both with *in vivo* MRS and *ex vivo* HR MAS MRS of the same tumor samples. Relatively lower signals from choline compounds were detected for the treated tumors, and can be explained by reduced proliferative activity, reduced cell density and increased cell death. These results are in agreement with other studies, where the choline metabolism has been of special interest with respect to tumor progression, proposing choline compounds as biomarkers both for malignancy and treatment effect (Eliyahu et al., 2007; Sitter et al., 2006; Glunde et al., 2006). MRS is a powerful tool with possibilities for longitudinal studies, quantification and for understanding response mechanisms. This has been and are further studied in our research group (Bathen et al., 2007; Bakken et al., 2001; Cao et al., 2009).

5.7 DCE–MRI and prognosis

A strong prognostic factor for breast cancer patients with primary inoperable disease is a complete pathologic response after NAC. MRI derived parameters may also be correlated to survival in this patient group, and was assessed in Paper III. Only a few additional studies with this focus have been published, and they all report a correlation between contrast enhancement parameters and survival (Pickles et al., 2008; Boné et al., 2003). Generally, patients with large tumors and high degree of contrast enhancement will be expected to have shorter overall survival. Both Paper III and an extended study of the patient cohort[3] showed that a higher pre–treatment contrast enhancement as assessed with RSI or curve types was correlated to poorer prognosis. This confirmed previous findings by Pickles et al. (2008), where both tumor volume and enhancement parameters were found to correlate to overall survival. In a study by Boné et al. (2003), patients with primary malignancy were examined pre–operatively, resulting in a different patient population than the other studies. However, despite poor temporal resolution (6 minutes), the findings were similar showing high contrast enhancement and larger tumor volumes for patients with shorter survival.

At the time of diagnosis a long process of tumor progression has formed the individual patient's cancer disease, and the tumor characteristics at this time point are the basis for evaluating patients' prognosis. One of the most important steps in tumor progression is the neoangigenic switch. When the tumor adapts the ability to initiate neoangiogenesis, blood vessels will supply the tumor cells, and one important premise for metastatic ability is "ensured". Highly proliferative and aggressive tumors are often highly vascularized, and associated with high degree of contrast enhancement. Thus, *in vivo* measurements of the angiogenic conditions in tumors could contribute to each patients prognosis, as measured by DCE–MRI (Jensen et al., 2009). DW–MRI could also play an important role as prognostic factor in breast cancer, and is an interesting topic for future studies.

[3] MG Heldahl et al. Prognostic value of pretreatment dynamic contrast–enhanced MR imaging in locally advanced breast cancer: overall survival predicted from single voxel classification of signal intensity time course data. Submitted 2009

5.8 Conclusion and future perspectives

In this thesis, MR protocols for assessing treatment effects in both pre–clinical and clinical studies have been established. The MR methods were DCE–MRI with pharmacokinetic analysis, DW–MRI, *in vivo* MRS and *ex vivo* HR MAS MRS. Differences in tumor vascularity were detected with DCE–MRI, both in breast cancer xenografts treated with docetaxel and in colon cancer xenografts influenced by the dietary fatty acid TTA. In breast cancer patients with locally advanced disease, changes in vascularity were also observed after only one cycle of NAC, although the pattern here were more diffuse. A correlation between DCE–MRI before treatment and survival was found for the same patient group. Furthermore, ADC parameters calculated from DW–MRI was significantly increased after therapy, both for MCF7 xenografts and for breast cancer patients. This could be a powerful measure for tumor response, more directly related to treatment effects compared to DCE–MRI. Differences in metabolism were seen with MRS in the breast cancer xenografts, with a relative decrease in choline compounds as the most dominating change.

For pre–clinical studies, MRI and MRS will still play an important role in characterizing tumor models and understanding mechanisms of therapy. The work with tumor model systems has developed in our research group, to new orthotopic breast cancer models. With the basis of the MR protocols presented in this thesis, these model systems are now being used to investigate new treatment regimes, as anti–angiogenic therapies. By using several tumor models, the diversity in human tumors can be elucidated, and further studies of the variation in treatment response between apparently similar tumors can be performed. The unique possibility for combining several MR methods during one examination may provide an important tool in evaluation of complex treatment effects in these tumor model systems.

For clinical MRI of breast cancer, derived parameters may be potential biomarkers for more individualized therapy, however this must be further explored to enhance sensitivity and specificity. Studies that investigate the reproducibility of DCE–MRI parameters have been published (Ah-See et al., 2008), however this should be done in a larger scale to adjust the clinical value of the method as a routine diagnostic tool. The trend moves toward using higher field strengths both for research and in the clinics, although the impact on sensitivity and specificity for both diagnosis and assessment of treatment response is not clear. This will among other factors depend on how the increased SNR is used, like improved temporal or spatial res-

olution in DCE–MRI. Studies addressing these questions would be highly relevant, as comparing 1.5 Tesla versus 3 Tesla in clinical trials. In addition, the use of combined sequences that can reconstruct both high temporal and high spatial resolution data from the same MRI acquisition has also evolved as promising (Han et al., 2008), although the quantitative reliability from these acquisitions should be compared to standard measurements. Several large multi–center trials are ongoing and are including breast cancer patients scheduled for NAC, as the ACRIN and MARIBS trials (Mann et al., 2008). DCE–MRI is performed before and after two cycles of treatment, and the results will be valuable for the future use of DCE–MRI in assessment of locally advanced breast cancer. For DW–MRI, including this acquisition in standard breast MRI may increase the information from the examinations. The use of ADC values in treatment monitoring seems feasible, however more investigations should be done to increase the knowledge of this promising parameter. Comparisons between systems and different methods need to be done, and improvements on imaging methods to increase SNR and decrease slice thickness should be prioritized.

The clinical studies designed today will be relevant for several years, when overall survival and disease free survival can be assessed. Thus providing high quality MRI data today is of great importance, such that new prognostic markers for locally advanced breast cancer can be established.

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131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.

138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.

166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
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169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
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183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
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186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS

197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE

222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
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227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
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232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS

249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
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266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES

278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
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292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY

303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
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308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
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