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MR determined brain metabolic pattern in patients with brain metastases and adolescents with low birth weight

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Sammendrag

In vivo MR spektroskopi (MRS) er en teknikk hvor biokjemisk informasjon kan hentes ut fra et definert volum, ofte på størrelse med en sukkerbit. Volumet velges ut anatomiske MR bildene tatt av pasienten på forhånd, og opptaket av et spekter gjøres i løpet av få minutter. Denne avhandlingen som består av fire studier, er basert på ideen om at MRS kan være et tilleggsverktøy i den kliniske hverdagen. I den første studien er MRS brukt i studie av ungdommer født med ekstra lav fødselsvekt i forhold til barn med normalvekt, mens i de tre siste studiene er det fokusert på kreftpasienter. Multivariat dataanalyse er benyttet for å klassifisere MR spektrene.

Ekstra lav fødselsvekt har vist seg å innebære en risiko for senere utvikling av nevrologiske lidelser. Artikkel I oppsummerer en studie av ungdommer med forskjellig fødselsvekt undersøkt med MRI og in vivo MRS av venstre frontallapp i hvit hjernesubstans. For å avdekke forskjeller av betydning i fordeling av hjernemetabolittene er det brukt både forholdsberegninger (ratio) og multivariat dataanalyse til analyse av. Klassifiseringen av ungdommene ble basert på forskjellene i de metabolske mønstrene som bare ble observert i de multivariate analysene. Resultatene var i overensstemmelse med observasjonene gjort i tidligere studier av barna, med hensyn på motoriske egenskaper og psykiatriske symptom.

Forskjellene i MR spekter av friskt og sykt vev er ofte så tydelige at man ved enkle metoder som for eksempel beregninger av metabolittforhold, kan klassifisere dem. Eksempler på slike spekter er vist i artikkel II, hvor både friske frivillige og pasienter med hjernemetastaser ble brukt til å vurdere effekten av økt magnetfeltstyrke. I denne artikkelen var målet å finne ut i hvor stor grad signalintensiteten (SNR) og oppløsningen i spektrene fra 3T-systemet ble forbedret i forhold til det som ble oppnådd ved 1.5T-systemet. Resultatene basert på beregning av metabolittforhold, viser at den spektral oppløsningen ble forbedret med 25 % i alle spektrene. Økningen i SNR var varierende og i mindre grad enn forventet. Dette kan forklares med ulike definisjoner for volumdefinisjon på de to ulike MR systemene, noe som gav mindre effektiv volumstørrelse ved 3T, til tross for lik volumstørrelse. Forskjellene var størst

ved kort ekkotid (TE 32), slik at det ble mindre økning i SNR ved økt magnetfeltstyrke, sammenlignet med lang ekkotid (TE 144).

Hjernemetastaser er blitt klassifisert som egen gruppe forskjellig fra de fleste primære hjernetumorer. De kan stamme fra mange typer primærkreft, men pasienter med lunge-, bryst- eller hudkreft (malignt melanoma) er blant de som oftest utvikler hjernemetastaser. Histologiske undersøkelser av vevsprøver fra metastasene viser ofte at de har likhet med den opprinnelige kreftsvulsten, noe som er med på å bestemme videre behandling av pasienten. Dersom in vivo MRS kan gi samme informasjon, vil det ha betydning for raskere valg av behandling og oppfølging uten kirurgisk inngrep. En hjernemetastase kan være første symptom på kreft hos en pasient og en klassifisering av denne kan spore opp den primære kreftsvulsten. Når operasjon er en del av behandlingen kan en høyoppløselig ex vivo MRS vevsanalyse gi utfyllende informasjon til standard histologiske analyser. Tidligere studier med bruk av MRS på hjernetumorer har vist at de ulike krefttypene har særtrekk i sine metabolske mønster. I artikkel III og IV er spekter av hjernemetastaser, henholdsvis in vivo og ex vivo blitt analysert. Ved hjelp av prinsipalkomponentanalyse og regresjonsanalyse ble spektrene klassifisert i forhold til primær tumor og klinisk utfall fem måneder etter start av behandling. Resultatene viser en signifikant korrelasjon mellom metabolske mønster og klinisk overlevelse for pasientene. Klassifiseringen i forhold til type primærtumor var mindre tydelig, som kan skyldes få pasienter undersøkt i studiene. En utvidet studie med et stort antall pasienter vil derfor være nødvendig for å få en bekreftelse på disse funnene. Både in vivo og ex vivo MR spektroskopi gir metabolske bilder som kan få høy klinisk relevans.

Acknowledgement

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Torill Anita Eidhammer Sjøbakk

Abbreviations

BM	brain metastasis (-es)
b.w.	body weight
ca.	carcinoma
CHESS	chemical shift selective sequence
Cho	choline
CI	confidence interval
COSY	correlated spectroscopy
Cr	creatine
CSI	chemical shift imaging
FID	free induction decay
FFT	fast Fourier transform.
FWHM	full-width-half-maximum
GABA	γ-aminobutyric acid
Glx	glutamine and glutamate
GPC	glycerophosphocholine
HR MAS	high resolution magic angle spinning
IDC	invasive ductal carcinoma
jMRUI	java-based magnetic resonance user interface
KPS	Karnofsky performance status
Lac	lactate
MR	magnetic resonance
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MRSI	magnetic resonance spectroscopy imaging
NAA	N-acetyl aspartate acid
PBS	phosphate buffered saline
PC	phosphocholine
PCs	principal components
PCA	principal component analysis
PLS	partial least square
ppm	parts per million
PRESS	point resolved spectroscopy pulse
PNN	probabilistic neural network
RPA	recursive partitioning analysis
SGA	small for gestational age
SNR	signal-to-noise ratio
SR	stereotactic radiosurgery
SVS	single volume spectroscopy
T	tesla
tCho	total choline containing compounds
TE	echo time
TR	repetition time
TSP	trimetylsilyl tetradeuteropropionic acid
VLBW	very low birth weight
VOI	volume of interest

List of papers

The thesis includes the following four original papers which will be referred to by their Roman numerals:

I
Bathen T.F., **Sjøbakk T.E.**, Brubakk A.M., Skranes J., Vik T., Martinussen M., Myhr G., Gribbestad I.S., Axelson D.E. *Cerebral metabolite differences in adolescents with low birth weight. Assessment with in vivo proton MR spectroscopy.*
Pediatric Radiology (2006) 36:802-809.

II
Sjøbakk T.E., Lundgren S., Kristoffersen A., Singstad T., Svarliaunet A.J., Sonnewald U., Gribbestad I.S. *Clinical ^{1}H MR spectroscopy of brain metastases at 1.5T and 3T.* Acta Radiologica (2006) 47 (5): 501-508.

III
Sjøbakk T.E., Johansen R., Bathen T.F., Sonnewald U., Kvistad K.A., Lundgren S., Gribbestad I.S. *Metabolic profiling of human brain metastases using in vivo proton MR spectroscopy at 3T.* Submitted BMC Cancer, 2007.

IV
Sjøbakk T.E., Johansen R., Bathen T.F., Sonnewald U., Juul R., Torp S., Lundgren S., Gribbestad I.S. *Characterization of brain metastases using HR MAS spectroscopy.*
Accepted by NMR in Biomedicine, 2007. In press.

Summary

The clinical applications of MRS have become a supplement to MR imaging (MRI) for diagnosis and treatment monitoring of several pathologies. In this thesis MR spectroscopy (MRS) has been used to assess brain metastases in adult cancer patients and cerebral metabolites in frontal lobe of adolescents.

Children born with very low birth weight are at risk of later neurodevelopment problems. Adolescents with different birth weight were examined using MRI and MRS and multivariate analyses for assessing differences in cerebral metabolites. The results from the multivariate analyses were consistent with observations in earlier published MRI findings, motor skills, psychiatric symptoms and disorders detected in the same participants. The classification of the adolescents was based on metabolic pattern differences which were only explored by the multivariate analyses. When the spectral information shows small or complex differences the interpretations become a challenge. In three of the four papers in this thesis, multivariate analyses were used as a tool to interpret the spectral information.

Brain metastasis is the dominating type of brain tumors which represent an oncologic challenge. The incidence of brain metastases is probably increasing due to improved treatment strategy of patient with primary cancer, prolonging their survival and brain metastases get time to develop. In some cases patients have an unknown primary cancer or several primary cancers. If MRS could provide metabolic information about brain metastases especially in differentiating it from the primary cancer, it might be a supplement to the conventional diagnostics and could help to optimize the cancer treatment. In the two last papers in vivo and ex vivo MRS of brain metastases were obtained before treatment and the spectra were analysed by using both principal component analysis and regression analysis. The spectra were classified according to primary cancer and clinical outcome five months after start of treatment. The results showed a significant correlation of spectral findings and clinical outcome of brain metastases patients.

From the MR theory, signal-to-noise ratio and resolution in MR spectra should increase by a factor of two with double the magnetic field strength. Different studies using in vivo MRS have shown that the situation varies. In Paper II the effect of increased magnetic field from 1.5T to 3T was investigated in spectra obtained in patients with brain metastases. The comparisons of spectral improvements in SNR and spectral resolution were made by ratio calculations. The gain was smaller than expected probably caused by various definitions of effective volume size at different clinical scanners.

In conclusion, in vivo and ex vivo MR spectroscopy can determine metabolic pattern on clinically highly relevant questions.

Introduction

Brain maturation

The brain and spinal cord constitute the central nervous system (CNS) which consists of mainly two types of cells; neurons (nerve cells) and neuroglia (glial cells). The hallmark of neurons is their specialization for electrical signalling over a range of distances. The neuroglia maintains the environment surrounding the neurons and they participate indirectly in signal transmission. Three types of glial cells have been identified in the CNS; astrocytes with great diversity of function, oligodendrocytes which form myelin around nerve cell extensions (axons) and microglia the defence cells near blood vessels. Myelinated nerve cells constitute the white matter while un-myelinated neurons form the grey matter in CNS (1).

Brain maturation is known as a complex and lifelong process where fetal development and childhood are of great importance. Histological evidence has shown brain development as a dynamic process of progressive and regressive changes. The entry of neuroimaging techniques such as magnetic resonance imaging (MRI) in the middle of the 1980s made it possible to study brain maturation in detail. MRI enabled longitudinal experiments and non-invasive investigations of living subjects. This has provided more detailed documentation of the large-scale changes within the brain (2). Brain maturation is characterized by changes in the myelination process, synaptic density and pathways of metabolism during the development from neonatal to adult brain. However, birth weight is an important factor in how successful this development will be. Follow-up studies of children with birth weight below 1500 g have documented increased prevalence of neurodevelopmental disabilities and cognitive deficits compared with children born at full term (3-5). Adolescents who had low birth weight have been studied by MRI and clinical assessment, showed correlation between cerebral abnormalities and psychiatric symptoms (6). Also, MR spectroscopy (MRS) provides a non-invasive tool for investigation of the physiology of the CNS and its postnatal development.

Brain metabolites

The chemical processes that occur when nutrients are absorbed to provide energy, build or repair body tissue and break down waste products to be extracted, are called metabolism. The chemicals involved are known as metabolites and some of them can be observed using MRS. The most prominent signals in water suppressed spectra from healthy brain tissue is due to N-acetyl aspartate (NAA), creatine (Cr) - and choline–containing compounds (tCho) (7-12). NAA appears as a singlet signal at 2.0 ppm in the spectra and decreases in diseases such as dementia, stroke and brain tumors where neuronal density and/or function are disturbed (13). The Cr signals at 3.0 ppm and 3.9 are due to both creatine and phosphocreatine (PCr) in spectra from low field magnets typically used for in vivo spectroscopy (10). Cr is reported to represent the cells mitochondrial activity and to appear in higher concentrations in oligodendrocytes and astrocytes than in neurons (8,13). In abnormalities such as brain metastases, aggressive brain tumors and hypoxic tissue the Cr signals decreases (8). The signal at 3.2 ppm is caused by compounds which are not separable in in vivo spectra at low field. The peak includes signals from free choline, phosphocholine (PC) and glycerophosphocholine (GPC) and is referred to as total choline (tCho) (14). It is reported to reflect cell membrane synthesis and degradation and also to appear in higher concentrations in glial cells than neurons (8,13). Abnormalities like brain tumors, white matter diseases and stroke are characterized by an elevated tCho signal while necrotic tissue show a decreased signal (8,15). In pathological tissue also lactate (Lac) and lipids can be observed in proton spectra, often as overlapping peaks at 1.3 ppm. A strong Lac signal indicates anaerobic metabolism due to impaired oxygen supply which is often seen in brain tumors. Several signals represent methyl- (0.9 ppm) or methylene groups (1.2-1.4 ppm) of lipids/fatty acids which are normally only seen in spectra from diseased brain tissue such as tumors, stroke and demyelinating disease (7-9,11,16,17). Provided short echo time and sufficient magnetic field (> 3T) also metabolites such as glutamine and glutamate (Glx) at 2.2-2.4 and 3.6-3.8 ppm or glycine (Gly) at 3.56 ppm and myo-Inositol (mI) at 3.52 can be separated and observed in spectra in vivo (10,18) (Fig. 1). Ex vivo spectra from intact tissue or extracts obtained using high resolution instruments, give further metabolic information about these and many other metabolites due to

increased spectral resolution as demonstrated in Paper IV and several previous papers (10,19-21).

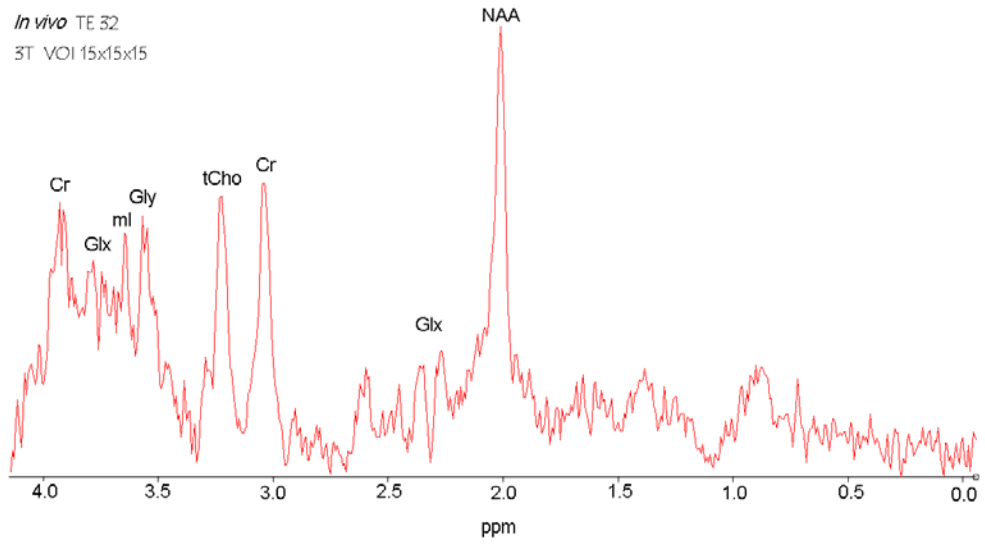


Figure 1. In vivo spectrum of healthy brain tissue (white matter) obtained at 3Tesla. Tentatively assigned peaks based on published chemical shift. Abbreviations are explained in the text above (MRI, MRS and processing parameters are described in paper II).

Brain metastases

Brain metastases (BM) are the dominating type of brain tumors and are most frequently caused by haematogenous spread from different primary cancers such as lung (40-50%), breast cancer (15-17%) and melanoma (10-11%) (22,23). BM often appear as multiple intracranial lesions in the cerebral hemisphere (80%), cerebellum (15%) or brain stem (5%) and the disease might change dramatically the patients' quality of life due to neurologic, cognitive and emotional difficulties (24-26). The patients represent a significant oncologic and health care providing challenge. Long-term survival after

development of BM is rare as median survival is estimated in months (23,27). The incidence of BM is expected to increase due to improved systemic treatment of primary cancers involving a larger number of patients who lives long enough to develop symptomatic BM. An increased incidence might also be a consequence of greater access to improved neuroimaging techniques and previously detecting small metastases (23,25,28,29).

All kinds of primary cancers are classified in subgroups related to the type of tissue or cells they originate from. The cancer cells might infiltrate into adjacent tissue and metastasize through the lymphatic system or hematogenous spread to distant organs, such as bone, liver, lung, or brain (30,31). The metastases are classified by the histopathological appearance and the medical terminology relates to the cell of origin (32). Malignant neoplasms of epithelial cell origin are called carcinomas which may be further classified after the tissue or organ of origin. Adenocarcinoma denotes a lesion in which the neoplastic epithelial cells grow in glandular tissue while squamous cell carcinoma denotes neoplasms in which the cells resemble stratified squamous epithelium. Metastases showing no distinct histopathological appearance are classified as undifferentiated carcinomas (32).

Certain primary cancers have a predilection to metastasize to the brain (22,33). Malignant melanoma and small-cell-lung carcinoma have been reported as the most aggressive contributors to secondary brain tumors while the metastasizing of breast and non-small lung carcinomas is not as pronounced. Patients with kidney or colon carcinoma are also within the risk group of developing BM, yet this is not as common as the cancer types mentioned above (33).

Diagnosis and treatment of brain metastases

Indications of elevated intracranial pressure or progressive focal neurologic signs, as well as an epileptic seizure in a patient with prior history of primary cancer are possible symptoms of brain tumors (25,26). In some cases BM cause the first symptoms of a

systemic cancer (34,35). The prognosis varies with type and grade of primary cancer, age and performance status at the time of diagnosis as well as extent of extracranial disease (28,35-37). Hence, identification of the origin of metastases is of clinical interest to get optimized treatment and control the systemic primary cancer (34).

In general, the use of non-invasive, neuroimaging modalities like magnetic resonance imaging (MRI) or computed tomography (CT) in brain tumor diagnosis is of great importance. A combination of MRI and MR spectroscopy (MRS) gives more detailed information and makes a further differentiating or classifications of brain tumors possible. However, a definite diagnosis can only be confirmed by histological analyses of tumor tissue samples. The specific diagnosis sets the guidelines for treatment strategies (Fig. 2). Provided surgically accessible, the treatment of single BM is most often surgical resection followed by radiotherapy and/or chemotherapy. Multiple and non-operable single BM might be treated by using whole brain radiation therapy (WBRT) and/or chemotherapy. Patients with BM and symptomatic peritumoral oedema are also treated with corticosteroids (33,38). Before any decision is made on treatment strategy the patient's performance status is evaluated. Karnofsky performance status (KPS) is one method of classification where KPS of 50 describes a person needing considerable help and medical care while a KPS 100 indicate a patient with no affliction or subjective symptoms of the disease (39). Three prognostic classes for patients with BM have been developed using recursive partitioning analysis (RPA) of a large database (40). The three-class system (Fig. 3) indicating clinical status involving the patient's KPS score, age, control of primary cancer, extracranial metastases and number of BM observed (36,40).

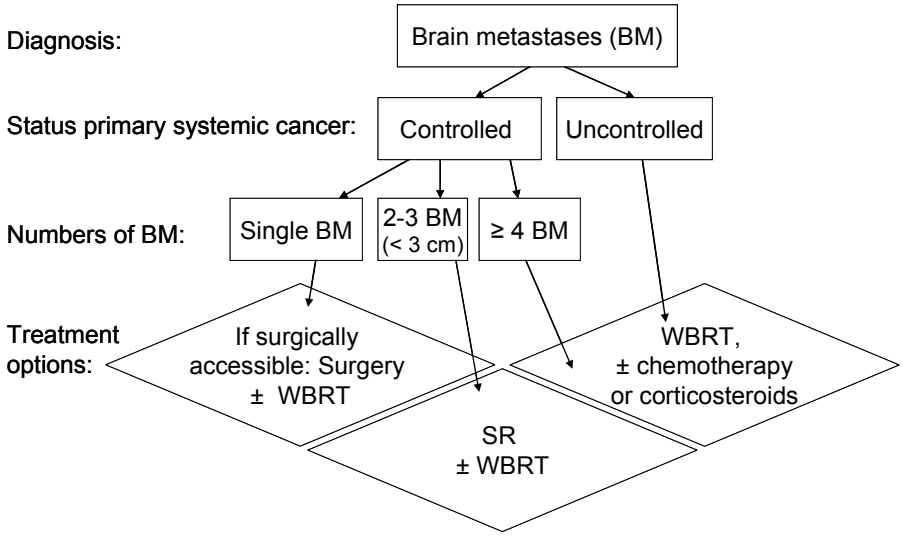


Figure 2. Simplified BM treatment decision diagram, modified after Ewend et al (27). SR: Stereotactic radiosurgery, WBRT: whole-brain-radiation therapy.

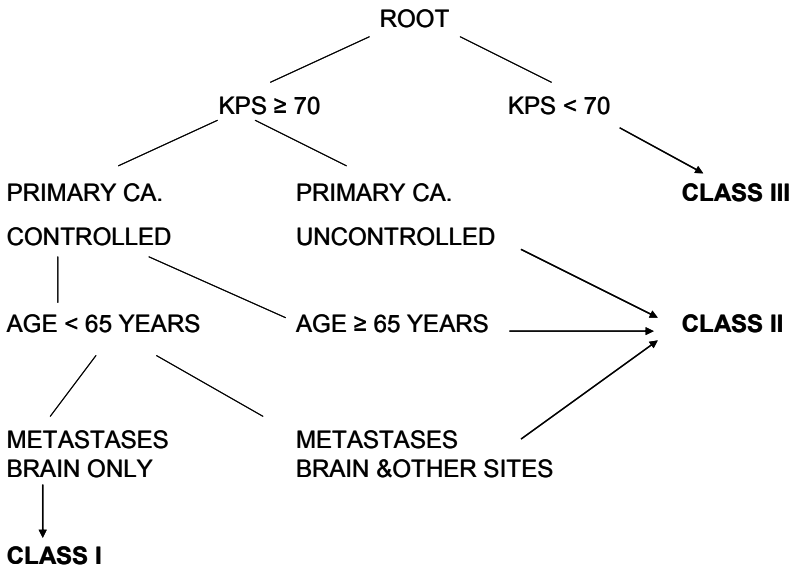


Figure 3. Scheme for RPA classification of BM patient (class I, II or III) modified after Gaspar et al. 2000 (36). KPS: Karnofsky performance status. Ca: cancer.

Histopathology

Histopathology is the gold standard for accurate diagnosis of tumor tissue samples. To prevent tissue degradation during storage, the samples are either frozen in liquid nitrogen or fixed in formalin. Microscopic sections are made and prepared for examinations by a pathologist. The histopathological investigations in this study include interpretation of tumor type and evaluation of any apoptosis, necrosis, gliosis, and fibrosis present.

Histopathological analyses reveal presumptive source of malignant tissue due to the cells characteristic, as well as tumor grade. Tissue samples of anaplastic carcinomas showing no distinct histological appearance are described as undifferentiated carcinomas. Apoptotic tissue is a result of programmed cell death which may occur after un-repairable cell damage or virus infection. The process can be induced by the cell itself, by the surrounding tissue or by the immune system. Apoptotic cells show several morphologic characteristic that can be seen under a microscope after appropriate staining. Necrotic tissue is a result of a non-controlled cell death called necrosis which can be seen in various pathological settings, such as malignant tumors, infarction and infection. Some malignant tumors induce a dense, abundant fibrous stroma, called desmoplasia (32,41). A phenomenon found in most pathological reactions where neuronal cell loss is involved, is the formation of gliotic tissue which consist of a dense fibrous network of proliferated astrocytes.

In vivo MRS

MRI was introduced as a clinical modality in the early 1980s and is now in worldwide use as a clinical imaging technique. No adverse biological effects from exposure to the magnetic fields or radiowaves used have been reported.

Gadolinium-enhanced MRI has become the most important imaging method for examination of brain tumors. BM appears as ring contrast enhancing lesions most often located in the gray-white matter junction. MRI combined with MRS might provide

evidence for cellular injury after traumatic brain injury, brain tumors not visible by conventional imaging techniques, and detailed characterization of lesions (16,17,42,43). A spectrum obtained from a chosen volume of interest (VOI) with standard gadolinium-enhanced MR images in all three planes of orientations are presented in Fig. 4.

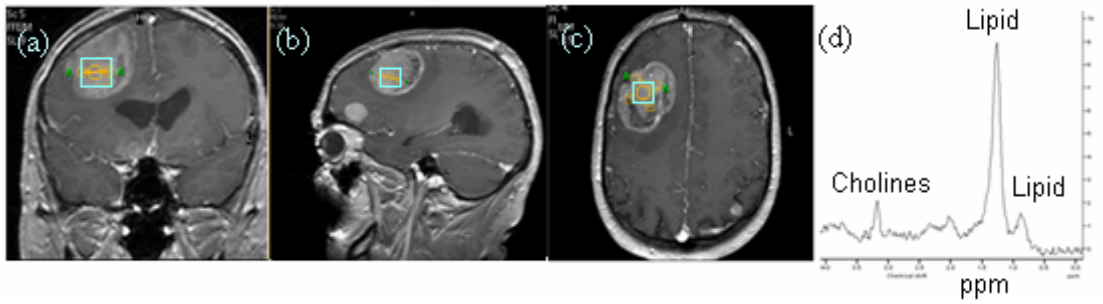


Figure 4. (a) Coronal, (b) sagittal and (c) axial planes of gadolinium-enhanced T_1-weighted MRI at 3T of a patient with BM from malignant melanoma, showing the VOI localized within one of the observed metastases. A short echo time spectra obtained in the VOI is presented (d).

MRS allowing investigations of brain metabolism in vivo is of great importance where resection of tissue for ex vivo analyzing is undesirable or unobtainable. Examination of proton (^{1}H) and phosphorous (^{31}P) are the most important nuclei used in clinical systems. However, proton spectroscopy is the preferred method due to the widespread distribution of proton in most compounds and because it has the sensitivity to provide adequate signal-to-noise ratio (SNR) from small VOI. It is also easier to apply using standard MRI systems.

To obtain high quality spectra some requirements must be fulfilled. First, a well shimmed static field is needed, secondly water suppression must be performed (due to the huge amount of abounded proton) and at last localization scheme must be used (44-46). On standard clinical MR systems the optimization of linewidths is done using an autoshim procedure developed by the system vendor. Water suppression might be

performed using the chemical shift selective sequence (CHESS) where presaturation pulses are used, or other techniques. The localization sequence PRESS (point resolved spectroscopy pulse) uses spin echo sequences which provide optimal signal-to-noise-ratios.

In vivo spectra might be obtained from single VOI or by multi-voxel spectroscopy (MRSI) from single or multi slices using long or short echo times (TE). Metabolites relaxation time (T_2) decides whether they are spectroscopic visible or not. Large molecules such as lipids move slowly and their T_2-values are short, hence these metabolites are observed only in short echo time spectra. Also the repetition time (TR) is important, since short TR might cause saturations and bad spectrum quality. Single volume MRS is particularly suited for studying lesions like brain tumors due to the short acquisition time needed. When an overall view of brain metabolism or investigations of brain tumors heterogeneities are needed MRSI will provide spectral data with spatial information (47).

The clinical applications of in vivo ^{1}H MRS have involved examination of a variety of diseases or abnormalities, from pediatric brain maturations differences to breast or prostate cancer and neurological disorders (11,48-50). MRS can classify brain tumors into different subgroups such as glioblastomas, astrocytomas and BM (7,51,52). Studies of cancer treatments effect have been performed using both single volume MRS and MRSI. Observed changes in metabolite ratios were interpreted as treatment effect (53,54). Appropriate analysis and interpretations of MR spectroscopic data have been proposed in previous work as additional tool together with more traditional clinical findings for predicting survival of patients with gliomas (55,56).

High resolution magic angle spinning (HR MAS)

High resolution magic angle spinning (HR MAS) is an ex vivo MRS technique which has become important for analyzing metabolic information from intact tissue specimens of different origins (57-62). Several metabolites have been identified and an example of

a typical HR MAS spectrum some is given in Fig. 5. Comparisons of HR MAS and conventional MR spectra of perchloric acid extract have reported similar results (20,62). The clue of the MAS method is the tilting of the solid sample by an angle of 54.7º to the direction of the static magnetic field and by spinning the sample at great speed about its own axis, the line broadening of signals is reduced due to a reduction of the anisotropic interactions in the tissue (63-65). Large molecules such as lipids have short T_2-relaxation time and might still appear as broad signals. These signals can be reduced in spin echo sequences, resulting in even better resolved spectra (66).

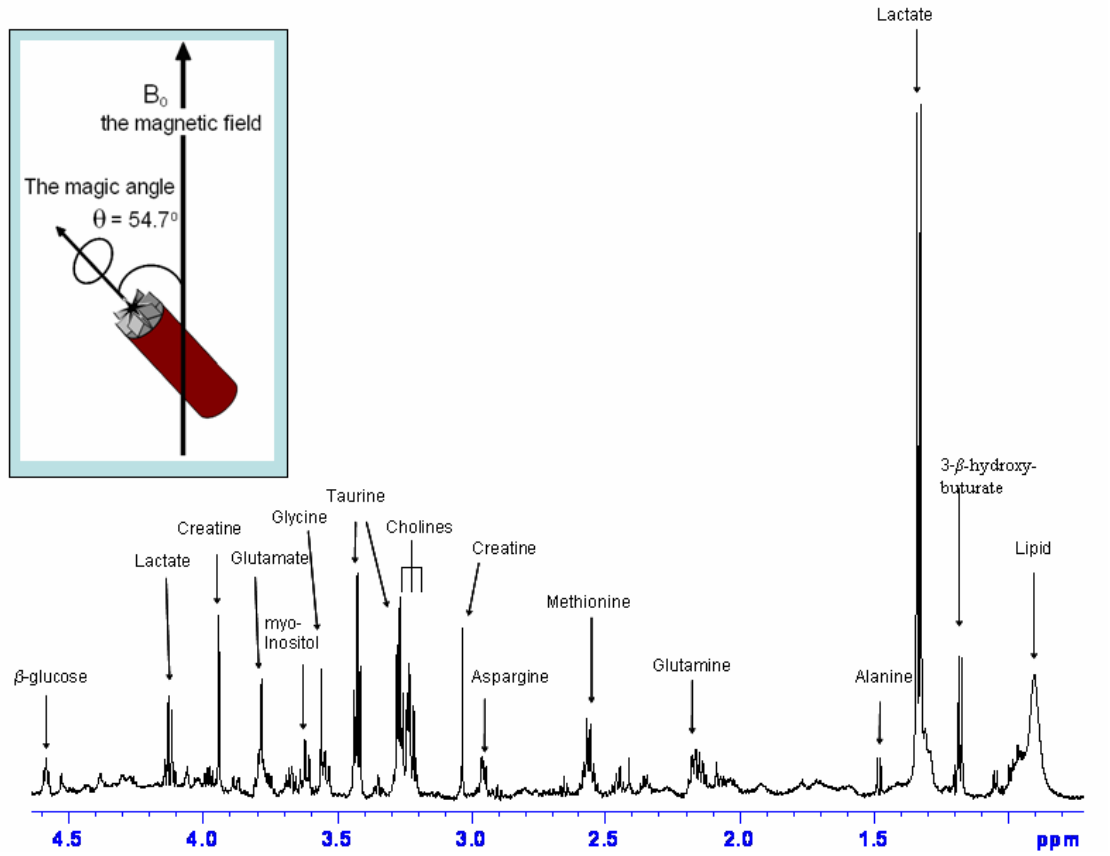


Figure 5. HR MAS spin echo spectrum (TE 32 ms) from brain metastasis of lung carcinoma, showing a selection of identified metabolites. *In frame:* Schematic presentation of magic angle spinning (MAS) principle (with permission from B. Sitter).

Assignments of spectra from biological samples are based on comparisons of peaks multiplicity and chemical shift with previously reported values (10,20,62). A one-dimensional (1D) spectrum as shown in Fig. 5 might be too complex for complete interpretation due to numerous metabolites. However, using an additional spectral dimension more detailed information becomes available. Two-dimensional (2D) homonuclear correlated spectroscopy (COSY) gives information originated from neighbour nuclei's interactions and their chemical shifts are extracted (Fig.6).

Examination of intact tumor tissues using HR MAS analysis has been suggested as a supplement to histopathology and a contribution to improve brain tumor diagnosis (57,58,67). The similarities between ex vivo and in vivo spectra found in studies of different primary brain tumors allow a better interpretation of in vivo MR spectra (20,61,68-70). Recent studies have shown that HR MAS metabolic phenotypes correlate to clinical parameters both in breast and prostate carcinoma (67,71).

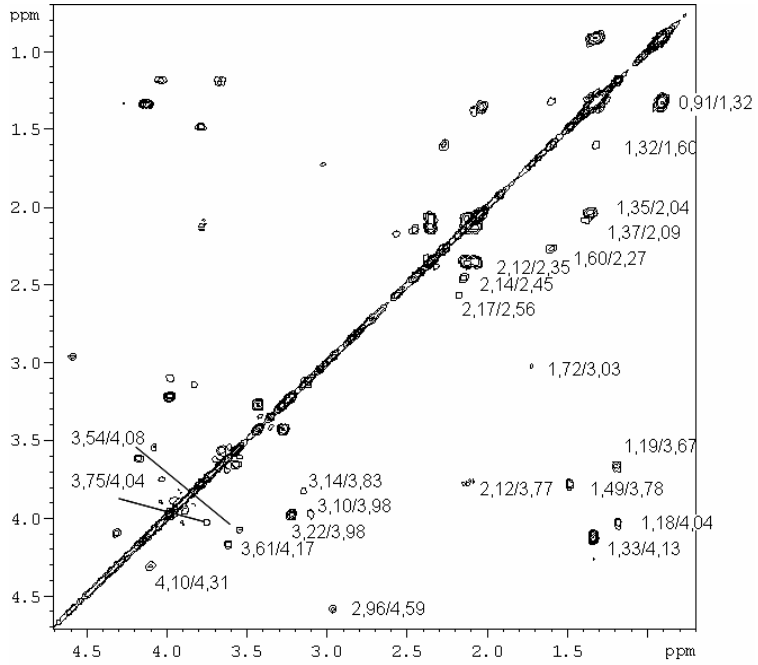


Figure 6. HR MAS 2D correlated spectroscopy obtained in intact tissue sample of BM from breast carcinoma. The numbers indicate chemical shifts for the observed cross peaks between neighbouring molecules.

Multivariate analyses

Multivariate analyses constitute an important statistical help to interpret complex data sets such as spectroscopic data (72). The use of multivariate analyses are mainly based on three groups of purposes; exploration, classification and prediction of spectral data. Both supervised and unsupervised methods are established. Unsupervised methods group the samples on basis of input variables only and are typically used for exploration and classification. Principal component analysis (PCA) is such a method, while principal least square (PLS) regression and probabilistic neural network (PNN) are examples of supervised methods. These methods utilize prior knowledge about pattern, groups or other measured variables directly in order to provide predictions, e.g. of outcome. Establishment of an adequate model, based on representative samples, makes a prediction of values from unknown samples possible.

PCA, compresses or simplifies high-dimensional data by finding a linear combination of the original variables so the variance is maximized and new uncorrelated variables, principal components (PC) are created. The resulting score plots and loading profiles visualize the differences and correlation between the samples. The score plot of PC1 and PC2, or PC3 gives the main information content in the data set. The correlations between the variables and PCs are called the PCs loadings. The loading profile for each PC give the importance of each variable or metabolite for the variation described.

PLS regression finds correlations between two data sets simultaneously, by using one set of variables to predict another. The spectral data are reduced into PCs which explain most of the variation in both predictors (MR spectra) and responses (e.g. clinical parameters). The regression coefficients summarize the relationship between all predictors and the given response(s). Classification based on differences between several classes with PLS is called PLS-discriminant analysis (PLS-DA). For both PCA and PLS the explained variance is measured as a percentage of the total variance in the data. It is the proportion of variation in the data accounted for by the current PC. The total residual and explained variance indicates how well the model fits the data set. An

optimal model shows explained variance close to 100 % and residual variance close to zero with few components (PC's) (72).

PNN is a type of radial basis network suitable for classification problems. PNN networks are organized in three layers: input, pattern and summation. The input layer has as many elements as there are individual parameters (selected chemical shift region) needed to describe the samples to be classified. The pattern layer organizes the training set such that an individual processing element (neuron) represents each input vector. The summation layer has as many processing elements as there are classes to be recognized and simply collects the outputs from all hidden neurons of each respective class. The products of the summation layer are forwarded to the output (one neuron for each data class), where the estimated probability of the new pattern being a member of that data class is computed. The stopping criterion involves minimizing the average percentage of incorrect classifications over all categories.

Validation of a model is important for evaluation of its modelling ability. An estimation of expected error when fitting new, similar data to the model is then made. Use of a separate test set is the optimum choice, but in practice not always obtainable. One of the major considerations in model development is that the training set must contain the extremes of the behaviour of the patterns associated with each class since the methods do not extrapolate. Thus, randomly selection of samples for external validation has limitations that can be mitigated by ensuring that the training data set is optimized with respect to this requirement. This can be done by using an algorithm such as the Kennard Stones, for splitting data sets into two subsets; calibration and test sets (73). Both subsets of samples have to be representative for the original data set to avoid high prediction error and a bias. Another option in validation is to simulate a test set by using full cross validation (leave-one-out), where the same samples for both estimation (calibration) and testing (validation) the model are used. During this process of modelling one sample is kept out while the calibration is performed on the rest of the samples. Values are then predicted for the left-out sample and prediction residuals are calculated. The process is repeated until all samples have been kept out once. Finally all prediction residuals are combined to find the overall root mean square error of

prediction (RMSEP). The number of PCs to retain in the model should be determined by the PC where RMSEP and residual variance are minimized (72).

Aims of present work

The main objective of this thesis was to investigate the feasibilities of proton MRS in four different studies as follow:

1. Implement multivariate analyses for assessing differences in cerebral metabolites in adolescents with low birth weight assessed by in vivo MRS at a 1.5T clinical system.

2. Address the effect of increased magnetic field from 1.5T to 3T, regarding signal-to-noise ratio and spectral resolution in spectra obtained in patients with brain metastases.

3. Investigate the benefits of in vivo MRS in characterization of brain metastases and correlation to clinical outcome.

4. Assess metabolite profiles of brain metastases using ex vivo HR MAS MRS and relate the spectral data to clinical outcome for the patients.

Materials and methods

A summary of the different MR systems and data analyses used in the four presented papers is given in Fig. 7.

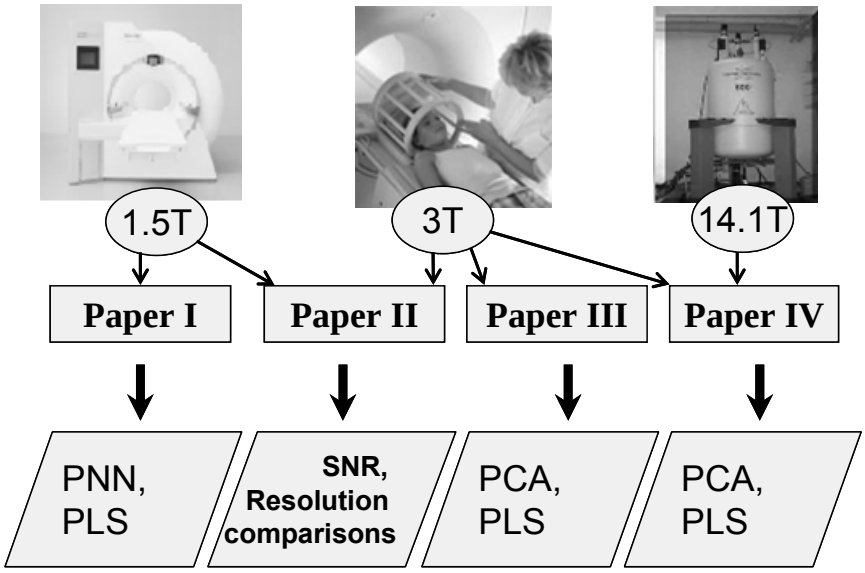


Figure 7. Schematic presentation of the MR-systems with different magnetic field strength and data analyses used in this work: PNN: probabilistic neural network, PLS: partial least square regression, PCA: principal component analysis and SNR: signal-to-noise ratio used in the different papers (I-IV).

Patients and healthy volunteers

The subjects in Paper I were enrolled during the period of year 2000-2003 in a follow-up study of 14-years old adolescents with different birth weights, including in vivo MRS as one of several examinations (74-77). During 1.5 years the patients for studies II-IV were recruited among cancer patients at St.Olavs Hospital in Trondheim with diagnosis BM. The inclusion criteria were the diagnosis and patient's age (> 18 year).

All projects in this thesis were approved by the Regional Committee for Medical Research Ethics. The enrolled patients and healthy volunteers gave written informed

consent to participate. For the study in Paper I, both the adolescents and their parents signed the informed consent.

Tissue samples

Tissue samples from different BM examined by HR MAS MRS are presented in paper IV. The tissue samples obtained from patients undergoing scheduled surgical resection were stored in liquid nitrogen immediately after dissection. In order to prevent biochemical and structural degradation the specimens were kept at this temperature until further analyses were made. In order to maintain the tissue frozen as much as possible the preparation were performed mostly on ice. The samples were sliced to fit the MAS rotor (4 mm o.d., 50 µl) filled with PBS-buffer (40 µl, a mixture of trimetylsilyl tetradeuteropropionic acid (TSP, 1mM), sodium formate ($CHNaO_2$, 1mM), and phosphate buffered saline (PBS) in deuterium water (D_20)). Excess PBS-buffer was removed when assembling the rotor. The mean ± SD sample weight was 10.0 ± 4.0 mg.

Histopathology

Routine histopathological were performed of tumor tissue from all patients. During surgery one part was sent for this analysis, while another part was analyzed after the HR MAS examinations. The histopathological information used in this work where the diagnosis from the routine histopathology and tissue composition of the HR MAS sample, such as the fraction of tumor, necrosis or other types of tissue.

In vivo MRS

Clinical MR systems with standard clinical head coils at both 1.5T (Siemens Magnetom Symphony, Erlangen, Germany) and 3T (Philips Intera, Best, The Netherlands) were used in Paper I, II and III. The examinations of patients and healthy volunteers were performed by radiographs. Patients were examined using intravenous contrast injection of 0.1 mg/kg b.w. Gadodiamide (Omniscan^{TM}, GE Healthcare).

The MRI protocol consisted of conventional T_1 - and T_2 - weighted images in all three directions (transversal, sagittal and coronal plane) before single voxel ^1H MRS was performed on a localized VOI. MRS was performed using the point resolved spectroscopy pulse sequence, PRESS, with 2000 ms in repetition times (TR) and different echo times (TE 30/32/135/144 ms). If necessary the volume was slightly rotated to optimize the VOI selection and reduce possible partial volume effects. Phantom measurements in Paper II were performed as quality checks of the examinations using the same sequences. The phantom consisted of an agar-mixture containing N-acetyl aspartate acid (NAA), choline (Cho), creatine (Cr) and lactate (Lac) which are compounds known as brain metabolites observed in spectra of healthy brain tissue (78-80).

The spectra were processed using the program "java magnetic resonance user interface", jMRUI (81,82). The FID was zero-filled to doubled number of points and a Lorentzian filter of 2Hz was applied before Fast Fourier Transformation (FFT). To suppress the residue peak of the water signal, Hankel Lanczos Singular Values Decomposition Filter (HLSVD) was used. Chemical shift referencing was set relative to the tCho signal at 3.2 ppm. Finally, the algorithm AMARES was applied to estimate the linewidth of each metabolite peak in the spectra (81,82).

HR MAS MRS

The HR MAS spectra were obtained using a Bruker Avance DRX600 spectrometer equipped with a $^1H/^{13}C$ HR MAS probe with magnetic field gradients aligned with the magic angle axis. The spin rate for all experiments was 5 kHz and the temperature within the probe was fixed at 4°C. A single pulse experiment (zgpr; Bruker) and spin echo experiments (cpmgpr; Bruker) using effective echo times of 32 and 285 ms were performed with water presaturation (83). All spectra from these one-dimensional experiments were obtained within 1 h and 30 minute. Immediately after the HR MAS

analysis the tissue specimens were fixed in formalin for subsequent histopathological examinations.

Two-dimensional homonuclear correlated spectroscopy (COSY) were performed to assist the spectral assignment of the one-dimensional spectra. The COSY spectra were zero-filled and multiplied with a sine window function in both dimension before Fourier transformation. Also previous reported HR MAS spectra were used to assist the spectral assignment (20,62,84,85).

The HR MAS spectra were processed using the program WIN-NMR (Bruker). Before Fourier transformation the FID was multiplied with a 0.3 Hz exponential line broadening. Chemical shift referencing was performed relative to the TSP signal at 0 ppm.

Multivariate analyses

Different methods of multivariate analyses were used in this work (Fig. 7). All spectra were checked and approved regarding technical quality criteria (FWHM of the water peak signal) before they were converted to ASCII-files and transferred to the software program Unscrambler (CAMO, Norway) (Paper III and IV) or Neuroshell Classifier (Ward System Groups)(Paper I). The chemical shift range of interest was selected and the spectra were either peak aligned with an algorithm (Paper I) or calibrated (Paper III and IV) to adjust for small chemical shift differences. Peak alignment was considered unnecessary for the spectra in Paper III and IV, since the PCA and PLS results showed no chemical shift variations within the three and four first PCs, respectively. Finally, baseline offset was corrected and the spectra mean normalized in order to eliminate the differences in sample weight (ex vivo spectra) or volume size (in vivo spectra) before the multivariate analyses were performed.

PCA was applied in order to identify clustering of spectra due to origin of metastases based on examination of score plots and loading profiles (Paper III and IV). The

chemical shift regions selected in these studies were the resonances from 3.4 - 0.7 ppm and 4.7 – 0.7 ppm, respectively. On the same spectral data PLS was applied in order to relate clinical outcome of the patients (survival or not at five months after first MR examination) to the spectral data (obtained at first MR examination) (Paper III and IV).

Both PNN and PLS-DA were used to compare in vivo ^{1}H spectra obtained from white matter in frontal lobe of adolescents with low birth weight and controls (Paper I). Only the chemical shift region containing the resonances from NAA (2.0 ppm), Cr (3.0 ppm) and tCho (3.2 ppm) were selected for these analyses.

General statistical analyses

Non-parametric tests were also applied to evaluate spectral differences. The Kruskal-Wallis test was used to compare means of metabolite ratios in Paper I, while Mann-Whitney U test was used to compare SNR and resolution differences between the spectra obtained at different magnetic field strength in Paper II. The significance of the estimated correlation factors between measured and predicted y-variables in both Paper III and IV was ascertained by using the Pearson correlation test (two-tailed).

Summary of results; the individual papers

Paper I

Bathen T.F., **Sjøbakk T.E.**, Brubakk A.M., Skranes J., Vik T., Martinussen M., Myhr G., Gribbestad I.S., Axelson D.E. *Pediatric Radiology (2006) 36: 802-809.*

CEREBRAL METABOLITE DIFFERENCES IN ADOLESCENTS WITH LOW BIRTH WEIGHT. ASSESSMENT WITH IN VIVO PROTON MR SPECTROSCOPY.

Children with very low birth weight (VLBW; birth weight ≤ 1500 g) are especially at risk of later neurodevelopment problems, while infants born at term but small for gestational (SGA; birth weight < 10^{th} percentile) are at some risk of evolving neurological impairments. The objective of this study was to evaluate possible differences in brain metabolites among VLBW and SGA children compared with a control group; children born at term with birth weight > 10^{th} percentile, using in vivo MRS at 1.5T and univariate and multivariate analysis. Spectra (n=54) were acquired from volumes localized in the left frontal lobe, containing mainly white matter. Peak areas of NAA, tCho and Cr were estimated and peak ratios determined. The calculated metabolite ratios NAA/Cr, tCho/Cr and NAA/tCho showed no significant differences between the groups when using the Kruskal Wallis test. By application of PNN a correct classification of 52 of the 54 adolescents with sensitivity and specificity exceeding 93% for all groups were achieved. Small, yet systematic, differences in metabolite distribution among the groups were thus confirmed.

Paper II

Sjøbakk T.E., Lundgren S., Kristoffersen A., Singstad T., Svarliaunet A.J., Sonnewald U. Gribbestad I.S. *Acta Radiologica (2006) 45 (5):501-508.*

CLINICAL ^{1}H MR SPECTROSCOPY OF BRAIN METASTASES AT 1.5T AND 3T

Previous studies of the effects of increased magnetic field have found variable improvements in signal-to-noise-ratio and spectral resolution in spectra when similar anatomic regions and analyzing parameters are compared. The aim of this study was to investigate whether improvements in SNR and spectral resolution were found in spectra from patients with BM obtained at higher magnetic field strengths using standard clinical instrumentation. Six patients with BM, thirteen healthy volunteers and a phantom containing brain metabolites were examined using two clinical MR instruments operating at 1.5T (Siemens) and 3T (Philips) with standard clinical head coils. The spectra were obtained using the PRESS pulse sequence, echo times 32 ms and 144 ms and repetition time 2000 ms from a volume-of-interest (VOI) with size 15x15x15mm^3. SNR and spectral resolution of the metabolites NAA, tCho and Cr were compared at 1.5T and 3T. In general spectral resolution was improved by 25-30 % at higher magnetic field strength. Only minor improvements in SNR were obtained at 3T using short echo time and 20-50% at long echo time. Several factors influence the SNR of MR spectra, such as definition of the actual VOI size, which can vary between different MR systems. The effective VOI sizes have great impact on the measured SNR.

Paper III

Sjøbakk T.E., Johansen R., Bathen T.F., Sonnewald U., Kvistad K.A., Lundgren S., Gribbestad I.S. Submitted BMC Cancer, 2007.

METABOLIC PROFILING OF HUMAN BRAIN METASTASES USING IN VIVO PROTON MR SPECTROSCOPY AT 3T.

Brain metastases are an oncologic challenge with general poor prognosis. Proton (^{1}H) in vivo MRS can be used to quantify metabolites and monitor response to therapy in brain tumors, thereby allowing non-invasive monitoring of tumor biochemistry. The objectives of this study were to investigate the feasibility of using proton MRS and multivariate analyses to characterize BM originating from different primary cancers, to assess changes in spectra during radiation treatment and to correlate the spectra to clinical outcome for the patients after treatment. Single volume ^{1}H MRS was performed on patients (n=26) with BM using a 3.0T clinical MR system. The spectra were obtained before start, immediately after and two months after end of treatment. Signals from lipids and choline containing compounds dominated the MR spectra. The spectral data were analyzed by using principal component analysis (PCA) and partial least square regression analysis (PLS) in order to identify any differences in the metabolic pattern due to origin of metastases and to relate clinical outcome (survival) of the patients to spectral data from the first MR examination. The PCA results indicated that BM from primary lung and breast carcinoma were separated into two clusters, while the metastases from malignant melanomas showed no uniformity. The PLS analysis showed a significant correlation between MR spectral data before start of treatment and survival five months after MRS.

Paper IV

Sjøbakk T.E., Johansen R., Sonnewald U., Juul R., Torp S., Lundgren S., Gribbestad I.S. Accepted by NMR in Biomedicine, 2007, in press.

CHARACTERIZATION OF BRAIN METASTASES USING HR MAS MR SPECTROSCOPY.

The overall prognosis for patients with BM is generally poor. Survival varies with type of primary cancer, age and performance status at the time of BM diagnosis as well as extent of extracranial disease. The objectives of this study were to explore spectral characteristics of BM with focus on origins of the primary cancer, and to evaluate the correlation with clinical outcome for the patients using multivariate analyses. HR MAS MR spectra (n=26) were obtained from patients (n=16) with BM using a Bruker Avance DRX600. Standard pulse-acquired ^{1}H and spin echo (TE 32 and 285 ms) spectra were obtained. The data was examined using PCA and PLS regression relating spectral data to clinical outcome. The PCA score plot of pulse-acquired HR MAS spectra showed a trend of clustering due to different origin of the metastases, mainly based on differences in the lipid signals at 1.3 and 0.9 ppm. The short echo time spectra gave the best PLS results. Spectra of patients who passed away before five months after surgery appeared to cluster in the lower left quadrant of the score plot. Due to the possibility of differentiating metastases related to origin and predicting survival by PCA and PLS analysis, these type of analyses have a great potential to be useful tools in diagnosis of cancer patients in the future.

Discussion

Characterization of brain metabolites in adolescents

The ability to noninvasively obtain biochemical information by using in vivo MRS has been utilized in several studies of the pediatric brain. These studies have revealed MRS as useful in characterization of brain maturation and malignancy of pediatric brain tumors, as well as assessing treatment response (42,86-88). MRS might also provide information relevant to understand disease processes in pediatric brain, such as genetically directed structural and metabolic diseases without surgery (48). Children with low birth weight have been found to be at some risk of evolving neurological impairments (3,4,89). In the purpose to evaluate cerebral metabolite differences in adolescent born with very low or normal birth weights, single volume MRS were performed in their frontal lobe where no MRI pathologies were observed (Paper I). The spectral differences between the groups were too small to be resolved by standard analyses such as peak ratios and univariate statistical test. This might be due to the uncertainties in the peak integrals estimation from in vivo spectra which might be inaccurate due to distorted base line and overlapping peaks such as tCho. As demonstrated in previous studies neural networks are able to resolve hidden spectral differences (90-92) and the use of PNN a classification of the three groups was achieved based on small, yet systematic variations in the metabolic distribution in the adolescents. This was consistent with clinical observations of motor skills, psychiatric symptoms and disorders diagnosed in the same participants in other studies (3,4).

Characterization of brain metastases

Biochemical monitoring of cerebral neoplasms using MRS has during the last two decades provided useful information about classification, type and grade of especially primary brain tumors (7,47,93). Also a decision support system for diagnosis and grading of brain tumors using in vivo MRS has been developed (52). In general BM are

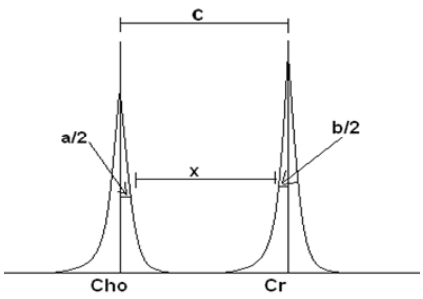
classified as one subgroup of brain tumors (52,94). However, the spectral data from the different BM described in Paper III and IV indicated that subgroups of BM exist. The PCA analysis of short echo time in vivo spectra indicated separation of metastases originating from breast and lung carcinoma in different clusters while the metastases from malignant melanomas showed no uniformity. In Paper IV only two patients with metastases of breast carcinomas were included and comparison to the previous study was not rational. However, the metastases from colorectal carcinomas were clearly separated from lung carcinomas and malignant melanoma metastases in the score plot (Paper IV). The differentiation was not based on single metabolites but rather on multiple differences in the metabolic patterns. Multivariate analyses were necessary to resolve these small, but systematic differences.

In vivo MRS

Use of higher magnetic field strength (≥ 3T) is now common in both research and clinical settings. With the increased access to 3T human MR scanners, comparisons of high field brain spectroscopy to standard clinical system are relevant. Theoretically, an increment by two in field strength should double the SNR and increase the spectral resolution (95-98) However, in addition to magnetic field strength, SNR depends upon the acquisitions parameters, RF coil sensitivity, T_1 and T_2 relaxation times and shimming. Studies comparing spectra from 1.5T and 3T/4T systems have indicated that only half of the theoretical increase in SNR and improvement in spectral resolution of 20 – 50% were obtained when similar anatomic regions and parameters were used (95-97,99). Our study (Paper II) of BM examined at both 1.5T and 3T systems demonstrated the same. The acquisition parameters were chosen as equal as possible at the two different MR systems. The VOI size for a selected metastasis was the same at both systems and the same radiographer performed both examinations. The position of the VOI was attempted to be equal. However, the phantom measurements showed no spectral improvement in SNR at short echo time and close to a two-fold increase at long echo time, indicating differences depending on the chosen acquisition parameters. The definitions of the fixed VOI sizes at the two MR systems gave different effective size of

VOIs, which is crucial for the SNR (Paper II). This effect was largest at short echo time. The T_2 relaxation times for each metabolite have been reported to decrease to various degrees with increased magnetic field (100,101). By correcting the SNR for the T_2 effect of each metabolite observed in Paper II, equal SNR for the two echo time measurements at 1.5T for healthy volunteers and phantom were obtained, while at 3T the values at long echo time become nearly double the corresponding SNR value at short echo time. The difference in effective volume size caused by the definition of pulse bandwidths might be the explanation.

The improvement in spectral resolution with increased magnetic field has in previous work been demonstrated by qualitatively comparisons (95-97). In Paper II we established the equation given in Fig. 8 to estimate the separation of the tCho and Cr peaks. The difference in resolution between the MR systems was thereafter given in percentage in the paper. A limitation of high field scanning is the increased susceptibility artifact caused by magnetic field inhomogeneities (102-104). In heterogeneous tissue like BM this might disturb both spectral resolution and SNR.



$$x = c - (a/2 + b/2)$$

Figure 8. Equation used for estimation of differences in resolution between spectra obtained at different magnetic field. X: resolution, c: distance between peaks, a and b: ½ Full-width-half-maximum of Cho and Cr peak, respectively. All variables are given in ppm.

MRS is an image-guided technique where the image quality of the anatomy and pathology of interest is of great importance for the selection of VOI localization. Of several localization sequences the pulse sequences PRESS and STEAM (stimulated

echo acquisition mode spectroscopy) are most common. STEAM is often used at short echo time when TE < 30 ms is required, while PRESS which provides better SNR is preferred when longer TE can be used. All spectra in this thesis were obtained using PRESS with different echo times, since STEAM was not implemented at 3T at the time. To obtain optimal quality of biochemical information from in vivo MR spectra it is also important to avoid motion artifact. Patient's movement might result in contribution from outside the chosen anatomical VOI. Care was taken to avoid this kind of artefact as much as possible.

HR MAS MRS

The HR MAS technique gives high quality MR spectra of whole tissue samples with no special pre-treatment (61,62,105). The storage of intact tissue and immediate analysis leads to minimal manipulation of the specimens. The effect of long time storage on biopsies biochemical profile has been discussed in previous studies (83,106). The effect of high spinning rate on the sample quality following histopathologic analysis has been shown to be of negligible importance (70,83,107). The HR MAS study of BM (Paper IV) confirm the potential of the technique demonstrated in previous studies where tissue samples of breast, prostate, cervix and primary brain tumors have been investigated (20,58,60,62,67,69). The use of both standard pulse-acquired and spin echo sequences gives information about both metabolites with short and long T_2 and complete the assignment of metabolic profiles. HR MAS spectra are also an important contributor for assigning in vivo spectra obtained in corresponding tissues, since they contain all resonances that can be observed in these (20,69).

Multivariate data analyses

In general, MRS differentiation of cancer tissue from normal brain tissue is often clear due to abnormal proportions of metabolite signals from choline containing compounds, NAA, Cr and lipids (7,18,47). Peak fitting analysis and ratio calculations have been reported as methods to distinguish between normal and abnormal brain tissue conditions

(108). When investigating spectra from same type of tissue (e.g. different BM), multivariate data analyses have demonstrated to be a useful tool to explore hidden spectral information (60,71,109-111). The capability of multivariate data analyses to use the entire spectrum with all its resonances simultaneously is one of the major advantages. No peak assignment is required, and overlapping resonances do not have to be separated in advance. The comparison of data analyses in Paper I shows how the multivariate analysis PNN is able to classify different groups while traditionally univariate analyses (Kruskal Wallis test) did not. Another advantage is the possibility to compare spectra obtained from samples with different sample weight or VOI by normalizing the spectra mutually before the analyses. This was utilized both in Paper III and IV where two sizes of VOI and a mixture of sample weights were used.

Which multivariate analysis to use, depends on the original data set and the investigation purposes. PCA and PLS are well established, simple methods to be used if linear combination of original variables gives an adequate model, while supervised non-linear method such as PNN might be useful in non-linear situations.

Correlation of ex vivo and in vivo MRS to clinical outcome

Implementing in vivo MRS, especially MRSI has been reported to be valuable for treatment planning and follow-up examinations of gliomas (112). Appropriate analysis of proton MRSI data is also suggested to predict survival in patients with supratentorial gliomas in comparison to clinical-pathological features that include invasively acquired data (56). When the treatment strategy is surgery, HR MAS analysis gives easily the metabolic profile of the tissue which might be useful in the further diagnostic of the disease (71).

Both Papers III (in vivo) and IV (ex vivo) present PLS results indicating a significant correlation between spectral data obtained before start of treatment and outcome five months later. The PLS results for both studies are presented in Fig. 9 as score plos of PC1 versus PC2 with corresponding regression coefficients. The spectra of patients

who passed away before five months are clustered in the lower left quadrant of both PLS score plots. The HR MAS spectra with short echo time gave the best PLS results regarding numbers of valid PC's and the significance of correlation coefficients (Paper IV).

These PLS results indicate that multivariate analysis of the MR spectra of BM before start of treatment can be used to predict survival in these patients on the basis of biochemical data of their tumors obtained by MR spectroscopy. This provides useful information for individualized patient prognosis which might be used in treatment planning of BM patients and also for deciding termination of further therapies. However, the relatively small number of subjects analyzed in these studies necessitates further validation in larger cohorts of patients before any clinical implementation.

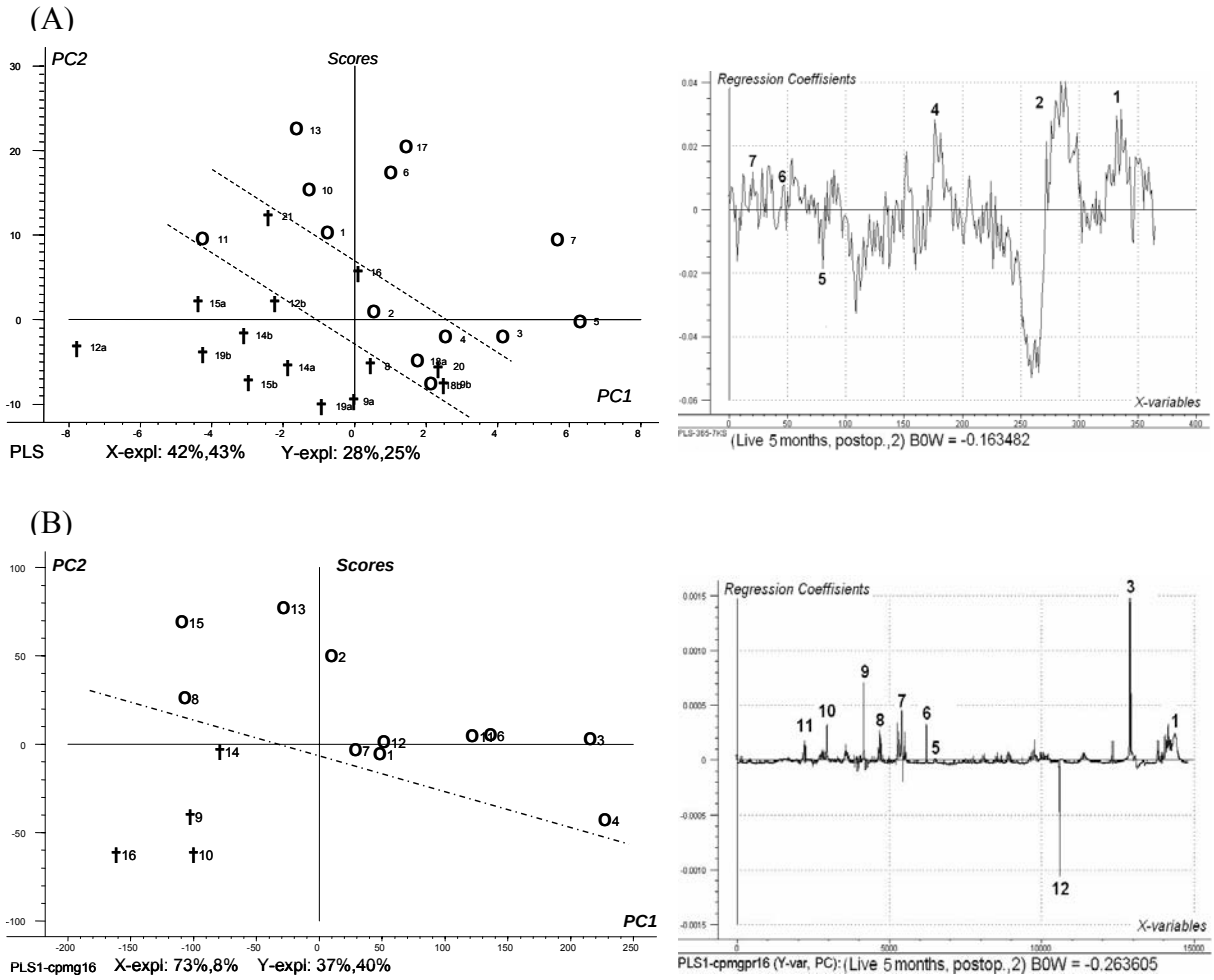


Figure 9. PLS score plots showing the dispersion of **A**) in vivo MR spectra (n=27) and **B)** ex vivo HR MAS spin echo spectra (n=15) from patients who lived longer than five months after the first MR examination, marked as **o**, and those who passed away before 5 months, marked as **†**. The two first principal components are shown with the corresponding regression coefficients; PC1 and PC2. The numbers represent following metabolites: 1: lipid (0.9 ppm), 2: lipid (1.3 ppm), 3: lactate (1.3 ppm), 4: lipid (2 ppm), 5: lipid (2.8 ppm), 6: creatine (3.0 ppm), 7: choline containing compounds (3.2 ppm), 8: taurine (3.4 ppm), 9: glycine (3.6 ppm), 10: creatine (3.9 ppm), 11: lactate (4.1 ppm), 12: acetate (1.9 ppm).

Conclusion

The work presented in this thesis demonstrates that the effect of doubling the magnetic field in BM spectra was much less than expected. This was mainly due to differences in effective size of VOI, caused by different instrumental set-up for VOI definition at the various clinical scanners. The improvement in spectral resolution was about 25 -30 % in the spectra from both BM and healthy brain tissue.

Proton in vivo spectra of brain tissue giving metabolic pattern with non-significant differences in metabolite ratios can be resolved and classified by non-linear multivariate analysis (PNN). Hence, it was possible to resolve differences in cerebral metabolite patterns in adolescents regarding whether they were low-birth-weight children or controls. These results were consistent with MRI findings, motor skills, psychiatric symptoms and disorders detected in the same participants.

Both in vivo and ex vivo proton spectra of different brain metastases analyzed by linear multivariate analyses show a possible differentiation related to origin. The present findings suggest that multivariate analysis of the different MR spectra can be used to predict survival in patient with BM on the basis of their tumors biochemical data obtained by MR spectroscopy. Hence, this provides useful information for individualized patient prognosis which might be used in diagnosis and treatment planning of BM and also for decisions of termination of further therapies. However, it is important that classification and prediction of survival of BM patients based on spectroscopic analyses is validated in larger cohorts of patients.

In conclusion, in vivo and ex vivo MR spectroscopy can determine metabolic pattern on clinically highly relevant questions.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
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
159. xxxxxxxxx (blind number)
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.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
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
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
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
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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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
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
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
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
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
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